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Antipsychotic Medications and Cognitive Behavior Therapy in Pregnant Women with Bipolar Disorder

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

One of the most difficult clinical tasks is treating pregnant women with bipolar disorder. Decisions that patients and physicians make are challenging, and no strategy is without risks nor prevents potential malpractice litigation. There is debate about whether to continue or discontinue antipsychotic medications during pregnancy. While discontinuation of antipsychotics may increase the risk of relapse, continued use of these medications may lead to fetal and maternal adverse outcomes. Some antipsychotics effectively treat symptoms related to bipolar disorder, including manic episodes and mood swings between mania and depression. Though antipsychotics may be useful for the treatment and management of bipolar disorder, the medications are not always favorable and are associated with adverse effects which have influenced some medical professionals to practice defensive medicine for decades that, in some cases, may coincide or conflict with medical ethics. While antipsychotics have a less safe yet effective impact on bipolar disorder in pregnant women, an alternative therapeutic approach such as Cognitive Behavior Therapy (CBT) should be considered. CBT psychotherapy is an evidence-based practice approach that can be beneficial in the treatment of bipolar disorder in pregnant women while bypassing the associated adverse reactions of antipsychotics. Attention is needed to explore the use and associated risks and benefits of antipsychotic medications during prenatal and postnatal, the debate of whether to continue or discontinue antipsychotic medication during pregnancy, and the role of

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CBT in the treatment of pregnant women with bipolar disorder. While antipsychotics may have beneficial effects that should not be underscored, the risks associated with the usage of antipsychotics during pregnancy cannot be minimized.

Keywords: Bipolar disorder; antipsychotic medication; pregnant women; cognitive behavior therapy; defensive medicine; medical ethics; teratogenic.

1. INTRODUCTION

The treatment of bipolar disorder in pregnant women involves significant challenges for both the woman and the developing fetus. Bipolar disorder is a severe mental disease with a lifelong course and considerable morbidity and mortality [12]. Bipolar disorder affects 0.5%–1.5% of individuals in the United States, [103] and it has an estimated lifetime prevalence of 3% to 7%, [56,57] with an annual incidence of three to ten cases per 100,000 people [80]. Bipolar I disorder and bipolar II disorder are severe, long-lasting mental conditions marked by alternating periods of mania or hypomania and extreme depression, or by combinations of manic and depressive symptoms [6]. Bipolar disorder can lead to the onset of family burden, emotional distress, declined coping ability, overwhelming stress, and disability in the affected individuals as well as psychiatric conditions in those caring for or supporting the individual diagnosed with bipolar disorder such as depression, anxiety, and post-traumatic stress disorder which is manifested by internal factors including endless efforts to assist the individual [71]. These factors are related to the increased importance of the treatment and management of bipolar disorder, particularly in women of reproductive age. While pregnancy has protective properties in bipolar I disorder, it is often associated with increased relapse risk which is evident upon the discontinuation of mood-stabilizing treatment [18]. Contrarily, the continuation of antipsychotic medications requires analyzing whether the benefits outweigh the risks of congenital malformations.

Women diagnosed with bipolar disorder may subject themselves and their developing fetuses to adverse factors when taking antipsychotic medications during pregnancy. It is estimated that 2.8 percent of adults have bipolar I disorder and bipolar II disorder and the prevalence of bipolar disorder among adolescents aged 13 to 18 is higher for females (3.3%) than for males (2.6%) [46,47,56,57,67]. Some females of childbearing age are of great concern because of their reproductive ability, chances of having bipolar disorder, and being prescribed an antipsychotic. Bipolar disorder is common among women of childbearing age whereby women with bipolar disorder are typically in their teens and early 20s at onset the of the illness, placing them at risk for episodes throughout their reproductive years [104]. Many women with bipolar disorder are prescribed antipsychotic medication, and the decision to continue or discontinue medication during pregnancy is challenging. Though antipsychotics may have some benefits, taking some medications during pregnancy may result in human teratogens [103]. With the number of women suffering from bipolar disorder, pregnant women with bipolar disorder must be informed of the possible benefits and risks associated with antipsychotic medications.

2. BIPOLAR DISORDER IN WOMEN

Bipolar II disorder is more common in women than men in which bipolar II disorder is characterized by episodes of hypomania and depression [76]. Most women are diagnosed with bipolar disorder between the ages of 18 and 30, when many women are in peak reproductive age [56,78]. Pregnancy and childbirth are major life transitions, so medical treatment must be close to perfect. Women who suffer from bipolar disorder may face more challenges with treatment decisions than men due to an increased risk of difficulties associated with pregnancy and childbirth.

Psychiatric problems appear to have more unfavorable characteristics to sexuality and reproduction in women [58]. Women who have bipolar disorder face a complex set of challenges that causes many lifelong clinical concerns. These challenges include sexually risky conduct during mania, health concerns for the mother and/or infant, medication decisions throughout pregnancy, unplanned or unwanted pregnancy, and sexually transmitted diseases/sexually transmitted infections [63,64]. Such factors complicate the treatment and case management efforts of treating bipolar disorder in women [66,72]. Treatment regimens can be compromised because bipolar disorder can affect

women differently than men. Women with bipolar disorder are more likely than men to experience mixed mania [76]. Treating pregnant women with bipolar disorder can result in direct and indirect expenses.

