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Review Article

A Review of Repercussions of Lithium Amalgamated with Antipsychotics for the Remedy of Bipolar Disorder

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Abstract

Bipolar disorder is a brain illness that causes mood, energy, and ability to function variations. Bipolar illness patients have extreme emotional states that often occur over a period of days to weeks, referred to as mood episodes. Manic/hypomanic (abnormally cheerful or angry mood) or depressed (sad mood) mood episodes are classified. People with bipolar disorder frequently have periods of neutral mood. People with bipolar disorder can live long and productive lives if they are treated. The management of BD may be summarized into 2 phases, acute treatment and long-term prevention. Lithium was observed to have a unique therapeutic profile, including mood-stabilizing effects, as well as anti-suicidal and neuroprotective properties.[13] It is available in many different salt forms, namely lithium carbonate, lithium citrate, lithium chloride, and lithium sulfate. A meta-analysis discovered that a combination regimen of haloperidol, olanzapine, risperidone, and quetiapine was substantially more effective in treating BD manic episodes than monotherapy with a mood stabiliser, but the combination regimen was less well tolerated than monotherapy.

Keywords: Bipolar Disorder, Lithium, Monotherapy, Combination therapy, Adverse effects.

INTRODUCTION:

Bipolar disorder (BD) was first described in the early nineteenth century[1], yet the management of this condition remains challenging and complicated even in the present day. The estimated prevalence of BD in the general population is approximately 4%; however, in the primary care setting, it may be as high as 21% to 26%.[2,3] Bipolar disorder (BD) is a chronic mental condition characterised by mood and energy changes in affected persons. Clinical manifestations include repeated episodes of mania and depression, which seriously impair personal life and result in unstable work performance, tense marital relationships, and increased incidence of psychosocial issues.[4] In adults, Lithium is the gold standard treatment for acute mania and the prevention of recurring BD episodes in adults (both manic and depressed).[5] Lithium inhibits glycogen synthase kinase-3 and decreases inositol signalling by depleting intracellular inositol, while the precise mechanism of action is uncertain.[6] Lithium has also been observed to reduce norepinephrine and dopamine release from nerve terminals while temporarily increasing serotonin release.[6] Slowly but steadily, the prescriptions of lithium were replaced by the recent psychotropics. This was mostly due to the time-consuming monitoring, adverse effect profile, limited therapeutic index, and common comorbidities in patients, which made lithium a second-choice medicine.[5,7] The most prevalent treatment for bipolar manic episodes has been the combination of mood stabilizers (MSs), lithium/valproate, and antipsychotics (APs).[8] The purpose of this review is to look into the efficacy differences of lithium combined with FGAs haloperidol, chlorpromazine, and SGAs olanzapine, risperidone, which are commonly used for the treatment of patients with bipolar disorder without intervention measures, as well as the incidence of adverse effects of combined drugs, in order to provide a reference for clinical and rational drug use.

THE PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER:

The management of BD may be summarized into 2 phases, acute treatment and long-term prevention. During the acute treatment phase, patients may present with either mania or depression or mixed episodes. According to the APA guidelines, for patients with severe acute mania or mixed episodes, a combination of an antipsychotic, particularly 2nd generation antipsychotics or atypical antipsychotics, and either lithium or valproate may be initiated. However, for those with modest symptoms, lithium, valproate, or an atypical antipsychotic alone may suffice. If the patient only shows a partial response to the previously established medication, a benzodiazepine may be administered for a brief period of time. However, given the high potential for abuse of benzodiazepines with this population, precautionary measures must always be implemented. Alternatively,

