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MENTAL HEALTH

Antidepressant Use in the Breastfeeding Patient

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ABSTRACT: It is well known that the peripartum period carries an increased risk of psychiatric disorders in the mother, and treatment is often necessary; however, given concerns about medication exposure in infants, uncertainty exists on how to safely manage treatment in breastfeeding patients with psychiatric illnesses. Additionally, the impact of the drug on milk production should be considered. However, pharmacologic treatment is not always incompatible with breastfeeding. As patients and providers may seek information on the use of antidepressants and other psychotropics while breastfeeding, pharmacists must consult current resources to keep abreast of risks, benefits, and treatment guidelines. By optimizing care for breastfeeding patients, pharmacists can help prevent adverse outcomes in both mother and baby.

It is well known that the first few months postpartum carry an increased risk of onset or worsening of mental illness in the mother. Mental-health conditions that may be experienced during this period include depressive and anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders, and (more rarely) psychotic disorders.[1] Major risk factors for the development of depressive and anxiety disorders in the peripartum period include a history of psychiatric illness, an insufficient support network, and prior adverse life events. Additionally, during the postpartum period, several other elements may contribute to the onset or worsening of mental disorders, including reduced quality and quantity of sleep, postpartum hormonal fluctuations, and genetic factors.[1] Many women choose to breastfeed, resulting in the necessity to address the safety of psychotropics use with regard to infant exposure. This article will chiefly discuss the use of antidepressants in breastfeeding women.

Pharmacologic Treatment of Psychiatric Disorders While Breastfeeding

It is recommended that breastfeeding women with milder psychiatric symptoms engage in lower-risk treatment such as psychological interventions; however, those with more severe symptoms may require pharmacologic treatment.[1] As with any clinical decision, the risks and benefits of continuing or initiating a medication should be carefully weighed against the risks and benefits of discontinuing or avoiding medications during breastfeeding.

Although breastfeeding is generally recommended for its benefits to the baby, many women experience challenges with latching, milk supply, and sleep disruption, so these factors should be assessed in order to limit resultant distress.[1,2] If sleep disruption caused by late-night breastfeeding sessions is having a significant negative impact on psychiatric symptoms, a discussion could be initiated about switching to formula feeding at night or

pumping breast milk so that the partner or spouse can handle nighttime feedings.[1] A patient already taking an antidepressant may either choose to continue it and switch to formula feeding if adverse effects (AEs) on the newborn become a concern or opt to forego the medication and try nonpharmacologic treatments, such as psychotherapy. It is important to recognize, however, that pharmacologic treatment is not always incompatible with breastfeeding.

The risks of remaining on medications while breastfeeding vary, but the main risks related to switching or discontinuing pharmacologic treatment during this period involve suboptimal outcomes including relapse, uncontrolled psychiatric symptoms, and adverse outcomes such as death from suicide.[3] The patient's mental-illness history, including symptom severity, history of suicidality, and history of impaired quality of life due to symptoms, should be considered. It should be kept in mind that untreated maternal mental illness can also affect the infant if it impairs the mother's ability to take care of the child properly or—in more severe cases—results in direct harm to the child. Additionally, the potential impact of the drug on milk production should be considered.

Finally, the infant's age must be taken into account. Hepatic functionality is still developing at age 3 to 6 months, so babies of this age may be unable to efficiently metabolize any medications they are exposed to via breast milk, which may result in elevated plasma concentrations beyond what is anticipated. This decreased ability to metabolize drugs may be even more pronounced in preterm infants.[4] Another consideration is whether the infant is taking any medications, as there may be interactions between the infant's medications and the mother's. Finally, the amount of milk the infant is consuming may also impact treatment decisions because, compared with partially breastfed infants, an exclusively breastfed infant is at higher risk for medication exposure. These factors must be considered on a case-by-case basis, with the healthcare team and the patient engaging in shared decision making. Breastfed infants of mothers who continue a medication from pregnancy into the postpartum period may be less likely to experience neonatal adaptation compared with formula-fed infants.[5] Treatment goals for postpartum psychiatric disorders are to reduce the psychiatric symptoms and support the relationship between mother, child, and family unit.[1]

To estimate an infant's potential exposure to medication during breastfeeding, the milk-to-plasma (M/P) concentration ratio is often used. The most common cutoff point for concern over drug accumulation in breast milk is when the M/P ratio exceeds 1.[6] Another way to measure exposure is the relative infant dose (RID) or percent maternal dose, which is calculated by dividing the mg/kg/day ingested via breast milk by the mg/kg/day maternal dose. It is generally accepted that an RID of 10% or more of the maternal dose is clinically significant and potentially concerning.[7-9]

