Antipsychotic Use in Pregnancy

Subjects: Psychology, Clinical

Contributor: Elyse Cornett, Alan David Kaye

Pregnant women constitute a vulnerable population, with 25.3% of pregnant women classified as suffering from a psychiatric disorder. Since childbearing age typically aligns with the onset of mental health disorders, it is of utmost importance to consider the effects that antipsychotic drugs have on pregnant women and their developing fetus. However, the induction of pharmacological treatment during pregnancy may pose significant risks to the developing fetus. Antipsychotics are typically introduced when the nonpharmacologic approaches fail to produce desired effects or when the risks outweigh the benefits from continuing without treatment or the risks from exposing the fetus to medication. Early studies of pregnant women with schizophrenia showed an increase in perinatal malformations and deaths among their newborns. Similar to schizophrenia, women with bipolar disorder have an increased risk of relapse in antepartum and postpartum periods.

Keywords: antipsychotics ; pregnancy ; teratogenicity ; complications ; psychosis

1. Antipsychotics Overview/Classes

Antipsychotic drugs are a class of drugs used to reduce psychotic symptoms in patients with psychiatric disorders. Bipolar disorder and schizophrenia are commonly treated with antipsychotics, but different variants of psychoses may also receive similar treatment, such as dementia-related psychosis, depression with psychotic features, and drug-induced psychoses. Antipsychotics are also available off-label for various disorders, including sleep disorders, obsessive-compulsive disorder, augmentation in depression, and dementia. In this regard, augmentation of depression with some antipsychotics is “on label” for select antipsychotics.

1.1. Classification

The classification scheme employing “typical” and “atypical” is the preferred nomenclature based on the liability to cause EPS. However, this should not be confused with other similar classification schemes such as “first” and “second” generation or “chlorpromazine-like” and “clozapine and related drugs.” The first and second-generation terminology describes the drugs discovered before and after clozapine, respectively. Clozapine and related drugs provide a more potent blockade of the $5HT_2$ serotonin receptor subtype, $5\text{-}HT_{2A}$, instead of the powerful D_2-receptor blockade characteristic of chlorpromazine-like drugs.

1.2. Receptor Binding

The serotonin hypothesis of schizophrenia started with discovering that LSD and mescaline were agonists of the serotonin (5-HT) receptor. Identifying various 5-HT-receptor subtypes led to finding the vital mediator for hallucination effects and, more importantly, the basis for the antipsychotic agents: the $5\text{-}HT_{2A}$-receptor antagonist in addition to dopamine receptor blockade. Blockade of this receptor is key to the atypical group of antipsychotics, of which clozapine represents the prototypical drug. $5\text{-}HT_{2A}$-receptors in the cortex, limbic region, and striatum modulate the release of several neurotransmitters such as dopamine, GABA, glutamate, and acetylcholine. Furthermore, stimulating the $5\text{-}HT_{2A}$-receptor depolarizes the glutamate neurons and stabilizes the N-methyl-D-aspartate (NMDA) receptors on post-synaptic neurons [1][2][3].

Serotonin’s role in schizophrenia receives less attention than the dopamine hypothesis of schizophrenia, but it should be discussed, especially when considering the positive and negative symptoms of schizophrenia. The dopamine receptors have important implications when assessing the antipsychotic mechanisms of action: many antipsychotics inhibit the postsynaptic D_2-receptors in the mesolimbic and striatal-frontal pathways. Additionally, it was found that dopamine receptor agonists aggravate symptoms in schizophrenia patients. Greater dopamine levels and increased density of dopamine receptors, specifically, D_2-receptors in the nucleus accumbens, caudate, and putamen, were discovered in patients with schizophrenia. The D_2-receptors provide G_i-coupled inhibition of adenylyl cyclase to decrease cAMP.

Calcium channels are inhibited while potassium channels remain open. The typical antipsychotics are known to produce antipsychotic effects with more selective D_2-receptor block and typically result in EPS when more than 80% of the D_2-receptors are occupied. However, despite the several lines of evidence associating dopamine's role in schizophrenia, the reduced dopamine activity found in newer antipsychotics has created a shift in the pharmacologic approach towards manipulating other receptors such as the 5-HT_{2A}-receptor subtype [3][4].

