Medicines Adverse Reactions Committee

Meeting date	**14 March 2019**	Agenda item	3.2.3
Title	**Use of methadone during breastfeeding**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Methadone	**Medicines** Biodone oral solution Methadone injection Methadone Molteni oral solution Methatabs tablet	**Sponsors** Biomed AFT Boucher & Muir PSM Healthcare	
Funding	Biodone, Methadone injection and Methatabs are fully funded by PHARMAC		
Schedule	Prescription medicine (controlled drug)		
Usage data	Approximately 5,314 people receiving opioid substitution treatment (with methadone, or buprenorphine + naloxone) in 2016 [1]		
Advice sought	The Committee is asked to advise whether there are any regulatory actions that should be taken to reduce the risk of adverse effects in infants exposed to methadone through breast milk.		

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1.0 PURPOSE

There have been worldwide cases of deaths in infants exposed to methadone through breast milk. Small amounts of methadone can be passed to infants through breast milk and this may lead to respiratory depression, heart problems and death.

Methadone is predominantly used for opioid substitution treatment (OST) in New Zealand. It is also used in treating moderate to severe pain. The pharmacokinetics of methadone varies greatly between individuals. Plasma concentrations can vary widely between patients and fluctuate greatly within the same patient. It is possible that genetic differences result in some infants being more sensitive to effects of methadone than others but these genetic factors are not well understood.

Although exclusive breastfeeding is recommended for the first 6 months of life, the Growing Up in New Zealand study found low adherence to this guideline (35% adherence). This could be due to social and environmental barriers (eg, lack of family and broad social support, returning to work, inappropriate or lack of facilities for breastfeeding, cultural beliefs and practices that limit breastfeeding duration and/or include early introduction of complementary foods) and clinical barriers (eg, lack of access to antenatal education and postnatal support, lack of routine follow-up care and home visits for mothers). These barriers as well as changes in timing of feeds and timing of methadone doses may affect the concentrations of methadone transferred into breast milk and to the infant. Furthermore, mothers taking methadone who suddenly stop breastfeeding may induce withdrawal symptoms in their infants.

The *New Zealand Practice Guidelines for Opioid Substitution Treatment 2014* and methadone data sheets for products indicated for opioid substitution generally encourage mothers on methadone to breastfeed. This is because breastfeeding has many benefits including mother-infant bonding, nutrition and prevention of childhood illness, and may reduce the severity of neonatal abstinence syndrome (NAS).

The purpose of this paper is to review information on the use of methadone during breastfeeding to ascertain if any regulatory action can be taken to reduce the risk of adverse effects in the infant.

2.0 BACKGROUND

2.1 Opioid dependence

Opioid dependence is a complex, relapsing condition requiring a model of treatment and care similar to other chronic health conditions.

Data from national drug surveys on recreational drug use conducted between 1996 and 2010 in New Zealand suggest levels of opioid use have remained constant over this period with <1% of those surveyed reporting current use [2]. The number of people in New Zealand with opioid dependence was estimated to be 9953 (95% CI 8940–10,967) in a 2008 survey [3, 4]. Half of these regular opioid users (n=4608) were not receiving opioid substitution treatment (OST) [4].

In New Zealand, the community cost of untreated opioid dependence is considerable indicating the importance of OST [5]. According to the results of a local cost-effectiveness analysis, reducing barriers to accessing OST would improve treatment of hepatitis C for injecting drug users on methadone maintenance therapy [6].

2.1.1 Opioid substitution treatment (OST) services usage

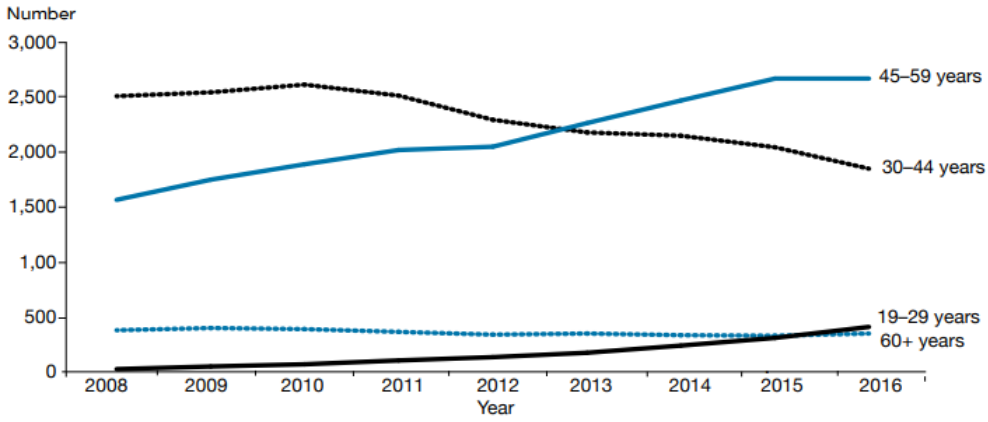
The *Office of the Director of Mental Health Annual Report 2016* contains data on opioid substitution treatment (OST) services including the number of people accessing these services (www.health.govt.nz/system/files/documents/publications/office-of-the-director-of-mental-health-annual-report-2016-dec17-v2.pdf) [1].

There are two medicines used for opioid substitution treatment (OST) in New Zealand: methadone, and buprenorphine + naloxone (Suboxone). One of the key objectives of OST is to improve the physical and

psychological health and wellbeing of the people who use opioids. There is movement away from a maintenance-treatment model towards a client-led, recovery-focused treatment. OST attempts to promote a tripartite partnership approach between the client, the specialist service or primary care team, and the client's nominated support people (eg, advisors, representatives, peer-support workers, and family and whānau) to improve outcomes for clients and services [2].

In 2016 there were 5314 people receiving OST. Of these 5314 people 78% were New Zealand European, 14% were Māori, 1% were Pacific peoples and 7% were of another ethnicity. Approximately 28% of people receiving OST were being treated by a GP in a shared-care arrangement.

OST clients are an aging population; those >45 years are the most likely to be receiving treatment (Figure 1). In 2016, the overall portion of clients >45 years was 58.2%.

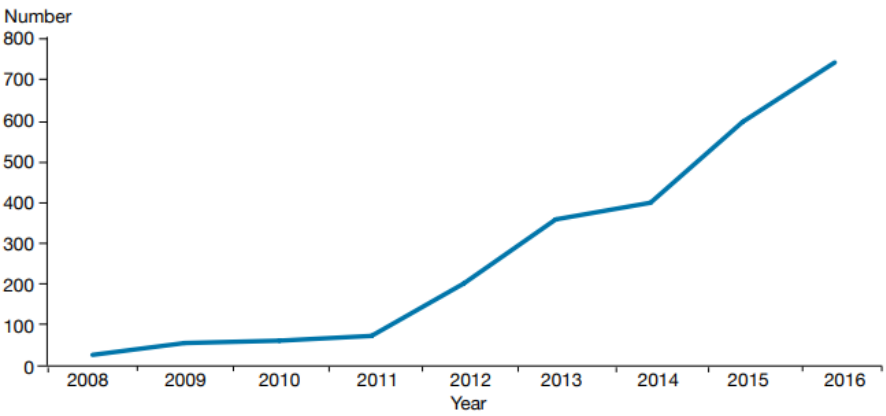


Source: Data provided by OST services in six-monthly reports

Figure 1: Number of opioid substitution treatment clients, by age group, 2008-2016

Between 2015 and 2016 the number of clients accessing OST services decreased by 69. This decrease is not consistent with previous years where services typically increased by 70–150 clients per year.

Since July 2012 PHARMAC has funded Suboxone (buprenorphine + naloxone) for OST (Figure 2). Since then there has been a steady increase in the number of people prescribed it. Suboxone lowers the risk of diversion and its misuse is lower than that associated with methadone. In addition, Suboxone can be given in cumulative doses that last several days, rather than the daily dosing regimen that is required with methadone.



Source: Data provided by OST services in six-monthly reports

Figure 2: Number of people prescribed Suboxone, 2008-2016

OST in New Zealand is provided by specialist addiction services and primary health care teams. Transferring care to a shared-care arrangement with primary care offers many benefits, including allowing specialist

services to focus on those with highest need and normalising the treatment process. Ensuring services are delivered seamlessly across providers will be an important focus in future. The Ministry of Health's target for service provision is 50:50 between primary and specialist care. Nationwide in 2016, general practice delivered approximately 28% of OST and specialist services approximately 71%.

Comments:

There were approximately 4500 patients prescribed methadone for OST in 2016 (based on the number of people prescribed Suboxone and the total number of people receiving OST). 58.2% of clients in 2016 were >45 years of age. The median age of women giving birth in 2015 was 30 years (see Ministry of Health report on maternity: www.health.govt.nz/system/files/documents/publications/report-on-maternity-2015-updated_12122017.pdf).

Although methadone is approved for use in both OST and moderate to severe pain, this paper focuses on the use of methadone in OST as there are other non-opioid and opioid alternatives to methadone for treating pain in breastfeeding women (see American College of Obstetricians and Gynecologists guidance: www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/CO742.pdf?dmc=1&ts=20190211T1754578416 and section 3.2.3.1).

2.1.2 Opioid substitution treatment (OST) in pregnant and breastfeeding women

The *New Zealand Practice Guidelines for Opioid Substitution Treatment 2014* is shown in Annex 1 and can be accessed electronically here: www.health.govt.nz/system/files/documents/publications/nz-practice-guidelines-opioid-substitution-treatment-apr14-v2.pdf.

According to these guidelines pregnant women are eligible for priority access to opioid substitution treatment (OST) and are encouraged to enter OST as early as possible [2, 7]. Methadone is currently the preferred treatment for pregnant women entering OST as there is a greater body of data about long-term efficacy and safety with respect to its use in both pregnancy and breastfeeding [2].

Illicit opioid use in pregnancy is associated with maternal and fetal acquisition of blood-borne viruses, preterm labour and delivery, intrauterine growth retardation, pre-eclampsia, placental abruption and intrauterine fetal death [2]. OST in pregnancy has been found to reduce illicit drug use, improve maternal engagement in antenatal care and improve neonatal birth weight [2].

During pregnancy, doses between 60–100 mg daily are considered therapeutic [8]. During the third trimester, dose increases are typical, and a higher concentration of methadone is transferred across the placental barrier as it becomes more permeable, resulting in reduced maternal plasma methadone concentrations despite an unchanged dose [9-11].

