Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders

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INTRODUCTION

The benefits of breastfeeding generally appear to outweigh the small risk posed by psychotropic medications that are used to treat postpartum mental disorders in lactating mothers [1,2].

This topic reviews the safety of antipsychotics, lithium, and medications for substance use disorders in breastfeeding infants. The safety of anticonvulsants, antidepressants, and benzodiazepines in breastfeeding infants; benefits of lactation; education of parents about breastfeeding; and initiation of breastfeeding are discussed separately, as is choosing a specific drug for treating postpartum psychiatric disorders.

- (See "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Breastfeeding'.)
- (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding".)
- (See "Infant benefits of breastfeeding".)
- (See "Maternal and economic benefits of breastfeeding".)
- (See "Breastfeeding: Parental education and support".)
- (See "Initiation of breastfeeding".)

- (See "Severe postpartum unipolar major depression: Choosing treatment".)
- (See "Bipolar disorder in postpartum women: Treatment".)
- (See "Treatment of postpartum psychosis".)
- (See "Obsessive-compulsive disorder in pregnant and postpartum patients".)

GENERAL PRINCIPLES

General principles to bear in mind when choosing a psychotropic drug for postpartum, lactating patients include:

- Patients who are successfully treated with drugs during pregnancy should generally not change medications for the purpose of breastfeeding
- Patients who start pharmacotherapy should be treated with medications that were efficacious in the past
- Avoid polypharmacy if possible

Additional information about the general principles of using psychotropic drugs in breastfeeding patients is discussed separately, as is choosing specific treatments for postpartum mental disorders.

- (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'General principles'.)
- (See "Severe postpartum unipolar major depression: Choosing treatment".)
- (See "Bipolar disorder in postpartum women: Treatment".)
- (See "Treatment of postpartum psychosis".)
- (See "Obsessive-compulsive disorder in pregnant and postpartum patients".)

Monitoring — Pediatricians should assess infant behavior, feeding, alertness, and sleep as well as physically examine infants to establish a baseline [3-6]. Infants exposed to medications via breast milk should then be monitored periodically (eg, monthly) for adverse events such as sleep disturbances, irritability, agitation, excessive crying, or poor weight gain. In addition, infants should be assessed for known drug effects; as an example:

- Infants exposed to antipsychotics should be monitored for extrapyramidal symptoms [7,8].
- Among infants exposed to lithium, weight should be closely monitored for the first two weeks (eg, postdischarge day one or two and then every three days, until weight gain is appropriate) [9]. Lactating mothers treated with lithium should be educated about monitoring infant symptoms such as dehydration, feeding problems, or lethargy.

Serum laboratory tests for infants should also be performed for all indices that can be affected by the medications that the mother is taking (table 1); tests should be scheduled at least as often as they are for adults, including those times when maternal drug doses are increased or side effects occur in the infant [10]. Laboratory monitoring is indicated especially for infants exposed to carbamazepine, lithium, or valproate [11].

If adverse events in infants are suspected, mothers should immediately reduce or suspend breastfeeding [4,10]. This may enable clinicians to determine whether maternal medications caused the adverse events.

ANTICONVULSANTS

Information about the safety of infant exposure to anticonvulsants through breast milk is discussed separately. (See "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Breastfeeding'.)

ANTIPSYCHOTICS

Based upon the limited evidence and our clinical experience, breastfeeding mothers can be encouraged to take antipsychotics if they are indicated and if a discussion of the risk of not treating reveals the possibility of significant negative outcomes for mother and child. The exposure of infants to antipsychotics via human milk generally appears to be low and clinically insignificant [12]. However, the literature remains scant and more research is needed to make evidence based recommendations [7].

First-generation — Small studies suggest that chlorpromazine and haloperidol may be compatible with breastfeeding.

Chlorpromazine — Multiple reviews of studies that examined secretion of chlorpromazine into breast milk and adverse effects in infants have concluded that chlorpromazine may be compatible with breastfeeding [7,13]. In one review of six observational studies that identified infants (n = 16) whose mothers were treated with chlorpromazine monotherapy, one baby had drowsiness, and no long-term adverse effects were observed among the 16 infants [7]. Another review concluded that chlorpromazine is excreted in breast milk in small amounts [14].

Haloperidol — Haloperidol is a reasonable choice for women who are starting a first-generation antipsychotic while nursing, based upon small observational studies of infants exposed to haloperidol through lactation. The use of haloperidol in breastfeeding women who

are treated with a first-generation antipsychotic is consistent with guidance from the National Library of Medicine's LactMed database (United States) [15]. In addition, multiple reviews of studies that examined secretion of haloperidol into breast milk and adverse effects in infants have concluded that haloperidol may be compatible with breastfeeding [7,13].

