


Clozapine Efficacy in a Case of Severe Treatment-Resistant Postpartum Psychosis

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Background: The postpartum period is a difficult time for mother and family. Unfortunately, in some cases, two psychiatric complications may occur: postpartum psychoses (PPP) with a prevalence of 0.2% and a very low incidence of 0.25–0.50 per 1000 deliveries, and post-natal depressions with an incidence of 10 to 20% per 1000 deliveries. The onset of postpartum psychosis is in the first 4 weeks after childbirth with symptoms such as emotional lability, cognitive disorganization, delusional beliefs and hallucinations. It requires hospitalization due to the high risk of suicide and infanticide. The studies reveal that the treatment can include FGAs (first-generation antipsychotics), such as haloperidol, and SGAs (second-generation antipsychotics), such as olanzapine, quetiapine and risperidone. The literature is scarce in what resistant PPP is concerned and no such cases treated with clozapine have been reported, according to our knowledge. The present case report focuses on a female diagnosed with PPP who was treated with clozapine due to the lack of response to adequate dosage of 2 second-generation antipsychotics.

Case Presentation: We present the case of a 30-year-old primiparous woman on her 3rd day after delivery, admitted in the psychiatric emergency unit for agitation, intrusive thoughts with a content frequently related to the infant, ideas of reference, disorganized speech, bizarre behavior, verbal stereotypes, insomnia and anxiety. Due to lack of response to adequate dosage of 2 second-generation antipsychotics, clozapine was initiated up to 250 mg/day. The symptoms remitted in the next 5 days and the patient was discharged. After discharge, at the patient's request, clozapine was replaced by olanzapine. Visit at 1 year revealed full remission of symptoms.

Conclusion: Although data is extremely limited, clozapine has been shown to be effective and safe in a severe case of treatment-resistant PPP.

Keywords: postpartum psychosis, antipsychotics, clozapine, suicide, treatment-resistant

Background

The postpartum period is a difficult time for mother and family. Unfortunately, in some cases, two psychiatric complications may occur: postpartum psychoses (PPP) with a prevalence of 0.2% and a very low incidence of 0.25–0.50 per 1000 deliveries and post-natal depressions with an incidence of 10 to 20% per 1000 deliveries. The postpartum psychosis is not only rare, but it is also not officially recognized as a distinct disorder in DSM-5.^{1,2}

The onset of postpartum psychosis (a psychiatric emergency) is in the first 4 weeks after childbirth; it is marked by symptoms such as emotional lability, cognitive disorganization, delusional beliefs and hallucinations and it is most likely an overt presentation of bipolar disorder.³ It requires hospitalization due to the high

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risk of suicide and infanticide.⁴ Infanticide is associated with imperative hallucinations that command to kill the child or delusions that the child is possessed.⁵

The risk of developing psychosis is higher in the first 30 days after childbirth, especially in primiparous. Women who are already vulnerable as a result of genetics or stressful environmental exposure are susceptible to mental disease in this period and this was attributed to neuro-hormonal factors.⁶ The levels of estrogen and oxytocin gradually rise during the pregnancy and drop sharply after delivery, returning to normal within 3 weeks. Considering that the occurrence of psychosis is associated in time with the abrupt decline of the two hormones, an increased sensitivity of dopamine receptors due to the sudden decrease in estrogen levels has been involved. Given the putative role of estradiol and oxytocin in the pathophysiology, both estrogens (sometimes associated with progesterone) and oxytocin have been tested as potential treatments for nonpsychotic and psychotic illness in the puerperium, but the results of the clinical studies available so far are inconclusive to sustain their use.⁶

Jones et al conducted a genome-wide linkage study in families with bipolar disorder in which at least one woman had suffered a manic or psychotic episode within 6 weeks postpartum. They reported significant linkage signal on chromosome 16p13 and a suggestive linkage signal on chromosome 8q24, which suggests that chromosome 16 and chromosome 8 may contain genes potentially involved in the predisposition to puerperal psychosis.⁷

The other risk factors include being unmarried, first baby, Caesarian section, perinatal death, all this under the name of psychological stress. Also, women with a history of manic or depressive episodes have a higher risk than women with schizophrenia.⁸ Almost 10% of women hospitalized for psychiatric morbidity before delivery develop postpartum psychosis after their first birth.⁹ Of all women with PPP, 70% to 90% have bipolar disorder or schizoaffective disorder, while approximately 12% have schizophrenia.^{10,11} The risk of non-puerperal admission is higher for women with schizophrenia and PPP is a part of a lifelong recurrent psychiatric disorder.¹²