1.3. Atypical Antipsychotic Drugs

The atypical antipsychotics include olanzapine, quetiapine, iloperidone, lurasidone, paliperidone, risperidone, and ziprasidone. These drugs are grouped based on a similar mechanism of action: more potent 5-HT_{2A}-receptor antagonism than D_2-receptor antagonism. These drugs are inverse agonists of the 5-HT_{2A}-receptor in which inhibit the constitutive activity of the receptors. Most are also 5-HT_{1A} partial agonists and either 5-HT_6 or 5-HT_7-receptor antagonists. 5-HT_{1A} partial agonism creates a synergistic effect with the 5-HT_{2A}-receptor antagonism [2][3]. Aripiprazole has a slightly different mechanism of action: it reduces dopaminergic neurotransmission as a partial D_2-receptor agonist [5].

A smaller group of antipsychotics is worth mentioning as these drugs have a mechanism of action that differs slightly from the larger group of atypical antipsychotics. It is suggested that amisulpride and cariprazine have greater D_2/D_3-receptor antagonism with a similar serotonergic profile to the clozapine-like drugs. Amisulpride is a potent 5-HT_7-receptor antagonist, whereas cariprazine is a 5-HT_{2B}-receptor antagonist and a 5-HT_{1A}-receptor partial agonist [6][7].

2. Antipsychotics in Pregnancy

Antipsychotic drugs are often prescribed to patients as the standard of care for bipolar disorder, schizophrenia, and other psychotic disorders. They are also prescribed to a lesser degree for depression, anxiety, insomnia, autism, and nausea in early pregnancy [8][9]. Over several decades, the availability of effective treatment for psychotic patients has led to an overall increase in wellness and fertility rates among women with psychosis; however, pregnancy complicates antipsychotic treatment options. Whether or not prescribing antipsychotic drugs to antepartum women would be beneficial is a challenging dilemma. Treating the mother with antipsychotics implies exposing the fetus to the drug, potentially harming the patient's child. It is known that antipsychotic medications can readily cross the placenta [10], and exposure to antipsychotic medication during pregnancy is associated with potential teratogenicity. Potential risks associated with antipsychotic use in pregnant women include congenital abnormalities [11], preterm birth [12], and metabolic disturbances [13], which could potentially lead to abnormal fetal growth. On the other hand, abstaining from antipsychotics may result in a worsened prognosis due to the deteriorated psychiatric condition of a mother, which is a more significant threat to the mother and child [14]. Furthermore, discontinuation of antipsychotic treatment during pregnancy may increase the risk of relapse of psychiatric disorders, including bipolar disorder and schizophrenia [15]. Thus, clinicians are often faced with the challenge of balancing the benefits and potential risks of antipsychotic use during pregnancy.

Changes in physiology during pregnancy also result in changes in the pharmacokinetics of multiple medications, including antipsychotics. For instance, an increased dose of antipsychotic medication may be required to achieve the same serum concentration of the antipsychotic during pregnancy because of the isozymes of the P450 enzyme system or increased blood flow and increased renal elimination of these drugs due to increased glomerular filtration rate during pregnancy [16][17].

The use of antipsychotics during pregnancy has obstetric implications. The major nonpsychiatric maternal health complications are the development of diabetes and weight gain, especially in second-generation antipsychotics (SGAs), some of which are known to increase the risk of diabetes mellitus in general adult patients [18]. While examining both atypical and typical antipsychotics during pregnancy, patients were observed with a nearly twofold increase in the gestational diabetes mellitus risk in women [18]. Additionally, maternal antipsychotic medication (both FGAs and SGAs) may be associated with low birth weight, cesarean delivery, or elevated risk for prematurity [18].

One of the biggest concerns regarding the use of any antipsychotics in pregnancy is the risk of teratogenicity to the fetus, especially during the first trimester, when it is the most critical period for organ formation. However, it remains unclear to what extent antipsychotics cause complications in the neonatal period. Most exposure to antipsychotics is unavoidably coupled with maternal psychiatric disorders and associated comorbidities such as malnutrition, smoking, substance abuse, alcohol abuse, physical illnesses, and traumas [11]. Thus, it is challenging to eliminate confounding variables to isolate the specific influence of antipsychotic medication on fetal outcomes. Finally, because conducting randomized

controlled trials in pregnant women is unethical, there is a lack of high-quality evidence for the risks of antipsychotics in pregnancy.

