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Opioid Use Disorder During Breastfeeding

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Opioid use disorder (OUD) in nursing is treated using the same medications as in other persons. In contrast to many drugs, a considerable amount of information is available on the main drugs used in maintaining abstinence in nursing mothers. Buprenorphine and methadone are the most commonly used drugs for maintenance, but naltrexone is also available. Naloxone plays a supportive role in OUD therapy. Information on the specific drugs during breastfeeding comes from LactMed® where additional information and references can be found.

Buprenorphine

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. This activity pattern makes the drug less likely to cause severe respiratory depression. Buprenorphine has poor oral bioavailability and is usually given by the sublingual or parenteral route. Sublingual bioavailability is 30–40% in adults and peak levels in blood occur 60–90 minutes after a dose. Buprenorphine is also available in long-acting formulations: a subcutaneous injection given monthly and subdermal implants inserted every 6 months.

These long-acting formulations have not been studied in nursing mothers, but in other individuals they result in serum levels similar to those of the sublingual product. Buprenorphine is metabolized to the slightly active metabolite, norbuprenorphine, and both are further glucuronidated.

Most information on buprenorphine during breastfeeding has come from women who were using the drug for long-term OUD maintenance. Twenty-seven nursing mothers using sublingual buprenorphine and four using it orally for maintenance therapy have had milk samples analyzed for buprenorphine. Buprenorphine generally had a relative infant dosage in milk of <1% of the maternal weight-adjusted dosage. Infant serum and urine levels of buprenorphine and its metabolites were very low to undetectable in 16 breastfed infants whose mothers were taking sublingual buprenorphine.

One exclusively breastfed 2-week-old infant was brought to the emergency department because of somnolence and decreased feeding. He had pinpoint pupils, lethargy, and a Glasgow coma score of 5. Two doses of naloxone resulted in infant crying and improved tone. The infant's mother had been taking buprenorphine 8 mg twice daily for several months and denied any illicit drug use. Sixteen hours after symptom onset, the infant's urine levels of norbuprenorphine and norbuprenorphine glucuronide were elevated, but buprenorphine and buprenorphine glucuronide urine levels were in the typical range.

Breastfeeding was stopped and the infant developed mild withdrawal symptoms that did not require treatment. The infant's symptoms were probably caused by buprenorphine, but the contribution by breastfeeding cannot be differentiated from prenatal exposure. It is also possible that the mother or infant metabolized buprenorphine atypically.

In contrast to the previous case, a large number of breastfed infants (>200) have been reported whose mothers were taking buprenorphine for maintenance therapy with no direct adverse events. What has been reported in several cases is opioid withdrawal among breastfed infants who were exposed in utero to buprenorphine, even though they were being breastfed. This reflects the fact that breastfed infants receive only low doses of the drug in milk, that is, not enough to completely prevent withdrawal.

Nevertheless, in most reports infants who were breastfed have had less severe and a shorter duration of withdrawal symptoms than infants who were not breastfed and some have lower morphine requirements for treating abstinence than nonbreastfed infants. The long-term outcome of infants breastfed during maternal buprenorphine therapy for OUD has not been well studied, but a few infants who were followed for durations up to 6 months showed no adverse developmental effects.

Up until January of 2023, only providers with the so-called X waiver on their Drug Enforcement Administration (DEA) registration were allowed to prescribe buprenorphine for OUD in the United States. That requirement has been lifted and all practitioners who have a current DEA registration that includes Schedule III authority may prescribe buprenorphine for opioid use if permitted by state law. This change should make buprenorphine more available and more commonly seen in nursing mothers.

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Methadone

Methadone is a long-acting mu-opioid receptor agonist with low affinity for delta and kappa receptors. Methadone exists as two isomers, *R*- and *S*-methadone. The *R*-isomer appears to have a receptor binding pattern similar to morphine and to be the active isomer. Its oral bioavailability ranges from 36% to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours after a dose. In other words, its pharmacokinetics are somewhat erratic and individual.

Like buprenorphine, most information on methadone during breastfeeding comes from women on long-term maintenance. Thirty-one mothers taking methadone have had milk analyzed. Data from these patients indicate that peak milk methadone levels occur variably at 2–6 hours after a dose. Most infants receive an estimated relative infant dosage of methadone of 1–3% of the mother's weight-adjusted dosage with a few receiving 5–6%. A study in 23 women indicated that levels of *R*-methadone in milk were higher than those of *S*-methadone. Methadone dosages received by the infants are less than the dosage used for treating neonatal abstinence.

Eight breastfed newborn infants whose mothers were receiving methadone maintenance in a median dose of 70 mg/day (range 50–105 mg/day) had methadone measured in their plasma on day 14 of life. Concentrations ranged from 2.2 to 8.1 mcg/L compared with maternal plasma concentrations ranging from 134 to 939 mcg/L. No correlation was found between the infant plasma concentrations and their mother's methadone dosage or whether the infant received treatment for neonatal abstinence.

