Pharmacological Aspects of Neonatal Antidepressant Withdrawal

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Depression is common in reproductive age women, and continued pharmacologic treatment of depression during pregnancy may be necessary to prevent relapse, which could be harmful for both the fetus and the mother. Although data on drug safety are imperfect and incomplete, the benefits of antidepressant therapy during pregnancy generally outweigh the risks. Neonates who are exposed to antidepressant medications during gestation are at increased risk to have neonatal withdrawal syndrome, although the exact incidence of this complication is unknown because the definition of the syndrome is not clear and withdrawal reactions are probably underreported. Tricyclic antidepressant withdrawal syndrome is most likely related to muscarinergic activity and individual drug half-lives, and selective serotonin reuptake inhibitor withdrawal may be due to a decrease in available synaptic serotonin in the face of down-regulated serotonin receptors, the secondary effects of other neurotransmitters, and biological or cognitive sensitivity. Other factors that influence neonatal toxicity or withdrawal include the normal physiologic changes of pregnancy, the altered activity of CYP450 enzymes during pregnancy, drug-drug transporter (Pgp and OCT3) interaction, and the presence of genetic polymorphisms in genes influencing drug metabolism. Further research is necessary.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to explain the importance of antidepressant therapy during pregnancy and postpartum, summarize the important neonatal effects of antidepressants, and describe the potential teratogenic effects of antidepressants.

It has been estimated that up to 70% of pregnant women experience symptoms of depression, with 10% to 16% of pregnant women fulfilling diagnostic criteria for a major depressive disorder (1–3). Women with depression have significantly lower health-related quality of life scores (4), and untreated maternal depression has been associated with obstetrical complications such as preterm birth and low birth weight, spontaneous abortion, preeclampsia, and substance abuse (5,6). Women with prenatal...
depressive disorders are less willing to initiate breast feeding, and untreated symptoms may also precipitate behavioral changes in the offspring (3).

Continued treatment of depression during pregnancy may be necessary to prevent relapses and postpartum depression. This was demonstrated by Cohen et al, who found that relapse of depression occurs in 68% to 75% of women who stop antidepressant therapy before conception or during the first trimester (7,8), and that nearly half of all pregnant women who stop antidepressant therapy before conception need to restart it during pregnancy to control depressive symptoms (9). This kind of relapse has not been reported for other psychiatric conditions (10). A review by Viguera showed that, compared with discontinuation of antidepressant therapy, continuous therapy for major depression during pregnancy is associated with a 30% lower rate of relapse per month (11). The factors which predict relapse of depression have not yet been fully identified.

Drug exposure registries reveal that antidepressants are used in 0.1% to 1.8% of pregnant women from the first trimester to delivery (12–20). In addition to depression, antidepressants are used to treat panic and stress disorders, major depressive disorders, obsessive compulsive disorders, phobias, anxiety disorders, and borderline personality disorders. Selective serotonin reuptake inhibitors (SSRIs) are the antidepressant drugs most commonly prescribed during pregnancy. However, concerns have recently been raised regarding paroxetine exposure during the first trimester, which may be associated with an increased risk of cardiovascular malformations in exposed fetuses (21).

In this systematic review, we summarize the current literature on the teratogenesis of antidepressant medications, and describe neonatal withdrawal from tricyclic antidepressants (TCAs) and SSRIs. We also discuss the possible pharmacological background, such as maternal pharmacokinetics, pharmacogenetics, and placental transporter mechanisms.

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LITERATURE SEARCH STRATEGY

Relevant articles for inclusion in this review were systematically selected by performing a literature search of publications, using PubMed (from 1968 until November 2006), the Excerpta Medica database EMBASE (1974 until November 2006), and Medline (1966 until November 2006), for the subheadings “neonatology,” “neonatal abstinence syndrome,” “antidepressive agents,” TCA, SSRI, “substance withdrawal syndrome,” pharmacogenetics, pharmacokinetics, placenta, pregnancy, polymorphism, and transporter. Cross-references from relevant articles were also screened for inclusion. Because human placentas are morphologically and functionally different than those of animals, animal data were not included. No reports from randomized controlled clinical trials (RCTs) were available, so the best evidence from case reports or case series or review articles was used. The absence of RCT results from major ethical considerations which prevent the study of drug effects in pregnant women.