3. DIRECT AND INDIRECT COSTS OF BIPOLAR DISORDER

In the United States, the direct and indirect costs of bipolar disorder were estimated to be 151 billion dollars in 2009 [20]. Millions of patients worldwide are affected by this severe mood illness, incurring costs of billions of dollars for the years lived with disability [31,37]. Individuals with bipolar disorder represent a range of diseases marked by repeated relapses, reoccurring symptoms, and persistent residual symptomatology [53]. An antipsychotic regimen may be necessary to help manage the symptomatology associated with bipolar disorder such as rapid mood swings, hypersexuality, grandiose, depressive moods, and mania. Though antipsychotics may be effective in the treatment of bipolar disorder, there is a chance of congenital abnormalities which would accrue direct and indirect costs for the pregnant mother and fetus. In the alternative, the discontinuation of antipsychotic medications during pregnancy may raise the chance of bipolar mood-episode relapses which also will accrue expenses.

The incidence and prevalence of bipolar disorder have increased over the past 20 years [10,31]. Because of the complexity of bipolar disorder, those diagnosed with it as well as family members and society may be adversely impacted. Bipolar disorder can contribute to increased health care costs, burdens on caregivers, strains on personal and professional relationships, inconsistencies with employment/career obligations, compromised marriages, unbalanced daily activities, and positive and negative experiences with systems (e.g., schools, hospitals, legal, family, social services) [71]. Bipolar disorder is a complex mental illness to treat, and the challenges of treating a pregnant woman present many concerns during prenatal and postnatal care. Some of the expenses associated with care exist because bipolar disorder can cause impaired cognition,[40] functional decline, [83,84] poor health outcomes,[17] and a high frequency of suicidal behavior [78].

Pregnant women with bipolar disorder may have the most direct and indirect costs due to the multiple services required for prenatal care, postnatal care, postpartum care, and psychiatric treatment. Individuals diagnosed with bipolar disorder have a greater amount of sick leave and have a lower employment rate and a lower income that is available to them, even though their education levels are comparable to those of the general population [10,67]. Bipolar disorder is associated with a significant increase in suicidal behavior. Suicidal behavior is an indication of the severity of the condition in which the risk is 20 to 30 times higher on average [10,31,67]. Such complexities make treatment regimens for pregnant women with bipolar disorder challenging which requires the women and physicians to evaluate the risks and benefits of every decision. Physicians are pressured to weigh treatment options to ensure the health and safety of the pregnant mother and developing fetus in a best practice and cost-effective manner while trying to implement strategies to minimize the peril of malpractice lawsuits which can be difficult.

4. TREATMENT OF BIPOLAR DISORDER IN PREGNANT WOMEN

The treatment and management of bipolar disorder in pregnant women or those planning to become pregnant are major challenges for physicians. Bipolar disorder complicates the treatment and management of pregnant women. The incidence of bipolar disorder in women peaks between the ages of 12 and 30 years, or in other words, during the critical reproductive years [92]. Women previously hospitalized for bipolar disorder may be at an increased risk of adverse perinatal outcomes when there is noncompliance with treatment recommendations. The treatment of bipolar disorder in pregnant women should include folate supplementation to minimize the risk of neural tube abnormalities in general [104]. Physical and mental health risks must also be assessed and minimized to ensure appropriate treatment and management. The selected treatment regime must also focus on proper fetal development and viability as well as ensure the limited impact of morbidity on the mother, fetus, and other related individuals [52,99].

Treatment planning for pregnant women with bipolar disorder should consider not only the relative risks of fetal exposure to antipsychotics but also the high chance of recurrence and morbidity associated with stopping maintenance

and treatment [100]. In contrast, there is a debate that the continuation of antipsychotics can present challenges for a pregnant woman and the fetus that outweighs the benefits of the medication during pregnancy. Not only should attention be placed on the prenatal and postnatal effects of antipsychotics, but attention should also be directed to potentially modifiable risk factors such as obesity, diabetes, and hypertension before and during pregnancy should be assessed to reduce the risk of adverse perinatal outcomes [5,65].

4.1 Undiagnosed, Untreated and Undertreated

There is a need to focus on undiagnosed, untreated, and undertreated pregnant women to bring attention to the necessity of proper treatment and management. Some pregnant women are associated with serious psychiatric disorders. Many women may receive substandard care or no care at all due to being undiagnosed, untreated, or undertreated. For those who seek treatment, many women may face difficulty deciding to continue or discontinue an antipsychotic. Thus, some women may lack knowledge about an alternative effective treatment approach such as Cognitive Behavior Therapy to address bipolar disorder. Cognitive Behavior Therapy is beneficial in treating pregnant women with bipolar disorder who face psychosocial stressors known to interrupt the disease course and increase the risk of relapse, [12,94,103] including negative events, family strife, other interpersonal problems, and disturbance of sleep and wake cycles or daily social routines [45,69].

Despite the availability of effective treatment regimens, whether antipsychotic regimens and/or psychotherapy, many pregnant women with bipolar disorder go undiagnosed, untreated, or undertreated. A lack of or inadequate treatment as well as failure to timely diagnose bipolar disorder may increase the risk of rapid cycling and suicide ideation. Suicide has been linked significantly related to pregnant women with bipolar disorder. Suicide is a leading cause of maternal death during pregnancy and up to a year after birth (the perinatal period) [79]. Even when bipolar disorder is diagnosed, women may face challenges to treatment such as some psychiatric professionals may be uncomfortable initiating, continuing, or discontinuing psychopharmacology treatment for pregnant women. These barriers can make it difficult for pregnant women to receive treatment. Access to treatment and ensuring that it is adequate are extremely important concerns, given that quitting medication is a controversial topic [98,100] and the lack of access to or participation in psychotherapy is also of concern [2,12,41,60]. All of which raises the probability of symptomology returning which further complicates treatment approaches for pregnant women.

