REVIEW ARTICLE

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Benefits and Risks to Mother and Infant of Drug Treatment for Postnatal Depression

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Contents

Abstract

The postnatal period presents a special problem to healthcare providers treating psychiatric disorders in women. Many new mothers who need antidepressant treatment may wish to breastfeed their infants, but are hesitant to do so for fear of passing on possible harmful effects of the medication through their milk.

The focus of this article will be on highlighting and interpreting the existing literature on the benefits and risks to mother and infant of drug treatment for postnatal depression, as well as outlining treatment guidelines for the use of antidepressants in breastfeeding mothers. The article will specifically focus on the use of fluoxetine, sertraline, paroxetine, fluvoxamine and citalopram, which are more commonly used and belong to the selective serotonin reuptake inhibitor group of antidepressants. The tricyclic and other newer antidepressant medications will also be discussed. As there are no published controlled studies on the use of antidepressants by breastfeeding women, publications of individual case reports, case series, and pharmacokinetic investigations serve as the basis for the development of treatment guidelines. Results from this growing body of literature are promising in that, with the exception of a few cases, no serious adverse events

have been reported in infants exposed to antidepressant medications through breast milk. In addition nonpharmacological treatments consisting of different types of psychotherapies will be discussed. It is critical that healthcare providers evaluate each mother-infant dyad on an individual basis when faced with the decision to prescribe antidepressant medications during the postnatal period.

The childbearing years are a time of increased vulnerability to the onset of major depression in women. Until recently, however, the association between depression and the perinatal period was not well researched. Recent literature indicates that between 10 to 16% of women fulfil the diagnostic criteria for major depression in pregnancy.[1] In the postnatal period, the prevalence of depression has been more systematically studied, with controlled studies reporting that 12 to 16% of women experience a major depressive episode.[2,3] This figure has been reported to be as high as 26% in adolescent mothers.[4]

It appears that some women may be at a higher risk of developing postnatal depression than others. Risk factors for postnatal depression include: depression in a previous pregnancy or postnatal period – this is associated with a 50 to 62% risk of subsequent illness,[5] a prior history of mood disorders,[6] depressive symptomatology during the pregnancy,[7] and a positive family history of psychiatric disorders.[1,3,6] In addition, a variety of contributing factors have been identified that may increase the risk for development of postnatal depression, including: younger maternal age, poor social support, adverse life events, marital instability, unwanted pregnancy, and the experience of abuse or violence.[1,4,6,8]

Pharmacotherapy in pregnant women is frequently necessary to treat chronic or relapsing depression and/or anxiety. The short-term effects of fetal exposure to antidepressants have been documented in several case reports and case series, while few long-term outcomes have been reported.[9-13] Only one study to date has described long-term effects in infants up to 86 months of age.[11] These infants, who were exposed to fluoxetine and tricyclic antidepressants during pregnancy, were found to have no differences in language abilities, IQ scores, or behavioural development when compared with a group of non-exposed infants.

Infant exposure to psychotropic medications is greater during pregnancy through placental passage than during the postnatal period through breast milk. The recommendations of the American Academy of Pediatrics for prescribing psychotropic medications during pregnancy are to prescribe the lowest dosage that will provide adequate control of the woman's illness while minimising the risks of fetal toxicity.[14] To date, there have been no systematic recommendations made to address the issue of infant exposure through breast milk. Longitudinal studies are needed to interpret the effects of small quantities of drug exposure through milk; at present, until these studies are conducted, clinicians must rely on the results of individual case reports and small case series when faced with the decision to prescribe an antidepressant medication to a postnatal breastfeeding woman.

All psychotropic medications are found in breast milk in varying amounts and are passed on to the nursing infant. Thus, when pharmacotherapy is indicated for postnatal women, the potential risks of medication exposure in the infant must be weighed against the risks of untreated maternal depression. The negative effects of untreated maternal depression during the beginning years of a child's life have been documented in several studies. Clinical data have shown that untreated postnatal depression has a moderate to severe negative effect on maternal-infant bonding during the first year of life,[15] and that exposure to postnatal depression has a significant adverse effect on the cognitive and emotional development of school-aged children.[16] In addition, several reports suggest that children of depressed mothers display more fear and anxiety,[17] and have more insecure and

disorganised attachment patterns than children who are not exposed to a depressed mother.[18]

The most commonly used medications to treat depression in the postnatal period are the selective serotonin reuptake inhibitor (SSRI) class of antidepressants and the tricyclic antidepressants (TCAs). There is only limited human and animal data available on the effects of the monoamine oxidase inhibitor (MAOI) class of antidepressants in pregnant and postnatal women.[19] In addition, the MAOIs have been reported to exacerbate hypertension, and they have extensive interaction profiles with food and other medications, which can lead to complications in treatment.[14] Therefore, the MAOIs are not recommended for use in treating depression in pregnancy or the postnatal period.

