Safety of infant exposure to antidepressants and benzodiazepines through breastfeeding

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INTRODUCTION

The benefits of breastfeeding generally appear to outweigh the small risk posed by antidepressant medications that are used to treat postpartum depression and other disorders in lactating mothers [1-3].

This topic reviews the safety of infant exposure to antidepressants and benzodiazepines through breastfeeding. The safety of anticonvulsants, antipsychotics, lithium, stimulants, and medications for substance use disorders 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 "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)
- (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

Overview — Information about the safety of psychotropic drugs during breastfeeding is based upon acute exposure in small observational studies and laboratory studies that typically last less than one year; no randomized trials have been conducted. Studies vary in multiple ways, including the severity of maternal psychopathology, maternal drug dose, onset and duration of infant exposure, whether infants were exposed to multiple concurrent medications, whether infants exclusively breastfed, and assessment of adverse effects and exposure. Adverse effects (eg, irritability, poor feeding, or sleep disorders) observed in babies who are exposed to antidepressants through breast milk are often nonspecific and may due to other causes such as viral infections [4,5].

Studies that assay infant serum concentrations provide a more direct assessment of infant exposure than studies of maternal serum and breast milk concentrations [6,7]. However, it is not established that a drug is safe if infant serum levels are undetectable, nor is it clear that measurable drug levels in infants are problematic [8].

Although one study defined elevated infant serum concentrations as those that exceeded 10 percent of maternal serum concentrations, this definition was arbitrary, and the study authors acknowledged that their findings did not show that these elevated levels were clinically significant [9]. Nevertheless, some authorities think that a ratio of infant to maternal serum drug concentration >10 percent may be clinically significant [10].

Another approach rates the safety of psychotropic drugs in breastfeeding mothers by utilizing all studies of a drug to derive multiple parameters, including the total number of infants exposed to the drug, maximum relative infant dose, infant serum drug concentrations, and the prevalence of adverse effects (all and serious) [11]. However, serum concentrations reported across different studies may vary due to different methods that are used to assay the quantity of a drug within a biologic sample [12].

Risks — Patients with postpartum mental disorders who require pharmacotherapy should generally not be discouraged from breastfeeding because the benefits of breastfeeding typically appear to outweigh the small risk posed by psychotropic medications [8,13,14]. However, formula feeding is a reasonable alternative for women who choose not to breastfeed

or who suffer from increased mood or anxiety symptoms due to difficulties with breastfeeding [6].

Effective treatment for postpartum depression is critical. Untreated postpartum depression poses risks to mothers and children that include impaired maternal-infant interactions and suboptimal parenting practices, such as reduced use of car seats, reduced talking and reading to children, and use of more harsh punishment [15]. In addition, postpartum maternal depression is associated with adverse neurobehavioral development [14], including delayed child cognitive development [16]. Although it is difficult to distinguish the adverse effects of infant exposure to psychotropic drugs from the effects of infant exposure to maternal psychopathology, the general consensus is that initiation or continuation of an effective psychotropic medication confers important benefits, such as preservation of mother-infant bonding [14]. Further information about the adverse outcomes of postpartum depression is discussed separately. (See "Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis", section on 'Adverse consequences'.)

Potential risks to the baby from exposure to medications through breast milk include drug toxicity and undetermined long-term effects on neurobehavioral development. All psychotropic medications are transferred to breast milk in varying amounts and are thus passed on to the nursing infant [3,6]. Milk is a fatty substance, and psychotropic medications are lipophilic. However, the amount of medication secreted into breast milk is highly variable across different patients [17,18].

Additional caution about exposure to medications through breastfeeding is warranted for low-birthweight or sick infants, as well as premature infants, whose ability to metabolize medications is less than that of full-term infants [6]. As an example, one preterm infant showed signs of serotonergic overstimulation (eg, tremor, myoclonus, and loose stools) during breast milk exposure to sertraline [19]. However, preterm labor is associated with developing postpartum symptoms [20], and the risks of untreated depression must be weighed against the risks of medication exposure.

Choosing a drug — General principles to bear in mind when choosing a psychotropic drug for postpartum, lactating patients with acute psychiatric illnesses include the following:

- Patients who are successfully treated with drugs during pregnancy should generally not change medications for the purpose of breastfeeding because fetal exposure to medications is substantially greater than it is for the breastfeeding infant [4,6-8,13,21-23]. One review estimated that antidepressant exposure is 5 to 10 times lower in breastfed infants compared with in utero exposure [4].