4.2 Psychiatric Comorbidity

Bipolar disorder is frequently diagnosed with other psychiatric disorders such as post-traumatic stress disorder, substance use disorders, obsessive-compulsive disorder, eating disorders, generalized anxiety, borderline personality disorder, attention deficit hyperactivity disorder, and other psychiatric conditions which can make the treatment planning process difficult [71,76]. For women who do not want to take medication or who are unable to tolerate the side effects, psychotherapy may be an effective alternative to address psychiatric comorbidities. Psychotherapy should be recommended for pregnant women with comorbidities that include bipolar disorder, regardless of whether they continue or discontinue antipsychotic medications.

Bipolar disorder in pregnant women has been associated with self-injury, suicide, high rates of premature mortality, general medical disorders, and even the intentional killing of their infants, all of which are negative results for both the mother and the child [18,32,38,61,79,95,98]. Therapeutic interventions are essential to minimize the chances of negative results, especially when treating psychiatric comorbidities. A collaborative treatment plan including psychotherapy, family support systems, and coordination of care with the treating physician to closely monitor the pregnant woman's mental and physical health, as well as medication regimen, is essential.

Pregnant women must be informed about and understand the risks associated with antipsychotic medications to make treatment-informed decisions. Treatment approaches must be a mutual decision between the pregnant women and treating physicians (i.e., obstetric, psychiatrist, etc.). Not only do antipsychotic medications present challenges, but treating pregnant women with comorbidity complexities raises concerns. For instance, investigations examining the risk of large-for-gestational-age birth related to prenatal antipsychotic medication

exposure were spurred by the well-known danger of clinically substantial weight gain and unfavorable alterations in glycemic profiles associated with particular antipsychotic medicines.[73] A small study included 45 babies who were treated with typical antipsychotics in utero, 25 babies who were exposed to atypical antipsychotics, and 38 controls who were not exposed to any drug, where data was prospectively gathered on gestational age and birth weight.[74] Infants exposed to atypical antipsychotics statistically showed a greater prevalence of large-for-gestational-age birth (20%) as compared to those exposed to typical antipsychotics (2%). [74] The risk of some atypical antipsychotic medications may be considerably greater than others during pregnancy.

4.3 Medical Comorbidity

Medical conditions are frequently presented in pregnant women with bipolar disorder which complicates treatment and management efforts. Risk factors associated with medical comorbidity must be assessed and minimized to ensure appropriate treatment and management for pregnant women with bipolar disorder. Not only do antipsychotic medications present challenges, attention to modifiable risk factors that commonly co-occur in women with bipolar disorder such as obesity, diabetes, migraines, thyroid disorders, polycystic ovary syndrome, and hypertension before and during pregnancy should be assessed to reduce adverse perinatal outcomes [34,65,76,77]. Medical comorbidity may contribute to the increased health care cost not only for those with complex conditions but also for pregnant women with bipolar disorder.

5. INITIATION, CONTINUATION OR DISCONTINUATION OF ANTI-PSYCHOTICS

5.1 During Pregnancy

Significant debates are challenging the decision to initiate, continue or discontinue the usage of antipsychotic medications during pregnancy. There is an argument that the common practice of abruptly stopping maintenance treatment for psychiatric disorders during pregnancy underscores the significant benefits of continuing medication with concerns of an overall reduction in recurrence risk and overall maternal morbidity (i.e., time spent ill during pregnancy) [30,100]. There is a concern that stopping effective pharmacotherapy during pregnancy exposes the patient and the baby to potential harm related to bipolar relapses and residual mood symptom-related dysfunction [32]. The relapse potential among pregnant women is of major concern. Women with bipolar disorder who relapse during the immediate postpartum period (or the third trimester) may require antipsychotic medications in the absence of significant risk factors for the pregnant women and fetus. [60,93,99,102] While some antipsychotic medications are related to the short-term treatment of bipolar disorder, certain medications are also useful for the long-term or maintenance treatment of bipolar disorder.

The use of short-term and long-term antipsychotics during perinatal and postnatal pregnancy may lead to an increased risk. Risks to the fetus may outweigh the empirical viewpoint for the continuation of mood stabilizers or antipsychotic medications. Neonatal problems, including extra pyramidal symptoms, respiratory distress, seizures, feeding issues, tachycardia, low blood pressure, gestational diabetes, abnormal fetal growth, preterm birth, macrocephaly, congenital malformations, preterm birth, transitory neurodevelopmental delay, and even long-term cognitive delays in infants exposed to antipsychotics in utero which have been linked to both typical and atypical antipsychotics [36,49,52,59,62]. The risks may be limited by close monitoring and maintenance but may be markedly increased by the abrupt discontinuation of such treatments [100]. Though continuation is recommended, antipsychotic drugs used to treat or protect against recurrences of bipolar disorder vary markedly in teratogens.

Different monitoring strategies must be implemented when considering whether to continue or discontinue an antipsychotic with pregnant women. When medication is continued, monitoring is needed for maternal and fetal exposures. In the alternative, when medication is discontinued, strategies to deter mood relapse and risk-taking behaviors are necessary. Some antipsychotics are prescribed with other medications such as mood stabilizers, anticonvulsants, and antiepileptics to achieve a greater effect of stabilizing moods and preventing relapse. There are low risks with typical neuroleptics, significant risks with lithium, higher risks with older anticonvulsants such as valproic acid and carbamazepine, and virtually unknown

risks with other newer generations of anticonvulsants and atypical antipsychotics [42,52,55,85,100]. When considering antipsychotics, decisions must be guided by whether the benefit of usage outweighs the adverse effects.