Despite this growing body of literature, there are many confounding factors that must be taken into account when interpreting the data. For example, some published case reports do not specify exposure details for the infants, thus making it difficult to determine if a particular effect is related to *in utero* versus breast milk exposure. In addition, the sensitivity of drug assay techniques varies widely, and in cases where infant clinical status is documented, it is often not based on standardised or widely used behavioural assessment tools. Therefore, the focus of this article will be on highlighting and interpreting the existing literature on the benefits and risks to mother and infant of drug treatment for postnatal depression, as well as outlining treatment guidelines for the use of antidepressants in breastfeeding mothers.

A MEDLINE search of the literature from the past 20 years was conducted to determine the use of antidepressants in breastfeeding women. Search items included each of the classes of antidepressants in association with postnatal depression, breastfeeding, breast milk, and lactation.

1. Antidepressants During Breastfeeding

1.1 Selective Serotonin Reuptake Inhibitors

The SSRIs are effective for the treatment of general depression, and have, for most patients, become the treatment of choice. The literature on use of these drugs in lactating women has also rapidly expanded in recent years and includes publications of individual case reports, case series, and pharmacokinetic investigations. However, as these agents have only been on the market for a relatively short period of time, the long-term developmental effects of SSRI exposure in infants through breast milk have yet to be evaluated. It is critical, therefore, to understand the potential risks of SSRI therapy during lactation, and to weigh these risks against the expected benefits to both mother and infant on an individual basis.

Table I is a summary of the existing published reports of SSRI use by postnatal women.

1.1.1 Fluoxetine

Fluoxetine is the SSRI with the most published data on use by postnatal women.[20-28] Norfluox-

Table I. Summary of the existing published reports of selective serotonin reuptake inhibitor use by postnatal women during breastfeeding

Medication	Number of nursing infants	Number of reports of adverse events	Adverse events
Fluoxetine[20-28]	57	7	Colic (3 infants),[20,27] irritability,[21] seizure activity,[a] [26] withdrawal symptoms (2 infants),[b] [27] reduced growth[28]
Sertraline[24,29-34]	46	1	Benign neonatal sleep myoclonus[32]
Paroxetine[24,35-38]	60	0	
Fluvoxamine[39,40]	2	0	
Citalopram[41-43]	5	1	Uneasy sleep[41]

a Infant was exposed to fluoxetine, carbamazepine, and buspirone both *in utero* and through breast milk. It is not clear what medication and timing of exposure is associated with the adverse event noted.

b Infants were both exposed *in utero* and through breast milk. It is not clear which exposure was responsible for the 'withdrawal symptoms' (irritability, crying, poor feeding) noted.

etine, the active metabolite of fluoxetine, has similar pharmacokinetics and pharmacological potency as fluoxetine; norfluoxetine also has a long half-life that may predispose to accumulation in the serum of nursing infants.[44] One case study described adverse effects such as colic, fussiness, crying, seizure activity, and reduced bodyweight gain with fluoxetine exposure.[20] Another report also found reduced bodyweight gain in infants breastfed by mothers who were taking fluoxetine, although the bodyweights reported were not statistically lower than the national mean.[28] Despite two studies that reported negative effects, the majority of studies on the use of fluoxetine for postnatal depression have reported low drug concentrations in maternal milk and infant serum, and no other adverse infant effects have been documented.

1.1.2 Sertraline

Sertraline and its weak metabolite, desmethylsertraline, have been detected in breast milk, but with low or undetectable serum levels in the infant.[24,29-34] A recent study examined sertraline exposure in 19 breastfeeding mother-infant pairs, and found that platelet serotonin uptake in these infants was unaltered, despite low concentrations of sertraline and its metabolite in their serum.[34]

1.1.3 Paroxetine

Paroxetine is also excreted into the breast milk of lactating women, however, unlike fluoxetine, sertraline, and citalopram, paroxetine does not have an active metabolite. Only low or undetectable serum concentrations have been reported in infants and no adverse effects have been reported.[24,35-38] Based on the available data, paroxetine may be preferable to the other SSRIs in postnatal women.