Potential long-term effects of prenatal methadone exposure on fetal and infant development are not well characterised [12]. Adverse outcomes result from both direct exposure to illicit opiates and/or therapeutic agents (eg, methadone), as well as companion interactive and additive effects from co-occurring risk factors (eg, abuse of alcohol, tobacco and other prescription medicine; socioeconomic status; education; nutrition and prenatal care etc.) [13]. It is possible environmental risk factors together with prenatal exposures promote epigenetic changes in gene expression and methylation patterns that have both immediate and long-term implications related to developmental programming [14].

The use of methadone during breastfeeding has many benefits, including mother-infant bonding, nutrition and prevention of childhood illness, and may reduce the severity of neonatal abstinence syndrome (NAS) [2, 15]. OST service providers should encourage opioid-dependent mothers to breastfeed, with the possible exception of HIV-positive mothers or those using alcohol or cocaine and amphetamine-like substances.

Methadone is transferred into breast milk at very low levels. The American Academy of Pediatrics classifies methadone as compatible with breastfeeding [16]. OST service providers should advise women who are breastfeeding while on high doses of methadone to wean slowly to minimise any risk of withdrawal in the infant.

Buprenorphine is also transferred into breast milk at low levels [2]. As infants swallow milk, absorption of buprenorphine from breast milk would be expected to be minimal due to hepatic first-pass metabolism [2]. However, the extent of oral bioavailability of buprenorphine in infants is unknown due to immature hepatic function [2]. The limited data regarding the effects of buprenorphine on the development of breastfed babies suggest it is safe to use however a cautious approach incorporating a risk-benefit analysis and fully informed maternal consent is recommended [2]. Like pregnant clients, breastfeeding clients should use the buprenorphine mono-product (Subutex) to avoid unnecessary exposure of the infant to naloxone [2].

Comments:

The buprenorphine mono-product (Subutex) is recommended for use in pregnant and breastfeeding women rather than Suboxone as it contains naloxone. Subutex is not an approved product in New Zealand.

The approved and funded OST products are methadone (Biodone) and buprenorphine with naloxone (Suboxone). Applications for funding for the buprenorphine mono-product (Subutex) in pregnant and breastfeeding women is via PHARMAC's named patient pharmaceutical assessment (NPPA) process and funding is not assured. There has been one approval for funding of Subutex for OST in a pregnant woman under the NPPA scheme during 1 March 2012 to 31 August 2017 (www.pharmac.govt.nz/tools-resources/forms/exceptional-circumstances/nppa-decisions/).

PTAC has previously considered the funding of Subutex in pregnant women in 2015. PTAC recommended declining the application to fund Subutex in women receiving Suboxone for OST who subsequently become pregnant. PTAC also recommended Subutex should not be funded for use in breastfeeding women.

2.1.3 Neonatal abstinence syndrome (NAS)

Neonatal abstinence syndrome (NAS) defines a set of symptoms that arise primarily in neonates who have been exposed to opioids during gestation [16]. It occurs in about 60–90% of neonates exposed to methadone in utero [2]. Babies born to mothers dependent on methadone show more frequent and severe signs than heroin-dependent mothers [17].

All infants of opioid-dependent women should be monitored for development of withdrawal symptoms which generally start within 48 hours of delivery but may be delayed by up to 7–14 days [2]. Symptoms include jitteriness, a high-pitched cry, diaphoresis and diarrhoea [16]. The severity of withdrawal should be measured using a validated scale such as the Modified Finnegan Scale [2].

Where possible, infants of opioid-dependent women should receive follow-up care and monitoring for developmental abnormalities from paediatricians with experience in managing children with in-utero exposure to substances of abuse [2].

A number of factors have been found to affect the occurrence and severity of NAS. Antenatal smoking and use of benzodiazepines are likely to increase incidence and severity [2]. Conversely, breastfeeding and neonates rooming with their mothers rather than in a nursery may improve symptoms [2]. A substantial decrease in neonatal withdrawal severity (decrease in number of infants requiring pharmacological treatment and length of treatment) in mothers who initiated breastfeeding while on methadone, buprenorphine or opiates for chronic pain has been found [12].

There have been studies on whether the prenatal maternal methadone dose is related to the diagnosis or severity of NAS [12]. Some studies have found the maternal methadone dose to be unrelated, while other studies exploring doses in the 3rd trimester have found an association with longer neonatal hospital stays.

Duration of drug exposure in utero is an additional factor that dictates the severity of withdrawal. Longer gestation contributes to NAS severity due to high permeability of the placental barrier during the 3rd trimester resulting in increased levels of fetal methadone exposure nearing delivery [12]. OST with methadone has been associated with shorter gestation [12]. There are also genetic contributions to whether postnatal pharmacological treatment is needed. Logan et al found single nucleotide polymorphisms (SNPs) of the μ-opioid receptor (OPRM1, variant A11AG) and catechol-o-methyltransferase (COMT) genes affect NAS severity and need for pharmacological treatment [12].

According to Starship Hospital's guidelines for infants born to drug dependent mothers (www.adhb.govt.nz/newborn/Guidelines/SubstanceUse/DrugDependentMothers.htm) [17] treatment of withdrawal is with morphine 1 mg/mL solution. A starting dose of 0.5 mg/kg/day in 4 divided doses (6 hourly) is used. It is administered directly into baby's mouth by syringe. The dose is reduced by 10–15% every 2–3 days if possible. An alternative treatment is chlorpromazine 2.2 mg/kg/24 hours given in 4 divided doses either orally or by injection. Breastfeeding is encouraged regardless of the drugs that have been taken by the mother. About half of affected infants requiring treatment need it for 10–20 days and one-third for up to 49 days after birth. Mortality is thought to be about 3% but with treatment should be virtually nil.

3.0 SCIENTIFIC INFORMATION

3.1 Methadone

3.1.1 Mechanism of action

Methadone is an opiate agonist interacting primarily with the μ receptor to suppress opiate withdrawal, cravings and the reinforcing effects of opioids [2, 16, 18]. Its precise mechanism of action in producing analgesia is not fully known but it alters the perception of pain in the spinal cord and higher levels in the central nervous system (CNS) and the patient's emotional response to pain [18]. In addition to analgesia, the effects of methadone in the CNS cause suppression of the cough reflex, respiratory depression, drowsiness, sedation, change in mood, euphoria, dysphoria, mental clouding, nausea and vomiting, and EEG changes [18].

It is thought that methadone exerts secondary effects by acting as an *N*-methyl-D-aspartate receptor antagonist blocking the actions of glutamate, the primary excitatory neurotransmitter in the CNS [16]. Opioids acutely inhibit the release of noradrenaline at synaptic terminals and with chronic exposure, tolerance develops as the rate of noradrenaline release over time increases toward normal [16]. Abrupt discontinuation of exogenous opioids results in supranormal release of noradrenaline and produces the autonomic and behavioural signs and symptoms characteristic of withdrawal [16].

Methadone is formed by a racemic mixture of (R) and (S) enantiomers where the (R) enantiomer accounts for the complete opioid effect felt by patients [19].

3.1.2 Pharmacokinetics

Methadone is readily absorbed after oral administration and has high oral bioavailability [18]. Peak plasma concentrations occur at 4 hours but this varies widely among individuals [18]. It takes an average of 4 days to reach steady state [2].

Methadone undergoes considerable tissue distribution and protein binding is reported to be 60 to 90% with a1,-acid glycoprotein being the main binding protein in the plasma [18]. Volume of distribution is 5 L/kg [18].

Methadone is a major substrate of CYP2B6 and CYP3A4; it is a minor substrate of CYP2C19, CYP2C9 and CYP2D6 [20]. Metabolism to the major metabolite 2-ethylidine-1,5-dimethyl, 3,3-diphenylpyrrolidine and the minor metabolite 2-ethyl-3,3-diphenyl-5-methyplyrrolidine, both of them inactive, occurs in the liver [18]. These metabolites are excreted in the faeces and urine together with unchanged methadone [18]. Other metabolites, including methadol and normethadol (reported to be pharmacologically active), have also been described but account for a small proportion of the dose [18]. The liver may also serve as a major storage site of unchanged methadone, which is taken up, bound non-specifically by the liver and released again mainly unchanged [18].

Marked inter-individual variations in kinetics have been observed with methadone. Elimination half-lives vary considerably (range of 15 to 60 hours has been reported) and careful adjustment of dose is necessary with repeated administration, after which there is a gradual accumulation in the tissues [18].

Plasma concentrations have been found to vary widely during methadone maintenance therapy with large differences between patients and wide fluctuations in individual patients [18]. Declining concentrations have been reported during methadone maintenance suggesting that tolerance occurs, possibly as a result of auto-induction of hepatic microsomal enzymes [18].

Comments:

Methadone mimics many of the pharmacological effects of morphine, but with a longer half-life. The pharmacokinetics of methadone varies greatly between individuals. Plasma concentrations can vary widely between patients and fluctuate greatly within the same patient. Methadone also accumulates in tissues with repeated doses.

Due to its mechanism of action, the undesirable effects of respiratory depression and QT prolongation are known to occur with methadone.

3.1.3 Genetic polymorphisms

A publication by Madadi et al [21] reported on two cases where methadone was detected in deceased neonates whose mothers were in methadone opioid substitution treatment (OST) programmes and were breastfeeding. The authors found that one of the deceased infants was homozygous for the CYP2B6*6 variant and both infants were heterozygotes for ABC1B1 variants 1236C>T, 2677G>T/A and 3435C>T. The medical cause of death was unascertained in both cases.

CYP2B6 is present at birth and the expression of CYP2B6 is correlated with increased age up to approximately age 1 at which time expression levels are similar to adults [22]. The CYP2B6 genotype (specifically *6/*6) appears to be associated with increased methadone concentrations in adults, likely through decreased metabolism via CYP2B6. Pharmacogenetic studies in the literature conducted in paediatric populations are limited to small case studies. However, the effect of CYP2B6 genotype is consistent throughout the literature (based on data from several reasonably-sized studies).

