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PHARMACOLOGICAL STRATEGIES FOR THE TREATMENT OF BIPOLAR DISORDER IN PREGNANT WOMEN: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Bipolar affective disorder (BAD) is a chronic mental disorder characterized by recurrent episodes of mania or hypomania and depression, with periods of remission in between. In women of reproductive age, BAD is associated with an increased risk of early pregnancy, perinatal complications, and postpartum relapse. The cornerstone of treatment is pharmacotherapy, including mood stabilizers as well as antipsychotic and antidepressant drugs. Pharmacological treatment during pregnancy reduces the risk of relapse but carries a potential risk of developmental defects and obstetric complications. Optimal therapeutic management requires individualized treatment.

Aim of the study: The aim of this work was to review the available literature on the pharmacological treatment of bipolar affective disorder (BAD) in pregnant women and to summarize the current state of knowledge. The safety profile of the drugs used and their effects on the mother and fetus during BAD pharmacotherapy are presented.

Methods and materials: A review of the literature available in the PubMed database was conducted using the following keywords: „treatment of bipolar disorder during pregnancy”, „teratogenicity”, „mood stabilizers”, „lithium”, „antidepressants”, „antipsychotic agents”, „congenital malformations”, „bipolar depression”, „valproate”, „lamotrigine”, „carbamazepine”, „postpartum relapse” and „anticonvulsants”.

Conclusion: Treatment of bipolar affective disorder in women of reproductive age is a significant clinical challenge. Continuation of pharmacotherapy during pregnancy is crucial for mood stabilization and prevention of postpartum episodes. Drug selection should be based on a risk–benefit assessment. Individualized pharmacotherapy and regular monitoring of mother and fetus are essential for optimal treatment outcomes and safety of both mother and child.

KEYWORDS

Bipolar Disorder, Treatment of Bipolar Disorder During Pregnancy, Mood Stabilizers, Psychopharmacology

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1. Introduction

Bipolar affective disorder is a severe and chronic mental illness characterized by the presence of depressive and manic or hypomanic states. The course of the disorder is marked by multiple recurrent episodes and periods of remission of varying duration (Merikangas et al., 2011). In individuals diagnosed with bipolar affective disorder, depressive symptoms usually predominate; however, the diagnostic hallmark is the presence of manic or hypomanic episodes (Zarate et al., 2000). Patients experience persistent residual symptoms, cognitive impairment, and psychosocial disability (Manji, Henter & Zarate, 2011). The etiology of bipolar affective disorder is associated with the interaction of multiple genetic, neurochemical, and environmental factors (Manji, Henter & Zarate, 2011), and the prevalence of the disorder in the adult population is approximately 2.4% (Merikangas et al., 2011). The mean age of onset in women falls within the reproductive period, around 25 years of age (Yatham et al., 2018). Young women with bipolar affective disorder have an approximately 20-fold higher risk of early pregnancy compared with women without a history of bipolar disorder (Yang et al., 2023). Additionally, in women diagnosed with bipolar affective disorder, both treated and untreated, the rate of pregnancy-related complications is higher than in healthy women (Giménez et al., 2019). The risk of disease relapse in the postpartum period is high. According to studies, up to 30% of pregnant women with bipolar affective disorder experience a mood episode postpartum. In bipolar disorder type I, the risk of severe postpartum episodes is six times higher than during pregnancy (Gilden et al., 2021). Continuation of treatment during pregnancy contributes to the maintenance of mood stability after delivery. Despite this, pregnancy is associated with a high risk of discontinuation of maintenance treatment due to women's concerns regarding the safety of medications used during pregnancy and their potential impact on fetal development (Stevens et al., 2019). In women who discontinue pharmacological treatment during pregnancy, the risk of relapse of a mood episode reaches as high as 71% (Viguera et al., 2007). Moreover, treatment discontinuation is associated with an increased risk of inadequate prenatal care, self-harm, and substance abuse (Bodén et al., 2007). Therefore, pharmacological treatment should not be discontinued in pregnant women with mental illness unless absolutely necessary (Newport et al., 2007). Efforts should be made to minimize the risks associated with untreated illness while simultaneously avoiding adverse effects of medications, such as congenital malformations and perinatal complications (Uguz et al., 2023). First-line therapy in the long-term pharmacological treatment of bipolar affective disorder includes mood stabilizers such as lithium, valproic acid, lamotrigine, and carbamazepine, as well as antipsychotic medications (Nierenberg et al., 2023).

