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Elizabeth Kramer
Ohio Northern University

Maria Patnella
Ohio Northern University

Rachel Bulko
Ohio Northern University

Allie Harrison
Ohio Northern University

Hannah Lamb
Ohio Northern University

See next page for additional authors

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Elizabeth Kramer, Maria Patnella, Rachel Bulko, Allie Harrison, Hannah Lamb, Manoranjan D'Souza M.D., Ph.D., assistant professor of pharmacology

Abstract

Neonatal abstinence syndrome (NAS) is a concern for infants born to mothers receiving treatment with a selective serotonin reuptake inhibitor (SSRI) throughout the pregnancy. The risk of NAS associated with SSRI use during pregnancy varies with the specific SSRI that is used by the patient during pregnancy. Common symptoms of NAS include premature delivery, gastrointestinal disturbances, irritability, low birth weight, short length and lack of response to various stimuli. Neonates that present with these symptoms can be scored using either the Finnegan or Lipsitz scoring tools. Neonates experiencing NAS can be calmed or treated using nonpharmacologic methods such as swaddling, rocking, exposure to calming scents, soft light and soothing music. Drugs such as morphine or phenobarbital may be used as needed. Monitoring children born with NAS is important as it is possible that these children may express long-term behavioral, social and intellectual developmental problems. While there are many health care professionals involved in the care of NAS, pharmacists can play a large role in both preventing and treating NAS. Importantly, pharmacists can work with pregnant mothers to help prevent NAS by recommending SSRIs that have less risk of causing high serotonin levels in neonates. Pharmacists can also help by offering nonpharmacologic treatment options, when appropriate, or by developing protocols for the treatment of NAS.

Key Terms

Depression; Neonatal Abstinence Syndrome; Therapeutics; Pregnancy; Antidepressive Agents; Breastfeeding; Mothers; Serotonin Uptake Inhibitors; Citalopram; Fluoxetine; Sertraline; Paroxetine; Nortriptyline

Introduction

Depression is a major concern for the overall population, including pregnant women, with about 7 to 19 percent of women experiencing depression at some point during their pregnancies.[1] Depression is associated with low levels of serotonin, and selective serotonin reuptake inhibitors (SSRIs), which increase levels of serotonin in the brain, form the mainstay of treatment in all patients suffering from depression, including pregnant women.[2] Most SSRIs have a pregnancy Category C classification which means that no controlled studies have been conducted in pregnant women, but adverse effects have been found in studies with animals, or no studies are given with either animals or women.[3] It is concluded that Category C medications can be given to the patient if the evaluated benefits of the medication outweigh the risks. Among the SSRIs, paroxetine is an exception as it has a Category D classification which means that studies have shown harm to a human fetus, but the drug can be used if the benefits are considerably greater than the risk. Some reports suggest that continuation of SSRI use during pregnancy affects the growth of the infant before and after birth. Furthermore, if a woman continues to use SSRIs in pregnancy there has been a link to neonatal abstinence syndrome (NAS) and other birth abnormalities.[2] However, discontinuation of therapy is likely to worsen symptoms of depression in the mother during pregnancy.[4] Therefore, carefully managing depression during pregnancy is warranted to avoid adverse outcomes for both the developing fetus and the mother.

Prevalence

It is estimated about 30 percent of newborns experience NAS after maternal-SSRI use.[5] Infants were more likely to experience NAS with SSRI use during the third trimester.[6] Particularly, paroxetine and fluoxetine have caused the most reported cases of NAS.[7] Sertraline and citalopram have also resulted in NAS.[1]

Symptoms

The signs and symptoms most commonly associated with NAS include premature delivery, low birth weight and short length of neonates at the time of birth. Symptoms of NAS may also include gastrointestinal (GI) disturbances, restlessness, irritability, tremors and respiratory distress.[8] Seizures, which are generally associated with opiate withdrawal, have also been reported in severe cases of NAS.

Infants whose mothers took SSRIs during the third trimester of pregnancy may exhibit reactional delays when exposed to positive and negative stimuli. Oberlander et al. reported a decreased rate of facial reactions to pain in infants exposed to SSRIs in utero.[9] The study further reported delayed responses including kicks, toe-curling and swatting away irritants as a result of SSRI exposure in utero. However, it must be known that motor skills in infants are not entirely coordinated at this stage of development.

In a study conducted by Sie et al., neonates reportedly expressed symptoms of NAS within 48 hours of birth.[10] Infants exposed to SSRIs in utero did not cry as loudly compared to infants who were never exposed to SSRIs in utero (control group). These unresponsive infants, who either cried sparingly or not at all, showed higher deviation from the control group symptomatically. The authors concluded that these symptomatic differences were most likely due to developmental alterations caused by in utero SSRI exposure.

