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A Review of Antidepressants in Pregnancy

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Abstract

Depression is a mentally debilitating, psychiatric disease affecting a person's day to day life. There are many risk factors and biological, psychological, and environmental causes that can contribute to the development and progression of depression. Medication is commonly used in addition to or after nonpharmacological options. In the general population, because of patient variability choosing and dosing an antidepressant involves a lot of trial and error and risk analysis to balance efficacy and safety. In pregnant women, additional challenges complicate an already difficult situation including additional risk analysis considerations for a growing fetus. Limited research is available regarding antidepressant use in pregnancy, therefore many clinical decisions are based on discussions between the patient and provider. Choosing a medication, dosing, altered pharmacokinetics, and monitoring are all key aspects to consider in this vulnerable population. Sound clinical judgment specific to the patient is critical in order to balance depression treatment and maternal, as well as fetal, outcomes.

Depression is an illness that affects about 1 in 10 women in the United States.[1] Statisitics also reveal that about 1 in 8 women experience symptoms of postpartum depression.[1]

The umbrella term, 'depressive illness' can describe many types of depression an individual may experience. Major depression describes an illness where the person has depressive symptoms most of the time and it affects the person's activities of daily life in a negative way.[2] Major depressive disorder (MDD) is a chronic and recurrent illness that can stem from many factors and present at any stage in life.[3] MDD is a clinical diagnosis that uses a patient's physical and mental status, family and social history, and past medical history to come to a final diagnosis. [3]

Depressive illness can have many root causes such as environmental, psychological, and genetic.[2] Familial history, major life changes, and certain illnesses or medications are all risk factors for developing or increasing the intensity of a depressive illness.[2]

No two people are ever going to present with the exact same symptoms, so sometimes it is difficult to get a fast and accurate diagnosis, especially with the many types.[2] MDD is diagnosed using the DSM-5 criteria that include: [3]

1. Persistently low or depressed mood
2. Reduced ability to experience pleasure
3. Feelings of guilt or worthlessness
4. Lack of energy
5. Poor concentration
6. Appetite changes
7. Psychomotor retardation or agitation
8. Sleep disturbances
9. Suicidal thoughts

A person must have 5 or more of these symptoms, with one being depressed mood or lack of ability to feel pleasure that causes social or occupational issues. [3]

Other types of depression include persistent depressive disorder, disruptive mood dysregulation, premenstrual dysphoric disorder, substance induced depressive disorder, and unspecified depressive disorder. [3]

In general, antidepressants are medications given to patients with the goal of relieving symptoms of depression. [4] Many classes of antidepressants now exist and can be used for similar or different indications. These classes include, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and tricyclic antidepressants (TCAs).[4] Choosing an antidepressant for a patient is largely based on anticipated side effects, familial history of response, and patient preferences. For example, some antidepressants may be better for sleep disturbances, while other may affect an individual's weight or appetite.[4]

Antidepressants in Pregnancy

Pregnancy brings about a whole other set of challenges when it comes to managing healthcare conditions with medication. It is no longer just the mother's health that must be taken into consideration, but also the fetus.

Treatment for depression in pregnancy is even less clear due to lack of data and inherent variability in patient response. The pharmacokinetics of a pregnant individual also is different and affect the efficacy and safety of antidepressant therapy. Up front, it may seem like the safest option is to simply discontinue the antidepressant for the extent of the pregnancy, but that is easier said than done.

The American College of Obestrics and Gynecology (ACOG) recommends that depression treatment be individualized and decisions be made for each specific patient.[5] Overall, the goals of depression treatment are the delivery of a healthy baby, management of depression symptoms, and preventing patient harm to herself or the fetus.[5] Worsening depression during pregnancy without treatment also has a risk of harming mom and baby due to unhealthy eating habits, inconsistency with medical care, and may also increase risk of postpartum depression.[5] Four meta-analyses have shown no statistically significant increase in risk of major malformations following antidepressant use in the first trimester of pregnancy.[6-7] A fifth meta-analysis has shown an increased risk of cardiac malformations in infants exposed to paroxetine in the first trimester.[8]

It is very important that pregnant, or women trying to get pregnant, get in contact with their physician to discuss the risks and benefits of starting, continuing, switching, or stopping their antidepressant therapy prior to becoming pregnant.[9] The decision will highly depend on current and preexisting disease status, information and safety data available, and patient acuity.[9]

SSRIs

SSRIs are considered a first line pharmacotherapy choice for moderate to severe depression and known to be effective.[10] Commonly prescribed agents include citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft) because of their efficacy and general safety profile. [11] SSRIs are the most studied class of antidepressants in pregnancy.[11] Historical data suggested SSRIs may be safe in pregnancy with no known risks, however more recent data has called this into question. There is growing evidence that SSRIs can lead to birth defects, persistent pulmonary hypertension of the newborn, and neonatal behavioral syndrome.[12-13] Paroxetine exposure in pregnancy has specifically been tied to cardiac malformations, such as atrial and ventricular septal defects.[13] No other SSRIs have been tied to cardiac deficits at this time. SSRI use during pregnancy has not been shown to increase risk of miscarriage, gestational diabetes, or higher blood glucose, but there is an increased risk of gestational hypertension and preeclampsia.[11-13]

When SSRIs are used late in pregnancy, it is possible for the neonate to develop symptoms related to withdrawal from the medication, a complication known as Neonatal Abstinence Syndrome (NAS).[14] NAS is a syndrome that develops within 48 hours after birth and can last up to a week. [14]

Some symptoms may appear as difficulty feeding, irritability, and tremors. [14]

