# Psychotropic Drugs in Lactation

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## ABSTRACT

Breast feeding is accompanied by numerous clinical and psychosocial advantages for both the mother and her child. Since most drugs will pass into human milk in some amount, the lactating mother who requires pharmacotherapy adds complexity to the risk-benefit assessment for clinicians making treatment decisions. In the case of psychotropic medications this issue is particularly worrisome since women who are not well controlled will have impaired bonding with their child.

Moreover, these women may not necessarily recognize adverse events or abnormal outcomes in her infants. In an ideal situation, the patient would receive pharmacotherapy to assist in disease management, while at the same time successfully breastfeed her child. This goal of this presentation is to discuss the disposition of drugs in lactating patients and to outline the available literature concerning the use of psychotropic drugs in lactating women. Part of the continuum of treating women with psychiatric disease in pregnancy concerns the treatment of women after delivery, and for many, this will include drug treatment during lactation. The goal of today's discussion is to describe the issues and outline what is currently known about the use of psychotropic drugs in breastfeeding women.

## INTRODUCTION

Breastfeeding is a biological norm for mammals, and is truly considered an ideal feeding method for most women. Research has clearly shown that breastfeeding is associated with numerous health advantages for both women and their children.[1] Infants who are breastfed experience lower risks of infection, including diarrhea, pneumonia, otitis media, meningitis and necrotizing enterocolitis. Breastfeeding also appears to have immunomodulating effects such that breastfed babies exhibit lower rates of diabetes, inflammatory bowel disease and other autoimmune disorders. A number of studies have also shown improved cognitive scores among breastfeed babies which appears to be more pronounced among premature infants.[2]

For clinicians, the situation of a breastfeeding mother requiring medication can be quite unique, because, in effect, there are two patients to consider. In most situations a risk-benefit analysis for pharmacotherapy is fairly straight forward. That is, do the benefits of taking a particular medication outweigh the risks that may be associated with its use? In the case of a lactating mother however, we must weigh the benefits that breast feeding provides for both the mother and the baby and the benefits of treating the mother's condition against the risks associated with the mother not taking the medication or the risks of her child ingesting unnecessary drug through milk. Almost all drugs will gain access to milk, just as they would any other tissue in the body. Generally drug excretion into milk is described as a

percentage of the maternal dose (per kg), the weight adjusted maternal dose. Drug excretion of less than 10% is generally considered compatible with breastfeeding as it is unlikely to lead to dose related adverse events in the infant.[3] Currently, it is believed that most drugs pass across the mammary barrier into milk by passive diffusion against the concentration gradient. However, active, or carrier-mediated transport, probably does occur for some agents. Drugs must pass from the maternal plasma, through the capillary walls into the alveolar cells lining milk duct. During the first few days of life there are large gaps between these alveolar cells which allow most molecules to easily cross. Once mature milk is established, these gaps are closed and drug access to the milk is more limited. Drugs must cross a lipid bilayer to reach the milk, and as such, extremely large molecules are unlikely to reach the milk. However, lipophilic drugs easily gain access the milk and may even accumulate.[3-5]

The amount of drug excreted into milk depends largely on pharmacokinetic parameters which have been used empirically to estimate the probability that a drug will enter milk.[6,7]
These characteristics include:

- the lipid solubility of the drug
- the molecular size of the drug
- the blood level attained in the maternal circulation
- protein binding in the maternal circulation
- oral bioavailability in the infant, and the mother
- the half-life in the maternal and infant's plasma compartments.