Risk factors associated with medications that are frequently prescribed with antipsychotics vary depending upon the pharmacological agent. For instance, embryonic exposure to lithium may increase the incidence of congenital cardiac abnormalities by up to 400 times [76,85]. Valproate carries a much higher risk of significant congenital abnormalities than other anticonvulsants like carbamazepine and lamotrigine, [13,58,74] in which maternal exposure has been linked to increased fetal congenital abnormalities (up to 20-fold) [54]. Carbamazepine exposure in pregnancy has been associated with microcephaly, growth retardation, small-for-gestational-age deliveries, coagulopathy, and temporary hepatotoxicity [54]. Therefore, the decision to continue or discontinue antipsychotics whether with or without other medications should be carefully evaluated.

The decision whether to continue or discontinue an antipsychotic must be determined beyond only the possibility of relapse and rapid mood swings, though they are important factors. Consideration must be focused on deterring suicidality of the mother, mortality of the baby, and risks to the pregnant mother and developing fetus, as well as identifying short-term and long-term effects of antipsychotic usage or lack thereof. The characteristics of the substance and the length of time the fetus is exposed to antipsychotics both may play a role in determining the risk of prenatal abnormalities related to maternal drug use. Exposure up to 32 days after conception has the potential to influence the development and closure of the neural tube; exposure between 21 and 56 days after conception has the potential to influence the formation of the heart, and exposure between days 42 and 63 has the potential to influence the development of the lip and palate [9]. Though it is perceived that the most potential critical prenatal exposure risks are in the first trimester, it is important to note that risks can occur thereafter. For instance, craniofacial abnormalities are not limited to occurring during the first trimester of pregnancy whereby if the mother is exposed to the toxin after the first trimester, neurobehavioral teratogenicity can occur [9]. Therefore, there is a need to explore the maternal and fetal risk factors associated with pregnant women with bipolar disorder who are prescribed antipsychotic medications and explore alternative available treatments.

6. DRUG SAFETY MEASURES WITH THE USAGE OF ANTIPSYCHOTICS DURING PREGNANCY

Drug safety measures have been issued about the usage of antipsychotic medications during pregnancy. In 2011, The United States Food and Drug Administration (US FDA) issued a drug safety communication informing medical professionals about the updates of the pregnancy component of drug labels for all antipsychotic medications that included warnings about the potential symptoms such as extra pyramidal signs and withdrawal symptoms in newborns babies whose mother was administered antipsychotics during pregnancy [96]. The US FDA's Adverse Event Reporting System database revealed 69 spontaneous reports of newborn withdrawal and extra pyramidal symptoms from both types of antipsychotic medications which served as the basis for warnings [96]. Many concerns arouse due to the health and safety of the newborns were affected. Though newborns recovered within several hours or days according to the severity of the symptoms and did not need any special therapy for these symptoms, patients had to recuperate in neonatal critical care units or had protracted hospital stays [96]. Such adverse effects of antipsychotic usage during pregnancy drew great attention which led to exploring risk factors with other medications used among pregnant women. The majority of instances contained potential confounding elements such as concurrent exposure to other medicines (e.g., benzodiazepines and opioids) linked to withdrawal, preeclampsia, early delivery, and other pregnancy problems [95].

7. DEFENSIVE MEDICINE, MEDICAL ETHICS AND ANTIPSYCHOTICS

Defensive medicine can result in favorable and unfavorable outcomes, depending upon the involved medical issue, medical error, and legalities. Strong debates differ about the usage and lack thereof of antipsychotics during pregnancy which has the propensity to foster malpractice litigation when adverse medical conditions occur. Differences of opinions among

medical professionals vary about antipsychotic usage for pregnant women with bipolar disorder which places constraints on treatment approaches. Not to mention, the driven demand for defensive medicine to minimize the risk of malpractice litigations that some perceive increases health care costs by performing countless tests while others presume that it creates a gateway to mask financial fraud within the health care system by performing unnecessary and expensive screenings. Though physicians are medically trained to use clinical knowledge and best judgment, medical education training does not include every possible clinical scenario which allows the possibility of uncertainties in some medical situations that can result in malpractice. Though malpractice liability insurance covers the majority, if not all, of a physician's litigation, there is the risk of negative impacts on the physician's career, reputation, patient relationship, interaction with colleagues, etc.

Defensive medicine stems from physicians' perception of being sued by patients or their relatives for presumed medical errors in which defensive medicine strategies are implemented with the hopes of reducing the chances of litigation [86] Some medical professionals believe that defensive medicine eliminates or reduces the chance of being sued. Such faulty thoughts not only deviate medical professionals from sound medical practice but also creates the false idea that ordering diagnostic tests, procedures, or visits is necessary to reduce the chance of misdiagnosis, medical uncertainties, adverse outcome, and malpractice litigation. Such actions may be deemed unethical and unlawful, depending upon the situation, which can be perceived more as suspicious and fraudulent actions than proper medical practices.