PLACENTAL TRANSFER OF ANTIDEPRESSANTS

The human placenta consists of 10 to 40 cotyledons containing chorionic villi. The chorionic villus is the functional unit of the human placenta, and is the site for exchange between the maternal and fetal circulations. The villus consists of a central fetal capillary, stroma, and an outer trophoblast layer. Trophoblastic cells are present as mononuclear cells called cytotrophoblasts and multinucleate cells called syncytiotrophoblasts. The composition of the trophoblast layer in the human placenta changes during pregnancy. During the first trimester, the villi have a nearly complete cytotrophoblast layer underneath the syncytiotrophoblast layer. Later in pregnancy, the cytotrophoblast layer becomes discontinuous. In addition to the trophoblast layer, the fetal and maternal circulations are separated by a trophoblast basement membrane, connective tissue space, an endothelial basement membrane, and fetal capillary endothelium (22).

Solute in the maternal circulation can reach the fetal circulation by passing through the apical brush-border (maternal facing) and basolateral or basal (fetal facing) membranes of the syncytiotrophoblast (23). Parameters which influence the rate of passage include the maternal-fetal concentration gradient of the unbound fraction of the drug, the surface and thickness of the placental membranes, and the biochemical characteristics of the diffusing molecules (lipid solubility, polarity, molecular weight, and pKa.
value) (23). Ion-trapping of drugs that are weak bases may occur because the fetal pH (pH = 7.3) is different from the maternal pH (pH = 7.4). The human placenta contains multiple enzyme systems, including those responsible for drug oxidation, reduction, hydrolysis, and conjugation (24). Cytochrome P-450 enzymes important for oxidative metabolism are designated CYP1A1, 1A2, 2C, 2D6, 2E1, 2F1, 3A4, 3A5, 3A7, and CYP34B1 (24,25). CYP2D6 is an important enzyme in antidepressant drug metabolism; the existing genetic polymorphisms of CYP2D6 make drug response and toxicity sometime unpredictable at first exposure.

Changes in drug permeability during pregnancy result from placental changes such as decreasing membrane thickness and increasing placental blood flow, the expression of active CYP-enzymes (1A1, 2D6, 2E1, 3A4) (26), and the regulation of different transporters.

Known placental transporters of antidepressants include P-glycoprotein (PgP), OCT3, and SERT transporters. The localization of the PgP efflux transporter determines the direction of the transport. If the transporter is located on the apical membrane, it will efflux into the maternal circulation. If it is located on the basolateral membrane, it will efflux into the fetal circulation (23). The role of the placenta as an efflux transporter has been established, and Molsa et al found that PgP is also involved in the transport of drugs from the placenta to the maternal circulation (27). Most drugs transported by PgP are basic, uncharged, hydrophobic, and contain multiple hydrogen bonds (28). An overview of drugs that interact with PgP has been presented by Balayssac et al (29). Of all antidepressants, desipramine, venlafaxine, and paroxetine are known to interact with PgP (30).

Some herb extracts (curcumin, ginsenosides, piperine, green tea, and silymarin from milk thistle) inhibit or accelerate the PgP-transporter mechanism, which hypothetically could be harmful to the fetus (31). Different polymorphisms for PgP have been found with no apparent clinical relevance (28). A 2-fold increase in PgP expression at the end of pregnancy compared to early pregnancy has been reported, but not yet confirmed in larger studies (32). Increased PgP expression may protect the fetus from xenobiotics (33). In contrast, a small study in mice showed that PgP-blocking drugs (digoxin, saquinavir) increase fetal exposure to these drugs (34).

The OCT3 transporter system, located in the basal syncytiotrophoblast, serves as the placental transporter for serotonin, dopamine, norepinephrine, histamine, amphetamines, clonidine, cimetidine, imipramine, and desipramine (23,24,26,35). Other TCAs may also be transported by the OCT3 transporter. Although OCT3 has been shown to transport imipramine, a recent study showed that imipramine may actually inhibit the OCT3-transporter (36). Fluoxetine has been shown to prevent serotonin from crossing the human placenta by blocking the serotonin transporter (37); the clinical relevance of this finding is not yet understood.

TERATOLOGY

Studies of the possible association between maternal drug use and adverse or teratogenic fetal effects are frequently complicated by methodological issues. These include the lack of appropriate controls, incomplete ascertainment of cases, imprecise information about the timing of drug use in relation to pregnancy, small numbers of reported cases with insufficient power, suboptimal study design (cohort or case-control), and the fact that most studies focus on the overall incidence of major malformations instead of specific birth defects. In addition, because most studies do not specify whether antidepressant use was started because of maternal depression about an existing pregnancy complication or whether the complication occurred after drug therapy was initiated for other reasons, it is difficult to ascribe cause and effect.