Stephannson et al. conducted a retrospective cohort study in Nordic countries looking at the use of SSRIs in pregnancy and

the birth outcome.[1] Not only did it look at neonatal mortality and stillbirths, but it also included data for postneonatal death which was defined as 28 to 364 days after birth. The study reported that citalopram, fluoxetine and sertraline were the most commonly used SSRIs, respectively. Importantly, the study did not find a difference in infant mortality rates, stillbirths or postneonatal death between mothers who had taken SSRIs during pregnancy compared to those who did not.

Management of Symptoms

The symptoms of SSRI-induced NAS usually resolve on their own.[11] However in some cases, active management is required. In such cases, treatment of NAS must begin within two hours of birth, as untreated NAS symptoms can cause irreversible physical and emotional damage to newborns.[12] The Finnegan Scoring Tool (Table 1) is a complex test utilized by health care professionals to determine the severity of withdrawal symptoms in neonates and to ensure that the best possible care is provided to these infants. Every four hours, the newborn suffering from NAS must be reassessed in order to determine the next appropriate steps in care, with three consecutive scores above eight indicating a need for pharmacologic therapy. Morphine (0.05 mg/kg) is utilized as a mainstay of treatment for withdrawal symptoms if the infant has three initial Finnegan scores that create a sum higher than 24. If the newborn suffers from polysubstance dependency, which indicates potential illicit drug use or polypharmacy in the mother, phenobarbital is utilized as a first-line therapy following morphine administration. Phenobarbital is not coadministered with morphine, but, instead, replaces morphine therapy if the Finnegan scores do not stabilize within two rounds of treatment.

The Lipsitz Scoring Tool (Table 1), an alternative test to the Finnegan Scoring Tool, simplifies the symptom assessment process and facilitates routine transfers of infants to different levels of care as needed.[13] This method requires a nurse to check the infant and assign a score every three hours within the first four days after birth. Parameters to be scored include timing of reflexes, irritability, bowel movements, respiratory distress and presence of vomitus. If a Lipsitz score of at least four is obtained, the infant must receive care and more intensive treatment. Table 1 compares the symptoms assessed in the Finnegan Scoring Tool and the Lipsitz Scoring Tool.

Several nonpharmacologic treatment methods can also help in the management of NAS symptoms in neonates. These treatments can be used independently or can help aid pharmacologic treatment. The nonpharmacologic treatment includes swaddling, rocking, exposure to calming scents, soft light and soothing music. These interventions possibly help by stimulating release of endogenous serotonin levels in infants suffering from NAS.[12] Additionally, administering maternal breast milk to the child whenever possible, preferably milk that does not contain traces of SSRIs or other addictive substances, aids in the recovery of serotonin pathways and stimulates natural growth and development of the infant. Alternating between bottle-feeding and use of a pacifier prevents emesis and occupies the infant, lessening bouts of harsh crying and calming the child during fits of withdrawal.

Long-Term Effects on Neonates

In addition to developing NAS, in utero exposure to SSRIs can have long-term consequences. Oberlander et al. compared neonatal exposure in the second or third trimester with either a single agent SSRI or paroxetine and clonazepam with a nonexposed control group.[5] In addition, they also grouped infants based on exposure and symptoms suggesting poor neonatal adaptation such as jitteriness, respiratory difficulty, hypoglycemia, lethargy and weak or absent cry. Regardless of exposure or neonatal symptoms, they did not find a difference in the mental development index (MDI) or psychomotor development index (PDI) from the Bayley Scales of Infant Development (BSID) at 2 months and 8 months of age.

Additionally, Nulman et al. prospectively compared child development between three groups of mother-child pairs, one that took fluoxetine throughout gestation, one that took tricyclic antidepressants, and one that did not have clinical depression and therefore not taking antidepressants.[14] Children were evaluated between the ages of 15 and 71 months. There were no differences found in cognitive and language outcomes, or in temperament between the groups.

A second study by Nulman et al. compared intelligence in four groups of children.[15] Group 1 was born to women that took venlafaxine, group 2 took SSRIs, group 3 was made up of women who had depression but took no medications and group 4 consisted of children born to healthy women that were not depressed. They completed a variety of age appropriate assessments between the ages of 3 and 6 years. In the groups exposed to antidepressants, 11.3 percent showed signs of NAS at birth. These children did not show any differences in cognitive function compared to children who did not show signs of NAS, however some did have differences in behavioral assessments. Children in groups 1 and 2 did not show any clinical significant differences compared to group 3 in any of the intelligence quotient (IQ) tests for cognition. There were differences in IQ and in the behavioral assessments for antidepressant exposed children versus children who were not exposed. However, the authors concluded that the cognition difference may have been accounted for by differences in the mother's IQ.

