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UPDATES IN PSYCHOPHARMACOLOGY

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Neonatal Risks from SSRI Exposure in Late Term Pregnancy

The lifetime risk of depression in women is 10-25%, with the prevalence peaking during childbearing years.[1] Untreated depression in pregnant women carries significant risk for both the mother and the fetus. Depression increases the risk of self-injurious or suicidal behaviors and it may contribute to inadequate self-care and poor compliance with prenatal care. Some studies have also found an association between maternal depression and factors that predict poor neonatal outcome, including preterm birth, lower birth weight, smaller head circumference, and lower APGAR scores.[2] Clinicians face significant challenges when making recommendations for the treatment of depression in pregnant women. Although selective serotonin reuptake inhibitors (SSRIs) have not been linked to congenital malformations, they have been linked to a number of other negative effects including serotonergic hyperstimulation (jitteriness, tachypnea, hypertonicity, temperature instability, and diarrhea), prematurity, respiratory distress and neonatal abstinence syndrome (NAS).[3] Two studies published in February of this year examined the risks of SSRI exposure in newborns.[4,5]

Neonatal Abstinence Syndrome (NAS)

Levinson-Castiel and colleagues examined the occurrence of NAS in neonates exposed to SSRIs compared to those who were not exposed in utero.[4] Clinical features of NAS include irritability, jitteriness, constant crying, shivering, increased tonus, and eating and feeding difficulties.[3] In this cohort study, symptoms of NAS were assessed in 60 full term neonates with prolonged in utero exposure to SSRIs (including paroxetine, fluoxetine, citalopram, sertraline and the serotonin norepinephrine reuptake inhibitor venlafaxine) and compared to 60 neonates with no exposure. NAS symptoms were evaluated with a Finnegan score, an objective scale used to monitor onset, progression and improvement of NAS symptoms in passively exposed neonates. Higher scores (>8) represent more severe NAS with a consequent risk of increased morbidity. Scores were assessed 2 hours after birth and every 8 hours after meals for 48 hours (longer if the score had not normalized in 48 hours).

Symptoms of NAS were present in 18 of the 60 SSRI-exposed infants (30%) compared to none of the 60 control infants ($p<0.001$). Eight (13%) of the SSRI-exposed infants had severe NAS (Finnegan score >8) and 10 (17%) had mild NAS (score 4-7). None of the infants had a score of ≥8 in 3 consecutive measurements which would have indicated a need for treatment. Maximum mean daily symptoms occurred within the first 48 hours of life, although maximum individual Finnegan scores occurred as long as 4 days after birth. The most common symptoms of NAS observed in this study were tremor, gastrointestinal or sleep disturbance, hypertonicity and high-pitched cry.

Due to the small sample size within each SSRI subgroup, the study was not able to determine which SSRI was the most likely to cause NAS symptoms. The majority of neonates in the experimental group (37/60) were exposed to paroxetine. Of these, 16% (n=6) had severe NAS symptoms. The paroxetine group was the only subgroup large enough to identify a dose-response effect. The maternal mean drug dose for neonates with no symptoms was 19mg, 23mg for those with mild symptoms, and 27mg for those with severe symptoms.

The results of this study show that 30% of infants exposed to SSRIs in utero have symptoms of NAS, but not significant enough to require treatment. The risk and benefits of continuing SSRI treatment during pregnancy should be evaluated in every patient. Neonates with significant in utero exposure to SSRIs should be evaluated for symptoms of NAS through at least the first 48 hours of life.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

As a part of the Birth Defects Study (Slone Epidemiology Center), Chambers et al. conducted a study to determine if exposure to SSRIs during late pregnancy is associated with an increased risk of PPHN.[4] PPHN is associated with substantial morbidity and mortality and is estimated to occur in 1 or 2 infants per 1000 live births.[6,7] PPHN is characterized by postnatal persistence of elevated pulmonary vascular resistance, resulting in right-to-left shunting of blood through the patent ductus arteriosus and/or foramen ovale, diminished pulmonary blood flow, and profound hypoxemia. Infants with PPHN will require intubation and mechanical ventilation. Suggested maternal risk factors for PPHN include a lower educational level, fever, urinary tract infection, diabetes, cesarean section, antenatal use of nonsteroidal anti-inflammatory agents (NSAIDs), and possibly tobacco use.[5]

In this case-control study, 377 infants with PPHN were matched to 836 controls. Maternal factors significantly associated with PPHN included lower educational level, black or Asian race, higher pre-pregnancy body mass index, and diabetes mellitus. Although the majority of infants were not exposed to an antidepressant during pregnancy, the authors found a significant association between PPHN and late exposure to SSRIs. Even after adjustment for other maternal risk factors (diabetes, race or ethnic group, and body mass index), the adjusted odds ratio was 6.1 (95 percent confidence interval, 2.2 to 16.8). As a possible mechanism for this association, the authors suggest that the accumulation of serotonin in the fetal lung might lead to the proliferation of smooth muscle cells. In addition, they note that SSRIs have an inhibitory effect on the synthesis of nitric oxide, a vasodilator that has a role in the regulation of vascular tone and reactivity.