Drug Passage Into Breast Milk

Multiple factors can affect a medication's ability to pass into breast milk.[9,10] For example, in the first 3 days postpartum, spaces between the mammary epithelial cells allow larger molecules to penetrate the milk. The amount of drug that the newborn may be exposed to during this time is limited owing to the small volume consumed.[9,10] Following this phase, milk production increases, and the spaces between the mammary epithelial cells close over a 1- to 2-week period. Subsequently, medications are able to penetrate breast milk primarily by passive diffusion across the mammary epithelium, which acts as a semipermeable lipid barrier. An exception occurs in the event of maternal infections such

as mastitis, wherein the passage of drug molecules may generally increase and larger molecules again may be able to pass through.[10]

The rate of passage from maternal plasma into breast milk is determined both by medication lipid solubility and by molecular weight, with smaller-molecular-weight molecules having increased passage. Psychotropic drugs are generally lipophilic, which permits them to dissolve in the mammary epithelial cell membrane and pass more easily into breast milk. It also allows the drug to concentrate in the milk fat, which ranges from 10% in hindmilk to 2% to 3% in foremilk.[9,10]

Medications that enter the milk compartment quickly will achieve a greater initial concentration, resulting in a higher M/P ratio. Those that enter the milk compartment slowly may not achieve concentrations as high as those in the maternal plasma, as the compartment is emptied at each nursing session, thus requiring new transport of the drug.[9,10]

Protein-binding also has an impact on medication passage into breast milk, as highly protein-bound drugs are less able to penetrate the milk compartment.[9,10] Additionally, the drug's pH has an effect on passage into breast milk. According to the pH partition theory, ionized forms of weak bases concentrate in the milk, whereas weak acids are trapped in the plasma.[9] To summarize, the ideal medication for passing into breast milk is nonionized and has a lower molecular weight, high lipophilicity, low protein-binding, and high pK_a. (pK_a, the negative log of the acid dissociation constant K_a, expresses the acidity of a weak acid, whereas a lower pK_a denotes a stronger acid.[9,10])

Antidepressants and Breastfeeding

All antidepressants pass into the breast milk to some degree.[2] Therefore, clinical-treatment guidelines for depression in postpartum breastfeeding mothers often recommend psychotherapy first-line, with second-line therapy including agents such as citalopram, escitalopram, and sertraline.[2,11] Other options may be considered in patients who have responded well to other agents in the past. In a pooled analysis of antidepressant concentrations in lactating mothers, breast milk, and nursing infants, infants who were exposed to nortriptyline, paroxetine, or sertraline were least likely to have detectable or elevated serum drug concentrations (>10% of maternal level).[8] In the same analysis, citalopram or fluoxetine use in a nursing mother often resulted in elevated serum drug concentrations in the infant.[8]

Although citalopram use sometimes leads to elevated serum drug concentrations in the infant that are beyond the 10% threshold, the reported AEs for infants are relatively mild and include drowsiness, weight loss, restlessness, irritability, and uneasy sleep.[5] Neonatal adaptation syndrome and withdrawal effects from citalopram have also been reported, including irregular breathing, apnea, disordered sleep, and hypotonia.[12]

Case reports have identified potential AEs associated with fluoxetine during breastfeeding, including fussiness, drowsiness, and impaired infant weight gain.[5] For this reason and because of the higher concentrations in infant serum, it is often recommended that an antidepressant with less excretion into the milk compartment be used when feasible.

Although escitalopram passes into breast milk only in low concentrations, there have been a few cases of AEs, including irritability, in nursing infants.[5] There has been a single case

report of necrotizing enterocolitis in an infant exposed to escitalopram via breast milk, but causality was not determined.[13] Additionally, in one report, seizure activity occurred in an infant exposed to both escitalopram and bupropion via breast milk, but this was thought to be related to the bupropion exposure.[14]

Because sertraline passes into breast milk in low concentrations, it is considered a preferred agent for breastfeeding women.[2,10] AEs in breastfed infants exposed to sertraline are rare, but diarrhea, drowsiness, restlessness, insomnia, and poor neonatal adaptation have been noted.[5] In one case report, an infant exposed to sertraline via breast milk who was later determined to have genetic polymorphisms of the CYP450 enzymes involved in sertraline metabolism experienced hyperthermia, alterations in muscle tone, and high-pitched crying related to elevated sertraline concentrations.[15] This case illustrates that medications can affect all infants slightly differently owing to individual characteristics.

