

**Academy of Breastfeeding Medicine
Annotated Bibliography**

“Breastfeeding among Drug Dependent Women”

INTRODUCTION

Illicit and licit substance abuse and dependency remain a significant problem among women of childbearing age. The 2007 National Survey on Drug Use and Health (NSDUH) revealed that among pregnant women aged 15 to 44 years, 5.2 percent used illicit drugs in the past month. Although the prevalence of prescribed opioid pain relievers/narcotic analgesics, such as hydrocodone and oxycodone, among pregnant women is not well known, there is growing evidence that abuse of opioid pain relievers/narcotic analgesics is increasing; prescription opioid pain relievers were the second most frequent drug of abuse after marijuana in 2007.

Substance dependent women frequently display some behaviors or conditions that can be harmful for the breastfed infant independently or in addition to the drug exposure per se. Use of multiple substances (licit and/or illicit), illicit drugs cut with dangerous adulterants, infections such as HIV or hepatitis B/C, poor nutrition, smoking, and psychiatric disorders that require psychotropic medications are common among this population, making breastfeeding a difficult choice for both the mother and health care provider. While methadone maintenance is currently the standard of care for opioid dependent pregnant and postpartum women, buprenorphine, a partial opioid agonist used during pregnancy in Europe, has shown promise as a therapeutic agent, and is undergoing safety trials in the U.S. Infants of drug dependent women stand to benefit substantially from breastfeeding and breast milk, however, there are currently no standardized guidelines for breastfeeding in this vulnerable population.

There exists sparse literature on this subject in total, with most emphasis on methadone and lactation. The large majority of literature in this area constitutes primarily case reports. There are 4 reviews of general drug dependence and breastfeeding, and only case reports for illicit drug use (PCP, cocaine, marijuana) and breastfeeding; most concluding that illicit drug use and breastfeeding are not compatible, and one providing non-evidence based guidelines for cocaine use and lactation. Only few studies, all regarding methadone and lactation, are level II, and only one of these was case controlled (II-1). There are 3 small case studies regarding buprenorphine and breastfeeding, which contain conflicting data. All suffer from small ns.

Twenty two studies are summarized in the attached document; 5 reviews of drug dependence and lactation, 9 regarding methadone maintenance and lactation, 3 small single case studies regarding buprenorphine and lactation, a single case report of a PCP using breastfeeding woman, 3 reports regarding cocaine use and lactation, and one report of marijuana using breastfeeders.

Abbreviations:

BM = breast milk

BF = breastfeeding

FF= formula feeding

MM = methadone maintained

NAS = Neonatal abstinence syndrome

Bup = Buprenorphine

NorBup = Norbuprenorphine

PCP = phencyclidine hydrochloride

Coc = cocaine

Citation	Comment	**Level of Evidence
Wilton JM. Breastfeeding and the chemically dependent woman. NAACOGS Clin Issu Perinat Womens Health Nurs. 1992;3(4):667-72	Review of the topic that includes several specific drugs of abuse. Includes a convenience sample (informal survey) study of women in drug treatment and rates of breastfeeding. Provides some criteria for breastfeeding in this population.	III-review
Howard CR, Lawrence RA. Breast-feeding and drug exposure. Ob and Gyn Clin of NA. Substance Abuse in Pregnancy 1998;25(1):195-217.	Review of the topic that includes maternal kinetic and milk kinetic and oral bioavailability information for several drugs of abuse and methadone.	III-review
American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108(3):776-89.	The most comprehensive review of drugs/chemicals in human milk, this document contains a small table entitled "Drugs of abuse for which adverse events on the infant during breastfeeding have been reported" (amphetamine, cocaine, heroin, marijuana, PCP). Reports that methadone intake by a lactating mother is not associated with any sign or symptom in the infant or effect on lactation.	III-review
Ito S. Drug therapy for breastfeeding women. N Eng J Med 2000; 343(2):118-26.	A review of the benefits/risks of multiple drugs, including drugs of abuse, and lactation. Concludes that the use of all drugs of abuse precludes breastfeeding.	III-review

Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation. J Hum Lact 2004;20(1):62-71.	A review of existing literature regarding methadone and lactation, this article provides an overview of issues surrounding this population and clinical advice to providers.	III
Geraghty B, Graham EA, Logan B, Weiss EL. Methadone levels in breast milk. J Hum Lact 1997;13:227-30.	Two case reports delineating concentrations of methadone in BM and maternal plasma, concludes that methadone transmitted into BM is negligible and unlikely to have adverse effects on the infant, regardless of maternal dose	III
Wojnar-Horton RE, Kristensen JH, Yapp P, Ilett KF, Dusci LJ, Hackett LP. Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. Br J Clin Pharmacol 1997;44:543-47.	Data collected on 12 BF MM women. Subjects provided pre and post feed BM and post feed plasma samples, as well as post feed infant plasma samples (from 8 infants). Concentrations of methadone in maternal plasma and BM were low. Methadone was detectable in the plasma of one infant at a low concentration. 64% of the infants developed NAS. The mean infant dose of methadone was calculated as a percentage of maternal dose (2.8%), and the average infant exposure (calculated from average milk intake figures and assuming 100% bioavailability) was low (17.4 µg/kg/day). Post feed methadone concentrations in BM were 33% higher than prefeed concentrations. The authors conclude that women in MM programs should not be discouraged from breastfeeding. BM meth was insufficient to prevent NAS. There were no adverse effects attributable to methadone in milk.	II-3
McCarthy JJ, Posey BL. Methadone levels in human milk. J Hum Lact 2000;16(2):115-20.	Paper offers a comparative summary of previous studies (Kreek 1974, Blinick 1975, Kreek 1979, Pond 1985, Wojnar-Horton 1997, Geraghty 1997). 14 BM samples were obtained randomly from 8 MM women at infant days 3-202. Mean BM concentrations of methadone were low, as were mean daily infant methadone ingestions (0.05 mg/ day), consistent with other reports. There were no adverse effects associated with BM or weaning. Supports the compatibility of BF with MM therapy.	II-3
Begg EJ, Malpas TJ, Hackett LP, Ilett KF. Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. Br J Clin Pharmacol 2001;52:681-85.	Eight medium to high dose MM mothers yielded blood and BM samples at intervals during the first 24 hours and 2 subjects again at 15 days. R- and S-methadone enantiomers in BM and infant dose were quantified. The BM to plasma ratio was not found to be dose-dependent, consistent with low dose studies, and higher for R-vs S-methadone. The amount of methadone received by the infant is likely to be insufficient to prevent NAS.	II-3

<p>Jansson LM, Choo RE, Harrow C, Velez M, Schroeder JR, Lowe R, Huestis M. Concentrations of methadone in breast milk and plasma in the immediate neonatal period. J Hum Lact 2007;23(2):184-190.</p>	<p>Twelve MM women provided 4 paired (pre and post feed) specimens of BM 1,2,3 and 4 days after delivery. Maternal plasma samples were collected at trough and peak plasma levels. Mean BM methadone concentrations were low, as were mean ingestible infant doses (.006-.084 mg/ day). Concentrations of methadone increased from pre to post feed by 10.5%. There were no correlations between maternal methadone dose and peak or trough maternal plasma concentrations, peak or trough BM methadone concentrations. There were no correlations between maternal plasma concentrations and BM concentrations. Data supports the recommendation for BF for MM women, and further, that women should not be denied BF based on their required dose of methadone.</p>	II-3
<p>Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of NAS among infants of drug-dependent mothers. Pediatrics 2006;117:1163-69.</p>	<p>A retrospective chart review of 190 drug-dependent (poly drug and MM) mother-infant pairs was conducted to evaluate the effects of BM/BF on NAS. In the BM group, mean Finnegan scores were lower and the mean time to withdrawal occurred later. Controlling for exposure to other drugs and prematurity, the BM group was associated with lower need for pharmacologic treatment for NAS</p>	II-3 (?)
<p>Jansson LM, Choo R, Velez ML, Harrow C, Schroeder JR, Shakleya DM, Huestis MA. Methadone maintenance and breastfeeding in the neonatal period. Pediatrics 2008;121:106-14.</p>	<p>Eight MM BF women case matched to 8 MM FF women yielded maternal blood and BM samples on days 1,2,3,4,14 and 30 after delivery at times of trough and peak maternal methadone levels. Paired specimens of foremilk and hindmilk were obtained at each sampling time. FF women yielded plasma samples on the same days. Infant blood was obtained on day 14. Methadone concentrations in maternal plasma were low, unrelated to maternal dose, and not different between groups. Concentrations of methadone in BM increased for all 4 sampling times over time. Concentrations of methadone in infant plasma were detectable and low in all samples (2.2-8.1 ng/mL), and unrelated to maternal dose, plasma concentrations, feeding condition, need for pharmacotherapy for NAS, or NAS scores. Infant neurobehavioral assessments on days 3, 13 and 30 demonstrated no effects of BF on neurobehavioral outcomes. Results support recommendations for BF among MM women.</p>	II-1

