

# Comparing Lithium With Valproate for Clinical and Social Status of Bipolar Disorder Patients in Inter-Episode Interval: A Retrospective Comparative Study

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## Abstract

**Background:** Our aim was to compare the efficacy of Na valproate with lithium in prolonging the time to mood episode recurrence in patients suffering from bipolar disorder (BD) type 1. Patients' social and occupational functioning in the inter-episode interval was also compared.

**Methods:** A total of 324 patients that were admitted in our psychiatry ward with diagnosis of BD, manic phase, were surveyed for their past psychiatry history. The patients entered the study if they had adhered to their mood stabilizing medications from their past mood episode till this current mood episode. A total of 169 patients were on lithium (mean dose: 785.7 mg) and 155 patients were on Na valproate (mean dose: 734.3 mg) while admitted. The time period the patients were in the inter-episode interval was compared between the two groups. The patients' occupational and social functioning in the inter-episode interval was also compared.

**Results:** The inter-episode interval was 28.7 months in the patients taking lithium and 29.4 months in the patients on Na valproate. There was no significant difference in this regard between the two groups ( $P = 0.564$ ). Furthermore, rates of substance abuse (0.561), divorce (0.543), suicidal attempt (0.693) and unemployment ( $P = 0.453$ ) in the inter-episode interval did not differ significantly between the lithium and valproate groups.

**Conclusions:** Na valproate was demonstrated to be as effective as lithium in preventing mood episode recurrence in bipolar patients. Our patients also demonstrated comparable occupational and social status in the inter-episode interval.

**Keywords:** Valproate; Lithium; Bipolar disorder

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## Introduction

Bipolar disorder (BD) is a recurrent major psychiatry disease that causes disability worldwide and is associated with significant healthcare costs [1]. BD is associated with elevated risk of suicide attempts and deaths [2].

In the past, emphasis was placed solely on the treatment of acute episodes of BD; recently, the importance of mood recurrence prevention and inter-episode functioning has been recognized [3]. The frequent recurrences of mood episodes in BD are associated with poorer functioning, psychiatric and medical comorbidities, and increased odds of sociality, disability, unemployment, and re-hospitalization [4, 5].

For many years, lithium was the only mood stabilizer in common use, and it remains an agent of first choice in treatment of manic phase of BD [6]. Valproate is an anticonvulsant drug whose efficacy in treatment of acute mania in BD has been also shown [6]. In several meta-analyses of trials of individual drugs versus placebo in treatment of mania, efficacy measures were similar for lithium and valproate and did not indicate clear superiority of one agent over the other [7-9].

In studies of mood recurrence prevention in BD patients, the long-term efficacy of lithium and valproate in preventing depressive or manic/mixed relapses has been shown in several studies [10-12]. Pharmacological treatments during bipolar maintenance should prevent manic and depressive relapse, reduce residual symptoms, suicidal risk, cycling frequency, and mood instability, and improve functioning [13].

Our objective in this survey is to compare Na valproate with lithium in regard with prolonging inter-episode interval in BD type 1. Also this study would compare valproate with lithium in the inter-episode phase of BD patients regarding: 1) Enhancing patients' functioning; 2) Preventing substance abuse; 3) Preventing suicide attempts; 4) Preserving marital stability; and 5) Reported adverse effects and medication satisfaction.

## Patients and Methods

### Patients

Our survey is a retrospective comparative study. The hos-

**Table 1.** The Patients' Clinical and Demographic Status

	Lithium group	Valproate group	P value
Age (mean year)	33.51	32.34	0.473
Sex (women %)	52	49	0.321
Education (years)	12.7	11.9	0.398
Positive FHx for BD (%)	38.4	36.9	0.543
Mood episode on admission	Mania	Mania	
Previous hospital admissions (N)	2.2	1.9	0.651

FHx: family history; BD: bipolar disorder; N: number.

