BREASTFEEDING MEDICINE
Volume 3, Number 1, 2008

DOI: 10.1089/bfm.2007.9978

ABM Protocols

ABM Clinical Protocol #18: Use of Antidepressants in Nursing Mothers

THE ACADEMY OF BREASTFEEDING MEDICINE PROTOCOL COMMITTEE

A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

BACKGROUND

With estimates of between 5% and 25% of women experiencing depression in the postpartum year,[1–3] it is critical that healthcare providers consider all treatment options, including the risks and benefits for nursing mothers. Many healthcare providers recognize the short- and long-term negative effects that postpartum depression can have on mothers and infants.[4–6] Despite this, postpartum depression often goes undetected and untreated.[2] Postpartum depression is a treatable illness. Treatment options include psychotherapy (cognitive-behavioral, interpersonal psychotherapy),[7–9] antidepressants,[8,10,11] or a combination of medication and therapy.[8] The choice and approach to treatment can be influenced by many factors, including the mother's wish to breastfeed. Women may not receive medication, or receive inadequate doses, because they are breastfeeding, or may decide not to breastfeed because they are concerned about medication use during lactation. Full consideration must be given to the risks of untreated depression, risks of the medication to the infant and mother, and the benefits of treatment. This Protocol discusses the importance of actively screening for and, when present, making the diagnosis of postpartum depression, how treatment can be determined, and specifically addresses the medications for which there is sufficient evidence to make recommendations and provide data (selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]/heterocyclics). We recognize that this is a complex issue, and that there are many other factors that impact the care of women with postpartum depression, but which are beyond the scope of this protocol to discuss.

CLINICAL APPROACH TO IDENTIFYING POSTPARTUM DEPRESSION

Postpartum depression is often missed by providers and mothers.[2,12–14] The symptoms of depression—depressed mood, sleep disruption, weight loss, fatigue, difficulty concentrating, anxiety, loss of interest in usual activities—

can be difficult for mothers and providers to distinguish from the normal experiences of new mothers. It is also important to differentiate mothers suffering from postpartum depression from those with postpartum blues as misdiagnosis of such mothers can lead to unnecessary treatment. To distinguish symptoms of depression from the "baby blues," the timing (>2 weeks in duration, all day nearly every day) and the severity (functional impairment) must be evaluated.[15]

For many women, acknowledgement of feelings other than happiness following the birth of their infant can be devastating and embarrassing. If mothers have thoughts of harming themselves or their infant, they are often afraid to bring these issues to their obstetrician, family physician, pediatrician, midwife, child health nurse, or other healthcare professional for fear that they will be labeled "crazy" or that their children will be taken away. Therefore, many women will not bring up their concerns or even identify them as a problem unless providers ask specific questions or use a screening tool (see Table 1). Depending upon the setting or the country, it is common for women to receive their peripartum and postpartum care from healthcare providers other than physicians. In these circumstances, communication between physicians and these other healthcare providers may be crucial to making an accurate diagnosis and initiating timely treatment.

CLINICAL APPROACH TO TREATING POSTPARTUM DEPRESSION

Once a woman is identified as suffering from postpartum depression, the choice of treatment must be considered. While no treatment is an option, it is not the preferred approach. Postpartum depression may last for months to years and can have long-term effects for the health and well-being of mothers and infants.[4,5,9,23] In breastfeeding women with mild to moderate depression, the first-line treatment, if available, is psychotherapy. Psychotherapy can be an effective treatment for women with postpartum depression and carries no risks for the infants. Psychotherapy may also have the benefit of providing lasting changes in coping skills and adaptation to the new role of motherhood.

