

# Sedating drugs and breastfeeding

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## Abstract

**Question** If a mother takes a sedating drug during breastfeeding, will it cause central nervous system (CNS) depression in her breastfed baby?

**Answer** In some cases (eg, with the use of codeine or oxycodone) sedating drugs will likely cause CNS depression in breastfed infants and in other cases (eg, with the use of benzodiazepines) they will likely not. Mothers using sedating drugs should monitor their breastfed infants for signs of CNS depression (eg, drowsiness; difficulty breathing, feeding, or latching; or cyanosis), paradoxical effects (eg, unusual excitement, irritability), or inadequate weight gain.

## Sédatifs et allaitement

### Résumé

**Question** Les sédatifs qu'une mère prend pendant qu'elle allaite pourraient-ils causer une dépression du système nerveux central (SNC) chez son enfant allaité?

**Réponse** Dans certains cas (p. ex. avec la codéine ou l'oxycodone), les sédatifs causeront probablement une dépression du SNC chez l'enfant allaité et, dans d'autres cas (p. ex. avec les benzodiazépines), ce ne sera probablement pas le cas. Les mères qui prennent des sédatifs devraient surveiller chez leur enfant allaité des signes de dépression du SNC (p. ex. somnolence, difficulté à respirer, à s'alimenter ou à prendre le sein, ou encore cyanose), des réactions paradoxales (p. ex. excitation inhabituelle, irritabilité) ou un gain de poids insuffisant.

Thirty percent of Motherisk's consultations deal with the safety of drugs during breastfeeding. Benzodiazepines (BZDs), antihistamines, and opioids are a few classes of sedating drugs commonly used by breastfeeding mothers.

As a general rule, when the relative infant dose (the amount of a drug excreted into breast milk relative to the maternal dose) is less than 10%, it is considered compatible with breastfeeding.<sup>1</sup> However, some drugs, such as codeine, can cause sedation even at relative infant doses lower than 10%.

### Benzodiazepines

In 2012, Motherisk conducted a follow-up study to assess adverse effects in infants exposed to BZDs through breast milk.<sup>2</sup> There were no signs of central nervous system (CNS) depression (eg, sleepiness, not waking up for breastfeeding, poor latching, limpness, or lack of response to stimuli) reported in 98.4% of infants exposed to BZDs, which was similar to the control group exposed to acetaminophen. Mothers who reported infant sedation used a significantly higher number of CNS depressants than mothers who reported no adverse outcomes in their infants did (mean [SD]=3.5 [0.71] vs 1.7 [0.9];  $P=.0056$ ). Moreover, mothers who used more antidepressants were

more likely to experience adverse effects (eg, sedation, confusion, headache, nausea, and vomiting) themselves.<sup>2</sup> The authors concluded that the use of BZDs was compatible with breastfeeding and the risk of adverse effects in both mother and infant could be reduced by limiting the number of CNS depressants used by the mother.<sup>2</sup>

### Antihistamines

Another Motherisk follow-up study involving 85 infants exposed to first- or second-generation antihistamines through breast milk reported 6 cases of irritability, 1 case of drowsiness, and 1 case of diarrhea.<sup>3</sup> After excluding multiple exposures, infants solely exposed to antihistamines through breast milk had an elevated risk of irritability (relative risk=3.3, CI 1.2 to 9.5).<sup>3</sup> A similar study involving 234 infants exposed to antihistamines through breast milk (54% were exposed to first-generation antihistamines and 46% were exposed to second-generation antihistamines) reported 53 cases (22.6%) of irritability, drowsiness, or decreased sleep in breastfed infants.<sup>4</sup>

Although exposure to first-generation antihistamines through breast milk is theoretically expected to cause adverse CNS effects in infants, both of the aforementioned studies did not report any adverse events that

required medical attention.<sup>4,5</sup> The risk of severe adverse effects is therefore believed to be low and is outweighed by the benefits of breastfeeding. It is recommended that mothers continue breastfeeding, provided the infant is monitored for potential adverse CNS effects.<sup>3,4</sup>