1.1.4 Fluvoxamine

Two small case studies of fluvoxamine exposure through breast milk have both reported very low concentrations in the breast milk, and no adverse events in the infants.[39,40] Another recent study of six women found that fluvoxamine was an effective treatment for postnatal depression, although no details on infant exposure were given in this report.[45] As there is limited information available regarding the effects of this medication, caution is advised when prescribing fluvoxamine in postnatal breastfeeding women.

1.1.5 Citalopram

Only three case studies examining citalopram exposure through breastfeeding have been published.[41-43] As with fluvoxamine, limited data exists regarding the effects of citalopram on nursing infants, and therefore caution is advised when prescribing this medication to postnatal breastfeeding women.

1.2 Tricyclic Antidepressants

Table II is a summary of the existing published reports of TCA use by postnatal women.

The TCAs are useful in the treatment of postpartum depression when the SSRIs have failed, or when the woman has shown a previous good response to these medications. All TCAs are excreted into human breast milk in low concentrations, and

Table II. Summary of the existing published reports of tricyclic antidepressant use by postnatal women during breastfeeding

Medication	Number of nursing infants	Number of reports of adverse events	Adverse events
Amitriptyline[46-50]	8	0	
Clomipramine[24,46,51,52]	9	0[a]	
Desipramine[24,53,54]	10	0	
Doxepin[55-57]	3	2	Respiratory depression;[55] poor sucking, muscle hypotonia, vomiting, jaundice, and drowsiness[56]
Imipramine[24,46,53]	7	0	
Nortriptyline[24,29,58-60]	18	0	

a One study reported 'toxic effects' in a neonate, but it was concluded that they were the result of *in utero* exposure.

a wide range of infant serum concentrations have been reported. However, no adverse effects have been documented for exposure to amitriptyline,[46-50] clomipramine,[24,46,51,52] desipramine,[24,53,54] imipramine,[24,46,53] or nortriptyline.[24,29,58-60] The active metabolite of doxepin has the longest half-life (37 hours) of all of the TCA medications, and may be potentially hazardous to nursing infants due to high accumulation in their sera. Doxepin exposure has been associated with adverse effects in two reports.[55,56] Caution is advised when prescribing doxepin to postnatal breastfeeding women; if possible, use an alternative medication with a shorter half-life and better documented infant effects.

1.3 Other Antidepressants During Breastfeeding

Table III is a summary of the data available on atypical antidepressants by postnatal women.

There is very limited data available on the use of atypical antidepressants such as bupropion,[61] trazodone,[62] and nefazodone by breastfeeding women and their infants. When possible, women should be advised to use an alternative antidepressant medication with more documented use in postnatal breastfeeding mothers.

Venlafaxine is a newer antidepressant medication that works by inhibiting the reuptake of both serotonin and norepinephrine (noradrenaline). A recent study of venlafaxine in 15 women found that it is an effective medication for the treatment of postnatal depression, however, no details were given in this report about infant exposure to the medication.[65] Only two case reports have been published to date regarding venlafaxine concentrations in nursing infants.[63,64] The first study reported high concentrations of the medication in the sera of three exposed infants, but no adverse effects were noted in the infants.[63] The second study involved measurement of venlafaxine concentrations in the sera of two mother-infant pairs.[64] The main metabolite of venlafaxine was present in low but detectable amounts in both infants; however, no adverse effects were noted in the infants, and they were developing normally over the first year of age. Although these results are promising, more data are needed before conclusions can be made regarding the safety of venlafaxine in breastfeeding.

Table III. Summary of the existing published reports of use of other antidepressants (not selective serotonin reuptake inhibitors or tricyclic antidepressants) by postnatal women during breastfeeding

Medication	Number of nursing infants	Number of reports of adverse events
Bupropion[61]	1	0
Trazodone[62]	6[a]	0
Venlafaxine[63,64]	5	0

a No details given on infant serum concentrations or clinical status.

2. Adjunctive Therapies During Breastfeeding

There are several non-pharmacological treatment alternatives available for the treatment of postnatal depression, including cognitive-behavioural therapy,[66] interpersonal psychotherapy,[67-69] and group therapy.[70,71] While these treatments have been documented to be effective in treatment of women with mild to moderate symptomatology, they may not be adequate for the woman who has more severe symptoms. However, the non-pharmacological treatments continue to play a major role as adjunctive therapies for pregnant and postnatal women with mood and anxiety disorders, and as first-line therapies for women who refuse pharmacological treatment.