It should be noted that the vague PPHN diagnostic criteria used in this study may have led to the inclusion of patients with diagnoses other than PPHN such as respiratory distress syndrome, pneumonia, sepsis or asphyxia. In addition, the inclusion criteria didi not necessarily correlate with clinically significant PPHN. Despite the fact that this study was limited to a small number of neonates with late exposure to SSRIs (14 with PPHN and 6 controls), the relative risk for PPHN is worth considering in light of other maternal and neonatal risk factors when assessing the risks and benefits of continuing SSRIs in late term pregnancy.

Conclusion

The treatment of depression in pregnancy is challenging and is largely guided by practical experience rather than definitive data from published trials. Clinicians should work collaboratively with their patient to identify their past psychiatric history, their current symptoms, and their attitude toward the use of psychiatric medications during their pregnancy. The relative safety of the antidepressants should then be evaluated and discussed with the patient.

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Weight Gain from Orally Disintegrating Olanzapine Tablets

Olanzapine (*Zyprexa*) can cause clinically significant weight gain.[1,2] In a study conducted to assess the prevalence of weight gain with olanzapine, 27 patients with schizophrenia or schizoaffective disorder took olanzapine over a mean duration of 22 months. The mean weight gain over the study period was 9.2 kg or 20.28 pounds.[3]

However, a single study suggests that orally disintegrating olanzapine tablets (*Zyprexa Zydis*) may not cause as much weight gain as the original tablets.[4] This study was not randomized and it was open-label introducing the possibility for observational bias. In addition, its power was limited by the inclusion of only 18 patients (all adolescents). Nine of the adolescents remained on oral olanzapine therapy and nine were switched from oral olanzapine to the orally disintegrating tablet. The nine who were switched lost an average of 6.6 kg over 16 weeks. The authors, de Haan and colleagues, theorized that orally disintegrating olanzapine causes less weight gain than oral olanzapine due to subtle pharmacokinetic differences. The authors proposed that the orally disintegrating tablets have a shortened interaction time with serotonin (5HT-2) receptors in the pylorus, thereby preserving food saturation feedback mechanisms and decreasing food intake.[4] Gastric 5HT receptors are proposed to mediate feelings of satiety and fullness.

The proposed pharmacokinetic rationale of de Haan *et al*. for reduced weight gain with *Zyprexa Zydis*, *i.e.* a more rapid onset of absorption leading to reduced interaction with pyloric 5HT-2 receptors, is illogical. Manufacturer conducted pharmacokinetic studies demonstrate that both oral and orally disintegrating dosage forms are bioequivalent.[5] To have an effect on pyloric neurotransmitter receptors, olanzapine must reach the bloodstream. Once in the bloodstream, olanzapine (either dosage form) interacts with both peripheral and central receptor sites until it is eliminated (olanzapine has a 21 to 54 hour half-life). Daily medication administration will keep the drug's presence in the bloodstream constant. In addition, although the exact mechanisms for weight gain with olanzapine are unknown, interaction with peripheral serotonin receptors is not a complete explanation. Olanzapine-induced weight gain most likely involves a combination of receptors and mechanisms, including alterations in feedback circuits within the central nervous system that regulate leptin levels.[6] Without more comprehensive study, the observed decreases in weight gain with *Zyprexa Zydis* reported by de Haan *et al*. are best attributed to observational bias.

Weight gain associated with olanzapine presents a clinical challenge to patients and their prescribing providers. While weight gain has been associated with improved psychiatric outcome in patients taking olanzapine[7], it has also been associated with significant metabolic abnormalities and treatment discontinuation.[2] Switching from oral tablets to the orally disintegrating tablets has not been shown to alter olanzapine's effect on weight gain, just as it should not affect its clinical effectiveness. For patients who are able to swallow medications and who do not require direct observation during medication administration, the oral olanzapine tablets are less expensive. For every 50 patients who take the oral tablet instead of the orally disintegrating tablet, an average $19,800 can be avoided annually.

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Potential New Warnings for Stimulant Medications

Stimulant medications, including amphetamines (Adderall) and methylphenidate (Ritalin, Concerta) products are currently under review with the Food and Drug Administration (FDA). On February 9, 2006, the Drug Safety and Risk Management Advisory Group of the FDA recommended the addition of a black box warning to product labels that would describe their cardiovascular risks.

During their meeting, the committee heard testimony indicating that 2.5 million children are currently taking stimulants for attention deficit hyperactivity disorder (ADHD), including approximately 10 percent of all 10-year-old boys in the United States.[1] In addition, 1.5 million adults now take stimulants, with 10 percent of users older than 50 years of age. Stimulant medications are known to exert potent stimulant effects on the cardiovascular and central nervous system. Long-term elevation of heart rate and blood pressure can increase morbidity and mortality.[2] Data from the FDA's Adverse Event Reporting System (AERS) identifies cases of myocardial infarction, stroke, and sudden death in children and adults taking stimulants.[1] Although the committee recognized the benefits of stimulant medications, they advocated for the judicious use of these potent sympathomimetic agents.[2]

In a follow-up meeting, the FDA's Pediatric Advisory Committee was asked to review the same issue, as well as reports that psychosis or mania can occur in some juvenile patients at normal doses of ADHD drugs. The Committee felt that the cardiovascular events were not of a similar risk in children as adults, except for those with cardiovascular abnormalities.[3] The committee declined to endorse the black box warning for cardiac events and psychiatric events, including aggression and suicidality. Instead, they recommended that the warnings section of the product labels for all ADHD drugs (including atomoxetine) describe these risks.

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