2. Description of the State of Knowledge

Lithium

Lithium is a primary drug in the treatment of bipolar disorder, particularly for long-term prophylaxis. It is highly effective in preventing manic and depressive episode relapses and suicidal behavior (Tondo et al., 2019). Lithium treatment is effective in mood stabilization in women both during pregnancy and postpartum (Wesseloo et al., 2016). Despite this, it is currently not a common choice for therapy in young women. A 2017 study of 336 women found a significant decrease in the proportion of women filling lithium prescriptions during pregnancy; only 16% filled at least one prescription (Broeks et al., 2017). Lithium use during pregnancy is associated with an increased risk of congenital malformations, especially with high doses and first-trimester exposure (Fornaro et al., 2020). A 2017 large cohort study of over 1.3 million pregnant women examined the risk of heart defects in infants exposed to lithium in the first trimester. The study showed that first-trimester use increased the risk of heart defects, but the effect was smaller than expected (Paterno et al., 2017). Another large 2018 meta-analysis of six studies found a higher risk of major malformations in fetuses exposed to lithium in the first trimester; however, for major heart defects, the difference was not significant (Munk-Olsen et al., 2018). A 2018 study reported a higher rate of fetal ultrasound abnormalities in women using lithium during pregnancy (Frayne et al., 2018). Research on the neuropsychological functioning of children exposed to lithium is reassuring. A 2022 study of 99 children aged 6–14, including 56 exposed to lithium in utero, found no significant changes in neuropsychological functioning compared to controls (Poels et al., 2022). Furthermore, studies show that the risk of obstetric complications in women using lithium during pregnancy is not higher than in women who discontinued lithium before pregnancy (Frayne et al., 2018).

Valproic Acid

Exposure to valproic acid during pregnancy carries the highest risk of congenital malformations compared to other antiepileptic drugs. The risk of birth defects is 2–7 times higher with valproic acid than with other drugs (Tanoshima et al., 2015). The literature describes a set of features called “fetal valproate syndrome,” which primarily includes spina bifida, as well as limb, craniofacial, and heart defects, cleft lip and palate, and anencephaly. Valproic acid use during pregnancy also carries a risk of autism spectrum disorders and lower IQ in children (Ornoy, 2009). In 2013, it was shown that the IQ of 6-year-old children exposed to valproic acid in utero was lower than in children exposed to carbamazepine, lamotrigine, or phenytoin. Additionally, valproate-exposed children scored worse on other tests compared to children exposed to other antiepileptic drugs (Meador et al., 2013). A Cochrane database review reported the risk of multiple congenital malformations with valproic acid at 9%–11%, dependent on dose and combination with other antiepileptic drugs (Weston et al., 2016). In 2017, a study of 240,071 women found that 6.6% of women using valproic acid during pregnancy gave birth to a child with a major congenital malformation (Petersen et al., 2017).

Lamotrigine

Lamotrigine is considered one of the safer antiepileptic drugs for use during pregnancy in women with bipolar disorder (Vieta et al., 2024). It is recommended for treating both acute depressive episodes and maintenance therapy in BD. Lamotrigine is also well tolerated (Yatham et al., 2018; Vieta et al., 2024). A 2011 study over 18 years reported 35 infants with congenital malformations among 1,558 infants exposed to lamotrigine monotherapy in the first trimester. This number was similar to that in general population cohorts, indicating no significant increase in congenital malformations in fetuses exposed to lamotrigine in the first trimester. No dose-dependent increase in malformations was observed (Cunnington et al., 2011). A large 2018 study also found that the risk of major congenital malformations in children exposed to lamotrigine during pregnancy was comparable to unexposed children (Tomson et al., 2018). A 2017 Danish cohort study showed that lamotrigine during pregnancy was similarly effective as lithium in preventing severe postpartum episodes in women with BD. The risk of postpartum psychiatric hospitalization was comparable between women using lamotrigine and those using lithium. However, this finding requires further research due to potential confounding factors and the small sample size (Wesseloo et al., 2017).

Carbamazepine

The risk of congenital malformations with carbamazepine monotherapy is approximately 3–6% (Tomson & Battino, 2012). Use of this drug during pregnancy is associated with an increased risk of various birth defects in exposed children compared to children born to women without epilepsy or women with untreated illness (Weston et al., 2016). Prospective studies including 1,255 cases showed that carbamazepine use during pregnancy is mainly associated with neural tube defects, cardiovascular and urinary tract defects, and cleft palate (Matalon et al., 2002). In 2010, it was reported that the only specific congenital malformation significantly associated with carbamazepine use is spina bifida, with a lower risk than exposure to valproic acid (Jentink et al., 2010). A large 2011 study showed that the risk of congenital malformations depends not only on the type of antiepileptic drug but also on dose and other factors that physicians should consider when selecting pharmacological treatment for women of reproductive age (Tomson et al., 2011). Carbamazepine monotherapy is less teratogenic than carbamazepine combined with other antiepileptic drugs (Matalon et al., 2002).

