



**LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY
VERSUS MONOTHERAPY IN TREATMENT OF BIPOLAR
DISORDERS: AN OBSERVATIONAL COHORT STUDY**

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ABSTRACT

Background: Bipolar disorder is one of the lifelong psychiatric illness affecting the population. Lithium and sodium valproate are each recommended as a monotherapy for preventing relapses in patients with bipolar disorders and are sometimes used in combination. However combination and monotherapy have never been compared rigorously. **Aim:** To compare the effectiveness of combination therapy

of lithium and sodium valproate with the monotherapy in the treatment of bipolar disorders in the clinical practice. **Methods:** An observational cohort study was performed in the psychiatric hospital settings among the individuals who were diagnosed with BPAD and randomly allocated to 3 groups among which one group received the lithium alone and another group received sodium valproate monotherapy and a third group with a combination of lithium and sodium valproate during the period from jan 2015 to march 2015. **Results:** A total of 75 participants were included in the study, among which 25 received the lithium monotherapy and 25 received the sodium valproate monotherapy. combination of lithium and sodium valproate was given to 25 patients. from the study, it was found that the reduction in the symptoms and better prognosis was observed among the participants who received the combination therapy. **Conclusion:** In daily clinical practice, treatment with combination of lithium and sodium valproate was found to be superior to individual monotherapy.

KEYWORDS: Bipolar Disorder, Lithium, Sodium Valproate, Treatment.

INTRODUCTION

Bipolar disorder is one of the illness of the brain which shows extreme cycles in person's mood, thinking, energy level and behavior. It is usually characterized by episodes of depression and mania or both at a time. Due to this unusual swings or shifts of mood it was previously called as "manic-depressive psychosis" and "dual form of mental illness". Bipolar disorder appears in four forms mania, depression, mixed episodes (both mania and depression) and hypomania (irritable moods).^[1] As the mood swings in this illness it is hard to diagnose and differentiate its type. It's a life long illness for many of the patients. Due to this impact of illness and swings of mood it effects relationships, career, distress, loss of life, longevity and self-esteem.^[3] Mostly adolescents are prone to onset of disease when compared to other age groups and there is a strong genetic basis proving this statement. Rapid cycling with or without psychotic features are associated with treatment resistance and adherence.^{[17][7]} This illness recovers overtime with usually longer duration of treatment, but there is a marked tendency of recurrence while mostly shows lifetime rapid cycling. This longer duration of treatment prevents relapse. Sudden discontinuation of treatment cause serious effects.^[18] Due to all these factors bipolar disorders causes significant psychological and socioeconomic burden on both patients and their care givers. If this disorder is not treated it leads to increased number of episodes, increased hospitalization.^[3]

TREATMENT OF BIPOLAR DISORDER

This unusual cyclic mood disorder can be treated with different types of medicines which belong to class mood stabilizers, anti depressants, antipsychotics and rarely anti convulsants. Mood stabilizers maintain the both elevated and depressive mood of the patient i.e; mania or depression or both phases of the patient. For this job Lithium has created its own identity from the past five decades. Antidepressants usually manage the bipolar depression. To an extent antipsychotics have been treating manic episodes as they too have some mood stabilizing properties. In simple words they might seem to prevent the future episodes of illness. As the medicines play a critical role in management of bipolar disorder they have to be given to the patient correctly which includes right drug with right dose at right time for effective treatment (either monotherapy or combination therapy). Along with the medications therapies like cognitive behavior therapy, speech therapy etc shows effectiveness in the treatment. In the severe stage Electroconvulsive therapy (ECT) may also be recommended. Some studies suggest that anti convulsants like valproic acid helps a lot in stabilizing the mood.^[11]

LITHIUM

Lithium is considered as gold standard drug for treatment of bipolar disorder and remains of first line treatment option yet its actual mechanism of action is unclear but it is said that it works with help of second messengers and enhancing 5-HT responses.^[3]

The plasma concentration of lithium should be monitored periodically. The usual therapeutic concentration maintained should be 0.8 – 1.2 mmol/l considering inter-patient variability, more than this range clinical vigilance is suggested as it may produce its adverse effects like hypothyroidism, weight gain, parathyroid problems etc. Usually lithium is more effective in treatment of mania. Now a days trials shows evidence that lithium is effective against depression and prevent the risk of suicide.^[2] Dose should be tapered before discontinuation of the therapy. Sudden cessation may cause decreased kidney function, cognitive impairment and tremor can occur. Discontinuation of lithium therapy should be done atleast within time period of 2-4 weeks except in medical emergency or overdose. Discontinued of lithium within a period of less than 2weeks may cause increased risk of manic relapse.^[7] Lithium has slow onset of action and a weak sedative property.