An understanding of drug disposition and how drugs reach the milk is critical to being able to better advise patients on what medications they can take while lactating. If the drug is given by mouth to the mother, then the oral bioavailability will influence the amount available to the systemic circulation. Drugs with poor oral absorption are less likely to reach the milk. Once a drug is absorbed, it can become protein bound, it can move into other tissue depots in the body or it can be metabolized by the liver or excreted by the renal system before it ever enters the mammary ducts. As a result of normal absorption and distribution, in most cases, very little drug will get into milk and infants are unlikely to ingest large quantities of drug. Only free drug concentrations will move across the biological membranes, therefore highly bound drugs are less likely to accumulate in milk. On the other hand, milk has a relatively high fat content as compared to serum. Therefore lipophilic drugs will easily pass into the milk and will tend to accumulate within the ducts. The pH of the milk is also plays a role in the drug disposition. Milk pH is lower than that of the plasma so that drugs which become ionized at this lower pH, usually basic drugs, are more likely to become ion trapped in the milk. After drugs reach the milk, once again, oral absorption plays a role. However it is the infant’s absorption that is critical at this stage. Infants, by default, are

ingesting drug through milk orally and therefore their own oral bioavailability will impact the likelihood that the drug will reach the infant's systemic circulation.

So what are the alternatives when a mother requires drug therapy while lactating?
Generally there are three options and the risks and benefits of each of them require full consideration:

- avoidance of drug therapy and continuation of breastfeeding
- discontinuation of breastfeeding during maternal drug therapy
- continuation of both breastfeeding and maternal drug therapy

Both of the first two options would present risks to the mother or child or both. In reality, the third option would be the most ideal, provided appropriate treatments are chosen. In fact, in most cases continued breastfeeding during maternal drug therapy is possible. To date, there are no specific protocols or guidelines for clinicians treating the lactating psychiatric patient. Therefore, clinicians should consider a number of issues when suggesting treatment alternatives. Looking at individual drugs, it is important that one considers the factors that influence infant serum levels as noted above, as well as the patient's particular clinical situation, including disease symptoms and treatments used in the past. It is important to note that, in most cases, the milk excretion data and reports of infant exposure are very limited. Generally, the literature is limited to single case reports or small case series describing several mother infant pairs.

**Selective Serotonin Reuptake Inhibitors (SSRIs) and Seotonine-Norepinephrine Reuptake Inhibitor (SNRIs)**

Most SSRI's and SNRIs are found in milk in relatively low amounts (Table 1). With paroxetine and sertraline, two of the more commonly used agents, the infants generally had low or undetectable serum drug levels.[8-19] The literature includes cases of adverse events, mainly with the use of fluoxetine, which included uneasy sleep, colic, irritability, poor feeding and drowsiness.[20-28] It is possible that this is merely due to the fact that fluoxetine was the first of its kind on the market. There does not appear to be any clear pattern of adverse event and most events were transient or self limited, rarely verified by a medical professional or objective measure.

**Heterocyclic Antidepressants**

Since the introduction of the SSRIs, heterocyclic antidepressants have fallen from first line therapy for depression. Tricyclic antidepressants (TCAs) generally had a less favorable side effect profile and a much higher risk of morbidity and mortality from overdose. However, for some patients they may still be

preferred agents. In particular, for patients who responded well to the TCAs in the past, there may be little clinical reason to switch. Some TCAs have been measured in milk with small amounts detected (Table 1). In a number of these cases the mothers continued to breastfeed. Follow up information is available for a number of infants who were breastfed during maternal amitryptyline, nortriptyline, clomipramine or imipramine therapy with no adverse events noted.[29-38] This includes some infants who were followed up to the age of 30 months showing normal neurological, psychological and motor development.[38]

Data with doxepin appears to be somewhat concerning. There is a case of an infant whose mother was taking 150 mg doxepin/day with no adverse events.[39] However, two other case reports reveal infants with serious adverse events during maternal doxepin therapy.[40,41] The first is the case of an infant admitted to hospital with respiratory depression; she was pale, limp and drowsy.[40] The mother's dose had been increased to 25 mg three times/day four days prior to the hospital admission. Breast milk levels of the drug were low, 0.3% of the weight adjusted maternal dose. The infant had very low levels of doxepin but therapeutic concentrations of the active metabolite, desmethyldoxepin. The infant returned to normal 1 day after breastfeeding was discontinued. A second infant was admitted to hospital with poor suck and swallow, hypotonia, and vomitting.[41] Symptoms resolved 48 hours after breastfeeding was stopped however there were undetectable drug concentrations in the infant. There are no published case reports of amoxepine, maprotiline or trimipramine in lactating women.