Not surprisingly, therefore, reports of the teratogenic risk of maternal TCA use have contradictory results. Although one Swedish study identified an association between maternal clomipramine use and congenital cardiovascular anomalies such as ventricular or atrial septal defects (38), other studies have found no teratogenic effects of TCA use during pregnancy or before conception (39–42). In addition, TCA exposure has not been associated with an increased incidence of perinatal complications (43). In general, the use of TCAs during pregnancy is considered safe, although the statistical power of published studies is low (44).

Several cohort studies that examined the use of SSRIs in pregnancy found no increased risk of major congenital malformations (45–49), whereas other cohort studies have reported an association between SSRI use and adverse pregnancy outcomes such as lower birth weight (but not low birth weight or intrauterine growth restriction), earlier gestational age at delivery, and an increased incidence of minor congenital anomalies (47,50). A recent meta-analysis suggested that spontaneous abortion is more common among women using antidepressants than among women not using any drugs (51), but the analysis
could not determine whether this was associated with the medication or with maternal depression itself.

One recent case-control study found a possible relationship between maternal use of SSRIs (particularly paroxetine) during early pregnancy and an increased risk of congenital cardiac defects (52), whereas another case-control study reported an association between third-trimester use of SSRIs and persistent fetal circulation (pulmonary hypertension) (53). However, many studies evaluating a variety of antidepressant medications have reported no teratogenic effects for TCAs, SSRIs, or any other antidepressant (45,46,49,52,54–58).

**PHARMACOKINETICS OF ANTIDEPRESSANTS IN PREGNANCY**

The pharmacokinetics of most drugs are altered by pregnancy, such that the doses of most drugs have to be increased to maintain therapeutic levels (59). The doses of nortriptyline and desipramine have to be increased during pregnancy (60), and Hostetter et al. found that 70% of pregnant paroxetine, sertraline, and fluoxetine users needed to increase their daily dose to control depressive symptoms (61). The responsible pregnancy-related pharmacokinetic changes include substantial first-pass metabolism in the gut, changes in protein binding, a large volume of distribution, altered hepatic clearance, and elimination half-lives up to 3 days (62–65). On the other hand, there is enhanced absorption related to progesterone-related slowed intestinal transport (62,63). Another factor may be the effects of fetal drug metabolism. Although neonatal drug metabolism is unpredictable, resulting in fluctuations in blood concentrations (44,66–68), it is unknown whether this occurs during prenatal life.

**Phase 1 Metabolism (Cytochrome P-450)**

A main factor influencing the pharmacokinetics of antidepressants during pregnancy is the cytochrome P-450 isoenzyme system (69). A study of drug metabolism by CYP1A2, CYP2D6, and CYP3A4 during pregnancy showed that the metabolism of drugs during pregnancy may be altered (70). Anderson reviewed CYP1A2 activity during pregnancy (59), and showed the activity of CYP1A2 is reduced about 65% to 70% at the end of pregnancy, compared with the postpartum period (59,71). This finding may be relevant for antidepressants that are metabolized by CYP1A2, such as amitriptyline, clomipramine, desmethylimipramine, fluvoxamine, and imipramine. Although data are lacking, blood concentrations of these antidepressants may be altered.

CYP2C19 is involved in demethylation reactions which occur during the metabolism of amitriptyline, clomipramine, desmethylimipramine, fluvoxamine, and imipramine (72).

CYP2D6 also regulates the hydroxylation of antidepressants, which are generally lipophilic bases with a protonable nitrogen atom (73), and this contributes to their therapeutic and adverse effects (72). CYP2D6 activity is increased by 47.8% at the end of pregnancy compared to the postpartum period (74,75). It is likely that blood concentration levels of antidepressants (except trazodon and nefazodon) are lowered by this mechanism, which could result in a relapse of depression during pregnancy.