Sodium Valproate

Among all the anticonvulsants studied only sodium valproate and carbamazepine showed effectiveness towards mania. Comparatively Sodium valproate seems to be more effective than carbamazepine.^[3] Some studies suggest that the efficacy of sodium valproate reaches equivalent to that of lithium in mania. Usually a plasma concentration of 43mg/l is considered as therapeutic range and concentration above 122mg/l is toxicity level. The effectiveness is accelerated by using loading dose. Dose of 30mg/kg/day is usually used. Due to high therapeutic index than lithium and equivalent efficacy to that of lithium it is being used in maintenance therapy. Side effects can be minimized by reducing the dose. Side effects usually include weight gain, sedation and hair loss are more common^[7]. The exact mechanism of action is still unclear but seems related to enhance GABA which is an inhibitory neurotransmitter.^[3]

Concept of double mood stabilizer

Recent studies show that combination therapy of lithium and sodium valproate is more effective than monotherapy i.e; lithium or sodium valproate alone in many patients.^[7] Among all combinations lithium and sodium valproate combination is considered as best. Combination therapy also includes addition of antipsychotics. This combination therapy can

be used during episodes of bipolar and also during maintenance therapy. Some of the studies in some countries include the combination therapy of sodium valproate and lithium carbonate is not effective in all patients. These combination treatments produce adverse effects like neurotoxicity and interact with most of drugs. In this article the main focus is given on the relationship of mutual actions of these drugs.^[14] The study of Chinese criteria of classification and diagnostic of mental disorder 3rd (ccmd-3) showed that patients showed significant improvement in the first week of treatment including verbal activity, flight of thoughts, self esteem, mood, hostility and sleep disturbance. In the second week patients showed improvement in sexual activity, social contact, noise level and verbal activity. In the fourth week a marked decrease in motor activity, hostility, mood, self esteem, social contact, sleep disturbance, sexual interest and verbal activity were observed. This treatment group of combination treatment is compared with lithium monotherapy group and sodium valproate monotherapy groups and results showed effective treatment towards combination therapy^[14]. For resistant bipolar disorder triple drug regimen (lithium, sodium valproate and an antipsychotic) is used.^[3]

INCLUSION CRITERIA

Both Males and females of age 20-50 years who were diagnosed with bipolar disorder in partial or complete remission was included in the study.

EXCLUSION CRITERIA

The patients suffering with any other comorbidities or systemic illness were excluded.

STUDY METHOD AND DATA COLLECTION PROCESS: Study includes the comparison of monotherapy and combination therapy with the lithium and sodium valproate to prevent mood episodes and follow up were done up to 3 months period. Reviewers extract the data concerning the individual patient characteristics, intervention details and outcomes measures.

RESULTS AND DISCUSSION

A total of 75 participants were included in the study, among which 25 received the lithium monotherapy and 25 received the sodium valproate monotherapy. Combination of lithium and sodium valproate was given to 25 patients. From the study, it was found that the reduction in the symptoms and better prognosis was observed among the participants who received the combination therapy. The results were compared with the another study by Geddes JR et al ;

in which it was found that For people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy.

The Bech-Rafaelsen Mania Scale (BRMS) and the Hamilton Depression Scale (HDS) have been used for assessing the severity of bipolar disorder. our results seem to indicate that the improvement in assessing manic-depressive states of bipolar disorders is best possible by using these two rating scales.

CONCLUSION

Compared to lithium, sodium Valproate is highly used in the treatment of bipolar disorders due to its safety and efficacy during the past 2 decades. In daily clinical practice, treatment with combination therapy of lithium and sodium valproate was found to be superior to individual monotherapy. we believe that this data provide supplemental evidence that adds to results from randomized controlled trials on lithium vs valproic acid.

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