Observational studies have found that most breastfeeding babies are not adversely affected by their mothers' use of haloperidol:

- Multiple case reports (total n = 14 infants) have found no acute adverse effects [16-19].
- A prospective observational study found that acute mental and psychomotor development was comparable for babies who were breastfed by mothers taking first-generation antipsychotics (n = 12; 9 of the 12 [75 percent] received haloperidol) and for nonbreastfeeding babies whose mothers were taking haloperidol or other drugs (n = 18) [17].

In addition, excretion of haloperidol in breast milk appears to be small [14].

Other drugs — Other first-generation antipsychotics may be compatible with breastfeeding, but the evidence of their safety is sparse. Small observational studies of breastfeeding infants whose mothers were taking chlorprothixene, flupenthixol, perphenazine, trifluoperazine, or zuclopenthixol (total n = 18 infants) found no acute adverse events [7]. In addition, a review concluded that perphenazine and trifluoperazine are excreted in breast milk in small amounts [14].

Second-generation — Olanzapine has been more widely studied in the setting of breastfeeding than other second-generation antipsychotics; these studies suggest that olanzapine may be compatible with breastfeeding [20]. The next most widely studied drugs appear to be quetiapine and risperidone, and the evidence suggest that they may also be compatible with breastfeeding.

Aripiprazole — Although definitive data regarding the use of aripiprazole during breastfeeding are lacking [20,21], a review concluded that the results from case reports, other literature reviews, and practice guidelines were reassuring [22]. As an example, one case report described a mother-infant pair in which the mother was prescribed aripiprazole; no acute adverse effects occurred in the infant [23]. Two separate case reports found that aripiprazole was detectable in breast milk [24,25], whereas one case report found that the drug was not detectable [23]. In addition, one treatment guideline suggests that aripiprazole is a reasonable option for lactating patients because infant exposure is relatively low compared with some other antipsychotics and adverse effects in nursing children have not been reported [12].

Asenapine — It is not clear if asenapine is compatible with breastfeeding because little information is available about its use in lactating women [15,20].

Clozapine — We typically encourage women treated with clozapine to not breastfeed, because infants may be vulnerable to the side effects that occur in adults (eg, hematologic toxicity and seizures) [14]. In addition, the safety of clozapine in breastfed infants has been studied in only a few patients, and the results suggest that the drug is problematic. A review of two observational studies (total n = 5 infants exposed to clozapine) found that one baby suffered agranulocytosis, one baby manifested lethargy, and one had speech delay [7]. In addition, a case report observed that the accumulation of clozapine in breast milk was high [26]. Using antipsychotics other than clozapine is consistent with guidelines from the United Kingdom's National Institute for Health and Clinical Excellence [6] and the British Association for Psychopharmacology [14], and several reviews have deemed it inadvisable to use clozapine in lactating patients [7,12,13,20,21,27].

Lurasidone — One case report of an infant exposed to lurasidone through breastfeeding found that the infant serum concentration was negligible and that during 39 days of follow-up, infant growth and development were normal [28].

Olanzapine — Olanzapine is a reasonable choice for women who require a second-generation antipsychotic while nursing. The use of olanzapine is consistent with guidance from the National Library of Medicine's LactMed database (United States), which reports that maternal doses up to 20 mg/day are associated with low levels in breast milk and undetectable levels in the serum of breastfed infants [15]. In addition, multiple reviews of observational studies that examined secretion of olanzapine into breast milk and adverse effects in infants have concluded that olanzapine may be compatible with breastfeeding [7,12,13,20,21,29].

Observational studies have found that most breastfeeding babies are not adversely affected by their mothers' use of olanzapine:

- A review of 10 studies (total n = 64 infants exposed to olanzapine) found that somnolence was observed in three (5 percent) infants, slow weight gain in two (3 percent), and developmental delay in three (5 percent) [7]. One of the better studies was a prospective study, which found that adverse events were comparable for breastfeeding infants whose mothers were taking olanzapine (3/22 infants, 14 percent), nonbreastfeeding infants of mothers taking olanzapine (1/15, 7 percent), and breastfeeding infants whose mothers were taking a drug known to be safe during lactation (4/51, 8 percent) [30].