Antipsychotic Drugs

Numerous studies suggest that the use of antipsychotic drugs in early pregnancy does not significantly increase the risk of congenital malformations, particularly heart defects, in the fetus (Huybrechts et al., 2016). A cohort study in 2023 involving over 26,000 pregnant women found no increase in the risk of major congenital malformations in children exposed to antipsychotic drugs during pregnancy. In that study, the risk of any major congenital malformation was 4.3% in infants exposed to atypical antipsychotics during fetal life, 3.1% in infants exposed to typical antipsychotics during fetal life, and 2.7% in unexposed children (Huybrechts et al., 2013). Research also indicates that children exposed to antipsychotic drugs in utero do not have an increased risk of neurodevelopmental disorders compared with a control group (Wang et al., 2021; Straub et al., 2022). Available sources also report studies suggesting that antipsychotic use during pregnancy is associated with an increased risk of adverse obstetric and neonatal outcomes. In 2015, it was reported that exposure to antipsychotic drugs during pregnancy increases the risk of developmental defects such as heart defects, preterm birth, and low birth weight (Coughlin et al., 2015). A 2020 meta-analysis including six cohort

studies showed that antipsychotic use during pregnancy increases the risk of gestational diabetes in women (Wang et al., 2021). However, further observation and the elimination of confounding factors are necessary, as a causal relationship between antipsychotic use during pregnancy and increased risk of adverse obstetric and neonatal outcomes does not necessarily exist (Coughlin et al., 2015).

Antidepressant Drugs

Data regarding maternal and fetal complications associated with prenatal antidepressant treatment are conflicting. Many studies question whether, despite a statistically significant association between antidepressant exposure and pregnancy and birth outcomes, these differences are clinically meaningful (Ross et al., 2013). A large cohort study in 2014 involving 949,504 pregnant women found no significant association between first-trimester antidepressant use and an increased risk of heart defects in offspring. The cohort was restricted to women diagnosed with depression to exclude potential confounding factors related to the presence of maternal psychiatric illness and conditions or behaviors that could increase the risk of heart defects in the child (Huybrechts et al., 2014). Furthermore, no association was found between fetal exposure to antidepressants and intellectual disability, speech development, or behavior in children (Nulman et al., 1997). However, some studies suggest that children of mothers who used antidepressants during pregnancy are at a significantly higher risk of low birth weight (Huang et al., 2014), congenital heart defects (De Vries et al., 2021), and persistent pulmonary hypertension (Masarwa et al., 2019) compared to unexposed children. A systematic review of 15 meta-analyses in 2020 also suggested an association between the use of SSRIs (particularly paroxetine and fluoxetine) and the occurrence of congenital malformations (Uguz, 2020). Several meta-analyses have also indicated a potential increased risk of autism spectrum disorders in children of women who used antidepressants during pregnancy (Kobayashi et al., 2016; Kaplan et al., 2016; Kaplan et al., 2017). In 2017, prenatal antidepressant exposure was reported to be associated with an increased risk of autism spectrum disorders in offspring (Andalib et al., 2017). Earlier studies, however, noted that when analyses were limited to children born to women with psychiatric disorders, no increased risk of autism spectrum disorders was observed in children exposed to antidepressants, highlighting maternal psychiatric illness as a potential confounding factor (Kobayashi et al., 2016). In 2018, a slightly increased risk of poorer motor development was reported in children prenatally exposed to antidepressants, although this study could not exclude the influence of bias or confounding factors (Grove, Lewis & Galbally, 2018). Additionally, a 2014 meta-analysis found that antidepressant use during pregnancy significantly increased the risk of preterm birth (Huang et al., 2014). Antidepressant exposure was associated with an increased risk of preterm delivery regardless of whether the control group included only unexposed women or both unexposed women and those with depressive disorders (Ross et al., 2014; Eke, Saccone & Berghella, 2016).

3. Summary

Continuation of pharmacotherapy in women with bipolar affective disorder during pregnancy is crucial for minimizing the risk of disease relapse, particularly in the postpartum period. Lithium is characterized by a relatively low teratogenic risk and may be considered for use in patients who respond well to it. Lamotrigine is one of the safer mood stabilizers for use during pregnancy. Valproic acid and carbamazepine carry a significantly higher risk of congenital malformations and should therefore be avoided in women of reproductive age. Antipsychotic and antidepressant drugs can be used during pregnancy; however, careful assessment of obstetric and developmental risks, as well as close monitoring of both mother and child, is necessary. Effective pharmacological treatment during pregnancy requires a balance between minimizing fetal risk and controlling maternal disease symptoms.

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- Research concept and design: PG, PK
- Data collection and/or compilation: PK, PG
- Data analysis and interpretation: PK, PG
- Writing: PG, PK
- Critical review of the article: PK
- Supervision, project administration: PG
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