If psychotherapy is unavailable or unacceptable to the mother, or the symptoms are severe, antidepressants are an effective option. The approach to choosing an antidepressant is based on a variety of factors. No antidepressant is

Table 1. Recommendations for Identifying Women with Postpartum Depression

- The preferred method for identifying women with postpartum depression is the systematic use of a validated screening tool such as the Edinburgh Postnatal Depression Scale[16] or the Postpartum Depression Screening Scale[17–19] at the obstetrical postpartum visit and at well childcare visits in the postpartum year.
- Ask mothers if they feel down or anxious. Many women with postpartum depression report anxiety as a primary symptom rather than depressed mood or anhedonia. Excessive worrying about the baby's or mother's health should be explored.
- Ask mothers if they are having trouble sleeping even when they are exhausted and their child is sleeping[20] or if they are sleeping all the time and are unable to get out of bed.
- Ask mothers if they are losing or gaining weight. Many women with postpartum depression report a poor appetite, but they eat because they need to keep their strength up or for nursing. Some mothers will gain weight.
- Ask mothers directly but in an open, nonthreatening manner about thoughts or fears of harming their children. For example, "Many new mothers experience anxiety about their new infants. They may have thoughts that are unusual or frighten them such as fears that they may harm their baby. Does this ever happen to you?"[21] Mothers who experience intrusive thoughts do not wish to harm their children and avoid the topics of their fears (i.e., a mother is afraid her baby will drown therefore will not bathe the baby and has her partner bathe the infant). It is important to distinguish the woman with postpartum depression whose intrusive thoughts or fears of harming the infant are incongruent with the mother's wish to keep her infant safe from the woman with postpartum psychosis who is delusional and who may have thoughts of harming her infant to "save the infant from the devil or a life of torment." Delusional mothers are at great risk of harming their infants or themselves and must be immediately evaluated by a psychiatrist.[22]
- Ask mothers if they have concerns or questions about adapting to a new baby.
- Consider the mother's interactions with the infant, including the responsiveness of mom and baby.
- Difficulty in breastfeeding, or not enjoying breastfeeding, may be a warning sign that should be further evaluated.

proven safer or more effective than another in the postpartum period or during lactation. The majority of drugs including all antidepressants are excreted in breastmilk. Data to inform clinical decisions are derived primarily from case reports or case series. Therefore, the initial treatment choice should be based on an informed clinical approach that takes into account the patient's previous treatments for depression, the targeted symptoms, family history of depression and their experiences with antidepressants, current and past medical disorders, current medications, allergies, side effects of the medications, and maternal wishes. An individualized risk-benefit analysis of the treatments must be conducted (see Table 2).[28]

TABLE 2. RISKS AND BENEFITS OF ANTIDEPRESSANT TREATMENT IN LACTATING WOMEN

- The risks of untreated postpartum depression include:
  - persistence of symptoms
  - possible increase in severity of symptoms, including deterioration in functioning, and thoughts (or even actions) of self-harm or harm to others
  - relationship discord
  - impaired parenting
  - child neglect
  - effects on the child's development (including behavior, social, and cognitive).
- The risks of treatment with antidepressants include:
  - Maternal: side effects of the medication, potential drug interactions
  - Infant: exposure through breastmilk transmission; limited data on the long-term effects on child development
- The benefits of treatment include the resolution of depressive symptoms that, in turn, will potentially improve maternal self-esteem, parenting, maternal-infant interaction, and child outcomes.[24]
- The medical and psychological benefits of breastfeeding to infants and mothers are well established.[25–27] Depressed mothers may benefit additionally from breastfeeding because of the sense of accomplishment and active, positive participation in their infant's care and development.
- The risks of breastfeeding for depressed mothers should be considered and may include:
  - Sleep deprivation due to total dependence on the mother may exacerbate or precipitate depressive symptoms.
  - If mothers are nursing and taking medications, the feelings of guilt and anxiety associated with exposing their infant to medication may exacerbate their depressive symptoms.

CLINICAL FACTORS AFFECTING ANTIDEPRESSANT CHOICE

- There is no algorithm for antidepressant treatment choices in postpartum or lactating women; however, articles by experts in the field provide clinical guidance.[28,29]
- Obtain a history of previous antidepressant treatment. In general, if a treatment was effective in the past and was tolerated, and there are no current contraindications, it is the likely first choice of treatment.
- Obtain a family history of treatment of depression. An immediate family member's history may be indicative of the mother's treatment response.
- Consider the primary symptoms that the medication will be targeting and the potential side effect profile of the antidepressant. For example, if the mother is particularly anxious, a medication that might heighten anxiety would not be the first choice. If the mother is experiencing hypersomnia, a medication with sedation as a side effect would not be the first choice. If a mother has somatic complaints such as nausea or diarrhea, a medication that may induce diarrhea would not be the first-line treatment.