Other than CYP2B6, a genome-wide association study (GWAS; n=~450) [23] evaluated methadone maintenance concentrations in adults. This GWAS study found rs17180299 (located in an intergenic region) accounted for ~9% of variation in methadone (R/S) exposure; variants of SPON1, GSG1L and CYP450 genes including CYP2B6 were also significantly associated with the plasma concentrations of methadone. In total, the identified genetic variations accounted for approximately 10% and 25% of the variations in plasma concentrations of methadone (R/S).

ABC1B1 gene variants were also detected in cases reported by Madadi et al. However, the impact of ABC1B1 variants on methadone concentrations are much less substantially validated. Few literature reports of p-gp variant (1236C>T, 2677G>T/A and 3435C>T) effects on methadone disposition are very small and marginally significant in almost all cases.

Comments:

Genetic polymorphisms of CYP2B6 appears to impact methadone pharmacokinetics in adults though data in infants are limited. In addition, the effect appears too small to result in infant fatalities from the amount of methadone that would be transferred through breast milk.

There are genetic polymorphisms of other enzymes that metabolise methadone (eg, CYP2D6, CYP2C19) but there are limited data on these effects on methadone pharmacokinetics, and methadone is a minor substrate of these enzymes.

3.2 Breastfeeding

3.2.1 Benefits of breastfeeding

The evidence for benefits of breast milk is obtained largely from observational cohort studies and epidemiological analyses [24]. However, the presence of biological plausibility as well as close and frequently observed associations between breastfeeding and various health benefits suggests a causal relationship exists [24].

Breast milk is thought to help protect infants from tummy upsets, ear infections and respiratory infections, and may reduce the risk of diabetes, obesity and sudden unexpected death of an infant (SUDI) [25]. Breastfeeding may reduce the chance of an infant developing allergies if there is family history of food allergies [25]. It helps mothers recover after birth, reduce weight gained in pregnancy and reduces the risk of breast cancer [25]. It also helps to promote bonding between mother and infant.

Any decision to stop breastfeeding should be carefully balanced with the benefits that breast milk is thought to provide.

3.2.2 New Zealand breastfeeding statistics

The Ministry of Health and World Health Organization (WHO) recommend mothers exclusively breastfeed their infants for their first 6 months of life [26, 27]. After 6 months, the Ministry of Health recommends starting solid food and to continue breastfeeding until the infant is at least 1 year old [26].

Plunket – Breastfeeding statistics 2013 to 2017

Breastfeeding statistics as published on Plunket's website (www.plunket.org.nz/news-and-research/research-from-plunket/plunket-breastfeeding-data-analysis/annual-breastfeeding-statistics/) for 2013 to 2017 are shown in Figure 3. The definitions are as follows:

- Exclusive: The infant has never, to the mother's knowledge, had any water, formula or other liquid or solid food. Only breast milk from the breast or expressed breast milk and prescribed medicines have been given from birth.
- Full: The infant has taken breast milk only. No other liquids or solids except a minimal amount of water or prescribed medicines in the past 48 hours.
- Partial: The infant/child has taken some breast milk and some infant formula or other solid food in the past 48 hours.
- Artificial: The infant/child has had no breast milk but has had alternative liquid such as infant formula with or without solid food in the past 48 hours.

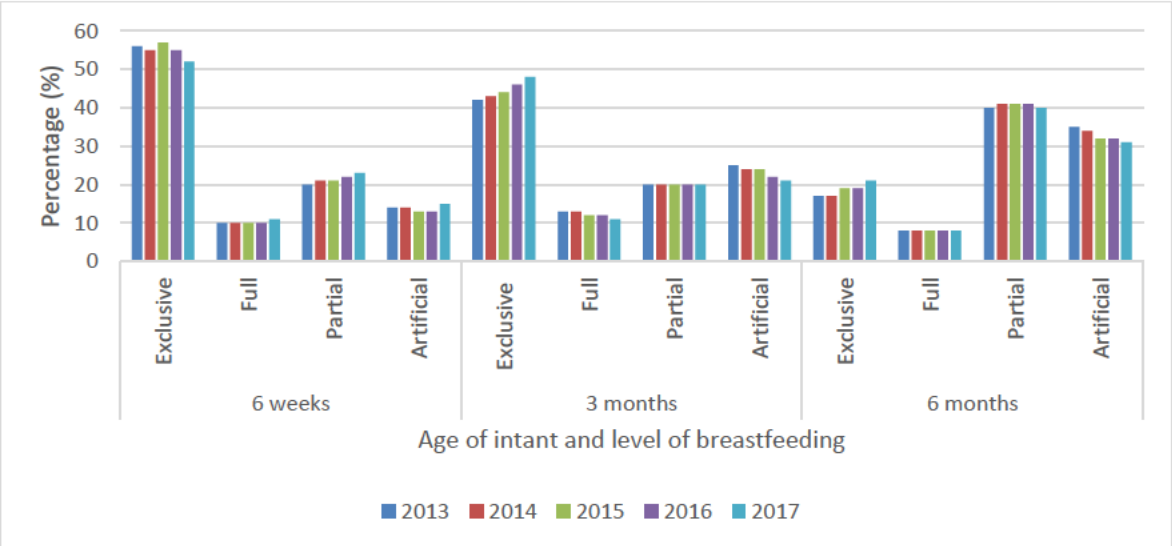


Figure 3: Plunket's annual breastfeeding statistics, New Zealand, 2013 to 2017 [28]

Ministry of Social Development – Report on infant feeding

A report on *Infant Feeding in New Zealand – Adherence to Food and Nutrition Guidelines among the Growing Up in New Zealand cohort* was published by the Ministry of Social Development in November 2018 (www.msd.govt.nz/documents/about-msd-and-our-work/publications-resources/research/infant-feeding/infant-feeding-in-new-zealand.pdf) [29]. Data was collected by the University of Auckland. A total of 6470 infants participated in this 9-month interview. 35 children had missing information and were excluded so the report presents data on 6435 infants.

A total of 13 indicators, including two indicators for breastfeeding, were included in this report:

- Breastfeeding duration to 12 months.
- Exclusive breastfeeding to around 6 months of age.

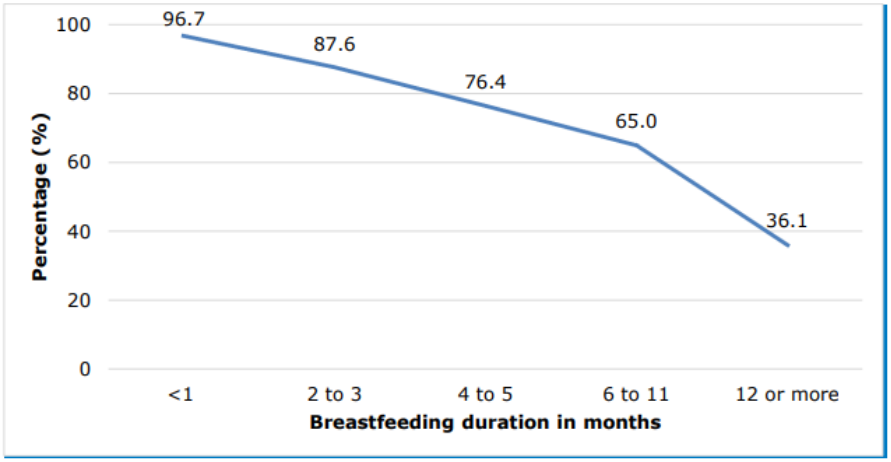
Overall of the 13 indicators, the breastfeeding domain had the lowest median score where 15.8% of infants met both the critical guidelines of exclusively breastfeeding to around 6 months, and breastfeeding for 12 months or beyond. There was generally low adherence to breastfeeding guidelines with a 35% adherence to exclusive breastfeeding duration to around 6 months and a 37% adherence to breastfeeding duration to 12 months or beyond.

Despite high rates of breastfeeding initiation, a large proportion of infants do not meet the national recommendations for duration of any and exclusive breastfeeding. This was also observed in Australian infants in 2010 (97% in NZ, 96% in Australia). In Australia, 15.4% of infants were being exclusively breastfed past 5 months of age while only 2.1% were exclusively breastfed to age of 6 months. Breastfeeding duration past 13 months of age was observed for less than 20% of Australian infants (18.2%). Despite better indicators for duration of any and exclusive breastfeeding observed in NZ when compared to Australia and other high-income countries, New Zealand is not on track to achieve the global nutrition target for 2025 of at least 50% of infants exclusively breastfed at the age of 6 months.

Further information on these two indicators are provided below.

1. **Breastfeeding duration**

The median breastfeeding duration was 8 months. Just over 1 in 3 children (36.1%) were breastfed for 12 months or beyond (Figure 4). A smaller proportion of twins and infants with a low birth weight were breastfed to 12 months compared to singletons and normal birth weight. First-born infants and those born prematurely, rather than normal gestation, were also statistically less likely to be breastfed to 12 months, but the difference between groups was small.

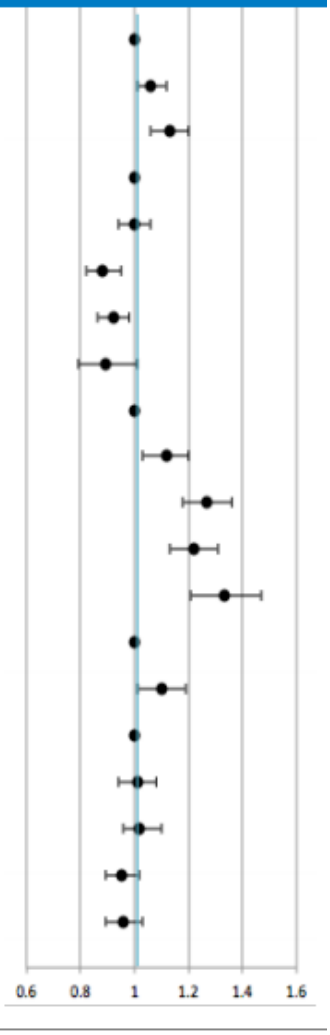


Notes: N=6303 (included the children that were never breastfed in the denominator; excluded children with missing information for total duration of breastfeeding).

Figure 4: Rates of breastfeeding duration according to infant age

After adjustment for differences between groups, women of Pacific and Asian ethnicity were significantly more likely to breastfeed their baby for 12 months or longer than Europeans. Women with a Bachelor's qualification or lower, aged under 35 years, and/or without a partner, were less likely to meet the 12 month breastfeeding duration guideline (Figure 5).