- A study examined the manufacturer's safety database, which included all spontaneously reported adverse events in breastfeeding infants (n = 102 exposed infants) [31]. No

adverse events were reported in 82 percent. The most common adverse events associated with exposure were nonspecific, such as somnolence (4 percent of infants), irritability (2 percent), tremor (2 percent), and insomnia (2 percent).

- A case report described a mother who began receiving long-acting injectable olanzapine during pregnancy and continued it during breastfeeding. Although the drug was excreted in breast milk, infant serum concentrations were very low and no adverse effects were observed in the infant [32]. Follow-up at age three years found that the child's somatic and psychomotor development was normal.

Several studies of serum assays of infants (total n = 12) exposed to olanzapine via breast milk have not detected the drug [8,14,33-36]. The mechanism may be due to low absorption and distribution of the drug in the large amounts of fat in children [8]. However, one case report described an infant who had a serum concentration that was approximately 40 percent of the maternal level; subsequent infant serum concentrations were very low or undetectable [37].

Paliperidone — Paliperidone, which is the active metabolite of risperidone, may be compatible with breastfeeding based upon studies of risperidone (see 'Risperidone' below). In addition, a study of two breastfed infants whose mothers were treated with risperidone found that infant serum concentrations of paliperidone (and risperidone) were not detectable, and there were no adverse effects [38].

Quetiapine — Most studies suggest that quetiapine may be compatible with breastfeeding [21,29]. A review of 10 studies (total n = 23 infants exposed to quetiapine) found that one infant became drowsy, which was attributed to the concomitantly prescribed mirtazapine, and two infants (who were also exposed to other concomitantly prescribed medications) manifested slight delays in mental and motor development [7]. The review concluded that use of quetiapine is compatible with breastfeeding. In addition, one treatment guideline suggests that quetiapine is a reasonable option for lactating patients [12].

Infant exposure to quetiapine through breast milk appears to be low [7,12,20]:

- A case report of a mother-infant pair in which the mother was prescribed quetiapine found that the infant serum concentration was 6 percent of the maternal concentration (some studies have arbitrarily defined elevated infant levels as those exceeding 10 percent of maternal levels) [39].

- Studies that assayed breast milk concentrations of quetiapine (total n = 16 women) found that quetiapine was not detectable in five patients and the mean infant dose of quetiapine was very small [27,40,41].

- Studies of breast milk levels (total n = 11 breastfeeding women taking quetiapine) concluded that maternal quetiapine therapy was unlikely to pose a significant exposure risk to breastfed infants [42-44].

Risperidone — Risperidone may be compatible with lactation [21], based upon studies (total n = 6 infants) that found no acute adverse effects occurred [38,45-47]. In addition, serum assays (total n = 4 infants) found that risperidone and the active metabolite were not detected, except for one infant in which the metabolite was present at minimal concentrations [38,46,47]. Consistent with these findings, a case report found that secretion of risperidone and the metabolite into breast milk was modest [48]. The use of risperidone in breastfeeding women who are treated with a second-generation antipsychotic is consistent with guidance from the National Library of Medicine's LactMed (United States) database, which reports that levels in breast milk are low [15]. In addition, a review of observational studies that examined secretion of risperidone into breast milk and adverse effects in infants concluded that risperidone is compatible with breastfeeding [7].

Ziprasidone — It is not clear if ziprasidone is compatible with breastfeeding due to the paucity of data [20,21,29]. A single case report found that infant exposure to ziprasidone through breast milk resulted in no acute adverse effects [49]. In another case report, ziprasidone breast milk concentrations were measured for 16 consecutive days; the drug was not detectable except on day 10, at which point the level was very low [50].

LITHIUM

There is no clear consensus on the safety of lithium in breastfeeding women [51]. Treatment with lithium versus other drugs thus needs to be considered on a case-by-case basis, and needs to account for patient values and preferences regarding risks such as relapse and infant exposure. As an example, a woman with bipolar disorder who has been well-controlled on lithium during pregnancy may not want to risk relapse by cross-tapering to a different medication following childbirth, when the risk for postpartum mood episodes is very high [6].

Among women who are breastfeeding, we suggest limiting the use of lithium to those cases in which each of the following criteria are met [52]:

- Patient is clinically stable and has participated in a discussion of the risks and benefits of using lithium while breastfeeding. (Clinically unstable patients who are hospitalized can pump their breast milk to maintain their supply.)

- Pharmacotherapy consists of lithium monotherapy or lithium plus one or two other drugs.

- Infant is healthy (eg, preterm babies may be more sensitive to medications, although data are limited).

