



Neonatal Benzodiazepines Exposure during Breastfeeding

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Objective To assess central nervous system depression and other adverse effects in infants exposed to benzodiazepines through breast milk.

Study design A prospectively recruited, retrospectively assessed **cohort study** of mothers who contacted the Motherisk program regarding the safety of benzodiazepines and were invited to participate in a follow-up program regarding the effects of these medications on their infants during lactation.

Results A total of 124 consenting women participated. Adverse outcomes, specifically sedation, was identified in only 1.6% (2 of 124) of infants and was not associated with benzodiazepine dose, number of hours breastfed, or any demographic trait. Mothers reporting adverse outcomes in themselves (26% [32 of 124]) were more likely to be taking concomitantly a greater number of central nervous system depressants.

Conclusions This study supports the continued recommendation to initiate breastfeeding while taking benzodiazepines postpartum. (*J Pediatr* 2012;161:448-51).

Although encouraging women to breastfeed is important, consideration must also be made in treating underlying maternal conditions during the postpartum period. Many women exhibit anxiety and insomnia in the postpartum period, leading them to take benzodiazepines while breastfeeding.¹⁻⁴ Adverse effects associated with the use of benzodiazepines include sedation, confusion, and withdrawal symptoms that vary in severity, from insomnia to seizures and psychosis.^{5,6} On the other hand, untreated maternal anxiety-related illness may adversely affect the mother's ability to care for herself and her baby.⁵ Currently, breastfeeding is not contraindicated in women using psychotropic medications such as benzodiazepines.^{7,8} Benzodiazepines include medications such as alprazolam, bromazepam, clonazepam, diazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, and triazolam, as well as several other less common molecules.⁹

Several benzodiazepines are transferred into breast milk as well as across the placenta.⁶ Passive diffusion and carrier-mediated transport through the organic cation transporter and the breast cancer resistance protein are thought to play a role in benzodiazepine transfer into breast milk.^{10,11} However, detailed knowledge of benzodiazepine transfer into human milk is limited and its clinical consequences in infants have yet to be elucidated. Rubin et al estimated the incidence of neonatal adverse drug reactions resulting from benzodiazepine use during lactation.¹² **Based on relatively small numbers, this study reported infant adverse event rates of 17% (1 of 6), 22% (2 of 9), and 50% (1 of 2) when exposed to alprazolam, diazepam, and clonazepam, respectively.** Adverse effects in these infants included lethargy, irritability, poor weight gain, and apnea. This study did not report any adverse drug reactions in infants exposed to oxazepam, lorazepam, or temazepam.¹² The small sample size and relatively limited benzodiazepine range need further exploration in order for informed decisions to be made regarding breastfeeding.

We examined the safety of infant exposure to benzodiazepines during lactation. We also determined the epidemiology of common benzodiazepines used in the breastfeeding population and the incidence of adverse drug reactions in mothers taking benzodiazepines. Finally, we compared these characteristics to other central nervous system (CNS) depressing drugs, mainly opioids, used by lactating mothers.

Methods

A **self-referred** population of mothers who called the Motherisk Program at the Hospital for Sick Children in Toronto, Ontario, between January 2010 and May 2011 for advice regarding the use of benzodiazepines during lactation were contacted for follow-up. Inclusion criteria consisted of women consenting to the follow-up procedure who were able to be reached, were fluent in English, and used benzodiazepines during breastfeeding. For the sake of confidentiality, calls from lactation consultants, family members, nurses, and physicians were excluded. Mothers taking concomitant CNS depressants were not excluded. The study protocol was approved by the institutional research ethics board.

We used the breastfeeding follow-up form to collect information from breastfeeding mothers regarding their medication use, frequency of breastfeeding, the

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CNS Central nervous system

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are you convinced even with a 100 vs 47% result?

health of their infants, and demographic characteristics during follow-up telephone interviews. Motherisk intake forms were completed when the mother first called the Motherisk program. (A copy of this form is in Koren.¹³) The intake form contains information regarding infant and maternal weight and age, parity, delivery details, and pregnancy complications.

good! **Informed verbal consent** was obtained from mothers prior to follow-up. Mothers were provided with the study objectives, the option to withdraw at any time, and assurance of privacy and confidentiality. All mothers who had called the Motherisk Helpline regarding the use of any benzodiazepine during breastfeeding were contacted. Participants who chose not to take any medication or chose not to breastfeed were excluded due to a lack of benzodiazepine exposure. Each follow-up call discussed any health concerns in the mother and as well as information regarding causes of medication use and dosing, **evidence of neonatal CNS depression**, and breastfeeding frequency. **CNS depression** was defined as sleepiness, not waking up for breastfeeding, poor latching, limpness, or lack of response to stimuli. Patients were offered the study coordinator's contact information in the event that they had further questions, comments, or concerns.

do u like this defin- ition?

