Medication Use for Trauma Symptoms and PTSD in Pregnant and Breastfeeding Women

Kathleen Kendall-Tackett, PhD, IBCLC, and Thomas W. Hale, PhD

Traumatic events are relatively common in the lives of pregnant and breastfeeding women. In our study, we found that 51% of new mothers had been exposed to at least one major traumatic event and multiple exposures were common. According to the National Center for PTSD, the most common traumatic experiences for women are rape, sexual molestation, physical attack, being threatened with a weapon, and childhood physical abuse (National Center for PTSD, www.ncptsd.va.gov). Trauma in the perinatal period can also be caused by previous pregnancy loss, preterm birth, neonatal death, or a life-threatening birth experience. Some trauma-exposed women will develop posttraumatic symptoms and others will meet full criteria for PTSD.

Kathleen Kendall-Tackett, PhD

Comprehensive trauma treatment involves a wide range of activities including patient education, peer support, EMDR, and trauma-focused psychotherapy. Clinicians treating women trauma survivors may also treat them while they are either pregnant or breastfeeding. Most of the standard treatments for PTSD are non-pharmacologic and therefore quite safe for both. But medications are also commonly used to treat PTSD and trauma symptoms. According to Friedman et al. (2009), medications have three potential benefits for patients: (1) they ameliorate PTSD symptoms, (2) they treat comorbid disorders, and (3) they reduce symptoms that can negatively affect both psychotherapy and daily living.

Medications for PTSD and Trauma Symptoms

The decisions about medication use become more complex when treating women who are pregnant or breastfeeding (Freeman, 2008). One challenge associated with medicating pregnant and breastfeeding women is making accurate risk/benefit analyses. Are the risks associated with using medication less than the risks associated with untreated depression? In many cases, the answer is likely to be yes. But it is not a decision to be made lightly. For example, in a recent study of pregnant women with depression, more than 20% of infants with continuous exposure to selective serotonin reuptake inhibitors (SSRIs) during pregnancy were delivered preterm (Wisner et al., 2009). However, the rate of preterm birth among the mothers with *untreated depression* was also 20%. The rate of preterm birth among the non-exposed or partially exposed groups ranged from 4% to 9%. Misri and colleagues also noted that "when a clinician is faced with the dilemma of managing mentally ill pregnant women, no decision is risk free" (Misri et al., 2006, p. 1031).

With regard to breastfeeding, risk/benefit analyses must also weigh the risks of infant exposure to mother's medications with the risks of *not breastfeeding*, which are well-established, and can lead to significant infant morbidity and mortality. In most cases, the risks associated with breastfeeding on medication are still less than the risk of not breastfeeding or the risks of infant exposure to ongoing, untreated maternal depression (Hale, 2008).

Transfer of Medications to the Infant in Pregnant and Breastfeeding Women

In this section, we give a brief overview of medication transfer to infants in utero and via breast milk, focusing on selective serotonin reuptake inhibitors (SSRIs). SSRIs are antidepressants and are often the frontline medications used to treat PTSD (Friedman et al., 2009). Researchers know a fair amount about how these medications affect infants after exposure in utero and via breastfeeding. This is a summary of a much larger literature. But it provides a starting place for understanding what we know about medication use in peripartum women.

In Utero Exposure. During pregnancy, medications transfer to babies via the placenta and amniotic fluid. The amount transferred via the placenta is significant and can equal the mother's dose. But medications differ in terms of how much they transfer, and using a medication that transfers in smaller amounts is one strategy for selecting a medication to use during pregnancy. For example, in a study of 38 pregnant women who were taking SSRIs, antidepressant and metabolite concentrations were found in 87% of umbilical cord samples. The mean serum ratios ranged from 0.29 to 0.89. The lowest ratios were for sertraline (Zoloft) and paroxetine (Paxil), and the highest for citalopram (Celexa) and fluoxetine (Prozac) (Hendrick et al. 2003).

Thomas W. Hale, PhD

With regards to SSRIs causing birth defects if administered during pregnancy, the Sloane Epidemiology Center Birth Defects Study recently confirmed that that the overall risk of having a child affected by SSRI use was only 0.2% (Louik et al., 2007). They did note increased risk of three birth defects with SSRI use in the first trimester: omphalocele and septal defects with sertraline, and the heart defect right ventricular outflow tract obstruction with paroxetine. But only 2% to 5% of infants with these defects were exposed to SSRIs.

In neonates, third-trimester exposure can lead to "discontinuation" syndrome due to SSRI withdrawal. Discontinuation syndrome includes acrocyanosis, tachypnea, temperature instability, irritability, and elevated drug levels (Oberlander et al., 2004). Fortunately, these symptoms are generally mild and self-limiting, and can be managed with supportive care. Severe symptoms are rare, and no reported neonatal deaths have occurred that are attributable to in utero SSRI exposure. Discontinuation syndrome can be distressing to both mothers and babies, but the symptoms are self-limiting, last for 24 to 48 hours, and do not require further treatment. Research from our lab also suggests that mothers who continue

on the medication while breastfeeding can ease discontinuation symptoms in their infants.

