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Case Report

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Lithium plus Olanzapine as One of the Most Effective Combinations for Bipolar Disorder. A Case Report and a Concise Review of the Literature

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Abstract

Background: The recurrent nature of Bipolar Disorder (BD) is the main cause of disability associated with the illness. Despite the proliferation of drugs approved for the maintenance phase of BD, the relapse rate is still high. The combination of drugs, especially the potentiation of mood-stabilizers with second generation antipsychotics, may reduce the risk of relapse and rehospitalization. However, studies on the efficacy of specific combinations are scarce.

Case presentation: The clinical case of a 28-year-old woman, who is involuntarily admitted to an Acute Psychiatric Unit, is presented. She suffers a manic postpartum episode with mixed and psychotic features. During the hospitalization, she is successfully treated with the combination of lithium plus olanzapine. In the discussion, a concise narrative review of the scientific literature on the efficacy of such a combination in BD is made.

Conclusions: The association of lithium plus olanzapine is one of the combinations with most evidence on its efficacy in BD, especially in mixed-featured episodes. Tolerability concerns should not be an obstacle to its use, although they must be considered.

Keywords

Lithium plus olanzapine, Bipolar disorder, Combination therapies, Maintenance phase, Mixed features

Introduction

Bipolar Disorder (BD) is a chronic and recurrent illness that affects more than 1% of the global population [1,2]. It is one of the main causes of disability among young people, because it can lead to significant cognitive and functional impairment, as well as an increase in mortality, associated with cardiovascular disease and suicide [3,4]. The recurrent nature of bipolar disorder is the most determining factor in the long-term prognosis and therefore, implementing an effective maintenance treatment to prevent relapses is crucial [5]. Nonetheless, recurrence rates in BD remain high, with two-year relapse rates of 50% [6]. In women with BD, the postpartum is a particularly critical period. According to a recent meta-analysis, the overall postpartum relapse risk is 37% in women with BD but 66% in those who were medication-free during pregnancy [7].

In recent years, there has been a clear trend towards the use of combination treatments in BD, especially those made up of second-generation antipsychotics with mood stabilizers [8-11]. This practice is supported by clinical experience and several recent studies [6,11,12]. Among all possible combinations, the sum of lithium and olanzapine could be particularly effective, both in the acute phase and in the maintenance phase of BD [13-16]. The following is a real clinical case, wherein this therapeutic combination is used to successfully treat a severe manic episode with psychotic and mixed features during the puerperium. Later, in the discussion, a narrative review of the literature on this topic is conducted.

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Case Description

A 28-year-old woman is involuntarily admitted to an Acute Psychiatric Unit at a third-level hospital for behavioral abnormalities. She presents expansive and irritable mood, racing thoughts, inflated-self-esteem, hyperactivity, rampant purchases, and decreased need for sleep. The patient claims to have special abilities and that her family and friends want to harm her out of envy. She also exhibits prominent dysphoria, hopelessness, and thoughts of death. These symptoms are causing the patient serious social and work disruptions, due to aggressive and inappropriate behaviors.

Her medical history highlights a vacuum-assisted delivery two months before. Regarding psychiatric history, a previous admission due to a psychotic episode in the context of multiple drug abuse (alcohol, cannabis, cocaine, amphetamine…) is reported two years earlier. That episode was successfully treated with 300 mg of aripiprazole long acting injectable (LAI) and the final diagnosis was a Substance-Induced Psychotic Disorder. During the subsequent follow-up, the patient suffered a depressive episode, which was treated with escitalopram. Few months later, when she became aware of the unplanned pregnancy and found herself clinically stable, she discontinued all psychopharmacological treatment.-

The current episode started in the postpartum and progressively had worsened within 2 months. At this time, in addition to mood-congruent and incongruent delusions, she presents affective symptoms of both poles, manic and depressive, with a predominance of the former. According to DSM-5 classification [17], this clinical picture corresponds to a manic episode with psychotic and mixed features. Regarding the complementary tests (urinalysis and complete blood analysis), the only pathological finding is the positive detection of cannabis in urine. The patient recognizes a sporadic and recreational use of cannabis (few times a month since adolescence) and she denies the use of other substances at present. A neuroimaging study is not performed because a cranial scan (computerized tomography) was made in the previous admission a year before, which was completely normal.

During current hospital admission, combination treatment with olanzapine plus lithium is started, until reaching a daily dose of 800 mg of lithium (0.9 mEq/L serum level) and 20 mg of olanzapine. Adequate tolerance and progressive remission of the symptoms are observed, obtaining a mood-stability, biorhythms restoration and functional recovery in a period of one month. 2 kg weight gain (with a BMI of 24.2 kg/m^2) was reported as a side effect. Young Mania Rating Scale shows a score of 40 at baseline and 7 at discharge from the hospital. The definitive diagnosis is Bipolar I disorder, current or most recent episode manic, with psychotic and mixed features, with peripartum onset (296.44 DSM-5, F31.2 ICD-10) [17].

Regarding the differential diagnosis, it is not considered a substance-induced disorder since the patient does not present the symptoms during or shortly after cannabis intoxication or withdrawal. Besides, the symptoms persisted during a significant period after cessation of drug use. The history of past depressive episode and the development of the symptoms during the postpartum are also helpful aspects for differential diagnosis.