Generally, the prognosis for a singular episode is favorable, with symptoms remission and good social and occupational functioning in 75–86% of the cases. However, it is considered as belonging to the bipolar spectrum, with potential recurrences¹³ or as a part of schizophrenia with 50% recoveries, 33% recurrent episodes and 5% treatment-resistant schizophrenia (TRS) cases.^{14,15}

Treatment for PPP is similar with non-puerperal episodes. The existing studies reveal that the treatment can include FGAs (first-generation antipsychotics), such as haloperidol, and SGAs (second-generation antipsychotics), such as olanzapine, quetiapine and risperidone. Olanzapine and quetiapine are preferred during breastfeeding, other antipsychotics are rarely mentioned.^{16,17}

Regarding the association of gonadal hormones with antipsychotic use, there are still many aspects to be elucidated. While convincing evidence on their benefits is still missing, many factors should be taken into consideration. For instance, pharmacokinetic interactions of hormones with CYP450 enzymes might change the plasma concentration of antipsychotics, thus influencing their effect on psychotic symptoms independent of the pharmacodynamics of estrogen. In this case, the outcome may depend on the antipsychotic agent; olanzapine and clozapine are metabolized by CYP1A2 liver enzyme, which is inhibited by estrogen; co-administration of estrogen will increase the antipsychotic level, while quetiapine is mainly metabolized by CYP3A4, which is induced by estrogens, so the antipsychotic level will decrease.⁶

The literature is very scarce in what resistant PPP is concerned and according to our knowledge no such cases treated with clozapine have been reported.

The present case report focuses on a female diagnosed with PPP who was treated with clozapine due to lack of response to adequate dosage of two SGAs. The Hospital Ethics' Committee approval was not necessary for the publication of this case report. The patient provided written consent for the anonymous publication of her case.

Case Presentation

We present the case of a 30-year-old primiparous woman, brought by her husband on day 3 postpartum and admitted in the psychiatric emergency unit for agitation, intrusive thoughts with a content frequently related to the infant, ideas of reference, disorganized speech, bizarre behavior, verbal stereotypes, insomnia and anxiety.

From her history, we noticed a previous psychotic episode at the age of 24, successfully treated with olanzapine 10 mg/day for 6 months and then stopped at her physician's recommendation. This episode was closely related to a stressful event. The patient had fully recovered without any residual symptoms. She got married and worked without any psychiatric problems. The biological investigations showed mild iron-deficiency anemia, mild hypercholesterolemia. The head computer tomography scan was normal. On

admission, she was treated with injectable haloperidol 5 mg/day, diazepam 20mg/day and cabergoline 1mg/day for two days for ab lactation. Due to extrapyramidal side effects (acute dystonia and rigidity), she was switched to olanzapine 20 mg/day, lorazepam 4 mg/day and trihexyphenidyl 4mg/day. Since no significant clinical response was registered after 2 weeks, the patient received add-on therapy with risperidone 4 mg/day. Despite the combination of two potent antipsychotics administered in proper doses, the patient remained intensely psychotic and 4 points mechanical restraint was often necessary. She started saying that she would kill herself to escape the terror caused by what was happening. She started being aggressive and presenting the Capgras delusion. Since she was non-responsive to adequate dosage of two second-generation antipsychotics, standard titration of clozapine was initiated up to 250 mg/day with ongoing monitoring in conformity with the current guidelines. Benzodiazepines were tapered off to discontinuation. The symptoms remitted in the next 5 days and the patient was discharged. After discharge, she continued the treatment for 6 months.

After 6 months the patient expressed the desire to switch from clozapine to olanzapine for several reasons: a) previous good outcome with olanzapine; b) less strict monitoring regimen; c) clozapine induced constipation. We chose the cross-tapering switch (6 weeks) in order to

avoid rebound symptoms, based on our previous experience as well as the expert's opinion on this topic.¹⁸ The cross-tapering switch is presented in Figure 1.

Visit at 1 year after discharge revealed full remission of symptoms and a good level of functioning on 10 mg/day olanzapine. We decided to gradually stop treatment with olanzapine during next 8 weeks. There were no signs of relapse at 6 months later. Family considered patient fully recovered.