Sociodemographic characteristic		Relative risk	95% confidence interval	Forest plot
Maternal age	≥35 years	Reference		
	25-34 years	1.06	1.01-1.12	
	≤25 years	1.13	1.06-1.20	
Self-prioritised ethnic group	European	Reference		
	Māori	1.00	0.94-1.06	
	Pacific	0.88	0.82-0.95	
	Asian	0.92	0.86-0.98	
	Other	0.89	0.79-1.01	
Maternal education	Higher/postgraduate	Reference		
	Bachelor's degree	1.12	1.03-1.20	
	Diploma/trade cert	1.27	1.18-1.36	
	Sec school / NCEA 1-4	1.22	1.13-1.31	
	No qualification	1.33	1.21-1.47	
Mother had a partner	Yes	Reference		
	No	1.10	1.01-1.19	
Neighbourhood deprivation (NZDep decile)	1-2 Least deprived	Reference		
	Decile 3-4	1.01	0.94-1.08	
	Decile 5-6	1.02	0.96-1.10	
	Decile 7-8	0.95	0.89-1.02	
	9-10 Most deprived	0.96	0.89-1.03	



Notes: Poisson regression model with robust estimation adjusted for maternal age, ethnic group, education, partner status and Neighbourhood deprivation at the antenatal interview. A statistically significant difference from the reference group is shown in bold (Wald chi square test p-value<0.05). Twins and infants born prematurely or with low birth weight were removed from the dataset (*n*=556). The model did not include participants with one or more missing data for maternal or household characteristics. Total N=5045. CI=confidence interval.

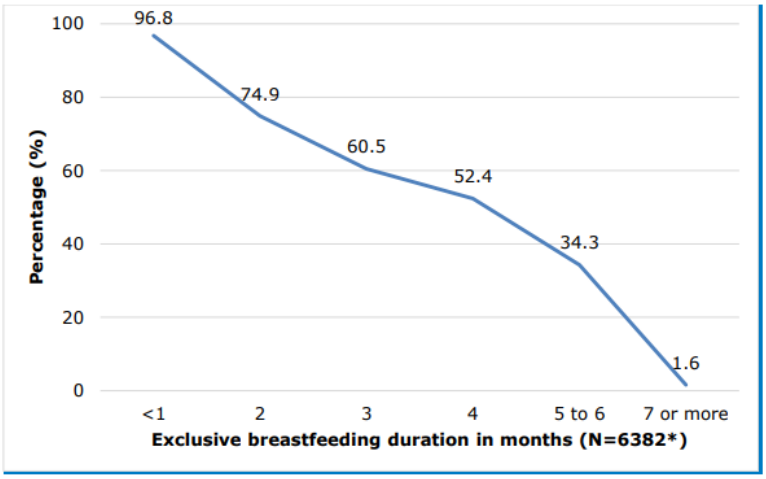
Figure 5: Risk of not meeting the guideline to breastfeed 12 months or more, by sociodemographic characteristics (adjusted)

2. Exclusive breastfeeding duration

The median duration of exclusive breastfeeding was 4 months. 1 in 3 children (34.3%) were exclusively breastfed to around 6 months and a small proportion of infants were exclusively breastfed beyond 6 months of age (Figure 6).

Maternal age and education were the largest drivers of disparities in exclusive breastfeeding duration. After adjustment for differences between groups, women with a Bachelor's qualification or lower were less likely to meet the guideline compared to a higher degree. Mothers aged under 25 years were less likely to meet

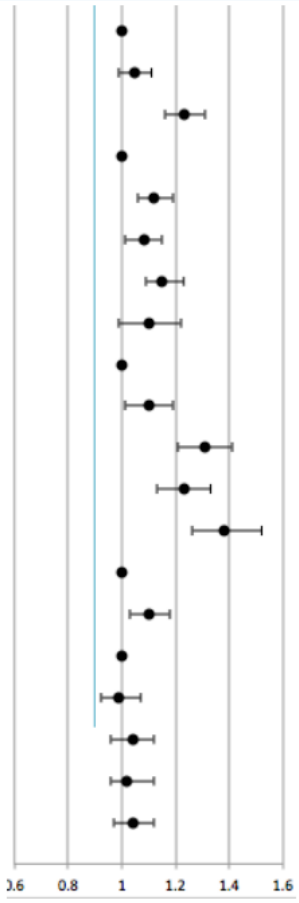
the guideline compared to mothers aged 35 years or older. Asian, Māori and Pacific mothers were also less likely to meet the guideline (Figure 7).



Notes: N=6382*(included the children that were never breastfed in the denominator; excluded children with missing information for total duration of breastfeeding).

Figure 6: Rates of exclusive breastfeeding duration according to infant age

Sociodemographic characteristic		Relative risk	95% confidence interval	Forest plot
Maternal age	≥35 years	Reference		
	25-34 years	1.05	0.99-1.11	
	≤25 years	1.23	1.16-1.31	
Self-prioritised ethnic group	European	Reference		
	Māori	1.12	1.06-1.19	
	Pacific	1.08	1.01-1.15	
	Asian	1.15	1.09-1.23	
	Other	1.10	0.99-1.22	
Maternal education	Higher/postgraduate	Reference		
	Bachelor's degree	1.10	1.01-1.19	
	Diploma/trade cert	1.31	1.21-1.41	
	Sec school / NCEA 1-4	1.23	1.13-1.33	
	No qualification	1.38	1.26-1.52	
Mother had a partner	Yes	Reference		
	No	1.10	1.03-1.18	
Neighbourhood deprivation (NZDep decile)	1-2 Least deprived	Reference		
	Decile 3-4	0.99	0.92-1.07	
	Decile 5-6	1.04	0.96-1.12	
	Decile 7-8	1.02	0.96-1.12	
	9-10 Most deprived	1.04	0.97-1.12	



Notes: Poisson regression model with robust estimation adjusted for maternal age, ethnic group, education, partner status and neighbourhood deprivation at the antenatal interview. A statistically significant difference from the reference group is shown in bold (Wald chi square test p-value<0.05). Twins and infants born prematurely or with low birth weight were removed from the dataset (n=556). The model did not include participants with one or more missing data for maternal or household characteristics. Total N=5045. CI=confidence interval.

Figure 7: Risk of not meeting the guideline to exclusively breastfeed to around 6 months, by sociodemographic characteristics (adjusted)

Comments:

The results from this study indicate sociodemographic factors are significantly related to diet quality, which is also described in the international literature. Among these sociodemographic factors maternal education was the strongest factor associated with adherence to the indicators.

3.2.3 Mechanism of drug transfer into breast milk

Recently in 2018, Ito published a study in the *Journal of Clinical Pharmacology* on the pharmacokinetic principles and clinical implications of opioids in breast milk [24]. Information from this study is summarised in this section.

Key indicators for levels of drug secretion into milk are diffusion-related factors (eg, ionisation characteristics, plasma protein binding, lipophilicity) and substrate specificity for BCRP [24]. These factors influence drug concentration in milk and collectively define the milk-to-plasma drug concentration ratio (MP ratio).

The MP ratio is defined as a ratio of the AUC curve (or average concentrations) between milk and maternal plasma [30]. The MP ratio is sometimes over-interpreted as a sole determinant of the infant drug exposure level which is untrue in most cases because infant exposure levels are also determined by drug clearance [24, 31].

The relative infant dose (RID) is a weight-adjusted time-averaged (eg, daily) dose of medicine in milk ingested by the infant, expressed as a percentage of the time-averaged maternal therapeutic dose on a body weight basis [24]. This PK principle can be visualised as a hyperbolic relationship between RID and clearance (Figure 8).

A RID of 100% is the same as directly receiving a therapeutic dose per weight; RID 10% means the infant dose of drug via milk is 10% of the therapeutic dose per body weight. RID of 10% is often considered a reference point as a safety threshold in risk assessment [30], but lower values such as 5% may be considered a threshold of breastfeeding acceptability for psychoactive drugs [32]. Most drugs are unlikely to achieve RID >10% as the reported MP ratios of most drugs are around 1 or lower and most have a clearance of >1 mL/kg/min [33].

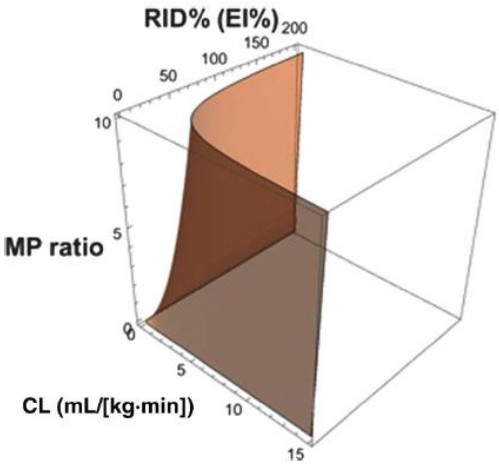


Figure 8: Infant exposure levels (exposure index [EI] or relative infant dose [RID]) to drug in milk [24]
Relative infant dose (RID%) is an infant dose of the drug in milk per time standardised by body weight, expressed as percentage of the corresponding maternal dose on a weight basis. Theoretically, it is defined by maternal drug clearance (CL) and milk-to-plasma (MP) ratio of drug. RID of 100% means the infant would be exposed to the drug in milk at a dose/time equivalent to the mother's dose/time per weight. MP ratios of most drugs are around 1 or less. CL is expressed as mL/kg/min. Bioavailability is assumed to be 1 in this graph.

3.2.3.1 Opioids

Regular use of opioids by the mother during breastfeeding for acute pain management should be limited to less than 2-3 days in unsupervised outpatient settings unless close monitoring of the infant condition is possible because adverse effect profiles of opioids are potentially life-threatening (eg, respiratory depression) [24]. Table 1 summarises some of the commonly used opioids during breastfeeding with key findings from selected studies.