- Patient and pediatrician can adhere to recommendations for monitoring the infant. (See 'Monitoring' above.)

Some authorities think that lithium is reasonable for patients who have been successfully treated with it [10,53,54], based upon evidence that nursing infants exposed to lithium generally do not suffer adverse events [21,55,56]:

- A prospective observational study of 10 mother-infant pairs found that growth and neurodevelopment was within normal limits [57]. All 10 infants had normal thyroid-stimulating hormone (TSH), blood urea nitrogen (BUN), and creatinine levels at birth, but during the course of breastfeeding one infant developed a slightly elevated TSH (which normalized after lithium was stopped); two developed a transient, slightly elevated BUN; and one a transient, slightly elevated creatinine.

- A retrospective study of nursing infants (n = 11) found that no adverse effects occurred [58].

- A review of case reports (n = 5 infants) found that no adverse events occurred [53].

However, lithium is often not used in breastfeeding mothers. Treatment guidelines from the United Kingdom's National Institute for Health and Clinical Excellence discourage the use of lithium in lactating patients [6], and some authorities maintain that lithium is contraindicated in the setting of lactation [13,59-61]. Exposure to lithium through breast milk may be associated with adverse events:

- One prospective observational study of breastfeeding infants (n = 4) whose mothers took lithium during pregnancy and lactation found that two infants developed feeding difficulties, which resolved with breastfeeding education and support; one of the two infants also had mild hypotonia [9].

- One case report described an infant who was exposed to lithium through breast milk during the first postpartum week and suffered cyanosis, heart murmur, and T-wave inversions on an electrocardiogram, hypothermia, hypotonia, and lethargy [62]. However, lithium and a diuretic were taken during the pregnancy, which may have at least partially accounted for the adverse events that occurred soon after delivery.

Breast milk and infant serum concentrations are frequently substantial, with infant levels of 10 to 60 percent of maternal serum concentrations [51,56,63]. Lithium can accumulate in

newborns because kidney function is immature [53]. In addition, infant serum levels may be less stable due to fluctuating hydration and intercurrent infections, which places infants at risk of lithium toxicity and necessitates invasive monitoring of infant levels [51].

STIMULANTS

Although theoretical concerns exist that exposure to stimulants via breast milk may adversely affect infant sleep, appetite, and growth [64], observational studies suggest that some stimulants may be compatible with breastfeeding:

- Small studies of women with attention deficit hyperactivity disorder or narcolepsy, who were prescribed amphetamine (n = 1) [65], dextroamphetamine (n = 4) [66], or methylphenidate (n = 4) [67-70], found that their breastfeeding infants had minimal exposure and/or suffered no adverse effects.

- In an older study of nursing infants (n = 103) who were exposed to dextroamphetamine that was prescribed for postpartum maternal depression, neonatal insomnia or stimulation did not occur [71].

In addition, stimulant drug concentration in breast milk and infant serum is often low [12,66-68], but varies substantially [72].

MEDICATIONS FOR SUBSTANCE USE DISORDERS

Buprenorphine — Buprenorphine may be compatible with breastfeeding. Multiple observational studies have found that the amount of buprenorphine and its metabolite that accumulates in breast milk is small and thus unlikely to negatively affect infants [73-75]. As an example, a prospective study of breastfeeding women treated with buprenorphine (n = 7) found that no adverse effects occurred in the infants [76]. Nevertheless, potential adverse effects that may occur include lethargy, respiratory difficulty, and poor weight gain [77].

Prenatal exposure to buprenorphine often leads to the neonatal abstinence syndrome and the need for postnatal pharmacotherapy (eg, oral morphine). The duration of pharmacotherapy may be shorter in breastfeeding infants (who are exposed to buprenorphine through breast milk due to ongoing maternal use of buprenorphine), compared with infants not breastfed [78].

Disulfiram — It is not clear if disulfiram is compatible with breastfeeding because little information is available about its use in lactating women [15,77].

Methadone — For opioid-dependent women who are engaged in substance abuse treatment and are abstinent from illicit drug use, methadone may be compatible with breastfeeding [73,79,80]. Potential adverse effects in infants exposed to methadone through breast milk include lethargy, respiratory difficulty, and poor weight gain [77]. However, studies have found that infant serum concentrations of methadone are typically low (<3 percent of maternal concentrations) or undetectable [77,79].