Since having maternal depression may have adverse neonatal outcomes, Casper et al. compared women who were diagnosed with major depressive disorder (MDD) that remained medication free versus women diagnosed with MDD that used SSRIs during pregnancy.[16] Children had follow-up after six to 40 months. Using BSID II, no significant differences were found in the MDI between the two groups. They did, however, find a slight difference on the PDI and the Behavioral Rating Scale (BRS). The group that was exposed to SSRIs in utero had lower scores than those that were not exposed to SSRIs. Casper et al. concluded that although there were differences in the PDI and BRS between the exposed

Table 1. Finnegan versus Lipsitz Scoring Tools[12,13]

Metabolic/Vasomotor/Respiratory Disturbances			
Finnegan	***Score***	***Lipsitz***	***Score***
High Pitched Cry Continuous High-Pitched Crying	2 3	Irritability or excessive crying	None (0) Minimal (1) Moderate (2) Marked or continuous (3)
Sleeps <1 hr after feeding Sleeps <2 hrs after feeding Sleeps <3 hrs after feeding	3 2 1		
Hyperactive Moro reflex	2	Hyperactive Moro reflex	Normal (0) Increased (1) Markedly increased (2)
Mild Tremors Moderate/severe tremors	1 2	Tremors	None (0) Minimal (1) Moderate (2) Marked increase or continuous (3)
Increased Muscle Tone	2	Muscle Tone	Normal (0) Increased (1) Rigidity (2)
Excoriation	1	Skin Abrasions	None (0) Redness of knees and elbows (1) Breaking of skin (2)
Myoclonic jerks	3		
Generalized convulsions	3		
Central Nervous System Disturbances			
Finnegan	***Score***	***Lipsitz***	***Score***
Sweating	1		
Fever <37.2-38 degrees Celsius Fever >38.4 degrees Celsius	1 2	Fever	No (0) Yes (1)
Frequent Yawning	1	Repetitive Yawning	No (0) Yes (1)
Mottling	1		
Nasal stuffiness	1		
Sneezing >3-4 times	1	Repetitive Sneezing	No (0) Yes (1)
Nasal Flaring	2		
Respiratory Rate > 60/min Respiratory Rate >60/min with retractions	1 2	Respiratory Rate	<55 (0) 55-75 (1) 76-95 (2)
Gastrointestinal Disturbances			
Finnegan	***Score***	***Lipsitz***	***Score***
Excessive Suckling	1		
Poor Feeding	2		
Regurgitation Projectile Vomiting	2 3	Vomiting	No (0) Yes (1)
Loose Stools Watery Stools	2 3	Stools	Normal (0) Explosive, normal frequency (1) Explosive, >8/day (2)

and nonexposed group, these differences may not be clinically significant.

A more recent study conducted by Klinger et al. also evaluated long-term outcomes following SSRI-induced NAS.[17] Two groups of children were assessed, one that had NAS symptoms as evidenced by a Finnegan score of greater than four, and another group that did not have withdrawal symptoms (Finnegan score 0-3). Developmental pediatricians evaluated children at around 3 years of age using the Denver Developmental Screening Test II (DDST-II), which evaluates four areas including gross motor, fine motor-adaptive, language and personal-social functioning. They did not find a difference in the overall scores on the DDST-II. However, in the group that had NAS, children were more likely to have an abnormal result on the social functioning component. There were no significant differences found in the intelligence tests. In summary, the combination of studies described above provides some evidence that SSRIs do not have long-term effects on neurocognitive development but may have long-term behavioral effects.

Role of the Pharmacist: Recognizing at-Risk Pregnant Women and Combating the Problem

It is important for the pharmacist to recognize NAS associated with SSRI use during pregnancy. The pharmacist may also play an important role in the inpatient setting by developing protocols for NAS induced by other drugs such as opiates, benzodiazepines and other medications. Importantly, pharmacists can contribute significantly in managing depression during pregnancy.