carbamazepine or oxcarbazepine can be used instead of lithium or valproate, and ziprasidone or quetiapine can be used in place of another antipsychotic.[9] The BAP guidelines suggested using haloperidol, olanzapine, risperidone, or quetiapine as first-line therapy to control short-term acute manic symptoms because they have the highest efficacy.[10] For those who have not been on long-term BD medication, valproate and lithium are feasible options. As an adjuvant therapy, the administration of a short-term benzodiazepine to promote sleep in agitated hyperactive patients may be considered. For individuals who are not adequately controlled with first-line medicine, a combination of lithium or valproate with a dopamine antagonist (e.g., haloperidol or olanzapine) or a partial agonist (e.g., aripiprazole) is recommended. Clozapine may be considered in cases with more refractory sickness. The American Psychological Association (APA) recommends lithium or lamotrigine alone as first-line treatment for acute depression. For people with a more severe condition, a combination of lithium and an antidepressant may be used.

THE PROPERTIES OF LITHIUM:

Lithium was observed to have a unique therapeutic profile, including mood-stabilizing effects, as well as anti-suicidal and neuroprotective properties.[13] It is available in many different salt forms, namely lithium carbonate, lithium citrate, lithium chloride, and lithium sulfate. The chloride and sulfate salt forms are relatively more soluble than the carbonate salt; therefore, their peak plasma concentration can be reached within 1 hour after ingestion compared with 4 hours for the carbonate formulation.[11,12,14,15] The concentration of lithium in the brain may peak around 24 hours after delivery. Lithium's precise method of action is still unknown, nevertheless, studies have shown it affects sodium transport in nerve and muscle cells, shifting the intraneuronal metabolism of adrenergic neurotransmitters.[16,17,18] Lithium has a fairly narrow therapeutic window, with long-term plasma levels ranging from 0.6 to 1.2 mEq/L.

DISCUSSIONS:

1. Sameer Jauhar and Allan H. Young **(2019)[19]** They discussed the use of 2nd generation antipsychotics in the maintenance treatment of bipolar disorder in this study. They will also compare their use to more established treatments in the past (particularly lithium, the gold standard). To this, literature should be added RCTs of long-acting injections (LAIs). A 52-week randomised placebo-controlled trial of aripiprazole depot demonstrated a positive benefit in Bipolar illness, with a hazard ratio of 0.45 in recurring of any mood episode, mostly manic episodes, echoing data for oral aripiprazole. Similar efficacy is also seen for risperidone LAI, versus placebo, from two trials, of 18 and 24 months duration, in relapse prevention, with combined risk ratio of 0.42 for manic, hypomanic or mixed symptoms, though not for depression relapse. This review summarizing the three trials comparing LAI to oral antipsychotics and discovered that there is no difference in relapse rates, though sensitivity analysis revealed benefit in people with rapid cycling illness. For any mood episode, the first trial evaluating the efficacy of antipsychotic monotherapy versus lithium for relapse prevention in BD compared olanzapine to lithium. This included open label concurrent treatment for 6–12 weeks, double blind taper over 4 weeks, and 48 weeks of double-blind monotherapy. It discovered no difference between olanzapine and placebo in terms of the primary outcome, hospitalisation for any mood episode. The antipsychotics examined were aripiprazole, olanzapine, paliperidone, quetiapine and risperidone LAI. It found all interventions were more effective than placebo in preventing relapse, apart from aripiprazole, carbamazepine, imipramine, and paliperidone. It should be noted that more current aripiprazole studies were not included. Only lithium and quetiapine showed a greater effect than placebo in avoiding depression relapse. The results of this systematic review are as follows: Second-generation antipsychotics are increasingly being used as monotherapy or adjunctive therapy for bipolar disorder maintenance treatment. Despite being classed as a single class, their pharmacological characteristics, efficacy, and tolerance in bipolar illness differ. This is particularly the case for prevention of depressive episodes, where their clinical effects appear less pronounced (with the exception of quetiapine, and possibly asenapine and lurasidone).