Categorical data for the infants where CNS depression was reported were compared with asymptomatic infants using the **Fisher exact test**. Continuous data in both groups were analyzed using a **Mann-Whitney test**. For all statistical analysis, a significance critical value of $P < .05$ was set.

Red alert!

Results

A total of 296 women contacted the Motherisk program concerning the use of benzodiazepines during lactation between January 1, 2010, and May 31, 2011, and 124 women consented to this investigation. Excluded mothers included 35 who did not take benzodiazepines, 23 who either could not recall details surrounding their benzodiazepine use or refused to participate, and 14 women who did not choose to breastfeed. **There were 52 women that could not be reached and 48 telephone numbers that were no longer in service.**

The most commonly used benzodiazepines during lactation *i wonder if the interns think this is a big deal*

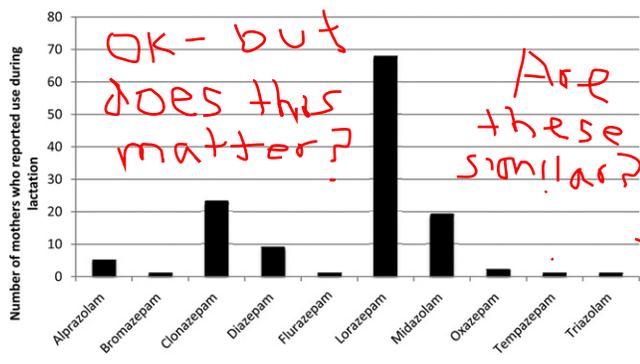


Figure 1. The frequency of benzodiazepines reported by breastfeeding mothers.

Table I. Comparison between those mothers who reported CNS depression in their infants and those who did not identify any adverse outcomes*

	Infant sedation reported (n = 2)	No adverse outcomes (n = 122)	P
Chronic benzodiazepine use	50% (1)	69% (84)	.43
Maternal sedation	50% (1)	13% (16)	.24
Caucasian	100% (2)	84% (102)	.70
Formula supplementation	100% (2)	47% (58)	.23

*Analyzed with a Fisher exact test, the p-value is > 0.05 so there must not be a difference, right?

were lorazepam (52%), clonazepam (18%), and midazolam (15%) (**Figure 1**). The mean age of the children at the time of follow-up was 11 months (range 2-24 months).

There were 2 reported cases (1.6%) of CNS depression in infants exposed to benzodiazepines. One mother reported using 0.25 mg of alprazolam on 2 occasions, and the other mother reported chronic use of 0.25 mg clonazepam twice per day bid and 1 mg of flurazepam daily. The sedated infant of the mother with chronic benzodiazepine use was also exposed to the drugs in utero and both were exposed throughout lactation. There were no differences in exposure periods, maternal sedation, ethnicity, or whether formula was used to supplement breast milk between the 2 cases with reported CNS depression and those who did not (**Table I**). There were no significant differences in maternal age or gestational age, benzodiazepine dose, or the length of time spent breastfeeding (**Table II**).

if you say so!

Mothers who reported CNS depression in their infants were not taking a higher weight-adjusted benzodiazepine dose and their infants were not sleeping longer per day. The **only significant difference** seen between mothers who reported adverse drug outcomes in their children and those who did not was the total number of CNS depressants taken. Those who reported sedated infants were taking a **mean of 3.5 ± 0.71 medications** that cause CNS depression compared with a mean of 1.70 ± 0.90 in those with no health concerns related to benzodiazepine use during lactation ($P = .006$). The first mother with a sedated infant was taking 50 mg of sertraline daily and 2.5 mg of zopiclone when necessary, or about once every 3 days. The second mother reporting a sedated infant was co-medicating with 1 mg of bupropion and 0.75 mg of risperidone.

maybe should have said "those two"

Maternal adverse outcomes were reported in 26% (32 of 124) of mothers. The number of CNS depressants used by

Table II. Clinical characteristics of participants represented as **mean \pm SD**