With the exception of doxepin there is little evidence to suggest that this group of medications is an absolute contraindication in breastfeeding. They have been used clinically for many decades and the lack of adverse events reported in the literature is reassuring.

**Monoamine Oxidase Inhibitors (MAOIs)**

Although MAOIs are not considered first line therapy for depression they may still be encountered clinically. Unfortunately there is very little data on their use in lactation. Excretion measurements suggests that the infant will ingest approximately 1% of the weight adjusted maternal dose (Table 1) however infants in this series were not breastfeed during this single dose study and were therefore not exposed to drug through milk.[42]

**Other Antidepressants**

Bupropion or it's active metabolite hydroxybupropion was undetectable in the sera of three breastfed infants.[43-45] Milk data suggests that the infant would be exposed to only 3% of the weight adjusted maternal dose. No adverse effects have been reported in any of the nursed infants.

**Benzodiazepines**

There is little data on the use of benzodiazepines in breastfeeding women. Excretion data is as low as 1% with oxazepam[46-48] and up to 8% with alprazolam.[49] Generally, since infants are more likely to accumulate drugs, due to their impaired clearance, benzodiazepines with shorter half lives are preferred.

**Mood Stabilizers**

Data on the use of carbamazepine and valproic acid in lactating women is found among women using these medications for seizure disorders.[50-54] Both carbamazepine and valproic acid have not been associated with adverse events in breastfed infants as small amounts are detectable in milk. They are considered compatible with lactation.[4] Lithium use in lactating patients is somewhat controversial. The literature is inconsistent as milk levels appear to vary widely among patients.[55] In our own setting the agent is used with caution in lactating patients and in consultation with the primary physician.[55] Patients are followed closely and individualized drug monitoring is performed with each mother-infant pair.

**Typical Antipsychotics**

Data for the typical antipsychotics has been located for only haloperidol, perphenazine and chlorpromazine.[56-60] All have shown low amounts in milk. No data is available for other agents in this class. Generally, if alternative treatments can be used agents with no data should be avoided.

**Atypical Antipsychotics**

Some cases of milk excretion data are reported for clozapine, olanzapine, quetiapine and risperidone.[61-68] All have low excretion into milk, <3% of the maternal weight adjusted dose.

**Summary**

The key to evaluating any particular mother infant pair is truly a balancing act; putting into perspective the benefits of breastfeeding, and optimal treatment of maternal disease. If maternal treatment has continued for some time, in most cases, the infant would have been exposed to significantly more drug prenatally and would also be exposed to breastmilk levels significantly below therapeutic doses. With such limited information it is clear that no agent within a given class has clearly proven to be safer than another for a lactating patient. The ability to monitor the infant, the patient's response to drugs in the past, concomitant medications and the available breastfeeding data all come together in this assessment of choosing the optimal psychotropic medication for a lactating patient.

**TABLE 1** Summary of Antidepressant Drug Excretion into Milk

| | |
|---|---|
| **SSRIs & SNRIs** | |
| Fluoxetine | 3-9% |
| Paroxetine | < 4%, |
| Sertraline | <2% |
| Citalopram | 5-10% |
| Fluvoxamine | < 2% |
| Venlafaxine | 2-3% (detectable metabolites) |
| **Heterocyclic antidepressants** | |
| Amitriptyline | 0.3 – 1.3% |
| Clomipramine | 2-3% |
| Desipramine | 1% |
| Doxepin | <1-2.5% |
| Imipramine | <1-5% |
| Nortriptyline | up to 2% |
| **Monoamine oxidase inhibitors** | |
| Moclobemide | 1% |
| **Other antidepressants** | |
| Bupropion | <1.0% |
| Nefazodone | <0.5% |
| Trazodone | up to 1% |