2. Stay Hyun Kyung Lee, Shruti Prabhudesai , Ramu Vadukapuram , Noha Eskander , Rikinkumar S. Patel**.(2020)[20]** conducted a study based on the effect of Lithium and antipsychotic combination regimen on adult hospitalization length of stay in Bipolar Manic Episodes. They used the NIS on 1,435 adult inpatients with bipolar disorder, manic episodes, and those pursuing lithium. To estimate the predictors with 95% CI, a logistic regression model was used to find the odds ratio (OR) for the combination regimen. The combination regimen reduced the LOS of BD patients by almost 2.8 days per inpatient hospitalisation, although there was no significant statistical difference in total charges. The combination regimen's higher efficacy and faster onset of action compared to monotherapy may result in a shorter hospital stay. This study discovered that a combination treatment of lithium and antipsychotic drugs reduced LOS for BD manic episodes by 2.8 days when compared to inpatients receiving lithium alone. As a result, starting the combo regimen on the first day of hospitalisation should be considered an effective model for quicker response.

3. Miguélez Rodríguez A* and Pérez de Mendiola Etxezarraga X **(2021)[21]** 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. The clinical case report of a 28-year-old woman, who has admitted to Psychiatric Unit. She had the complaints of a manic postpartum episode with mixed and psychotic features. During the treatment, she was treated with the combination of lithium carbonate and olanzapine with daily dose of 800 mg of lithium (0.9 mEq/L serum level) and 20 mg of olanzapine. A continuous progression including the psychotic features were observed for a period of one month. By Observation the patient gain the 2 kg of body weight (with a BMI of 24.2 kg/m2) was reported as a side effect. Young Mania Rating Scale results 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. In the first, adding olanzapine to lithium or valproate significantly improved treatment efficacy in manic or mixed episodes. The third controlled trial found similar results, demonstrating that patients who maintained combination therapy (olanzapine plus lithium or valproate) had a longer time to relapse than those who discontinued antipsychotic treatment. The final study is a cohort study that demonstrates that rehospitalization following a manic episode is much lower in patients getting combination medication (olanzapine + lithium or valproate) than in those receiving lithium alone. In a summarised case report reflected in the use of combination therapies (concurrent use of SGA with mood stabilizers) is a suitable treatment in BD. In certain

therapeutic conditions, including as severe episodes with psychotic or mixed features, it may be more beneficial than monotherapy. According to the study's findings, the combination of olanzapine and lithium may be one of the combinations with the best scientific evidence in its favour.

4. Shoja Shafti S **(2020)**[22] conducted a double blind clinical trial using Mood Stabilizer and Third Generation Antipsychotic in an acute manic phase investigation. The current trial's goal is to compare lithium with aripiprazole in a group of patients with a diagnosis of acute mania. For four weeks, 30 male inpatients with bipolar I disorder were included in the trial and given either lithium carbonate (800-1200mg/day) or aripiprazole (20-30mg/day) (n=15 in each group). (MSRS) was the primary assessment scale for the outcomes and other scales such (BRMS), (SAI) (CGI-G) have been used as secondary outcome measures. According to this study, while both aripiprazole and lithium were effective in treating manic symptoms, lithium treatment was superior.

5. Harald Scherk, MD; Frank Gerald Pajonk, MD, PhD; Stefan Leucht **(2007)**[23] A meta-analysis of the efficacy and safety of SGAs in the treatment of acute mania was undertaken using a systematic review and meta-analysis of randomised controlled trials. In this metanalysis , Data Sources were taken by a randomized controlled trials comparing SGAs with placebo, first-generation antipsychotic drugs, or mood stabilizers (MSs) in the treatment of acute mania were searched for in the PsiTri and MEDLINE databases (last search: May 2006).then the data's was extracted based in the Data on efficacy, global dropout, drop out due to adverse events, dropout due to inefficacy, weight gain, rate of somnolence, and extrapyramidal symptoms were extracted and combined in a meta-analysis. A total of 24 trials with a total of 6187 patients were included. SGAs were much more effective than placebo. The results revealed that combining antipsychotic drugs with mood stabiliser treatment was substantially more beneficial than mood stabiliser treatment alone.