	Infant sedation reported (n = 2)	No adverse outcomes (n = 122)	P
Maternal age (y)	33.5 ± 5.0	33.6 ± 10.6	.98
Gestational age at delivery (wk)	40.5 ± 0.7	38.9 ± 3.2	.47
Amount breastfeeding (min/d)	68.0 ± 26.5	93.1 ± 64.2	.60
No. of hours infant slept per day	15.3 ± 0.4	13.2 ± 10.0	.77
Benzodiazepine dose (mg/kg/d)	0.016 ± 0.01	0.038 ± 0.12	.80
No. of CNS depressants	3.5 ± 0.7	1.7 ± 0.9	.0056

*All variables were analyzed using the Mann-Whitney U test.

this table caused one of the people in Heroes 3007 to get hives. does this make you uncomfortable?

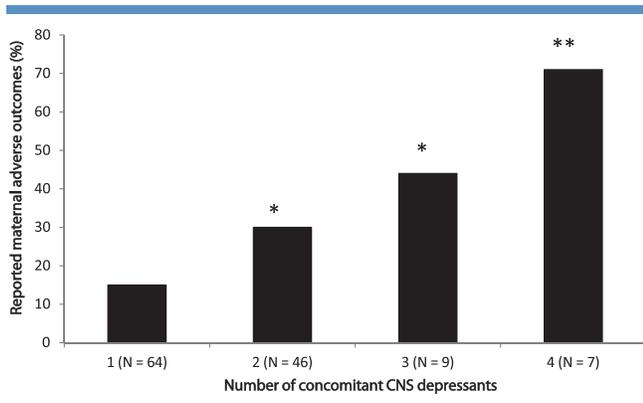


Figure 2. The frequency of reported maternal adverse outcomes as determined by the number of concomitant CNS depressants used where $*P < .05$, $**P < .001$ when analyzed with a Fisher exact test. Concomitant medications included selective serotonin reuptake inhibitors (sertraline, paroxetine, citalopram, fluvoxamine), serotonin-norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine), opioids (codeine, oxycodone, fentanyl, morphine), atypical antipsychotics (risperidone, quetiapine), domperidone, zopiclone, trazodone, phenytoin, clobazam, and bupropion.

Wow! I wonder if the DEA flagged the doc who prescribed for this mother

mothers correlated with the risk of developing maternal adverse effects such as sedation, headache, and confusion (Figure 2). There were no women taking 5 CNS depressants and only 1 mother who reported using 6 concomitant CNS depressants who did not report any adverse effects. Those using only 1 CNS depressant were only taking a benzodiazepine and were significantly less likely to experience adverse effects compared with those taking 2, 3, or 4 CNS depressants ($P = .03$, $P = .05$, $P = .003$, respectively).

Discussion

The primary objective of the present study was to develop a better understanding of the safety and pharmacodynamics of infant exposure to benzodiazepines during lactation. We detected only 2 cases of sedated infants, and overall, there were no serious adverse drug reactions in participating mothers and children. In both sedated infants, mothers used drugs that are not among the most commonly prescribed in this class: alprazolam and flurazepam combined with clonazepam. There were no significant differences in infant gestational age, maternal age, amount of breastfeeding, formula supplementation, and ethnicity. In addition, the length of infant sleep did not correlate with the weight-adjusted dose of benzodiazepines taken by the mother. Therefore, the incidence of reported sedation in infants cannot be explained by aforementioned factors.

A study conducted by the American College of Obstetricians and Gynecologists reported that women with postpartum depression taking benzodiazepines in combination with an antidepressant for anxiety reported sedation in infants following breastfeeding.¹⁴ This trend was also ob-

served in our study where the total number of CNS depressants taken by mothers who reported sedated infants was significantly greater than those who did not report sedation. This suggests that when benzodiazepines are used as an adjunctive medication, there exists the potential for drug-drug interaction and an increased risk for CNS depression. For example, the opioid analgesic morphine and anxiolytic diazepam when taken together potentiate CNS depression.^{15,16} This relationship was further demonstrated by the increased adverse event frequency in mothers taking >1 CNS depressant, demonstrated in Figure 2.