CHOOSING AN ANTIDEPRESSANT DURING BREASTFEEDING

When considering the use of any medication in a lactating woman, providers must consider the factors that influence infant serum levels, the most accurate measure of infant exposure. Factors affecting the passage of medication into breastmilk must be considered (route of administration, absorption rate, half-life and peak serum time, dissociation constant, volume of distribution, molecular size, degree of ionization, pH of plasma [7.4] and milk [6.8], solubility of the drug in water and in lipids, greater binding to plasma protein than to milk protein), factors affecting the amount of drug received by the infant (milk yield, colostrum vs. mature milk, concentration of the drug in the milk, how well the breast was emptied during the previous feeding), and an infant's ability to

absorb, detoxify, and excrete the drug. Up-to-date information about medication use during lactation is available on TOXNET lactmed at http://toxnet.nlm.nih.gov.

Most antidepressant studies provide milk levels, or milk to mother's plasma ratio, that are not constant and depend on factors such as dose, frequency, duration of dosing, maternal variation in drug disposition, drug interactions, and genetic background. Few studies provide infant serum levels, although they are the best measure of infant exposure. Most studies suggest that infant daily dosages (calculated based on maternal dose and milk levels) are safest if the level is 10% or less of the "therapeutic dose for infants (or the adult dose standardized by weight)."

SPECIFIC ANTIDEPRESSANTS

Data from a recent meta-analysis indicated that all antidepressants were detected in breastmilk but not all were found in infant serum.[30] Infant serum levels of nortriptyline, paroxetine, and sertraline were undetectable in most cases. Infant serum levels of citalopram and fluoxetine exceeded the recommended 10% maternal level in 17% and 22% of cases, respectively. Few adverse outcomes are reported for any of the antidepressants. There were an insufficient number of cases for all other antidepressants to make conclusions.

SSRIs

The SSRIs are the most widely prescribed antidepressant class and include citalopram (20–60 mg), escitalopram (10–20 mg), fluoxetine (20–80 mg), fluvoxamine (50–300 mg), paroxetine (20–60 mg), and sertraline (50–200 mg). SSRIs improve depression and anxiety by blocking the serotonin transporter and thereby increasing serotonin availability in the synapse. The medications are usually prescribed for depressive or anxiety disorders but may be prescribed for fibromyalgia, neuropathic pain, and premenstrual symptoms and disorders. Common maternal side effects include gastrointestinal distress, headaches, sexual dysfunction, nervousness, or sedation. Except for fluoxetine, which has a half-life of 4–6 days, most SSRIs have a half-life of 24–48 hours. A newer, related class of antidepressants, selective serotonin and norepinepherine reuptake inhibitors (SSNRIs or SNRIs), are becoming more widely used because of what appears to be better efficacy with fewer side effects, especially for neuropathic pain. Since the SSRIs have been in use longer and there are more data concerning lactation, this discussion will focus on the SSRIs.

All SSRIs have been detected in breastmilk, although paroxetine[31–33] and sertraline[33–38] usually produced undetectable infant serum levels.[30] Neither of these medications has been found to exceed the recommended 10% maternal level. In contrast, fluoxetine,[39–44] in 22% of cases, and citalopram,[33,45,46] in 17% of cases, have exceeded the 10% maternal level.[30] There are virtually no case reports of escitalopram and few case reports of fluvoxamine[47–52] in nursing mothers, most likely because escitalopram is only recently available and fluvoxamine was indicated for obsessive compulsive disorder, not depression, and therefore is not used as frequently. In most studies, no infant adverse events are reported for any of these medications. The few infant adverse events reported include uneasy sleep, colic, irritability, poor feeding, and drowsiness.[53–55] In one case, an infant seizure was reported during the time that the mother was taking fluoxetine.[56] However, the relationship of fluoxetine to the reported seizure was confounded by other medication exposures, and infant serum concentration was not obtained.