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## REFERENCES


1. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005 Feb;115(2):496-506.
2. Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. BMJ 2006 Nov 4;333(7575):945.
3. Bennett PN, Jensen AA. Drugs and human lactation-a comprehensive guide to the content and consequences of drugs, micronutrients, radiopharmaceuticals, and environmental and occupational chemicals in human milk. 2nd ed . Amsterdam: Elsevier; 1996.
4. American Academy of Pediatrics Committee on Drugs: The transfer of drugs and other chemicals into human milk. Pediatrics 1994 Jan;93(1):137-50.
5. Anderson PO. Drug use during breast-feeding. Clin Pharm 1991 Aug;10(8):594-624.
6. Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. Clin Pharmacokinet 1990 Feb;18(2):151-67.
7. Begg EJ, Atkinson HC. Modelling of the passage of drugs into milk. Pharmacol Ther 1993 Sep;59(3):301-10.
8. Begg EJ, Duffull SB, Saunders DA, Buttimore RC, Ilett KF, Hackett LP, et al. Paroxetine in human milk. Br J Clin Pharmacol 1999 Aug;48(2):142-7.
9. Stowe ZN, Cohen LS, Hostetter A, Ritchie JC, Owens MJ, Nemeroff CB. Paroxetine in human breast milk and nursing infants. Am J Psychiatry 2000 Feb;157(2):185-9.
10. Hendrick V, Stowe ZN, Altshuler LL, Hostetter A, Fukuchi A. Paroxetine use during breast-feeding. J Clin Psychopharmacol 2000 Oct ;20(5):587-9.
11. Misri S, Kim J, Riggs KW, Kostaras X. Paroxetine levels in postpartum depressed women, breast milk, and infant serum. J Clin Psychiatry 2000 Nov;61(11):828-32.
12. Stowe ZN, Owens MJ, Landry JC, Kilts CD, Ely T, Llewellyn A, et al. Sertraline and desmethylsertraline in human breast milk and nursing infants. Am J Psychiatry 1997 Sep;154(9):1255-60.
13. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. Am J Psychiatry 1996 Sep;153(9):1132-7.
14. Altshuler LL, Burt VK, McMullen M, Hendrick V. Breastfeeding and sertraline: a 24-hour analysis. J Clin Psychiatry 1995 Jun;56(6):243-5.
15. Epperson N, Czarkowski KA, Ward-O'Brien D, Weiss E, Gueorguieva R, Jatlow P, et al. Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. Am J Psychiatry 2001 Oct;158(10):1631-7.
16. Kristensen JH, Ilett KF, Dusci LJ, Hackett LP, Yapp P, Wojnar-Horton RE, et al. Distribution and excretion of sertraline and N-desmethylsertraline in human milk. Br J Clin Pharmacol 1998 May;45(5):453-7.
17. Stowe ZN, Hostetter AL, Owens MJ, Ritchie JC, Sternberg K, Cohen LS, et al. The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. J Clin Psychiatry 2003 Jan;64(1):73-80.
18. Dodd S, Stocky A, Buist A, Burrows GD, Maguire K, Norman TR. Sertraline in paired blood plasma and breast-milk samples from nursing mothers. Hum Psychopharmacol 2000 Jun;15(4):161-264.
19. Dodd S, Stocky A, Buist A, Burrows GD, Norman TR. Sertraline analysis in the plasma of breast-fed infants. Aust N Z J Psychiatry 2001 Aug;35(4):545-6.
20. Isenberg KE. Excretion of fluoxetine in human breast milk. J Clin Psychiatry 1990 Apr;51(4):169.
21. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. Pediatrics 1992 Apr;89(4 Pt 1):676-7.