Table 1: Opioid excretion in milk and relative infant dose [24]

Opioid	Main Metabolic Pathway	Active Component	Absolute Infant Dose (μg/[kg·day])[a]	Relative Infant Dose (%)[b]	Comments
Pain management					
Morphine	UGT2B7	M6G[c] is a potent μ-opioid receptor agonist with a significant role in morphine therapy, particularly in chronic therapy.	1-10 (M6G[b] 26-64) [Maternal dose range 60-150 mg/48 h IV[c]]: n = 12[38,39] 15 (based on peak level) [Maternal dose 40 mg/24 h PO]: n = 1[40]	~3% (based on absolute infant dose of 15 μg/[kg·day]; M6G is not taken into account)	Because oral bioavailability of M6G in infants is unknown (10% in adult), clinical significance of M6G in milk is difficult to evaluate.
Codeine Not recommended for breastfeeding women, and contraindicated in children younger than 12 years old.[64]	CYP2D6	Morphine	53 (Morphine 6) [Maternal dose 60 mg q4h PO at steady state]: n = 2[41]	~1% (including morphine; M6G is not taken into account)	Exposure levels to codeine and morphine vary widely among individuals due to factors including CYP2D6 gene variants. Data on M6G levels in milk during codeine therapy are lacking.
Oxycodone	CYP3A CYP2D6 (minor pathway)	Noroxycodone (via CYP3A4) Oxymorphone (via CYP2D6) Contribution of the active metabolites to oxycodone effects in vivo is small.	8.7; range <0.3-20 [Maternal mean dose 60 mg/24 h PO: range 30-90]: n = 50[42]	1% (range <0.1% to 3%)	Wide variations are anticipated in oxycodone clearance in both mother and infant.
Tramadol Not recommended for breastfeeding women, and contraindicated in children younger than 12 years old.[64]	CYP2D6	O-Desmethyltramadol (also known as M1)	112; range 15-390 (M1[d] β2; range 8-111) [Maternal dose 400 mg/24 h PO]: n = 75 (population PK analyses)[43]	2% (range 0.2% to 6%). Relative infant dose combining tramadol and M1 was 3%.	Variable infant exposure. Analgesic effects are due to μ-opioid receptor activation and reuptake inhibition of serotonin and norepinephrine.
Fentanyl	CYP3A	none	1 [Maternal dose 100 μg/h transdermal patch]; n = 1[44] 0.06; range 0.01-0.15 [Maternal mean dose 2 μg/kg IV]; n = 13[45]	~3% compared to the maternal transdermal dose (based on absolute infant dose of 1 μg/[kg·day] via milk)	In adults, oral bioavailability is 30% to 50%; transdermal bioavailability is >90%. Oral bioavailability of infant is not known.
Opioid dependence treatment					
Methadone	CYP2B6/CYP3A	none	17.4: range 6-35 [Maternal dose range 20-80 mg/day]; n = 12[46] 36: range 10-58 [Maternal dose range 40-105 mg/day]; n = 8[47] 33: range 6-170 [Mainly at a peak during maternal dose 40-200 mg/day]; n = 20[48]	~3% (range 0.5%-9%)	Highly variable and relatively high infant exposure compared to other opioids. May contribute to alleviation of neonatal withdrawal symptoms.
Buprenorphine	CYP3A	Norbuprenorphine Significant contribution to buprenorphine therapy is unlikely.	0.55; range 0.12-1.24 [Maternal mean dose 9.3 mg/day sublingually (range 2.4-24)]; n = 7[49]	0.4% (range 0.04% to 0.63%)	Exposure levels of the infant are predicted to be very low.

IV indicates intravenous; PO, oral dose; q4h, every 4 hours.

[a]Amount of drug ingested by an infant via milk at 150 mL/[kg·day] milk intake. Maternal dose in square brackets. n = total number of subjects in cited references.

[b]Compared to mother's dose per kilogram.

[c]Morphine 6-glucuronide.

[d]Expressed as a molar-equivalent parent drug.

[e]Patient-controlled analgesia with morphine.

Opioid RID is usually low on average in the range of 1% to 5% of the mother's therapeutic dose on a weight basis, although individual variations exist [24]. Avoiding long-term use (more than 3-4 days) helps to avoid potential drug accumulation in the infant in case of significantly reduced drug clearance, which can't always be reliably predicted. This is reasonable for the purpose of acute pain control. Safety data are relatively scarce on long-term opioid use (eg, 1-2 weeks) for analgesic purposes during breastfeeding compared to methadone therapy for OST [24]. Infant populations in these two circumstances differ in gestational opioid exposure affecting infant sensitivity to opioids. Whether to continue breastfeeding with opioids if long-term pain management is needed in pregnancy and breastfeeding remains a difficult clinical decision.

3.2.3.2 Methadone

Although multiple CYP enzymes and glomerular filtration are involved with methadone, CYP2B6 and CYP3A are considered the enzymes for methadone elimination and there are no major active metabolites [34]. The RID of methadone in breastfeeding is around 1–3% which may be as high as 5–6% in a few cases [35]. At a maternal dose of 90 mg/day of methadone, a RID of 1–3% amounts to an infant dose of about 0.015–0.045 mg/kg/day which seems too small to cause respiratory depression. However, this can be put into perspective by comparing with the methadone treatment dose for NAS. An initial dose of methadone for treatment of neonatal withdrawal is 0.1–0.2 mg/kg/day and a maximum dose is 1 mg/kg/day [36], indicating that a breastfed infant of a mother receiving 90 mg/day of methadone is exposed to the medicine at a dose ranging from 15–45% of the low end of the typical starting dose of methadone for NAS.

Because RID is based on 150 mL/kg/day of infant milk intake, this overestimates the actual infant dose during the first several days when milk intake is relatively low. However, in a subset of infants, methadone dose through milk may reach 45% of the low-end therapeutic dose for NAS.

It is known that breastfeeding during methadone-assisted treatment for maternal OST alleviates infant withdrawal symptoms [37, 38]. More research is needed on the pharmacokinetics of methadone and its individual variations among breastfeeding women on methadone OST including those with a relatively high dose (eg, >100 mg/day).

As long as infant conditions are monitored and regular paediatric follow-up is provided, breastfeeding is encouraged during methadone OST of the mother [24]. Intrauterine exposure to methadone may make these infants less sensitive to opioid in breast milk, but this also remains to be systematically examined [24].

Comments:

Using an RID of 1–3% and a maternal dose of 90 mg/day of methadone, the amount of methadone that would reach the infant is expected to be too low to cause respiratory depression, and ranges from 15–45% of the low end of typical starting doses of methadone for NAS. However, wide variation in methadone pharmacokinetics could translate to higher doses reaching some infants.

3.2.3.3 Buprenorphine

Buprenorphine is another opioid used sublingually for the treatment of pregnant women with opioid dependence. Compared to methadone, buprenorphine-assisted therapy of opioid addiction of pregnant women may result in milder withdrawal in neonates [39].

Buprenorphine is a partial agonist of the μ-opioid receptor and is extensively metabolised by CYP3A [40]. It is a high-extraction-ratio drug and its oral bioavailability is about 10% due to extensive presystemic elimination [41]. Bioavailability of the sublingual formulation is still around 30–50% [40].

During maternal buprenorphine (sublingual)-assisted therapy for opioid addiction at a mean dose of 9.3 mg/day, milk levels were 3.7 ng/mL on average, resulting in an estimated infant dose of 0.55 μg/kg/day [42]. Other reports also indicate a similar range of milk levels and infant doses [43-45].

The RID of buprenorphine based on the reported average milk levels is less than 1–2% of the maternal sublingual dose adjusted by body weight [42, 43]. Compared to infant sublingual doses for opioid

withdrawal (15–60 µg/kg/day) the infant exposure levels to buprenorphine in milk in those reports are also in the range of <1% to 4% of the low end of the therapeutic infant dose.

In the context of buprenorphine-assisted treatment for maternal opioid addiction, breastfeeding should be encouraged with regular monitoring of infant conditions unless there is a contraindication such as HIV infection [24].

Comments:

Overall Ito concludes based on opioid transfer into breast milk, opioids use by the mother during breastfeeding should be limited to 2–3 days for acute pain management in unsupervised outpatient settings, while breastfeeding should be encouraged during maternal treatment of OST using methadone, particularly when the treatment is started before or during pregnancy, but the mother-infant pairs should be monitored regularly.

3.3 Data sheets and guidelines for use in breastfeeding

3.3.1 New Zealand

A summary of the information on breastfeeding contained in methadone New Zealand data sheets and treatment guidelines is shown in Table 2.

Table 2: Breastfeeding information summary from methadone New Zealand data sheets and treatment guidelines

Source	Indications	Use in breastfeeding
Biomed oral solution https://medsafe.govt.nz/profs/Datasheet/b/Biodoneoralsoln.pdf	Opioid substitution treatment	Except where contraindicated for other medical reasons the benefits of breastfeeding outweigh the risks (except in the case of maternal HIV positive status) and therefore is to be encouraged. The amount of methadone present in breast milk is minute and unlikely to harm the infant in the first three to six months of life. Breastfeeding mothers should be advised to wean slowly off breastfeeding when they decide to stop to reduce the possibility of mild withdrawal symptoms being experienced by the baby. Breastfeeding mothers should be under the care of a specialist midwifery drug and alcohol service or a GP approved or authorised to prescribe controlled drugs for the treatment of dependence under the Misuse of Drugs Act 1975.
Methadone Molteni oral solution https://medsafe.govt.nz/profs/Datasheet/m/methadonemoltenisol.pdf	Opioid substitution treatment	Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breastfeeding is usually not recommended but a careful risk-benefit assessment case by case is suggested. Methadone could prevent the possibility of an overdose syndrome in the newborn, and the benefits of breastfeeding may outweigh the risks (except in the case of maternal HIV positive status). Breastfeeding mothers should be advised to wean slowly off breast feeding when they decide to stop to reduce the possibility of mild withdrawal symptoms being experienced by the baby. Breastfeeding mothers should be under the care of a specialist midwifery drug and alcohol service or a GP approved or authorised to prescribed controlled drugs for the treatment of dependence under the Misuse of Drugs Act 1975.