Discussions and Conclusions

To our knowledge, PPP are very rarely treated with clozapine and data is limited on this topic. Most data are available from case reports and small studies. The term “resistant postpartum psychosis” is an analogy to the treatment-resistant schizophrenia, in which patients have persistent symptoms despite at least two adequate trials of neuroleptic drugs, over a prolonged period of time.^{18,19} In treatment-resistant schizophrenia clozapine is the gold standard.²⁰

The risks for infants exposed to clozapine from breast milk are unknown. However, Imaz et al²¹ did not find any acute toxicological effect in the exposed newborns. Meanwhile, the majority of women stop breastfeeding during psychiatric hospitalization and therefore clozapine could be an alternative for the patients that are unresponsive to other antipsychotics. The treatment generally

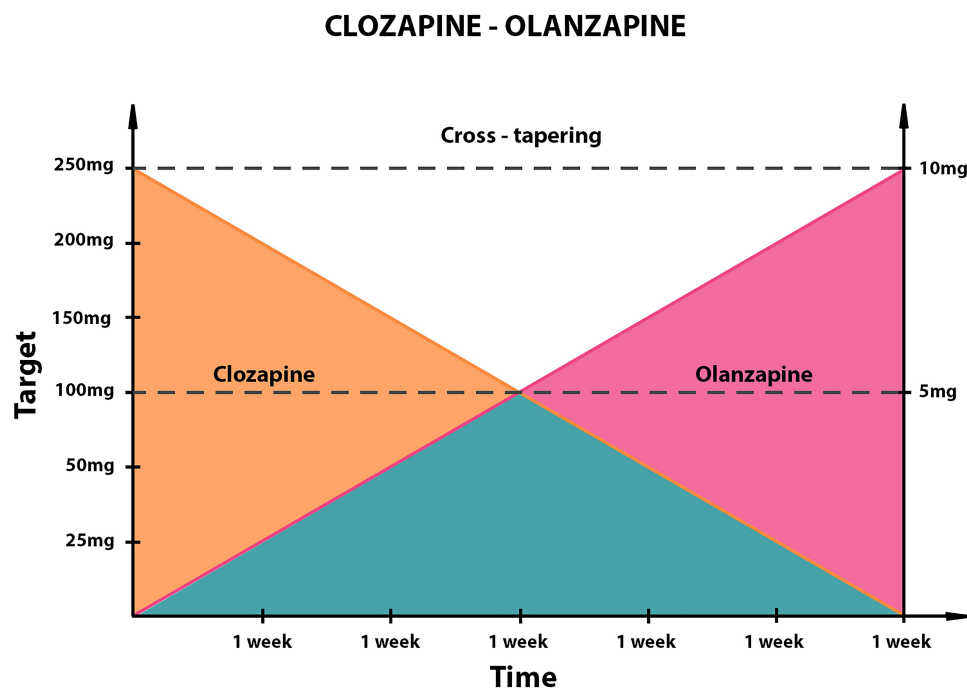


Figure 1 Clozapine to olanzapine cross-tapering.

includes sequential administration of short-term benzodiazepines, antipsychotics, and lithium, with response monitoring.²²

Insufficient response to an antipsychotic is most often followed by changing the antipsychotic, which is associated with an increased risk of side effects, prolonged hospitalization and major psychological consequences for the patient and family. Cases of long-term treatment-resistant psychoses with onset during the postpartum period have been reported and a few studies have explored the efficacy of electroconvulsive therapy, but data sustaining the best therapeutic attitude for these cases is lacking.^{22,23}

The recognition of treatment-resistant postpartum psychosis as a rare but severe condition will probably make the clinicians weigh clozapine as an efficient and safe treatment.

In Romania clozapine is indicated for TRS and psychosis in Alzheimer's Disease. According to our Hospital's protocols, we are allowed to use clozapine in patients with another psychiatric diseases in cases with severe agitation, aggressiveness, recurrent suicidal or self-mutilation behavior. This experience resulted from the numerous cases that needed to be resolved quickly in order to prevent prolonged mechanical restraint, loaded therapeutic regimens, prolonged hospitalization, etc.²⁴

An important aspect of our report was the duration of antipsychotic treatment after discharge. Due to the high risk of relapse after postpartum psychosis, we considered necessary to continue the treatment for at least 1 year.²⁵ A recent meta-analysis shows that more than 40% of women were classified as having "isolated postpartum psychosis" which could be considered a distinct diagnostic category. The remaining 60% of women had severe non-puerperal psychotic episodes during longitudinal follow-up.^{26,27}

Although data is extremely limited, clozapine has been shown to be effective and safe in this severe case of treatment-resistant PPP. Further studies will show whether clozapine might be an option for all patients with treatment-resistant postpartum psychosis.

Abbreviations

PPP, Postpartum psychosis; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; TRS, treatment-resistant schizophrenia; FGAs, First-generation antipsychotics; SGAs, Second-generation antipsychotics; CYP450, Cytochrome P450; CYP1A2, Cytochrome P1A2; CYP3A4, Cytochrome P3A4.

Data Sharing Statement

Not applicable.

Ethics Approval

Not applicable.

Consent for Publication

The patient signed a voluntary written informed consent form authorizing the publication. A copy is available if requested.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Disclosure

All authors declare that they have no conflict of interests for this work.

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