22. Lester BM, Cucca J, Andreozzi L, Flanagan P, Oh W. Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adolesc Psychiatry 1993 Nov;32(6):1253-5.
23. Taddio A, Ito S, Koren G. Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. J Clin Pharmacol 1996 Jan;36(1):42-7.
24. Brent NB, Wisner KL. Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. Clin Pediatr (Phila) 1998 Jan;37(1):41-4.
25. Yoshida K, Smith B, Craggs M, Kumar RC. Fluoxetine in breast-milk and developmental outcome of breast-fed infants. Br J Psychiatry 1998 Feb;172:175-8.
26. Hale TW, Shum S, Grossberg M. Fluoxetine toxicity in a breastfed infant. Clin Pediatr (Phila) 2001 Dec;40(12):681-4.
27. Suri R, Stowe ZN, Hendrick V, Hostetter A, Widawski M, Altshuler LL. Estimates of nursing infant daily dose of fluoxetine through breast milk. Biol Psychiatry 2002 Sep 1;52(5):446-51.
28. Heikkinen T, Ekblad U, Palo P, Laine K. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. Clin Pharmacol Ther 2003 Apr;73(4):330-7.
29. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. Am J Psychiatry 1980 Jul;137(7):855-6.
30. Breyer-Pfaff U, Nill K, Entenmann KN, Gaertner HJ. Secretion of amitriptyline and metabolites into breast milk. Am J Psychiatry 1995 May;152(5):812-3.
31. Brixen-Rasmussen L, Halgrener J, Jorgensen A. Amitriptyline and nortriptyline excretion in human breast milk. Psychopharmacology (Berl) 1982;76(1):94-5.
32. Pittard WB, III, O'Neal W, Jr. Amitriptyline excretion in human milk. J Clin Psychopharmacol 1986 Dec;6(6):383-4.
33. Matheson I, Skjaeraasen J. Milk concentrations of flupenthixol, nortriptyline and zuclopenthixol and between-breast differences in two patients. Eur J Clin Pharmacol 1988;35(2):217-20.
34. Wisner KL, Perel JM. Nortriptyline treatment of breast-feeding women. Am J Psychiatry 1996 Feb;153(2):295.
35. Wisner KL, Perel JM, Foglia JP. Serum clomipramine and metabolite levels in four nursing mother-infant pairs. J Clin Psychiatry 1995 Jan;56(1):17-20.
36. Wisner KL, Perel JM. Serum nortriptyline levels in nursing mothers and their infants. Am J Psychiatry 1991 Sep;148(9):1234-6.
37. Birnbaum CS, Cohen LS, Bailey JW, Grush LR, Robertson LM, Stowe ZN. Serum concentrations of antidepressants and benzodiazepines in nursing infants: A case series. Pediatrics 1999 Jul;104(1):e11.
38. Yoshida K, Smith B, Craggs M, Kumar RC. Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. J Affect Disord 1997 May;43(3):225-37.
39. Kemp J, Ilett KF, Booth J, Hackett LP. Excretion of doxepin and N-desmethyldoxepin in human milk. Br J Clin Pharmacol 1985 Nov;20(5):497-9.
40. Matheson I, Pande H, Alertsen AR. Respiratory depression caused by N-desmethyldoxepin in breast milk. Lancet 1985 Nov 16;2(8464):1124.
41. Frey OR, Scheidt P, von Brenndorff AI. Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. Ann Pharmacother 1999 Jun;33(6):690-3.
42. Pons G, Schoerlin MP, Tam YK, Moran C, Pfefen JP, Francoual C, et al. Moclobemide excretion in human breast milk. Br J Clin Pharmacol 1990 Jan;29(1):27-31.
43. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. J Clin Psychiatry 2004 Jun;65(6):881-2.
44. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. Am J Psychiatry 1996 Sep;153(9):1132-7.
45. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. Ann Pharmacother 1993 Apr;27(4):431-3.