References

1. Kaar, S.J.; Natesan, S.; McCutcheon, R.; Howes, O.D. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology 2019, 172, 107704.
2. Zhang, A.; Neumeyer, A.J.L.; Baldessarini, R.J. Recent Progress in Development of Dopamine Receptor Subtype-Selective Agents: Potential Therapeutics for Neurological and Psychiatric Disorders. Chem. Rev. 2006, 107, 274–302.
3. Shapiro, D.A.; Renock, S.; Arrington, E.; Chiodo, L.A.; Liu, L.-X.; Sibley, D.R.; Roth, B.L.; Mailman, R. Aripiprazole, A Novel Atypical Antipsychotic Drug with a Unique and Robust Pharmacology. Neuropsychopharmacology 2003, 28, 1400–1411.
4. Abbas, A.I.; Hedlund, P.B.; Huang, X.-P.; Tran, T.B.; Meltzer, H.Y.; Roth, B.L. Amisulpride is a potent 5-HT7 antagonist: Relevance for antidepressant actions in vivo. Psychopharmacology 2009, 205, 119–128.
5. Kiss, B.; Horváth, A.; Némethy, Z.; Schmidt, E.; Laszlovszky, I.; Bugovics, G.; Fazekas, K.; Hornok, K.; Orosz, S.; Gyertyán, I.; et al. Cariprazine (RGH-188), a Dopamine D3 Receptor-Preferring, D3/D2 Dopamine Receptor Antagonist–Partial Agonist Antipsychotic Candidate: In Vitro and Neurochemical Profile. J. Pharmacol. Exp. Ther. 2010, 333, 328–340.
6. Minami, F.; Zohar, J.; Suzuki, T.; Koizumi, T.; Mimura, M.; Yagi, G.; Uchida, H. Discrepancies Between Nomenclature and Indications of Psychotropics. Pharmacopsychiatry 2018, 52, 175–179.
7. Hálfdánarson, Ó.; Zoega, H.; Aagaard, L.; Bernardo, M.; Brandt, L.; Fusté, A.C.; Furu, K.; Garuoliené, K.; Hoffmann, F.; Huybrechts, K.F.; et al. International trends in antipsychotic use: A study in 16 countries, 2005–2014. Eur. Neuropsychopharmacol. 2017, 27, 1064–1076.
8. Iqbal, M.M.; Aneja, A.; Rahman, A.; Megna, J.; Freemont, W.; Shiplo, M.; Nihilani, N.; Lee, K. The Potential Risks of Commonly Prescribed Antipsychotics. Psychiatry 2005, 2, 36–44.
9. Huybrechts, K.F.; Hernández-Díaz, S.; Patorno, E.; Desai, R.J.; Mogun, H.; Dejene, S.Z.; Cohen, J.; Panchaud, A.; Cohen, L.; Bateman, B.T. Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations. JAMA Psychiatry 2016, 73, 938–946.
10. Tosato, S.; Albert, U.; Tomassi, S.; Iasevoli, F.; Carmassi, C.; Ferrari, S.; Nanni, M.G.; Nivoli, A.; Volpe, U.; Atti, A.R.; et al. A Systematized Review of Atypical Antipsychotics in Pregnant Women. J. Clin. Psychiatry 2017, 78.
11. Seeman, M.V. Gender Differences in the Prescribing of Antipsychotic Drugs. Am. J. Psychiatry 2004, 161, 1324–1333.
12. Lin, H.-C.; Chen, I.-J.; Chen, Y.-H.; Lee, H.-C.; Wu, F.-J. Maternal schizophrenia and pregnancy outcome: Does the use of antipsychotics make a difference? Schizophr. Res. 2010, 116, 55–60.
13. Bodén, R.; Lundgren, M.; Brandt, L.; Reutfors, J.; Kieler, H. Antipsychotics During Pregnancy. Arch. Gen. Psychiatry 2012, 69, 715–721.
14. Zhong, Q.-Y.; Gelaye, B.; Fricchione, G.L.; Avillach, P.; Karlson, E.W.; Williams, M.A. Adverse obstetric and neonatal outcomes complicated by psychosis among pregnant women in the United States. BMC Pregnancy Childbirth 2018, 18, 120.
15. Viguera, A.C.; Whitfield, T.; Baldessarini, R.J.; Newport, D.J.; Stowe, Z.; Reminick, A.; Zurick, A.; Cohen, L.S. Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation. Am. J. Psychiatry 2007, 164, 1817–1824.
16. Anderson, G.D. Pregnancy-Induced Changes in Pharmacokinetics. Clin. Pharmacokinet. 2005, 44, 989–1008.
17. Reis, M.; Källén, B. Maternal Use of Antipsychotics in Early Pregnancy and Delivery Outcome. J. Clin. Psychopharmacol. 2008, 28, 279–288.
18. Patton, S.W.; Misri, S.; Corral, M.R.; Perry, K.F.; Kuan, A.J. Antipsychotic Medication during Pregnancy and Lactation in Women with Schizophrenia: Evaluating the Risk. Can. J. Psychiatry 2002, 47, 959–965.