hospital charts of all the patients with diagnosis of BD type 1 (manic type) that were admitted in our psychiatry ward from June 2011 to June 2016 were reviewed. A patient's hospital chart was selected for study based on the following criteria: diagnosis of BD type 1, manic episode, on admission by a board certified psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria; age between 18 to 65; and treatment adherence to Na valproate or lithium in their recent inter-episode interval. Treatment adherence was evaluated by both patients and care givers' reporting. Exclusion criteria were: taking other medications or psychology interventions during inter-episode interval, having medical problems, substance abuse before the recent inter-episode interval and being mentally retarded. Of 483 charts that were reviewed, 369 met our study criteria. Necessary information for our survey could be obtained only from 324 charts (169 patients in the lithium group and 155 patients in the Na valproate group). The mean dosage of lithium was 785.7 mg and the mean dosage of valproate was 734.3 mg during the recent inter-episode interval.

### Assessments

Information regarding the time in remission, employment status, marital stability, substance abuse, suicidal attempt and satisfaction about the administered mood stabilizer was gathered from the patients' hospital charts. If there was missing information in the charts, we tried to collect that by asking directly from the patients or their families.

The patients were monitored for mood symptoms in the interval between their past mood episode till their current mania recurrence by their psychiatrists. Inter-episode interval was measured by the time the patients were reported to be stable by their psychiatrists following them in the inter-episode interval. Employment status was assessed by the number of months being at work. Marital stability in each group was measured by the number of divorces in that group. Substance abuse in the groups was evaluated by the number of patients that had started substance abuse. The patients were not abusing any substance before the recent inter-episode interval. Patients' satisfaction about mood stabilizer and adverse effects were evaluated by special questions from the patients. The number of the patients that reported satisfaction with their mood stabilizer was com-

pared between the two groups.

### Statistical analysis

Necessary information was collected from the patients' charts or directly asking the patients and their care givers. Obtained data were statistically analyzed with IBM SPSS Statistics 21.0 for Windows (IBM Corp., Armonk, NY, USA). Chi-square and independent *t*-tests were used, as appropriate, to compare the demographic and clinical characteristics of the two groups. *P* values less than 0.05 were considered as statistically significant.

The study was approved by the ethics committee of Shiraz University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research, 1964.

### Results

Our retrospective study surveyed the past psychiatry history of BD patients that were admitted in Ebnesina Hospital from June 2011 to June 2016. The patients' demographic and clinical data at baseline are depicted in Table 1. The two groups did not differ significantly in regard with age, sex, education, family history of BD and previous hospital admissions.

The mean time of remission period in lithium and Na valproate groups were 28.7 and 29.4 months, respectively. Indeed, our study showed that lithium or Na valproate did not differ significantly in prolonging the time to mood episode recurrence (*P* = 0.564).

Table 2 demonstrates the patient's clinical and social status in their recent inter-episode interval. The patient's employment status (number of months being employed) did not differ significantly (*P* = 0.453) between the two groups. The number of patients that had started any substance during the recent inter-episode interval did not differ significantly between the groups (*P* = 0.561) as well.

The adverse events mainly reported by patients taking lithium were dizziness, dysphoria, memory problem and sleepiness. In the other group the patients complained more about drowsiness, sleepiness, tremor and weight gain. The number of the patients in the lithium and valproate groups that reported satisfaction with their mood stabilizers did not differ signifi-

**Table 2.** Patients' Inter-Episode Status

	Lithium group	Valproate group	Statistics (P value)
Inter-episode duration (months)	28.7	29.4	0.564
Unemployment (months)	10.7	11.4	0.453
Substance abuse, N (%)	25 (14.7)	20 (12.9)	0.561
Patients' satisfaction with medication (%)	74.5	72.9	0.632
Divorce, N (%)	44 (25.8)	42 (27.1)	0.543
Suicide attempt, N (%)	15 (8.8)	14 (9.03)	0.693

N: number.

cantly between the two groups ( $P = 0.632$ ).