Pregnant women struggling with depression can be divided into two categories; those who may need to be started on antidepressants while pregnant and those who are already being treated who will continue their therapy while pregnant.[18] In either category, a woman should consult a health care professional to decide whether to start, change or continue her therapy regimen while pregnant. This should include a discussion of both pharmacologic and nonpharmacologic treatments as leaving depression untreated could have serious health consequences for both the mother and baby. Counseling pregnant women with depression about consequences of antidepressant use during pregnancy and the effects on the developing infant is an important role for pharmacists in both outpatient and inpatient settings. Doctors, OBGYNs, psychiatrists, pharmacists and all other personal health care providers are important in the decision-making process.[18] Further, pharmacists can look at the diagnosis, confirm the severity of the depression and identify comorbidities that may complicate treatment. Discussing a treatment plan with the patient can be complex, as the decision to stop or change medications can come with a risk of relapse, and generally should not be changed if a patient is well-controlled on a medication.

Pharmacists can discuss some nonpharmacologic treatment options that may be useful in patients with mild-moderate depression to use as substitutes to antidepressant medications if it is determined that tapering off SSRIs is safe by the pharmacist and other health care professionals. Two of these alternative treatments are acupuncture and psychotherapy. In studies comparing acupuncture and psychotherapy to SSRIs during pregnancy, treatment for both was found to be comparable to SSRIs and well-tolerated, with mild to no side effects reported.[19,20] It was found that acupuncture yielded response rates comparable to the rates observed in standard treatments for depression and was associated with little to few side effects. However, in the acupuncture study, 90 percent power was not met and included only nine people in the analysis that did not receive the treatment at all.[19] In the psychotherapy study, although power was not calculated and there was a small sample size, recovery criteria was met in 60 percent of women treated and there was a significant correlation between maternal mood and mother-infant interaction.[20] By recognizing these safer alternatives to pharmacologic therapy, the pharmacist can recommend these options to patients and, in consultation with the physician or psychiatrist, undertake a bigger role in managing patients' depression.

If nonpharmacologic treatment is not a viable option, as in severe cases of depression, SSRIs can be used under the direction and supervision of health care providers. However, SSRI choice and timing are important considerations when evaluating therapy options. A study by Chambers et al. looked at birth outcomes in pregnant women taking fluoxetine.[21] Specifically, adjusted relative risks were calculated in those who were exposed to fluoxetine in the third trimester compared to those who had been exposed to it earlier in the pregnancy. The study reported that women had a much greater risk for neonatal problems from later exposure to antidepressants. The relative risk was 4.8 for prematurity, 2.6 for admission to special care nurseries and 8.7 for NAS. In summary, the study concluded that women taking fluoxetine in the third trimester were at increased risk for SSRI-induced NAS.

As for the other SSRIs, a placental passage study was done at UCLA Pregnancy and Postpartum Mood Disorders Program comparing SSRI levels in the mother to the levels in the umbilical cord.[22] The women were receiving one of four SSRIs; citalopram, paroxetine, sertraline or fluoxetine. Each woman had been taking the medications for at least five half-lives before delivery. A blood sample was taken from the umbilical vein before delivery of the placenta. This study found that the umbilical cord serum concentrations were lower than the maternal concentrations. The ratio of cord to maternal concentrations of antidepressants ranged from 0.29 to 0.89. Citalopram produced the highest ratio, followed by fluoxetine, paroxetine and then sertraline. Sertraline had a significantly lower ratio than the rest, which suggests that sertraline might be the best agent in treating depression in pregnancy.

Many mothers on antidepressant therapy may want to start breastfeeding, so it is important to also take this into consideration. In a pooled analysis of 67 appropriate studies on

antidepressant levels in lactating mothers, breast milk and infants; nortriptyline, paroxetine and sertraline produced undetectable levels in the infants, making them safest to use while breastfeeding.[23] Fluoxetine produced the highest proportion (22 percent) of infant levels that were elevated above 10 percent of the average maternal level with citalopram only slightly lower (17 percent). Further research is needed on this topic. However, it was noted that based on current evidence, breastfeeding women may reasonably choose to continue to use antidepressants. Although it appears that sertraline may be the safest option in both populations of women, choosing an antidepressant for pregnant and breastfeeding mothers is something that should always be discussed with a doctor and other health care professionals.

Conclusion

With increasing evidence becoming available that SSRI use during pregnancy may cause NAS, it is becoming more important that health care professionals are aware of the potential short-term and long-term effects of SSRI use during pregnancy and how they will affect a newborn. Health care professionals must also be prepared to weigh the risks versus benefits of treating a mother with SSRIs. In addition, pharmacists play a unique role in recognizing the potential for NAS and educating other health care professionals to make them aware of the risk. Then, if needed, the team is prepared to handle the symptoms. The health care team, particularly pharmacists, can provide both pharmacologic and nonpharmacologic therapies to expecting mothers needing antidepressant treatment as well as treat infants that are experiencing NAS.

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