<p>Jansson LM, Choo , Velez ML, Lowe R, Huestis MA. Methadone maintenance and long-term lactation. Breastfeed Med 2008;3(1):34-7.</p>	<p>Five MM women provided BM and plasma samples monthly for up to 12 months. Consistent with previous reports, concentrations of methadone in BM and plasma were low. Calculated ingestible infant dose was also low (less than 1/3 mg per day). One infant yielded plasma at one year; methadone concentration in this infant's plasma was detectable and low (2.0 ng/mL). Contributes to the recommendation for BF beyond the neonatal period in MM women.</p>	<p>II-3</p>
<p>Grimm D, Pauly E, Poschl J, Linderkamp O, Skopp G. Bup and Norbup concentrations in human BM samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit 2005;27(4):526-30.</p>	<p>A case report of 1 Bup maintained subject yielding 10 random BM and plasma samples over postpartum days 8-12. Concentrations of Bup in BM and plasma were variable and low. Concludes that Bup exposure of the infant via BM may be considered low.</p>	<p>III</p>
<p>Marquet P, Chevral J, Lavignasse P, Merle L, Lachatre G. Buprenorphine withdrawal syndrome in a newborn. Clin Pharmacol Ther 1997;62:569-71.</p>	<p>A case report of 1 Bup maintained subject yielding single prepartum plasma, postpartum (20 hours) BM and infant plasma, meconium and urine samples. Analysis for Bup and NorBup revealed low concentrations of Bup and NorBup in all samples, however, infant plasma Bup concentrations were 6 times maternal plasma Bup concentrations. The dose of Bup and NorBup delivered to the baby via BM was evaluated at 4 weeks over 24 hours; the dose was determined to be negligible. No withdrawal was seen when lactation was abruptly discontinued.</p>	<p>III</p>
<p>Johnson RE et al. Bup treatment of pregnant opioid dependent women: maternal and neonatal outcomes. Drug Alcohol Depend 2001;63:97-103.</p>	<p>A case report of 1 Bup maintained woman who elected to BF until day 4. BM Bup concentrations were obtained on postpartum days 3, 6 and 9. Concentrations of Bup in BM were low and similar to plasma concentrations on day 3.</p>	<p>III</p>
<p>Kaufman R, Petrucha RA, Pitts FN, Weekes ME. PCP in amniotic fluid and breast milk: case report. J Clin Psych 1983;44(7):269-70.</p>	<p>A single case report of a woman with "phencyclidine psychosis and reactive depression", who provided BM for PCP analysis. PCP appeared in high concentrations in BM, leading to the conclusion that women who have used PCP should not breastfeed.</p>	<p>III</p>