**Pharmacogenetic Variations in Phase 1 Metabolism**

Phase I metabolism is also subject to genetic variability. Much of the available information relevant to antidepressants regards the CYP2D6 sub-enzyme. The activity of CYP families, as well as several drug transporters, is regulated by a variety of nuclear receptors: pregnan X (PXR), constitutive androstane receptor (CAR), hepatic nuclear factors, and the aromatic hydrocarbon receptor (AhR) (76,77). The CYP2D6 gene is highly polymorphic, with over 70 known variants. It has been estimated that 36% of the world population has a variant gene, with relevant clinical consequences (78). Homozygosity of the null alleles of CYP2D6 is associated with poor metabolism (debrisoquine). Null allele heterozygosity, or homozygosity for intermediate metabolic alleles, gives rise to intermediate enzyme activity, whereas CYP2D6 gene duplications give rise to ultrarapid metabolic activity (78). Although the different allelic forms of CYP2D6 have not been associated with depression during pregnancy and in the postpartum period (79), they may result in a 2-fold difference in the required clomipramine and imipramine doses, a 8-fold difference in the desipramine doses, a 3-fold difference in the required nortriptyline doses, a 10-fold difference in the trimipramine doses, a 2-fold difference in the fluoxetine and paroxetine doses, a 5-fold difference in the mianserin doses, and a 4-fold difference in the venlafaxine doses (78). The C/C genotype of the CYP2D6 enzyme, 5-hmt2AT102C CY2D6, has been associated with severe paroxetine side effects (80), although it is not known whether plasma levels are increased.
Wadelius et al found that in extensive metabolizers of CYP2D6, the metabolism was decreased by 53% during pregnancy, whereas for poor metabolizers the metabolism was increased by 63% (75). Genetic variability in the activity of the CYP2C19 enzyme may result in a 2-fold difference in amitriptyline, clomipramine, imipramine, citalopram, and moclobemide doses and a 3-fold difference in fluoxetine doses (78).

**Phase 2 Metabolism**

Uridine diphosphate glucuronyltransferases (UGT) are extensively involved in the phase 2 metabolism of TCAs and SSRIs. Fluctuations in activity may occur, due to high interindividual expression of some UGT isoforms and their activity (81), the activity of promoter genes of UGT expression genes, and decreasing enzyme activity during pregnancy (62).

**Receptor Polymorphism**

Polymorphisms of serotonin (5-hydroxytryptamine, 5-HT) receptors and variations in 5-HT synthesis, 5-HT storage, and 5-HT membrane uptake may lead to variations in drug response (82). Of all serotonin receptors, 5-HT, 5-HT1, and 5-HT2a are of particular interest. Polymorphisms of the 5-HT1a receptor gene have been reported, although their clinical relevance has not yet been established yet. The A50V polymorphic variant has been shown to result in loss of a detectable 5-HT response (83). Polymorphisms of variable number tandem repeats (VNTRs) have been associated with altered responses to fluvoxamine therapy and an altered prolactin response to clomipramine therapy (83).

Murphy and coworkers showed that the C/C genotype of the 5-HT2a receptor (HTR2A) has been associated with both paroxetine withdrawal symptoms and the severity of paroxetine side effects in adults (80). This relevant finding should be explored in neonates.

Alterations in the SERTPR gene may lead to alterations in the response to fluvoxamine, paroxetine, citalopram, and fluoxetine (10). The A/A and A/C genotypes of TPH A218C gene have been associated with a slowed response to paroxetine (10).

DeVane et al tried to predict the effects of the PgP C3435T genotype on fetal exposure to substrate drugs (84). Of particular interest are the TT genotypes of both maternal and fetal/placental PgP receptors. This combination is suspect for high exposure to antidepressants (imipramine, desipramine, venlafaxine, paroxetine) and may be a key factor in the explanation of antidepressant withdrawal.

**NEONATAL SYMPTOMS AFTER PRENATAL EXPOSURE TO ANTIDEPRESSANTS**

The most important neonatal morbidity associated with maternal antidepressant use is the occurrence of neonatal withdrawal symptoms. The increasing prevalence of the neonatal withdrawal syndrome is not surprising, in light of the increase in maternal antidepressant use and the high frequency of the corresponding syndrome in adults. According to Haddad, the criteria that define withdrawal syndrome include onset shortly after the drug is discontinued or the dosage is reduced, short duration, rapid reversal on restarting the original drug, symptoms distinct from a reappearance of the underlying disease for which the drug was prescribed, and symptoms not attributable to other causes (85). The definition proposed by Desmond also includes central nervous excitation and respiratory and gastrointestinal dysfunction (86).

Prevention of withdrawal symptoms in adults by tapering the medication dose instead of abruptly discontinuing it has been recommended, but data from randomized controlled trials are lacking. The British National Formulary recommends that antidepressants administered for 8 weeks or more should be reduced over a 4 week period (85). It has also been suggested that discontinuing the drug over the course of a year, by reducing the dose by 25% every 3 months, is optimal (85), but this would be inappropriate for pregnant women who wish to prevent withdrawal symptoms in their offspring. No data are available on the prevention of neonatal withdrawal signs by tapering the maternal antidepressant dose during the last weeks of pregnancy or treating the newborn with low doses of the maternal medication. Recently, in a study by Abdel-Latif of mothers using opioids during pregnancy, it was found that neonates that were breastfed by mothers who continued their antidepressants showed significantly fewer withdrawal symptoms than those who were bottle-fed (87). These results may be the starting point for preventing neonatal withdrawal from other pharmacological agents, including antidepressants.