Medical ethics play a critical role in the practice of medicine. The decision of whether to continue or discontinue an antipsychotic during pregnancy requires a balance between medical ethics and defensive medicine. For some medical professionals, applying accurate defensive medicine strategies and adhering to medical ethics guidelines can be difficult and stressful. Medical professionals may feel pressured to order extra tests. Ordering additional or unnecessary tests can be perceived as an unethical medical measure to minimize liability or a fraudulent financial incentive that benefits medical professionals. Both approaches are potentially serious violations of the standard of care and could result in malpractice litigation. A serious ethical or fraudulent violation not only subjects medical professionals to litigation but also can result in the loss of a medical license. Physicians must constantly minimize risks even when the best course of action is performed while contemplating whether to practice defensive medicine. Of particular concern with defensive medicine are methods to treat patients suffering from aggression and mania associated with bipolar disorder [4].

There is no secret that treating pregnant women with bipolar disorder can be challenging which may foster decisions to practice defensive medicine. While some physicians may be trained to treat pregnant women with bipolar disorder, one of the many challenges with defensive medicine is ordering medical tests that are deemed medically and legally necessary and absent of financial fraudulent gains and adverse medical outcomes. Though the continuation of antipsychotic medications may be effective in reducing relapse, managing depressive moods, and controlling rapid mood shifts, medical professionals must understand not only what defensive medicine is, but also how to ensure compliance, ethical standards, and risk management when treating pregnant women. Even though no supervision is required for physicians to make treatment decisions for patients, including pregnant women, only medically necessary diagnostic measures, imaging tests, invasive procedures, surgeries, utilization of specialized equipment, medical transportation, prescriptions, hospitalizations, referrals to medical specialists, etc. must be done to minimize the risk of litigations.

The highly litigious nature of legal systems combined with medical professionals' lack of understanding of and communication about golden standard risk management, quality assurance, and quality improvement measures has led some physicians to erroneously presume that they must practice defensive medicine to avoid liability due to fear of litigation which has influenced treatment methods. Medical professionals must understand that the act of practicing defensive medicine alone does not, in itself, prevent litigations. The complexity of deciding on an accurate treatment regime for patients, especially pregnant women with bipolar disorder, can be challenging when intertwined with defensive medicine. Not only should medical knowledge be considered in the decision of whether to continue or discontinue an

antipsychotic, but medical best practices, medical ethics, ethical standards, standard health care practices, hospital/clinic procedures, accreditation guidelines, and medical licensure requirements as well as awareness of prior malpractice litigation within the health care industry, etc. are beneficial to know and seriously considered. Even though medical sound judgment may be applied and various defensive medicine strategies may be implemented, it is important to know that some risks are inevitable. For instance, antipsychotics of both types, typical and atypical, can cause serious complications when given to pregnant women during the perinatal time in which some major symptoms are tachycardia, hypotension extrapyramidal symptoms, neuro-developmental delay in the fetus, seizures, and respiratory distress [36]. Even some self-limiting extrapyramidal signs associated with tremors, somnolence, feeding problems, irritability, and jitteriness were also reported for exposure during the antenatal period along with other symptoms [16].

There is no requirement for medical professionals to obtain a legal education unless it is a preferred choice, but it is highly recommended for medical professionals to understand the risks and benefits of defensive medicine when considering to initiate, continue, or discontinue an antipsychotic for pregnant women with bipolar disorder. When considering defensive medicine, building physician-patient trust and rendering appropriate care are essential in the treatment and management process instead of basing care primarily on potential consequences for the physician, patient, health care expenses, and health care system. Recommendations have been made for physicians to focus first on efficiency and safety of patient care as well as the use of informed consent, evidence-based medicine, integration of specialized medicine, and thorough patient follow-up [4]. Whether it is to minimize fear of litigation, avoid being financially ruined, or prevent loss of a medical license, defensive medicine and medical ethics must be practiced with serious consideration of medical and legal standards of care. Therefore, in-depth knowledge of medical evidence-based approaches, risk management concepts, clinical golden standards, medical ethics, and risk and benefits of antipsychotic medications as well as a thorough understanding of defensive medicine are necessary to consider when treating pregnant women with bipolar disorder.

8. ANTIPSYCHOTIC MEDICATION USAGE DURING PREGNANCY

First-generation and second-generation antipsychotic medications are categorized as typical and atypical, respectively. The main difference between the two types of antipsychotics is that the first-generation drugs inhibit dopaminergic neurotransmission, and the second-generation is considered serotonin-dopamine antagonists which block D2 dopamine receptors as well as serotonin receptor antagonist action [29,33,50]. Antipsychotic drug use during pregnancy was linked to an increased risk of gestational diabetes set side by side with the normal population of births in a retrospective cohort study of a very large number of 357, 696 antipsychotic-unexposed and 169,338 antipsychotic-exposed pregnancies, after arranging for order of birth and mother's age, birth country, cohabitation, height, and smoking. [8] Arguments are made to continue antipsychotic medications because of the reducion in recurrence risk and overall maternal morbidity, [100] and prevention of relapses and residual mood symptom-related dysfunction [32]. In contrast, for newborns exposed to some antipsychotic medications, clozapine, and olanzapine, the large head circumference of babies than normal gestational age substantially increased [8].

Few studies have analyzed the potential negative effects of antipsychotic drug exposure on fetal neurodevelopment. In one prospective, controlled trial, 309 mother-infant pairs were examined at six months postpartum, 22 had used antipsychotics during pregnancy, 202 had taken antidepressants, and 85 had taken no psychotropic medications [51]. The findings should be considered when determining whether to continue or discontinue antipsychotic medications. For instance, the infants who were exposed to prenatal antipsychotic drugs conspicuously had lower neuromotor-performance scores as compared to infants who were exposed to antidepressants as determined by the Infant Neurological International Battery, a standardized assessment of muscle tone, posture, motor skills, and reflexes [51] Some prenatal and postnatal risks may be contributed to factors independent of the usage of antipsychotic usage. Even though a higher risk of anomalies may be due to genetics or habits like smoking, drug abuse, or inadequate prenatal care,[1] there still exists a risk of maternal and fetus exposure to antipsychotic medications.