In addition, using the same drug regimen during lactation as was used during pregnancy may prevent withdrawal in the neonate; one study of infants exposed to mirtazapine in the third trimester found that poor neonatal adaptation occurred in fewer children who were breastfed than formula fed (19 percent [8/43] versus 55 percent [6/11]) [24]. However, it is not known if cumulative effects occur through fetal and infant exposure to medications during pregnancy plus breastfeeding. Neonatal withdrawal from antidepressants is discussed separately. (See "Antenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs): Neonatal outcomes", section on 'Poor neonatal adaptation'.)

- Postpartum patients who start pharmacotherapy should be treated with medications that were efficacious in the past [6,13]. Using a different drug because there are more data regarding breastfeeding may place mothers at risk for nonresponse.

- Infant exposure to medications through breast milk can generally be decreased by choosing medications with shorter half-lives and greater protein binding [2,25].

- Psychotropic polypharmacy should be avoided, if possible, and mothers should avoid other concomitant medications that increase infant exposure [6,8,26]. As an example, should minimize their use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Other general principles as well as choosing a specific drug for treating postpartum mental disorders are discussed separately. (See "Unipolar depression in adults and initial treatment: General principles and prognosis", section on 'General principles' and "Severe postpartum unipolar major depression: Choosing treatment" and "Bipolar disorder in postpartum women: Treatment" and "Treatment of postpartum psychosis" and "Obsessive-compulsive disorder in pregnant and postpartum patients".)

Medication administration — For lactating women who commence pharmacotherapy, the medication should be started at the lowest effective dose and titrated slowly because infant exposure through breast milk may be dose-related [26]. Nevertheless, the goal is to ameliorate the illness quickly.

Efforts to reduce infant exposure by taking medication immediately after nursing or by discarding breast milk obtained at the time of peak drug concentration are not recommended [3,5,13]. There is little evidence to support either timing drug administration or discarding breast milk, which are both impractical and can potentially make breastfeeding more difficult.

Preserving sleep — If mothers with psychiatric illnesses choose to breastfeed, they should try to minimize chronic sleep deprivation. The goal is to work towards both preservation of

maternal sleep and successful breastfeeding, while making necessary accommodations [27]. As an example, mothers can pump milk during the day so that family members can bottle-feed the baby, to allow for at least four to five hours of uninterrupted sleep. If the mother is not able to pump an adequate supply for the nighttime feeding, a bottle of formula may be given during the block of time that the mother's sleep is protected. Breastfeeding typically disrupts sleep, which can exacerbate mental disorders [6].

Monitoring — Pediatricians should assess infant behavior, feeding, alertness, and sleep as well as physically examine infants to establish a baseline [3,8,14,26]. Infants exposed to medications via breast milk should then be monitored periodically (eg, monthly) for adverse events such as irritability, agitation, excessive crying, poor weight gain, or sleep disturbances.

If adverse events in infants are suspected, mothers should immediately reduce or suspend breastfeeding [6,14]. This may enable clinicians to determine whether maternal medications caused the adverse events.

For breastfeeding infants who are exposed to antidepressants, routine assessment of serum concentrations is not recommended [3,6,13]. However, a serum assay can be helpful if the infant appears to be suffering an adverse event [3,13]. In addition, infant serum samples that reveal minimal drug levels can reassure breastfeeding mothers who are taking antidepressants but are anxious about infant exposure.

Severely ill patients — Patients with psychiatric disorders who are acutely and severely ill, especially women who are psychotic, should not be left alone the infant. However, patients may breastfeed their infants, provided that a member of the nursing staff is present to provide support and ensure safety. In addition, women can pump milk if the child is not present.

Severe illness is characterized by one or more of the following:

- Suicidal or homicidal behavior or ideation with a specific plan and intent (see "Suicidal ideation and behavior in adults")
- Psychotic features (eg, delusions or hallucinations) (see "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Clinical manifestations')
- Catatonia (see "Catatonia in adults: Epidemiology, clinical features, assessment, and diagnosis")
- Poor judgement that places the patient or others at imminent risk of being harmed

- Grossly impaired functioning (eg, food and fluid refusal leading to malnutrition and dehydration)

Severely ill patients should be referred to a psychiatrist for management and generally require hospitalization.

ANTIDEPRESSANTS

Composite data — Prescribing antidepressants to lactating women involves possible risks to infants because all antidepressants are secreted into breast milk [13,28]. However, reviews have concluded that the risk to infants from most antidepressants is relatively low [3] because the frequency of adverse events in babies who are exposed to antidepressants is low [27,29]. As an example:

- In a study of a nationwide database that included reports of adverse reactions to drugs transmitted through breast milk (n = 174 breastfed children), the list of drugs that were most frequently implicated did not include any antidepressants [30].