A prospective study showed that both maternal TCA and SSRI use significantly increased the risk of neonatal respiratory distress, hypoglycemia, and neonatal convulsions (88). No statistically significant differences were found between both groups. This study also showed that women using antidepressants...
often use other medications as well during pregnancy, making the interpretation of antidepressant withdrawal symptoms difficult (88).

Maternal depression is a major confounding factor in determining whether neonatal symptoms are due to withdrawal from in utero exposure to antidepressants. Oberlander and colleagues showed that only neonatal respiratory distress was a symptom of antidepressant withdrawal, whereas other neonatal symptoms such as feeding problems, jaundice, and even convulsions were found in both medication exposed and nonexposed neonates of depressed mothers (89).

Neonatal Symptoms After Maternal TCA Exposure

It is estimated that, overall, 50% of adults exhibit withdrawal symptoms after discontinuing TCA use (90). It is hypothesized that short half-lives, high doses, long-term use, and abrupt discontinuation of TCA therapy increase the likelihood of withdrawal symptoms (91). TCA withdrawal syndromes in neonates have been described and include jitteriness, irritability, convulsions, bowel obstruction, and urinary retention (92–96). It has been estimated that 20% to 50% of neonates might develop TCA withdrawal reactions as a result of maternal use (97–99).

Two theories regarding the development of TCA withdrawal are described: the cholinergic theory and the adrenergic theory (100,101). The cholinergic theory is based on the fact that TCAs bind to peripheral and central muscarinic receptors, and this binding—essentially cholinergic blockade—eventually produces muscarinic up-regulation (which incidentally is one explanation for the tolerance of side effects). When TCAs are discontinued, the muscarinic receptor up-regulation results in “cholinergic overdrive” in some patients (100). The adrenergic theory holds that TCA therapy causes inhibition of norepinephrine reuptake, so that the synaptic concentration of norepinephrine increases. This leads to a decrease in both the firing rate and norepinephrine turnover; with prolonged use, there is a decrease in α2-receptor sensitivity, leading to a further increase in norepinephrine release. With abrupt cessation of TCA therapy, synaptic norepinephrine levels decrease. Decreased norepinephrine levels and decreased receptor sensitivity lead to a sudden increase in norepinephrine release and turnover, and an increase in the synaptic firing rate (101).

Table 1 lists all published antidepressant neonatal withdrawal signs, classified by antidepressant and category according to Dilsaver and Moses-Kolko (100,102). Although the nature of the data (case reports and small series) makes it hard to draw conclusions, it is interesting that withdrawal from SSRIs is associated with more cardiac problems and abnormal crying and aberrant stool than withdrawal from other agents. At the present time, only one case report has described the use of phenelzine (MAO inhibitor) during pregnancy, but no abnormalities were observed in the neonate (103). Specific findings for each TCA are given below.

Desmethylimipramine and Imipramine

A case report describing neonatal withdrawal from antenatal desmethylimipramine exposure described breathlessness, tachypnea, tachycardia, and cyanosis (104). Symptoms related to withdrawal from imipramine include irritability, weight loss, breathlessness, cyanosis, tachypnea, and profuse sweating (104,105). One neonate who was exposed to imipramine required hospitalization for 30 days, but was discharged in good health (105).

Nortriptyline

Symptoms of neonatal withdrawal from nortriptyline have included respiratory distress, cyanosis, hyperhydrosis, lethargy, poor suck reflex, and tachycardia (105–107). Urinary retention has also been described, but may have been due to nortriptyline toxicity and not withdrawal; regardless, it resolved within 40 hours after delivery (105,107).

Neonatal Symptoms After Maternal SSRI Exposure

The neonatal SSRI withdrawal syndrome has been described by Moses-Kolko (102) and appears to be similar to the TCA withdrawal syndrome in adults described earlier by Dilsaver (100). Often the term “poor neonatal adaptation” (PNA) has been used to describe these symptoms, which include convulsions, jitteriness, poor muscle tone, weak or absent cry, respiratory distress (within 3 days after birth), hypoglycemia, low Apgar score, and seizures (54,108). Other symptoms of in utero exposure to SSRIs include increased motor activity, fewer different behavioral states, lower neonatal platelet serotonin levels, and deviant neonatal sleep patterns (109,110). The timing and intensity of neonatal SSRI discontinuation signs appear to be related to dose and duration of treatment, enzymatic activity levels of serotonin...
synthesis and metabolism, and the availability of serotonin precursors (90).