8.1 First-Generation Antipsychotic Medications

First-generation antipsychotic medications have benefits and risks in treating bipolar disorder. Some antipsychotics are initiated, continued, and discontinued during pregnancy. Though there is a chance of negative outcomes for some pregnant women and fetuses, close monitoring of pregnant women is highly recommended to reduce or eliminate risk factors as well as determine the medical necessity to continue or discontinue antipsychotics. Typical antipsychotic agents continue to have a role in the acute treatment of mania during pregnancy, and some experts consider the risk associated with typical antipsychotics to be less than the risk associated with mood stabilizers [76].

Table 1 below illustrates risks associated with typical antipsychotic medication usage by pregnant women with bipolar disorder during pregnancy[7,24,25,27,28,36,43,44,49,87,88,89,97]. Though Table 1 is not an exhaustive list of information about antipsychotic medications, it provides available information discovered in the literature.

8.2 Second-Generation Antipsychotic Medications

Atypical antipsychotics are considered second-generation medications. Atypical antipsychotics can cross the placenta [42,76]. The ability to cross the placenta may subject the developing fetus to greater risks, especially during the first trimester. Though risks can occur at any time between the first through the third trimester with the usage of either typical or atypical antipsychotic medications, the ability to cross the placenta should be of greater concern.

Table 2 below illustrates atypical antipsychotic medication risks associated with pregnant women with bipolar disorder during pregnancy [3,19,21,22,23,26,35,59,65,67,73,82,90,91,101]. Though Table 2 is not an exhaustive list of information about antipsychotic medications, Table 2 provides available information identified in the literature.

Table 1. Risks associated with first-generation (Typical) antipsychotics usage during pregnancy

*Medication	Risk for fetus/neonate/baby	Risk for pregnant women	Recommended screening
Haloperidol	Limb reduction Tongue thrusting Feeding difficulty Abnormal hand posturing Tremor of all extremities Aortic valve defect Phocomelia Transient fetal heart block	Aphasia with drug-overdose Teratogenic properties Neuroleptic Malignant Syndrome	Monitor drug serum levels Ultrasound monitoring of the fetus
Chlorpromazine	Risk of malformation Hypertonicity Tremors Spasticity Difficulty with feeding	Nausea Vomiting Drop in blood pressure	Monitor blood pressure Dose adjustment Ultrasound monitoring of the fetus
Fluphenazine	Severe rhinorrhea Respiratory distress Delayed extrapyramidal symptoms	Risk was not found in the literature	Ultrasound monitoring of the fetus Routine monitoring of mother
Perphenazine	Agitation Hypertonia Hypotonia tremor Somnolence Respiratory distress Feeding disorder Extrapyramidal syndrome	Gestational diabetes	Ultrasound monitoring of the fetus Routine monitoring of mother
Trifluoperazine	Agitation Hypertonia Hypotonia Tremor Somnolence	Risk was not found in the literature	Ultrasound monitoring of the fetus Routine monitoring of mother

*Medication	Risk for fetus/neonate/baby	Risk for pregnant women	Recommended screening
	Respiratory distress Feeding disorder Extrapyramidal syndrome		
Pimozide	Agitation Hypertonia Hypotonia Tremor Somnolence Respiratory distress Feeding disorder Extrapyramidal syndrome	Risk was not found in the literature	Ultrasound monitoring of the fetus Routine monitoring of mother
Thioridazine	Agitation Hypertonia Hypotonia Tremor Somnolence Respiratory distress Feeding disorder Extrapyramidal Syndrome	Risk was not found in the literature	Ultrasound monitoring of the fetus Routine monitoring of mother

**While some associated risks were found in the literature with first-generation (typical) antipsychotic medications, this does not exclude the possibility of additional risks. Though associated risks were not found in the literature for some first-generation (typical) antipsychotic medications, this does not preclude the possibility that additional potential risks do not exist. The recommended screenings do not eliminate the possibility that additional screenings may be required.*

Table 2. Risks associated with second-generation (atypical) antipsychotics usage during pregnancy

*Medication	Risk for fetus/neonate/baby	Risk for pregnant women	Recommended screening
Olanzapine	Neural tube defects Risk of complications	Weight gain Obstetric complications Insulin resistance Gestational diabetes Preeclampsia Folate deficiency	Monitor and control weight Monitor blood sugar level Monitor blood pressure Monitor increase of required folate in a dose of 5mg instead of 0.5mg Monitor risk of neural tube defects
Clozapine	Risk of malformation Risk of agranulocytosis	Gestational Diabetes	Monitor drug serum levels Ultrasound monitoring of the fetus
Risperidone	Neonatal withdraw Low birth weight Stiff muscles Floppy muscles Drowsiness Agitation Tremors Difficulty breathing Feeding problems	Weight Gain Difficulty controlling blood sugar levels	Ultrasound monitoring of the fetus Routine monitoring of mother Monitor blood sugar level
Quetiapine	Agitation Tremors Difficulty breathing Feeding problems	Gestational Diabetes	Monitor blood sugar level Routine monitoring of mother Ultrasound monitoring of the fetus
Amisulpride	Agitation Tremors Difficulty breathing Feeding problems	Risk was not found in the literature	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of the fetus
Ziprasidone	Breathing problems	Risk was not found in the	Serum level monitoring