- A prospective study included 280 lactating mothers treated with psychotropic drugs (more than 80 percent received antidepressants) and 152 lactating mothers treated with antibiotics compatible with breastfeeding [28]. The frequency of adverse reactions in the two groups of breastfeeding infants was similar. In addition, growth and gross motor development were in the normal range in both groups of children.

Infant exposure to selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants through lactation is generally low or negligible [13]. Among these antidepressants, infant serum concentrations appear to be lower with paroxetine and sertraline and higher with citalopram, fluoxetine, and venlafaxine plus desvenlafaxine [8,13,31]. However, these data do **not** indicate that women who have given birth while taking citalopram, fluoxetine, or venlafaxine and have responded well should be switched to a different antidepressant if they decide to breastfeed.

Selective serotonin reuptake inhibitors — SSRIs are probably the most widely prescribed antidepressants in lactating women [32], and several studies have concluded that women treated with SSRIs should not be discouraged from breastfeeding [1,7,14]. The literature on using SSRIs is generally reassuring regarding short-term adverse effects [13,14,33,34]. As an example:

- A study of breastfeeding infants (n = 20) exposed to SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) and infants (n = 68) whose mothers were not treated with medications found that adverse events (eg, irritability, loud crying, feeding problems, and decreased sleep) were comparable [1].

- A six-month prospective study of 75 lactating mothers treated for major depression with SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that infant weight gain was comparable to published national norms [35]. However, infant weight gain was less among mothers who suffered depressive relapses lasting at least two months, compared with infants of mothers who did not relapse or who suffered relapses lasting less than two months.

- Multiple reviews concluded that serum concentrations of SSRIs in breastfed infants are often undetectable and that signs of drug toxicity are rare [14,32].

Among SSRIs, paroxetine and sertraline may be preferable in lactating women who are starting an antidepressant, because the amount of paroxetine or sertraline that is secreted into breast milk may be less, compared with other SSRIs [1,8,31,32]. A review of 34 studies that examined SSRI use in breastfeeding mother-infant pairs found that paroxetine and sertraline usually produced undetectable infant serum levels, whereas fluoxetine appeared more likely to accumulate in nursing infants [9]. In addition, the review (arbitrarily) defined elevated infant serum drug concentrations as those that exceeded 10 percent of maternal concentrations and found that the proportion of infants with elevated serum levels of specific drugs was as follows:

- Citalopram (n = 12 infants) – 17 percent
- Fluoxetine (n = 36 infants) – 22 percent
- Fluvoxamine (n = 4) – 0 percent
- Paroxetine (n = 47 infants) – 2 percent
- Sertraline (n = 60 infants) – 7 percent

However, these data do **not** indicate that women who have given birth while taking citalopram or fluoxetine and have responded well to citalopram or fluoxetine should be switched to a different SSRI if they decide to breastfeed.

A subsequent study included 12 lactating women taking escitalopram or sertraline; although each drug was evident in mother milk, the concentration was very low [36].

The use of paroxetine and sertraline in breastfeeding women who are starting treatment is consistent with guidance from the National Library of Medicine's LactMed database (United

States) [37] and the Canadian Network for Mood and Anxiety Treatments [31], as well as literature reviews [3].

The following sections discuss the adverse effects of specific SSRIs in infants who are exposed via breast milk, as well as infant serum concentrations that have been observed. General information about the pharmacology, administration, and side effects of SSRIs in adults is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Citalopram — Citalopram may be compatible with breastfeeding; adverse events in infants exposed to citalopram through lactation appear to be minimal [35]. A review identified 13 studies that assessed adverse effects in neonates exposed to citalopram through breast milk (total n = 79 neonates); there were six cases with adverse events, which included sleep disorders, colic, irritability, and neurodevelopmental delay [38]. All of the adverse effects resolved spontaneously, with dose reduction or cessation of lactation. Two of the more informative studies included the following:

- A prospective study found that the incidence of adverse events was comparable for breastfeeding infants of depressed mothers taking citalopram (3 out of 31, 10 percent), depressed mothers not taking citalopram (0 out of 12), and healthy mothers not taking citalopram (1 out of 31, 3 percent) [39].

- A one-year prospective study compared infants whose mothers were treated with citalopram (n = 11) with a control group of infants who were not exposed to any medications through breastfeeding (n = 10); neurologic development and body weight were normal in both groups [21].