NAS symptoms are similar to symptoms experienced when an SSRI is abruptly stopped. [14] Up to 30% of exposed infants develop NAS and the risk has been noted particularly with fluoxetine and even more commonly, paroxetine. [14] Fetal SSRI drug concentrations have been found to be lower than maternal concentrations with sertraline and paroxetine being lowest and citalopram and fluoxetine exposure being highest.[14] These risks have predominantly been associated with exposures late in pregnancy. [14] To reduce this risk, it has been recommended that SSRIs be tapered to discontinuation starting 2 weeks before the due date with resumption after delivery.[14] Breastfeeding is also highly recommended as small concentrations of SSRI can pass into breastmilk allowing for a gradual exposure taper for the baby and reduced withdrawal symptom severity. [14] The majority of babies with SSRI exposure have self-limiting symptoms for a short duration and only require a few days of monitoring following birth.[14]

Increased risk for persistent pulmonary hypertension with SSRI use during pregnancy has been noted however data is not strong enough at this time to draw definitive conclusions.[15-16] Sertraline is the SSRI that currently has shown a potentially lower risk overall compared to others in the class with a favorable safety profile.[17]

SNRIs

SNRIs are another medication class considered first line therapy for moderate to severe depression.[10] Medications in this class include duloxetine (Cymbalta), venlafaxine (Effexor), and desvenlafaxine (Pristiq).[10] SNRIs have been tied to an increased risk of NAS when exposure occurs late in pregnancy.[14] Similar tapering prior to the due date is also recommended as discussed with SSRIs.[14]

In a 2020 retrospective cohort study aiming to compare individual SNRIs and SSRIs safety profiles, it was found that duloxetine was associated with the highest rate for adverse outcomes in newborns.[18] Early pregnancy exposure increased the risk of any abstinence or adaptation syndrome, and third trimester exposure was associated with increased odds of NICU admission.[18]

Venlafaxine has been found to have an increased risk of transient tachypnea of the newborn (TTN) and neonatal abstinence syndrome (NAS) when compared to other serotonergic antidepressants.[18,19]

Desvenlafaxine has a lower instance of being prescribed, especially to pregnant women as preliminary data shows increased risk of neonatal growth deficiency during pregnancy, which may result in negative consequences in brain development.[19]

TCAs

Tricyclic antidepressants are not considered first line but may be considered when first line options are exhausted.[10] This class contains amitriptyline (Elavil), clomipramine (Anafranil), desipramine

(Norpramin), nortriptyline (Pamelor), doxepin (Silenor) among others.[10] Several comparative studies reviewing adverse fetal outcomes in TCAs vs. SSRIs found no significant difference between classes.[20]

Research suggests that TCAs may increase risk for developing preeclampsia during pregnancy.[21] Some research also suggests clomipramine primarily may be associated with a higher risk of teratogenicity.[20]

In a 2022 study published in the Journal of Psychiatric Research, TCAs still showed an increased association of preeclampsia against SSRIs regardless of the rate of continuation or discontinuation throughout the pregnancy.[21] This study, along with another study revealed that taking a TCA in the first trimester may have a major role in the later development of the preeclampsia.[21] Researchers found an increased risk of preeclampsia in women who took a TCA in the first trimester regardless of continuation or discontinuation status by looking at women who:[21]

1. Discontinued the TCA in the first trimester
2. Continued past the first trimester
3. Initiated after the first trimester

For the fetus, TCAs have shown to cause withdrawal symptoms right after birth.[22] Similarly to SSRIs, this is self-limiting and usually resolves within 2 weeks.[22] Symptoms may include jitteriness, and irritability, with seizures happening only on rare occasions. [22]

Other Medications

Mirtazapine (Remeron) is an atypical antidepressant considered first-line for major depressive disorder with questionable data.[5,22] There has been some cases reported of spontaneous abortion and major malformations following use of mirtazapine.[22] This is a medication that has little data in pregnancy, so the risks should be considered, but until more data is available to offer better insight into possible risks, use of other first-line agents during pregnancy is likely prudent.[22]

Bupropion (Wellbutrin) is a norepinephrine and dopamine reuptake inhibitor used first-line for depression, as well as smoking cessation.[23] This extra indication may appeal to pregnant patients who are attempting to stop smoking.[23] Tobacco use in pregnancy has been associated with birth complications including low birth weight and pre-term delivery.[23] A key manufacturer of bupropion, GlaxoSmithKline established a Bupropion Pregnancy Register which by 2008 found ~3.6% of exposed infants had congenital abnormalities.[24] Cardiac malformations have also been reported inconsistently and the absolute risk appears low at 2.1/1000 births in exposed infants.[24] More data is needed to confirm a true correlation.[23]

Clinical Application

Depression affects many pregnant women, but there is so little research and data to base clinical decisions from. Ultimately, the safety profiles that are available for each

medication can be used for discussion between the patient and the provider.

For patients already on a medication before their pregnancy, risk and benefit should be evaluated and a monitoring plan should be discussed. It may be more harmful to mom and baby to attempt to stop or switch the medication than to continue and monitor.

For pregnant women who want or need treatment, psychotherapy is an important first step before jumping to medication.[10] If medication is warranted, SSRIs are typically first line, then SNRIs.[10] Medications vary in each class, so that should also be considered. Citalopram and sertaline have the best and most complete safety profiles of the SSRIs, while fluoxetine and paroxetine have more known risks.[6,7] TCAs have also been used and considered in pregnancy but are not typically first line.[10] Other medications for depression have little safety research available and their use should be based on a risk versus benefit evaluation.

Conclusion

Pregnancy is complicated when trying to make medication decisions. Not only is it the patient that needs to be considered, but also the fetus. Medication adjustments or changes need to be closely monitored and there needs to be open communication to and from the patient regarding their care. Special considerations need to be made when stopping, initiating, switching, or changing the dosage of antidepressants.

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