*Medication	Risk for fetus/neonate/baby	Risk for pregnant women	Recommended screening
	Feeding problems Fussiness Tremors Limp muscle Stiff muscles	literature	Routine monitoring of mother Ultrasound monitoring of the fetus
Aripiprazole	Low birth weight	Hypertension Shorter gestation period	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of the fetus
Lurasidone	Fussiness Respiratory issues, Neuromuscular changes (floppiness or stiffness) Gastrointestinal problems	Gestational Diabetes	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of the fetus
Asenapine	Agitation Hypertonia Hypotonia Tremor Somnolence Respiratory distress Feeding disorder Neonatal toxicity	Gestational Diabetes	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of the fetus
Iloperidone	Muscle stiffness Shakiness Drowsiness Feeding difficulties Breathing difficulties Constant crying	Risk was not found in the literature	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of thefetus
Paliperidone	Agitation Hypertonia Hypotonia Tremor Somnolence Respiratory distress Feeding disorder	Risk was not found in the literature	Serum level monitoring Routine monitoring of mother Ultrasound monitoring of the fetus

**While some associated risks were found in the literature with second-generation (atypical) antipsychotic medications, this does not exclude the possibility of additional risks. Though associated risks were not found in the literature for some second-generation (atypical) antipsychotic medications, this does not preclude the possibility that potential risks do not exist. The recommended screenings do not eliminate the possibility that additional screenings may be required.*

9. COGNITIVE BEHAVIORAL THERAPY

Evidence-based practices are beneficial and cost-effective for a wide range of psychiatric conditions, and psychotherapy concepts have been used as a treatment approach with and without the usage of antipsychotics. Cognitive Behavior Therapy (CBT) is an evidence-based psychotherapeutic intervention that aims to reduce depressive symptoms in patients with bipolar disorder as well as improve self-esteem while enhancing the quality of life and social functioning in individuals [15,39,48] CBT was developed in the 1960s by Aaron Beck and was found to be safe and effective in the treatment of psychiatric disorders. The treatment model is based on the three aspects of cognition that include schemas or underlying beliefs, automatic thoughts, and cognitive distortion which is designed as a goal-oriented structured therapy [11,48,81]. While the pharmacological approach is the mainstay of the treatment and management of some individuals with bipolar disorder, CBT should gain immense attention because of its effectiveness.

CBT, as well as other evidence-based psychotherapy approaches (e.g., Interpersonal and Social Rhythm Therapy, Family-Focused Therapy, Dialectal Behavior Therapy, and Systematic Care Management), have been used in the treatment of bipolar disorder and depression and preventing relapses which have shown to be effective in the absence and presence of drug therapy usage [15,48,68,69,81,93]. CBT has proven to be a

beneficial adjunct to medication in pregnant women with bipolar disorder who face psychosocial stresses known to interrupt the disease course and increase the risk of relapse,[14,68,82,94,103] including bad life events, family strife, other interpersonal problems, and disturbance of sleep and wake cycles or daily social routines [44,45,68].

CBT is effective in helping individuals to learn to recognize and change negative thinking and behavior patterns. CBT is an effective treatment for bipolar disorder and it helps in reducing depression [2,70]. CBT is a promising effective approach to helping individuals to manage bipolar disorder symptoms which may be considered beneficial in assisting pregnant women to manage bipolar disorder with minimal or no usage of antipsychotic medication [12,94].

9.1 CBT Psychoeducation

CBT psychoeducation is the hallmark of the clinical interaction between a patient and a psychiatric professional (e.g., psychiatrist, clinical therapist). Psychoeducation allows continuously learned concepts and supports that can be used outside of an outpatient psychotherapy session. Psychoeducation concepts can help individuals, including pregnant women, learn to apply concepts to deter self-destructive thoughts, promote changed behaviors, develop adaptive skills to manage impulses and urges, encourage self-management of actions, and identify shifts in moods. CBT strategies such as journals, calendars, therapeutic worksheets, self-care activities, self-awareness/monitoring exercises, family and support system collaboration, etc. are useful tools to assist individuals to track information associated with a diagnosis of bipolar disorder as well as other psychiatric conditions.

CBT psychoeducation is beneficial for pregnant women because the concepts can be used to help pregnant women by providing support and education to both the woman, spouse/partner, and her family. CBT may be beneficial in the combination of or the absence of an antipsychotic to help reduce the recurrence of symptoms of bipolar disorder. Hence, CBT is an effective therapeutic approach for individuals with bipolar disorder and poses no risk of malformations in the fetuses should the mother decide to remain unmedicated or be medicated during pregnancy.

Psychiatric disorders are prevalent worldwide and associated with high rates of disease burden as well as elevated rates of co-occurrence with medical disorders which has led to an increased focus on the need for evidence-based psychotherapies. Several useful strategies related to CBT have been developed for controlling the symptoms of bipolar disorder and mediating the quality of life [11,12,48,68,69,94]. Certain factors may trigger or worsen manic episodes in individuals with bipolar disorder. Factors may include but are not limited to sleep deprivation, use of recreational drugs, alcohol use, medication noncompliance, personal and familial stressors, etc.

Psychiatric professionals play important roles in using psychoeducation to educate patients to identify and implement self-control of triggering factors. Incorporating CBT can be beneficial for a pregnant woman. Strategies are designed to identify factors that contribute to the development or worsening of manic episodes in which the patient is encouraged to make safe decisions to prevent the onset of manic episodes, avoid relapse, learn positive behavior modifications, and develop self-regulation of actions [11,39,68,71,93]. Coordination of care is also essential among the treating physician, therapist, client, community resources, and family support systems to maximize treatment potential for pregnant women with bipolar disorder.