<p>Winecker RE, Goldberger BA, Tebbett IR, Behnke M, Eyley FD, Karlix JL, Wobie K, Conlon M, Phillips D, Bertholf. Detection of Cocaine and its metabolites in breast milk. J Forensic Sci 2001;46(5):1221-23</p>	<p>A method was developed for the detection of Coc and its metabolites and applied to BM samples from 11 Coc users and 10 control subjects (5 of whom admitted prenatal use, 5 were non users). Coc was detected in 6 of 11 users and none of the non-using sample. In one woman who admitted use 5 days prior to sampling, Coc concentrations in BM were detectable at high doses, which if ingested by an infant would yield comparable blood concentrations in adults after a 16 mg IV dose. Since not all Coc user samples were positive on analysis for Coc, the authors conclude that BM analysis is not sensitive enough to detect gestational Coc exposure.</p>	<p>II-2 - 3</p>
<p>Sarkar M, Djulus J, Koren G. When a cocaine-using mother wishes to breastfeed: Proposed Guidelines. Ther Drug Monit 2005;27(1):1-2.</p>	<p>This case description of a Coc using mother offers the recommendation that there exists scanty evidence to deny infants of Coc using mothers BM, and provides subjective (non-evidence based) guidelines for this group, which include maternal urine testing at birth and weekly, addiction services, frequent infant follow-up.</p>	<p>III</p>
<p>Tennes K et.al. Marijuana: prenatal and postnatal exposure in the human. NIDA Res Monograph 1985;59:48-60.</p>	<p>In this report, a sample of 62 marijuana using women breastfed their infants, 27 using marijuana during breastfeeding; 12 once a month or less, 9 weekly and 6 daily. No difference was found between users and non users for age at weaning, infant growth or mental or motor development.</p>	<p>III</p>
<p>Chasnoff I, Lewis DE, Squires L. Cocaine intoxication in a breast fed infant. Pediatrics 1987;80:836-8.</p>	<p>A case report of a 2 week old infant with cocaine intoxication after breastfeeding from a mother who had used intranasal cocaine.</p>	<p>III</p>
<p>AAP, Work Group on Breastfeeding. Pediatrics 1997;100(6):1035-39.</p>	<p>Concludes that breastfeeding is contraindicated in mothers who use illegal drugs</p>	<p>III</p>

Suggestions for Areas of Future Research:

Summary of evidence and areas of research deficiency

1. **Can infants of methadone maintained women safely breastfeed?**

Conclusion: despite small numbers of reports with small numbers of subjects, no randomized trials and only one controlled trial, the literature is consistent regarding the small amounts of methadone transmitted via breast milk and negligible ingestible infant dose. Further, methadone concentrations in breast milk appear to be unrelated to maternal

dose or plasma levels, leading to the conclusion that lactation is safe regardless of maternal dose for stable methadone maintained women.

2. **Can infants of buprenorphine maintained women safely breastfeed?**

Conclusion: While it appears from 3 case reports that the concentrations of buprenorphine in breast milk are small, too few and conflicting data exist to draw firm conclusions.

3. **Can infants of poly-drug (opioid, non-methadone and/or illicit drug) dependent women safely breastfeed?**

Conclusion: Only case reports of illicit drug use and breast milk drug concentrations exist. Most literature concludes that current illicit drug use is incompatible with breastfeeding. However, one report offers guidelines for cocaine dependent women and lactation; these are not evidence based. There is insufficient evidence to draw conclusions regarding the safety of breastfeeding among poly drug dependent women.

Areas of research deficiencies:

1. Little evidence exists regarding buprenorphine maintenance and lactation; this medication is becoming more commonly used in the US to treat opioid dependence. Currently, there is insufficient evidence to recommend breastfeeding among buprenorphine maintained women, though from case reports it is likely to be safe.
2. Despite the relatively large body of literature on methadone and breast milk, there is no literature regarding the developmental effects of small amounts of methadone received by the infant via breast milk over time, or effects on the developing infant brain.

There is insufficient research to support evidence based guidelines for poly-drug (including cocaine, methamphetamines, marijuana, benzodiazepines, PCP) dependent women who wish to breastfeed.

Suggestions for Further Research

1. Case controlled studies evaluating buprenorphine and lactation, to include investigations of concentrations of medication in maternal plasma and breast milk and amount ingestible by the infant, in addition to evaluations of infant neurobehavior among neonates of buprenorphine maintained women.
2. Long term RCT evaluations of infants exposed to methadone or buprenorphine via breastmilk, to include infant developmental assessments.
3. Establishment of standardized guidelines for the opioid dependent woman who chooses to breastfeed.
4. Establishment of consensus regarding the safety of lactation among illicit drug (cocaine, marijuana, benzodiazepine, PCP, methamphetamines) dependent women.

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****US Preventive Services Task Force Ranking of Evidence from Scientific Studies**

- I Evidence obtained from at least one properly randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

The Academy of Breastfeeding Medicine

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The Academy of Breastfeeding Medicine Protocol Committee

Nancy Brent, MD

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Nancy G. Powers, MD, FABM

Julie Scott Taylor, MD, MSc, FABM

Contributor(s)

* Lauren M. Jansson MD

*Lead Author(s)

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