In addition, a rating system that evaluates the safety of a psychotropic drug in breastfeeding mothers by utilizing all studies of the drug to derive multiple parameters, including the total number of infants exposed to the drug and infant serum concentrations of the drug, found that citalopram had a good safety profile [11].

The level of measurable citalopram concentrations in exposed infants varies among studies. A review of seven studies found that infants exposed to citalopram through breastfeeding often manifest detectable or elevated serum concentrations [9] (see 'Selective serotonin reuptake inhibitors' above). By contrast, other studies of infants whose mothers were treated with citalopram (total n = 21) found that infant serum concentrations of citalopram and its metabolites were minimal or undetectable [1,21]. Reducing the maternal dose may decrease infant exposure [9].

Escitalopram — Escitalopram has been studied in fewer nursing infants, compared with citalopram, fluoxetine, paroxetine, and sertraline. However, the safety data for citalopram may apply to escitalopram (which is the s-enantiomer of citalopram).

Escitalopram may be compatible with breastfeeding [40]:

- A review included seven studies that assessed adverse effects in neonates exposed to escitalopram through breast milk (total n = 19 neonates), and found that there were no short-term adverse effects except for one infant [38]. In addition, infant serum concentrations of the drug and its metabolite could not be detected [41,42].

- A prospective study of 33 women who were taking escitalopram or citalopram yielded reassuring results, insofar as the milk-to-plasma ratio for both the parent drug and metabolite was 1.9, and simulation models estimated that an exclusively breastfed infant would ingest 3.3 percent of the maternal dose [43].

However, a single case report described necrotizing enterocolitis in a term infant exposed to escitalopram throughout pregnancy and during the first five days of breastfeeding [44]. The infant initially had transient tachypnea after birth and was placed on mechanical ventilation for five hours and then weaned. The infant was then discharged on postnatal day three, but presented with necrotizing enterocolitis on postnatal day five; no known risk factors for necrotizing enterocolitis were identified, and symptoms resolved after two weeks of medical management. Although this case report adds to the literature, it does not indicate that women who have given birth while taking escitalopram and have responded well to the drug should be switched to a different drug.

Fluoxetine — Fluoxetine is one of the most widely studied drugs in lactation, and appears to be compatible with breastfeeding. Most studies suggest that infant exposure to fluoxetine through breast milk does not cause acute problems:

- A review identified 20 studies that assessed adverse effects in neonates exposed to fluoxetine through breast milk (total n = 217 neonates); there were 11 cases with adverse events, which included decreased postnatal growth, sleep disorders, colic, irritability, fever, emesis, watery stool, and possible seizure [38].

- In a six-month prospective study of breastfeeding mothers who were treated with fluoxetine (n = 29), the average weight gain for infants was comparable to published population norms [35].

However, one study suggested that exposure to fluoxetine via breast milk may possibly decrease postnatal growth. This retrospective study of women who took fluoxetine during pregnancy found that weight gain was less in the infants breastfed by mothers who continued taking fluoxetine for at least two weeks during lactation (n = 26), compared with infants breastfed by mothers who discontinued fluoxetine after delivery (n = 38) [45]. Nevertheless, weights in the infants exposed to fluoxetine through breast milk were judged to be adequate, based upon national norms.

Fluoxetine has a long half-life (four to six days during chronic use), and is often detectable in the serum of breastfeeding babies whose mothers are taking the drug. One review concluded that fluoxetine is more likely to accumulate in nursing infants compared with other antidepressants, and that infants exposed to fluoxetine may be at higher risk of experiencing elevated serum concentrations [9] (see 'Selective serotonin reuptake inhibitors' above). A second review also found that fluoxetine is often detected in the serum of infants exposed to the drug through breast milk [38]. In addition, norfluoxetine, the active metabolite of fluoxetine, has a long half-life (about nine days) that may predispose to accumulation in the infant. A prospective study (n = 8 nursing infants whose mothers were taking fluoxetine) found that norfluoxetine was detectable in the serum of six (75 percent) infants [22].

Fluvoxamine — Fluvoxamine has been studied in fewer nursing infants, compared with citalopram, fluoxetine, paroxetine, and sertraline [38]. The data for fluvoxamine suggest that it may be safe for breastfeeding [32,46]:

- A review identified 10 studies that assessed adverse effects in neonates exposed to fluvoxamine through breast milk (total n = 16 neonates); there was one case with an adverse event that consisted of neonatal jaundice, which resolved spontaneously despite continued breastfeeding [38].

- A six-month prospective study of breastfeeding mothers who were treated with fluvoxamine (n = 3) found that the average weight gain for infants was comparable to published population norms [35].