There are at least 3 possible mechanisms explaining SSRI withdrawal. These include: 1) a decrease in available synaptic serotonin in the face of downregulated serotonin receptors, 2) the secondary effects of other neurotransmitters (e.g., dopamine) or biological or cognitive sensitivity in individual pa-

### TABLE 1
Symptoms of the neonatal antidepressant syndrome, specified for SSRI and TCA

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
<th>SSRI</th>
<th>TCA</th>
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<tbody>
<tr>
<td>Sleep/energy</td>
<td>Somnolence</td>
<td>Sertraline (148)</td>
<td>Clomipramine (149)</td>
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<tr>
<td>Central nervous system</td>
<td>Irritability</td>
<td>Fluoxetine (44,150–152)</td>
<td>Clomipramine (93)</td>
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<td></td>
<td></td>
<td>Paroxetine (89,150,153,154)</td>
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<td></td>
<td></td>
<td>Citalopram (89,150,153,154)</td>
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<td></td>
<td>Convulsions</td>
<td>Fluoxetine (68,120,152,154)</td>
<td>Clomipramine (93,93,149,157–159)</td>
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<td></td>
<td></td>
<td>Paroxetine (155,156)</td>
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<td></td>
<td>Abnormal cry patterns</td>
<td>Fluoxetine (68,44)</td>
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<td></td>
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<td>Sertraline (148)</td>
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<td></td>
<td></td>
<td>Paroxetine (44,128,153,154)</td>
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<td>Citalopram (44,153)</td>
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<td>Gastrointestinal</td>
<td>Aberrant stool</td>
<td>Fluoxetine (160)</td>
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<td>Paroxetine (161)</td>
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<td></td>
<td>Poor suck necessitating tube feeding</td>
<td>Fluoxetine (68,150,153)</td>
<td>Clomipramine (93,162,163)</td>
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<td></td>
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<td>Sertraline (148)</td>
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<td>Paroxetine (150,154,156)</td>
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<td>Motor</td>
<td>Agitation</td>
<td>Fluoxetine (44,68,150,152,154,160,164)</td>
<td>Clomipramine (93,149,158,163,166)</td>
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<td>Paroxetine (127,129,150,156,165)</td>
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<td>Citalopram (154)</td>
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<td></td>
<td>Tremors, jitteriness, shivering</td>
<td>Fluoxetine (44,152)</td>
<td>Clomipramine (158,159,162,163,167)</td>
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<td>Paroxetine (127,154,161,165)</td>
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<td></td>
<td>Decreased tone</td>
<td>Fluoxetine (68,89,121)</td>
<td>Clomipramine (159,162,163,167)</td>
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<td>Citalopram (89,153)</td>
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<td>Increased tone rigidity</td>
<td>Fluoxetine (44,120,150,160,164)</td>
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<td>Paroxetine (44,112,127,129,153,154, 156,165)</td>
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<td>Apathy</td>
<td>Fluoxetine (44,68,150,160)</td>
<td>Clomipramine (162)</td>
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<td>Paroxetine (128,150,153)</td>
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<td>Somatic</td>
<td>Temperature instability</td>
<td>Paroxetine (156)</td>
<td>Clomipramine (162,166,167)</td>
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<td>Hypoglycemia</td>
<td>Fluoxetine (68,160)</td>
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<td>Paroxetine (128,166)</td>
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<td>Respiratory/cardiovascular</td>
<td>Tachypnea</td>
<td>Fluoxetine (120,160)</td>
<td>Clomipramine (162)</td>
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<td>Dyspnea</td>
<td>Fluoxetine (121)</td>
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<td>Paroxetine (155)</td>
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<td></td>
<td>Respiratory distress</td>
<td>Fluoxetine (68,120,121,160)</td>
<td>Clomipramine (93,159,162,163,167)</td>
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<td>Sertraline (89)</td>
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<td>Paroxetine (168)</td>
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<td>Arrhythmias</td>
<td>Fluoxetine (169,170)</td>
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<td>Tachycardia</td>
<td>Fluoxetine (152)</td>
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<td>Unstable blood pressure</td>
<td>Fluoxetine (89)</td>
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<td>Bradycardia</td>
<td>Paroxetine (155,156)</td>
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<td></td>
<td>Cyanosis</td>
<td>Fluoxetine (44,89)</td>
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<td>Preterm delivery</td>
<td>Fluoxetine (154)</td>
<td>Clomipramine (93,162,167)</td>
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<td>Sertraline (121,153)</td>
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<td>Paroxetine (89,150,153)</td>
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tients, or 3) cholinergic rebound (seen in withdrawal from paroxetine), comparable to the postulated mechanism of symptoms of withdrawal from TCA (111). It is hypothesized that the frequency of the SSRI withdrawal syndrome is determined by antagonist potency at the serotonin reuptake site (111).