Although the association between fluoxetine and observed effects is uncertain, the long-term effects on neurobehavior and development from exposure to this potent serotonin reuptake blocker, or any of the SSRIs, during a period of rapid central nervous system development have not been adequately studied.[57] In addition, the reduced weight gain identified in one study may have clinical significance in some situations, and should be monitored carefully in any breastfeeding baby whose mother is on fluoxetine.[58] The U.S. Food and Drug Administration specifically advised the manufac-

turer to revise the labeling of fluoxetine to contain a recommendation against its use by nursing mothers.[59] The current labeling contains this revision.

Bearing all this information in mind, sertraline and paroxetine are often the most likely to be prescribed, because of their low to zero concentrations in breastmilk. This is based on a presumption that there will be lower central nervous system effects compared to some of the other SSRIs with higher breastmilk concentrations.

TCAs/heterocyclics

The TCAs (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, maprotiline, nortriptyline, protriptyline, and trimipramine) are one of the older classes of antidepressants. They are effective for the treatment of depressive and anxiety disorders and are often used in low doses for sleep and chronic pain. The therapeutic mechanisms are most likely related to the blockade of the norepinephrine transporter, which thereby increases norepinephrine availability in the synapses. These medications also block the dopamine and serotonin pumps, which may contribute to their therapeutic mechanisms. Unfortunately, they also block muscarinic cholinergic receptors, H1 histamine receptors, and alpha-1-adrenergic receptors, which most likely account for their wide array of unpleasant side effects. Despite being effective and inexpensive they are not used as frequently as SSRIs because of their side effects, which can include hypotension, sedation, dry mouth, urinary retention, weight gain, sexual dysfunction, and constipation. In addition, in an overdose, these medications can cause cardiac arrhythmias and death. Among this class of medications, only nortriptyline has a sufficient number of reported cases to comment on its use during lactation. In most cases, nortriptyline is undetectable in infant serum. Its metabolite has been detected, but no adverse events have been reported.[60–62] Insufficient numbers of cases have been reported on the other medications; however, use of doxepin is often cautioned because of a case report of hypotonia, poor feeding, emesis, and sedation in a breastfeeding infant that resolved after discontinuation of nursing.[63]

Other antidepressants

Other common antidepressants include mirtazapine, an antidepressant that works by blocking the presynaptic noradrenergic receptors that control norepinephrine and serotonin release, venlafaxine[33,64] and duloxetine, which are SNRIs, and bupropion, which is a norepinephrine and dopamine reuptake inhibitor. Sporadic case reports were found for these medications,[65,66] and there are an insufficient number to report significant outcomes for nursing infants. One case report of a seizure in an infant exposed to bupropion through breastmilk is published, but attributing causation is cautioned.[67]

Herbal/natural

St. John's Wort, an herbal medication, has been used for the treatment of mild to moderate depression for many years, especially in Europe. Its use as a treatment for depression is controversial in the United States. Only one study of sufficient numbers was available for review.[68] In this study there were increased rates of colic, drowsiness, and lethargy in the St. John's Wort group compared to controls, but this was confounded by concomitant antidepressant treatment in the study group. No long-term effects were noted, and no effect on milk production.

Omega-3 fatty acids are currently being studied as a treatment for depression during pregnancy and the postpartum period.[69] Omega-3 fatty acids appear to be of little risk to mothers and infants as they are natural essential elements of one's diet and are often depleted during pregnancy and breastfeeding. The primary negative side effect is the "fishy smell" and the lack of sufficient evidence at this time to consider it a treatment for depression.

There is little or no evidence that ethnic or regional "medicines" are safe or effective; thus their use by healthcare providers is strongly cautioned.