Among infants who are exposed prenatally to methadone, breastfeeding may help prevent the neonatal abstinence syndrome. An observational study included infants (n = 78) who were exposed in utero to methadone and whose mothers continued methadone treatment following childbirth [78]. The neonatal abstinence syndrome occurred in fewer infants who were breastfed than infants not breastfed (53 versus 80 percent). Among those infants who developed neonatal abstinence syndrome, the duration of pharmacotherapy (eg, oral morphine) was shorter in breastfed infants than infants not breastfed (26 versus 39 days).

Breastfeeding mothers treated with methadone should gradually wean their infants from breast milk; abrupt discontinuation of breastfeeding may cause the neonatal abstinence syndrome [77].

Naltrexone — It is not clear if naltrexone is compatible with breastfeeding due to the paucity of data. In a case report of a patient with opioid use disorder who was treated with naltrexone and was breastfeeding, no acute adverse effects occurred [81]. In addition, the infant serum concentration of naltrexone was not detectable, and the concentration of the primary metabolite was very low.

Nicotine replacement therapy — Nicotine replacement therapy (gum, lozenges, or patches) is compatible with breastfeeding, according to the 2013 report from the American Academy of Pediatrics Committee on Drugs [77]. The suggested daily dose for these three products is less than the number of cigarettes typically smoked per day, based upon the assumption that one cigarette delivers approximately 1 mg of nicotine.

Shorter-acting gum or lozenges are preferable for lactating patients, but longer-acting patches are a reasonable alternative. A study of breastfeeding women who were smokers and treated with nicotine patches (n = 15) found that infant cognition and behavior were normal and that infant serum concentrations of nicotine were not detectable [82].

Varenicline — Little information is available about the safety of varenicline in breastfeeding women [15,77].

DRUG SAFETY INFORMATION

Multiple resources provide information about the safety of medications in women who are breastfeeding [83]:

- National Library of Medicine's LactMed
- The Breastfeeding and Human Lactation Study Center
- The Breastfeeding Network
- Reprotox
- MotherToBaby

EDUCATIONAL RESOURCES FOR PATIENTS

Educational resources for patients about breastfeeding are discussed separately. (See "Breastfeeding: Parental education and support", section on 'Programmatic approaches and professional resources'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders" and "Society guideline links: Breastfeeding and infant nutrition".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a

variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Health and nutrition during breastfeeding (The Basics)" and "Patient education: Coping with high drug prices (The Basics)" and "Patient education: Depression during and after pregnancy (The Basics)")

- Beyond the Basics topics (see "Patient education: Health and nutrition during breastfeeding (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY

- Patients with postpartum mental disorders who require pharmacotherapy should generally not be discouraged from breastfeeding. Low-quality studies suggest that the benefits of breastfeeding typically outweigh the small risk posed by psychotropic medications that are used to treat postpartum mental disorders in lactating mothers. (See 'Introduction' above and "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'General principles'.)

- All psychotropic medications are transferred to breast milk in varying amounts and thus are passed onto the nursing infant. Exposure can generally be decreased by choosing medications with shorter half-lives and greater protein binding. The drug should be started at the lowest effective dose and titrated slowly. Additional caution about exposure through breastfeeding is warranted for premature, low birthweight, or sick infants. If adverse events in infants are suspected, mothers should immediately suspend breastfeeding. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'General principles'.)

- Patients who are successfully treated with psychotropic drugs during pregnancy should generally not change medications for the purpose of breastfeeding. In addition, breastfeeding patients who initiate pharmacotherapy should be treated with medications that were efficacious in the past. Polypharmacy should be avoided if possible. (See "Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding", section on 'Choosing a drug'.)

- Infants exposed to medications via breast milk should be assessed by pediatricians at baseline and subsequently monitored periodically for adverse events. Serum laboratory tests for infants should also be performed for all indices that can be affected by the medications that the mother is taking (table 1). (See 'Monitoring' above.)

- Most of the evidence regarding the safety of anticonvulsants during lactation comes from patients with epilepsy. (See "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Breastfeeding'.)

- Haloperidol and chlorpromazine may be compatible with breastfeeding. (See 'First-generation' above.)

- Olanzapine, quetiapine, and risperidone may be compatible with breastfeeding. By contrast, breastfeeding is typically discouraged in patients treated with clozapine. (See 'Second-generation' above.)

- There is no clear consensus on the safety and use of lithium in breastfeeding women. (See 'Lithium' above.)

- Buprenorphine, methadone, and nicotine replacement therapy may be compatible with breastfeeding. (See 'Medications for substance use disorders' above.)

- Multiple resources provide information about the safety of medications in women who are breastfeeding. (See 'Drug safety information' above.)

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