Methatabs tablets https://medsafe.govt.nz/profs/Datasheet/m/Methatabs.pdf	Opioid substitution treatment Severe pain	Breastfeeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation. Assays of breast milk from methadone-maintained mothers showed methadone concentrations of 0.17 to 5.6 mcg/mL.
Methadone injection https://medsafe.govt.nz/profs/Datasheet/m/Methadoneinj.pdf	Moderate to severe pain	Methadone should generally not be taken by nursing women. However, concentrations in the breast milk are considered unlikely to have any clinical effect, and methadone may be used if, in the opinion of the physician, the benefits outweigh the likely effects on the infant.
Opioid substitution guidelines 2014 www.health.govt.nz/publication/new-zealand-practice-guidelines-opioid-substitution-treatment-2014	n/a	Breastfeeding has many benefits, including mother-infant bonding, nutrition and prevention of childhood illness, and may reduce the severity of neonatal abstinence syndrome (NAS). Service providers should encourage opioid-dependent mothers to breastfeed, with the possible exception of HIV-positive mothers, or those using alcohol or cocaine and amphetamine-type substances. Methadone is transferred into breast milk at very low levels. The American Academy of Paediatrics classifies methadone as compatible with breastfeeding. Service providers should advise women who are breastfeeding while on high doses of methadone to wean slowly, to minimise any risk of withdrawal in the infant.
NZF guidance for opioid substitution therapy https://nzf.org.nz/nzf_2859#nzf_2864	n/a	Breastfeeding is still the preferred form of feeding, even in the context of maternal methadone. The dose of methadone should be kept as low as possible without reducing stability in breast feeding mothers and the infant should be monitored for sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate). Women who are breastfeeding and are on high doses of methadone must wean slowly to minimise risk of withdrawal in the infant.

Comments:

Breastfeeding is generally encouraged for mothers taking methadone for opioid substitution treatment; however it is discouraged when used for pain. Breastfeeding helps to decrease the risk of withdrawal and to increase bonding with the infant.

3.3.2 Australia

The Australian methadone data sheets generally state methadone is distributed into breast milk, with a mean ratio of milk to plasma concentration of 0.44. However, doses of methadone to the infant via breast milk are low, estimated at 3% of maternal doses, on average, and insufficient to prevent neonatal abstinence syndrome in infants born to mothers on methadone maintenance. Breastfeeding is permissible in mothers receiving methadone for maintenance therapy but the baby should be monitored to avoid sedation.

[redacted]

The Australian *National guidelines for medication-assisted treatment of opioid dependence 2014* (www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf) contains information on breastfeeding. Although methadone is detectable in breast milk, levels are low and are not thought to significantly affect the infant. Breastfeeding has many benefits, including mother-infant bonding, nutrition and prevention of childhood illness, and may reduce the severity of neonatal withdrawal syndrome as well as providing substantial financial advantages for mothers on low incomes. Opioid-dependent mothers should be encouraged to breastfeed, with the possible exception of women who continue to use substances, especially where there is a risk of over-sedation and smothering of an infant (eg, benzodiazepines, alcohol).

Comments:

The Australian Guidelines are the same as the World Health Organization (WHO) *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence 2009* (http://apps.who.int/iris/bitstream/handle/10665/43948/9789241547543_eng.pdf;jsessionid=F476771A805471EB9F6A47677AE0224F?sequence=1).

3.3.3 United Kingdom

The UK data sheets for methadone generally state that methadone is excreted into breast milk. Specialised care from obstetric and paediatric staff with experience in such management is required. If breastfeeding is considered, the dose of methadone should be as low as possible and the infant monitored to avoid sedation. Breastfed infants may develop physical dependence and exhibit withdrawal symptoms.

The NHS has published a document *Pregnancy and breastfeeding treatment of psychiatric and substance misuse disorders* implemented in 2017 (www.sps.nhs.uk/wp-content/uploads/2017/10/CNWL_MHAS_Pregnancy_and_breast_feeding_guideline.pdf). Methadone is the mainstay of the treatment of opioid drug dependence and breastfeeding has benefits to an infant who has been exposed in utero to maternal opioids. Methadone is not contraindicated in breastfeeding but the dose should be kept as low as possible while maintaining stability, and the infant should be monitored to avoid sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate).

[redacted]

Comments:

The publicly available NICE guidelines on methadone and buprenorphine for the management of opioid dependence does not contain any guidance on methadone use during breastfeeding.

3.3.4 Europe

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has a 2015 clinical practice guideline for methadone prescribing and administration in pregnancy (www.emcdda.europa.eu/attachements.cfm/att_231326_EN_IE10_Opiate%20treatment%20in%20Pregnancy.pdf).

International clinical guidelines from the US, Canada, Australia and New Zealand encourage women on methadone OST to breastfeed in the absence of contraindications.

- Breastfeeding should be encouraged in women who are stable on methadone OST unless there are other medical contraindications.
- Clinical judgement should be used in determining whether breastfeeding is appropriate for an individual woman and her baby. Contraindications to breast feeding include HIV infection, and ongoing illicit drug use.
- Minimal levels of methadone are found in breast milk regardless of dose.
- Breastfeeding may attenuate the severity of NAS and lead to earlier hospital discharge.
- Abrupt weaning of breastfed infants of women on methadone maintenance can result in infant withdrawal symptoms.
- Diazepam and other commonly used benzodiazepines are excreted into the breast milk and have active metabolites. Accumulation may occur with repeated doses, leading to sedation, particularly in a newborn or preterm infant.
- Seek advice on the safety of other concomitantly prescribed medicines in breastfeeding.

3.3.5 Canada

[redacted]

[redacted]

The Canadian Pediatric Society published guidelines on managing infants born to mothers who have used opioids during pregnancy in 2018 (www.cps.ca/en/documents/position/opioids-during-pregnancy). Breastfeeding should be encouraged because it can delay the onset and decrease the severity of withdrawal symptoms as well as decrease the need for pharmacological treatment [37]. HIV-negative mothers who are stable and on opioid maintenance treatment with methadone should be encouraged to breastfeed [46]. Breastfeeding provides optimal nutrition, promotes maternal-infant attachment and facilitates parenting competence. Mothers with a dependency who wish to breastfeed may require extra support as they are less likely to initiate breastfeeding successfully and more likely to stop breastfeeding early [47].

3.3.6 United States

Methadone data sheets acknowledge there are low levels of methadone in breast milk based on results of two clinical lactation studies in 22 women. Due to rare case reports, the data sheets also recommend prescribers to advise breastfeeding women to monitor the infant for increased drowsiness, difficulty breastfeeding, breathing difficulties or limpness.

US clinical guidelines encourage breastfeeding by mothers who are stable on methadone unless there are other contraindications such as HIV infection or use of illicit drugs. Information from some of these guidelines are detailed below:

- *Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants 2018* (https://store.samhsa.gov/system/files/sma18-5054.pdf) has been produced by the Substance Abuse and Mental Health Services Administration (SAMHSA). This clinical guidance has a number of fact sheets.

  Factsheet #11 on breastfeeding considerations for infants at risk of NAS states levels of methadone are very low in breast milk and pose little risk to infants [42, 48, 49]. Any breastfeeding, however brief, can decrease the infant's need for pharmacological treatment for NAS and the length of pharmacological therapy and hospitalisation [37, 48-52]. The benefit that the infants with NAS derive from breastfeeding is attributed to the act of breastfeeding (eg, making skin-to-skin contact, holding infant closely) rather than to the amount of maternal opioid agonist secreted into the breast milk [53].

  Although a stable mother being treated for opioid use disorder with pharmacotherapy is encouraged to breastfeed her infant, there are some situations where breastfeeding is not recommended (eg, HIV positive, tuberculosis, cracked or bleeding nipples, hepatitis C positive, using illicit drugs including cannabis). Mother who are hepatitis B surface antigen positive or who are infected with HCV may breastfeed [16]. The CDC describes other situations in which a mother should avoid breastfeeding.

  Figure 9 shows the breastfeeding recommendations contained in Factsheet #11.

Factors	Breastfeeding May Not Be Recommended*
The mother is enrolled in a medication-assisted treatment program (with either buprenorphine or methadone) with significant social support and plans to continue treatment. She has demonstrated that she is stable in treatment.	The mother has a medical condition or takes medications that are contraindicated for lactation.
The mother has given written informed consent for healthcare professionals to discuss her SUD treatment.	The mother did not receive prenatal care
The mother's pain management medications after delivery are not contraindicated for newborns.	Close to delivery, the mother has a pattern of regular illicit drug use or licit substance use meeting criteria for an active SUD.
The mother's urine toxicology results were negative except for prescribed medications at delivery.	The mother is not willing to engage in SUD treatment or is engaged in treatment but is not willing to provide consent for contact with anyone in the program.
The mother has received consistent prenatal care.	The mother's urine toxicology results were positive for substances or their metabolites indicating recent use of alcohol or other substances that are not prescribed to her for the treatment of a medical condition.
The mother plans to consider SUD treatment in the postpartum period.	The mother does not have confirmed plans for postpartum SUD treatment and pediatric care.
The mother has been advised of the risk and benefits of taking antidepressants, anxiolytics, and mood stabilizers during the breastfeeding period.	The mother demonstrates behaviors or other indicators of an active SUD
If the infant has significant NAS, lactation support is available.	

* If the mother meets one or more of these criteria, further evaluation should be conducted to determine whether she can support safe infant breastfeeding. Evidence is accumulating to recommend eliminating cannabis use during pregnancy, while breastfeeding, or through secondhand smoke exposure (Jansson, Bunik, & Bogen, 2015).

Sources: AAP, Section on Breastfeeding, 2012; CDC, 2016; Committee on Obstetric Practice, ACOG, 2017; Hudak et al., 2012; Jansson et al., 2008a, 2008b, 2016; Jansson & Velez, 2015; Reece-Stremtan et al., 2015; WHO, 2014.

Figure 9: Breastfeeding recommendations from the United States Substance Abuse and Mental Health Services Administration (SAMHSA)

- The American College of Obstetricians and Gynecologists (ACOG) has a Committee on Obstetric Practice. This committee released an opinion No. 711 on *Opioid use and opioid use disorder in pregnancy* (www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co711.pdf).

  The opinion states breastfeeding should be encouraged in women who are stable on their opioid agonists, who are not using illicit medicines, and who have no other contraindications (eg, HIV infection).

  Women would be counselled about the need to suspend breastfeeding in the event of a relapse. Because breastfeeding should be encouraged in women who are stable on their opioid agonists, who are not using illicit drugs, and who have no other contraindications, obstetrician-gynecologists and other obstetric care providers should provide anticipatory breastfeeding guidance during the antepartum period.

  Breastfeeding is beneficial in women taking methadone and has been associated with decreased severity of neonatal abstinence syndrome symptoms, less need for pharmacotherapy, and a shorter hospital stay for the infant. In addition, breastfeeding contributes to attachment between a woman and her infant, facilitates skin-to-skin care, and provides immunity to the infant.