RECOMMENDATIONS FOR ANTIDEPRESSANT TREATMENT IN LACTATING WOMEN

- Current evidence suggests that the risks of untreated maternal depression can have se-

rious and long-term effects on mothers and infants and that treatment may improve outcomes for mothers and infants. Therefore treatment is strongly preferred.
- However, it is important not to label mothers who are only suffering from mild cases of "baby blues" as "depressed." We must make a distinction. If symptoms are mild, there is no reason to initiate antidepressant medication treatment in the first 2 weeks postpartum.
- When available and when symptoms are in the mild–moderate range, psychotherapy is the first line of treatment for lactating women as it carries no known risk for the infant. Mothers must be monitored and reevaluated. If they are not improving or their symptoms are worsening, antidepressant drug treatment must be considered.
- Psychotherapy in addition to antidepressant medication is recommended for women with severe symptoms.
- Women with moderate to severe symptoms may request only antidepressant drug treatment, and this must be considered as the benefits of treatment likely outweigh the risks of the medication to the mother or infant.
- There is no widely accepted algorithm for antidepressant medication treatment of depression in lactating women. An individualized risk-benefit analysis must be conducted in each situation and take into account the mother's clinical history and response to treatment, the risks of untreated depression, the risks and benefits of breastfeeding, the benefits of treatment, the known and unknown risks of the medication to the infant, and the mother's wishes.
- If a mother has no history of antidepressant treatments, an antidepressant, such as paroxetine or sertraline, that has evidence of lower levels in breastmilk and infant serum and few side effects is an appropriate first choice.
- If mothers have been successfully treated with a particular SSRI, TCA, or SNRI in the past, the data regarding this particular antidepressant should be reviewed, and it should be considered as a first-line treatment if there are no contraindications.
- Mothers should be provided the information regarding the known and unknown risks and benefits of the treatment to make an informed decision.
- Mothers should be monitored carefully in the initial stages of treatment for changes in symptoms, including worsening of symptoms. Specifically, women with histories of bipolar disorder, which may be undiagnosed, are at increased risk of developing a mood episode of depression, mania, or psychosis in the postpartum period. While this is rare, mothers and partners should be made aware of the symptoms to watch for such as increased insomnia, delusions, hallucinations, racing thoughts, and talking/moving fast and contact their mental health provider immediately.
- Infants should be evaluated prior to the initiation of a new medication during breastfeeding and monitored carefully by the pediatrician, including carefully following growth. Serum levels are not indicated on a regular basis without a clinical indication or concern.
- Strategies that may be used to decrease infant exposure, but for which there is little evidence, include medication administration immediately after feedings and pumping and discarding the breastmilk obtained during the peak serum levels.

CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

Despite many publications of antidepressants and breastfeeding, the scientific literature lacks both the breadth and depth for clinicians and mothers to make confident decisions about individual medications. Multiple reviews of the literature broadly suggest TCAs and serotonin reuptake inhibitors are relatively safe, and all recommend individual risk-benefit assessments.

The literature suffers from a lack of any randomized clinical trials in lactating women for any class of antidepressant. The majority of studies are case reports or case series, and most have small samples sizes. Those studies that report larger samples ($n > 25$) primarily report a variety of medications. Only six controlled studies (one retrospective,[70] five prospective[42,45,46,54,71]) were found that used a variety

of controls—some control for depression, while others do not. None of the studies sufficiently controlled for level of depression. In addition, the case reports are limited by confounding with in utero exposure, the range of infant ages, inconsistencies in the timing of when samples were obtained, lack of information about the amount of medication in foremilk versus hindmilk, and no information about infant consumption as average breastmilk volumes are not provided. The majority of studies provide information about the amount of medication detected in breastmilk and maternal serum. Some studies also provide information about infant serum levels of medication. Few studies report infant behavioral outcomes.

ACKNOWLEDGMENTS

This work was supported in part by a grant from the Maternal and Child Health Bureau, U.S. Department of Health and Human Services.

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ABM protocols expire five years from the date of publication. Evidenced-based revisions are made within five years, or sooner if there are significant changes in the evidence.

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