- A review of six studies concluded that infants exposed to fluvoxamine through breastfeeding are unlikely to manifest detectable or elevated serum concentrations [9] (see 'Selective serotonin reuptake inhibitors' above). In two other studies (total n = 6 infants), no detectable medication was present in serum assays [47,48].

Paroxetine — For postpartum, lactating patients who are starting treatment with an antidepressant, paroxetine is generally regarded as a first-line choice because of its safety record [2,3,32,35,38,49,50]:

- A review identified 16 studies that assessed adverse effects in neonates exposed to paroxetine through breast milk (total n = 150 neonates); there was one case of irritability and a second case with lethargy, poor weight gain, and hypotonia [38].

- In a one-year prospective study of mothers who sought information about the use of paroxetine during lactation (n = 73), weight gain was comparable for breastfeeding infants of mothers who were treated with paroxetine, breastfeeding infants of medication-free mothers, and bottle-fed infants of medication-free mothers [51].

- Multiple reviews have concluded that infants exposed to paroxetine through breastfeeding are unlikely to manifest detectable or elevated serum concentrations [4,9,38] (see 'Selective serotonin reuptake inhibitors' above). In addition, a review of studies that examined secretion of paroxetine into breast milk and adverse effects in infants concluded that paroxetine is compatible with breastfeeding [46].

In addition, a rating system that evaluates the safety of a psychotropic drug in breastfeeding mothers by utilizing all studies of the drug to derive multiple parameters, including the total number of infants exposed to the drug and infant serum concentrations of the drug, found that paroxetine had a very good safety profile [11].

Sertraline — For postpartum, lactating patients who are starting treatment with an antidepressant, sertraline is generally regarded as a first-line choice because of its safety record [2,3,5,32,38,46,49,50,52]:

- Multiple reviews have found that maternal use of sertraline is not associated with adverse effects in breastfeeding infants [52]. As an example, one review identified 16 studies that assessed adverse effects in neonates exposed to sertraline through breast milk (total n = 192 neonates) and found that no adverse effects occurred [38].

- A six-month prospective study of breastfeeding mothers (n = 25) who were treated with sertraline found that the average weight gain for infants was comparable to published population norms [35].

- Among infants exposed to sertraline through breast milk, serum concentrations are generally low or undetectable [4]. A review identified 14 studies of sertraline serum concentrations in breastfeeding infants (n = 167) whose mothers were taking sertraline, and found that [52]:

    - Sertraline levels were below the limit of detection in 87 percent, and low in the remaining infants

- Desmethylsertraline (the less active metabolite) levels were undetectable in 70 percent, and low in the other babies

In addition, a rating system that evaluates the safety of a psychotropic drug in breastfeeding mothers by utilizing all studies of the drug to derive multiple parameters, including the total number of infants exposed to the drug and infant serum concentrations of the drug, found that sertraline had a very good safety profile [11].

Serotonin-norepinephrine reuptake inhibitors — The SNRIs venlafaxine and desvenlafaxine appear to be safe to use in breastfeeding women, based upon observational studies of exposed infants and the lack of adverse events. However, infant exposure appears to be greater with venlafaxine and desvenlafaxine than it is for some other antidepressants.

The following sections discuss the adverse effects and infant serum concentrations of specific SNRIs in babies who are exposed via breast milk. General information about the pharmacology, administration, and side effects of SNRIs in adults is discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Duloxetine — Duloxetine may be compatible with breastfeeding, but the evidence of its safety is sparse. Case reports of infants (total n = 2) exposed to duloxetine via breast milk found no acute adverse effects [53,54] and one of the case reports found that duloxetine was undetectable in the infant's serum [53]. In addition, pharmacologic studies of lactating women (total n = 8) examined the transfer of duloxetine into breast milk; the results suggested that systemic drug concentrations in infants would be very low or undetectable [55,56]. One treatment guideline suggests that duloxetine is a reasonable option for lactating patients because infant exposure is relatively low compared with some other antidepressants and adverse effects in nursing children have not been reported [50].

Milnacipran — It is not clear if milnacipran is compatible with breastfeeding because little information is available about its use in lactating women [32,37].