Exposure via Breast Milk. Infants can also be exposed to maternal medications via breast milk, but the amount of exposure is substantially less than in utero exposure. Some medications are better than others in terms of amount of exposure the infant receives. A recent meta-analysis of 67 studies of antidepressant levels in breastfeeding infants pooled data from 337 research cases, including 238 infants (Weissman et al., 2004). The researchers had access to data on 15 different antidepressants and their major metabolites. They found that antidepressants were detectable in the breast milk for all the antidepressants they studied. Fluoxetine produced the highest proportion of elevated infant levels and the highest mean infant level (Weissman et al., 2004). Citalopram was also relatively high. Only one infant across studies had an elevated paroxetine level, and that infant had also been exposed prenatally. All other infant paroxetine levels were zero, and this included three infants with prenatal exposure. Maternal dose was highly correlated with infant plasma level for citalopram. The correlation was weak for sertraline. And maternal dose did not predict infant level for fluoxetine, nortriptyline, or paroxetine. Compared with other antidepressants, fluoxetine was more likely to accumulate in breastfeeding infants.

With regard to long-term effects, the authors noted that low or undetectable infant plasma concentrations alone cannot reassure us that the antidepressant will have no effect on the rapidly developing brain, and whether chronic, low-dose exposure poses a risk. However, they noted that the studies with asymptomatic infants are reassuring. Moreover, they noted that although antenatal exposure differs from exposure via breastfeeding, the antenatal data suggests little or no long-term effects on developmental outcomes. They noted that we must factor in whether there was prenatal exposure as that provides a "loading dose" that far exceeds any exposure from breast milk and can thus distort findings regarding exposure via breast milk. (Weissman et al., 2004).

In summary, they noted that breastfeeding infants' exposure to paroxetine, sertraline and nortriptyline are unlikely to have detectable or elevated plasma drug levels. In contrast, infants exposed to fluoxetine had higher medication levels, especially if they had also been exposed prenatally. Citalopram may lead to elevated levels in some infants, but more data are needed. Although these appear safe for the majority of babies, some adverse effects have been identified through case studies. Therefore, breastfeeding mothers should be advised to watch for any possible signs of adverse reactions including irritability, poor feeding, or uneasy sleep. Premature babies or other with impaired metabolite efficiency should especially be monitored for adverse effects (Weissman et al., 2004).

*T*able 1
FDA Pregnancy Risk Categories

Pregnancy Risk Category	What it Means
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women; or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Medications for PTSD in Pregnant and Breastfeeding Women

Two recent articles have outlined the state of the art in terms of medication choices for trauma symptoms and trauma symptoms and PTSD (Alderman et al., 2009; Friedman et al., 2009). The classes of medications used to treat PTSD include SSRIs, SNRIs, mirtazapine, SARIs, adrenergic agents, and atypical antipsychotics. Benzodiazepines, anticonvulsants, cyproheptadine, and buspirone cannot be recommended at this time (Friedman et al., 2009).

In each of these classes of medications, there are safer choices for pregnant and breastfeeding women. In perinatal health, the standard reference regarding medication use in this population is *Medications and Mothers' Milk* (Hale, 2008). Following this article is a summary of current medications recommended for trauma symptoms/PTSD, with their pregnancy and lactation risk categories. The pregnancy risk categories are based on U.S. FDA guidelines.

Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs address all three symptom clusters of PTSD: intrusive thoughts, avoidance and numbing, and hyperarousal (Friedman, 2001; Friedman et al., 2009). In the U.S., sertraline (Zoloft) was the first SSRI that was FDA-approved as a treatment for PTSD. Paroxetine (Paxil) is the treatment of choice in the U.K, and the only drug listed with a current U.K. product license for PTSD (National Institute for Clinical Excellence, 2005). Zoloft is also

continued on p. 14

Medication Use for Trauma Symptoms...

continued from p. 13

the preferred SSRIs for breastfeeding mothers because its inert metabolites mean that babies are exposed to less than one percent of the mothers' dose (Hale, 2008). Paxil also results in low levels of exposure for breastfeeding infants, but there is currently a black-box warning against using it during pregnancy. Lexapro (escitalopram) is another good choice for breastfeeding mothers.

Other SSRIs, including fluoxetine (Prozac) and citalopram (Celexa), can also be used to treat PTSD, but result in higher levels of exposure for infants. None of these are contraindicated for breastfeeding mothers, but sertraline, paroxetine and escitalopram are better choices whenever possible (Hale, 2008).

Newer Antidepressants

Some newer types of antidepressants can also be used (Friedman et al., 2009). These include venlafaxine (Effexor) and mirtazapine (Remeron). Venlafaxine is a selective norepinephrine reuptake inhibitor (SNRI) and is a frontline treatment for PTSD. Mirtazapine is also showing promise (Friedman et al., 2009). Both have a rating of L3 ("moderately safe"), and should be prescribed only if the benefit outweighs the potential risk to the infant (Hale, 2008).

Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs)

Trazodone (Desyrel) is a SARI with modest efficacy, but can be a useful adjunctive treatment to promote sleep (Friedman et al., 2009). Trazodone suppresses REM sleep, which reduces the number of nightmares patients experience (Lange et al., 2000). Because trazodone is a sedative, breastfeeding women should not share a bed with their babies while taking it. (Nefazodone, the other medication in this class, has been removed from the U.S. market due to liver toxicity.)

Adrenergic Agents

The adrenergic agents are another class of medications used to treat trauma symptoms/PTSD. Adrenergic agents work by blocking norepinephrine receptors and include clonidine (Catapres) and guanfacine (Tenex). (Propranolol [Inderal] is also used, but *not* when a patient has comorbid depression [Friedman, 2001].) Adrenergic agents are frequently prescribed to control hypertension, but in patients with PTSD, they also control symptoms of intrusive memories and hyperarousal. Prazosin (Minipress), an alpha blocker, can be helpful in reducing PTSD-related nightmares (Friedman et al., 2009), but has a rating of L4 ("possibly hazardous"), and should be used with extreme caution in breastfeeding women.

Clonidine is excreted into human milk, with the baby receiving about 6.8% of the mother's dose. It may also reduce prolactin, which can influence milk production (Hale, 2008). Guanfacine has not been studied with regard to human milk. However, since this medication has low molecular weight, a high volume of distribution, and penetrates the central nervous system at high levels, it is likely to penetrate the milk, so caution is advised (Hale, 2008).

Atypical Antipsychotics

Atypical anti-psychotics may also be added to the treatment regimen as an adjunct therapy for partial responders. These medications may help lessen anxiety responses. The medications within this class include risperidone (Risperdal), quetiapine (Seroquel), and olanzapine (Zyprexa). Olanzapine and quetiapine are rated L2. Risperidone has a risk category of L3. All have a C rating for use during pregnancy.

Summary

Although medications are not the central treatment modality for PTSD, they can be helpful in women's recovery. Medications can be used safely in pregnant and breastfeeding women with

Table 2
Lactation Risk Categories

Lactation Risk Category	What it Means
L1: Safest	Drug has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.
L2: Safer B	Drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.
L3: Moderately Safe	There are no controlled studies in breastfeeding women, however, the risk of untoward effects is possible; or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.
L4: Possibly hazardous	There is positive evidence of risk to a breastfed infant or to breast milk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk of the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)
L5: Contraindicated	Studies in breastfeeding mothers have been demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

From Hale, T. (2008). *Medications and Mothers' Milk* (13th ed.). Amarillo, TX: Hale Publishing. Used with permission.

trauma symptoms and there are safer choices within each medication category. Medications can also be used in addition to traditional trauma treatments, such as EMDR, psychotherapy, peer support, and psychoeducation.

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Kathleen Kendall-Tackett, PhD, IBCLC, is Clinical Associate Professor of Pediatrics, Texas Tech University School of Medicine, and Secretary of Division 56.

Thomas Hale, PhD, is Professor of Pediatrics, Texas Tech University School of Medicine.

Table 3
Pregnancy and Lactation Risk Categories for Medications for PTSD

Medication Classification	Medication Names	Pregnancy Risk Category	Lactation Risk Category	Symptoms Addressed
Selective Serotonin Reuptake Inhibitors (SSRIs)	Sertraline (Zoloft) Escitalopram (Lexapro) Paroxetine (Paxil) Fluoxetine (Prozac) Citalopram (Celexa)	C C D C C	L2 L2 L2 L2 L2	Well-tolerated; addresses comorbid symptoms; leads to global improvement and enhanced quality of life
Mixed-function Antidepressants	Venlafaxine (Effexor) Mirtazepine (Loniten)	C C	L3 L3	Demonstrated efficacy in PTSD
Serotonin-2 Antagonists/Reuptake Inhibitors (SARIs)	Trazodone (Desryl)	C	L2	Lowers incidence of nightmares by reducing REM sleep. Sedating, mothers cannot bedshare with their babies while on this medication.
Adrenergic agents	α-2 adrenergic antagonists (prazosin, clonidine, guanfacine) β-adrenergic blockers (propranolol)	C, C, B C	L4 L3 L3 L2 L2	Blocks norepinephrine, decreases nightmares and intrusive thoughts. Acute administration may prevent long-term symptoms. Some concern about this medication when there is co-morbid depression.
Atypical Antipsychotics	Olanzapine Quetiapine Risperidone	C C C	L2 L2 L3	These can be useful adjuncts for co-occurring psychotic symptoms or when first-line medications have failed. Can also help with extreme hypervigilance/paranoia, physical aggression, trauma-related hallucinations