10. METHODOLOGY

This narrative review was conducted to explore antipsychotic medications and cognitive behavior therapy in pregnant women with bipolar disorder. A literature review search was conducted by using Saint James School of Medicine's library resources, the University of Lahore's library resources, PubMed, PsycINFO, and Google Scholar. The text words "pregnant women," "bipolar disorder," "antipsychotic medications," "first-generation antipsychotics," "second-generation antipsychotics," "cognitive behavior therapy," "teratogenic," "defensive medicine," "medical ethics," "evidence-based psychotherapy," with the use of Boolean operator "AND" the term "pregnancy" was used to identify studies on antipsychotic medications and cognitive behavioral therapy in pregnant women with bipolar disorder. The inclusion criteria consisted of a) scholarly or peer-reviewed sources; b) relevant books and sources; c) articles published in the English language only; d) pregnant women with bipolar disorder; e) pregnant women who are taking antipsychotic medications; f) pregnant women who discontinued antipsychotic medications; and g)

pregnant women receiving evidence-based psychotherapy. The inclusion of literature was selected based on quality and relevance.

11. RESULTS AND DISCUSSION

This research was essential to not only explore the risks and benefits associated with antipsychotic medications during the prenatal and postnatal periods but also to analyze the debate about whether to continue or discontinue antipsychotics during pregnancy as well as understand the role of CBT in the treatment and management of pregnant women with bipolar disorder. A remarkable finding revealed that CBT is effective with minimum risks in comparison to antipsychotics, though CBT does not have similar physiological effects on the human body [12,39,41,70,94]. While both psychotherapeutic and pharmacologic interventions are effective in the treatment and management of manic episodes and depression in bipolar disorder, it is important to evaluate which of these modalities is safe during the pregnancy and has more favorable outcomes on maternal and fetal health as well as the health of family members.

Psychotropic medications including atypical antipsychotic medications tend to cross the placenta, [75] contributing to fetal exposure to antipsychotic medications [49], A noteworthy finding asserted that the first trimester of pregnancy is the period during which the fetus is highly susceptible to teratogens, which can have negative consequences on the viability, development, and health of the fetus [9,42,76]. Antiepileptic medications are often prescribed in addition to antipsychotic medications and can potentially increase the risk of the development of neural tube defects in the first trimester of pregnancy [59]. Since there are some benefits to the usage of antipsychotics that cannot be excluded, close monitoring of a pregnant woman should be a priority to detect risk factors. Discontinuation of antipsychotic medication is found in some women who are pregnant or planning to become pregnant to prevent fetal harm.

CBT is an effective adjunct to pharmacotherapy in the treatment of bipolar disorders in pregnant women. CBT treatment approach can be useful for pregnant women who are subjected to psychosocial, familial, and personal stressors that contribute to the relapse and disruption of the illness course. Psychotherapeutic interventions have no known risks related to bipolar disorder in pregnant women nor do these interventions have adverse pregnancy-related, maternal, and neonatal outcomes [32,41] An interesting finding revealed that the benefits of CBT interventions may prove to be a promising adjuvant to pharmacotherapy in the treatment of women with bipolar disorder, even though CBT has no similar physiological effect as medication [12,14,68,82,94,103]. Though CBT lacks pharmacological capabilities, it has therapeutic strategies that are appropriately designed to target similar symptoms of bipolar disorder as antipsychotic medications. For instance, CBT is effective in decreasing the relapse rate and improving depressive moods, mania severity, and psychosocial functioning [12,70].

When considering the use of antipsychotic pharmacologic interventions during pregnancy, monotherapy (if necessary) instead of polytherapy is recommended, to reduce the risk of congenital defects in the fetus which was the most compelling finding [52,54]. Preconception planning and psychiatric evaluation in women with bipolar disorder are critical to ensure safe and effective treatment and management. CBT may prove to be helpful in combination with or without pharmacological interventions since it improves compliance with the treatment, enhances social and occupational function, minimizes stressors, and alleviates sleep deprivation [45,70] The most surprising discovery was that CBT not only provides an effective method to treat pregnant women with bipolar disorder through psychotherapy, but it also provides strategies to teach ways to gain self-control of actions, thoughts, emotions, and behaviors that are necessary for the treatment and management of complex psychiatric conditions [11,39,41,68,71,93].

12. CONCLUSION

Antipsychotic medications are widely used in the treatment and management of bipolar disorder. A major challenge is the treatment and management of bipolar disorder in pregnant women. While discontinuation of antipsychotics may increase the risk of relapse, continued use of these medications may lead to fetal and maternal adverse outcomes. The recommended treatment of bipolar disorder in pregnant women is the use of CBT as an adjuvant therapy with monotherapy when an antipsychotic is necessary. While CBT is safe, effective, and improves treatment adherence, monotherapy ensures reduced risk of relapse and possibly

decreased chances of congenital anomalies in the neonate. No treatment decision is without risks when treating pregnant women with bipolar disorder which could potentially result in malpractice litigation. Medical professionals must not only be knowledgeable of medical approaches, medical ethics, and risk management in the treatment of bipolar disorder in pregnant women but also understand when to utilize appropriate defensive medicine strategies as well as recommend CBT to help maximize treatment efforts while reducing risks. Whether incorporating CBT or not, antipsychotic medications should be used to treat pregnant women with bipolar disorder only if the benefits outweigh the risks to the mother and fetus.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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