In addition, electroconvulsive therapy has been reported to be a safe treatment option for specific postnatal conditions such as severe depression with psychotic symptoms, acute mania, and in mothers who are at a risk for suicide or infanticide.[72,73]

3. Treatment Guidelines for Postnatal Depression

A new mother diagnosed with postnatal depression is faced with many difficult decisions. If she chooses to breastfeed her infant while taking an

antidepressant medication, she must consider the effects that exposure to the medication may have on her infant. However, if she chooses to discontinue breastfeeding, her infant may be at higher risk of developing a host of medical difficulties for which breastfeeding is considered to be protective against, including gastrointestinal disease, respiratory problems, and allergies.[74,75] On the other hand, if she chooses to continue breastfeeding her infant, but discontinues her antidepressant medication, she will likely relapse, resulting in infant exposure to maternal psychiatric illness, which has been shown to have negative consequences on emotional and behavioural development. When faced with this situation, it is critical that the patient, her family, and her healthcare givers take all of these factors into account, in an effort to make the best possible informed decision for the mother and her infant.

If the decision is made to commence or continue antidepressant therapy in the postnatal period, the following treatment guidelines are recommended:

1. Selection of an antidepressant medication should be based on: the patient's prior response to a particular agent; the patient's prior adverse effect experiences with a particular agent; concurrent medications and risk of interactions; published adverse effects associated with a particular agent when used by breastfeeding women and their infants.

2. Maternal doses should be monitored – maternal, fetal, and neonatal systems of drug absorption, distribution, metabolism, and elimination are all constantly changing throughout pregnancy and the postnatal period. Some of these variations require an increased or decreased dose of a specific medication, thus potentially increasing or decreasing drug exposure to the fetus or nursing infant. The effectiveness of a particular medication should therefore be monitored throughout the entire pregnancy and postnatal period in order to aim for the lowest possible dose that provides complete control of the depressive symptoms. Doses that are so low that they are ineffective compromise the mother by putting her at an increased risk for relapse, and compromise the infant through unnecessary exposure to medication.

3. When possible, a medication that is known to result in lower infant exposure, either through lower accumulation in breast milk, and/or through lower documented accumulation in neonatal serum, should be used. If possible, the use of recently released medications in the postnatal period should be discouraged until more information is available regarding the effects of the medication.

4. The use of a single medication at any dose is preferable to multiple medications during both pregnancy and lactation. Switching medications during either pregnancy or the postnatal period increases the exposure to the fetus or infant.

5. The infant's clinical status and drug concentrations should be assessed regularly. The infant should be assessed prior to (if possible), and throughout, medication exposure by a paediatrician. Parents should also be educated about possible adverse signs and symptoms that an exposed infant may exhibit. Tables I to III list the documented adverse events that have been associated with the use of antidepressants by breastfeeding women. If possible, infant serum samples may also be taken. It is important to remember, however, that drug assay techniques vary widely, and that 'undetectable' drug concentrations do not necessarily indicate that the medication is not present in the serum of the infant. Therefore, the best assessment of an infant's well being is a regular clinical evaluation by the paediatrician.

6. The patient should be advised to time her breastfeeding to when the medication concentrations are likely to be at their lowest in her breast milk. This can be done by educating her about the peak levels of the drug in the blood, where appropriate. In addition, when faced with a choice between several different types of medications with similar efficacy and adverse effect profiles, one with few or no active metabolites is recommended.

7. The use of SSRIs and TCAs by breastfeeding women is not contraindicated. With the exception of a few cases, no serious adverse events have been reported in association with these medications.

Antidepressant therapy should be considered in women who have moderate to severe symptoms, who have not responded to supportive therapy or other types of non-pharmacological treatments, or who are at a risk of suicide or infanticide. In these cases, the benefits of antidepressant therapy should be discussed with the patient and her partner, in order to help them make an informed decision that will benefit the well being of both mother and infant.

4. Conclusions

The existing literature on the use of antidepressants by postnatal breastfeeding women is limited to case reports and small studies making it difficult to formulate any generalisations about the safety of these medications. However, the results are promising in that very few adverse effects as a result of infant exposure to SSRIs or TCAs have been reported to date. All psychotropic medications pass through the breast milk in varying amounts, resulting in infant exposure. While a clear relationship between drug concentrations and infant development and behaviour is yet to be elucidated, preliminary reports in which children have been followed-up into the school age years are encouraging.

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