Several clinical studies indicate the relative frequency of neonatal withdrawal symptoms. Oberlander et al prospectively studied 46 women taking SSRIs over a 4-year period and found that 30% of the exposed neonates (14 of 46) experienced perinatal complications, such as transient respiratory distress and cardiac arrhythmias, which required continued hospital admission for observation, compared to 9% (2 of 23) of an unexposed group (44). Another study by the same group that included nearly 16,000 pregnancies found that 13.9% of SSRI exposed neonates experienced respiratory distress compared to only 7.8% of nonexposed neonates, as well as a higher incidence of feeding problems and jaundice (89).

Laine et al reported that neonates who were prenatally exposed to SSRIs had a 4-fold higher serotonergic symptom score than unexposed neonates (121 vs. 30), of which the most prominent symptoms were tremor, restlessness, and rigidity (112). These results suggested that SSRI withdrawal symptoms may reflect serotonin overstimulation or toxicity rather than withdrawal (112–114).

An overview of all case reports, cohort studies, unpublished FDA databases, and case series describing SSRI withdrawal symptoms was recently presented by Moses-Kolko et al (102). In 2005, Sanz et al published the results of an analysis of the WHO database of adverse drug reactions regarding the neonatal effects of withdrawal from prenatal SSRI exposure (115). Although it is difficult to compare these 2 reports because of differences in datasets and reporting systems, these data indicate an overall risk ratio of 3 (95% CI, 2.0–4.4) for relatively mild and transient neonatal SSRI withdrawal symptoms (CNS, motor, respiratory, and gastrointestinal symptoms) (102). The Sanz study, which included data from 102 cases, concluded that prenatal exposures to paroxetine and fluoxetine were most likely to result in signs of neonatal withdrawal such as convulsions. An accompanying editorial comment by Ruchkin suggested that a higher threshold be used for prescribing SSRIs during pregnancy (116). This warning indicated concern not only about neonatal withdrawal symptoms, but also referred to studies reporting longer-lasting effects, such as an attenuated pain response or changes in physiological reactivity and behavioral activations. However, other studies, such as those of Nulman and Gentile, have found that prenatal SSRI exposure has no long-term effects on neurodevelopment (41,117,118). Of all SSRIs, paroxetine appears to be the drug with the highest risk of causing neonatal withdrawal, although this finding is hard to interpret because paroxetine is the most widely prescribed SSRI. Other SSRIs associated with newborn withdrawal include citalopram, fluoxetine, and venlafaxine.

The symptoms of withdrawal from 8 specific SSRI antidepressants are listed below.

**Fluoxetine**

Case reports have described neonatal problems associated with prenatal fluoxetine exposure, including abnormal white blood cell counts and reduced pain response (119), erythematous rash and petechiae (120), neonatal encephalopathy (121), hypertonia, restlessness, and jitteriness (122). However, there have also been reports documenting no signs of neonatal withdrawal or any associated morbidities after prenatal fluoxetine exposure, possibly because these studies controlled for confounding factors. For example, Suri et al (123) presented a study of 62 patients in which women with a history of smoking, marijuana use, prenatal stress, or anxiety were excluded, because these factors have been independently associated with low birth weight, decreased gestational age, and risk of preterm birth (124–126). They found that obstetrical complications and abnormal pregnancy outcomes were not more frequent after prenatal exposure to fluoxetine.

**Paroxetine**

Reported neonatal problems associated with in utero exposure to paroxetine include elevated creatinine kinase levels, respiratory distress, convulsions, jitteriness and hyperreflexia (127), reduced pain response (128), hypertonia, irritability, feeding problems, myoclonic activity, and hypothermia (122). Profuse neonatal salivation has also been reported, but the mother was also taking olanzapine (129). Although there is one case report of a neonate prenatally exposed to paroxetine who suffered a severe intraventricular hemorrhage (130), other reports have failed to demonstrate abnormal platelet counts in exposed neonates (130).