Benzodiazepines have shown lower milk/plasma ratios than other classes of psychotropic CNS depressants such as opiates and barbiturates.^{17,18} The incidence of adverse infant outcomes we detected (1.6%) resulting from exposure to benzodiazepines in infants is significantly lower than the incidence of adverse outcomes of codeine (16.7%) or oxycodone (20.1%) exposure ($P < .001$). A cohort of patients taking only acetaminophen during breastfeeding, which was not expected to result in CNS depression, was also examined. The infant sedation rate in our study was similar to that reported with acetaminophen exposure during lactation (0.5%).¹⁹ All 4 of these prospectively recruited, retrospectively analyzed pharmacodynamics studies were collected via the same follow-up procedure. Retrospective data collection may sometimes introduce the potential for recall bias. The very low reported adverse events rate for the acetaminophen cohort suggests that mothers have an accurate recollection of their child's health while breastfeeding. Although concomitant use of opioids was not an exclusion factor in the present study, none of the women reporting symptomatic infants were taking opioids chronically. The stark differences between high rates of CNS depression in suckling infants exposed to opioids compared with the lack of CNS depression with benzodiazepines illustrates potential differences in penetration through the blood-brain barrier. In the case of morphine, P-glycoprotein effluxes the drug out of the CNS, and the expression of this carrier in neonates is greatly reduced. The reduced expression of this essential transporter may explain increased morphine sensitivity in neonates. More work is needed to investigate brain penetration of benzodiazepines in neonates.

As a secondary objective, maternal benzodiazepine-induced adverse effects were studied. Sedation, confusion, headache, nausea, and vomiting were reported in 26% (32 of 124) of mothers. Unlike the observation in breastfeeding mothers using codeine or oxycodone, adverse maternal effects in mothers using benzodiazepines were not a predictor of adverse outcomes in breastfed infants.¹⁹ Clonazepam had the highest rate of adverse outcomes in 42% (8 of 19) of breastfeeding mothers. The most commonly used benzodiazepine, lorazepam, had a much lower rate of adverse outcomes in 21% (14 of 64) of mothers ($P = .05$). Mothers taking >1 benzodiazepine reported a 50% (3 of 6) rate of side effects.

There are several potential limitations to this study, including the lack of breast milk benzodiazepine concentration analysis. Several benzodiazepines are metabolized by

polymorphic enzymes such as cytochrome P450 (CYP) 2C19 (CYP2C19) and CYP3A4/5. These polymorphisms can affect a wide variety of benzodiazepines including alprazolam, clonazepam, diazepam, midazolam, and triazolam.^{20,21} The contributions of these polymorphisms were not analyzed in the current study. However, we suggest that such polymorphisms are not likely to be a major predictor, as CNS depression in nurslings is very rare. Furthermore inaccurate recall by mothers of their benzodiazepine dose and infant sleeping patterns at the time of lactation is possible as the average age at the time of follow-up was 11 months. Importantly, we excluded women who claimed not to have accurate recollection. A future trial limiting concomitant CNS depressants is necessary in order to isolate the sedative effects of benzodiazepines only as both mothers in this cohort who observed adverse effects were co-medicated with other CNS depressants. Because anxiolytics are commonly taken in combination with other medications, we thought that excluding these women would decrease the generalizability of the data.

In conclusion, the sedative effects of benzodiazepine exposure through breast milk appear to present minimal risk of CNS depression in infants. Mothers taking >1 benzodiazepine are more likely to experience adverse drug effects themselves. Infant sedation was also more likely in mothers taking a greater number of concomitant CNS depressants. The data suggest that limiting the number of CNS depressants taken while breastfeeding will further decrease the risk of both maternal and infant adverse outcomes. This study supports the recommendation that benzodiazepines are compatible with breastfeeding. ■

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go back to the abstract and read it again now that you've scrutinized the article

here's a linkedin bio of the lead author



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Canada was built on the fur trade so it is very popular fashion

here's a bio of the senior author.



Dr. Gideon Koren

Dr. Koren is the founder and director of the Motherisk Program and professor of Pediatrics, Pharmacology, Pharmacy, and Medical Genetics at the University of Toronto. He is also the Richard and Jean Ivey Chair in Molecular Toxicology in the Schulich School of Medicine, at The University of Western Ontario, where he holds the rank of professor in Medicine and Pediatrics. Author of 1300 peer review scientific papers and editor of over a dozen medical books, Dr. Koren does research on drug safety, the molecular mechanisms and clinical effects of adverse drug and chemical reactions, with focus on pregnancy and children. He has received numerous national and international awards. In 2000 Dr. Koren established the FACE (Fetal Alcohol Canadian Expertise) Research Network and in 2002 he created the peer review medical journal, *Fetal Alcohol Research*.