Venlafaxine and desvenlafaxine — Venlafaxine may be compatible with breastfeeding [32,40]. A study of five lactating women taking venlafaxine found that venlafaxine/desvenlafaxine was evident in mother milk but in very low concentrations [36]. In addition, a review of eight studies of nursing infants (total n = 41) who were exposed to venlafaxine and the active metabolite desvenlafaxine through breastfeeding found that no acute adverse events occurred [38]. However, infant serum concentrations of venlafaxine and desvenlafaxine are often detectable [38]:

- A prospective study of mother-infant pairs (n = 5) found that in three infants, the serum concentration of venlafaxine plus desvenlafaxine was 20, 57, and 107 percent of maternal concentrations [18]. In addition, breast milk concentrations suggested that for breastfeeding infants, maternal use of venlafaxine appears to result in a marginally higher exposure than that for other antidepressants. Desvenlafaxine was a larger contributor to exposure than the parent compound, indicating that administration of desvenlafaxine alone would not appreciably reduce exposure.

- Three prospective studies of infants (total n = 8) found that venlafaxine and/or desvenlafaxine was detected in all infants [1,57,58].

- In a prospective study of infants (n = 7), venlafaxine was detected in one infant and desvenlafaxine in four infants, all at low concentrations [59].

One treatment guideline suggests not using venlafaxine in lactating patients because infant exposure is relatively high, compared with some other antidepressants [50]. Nevertheless, the guideline acknowledges that adverse effects in nursing children have not been reported.

Atypical — Most atypical antidepressants have been studied in fewer nursing infants than SSRIs and SNRIs; however, mirtazapine may be compatible with breastfeeding. General information about the pharmacology, administration, and side effects of atypical antidepressants in adults is discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects".)

Agomelatine — It is not clear if agomelatine is compatible with breastfeeding because little information is available about its use in lactating women [37]. In one case report, a breastfeeding patient was treated for 12 weeks [60]. Taking advantage of the relatively short half-life of the drug (one to two hours), the patient was encouraged to breastfeed before taking agomelatine at night, cease breastfeeding until she pumped all her milk the next morning, and resume breastfeeding during the day. No adverse effects were observed in the infant, and laboratory tests (unspecified) and development of the infant were normal.

Bupropion — Although infant exposure to bupropion through breast milk may be low, it is not clear if bupropion is compatible with breastfeeding due to the few studies that have been conducted and the possible association between infant exposure and seizures:

- Multiple studies of infants (total n = 5) found that no adverse events occurred, and that infants did not have quantifiable serum levels of bupropion or its metabolite [61-63].

- Pharmacologic studies (total n = 14) concluded that exposure to bupropion in breastfed infants was minimal [64,65].

- However, a single case report described a seizure in a breastfed infant that was possibly related to bupropion [66]. Another case report described tonic seizure-like symptoms as well as emesis in an infant that was probably due to exposure to bupropion plus escitalopram through lactation [67].

Mirtazapine — Mirtazapine may be compatible with breastfeeding [32,46]. Studies of infants exposed to mirtazapine through lactation have reported that there were no short-term adverse effects [46]; as an example, one study (n = 44 infants) reported that there were no problems with eating or sleeping [24]. Other studies suggest that infant serum concentrations of the drug are generally below the limit of detection [68-70].

However, a case report described a healthy infant exposed to mirtazapine throughout pregnancy and during the first two months of breastfeeding, at which point the mother expressed concern that the infant was sedated and its weight was greater than that of its older siblings at age two months. The infant's serum concentration was 37 percent of the mother's serum concentration, which was considered high [71].

Vortioxetine — It is not clear if vortioxetine is compatible with breastfeeding because little information is available about its use in lactating women [37]. In a study of three cases, breast milk concentrations were relatively low and the mothers observed no adverse effects in their infants [72]. In addition, at a maternal dose of 10 mg/day, the relative infant dose was 1.1 percent; at a dose of 20 mg/day, the relative infant dose was 1.7 percent. Each relative infant dose was well below the (arbitrary) standard of 10 percent. (See 'Overview' above.)

Serotonin modulators — There are few data regarding serotonin modulators in breastfeeding patients. General information about the pharmacology, administration, and side effects of serotonin modulators in adults is discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

Nefazodone — Nefazodone is generally not used during breastfeeding due to the paucity of data regarding its safety during lactation. A single case report described an infant who was exposed to nefazodone through breast milk and suffered drowsiness, lethargy, difficulty feeding, and hypothermia [73]. After breastfeeding was discontinued, the symptoms resolved over 72 hours. In addition, nefazodone is often avoided due to concerns about hepatotoxicity in patients treated with the drug. (See "Serotonin modulators: Pharmacology, administration, and side effects", section on 'Side effects'.)