### Opioids

After the death of a baby whose mother was using codeine during breastfeeding in 2005,<sup>6</sup> Motherisk conducted a case-control study involving 72 mother-infant pairs in which the mothers used codeine while breastfeeding; 17 infants demonstrated signs of CNS depression.<sup>7</sup> Compared with mothers of asymptomatic infants, mothers of symptomatic infants used, on average, 59% higher doses of codeine. Hence, the authors suggested that the occurrence of opioid toxicity in infants might be associated with the maternal dose of codeine. Additionally, 12 of the 17 mothers with symptomatic infants reported symptoms of CNS depression in themselves, suggesting a high concordance of CNS depression. Severe neonatal opioid toxicity occurred in 2 of the 17 cases. The mothers in both cases used a high dose of codeine for a long period (>4 days) and had a genotypic combination of the cytochrome P450 (CYP) 2D6 ultrarapid metabolizer and uridine 5'-diphosphoglucuronosyltransferase 2B7\*2/\*2 (fast metabolizer), likely leading to high production of pharmacologically active metabolites (morphine and morphine-6-glucuronide).<sup>7</sup> Together with slow elimination and accumulation in the neonates, neonatal opioid toxicity resulted.<sup>7</sup>

Owing to these concerns over the safety of codeine in breastfeeding, some physicians have switched to prescribing oxycodone.<sup>8</sup> However, opioid toxicities have occurred in infants breastfed by mothers using oxycodone, suggesting that it might not be a safer alternative to codeine.<sup>8,9</sup> This was supported by a recent Motherisk follow-up study, which compared the rates of adverse events in breastfed infants of mothers who used oxycodone, codeine, and acetaminophen for postpartum pain.<sup>8</sup> Rates of infant CNS depression were significantly higher among mothers who used oxycodone (20.1%, n=139;  $P<.001$ ) and codeine (16.7%, n=210;  $P<.001$ ) when compared with those who used acetaminophen (0.5%, n=184). Additionally, mothers of infants with CNS depression used significantly higher doses of codeine or oxycodone compared with mothers of infants without CNS depression ( $P<.001$ ). Furthermore, the rate of maternal sedation was significantly higher in the oxycodone group compared with the codeine group ( $P<.001$ ).<sup>8</sup>

Lam et al<sup>10</sup> further performed genotyping for 67 mothers from the oxycodone group for 4 polymorphic genes involved in oxycodone metabolism and response (ie, CYP 2D6; CYP 3A5;  $\mu$  opioid receptor; and ATP-binding cassette, subfamily B, member 1 [ABCB1]). No gene polymorphisms were associated with infant sedation, but ABCB1 2677G>T/A was associated with an

increased risk of maternal sedation. Additionally, compared with mothers with asymptomatic infants, mothers with infants showing CNS depression used oxycodone for a significantly longer period ( $P<.001$ ) and had shorter breastfeeding sessions ( $P<.001$ ).<sup>10</sup>

In 2009, *Canadian Family Physician* published a set of Motherisk guidelines for codeine use while breastfeeding.<sup>11</sup> In 2013, Kelly et al evaluated the effectiveness of these guidelines in 238 mother-infant pairs, based on the rate of adverse effects observed in neonates.<sup>12</sup> Mothers were provided with a copy of the guidelines when prescribed codeine for postpartum pain. There were only 5 reports (2.1%) of neonate sedation, which is 8-fold lower than in our previous study (16.7%).<sup>8,12</sup> Mothers of sedated infants used codeine for a significantly longer period than mothers of non-sedated infants did (mean [SD] = 4.8 [2.6] days vs 2.52 [1.58] days;  $P=.0018$ ). Furthermore, infant sedation was not associated with maternal genetic polymorphisms in ABCB1, CYP 2D6, catechol-O-methyltransferase, uridine diphosphate-dependent glucuronosyltransferase 2B7, and  $\mu$  opioid receptor. The authors concluded that the Motherisk guideline is effective in lowering the risk of neonatal CNS depression, even for those who are at high risk due to genetic polymorphisms.<sup>12</sup>

For women taking opioid maintenance treatment (eg, buprenorphine, methadone), studies have generally supported breastfeeding unless there are other contraindications.<sup>13,14</sup> Studies have suggested that breastfeeding improves clinical outcomes of infants with neonatal abstinence syndrome.<sup>13,14</sup>

### Conclusion

Maternal use of sedating drugs during breastfeeding is generally acceptable, provided that the infants are monitored for adverse CNS effects. Mothers should contact their physicians if any adverse events are observed in their infants. 🌿

#### Competing interests

None declared

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## MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in

Toronto, Ont. Mr Chow is a member and Dr Koren is Director of the Motherisk Program. Dr Koren is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation.

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