  Although most pregnant women who take methadone will experience dose increases during pregnancy, and a need for dose reduction might be expected postpartum, one study demonstrated little need for immediate postpartum methadone dose reduction [54]. Significant dose reductions postpartum should not be done routinely but should be titrated to signs and symptoms of sedation, particularly at the peak of the dose (2–6 hours). Other medicines that can produce sedation (eg,

benzodiazepines, zolpidem, antihistamines) should be used with caution, as they may add to the risk of maternal respiratory depression [55].

Long-term outcomes of infants with in utero opioid exposure have been evaluated in several observational studies. A major challenge in assessing these outcomes is isolating the effects of opioid agonists from other confounding factors such as use of other substances (tobacco, alcohol, nonmedical drugs) and exposure to environmental and other medical risk factors (eg, low socioeconomic status, poor prenatal care) [56]. For the most part, studies have not found significant differences in cognitive development between children up to 5 years of age exposed to methadone in utero and control groups matched for age, race and socioeconomic status, although scores were often lower in both groups compared with population data [57]. Preventive interventions that focus on supporting the woman and other caregivers in the early and ongoing parenting years, enriching the early experiences of children and improving the quality of the home environment are likely to be beneficial [58].

- LactMed is a database that contains information on medicines that breastfeeding mothers may be exposed to, including methadone (CASRN: 76-99-3) (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~eunFbW:6).

  Most infants receive an estimated dose of methadone ranging from 1 to 3% of the mother's weight-adjusted methadone dose with a few receiving 5 to 6%, which is less than the dose used for treating neonatal abstinence.

  Women who received methadone maintenance during pregnancy and are stable should be encouraged to breastfeed their infants postpartum, unless there is another contraindication, such as use of street drugs [36, 50, 51, 59-65]. Breastfeeding may decrease, but not eliminate, neonatal withdrawal symptoms in infants who were exposed in utero. Some studies have found shorter hospital stays, durations of neonatal abstinence therapy and shorter durations of therapy among breastfed infants, although the dose of opiates used for neonatal abstinence may not be reduced [63-72]. The long-term outcome of infants breastfed during maternal methadone therapy for opiate abuse has not been well studied [73]. Abrupt weaning of breastfed infants of women on methadone maintenance might result in precipitation of or an increase in infant withdrawal symptoms, and gradual weaning is advised. The breastfeeding rate among mothers taking methadone for opiate dependency has been lower than in mothers not using methadone in some studies, but this finding appears to vary by institution, indicating that other factors may be important.

  See section 3.4.1 for information from LactMed on effects of methadone in breastfed infants.

- American Academy of Pediatrics released a clinical report on *Neonatal drug withdrawal* in 2012 (http://pediatrics.aappublications.org/content/129/2/e540) [16]. The report discusses the use of analgesics or sedatives during pregnancy and the effects these have on the infant.

  In general, the report recommends breastfeeding and the provision of expressed human milk should be encouraged if not contraindicated for other reasons. Mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed so long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that presents later and less frequently requires pharmacologic intervention [37, 66].

3.4 Effects of methadone in breastfed infants

3.4.1 LactMed

LactMed contains information on methadone's effects in breastfed infants that have been reported in the literature (https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~eunFbW:6).

3.4.1.1 Summary

The reports in LactMed can be summarised as follows:

- *Minimal adverse effects:* 3 studies reported minimal adverse effects in infants some of whom were followed for up to 6 months. One of these studies warned against stopping breastfeeding abruptly as withdrawal symptoms may develop.
- *Withdrawal symptoms or NAS:* 13 studies reported on these effects:
    - 4 studies reported on outcomes in breastfed infants only (eg, methadone withdrawal may occur despite breastfeeding, withdrawal symptoms developed after stopping breastfeeding abruptly, trend towards shorter duration of hospitalisation for NAS).
    - 7 studies compared outcomes in breastfed infants vs. non-breastfed infants and generally reported breastfed infants had better outcomes (eg, shorter hospital stays, lower frequency of NAS, lower NAS scores, longer time to withdrawal symptoms, less likely to require pharmacologic treatment, lower doses of morphine).
    - 2 studies compared outcomes in breastfed infants vs. non-breastfed infants with mixed results (eg, delayed onset of NAS in breastfed infants but no decreased need for treatment of NAS, shorter hospital stays in breastfed infants but same rate of NAS and hospitalisation).
- *Other adverse effects:* 5 studies reported on adverse effects (eg, cyanosis requiring resuscitation and intubation after methadone and hydrocodone+acetaminophen, jaundice and convulsions less frequent despite higher average maternal methadone dose, shorter hospital stays in breastfed infants, weight loss outcomes after birth, cyanosis and decreased breathing after substitution of methadone with hydrocodone+acetaminophen).
- *Fatal outcome:* 4 infants with a fatal outcome.

Further detail on these studies are provided below.

3.4.1.2 Further details

<u>Minimal adverse effects</u>

One centre reported on 10 women who breastfed during methadone opioid substitution treatment (OST) with no observed adverse effects in their infants [74].

Three breastfed term infants of mothers taking oral methadone OST 45 to 70 mg daily during pregnancy and breastfeeding had no reported adverse effects. They were cared for in a well-baby nursery after birth and discharged home in good health with their mothers at 2 to 3 days of age. At follow up over 3 weeks to 6 months of age, the infants had no symptoms of sedation or methadone withdrawal while breastfeeding. One infant who had breastfeeding discontinued at 3 weeks of age developed withdrawal symptoms of hyperirritability and sleeplessness. The other 2 infants were slowly weaned over 4 to 6 months and did not experience withdrawal upon breastfeeding discontinuation. The authors cautioned against abrupt breastfeeding discontinuation during methadone maintenance [75].

Eight breastfed and eight formula-fed newborn infants whose mothers were receiving methadone OST in a median dose of 70 mg daily (range 50 to 105 mg daily). No differences were noted between infants in the two groups on days 3, 14 or 30 in nine neurobehavioural measures or on the percentage requiring pharmacologic management of withdrawal [48]. Four of these breastfed infants were followed for six

months. No health concerns arose during this time. Another infant who was partially breastfed for 1 year had no important health or developmental problems during this time [49].

Withdrawal symptoms or neonatal abstinence syndrome (NAS)

Twelve term breastfed newborns of mothers taking oral methadone maintenance (range 20 to 80 mg daily) during pregnancy and breastfeeding were observed during their first week of age. Seven of these infants developed methadone withdrawal and 6 required treatment. The authors considered maternal methadone OST to be compatible with breastfeeding in the first week of a newborn's life but cautioned that newborn methadone withdrawal may occur despite breastfeeding [76].

The hospital course of 88 breastfed newborns were compared to 32 non-breastfed newborns. All had mothers taking oral methadone OST at an average dose of 40 mg daily (range 5 to 175 mg daily). Although the breastfed newborns developed neonatal abstinence syndrome (NAS) and required rehospitalisation after discharge at the same rate as bottle-fed infants, they had a shorter hospital stay than bottle-fed newborns [77].

Two fully breastfed term infants of mothers taking oral methadone maintenance 70 to 130 mg daily during pregnancy and breastfeeding had no adverse effects and required no treatment for methadone withdrawal prior to postpartum hospital discharge at 8 and 6 days of age, respectively. Both infants were re-hospitalised and treated for methadone withdrawal symptoms at 6 weeks and 17 days of age, respectively, shortly after their mothers abruptly discontinued breastfeeding. The authors surmised the appearance of symptoms were probably due to withdrawal from methadone in breast milk [78].

A Swiss descriptive report found among newborns of 84 mothers on methadone OST, NAS was less frequent in breastfed infants than in non-breastfed infants, 26% and 78%, respectively. 27 infants were breastfed and 54 were formula-fed. "Breastfed" was defined by the authors as more than 50% of feeding from breast milk while in hospital [79].

A retrospective review from Australia was conducted on the medical records of 190 drug-dependent mothers and their infants. 149 of the mothers were taking methadone at delivery, 62 mothers taking methadone (average dose 68.5 mg daily, maximum dose 150 mg daily) breastfed their infants and 87 mothers taking methadone (average dose 79.6 mg daily) formula-fed their infants. Breastfed infants had a longer median time to withdrawal symptoms (10 days) than formula-fed infants (3 days). Breastfed infants were less likely to require pharmacologic treatment and doses of morphine required to treat withdrawal were lower in breastfed infants. Treatment duration was also shorter in breastfed infants (85 vs. 108 days) [37].

A retrospective review of charts of 68 newborn infants exposed to methadone in utero found that infants who were breastfed had a trend towards requiring shorter durations of treatment for NAS, although the trend was not statistically significant [80].

A retrospective cohort study reviewed records of 437 newborn infants whose mothers were taking methadone OST. Infants who were breastfed for ≥72 hours had a 45% reduced risk of experiencing NAS compared to those who were not. NAS was more likely in mothers who were also receiving a benzodiazepine [81].

A retrospective study in the US of 128 infants exposed during pregnancy and breastfeeding to methadone found an inverse relationship between the amount of breastfeeding and duration of hospitalisation for NAS. Five of the breastfed infants were re-admitted for withdrawal symptoms after discontinuing or markedly reducing breast milk intake after discharge [66].

A retrospective review of charts of infants of mothers taking methadone during pregnancy and postpartum at 2 hospitals in Maine was made. Infants who breastfed (n=8) had lower neonatal abstinence scores than infants who were formula-fed (n=9) or had mixed feeding (n=11) [82].

A tertiary care hospital in British Columbia analysed the charts of 295 women receiving methadone maintenance who delivered an infant over a 39-month period. Infants who were breastfed had a 79% reduced chance of requiring morphine to treat withdrawal symptoms than non-breastfed infants. All infants were rooming-in which may have assisted by increasing on-demand feeding and skin-to-skin contact [83].

A cohort of 124 infants exposed during pregnancy to maternal OST were followed postpartum in a Norwegian study. 78 infants were born to mothers taking methadone. Overall, infants who were breastfed had a lower rate of NAS and a shorter duration of therapy for neonatal abstinence. Among infants exposed to methadone, 53% of breastfed infants and 80% of non-breastfed infants required treatment. Breastfed infants required treatment for an average of 31 days compared with an average of 49 days among non-breastfed [68].