Trazodone — It is not clear if trazodone is compatible with breastfeeding due to the paucity of data [32]. In case reports of infants (total n = 4) exposed to trazodone through breast milk, no acute adverse effects occurred [18,74-76]. In addition, a pharmacologic study of nursing women (n = 6) examined the transfer of trazodone into breast milk following the administration of a single 50 mg dose; the results led the investigators to conclude that exposure to trazodone in nursing infants would be minimal [77].

Vilazodone — It is not clear if vilazodone is compatible with breastfeeding because little information is available about its use in lactating women [37].

Tricyclics — Several tricyclic antidepressants are compatible with breastfeeding because infant exposure is relatively low compared with some other drugs, and serious side effects in nursing children have not been reported (except for doxepin) [32,40,46,50]. For women who start a tricyclic during lactation, nortriptyline is usually favored due to its safety record [78]. General information about the pharmacology, administration, and side effects of tricyclic antidepressants in adults is discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Nortriptyline — For postpartum, lactating women who start treatment with a tricyclic antidepressant, nortriptyline is preferable because of its safety record [78]:

- Multiple studies of infants (total n = 34) who were exposed to nortriptyline through breastfeeding found that adverse events did not occur in any of the infants [8,25].
- A review (total n = 36 infants) concluded that detectable or elevated infant serum concentrations of nortriptyline were unlikely to occur (elevated was arbitrarily defined as infant serum drug concentrations that exceeded 10 percent of maternal concentrations) [9]. A subsequent study (n = 16 infants) found that infant serum levels were low or nondetectable [8].

The use of nortriptyline in breastfeeding women who are starting treatment is consistent with guidance from the National Library of Medicine's LactMed database (United States) [37] and the Canadian Network for Mood and Anxiety Treatments [31].

Other drugs — Amitriptyline, clomipramine, desipramine, and imipramine are compatible with breastfeeding [40,46], based upon many small studies that found these tricyclics were not associated with adverse effects [25,75,79-87]. Although a wide range of infant serum concentrations have been reported for infants exposed to tricyclic antidepressants through nursing, serum concentrations are usually low or below the limits of detection.

However, doxepin is generally not prescribed to lactating patients [2,7,8]. The active metabolite of doxepin has a long half-life (approximately 30 hours) and may be hazardous due to high accumulations in nursing infants. Reviews have found that doxepin exposure in one infant was associated with sedation and respiratory depression, and in another infant with hypotonia, poor sucking and swallowing, vomiting, and weight loss; symptoms resolved within 24 hours after breastfeeding ceased [9,78]. A case report of a third infant reported no adverse effects [78].

Monoamine oxidase inhibitors — Monoamine oxidase inhibitors (MAOIs) are generally not used during breastfeeding and little information is available about the use of isocarboxazid, phenelzine, and tranylcypromine in lactating women [37]. Two studies, which included a total of 13 breastfeeding infants whose mothers were treated with moclobemide, suggested there were no adverse effects in the infants [88,89]. In addition, one case report of an infant exposed to selegiline through breastfeeding found that the drug and its metabolite were not detectable in the infant's serum; in addition, follow-up at age five months found that infant development was normal [90].

MAOIs are seldom prescribed to the general population of depressed patients because of potentially lethal drug-drug and drug-food interactions, and the danger that MAOIs pose in overdoses. General information about the pharmacology, administration, and side effects of monoamine oxidase inhibitors in adults is discussed separately. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

BENZODIAZEPINES

For breastfeeding women who require benzodiazepines (eg, patients with severe anxiety or agitation [26]), we suggest using low doses of drugs that have a short half-life and no active metabolites, such as lorazepam [7,32,87]. Although clonazepam has no active metabolite, it may accumulate in infants due to its long half-life; a study of adverse reactions to medications transmitted through breast milk (n = 174 breastfed children) found that clonazepam was implicated in five cases (3 percent), including one infant who suffered hypotonia and apnea that resolved [30]. When benzodiazepines are used as part of a multidrug regimen, it is often possible to taper benzodiazepines once the primary drug produces a therapeutic effect. The use of benzodiazepines is consistent with practice guidelines from the United Kingdom National Institute for Health and Care Excellence [91] and the British Association for Psychopharmacology [5].

Multiple studies suggest that infant exposure to benzodiazepines through breast milk is small:

- In one study that included 11 patients who were treated with a benzodiazepine, the milk to plasma ratios were low (less than 1) and no adverse events were noted. In addition, the relative infant doses for all but one of the drugs was less than 10 percent, which is the (arbitrary) standard of safety [92]. (See 'Overview' above.)

- Across two studies of lactating women (total n = 5) taking alprazolam, the relative infant dose ranged from 1.4 to 4.6 percent [93,94].