Paroxetine is not recommended in pregnancy based on the risk of cardiovascular malformations if used in the first trimester; however, because it has been shown to pass into breast milk only in low concentrations, it may be more acceptable for use during lactation.[8] AEs in nursing infants exposed to paroxetine through breast milk are rare and generally mild; restlessness, constipation, insomnia, poor neonatal adaptation, alertness, agitation, and poor feeding have been reported.[5]

Venlafaxine and its active metabolite have been shown to pass into breast milk in higher concentrations (M/P ratio >1).[16] The literature notes several cases of suspected withdrawal in breastfeeding newborns whose mothers were taking venlafaxine during pregnancy and postpartum.[5]

Not much literature is available on nursing mothers taking mirtazapine, but there is one report of infant restlessness in a breastfeeding mother who was taking both mirtazapine and paroxetine.[5,17] Similarly, few studies exist on bupropion use in breastfeeding women; however, two cases of seizures in infants exposed to bupropion via breast milk have been reported.[14,18] There are no published reports on mother and nursing infant pairs for newer antidepressants such as vortioxetine and vilazodone, so little is known about their effects; therefore, it may be best for patients who are planning to breastfeed to opt for an alternative agent.[5]

Antidepressants' Impact on Milk Production

One important factor to consider regarding medication use during breastfeeding is the agent's impact on milk production. It has been observed that increases in serotonin levels cause early involution of mammary glands, thereby reducing milk production, which has led to theoretical concerns about milk supply in nursing mothers taking antidepressants with serotonergic properties.[19] Additionally, postmarketing reports of selective serotonin reuptake inhibitors have identified proposed "dopamine-dependent" AEs that may affect milk production, such as galactorrhea, mammary-gland hypertrophy, and hyperprolactinemia.[20] However, in a retrospective cohort study that used the galactogogue domperidone as a marker of low milk supply, no association was found between late-pregnancy serotonin reuptake inhibitor (SRI) use and domperidone use, indicating that SRIs do not adversely affect milk supply.[19]

Resources for Drugs in Lactation

Several rating scales exist for determining risks of medications used in lactation. The most widely used resources include Briggs and colleagues' *Drugs in Pregnancy and Lactation*, which rates drugs according to seven risk categories, and *Hale's Medications and Mothers' Milk*, which uses five lactation-risk categories.[9,21,22] Categories range from "contraindicated in breastfeeding" to "compatible/safest," which is reserved for agents that have been studied in breastfeeding humans and have not demonstrated any AEs in infants.[9,21] Uguz recently proposed a third scoring system specifically for psychotropic medications that rates each agent on a 10-point scale incorporating data on six items: reported total sample, reported maximum RID, reported sample size for RID, infant plasma drug concentrations, prevalence of observed AEs, and reported serious AEs.[22]

Although these categorical ratings are important to keep in mind and may be a good starting point for researching the effects of medications during breastfeeding, more in-depth resources should be consulted in order to fully inform clinical decisions. Other resources include the drug's package insert (PI), the LactMed online database, MotherToBaby, and the InfantRisk Center.[5,23,24] Each PI contains a lactation section organized into three distinct topics: risk summary, clinical considerations, and data. LactMed, which is maintained by the National Library of Medicine, includes information on medication concentrations in breast milk as well as summaries of AEs noted in the literature and any effects on milk production.[5] MotherToBaby is a telephone- and Web-based service of the Organization of Teratology Information Specialists that is available to both patients and healthcare providers.[23] The InfantRisk Center, a global call center located at the Texas Tech University Health Sciences Center School of Medicine, helps providers and patients evaluate the risk of multiple drug exposure to the infant.[24]

The Pharmacist's Role

During the postpartum period, mothers may be seeking information regarding the compatibility of their medications with lactation. Likewise, patients' healthcare providers may seek input from the pharmacist on this issue. Although many resources are available, much remains unknown about the passage of specific drugs into breast milk and about related AEs. In determining the safety of any medication in a breastfeeding woman, it is important for the pharmacist to keep in mind that there are essentially two patients: the mother and the infant. Information gathered should include not only the mother's health conditions and current medications, including indications, dosing, and anticipated duration of therapy, but also the infant's age, weight, preterm/term status, current health conditions, current medications, and percentage of breast milk in the diet.[22] The use of evidence-based resources will help the pharmacist evaluate and share the most up-to-date information regarding medication use in breastfeeding. Breastfeeding women who are thinking about discontinuing maintenance antidepressant therapy should be encouraged to discuss their concerns with the prescriber in order to avoid any risk of relapse, withdrawal, or other unintended harmful effects.