46. Dusci LJ, Good SM, Hall RW, Ilett KF. Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. Br J Clin Pharmacol 1990 Jan;29(1):123-6.
47. Stebler T, Guentert TW. Determination of diazepam and nordazepam in milk and plasma in the presence of oxazepam and temazepam. J Chromatogr 1991 Mar 8;564(1):330-7.
48. Wretlind M. Excretion of oxazepam in breast milk. Eur J Clin Pharmacol 1987;33(2):209-10.
49. Oo CY, Kuhn RJ, Desai N, Wright CE, McNamara PJ. Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk. Br J Clin Pharmacol 1995 Sep;40(3):231-6.
50. Froescher W, Eichelbaum M, Niesen M, Dietrich K, Rausch P. Carbamazepine levels in breast milk. Ther Drug Monit 1984;6(3):266-71.
51. Bar-Oz B, Nulman I, Koren G, Ito S. Anticonvulsants and breast feeding: a critical review. Paediatr Drugs 2000 Mar;2(2):113-26.
52. Hagg S, Spigset O. Anticonvulsant use during lactation. Drug Saf 2000 Jun;22(6):425-40.
53. Nau H, Kuhnz W, Egger HJ, Rating D, Helge H. Anticonvulsants during pregnancy and lactation. Transplacental, maternal and neonatal pharmacokinetics. Clin Pharmacokinet 1982 Nov;7(6):508-43.
54. von Unruh GE, Froescher W, Hoffmann F, Niesen M. Valproic acid in breast milk: how much is really there? Ther Drug Monit 1984;6(3):272-6.
55. Moretti ME, Koren G, Verjee Z, Ito S. Monitoring lithium in breast milk: an individualized approach for breast-feeding mothers. Ther Drug Monit 2003 Jun;25(3):364-6.
56. Stewart RB, Karas B, Springer PK. Haloperidol excretion in human milk. Am J Psychiatry 1980 Jul;137(7):849-50.
57. Whalley LJ, Blain PG, Prime JK. Haloperidol secreted in breast milk. Br Med J (Clin Res Ed) 1981 May 30;282(6278):1746-7.
58. Wiles DH, Orr MW, Kolakowska T. Chlorpromazine levels in plasma and milk of nursing mothers. Br J Clin Pharmacol 1978 Mar;5(3):272-3.
59. Uhlir F, Ryznar J. Appearance of chlorpromazine in the mother's milk. Act Nerv Super (Praha) 1973 May;15(2):106.
60. Olesen OV, Bartels U, Poulsen JH. Perphenazine in breast milk and serum. Am J Psychiatry 1990 Oct;147(10):1378-9.
61. Ambresin G, Berney P, Schulz P, Bryois C. Olanzapine excretion into breast milk: a case report. J Clin Psychopharmacol 2004 Feb;24(1):93-5.
62. Goodwin G, Young AH. Using guidelines in real clinical situations: clozapine and breast feeding in bipolar disorder. J Psychopharmacol 2005 May;19(3):317-8.
63. Barnas C, Bergant A, Hummer M, Saria A, Fleischhacker WW. Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk. Am J Psychiatry 1994 Jun;151(6):945.
64. Lutz UC, Wiatr G, Orlikowsky T, Gaertner HJ, Bartels M. Olanzapine treatment during breast feeding: a case report. Ther Drug Monit 2008 Jun;30(3):399-401.
65. Gardiner SJ, Kristensen JH, Begg EJ, Hackett LP, Wilson DA, Ilett KF, et al. Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. Am J Psychiatry 2003 Aug;160(8):1428-31.
66. Croke S, Buist A, Hackett LP, Ilett KF, Norman TR, Burrows GD. Olanzapine excretion in human breast milk: estimation of infant exposure. Int J Neuropsychopharmacol 2002 Sep;5(3):243-7.
67. Rampono J, Kristensen JH, Ilett KF, Hackett LP, Kohan R. Quetiapine and breast feeding. Ann Pharmacother 2007 Apr;41(4):711-4.
68. Lee A, Giesbrecht E, Dunn E, Ito S. Excretion of quetiapine in breast milk. Am J Psychiatry 2004 Sep;161(9):1715-6.