We generally avoid diazepam for lactating patients [32]. A review of studies that examined secretion of diazepam into breast milk and adverse effects in infants found that among infants who were exposed to diazepam through breast milk (n = 14), sedation occurred in two; the review concluded that diazepam is not compatible with breastfeeding [46]. A subsequent study concluded that diazepam transmitted through breast milk was certainly involved in the case of an infant who developed hypotonia and apnea that resolved [30]. Diazepam may accumulate in neonates due to its long half-life.

The primary concern in using benzodiazepines in women who are lactating is withdrawal in infants.

Sedation is a potential problem in infants exposed to benzodiazepines through breast milk; however, this risk generally appears to be low. In a prospective study of 124 mothers who used benzodiazepines (primarily lorazepam, clonazepam, and midazolam) during lactation, central nervous system depression (defined as sleepiness, poor latching, limpness, or lack of response to stimuli) occurred in two (1.6 percent) of the infants [95]. One of the mothers took clonazepam and flurazepam during the pregnancy as well as lactation, and the other mother took alprazolam on two occasions; both mothers were taking other medications.

Hypnotics — A review of studies that examined secretion of zaleplon, zolpidem, and zopiclone into breast milk and adverse effects in infants concluded that these hypnotics are compatible with breastfeeding [46].

DRUG SAFETY INFORMATION

Multiple resources provide information about the safety of medications in women who are breastfeeding [96]:

- 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".)

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: Breastfeeding and infant nutrition" and "Society guideline links: Depressive disorders".)

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

- **General principles**
  - **Risks** – Patients with postpartum mental disorders who require pharmacotherapy should generally not be discouraged from breastfeeding. Untreated maternal depression is associated with risks to the child, and 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.

    All psychotropic medications are transferred to breast milk in varying amounts and thus are passed onto the nursing infant. Additional caution about exposure through breastfeeding is warranted for premature, low-birthweight, or sick infants. (See 'Risks' above.)
  - **Choosing a drug** – Patients who are successfully treated with psychotropic drugs during pregnancy should generally not change medications for the purpose of breastfeeding. In addition, lactating patients who initiate pharmacotherapy should be treated with medications that were efficacious in the past. Exposure can generally be decreased by choosing medications with shorter half-lives and greater protein binding. Polypharmacy should be avoided if possible. (See 'Choosing a drug' above.)
  - **Medication administration** – The drug should be started at the lowest effective dose and titrated slowly. (See above.)
  - **Monitoring** – Infants exposed to medications via breast milk should be assessed by pediatricians at baseline and subsequently monitored periodically for adverse events. If adverse events in infants are suspected, mothers should immediately suspend breastfeeding. (See 'Monitoring' above.)
- **Safety of specific drug classes**
  - **Selective serotonin reuptake inhibitors** – Selective serotonin reuptake inhibitors (SSRIs; eg, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) appear to be compatible with breastfeeding because adverse events in exposed infants are typically minimal. Postpartum, lactating patients who start treatment with an antidepressant are often prescribed paroxetine or sertraline because of their safety record. In addition, the amount of paroxetine and sertraline that is

secreted into breast milk is generally low or undetectable, and may be less compared with other SSRIs. (See 'Selective serotonin reuptake inhibitors' above.)

- **Serotonin-norepinephrine reuptake inhibitors** – The serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine and desvenlafaxine appear to be safe to use in breastfeeding women, based upon observational studies of exposed infants and the lack of adverse events. However, infant exposure may be greater with venlafaxine and desvenlafaxine than it is for some other antidepressants. (See 'Serotonin-norepinephrine reuptake inhibitors' above.)

- **Atypical antidepressants** – Most atypical antidepressants have been studied in fewer nursing infants than SSRIs and SNRIs; however, mirtazapine may be compatible with breastfeeding. (See 'Atypical' above.)

- **Serotonin modulators** – There are few data regarding the safety of serotonin modulators in breastfeeding patients. (See 'Serotonin modulators' above.)

- **Tricyclics** – Several tricyclic antidepressants are compatible with breastfeeding. For women who start a tricyclic during lactation, nortriptyline is usually favored due to its safety record; by contrast, doxepin is generally avoided. (See 'Tricyclics' above.)

- **Benzodiazepines** – Benzodiazepines that have short half-lives and no active metabolites (eg, lorazepam) are generally preferred in the context of breastfeeding. Potential adverse effects of benzodiazepines include withdrawal and sedation in infants. Diazepam appears to be incompatible with breastfeeding. (See 'Benzodiazepines' above.)

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

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