A study of pregnant women being treated with OST with methadone at a clinic in Vienna were followed as were their newborn infants. Compared to infants who were not breastfed (n=118), breastfed infants (n=48) had lower average measures of neonatal abstinence, lower dose requirements of morphine (4.35 mg vs. 12.65 mg), shorter durations of treatment for neonatal abstinence (8.1 vs. 17 days) and shorter hospital stays (17.2 vs. 29.4 days) [84].

A retrospective chart review of 194 new mothers who were on methadone maintenance and their infants found that predominant breastfeeding during the first 2 days postpartum delayed the onset of NAS in infants compared to formula feeding. However, breastfeeding did not decrease the need for treatment of the infant for NAS [85].

Other adverse effects

A 5-week-old breastfed infant became cyanotic and required mouth-to-mouth resuscitation and intubation. The infant's urine was positive for opioids and the infant responded positively to naloxone; the level of consciousness improved over 2 days and extubation was accomplished. The infant's mother admitted to taking methadone and a hydrocodone-acetaminophen combination product that had been prescribed for migraine headache before she was breastfeeding [86].

A hospital in England reported outcomes among infants whose mothers were taking methadone OST during pregnancy over 2 time periods. Several changes were made in the management of mothers taking methadone between the 2 time periods. In the 1st time period (1991-1994) only 10% breastfed their infants (4% exclusive). In the 2nd time period (1997-2001) 30% breastfed their infants (20% exclusive). During the 2nd time period, the frequency of jaundice and convulsions were less frequent in all infants even though the average maternal methadone dose was twice as high as the earlier period. Pharmacologic treatment of the infants for withdrawal, days of hospitalisation, days in intensive care and percentage of infants admitted to intensive care were all lower during the second time period [38].

A retrospective review of charts of infants of mothers taking methadone during pregnancy and postpartum at an Ontario Canada hospital was made. Infants who were breastfed (n=14) had statistically significant shorter hospital stays than those who were given formula or mixed feeding (n=118) [67].

A retrospective cohort study of infants of 354 mothers taking methadone OST in Glasgow, Scotland compared weight loss of infants who were breastfed to those who were given formula. Infants in the entire breastfed (including partial) group lost a maximum of 10.2% of body weight after birth compared with a weight loss of 8.5% in the formula-fed group and 9.3% in the exclusively breastfed subgroup. Weight loss was less in infants who were small for gestational age compared to infants with normal birth weights. Median maximal weight loss occurred on day 5 postpartum except for exclusively breastfed infants in whom it occurred on day 4. Neither methadone dose nor polydrug abuse correlated with weight loss. These weight loss values were greater than local values for infants who were not exposed to drugs [87].

A 13-month-old infant was being primarily breastfed by a mother who was taking hydrocodone and acetaminophen for pain. On 2 occasions 4 hours apart she substituted a dose of 40 mg of methadone for the acetaminophen-hydrocodone combination. The child breastfed 2 and 6 hours after the 2nd dose for 45

minutes each time then fell asleep for 45 minutes. 45 minutes later the infant's mother noted the infant was drowsy and not responsive. Emergency responders confirmed the baby had cyanosis, myosis and decreased breathing. Upon arrival at the emergency room, the child was unarousable but had normal vital signs. The baby awoke after naloxone 0.2 mg was given intravenously. The infant's urine drug screen was positive for opiates including methadone metabolites. 18 hours after the mother's first dose, the infant remained intermittently drowsy with oxygen saturation dropping as low as 91%. During this 18-hour time period the infant received 4 doses of naloxone intravenously. Eventually the baby returned to normal state of good health [88].

Fatal outcome

The death of a 5-week-old infant who was born 1 week prematurely to a former heroin-abusing mother was possibly related to methadone in breast milk. The infant had been breastfeeding since birth and the mother was taking an unreported daily dose of oral methadone OST. The medical examiner's diagnosis was methadone intoxication. A high level of methadone was found in the infant's serum at autopsy; however, the high level might have been caused by postpartum redistribution, which can be 2- to 10-fold [21]. The infant was noted to be "obviously malnourished". Abnormal brain, liver and other organs on autopsy were also found and it appeared that the infant had been neglected [89, 90].

A partially breastfed 3.5-month-old infant of a mother taking oral methadone maintenance 73 mg once daily died of sudden unexplained death in infancy (SUDI). The mother was reportedly mostly bottle feeding the infant due to diminished milk supply. There was no methadone detected in the infant's blood at autopsy and the lower limit of assay was not reported [91].

Two infants whose mothers were on methadone OST died. Both infants were heterozygous for the lower activity form of the P-gp transporter and one had a pharmacogenetic variant for CYP2B6 thought to reduce methadone metabolism. Both also had other factors that could have contributed to their deaths. The authors state it would be inappropriate to assume that methadone from breast milk was the sole cause of death in these infants [21].

3.4.2 New Zealand

Fatal cases

There are no known cases of infant deaths due to methadone exposure through breast milk.

[redacted]

[redacted]

Non-fatal cases

CARM holds a total of 44 reports in their database where methadone is the suspect medicine. Of these 44 reports, one relates to an adverse effect in an infant (CARM ID 74394). There is no information in this case on exposure during breastfeeding. This was a male infant with the coded reaction of pulmonary hypertension. He was exposed in utero to methadone, mexiletine and amitriptyline and all were considered suspects. This case was reported to CARM by a pharmaceutical company following the publication of the article described below by Sharpe and Kuschel (2004) [92].

The authors performed a retrospective audit of infants exposed in utero to methadone administered for the treatment of maternal pain and compared the outcomes for these infants with a group of infants born to mothers who were managed with methadone in pregnancy for opioid substitution treatment (OST).

Cases were identified from a database kept by the pain service at the National Women's Hospital in Auckland. 19 mothers were identified between August 1997 and November 2000 in whom methadone was used for pain management. A further 24 women in whom methadone was used for OST from August 1999 to May 2001 were used as a comparison group. The authors note in some patients amitriptyline was used to treat neuropathic pain and visceral spasm and as headache prophylaxis and mexiletine was used to treat neuropathic pain.

Infants in the pain group were exposed to significantly smaller methadone doses for shorter periods starting later in pregnancy. 11% of them required treatment for neonatal abstinence syndrome (NAS) whereas 58% of infants in the OST group required treatment. Other neonatal morbidity in the pain group was considerable, probably related to prematurity. Infants in the pain group had significantly higher z scores for birth weight and head circumference, but not length, than the infants in the OST group.

The authors conclude methadone used for treatment of maternal pain resulted in a low incidence of NAS. Infants were normally grown. However, there was a significant morbidity related to slight prematurity and delivery in this group should be delayed until term if possible.

Comments:

There are confounding factors when assessing the outcomes of infants born to mothers using methadone for OST. These confounders include maternal health and nutrition, other drug use, smoking and socioeconomic status. These problems were less common in the pain group which could in part help to disentangle the many complex social and environmental factors that contribute to assessing this risk.

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3.4.5 Canada

Health Canada published a safety review assessing the potential risk of serious harm in children exposed to methadone through breast milk in August 2018 (https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00207).

At the time of the review, there were two fatal cases of methadone toxicity in children exposed through breast milk. Both reports were found to have a possible link between methadone and serious harm.

The safety review also looked at 13 international cases of methadone toxicity in children exposed through breast milk, 10 of which involved death. A possible link between methadone and the risk of serious harm (including death) in children exposed through breast milk was found in 12 of these cases. The remaining case did not have enough information to be assessed. It is possible that genetic factors may be a reason why some children are more sensitive to the effects of methadone than others, but these genetic factors are not well understood.

In all cases that were reviewed there were factors that made assessment of the cases difficult. These included lack of information about the mother's methadone dose, cause of death, and medical history of drug use that may have contributed to the serious side effects.

[redacted]

[redacted]

4.0 DISCUSSION AND CONCLUSIONS

Methadone is an opioid that mimics many of the pharmacological effects of morphine, but has a longer half-life than morphine. It blocks opioid withdrawal, cravings and the reinforcing effects of opioids. These characteristics make it suitable for opioid substitution treatment (OST). Methadone is also used in moderate to severe pain though its precise mechanism as an analgesic is not fully known. Due to other analgesics, both opioid and non-opioid, available for use during breastfeeding this paper has focused predominantly on the use of methadone for OST in breastfeeding women.

Pregnant women in New Zealand are eligible for priority assessment for access to OST. This is because illicit opioid use during pregnancy is associated with maternal and fetal acquisition of blood-borne viruses, preterm labour and delivery, intrauterine growth retardation, pre-eclampsia, placental abruption and intrauterine fetal death. OST in pregnancy has been found to reduce illicit drug use, improve maternal engagement in antenatal care and improve neonatal birth weight.

The preferred OST treatment for pregnant women in New Zealand is methadone due to greater data on its efficacy and safety during pregnancy and breastfeeding compared with buprenorphine. Both nationally and internationally, OST guidelines and methadone data sheets generally encourage mothers on methadone to breastfeed. There is some evidence indicating breastfeeding helps with mother-infant bonding, provides nutrition and prevention of childhood illness, and may reduce the severity of neonatal abstinence syndrome (NAS). In New Zealand, the main contraindication to this is mothers who are HIV-positive, however in the United States there are additional situations where breastfeeding is not recommended such as in mothers who are using illicit substances.

There are reports in the literature of methadone's effects in breastfed infants. Studies reporting on withdrawal symptoms or NAS generally show better outcomes in breastfed infants compared with non-breastfed infants such as shorter hospital stays, lower NAS scores, less likely to require pharmacologic treatment, and lower doses of morphine required to treat NAS. However, there have also been fatal cases reported in infants exposed to methadone through breast milk, none of which are known to have occurred in New Zealand.

Most breastfed infants receive an estimated dose of methadone ranging from 1 to 3% of the mother's weight-adjusted methadone dose with a few receiving 5 to 6%. This is a lower dose than that used for treating NAS. Infants should be monitored for sedation and respiratory depression and mothers should know how to recognise the signs and symptoms of these conditions. Mothers should also be warned not to stop breastfeeding abruptly as this can lead to withdrawal symptoms in her baby.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether there are any regulatory actions that should be taken to reduce the risk of adverse effects in infants exposed to methadone through breast milk.

6.0 ANNEXES

1. New Zealand Practice Guidelines for Opioid Substitution Treatment 2014

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