6. Yang Liu, Jun Liang, Qingrong Xia, Xin Zhou, Xuefeng Xie. (2020)[24] investigated the therapeutic efficacy of lithium combined with second-generation antipsychotics, specifically quetiapine, clozapine, olanzapine, and risperidone, for the treatment of manic episodes in bipolar disorder patients (BD). They looked at data from individuals with bipolar disorder who had manic episodes and were admitted to a Class 3A Psychiatric Hospital in Anhui Province between January 2015 and October 2019. The Bech-Rafaelsen Mania Rating Scale (BRMS) was used to enroll patients before and after treatment, and relevant adverse drug reactions were monitored. The analysis of 182 patients' case data revealed substantial differences in BRMS scores on admission and discharge of patients treated with lithium carbonate in combination with each SGA. The chi-square test was done, and the results reveal that there is no discernible difference in the combo therapy. The occurrence of side effects was associated to the length of hospital stay and clozapine medication, according to a logistic regression analysis. The rate of remission after 2 weeks was related to hospital stay, clozapine medication, and age of onset. According to the study's findings, lithium carbonate mixed with 2nd generation anti-psychotics (quetiapine, clozapine, olanzapine, and risperidone) successfully improves the manic symptoms of BD patients who have manic episodes. In terms of efficacy and adverse effect incidence, lithium combined with quetiapine for the treatment of bipolar manic episodes shows advantage.

COMBINATION THERAPY:

According to the 2018 standards, the first-line pharmacological treatment for bipolar disorder manic episodes can be decided between monotherapy and combination therapy based on the need for rapid response, severity of mania, previous history of response, and tolerability concerns. Monotherapy with lithium, quetiapine, valproate, asenapine, or aripiprazole (recommended to try first in order) or combination therapy with SGAs (quetiapine, risperidone, aripiprazole, or asenapine) and lithium or valproate25 are first-line treatments. Unless there are tolerability concerns, combination therapy is more effective (by around 20%) than mood stabiliser monotherapy and is preferred when a faster response is required, in severe manic episodes, or in a history of partial response to monotherapy.[26,27] Combining SGAs and lithium has been shown to be more effective at treating manic and mixed BD episodes, as well as reducing acute illness morbidity, than lithium alone. SGAs taken during the first week of treatment one year after a BD manic episode drastically reduces manic symptoms and prevents re-hospitalization. SGAs are useful for long-term maintenance therapy for bipolar disorder mania, and they reduce relapse rates due to their potent efficacy and improved compliance.[28,29] Even though SGAs have an antagonistic effect on the serotonin 2A (5-HT2A) receptor and the dopamine D2 receptor, there is more dopamine in the mesolimbic system, which improves manic symptoms.[30] Since combination therapy seems to be more effective and has a faster onset of action than monotherapy, hospitalisation time may be reduced.[29] Clinical trials suggest that a combination regimen will help nearly 20% more patients, and studies have also shown that the combination regimen reduces relapse rate and re-hospitalization for BD.[26]

CONCLUSION:

A meta-analysis discovered that a combination regimen of haloperidol, olanzapine, risperidone, and quetiapine was substantially more effective in treating BD manic episodes than monotherapy with a mood stabiliser, but the combination regimen was less well tolerated than monotherapy. The recurrence time of events (mania, depression, or mixed) after a manic episode was longer in those treated with a combination regimen, especially with atypical antipsychotics in combination with lithium/valproate, than in those treated with placebo. According to the APA recommendations, Because of their lower risk of adverse effects, SGAs are preferable over FGAs. The combination regimen had been associated with more adverse effects than monotherapy, and the patterns of safety and tolerability ranged depending on the type of combination, such as tremor, weight gain (with olanzapine), increased sedation (with quetiapine, haloperidol, and asenapine), and akathisia (with aripiprazole). Lithium combined with quetiapine has advantages in terms of efficacy and adverse effects for the treatment of bipolar manic episodes.

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