Reports and studies in the literature on hundreds of infants indicate that breastfeeding by infants whose mothers were on methadone maintenance during pregnancy and postpartum is not only safe, but may also reduce the dosage requirement of medications for neonatal abstinence. The infant dosage requirement for abstinence and length of hospital stay may be dependent on genetic polymorphisms of the catechol-o-methyltransferase and mu-opioid receptor genes.[1] Abrupt weaning of breastfed infants by women on methadone maintenance might result in precipitation of, or an increase in, infant withdrawal symptoms, so gradual weaning is advised.

Regardless of its general safety during methadone maintenance, methadone is a potent long-acting opioid and cases of severe respiratory depression and some possible infant deaths due to methadone in breast milk have been reported. These occurred in the infants of mothers who were not on continuous maintenance, but took methadone acutely, sometimes with other opiates. Initiation of methadone postpartum, increasing the maternal therapeutic dosage to >100 mg/day, or abuse while breastfeeding all pose a risk of sedation and respiratory depression in the breastfed infant, especially if the infant was not exposed to methadone in utero. In this respect, methadone is riskier than buprenorphine during breastfeeding.

Naltrexone

Naltrexone is a pure opioid antagonist. It is used as maintenance treatment of OUD in opiate-detoxified patients and is available as oral tablets and as pellets for intramuscular insertion once a month. After an oral dose, peak plasma levels of 40–50 mcg/L at 1 hour and average plasma levels of 3–5 mcg/L have been reported in adults taking daily maintenance doses. Oral bioavailability is 5–40% in adults. After administration of the pellet, total exposure is three- to four-fold higher than with the oral tablets over the period of a month. Naltrexone is metabolized to beta-naltrexol, which is active, and to other inactive metabolites.

Information on naltrexone's use in breastfeeding is limited to one lactating woman who was 1.5 months postpartum and took 50 mg of oral naltrexone daily during pregnancy and lactation. Her milk was sampled several times between 3.7 and 23 hours after her dose. Naltrexone milk levels were undetectable (<2 mcg/L) by 8 hours after the dose, whereas beta-naltrexol milk levels remained detectable throughout the study period and averaged 46 mcg/L. The half-lives of elimination from milk were 2.5 and 7.7 hours for naltrexone and beta-naltrexol, respectively.

The authors estimated that an exclusively breastfed infant would receive ~7 mcg/kg per day of naltrexone including the active metabolite, equivalent to 0.86% of the maternal weight-adjusted dosage. The mother's 1.5-month-old breastfed male infant had undetectable (<2 mcg/L) plasma levels of both naltrexone and beta-naltrexol 9.5 hours after the maternal dose, 30 minutes after starting a feeding. The infant was reportedly healthy with no naltrexone-related adverse effects. The long-term outcome of infants breastfed during maternal naltrexone therapy for opiate abuse has not been studied. Theoretically, naltrexone given to the mother might result in precipitation of withdrawal in an infant who is opioid tolerant.

Naloxone

Naloxone is a pure opioid antagonist with no oral bioavailability. No information is available on the excretion of naloxone into breast milk, but since it is not orally bioavailable, it will not precipitate withdrawal or otherwise affect the breastfed infant if it does reach the milk. With the over-the-counter availability of naloxone, more nursing mothers might be receiving naloxone in the future. In case of a suspected opioid overdose by a nursing mother, naloxone should be administered without concern for adverse effects on the breastfed infant. Naloxone is added to some dosage forms of buprenorphine to prevent the misuse of buprenorphine by injection or nasal inhalation by attenuating the opioid ''high.''

Effects on Breastfeeding

The breastfeeding rates among mothers with OUD may be lower than in other mothers; however, among women taking buprenorphine as part of an abstinence program, the retention rate may be better in nursing mothers than in non-breastfeeding mothers. The breastfeeding rate among mothers taking methadone for opiate dependency has been lower than in mothers not using methadone in some studies, but this finding appears to vary by institution, indicating that institutional factors might be important.

Summary

Nursing mothers with OUD can be safely treated with the conventional drugs used for the condition. Breastfeeding can

improve infant outcomes and reduce the rate of relapse in mothers with OUD. The low levels of buprenorphine in breast milk, its poor oral bioavailability, and the low drug concentrations found in the serum and urine of breastfed infants make it a safe option for nursing mothers. Methadone is acceptable to use in nursing mothers on maintenance therapy, but starting the drug while nursing an opioid-naive infant can be risky and abruptly weaning or discontinuing methadone can lead to infant abstinence symptoms. Abrupt discontinuation of buprenorphine is less likely to cause infant withdrawal symptoms than with methadone.

Women who received buprenorphine or methadone maintenance during pregnancy and are stable should be encouraged to breastfeed their infants postpartum, unless there is another contraindication, such as the use of street drugs. The family and health care providers should monitor infants for drowsiness, respiratory depression, adequate weight gain, and developmental milestones, especially in younger exclusively breastfed infants. If the baby shows signs of increased sleepiness, breathing difficulties, or limpness, a physician should be contacted immediately. Infants should be observed for withdrawal signs if breastfeeding is stopped abruptly.

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Reference

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