Discussion

The clinical case described is a paradigmatic example of a postpartum onset manic episode with psychotic and mixed characteristics, successfully treated with lithium plus olanzapine. In order to study the effectiveness of this combination in BD, a comprehensive literature search was conducted using the MEDLINE database in January 2021. Search terms included the following: (Bipolar disorder) and (lithium) and (olanzapine). The main findings of the bibliographic retrieval are summarized below.

Antipsychotics, particularly olanzapine, have shown to be more effective, essentially faster, than mood stabilizers in the manic episodes [18,19]. Olanzapine also turns out to be one of the drugs with greater acceptability and with the lowest discontinuation rate in the manic episodes [18,20]. Furthermore, olanzapine monotherapy has proven to be effective in preventing recurrences, surpassing the rest of antipsychotics in this regard [21]. Its prophylactic action is eminently antimanic, although with a polarity index more balanced than other antipsychotics, for example aripiprazole or risperidone [4,22], which implies a greater effect of olanzapine in the prevention of depressive relapses.

The efficacy of olanzapine in episodes with mixed features deserves special mention. In fact, in the latest clinical guidelines, it is listed as the treatment of choice for the mixed states [23-25]. This aspect is highly relevant, since mixed symptoms are the most common in the BD, they are the most difficult to treat and are associated with a worse prognosis, higher suicide rate and substance abuse [24,26-28].

On the other hand, lithium is still considered the Gold Standard treatment for the BD [29,30]. It prevents manic, depressive, and mixed episodes effectively, with a robust evidence [26,31], supported by recent both controlled and observational studies [32,33]. Independently of its mood-stabilizing effect, lithium has unique anti-suicide and neuroprotective properties [34]. In addition, it is the only drug that has been shown to be highly effective for the acute and maintenance treatment of postpartum psychosis [35].

Therefore, if we consider the favorable data for the use of lithium and olanzapine in monotherapy in the BD, it would be expected that the combination of both could provide additional benefits. Four recent papers support this hypothesis. In the first of these [13], the addition of olanzapine to lithium or valproate significantly increased the efficacy of the treatment in manic or mixed episodes. In the second study [14], symptomatic remission was found to be longer with combination therapy (olanzapine plus lithium or valproate) than with monotherapy (lithium or valproate alone), in a group of patients who had recently achieved remission after a manic or mixed episode. Similar results were found in the third controlled trial [15], which showed that in patients who maintained combination therapy (olanzapine plus lithium or valproate) the time to relapse was longer, compared to those who discontinued antipsychotic treatment. The last

one is a cohort study [16], in which it is suggested that the rehospitalization rate, after a manic episode, is significantly lower in patients with combination therapy (olanzapine plus lithium or valproate), compared to lithium monotherapy.

The main limitations for the use of the combined treatment are the problems of tolerability and the increased risk of adverse effects [11,36]. However, this does not always lead to discontinuation of the treatment, since the benefit perceived by the patient, in terms of symptomatic or syndromic remission, could prevail over the negative effects of the treatment [6]. This would explain the aforementioned increase in the use of combination therapies in real-world practice. Furthermore, there are effective strategies to prevent some of the most worrisome adverse effects, such as weight gain and diabetes in the case of Olanzapine [37] or renal dysfunction in the case of lithium [38,39]. It should not be forgotten that the alternatives are not risk free: quetiapine has a similar metabolic and sedative profile to Olanzapine [40], risperidone causes more extrapyramidal and sexual side-effects [41] and valproate is related to a high teratogenic risk [42]. Despite its side effects, olanzapine presents a lower risk of discontinuation than aripiprazole [43] and is one of the best rated antipsychotics, both by psychiatrists and by the patients [44]. Concerning lithium use, it is now recognized that its adverse effects, specifically the most serious (renal and teratogenic), could have been overestimated in the oldest studies [38,45], which could have generated an excessively negative perception of its “toxicity” [34,46,47].

The study's main limitation is the narrative nature of the review, with the risk of selection bias that this implies. However, given the sparse studies evaluating the effectiveness of the association of lithium and olanzapine in BD, we consider that it is an adequate approach to the topic. This review raises the need for future research comparing the efficacy of different combination treatments, both with each other and with monotherapy.

Conclusions

In summary, as reflected in the current clinical guidelines and real-world clinical practice, the use of combination therapies (second-generation antipsychotics associated with mood stabilizers) is a suitable treatment in BD [23-25]. It could be more effective than monotherapy in certain clinical situations, as severe episodes with psychotic or mixed features. Considering the results of this review, the association of olanzapine and lithium could be one of the combinations with the most scientific evidence in its favor. Therefore, we conclude that it is an appropriate therapeutic strategy in resistant or difficult cases, like the one exposed, despite the reasonable tolerability concerns.

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Both authors declare that the elaboration, review and submission process of the present manuscript has been equitably carried out. Both authors have contributed equitably in conceptualization, investigation, project administration, supervision, visualization, writing the original draft, reviewing and editing of this article.

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