## Discussion

Our retrospective study showed that Na valproate is as effective as lithium in prolonging the time to mood episode recurrence. It also demonstrated that rates of unemployment, divorce, substance abuse and suicidal attempt were not significantly different between the groups in the inter-episode interval. Patients of the two groups also had similar rate of satisfaction about their medication.

For many years, lithium was the only mood stabilizer in common use, and it remains an agent of first choice in the treatment of acute mania and maintenance of BD [6]. Moreover, several studies have revealed the efficacy of valproate in both treating mania and preventing mood episodes in BD patients [14-16]. Several studies have compared valproate with lithium for both acute and maintenance phases of BD. In a randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in patients with BD, both lithium and divalproex were adequately tolerated and efficacious [17]. In another trial comparing divalproax with lithium for initial treatment of mania in adolescent patients, both treatments had comparable results [18]. A systemic review of pharmacological treatments in maintenance phase of BD patients revealed efficacy for both valproate and lithium [15]. However, in a long-term maintenance therapy of BD patients, divalproex was superior to lithium in longer duration of successful prophylaxis in the study and less deterioration in depressive symptoms and Global Assessment Scale scores [19]. Our study revealed that Na valproate was as effective as lithium in preventing mood episode recurrence.

Patients suffering from BD are at elevated risk of suicide attempts and suicide [20-22]. The extensive literature on the impact of lithium use on both suicide attempts and suicide deaths in BD samples demonstrated that lithium was significantly associated with a reduced risk of suicide compared to placebo [23, 24]. Nonetheless, several studies have found higher rates of suicidal events in patients on valproate compared to lithium [25, 26]. However, there are surveys that have failed to find differences in suicidal behavior between valproate and lithium [27, 28]. Our research did not find any significant difference between lithium and valproate groups regarding suicidal behavior.

Patients with BD frequently report co-occurring substance use disorders more than that in the general population [29]. A current or past comorbid substance use disorder may lead to worse outcomes for BD, including more symptoms, more suicide attempts, longer episodes, greater treatment non-adherence and lower quality of life [30-32]. Other studies have reported better functioning and quality of life and less suicidal attempts in bipolar patients without history of substance abuse compared to those with current or past history of substance abuse [33, 34]. Valproate has shown efficacy in reducing alcohol consumption in patients with BD and comorbid alcohol dependency in one study [35]. Evidence from several studies suggests the rate of substance abuse in rapid cycling bipolar patients to be about 40% [36, 37]. Our study reveals the rate of substance abuse in the lithium and valproate groups to be 14.3% and 12.9%, respectively. Our study shows that the rate of substance abuse by our patients in both lithium and valproate groups did not differ significantly.

There are researches indicating that there are high rates of divorce and volatility in marital relationships of patients with BD. Care-giving burden and psychological distress among spouses of patients with BD have been reported to be high [38, 39]. Therefore, studies on BD patients need to survey all aspects of their social life. Two previous studies had reported the rate of divorce in bipolar patients to be 24% and 28% respectively [40, 41]. Our study showed that about 25.7% of marriage of BD patients on lithium and 27.1% of marriage of BD patients on valproate had led to divorce. There were no significant differences in this regard between the two groups.

Our study is a retrospective survey. Most of our information was gathered from the patients' hospital charts. Clinical trials are needed to better compare lithium and valproate for their efficacy in preventing mood episode recurrence. Patient's occupational and social functioning in the inter-episode intervals also can be monitored and surveyed more precisely in prospective studies.

## Conclusions

Our study showed that valproate is as effective as lithium in preventing mood episode recurrence in bipolar disorder. Furthermore, patients taking Na valproate and lithium did not reveal significant difference regarding occupational functioning, rate of divorce, substance abuse, suicidal attempt and medica-

tion intolerability in inter-episode interval.

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## Conflict of Interest

None to declare.

## Informed Consent

All patients provided written informed consent to participate in the study.

## Author Contributions

All the authors were involved in designing the method of this research and contributed to carrying it out. AM wrote the paper and submitted it to the journal.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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