REFERENCES

1. Meltzer-Brody S, Howard LM, Bergink V, et al. Postpartum psychiatric disorders. *Nat Rev Dis Primers*. 2018;4:18022.

2. Sriraman NK, Melvin K, Meltzer-Brody S. ABM clinical protocol #18: use of antidepressants in breastfeeding mothers. *Breastfeed Med*. 2015;10(6):290-299.

3. Johannsen BM, Larsen JT, Laursen TM, et al. All-cause mortality in women with severe postpartum psychiatric disorders. *Am J Psychiatry*. 2016;173(6):635-642.

4. Berle JØ, Spigset O. Antidepressant use during breastfeeding. *Curr Womens Health Rev*. 2011;7(1):28-34.

5. Drugs and lactation database (LactMed) [Internet]. Bethesda, MD: National Library of Medicine; 2021. www.ncbi.nlm.nih.gov/books/NBK501922/. Accessed April 2, 2021.

6. Ito S. Mother and child: medication use in pregnancy and lactation. *Clin Pharmacol Ther*. 2016;100(1):8-11.

7. Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132(3):e796-e809.

8. Weissman AM, Levy BT, Hartz AJ, et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. *Am J Psychiatry*. 2004;161(6):1066-1078.

9. Berens PD, Hale TW. Principles of drug therapy in pregnancy and lactation. In: O'Connell MB, Smith JA, eds. *Women's Health Across the Lifespan: A Pharmacotherapeutic Approach*. 2nd ed. New York, NY: McGraw-Hill Medical; 2019.

10. Anderson PO, Sauberan JB. Modeling drug passage into human milk. *Clin Pharmacol Ther*. 2016;100(1):42-52.

11. MacQueen GM, Frey BN, Ismail Z, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 6. Special populations: youth, women, and the elderly. *Can J Psychiatry*. 2016;61(9):588-603

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12. Franssen EJF, Meijs V, Ettaher F, et al. Citalopram serum and milk levels in mother and infant during lactation. *Ther Drug Monit*. 2006;28(1):2-4.

13. Potts AL, Young KL, Carter BS, Shenal JP. Necrotizing enterocolitis associated with in utero and breast milk exposure to the selective serotonin reuptake inhibitor, escitalopram. *J Perinatol*. 2007;27(2):120-122.

14. Neuman G, Colantonio D, Delaney S, et al. Bupropion and escitalopram during lactation. *Ann Pharmacother.* 2014;48(7):928-931.

15. Müller MJ, Preuss C, Paul T, et al. Serotonergic overstimulation in a preterm infant after sertraline intake via breastmilk. *Breastfeed Med*. 2013;8(3):327-329.

16. Schoretsanitis G, Augustin M, Sassmannshausen H, et al. Antidepressants in breastmilk; comparative analysis of excretion ratios. *Arch Womens Ment Health*. 2019;22(3):383-390.

17. Uguz F. Short-term safety of paroxetine plus low-dose mirtazapine during lactation. *Breastfeed Med*. 2019;14(2):131-132.

18. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry*. 2004;65(6):881-882.

19. Grzeskowiak LE, Leggett C, Costi L, et al. Impact of serotonin reuptake inhibitor use on breast milk supply in mothers of preterm infants: a retrospective cohort study. *Br J Clin Pharmacol*. 2018;84(6):1373-1379.

20. Damsa C, Bumb A, Bianchi-Demicheli F, et al. “Dopamine-dependent” side effects of selective serotonin reuptake inhibitors: a clinical review. *J Clin Psychiatry*. 2004;65(8):1064-1068.

21. Instructions for use of the reference guide. In: Briggs GC, Freeman RK, Towers CV, Forinash AB, eds. *Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.
22. Uguz F. A new safety scoring system for the use of psychotropic drugs during lactation. *Am J Ther.* 2021;28(1):e118-e126.

23. MotherToBaby. Is it safe for me and my baby? https://mothertobaby.org/. Accessed February 28, 2021.

24. InfantRisk Center. About the InfantRisk Center. www.infantrisk.com/about-infantrisk-center. Accessed February 28, 2021.