**Citalopram**

In a pharmacokinetic study of maternal citalopram therapy during pregnancy, delivery, and lactation in...
11 women, no neonatal problems were reported (131). Franssen et al described a case of severe respiratory distress, sleep disorder, hypotonia, and hypertonia in a neonate exposed to citalopram prenatally (66). Sivojelezova et al reported that 20 of 63 fetuses exposed to citalopram in utero had neonatal problems, including pneumothorax (n = 2), fetal distress (n = 10), decreased heart rate (n = 3), heart rate variability (n = 1), breathing difficulties (n = 2), and meconium staining/aspiration (n = 10) (132). In the same study, exposed neonates were 4 times more likely to require intensive care than infants who had not been exposed.

**Bupropion**

In a study of in 136 women who took buproprion during pregnancy, there were no differences in exposed versus nonexposed neonates, although significantly more spontaneous abortions were reported by the exposed group (P = 0.009) (133). According to the authors, the observed rate of spontaneous abortion was comparable to that associated with exposure to other antidepressants (133).

**Fluvoxamine**

Evaluation in 92 pregnant women revealed no increased risk of adverse neonatal events (134).

**Venlafaxine**

No differences in maternal or neonatal outcomes were observed in women who used venlafaxine parentally compared to a matched control group of non-SSRI users (47). A case report of de Moor et al described a neonate with hypoglycemia, tremor, jitteriness, and feeding problems after prenatal venlafaxine exposure. However, these symptoms disappeared within 8 days (135). Data kept on file by the manufacturer of venlafaxine (Wyeth Pharmaceuticals, The Netherlands) indicate that antenatally exposed infants have displayed respiratory distress, feeding difficulties, cyanosis, apnea, seizures, temperature instability, vomiting, hypotonia, hyperreflexia, irritability, and constant crying (136).

**Mirtazapine**

One case report described a neonate with persistent fetal circulation and pulmonary hypertension after prenatal exposure to mirtazapine (137).

**Sertraline**

Enhanced startle response and reduced pain response (54), an exaggerated MORO-response (138), and a case of nystagmus (139) have been reported after prenatal exposure to sertraline. Bot et al described a prenatal exposed neonate with myoclonic activity, lip smacking, irritability, jitteriness, opisthotonus, and EEG abnormalities (122).

**MEASUREMENT OF THE NEONATAL ANTIDEPRESSANT WITHDRAWAL SYNDROME**

One problem with the published literature is that there are currently no objective diagnostic criteria or a validated scoring system for identifying and quantifying signs and symptoms of neonatal withdrawal from prenatal exposure to antidepressants. Another problem is that neonatal symptoms may not develop until after the first week of life, when the infant has been discharged from the hospital. Although monitoring for 1 week after birth has been recommended (85), this is currently not part of standard neonatal care. With no alternatives, the Committee on Drugs of the American Academy of Pediatrics has stated that neonatal withdrawal symptoms related to in utero exposure to clomipramine may be compared to symptoms associated with withdrawal from exposure to maternal narcotics (140). Several existing scoring systems are described below, but none has been validated for the evaluation of antidepressant withdrawal.

In the early 1970s, the Finnegan score was developed to evaluate neonates who had been parentally exposed to opiates and cocaine (141). If the score was higher than a specified threshold, treatment according to a standard protocol, which frequently included phenobarbital therapy, was recommended. The Finnegan score has been widely used, but has been validated only for opiates. The neonatal intensive care unit network neurobehavioral scale (the NNNS scale) was developed for the Maternal Lifestyle Study (142–144). It assesses and scores the full range of infant neurobehavioral performance, including infant stress, abstinence and withdrawal, and neurological functioning. The scale has been validated for both low- and high-risk infants who have been stabilized after withdrawal from prenatal exposure to opiates, cocaine, and nicotine (143). The neonatal evaluation required for the NNNS scale is labor intensive, and training is required for valid testing. Other scoring systems, such as the Neonatal Drug Withdrawal Scoring System (NDWSS), the
Neonatal Narcotic Withdrawal Index (NNWI), and the Neonatal Withdrawal Inventory, were developed for other pharmacologic classes of drugs and/or have not been empirically validated (145). All of these scoring systems were developed for drugs of abuse. Serious methodological problems affecting the score’s validity may rise if these scoring systems are used to assess antidepressant drug withdrawal (146).

Laine et al (112) used a nonvalidated scoring system (the serotonergic symptom score), based on the definition of the serotonin syndrome (147). The evaluation includes assessment of blood pressure, heart rate, and body temperature, and examination for myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination, and rigidity (112). Compared to the other scoring systems described above, this method seems more suitable for evaluating neonatal withdrawal from serotonergic/antidepressant drugs. However, this method has not been validated (yet). As these data make obvious, a scoring system specifically for neonates with in utero exposure to maternal antidepressants is needed and is being developed (112).

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