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Original Research Article

A Prospective Observational Comparative Study of Efficacy and Safety of Lithium vs Quetiapine and Divalproex Sodium in Treating Bipolar Disorder

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Abstract

Aim and Objective: Bipolar disorder is a very common illness that significantly affects how well people operate. Over 50% of people experience depressive symptoms during their disease, which can result in suicidal thoughts and actions or self-harm. There are no direct clinical studies comparing efficacy and safety of lithium versus quetiapine and divalproex for treating bipolar disorder. We performed this open-label, enriched, naturalistic study with a 24 week follow-up in bipolar disorder patients to examine the efficacy and safety of quetiapine and divalproex sodium (QTP+DVP) and Lithium (Li) in maintenance treatment.

Methods: Participants (n = 313) with bipolar illness were treated with either lithium (Li) monotherapy or divalproex plus quetiapine (DVP + QTP) combination therapy in this prospective observational real-world experiment.

Results: In terms of pole-specific recurrence, the groups of quetiapine and divalproex outperformed the lithium group statistically in preventing the recurrence of depressive episodes ($\chi 2 = 6.62$, $p = .001$). During the study phase, the Li group experienced higher increase in lipid and glucose levels than the QTP+DVP group.

Conclusion: According to this prospective naturalistic study, quetiapine and divalproex are more effective than lithium in preventing both mania and depression episodes in bipolar disorder patients. There is no significant difference in the safety profile of lithium in comparison to quetiapine and divalproex sodium. Large-scale randomized trials are necessary in the future to confirm our findings.

Keywords: Quetiapine; Maintenance; Bipolar disorder; Lithium; Divalproex.

Introduction

The majority of bipolar disorder cases start in adolescence, and patients usually have recurrent emotional outbursts that are worse and more frequent during the course of their illness, especially in the early stages [1]. Additionally, compared to their counterparts who are not afflicted, young people with bipolar disorder have a much higher disability [2], a higher risk of suicide [3], a lower quality of life [4], and a severe functional impairment [5]. The hallmark clinical symptom of bipolar I disorder is mania, which is defined by times of unusually high or irritable mood along with an unusual and sustained increase in energy or activity.

Mania in young people can be effectively treated with a number of pharmaceutical drugs [6- 8]; nevertheless, treatment response varies greatly, and choosing the best pharmacological agent for a given patient is still primarily an empirical process. There is currently no trustworthy way to identify patient subgroups that have a higher chance of responding to a particular drug. Furthermore, diverse molecular targets and unique neurophysiologic effects may be exhibited by pharmaceutical drugs with comparable antimanic capabilities. Lithium and quetiapine appear to have distinct molecular targets and neurophysiological effects among the medications that are useful in treating mania in young people. In randomized, placebo- controlled clinical trials, lithium [9] and quetiapine [10] have both shown promise in treating mania in kids and teenagers.

Few trials comparing the effectiveness of various drugs used to treat mania in young people with bipolar disorder have been conducted to date. In a randomized controlled trial of early age mania,

lithium and risperidone were evaluated; risperidone produced greater response rates than lithium [11]. Furthermore, quetiapine has been shown to be more effective than divalproex in terms of response and remission when used to treat mania in adolescents [12]. There are no direct clinical trials comparing lithium and quetiapine or quetiapine and divalproex for mania in this age group, despite comparisons between the two medications in adult populations.

There is debate on the effectiveness and possible drawbacks of long-term prophylactic treatment for bipolar disorder patients. Although mortality following anticonvulsant treatment has been documented [12,13], mood stabilizers may be considered for maintenance treatment due to fewer side effects despite the modest therapeutic performance [14,15], given the growing concern about the increased morbidity and mortality associated with atypical antipsychotics [16,17]. However, there is currently inadequate data to evaluate the balance between the benefits and acceptability of atypical antipsychotics and mood stabilizers in clinical practice because few research have examined their efficacy. We performed this open-label, enriched, naturalistic study with a 24 week follow-up in bipolar disorder patients to examine the efficacy of quetiapine and divalproex sodium (QTP+DVP) and Lithium (Li) in maintenance treatment.

Methods

Study

This observational study was conducted by pharmacology department of Jawarhar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar in a collaboration with the department of psychiatry from January 2024 to June 2025. The patients had to be at least eighteen years old, diagnosed with bipolar I disorder according to the DSMIV, have experienced at least one mixed episode, mania, or depression in the two years before the study, have an acute mixed episode, mania, or depression at enrollment, or have experienced a mixed episode, mania, or depression within 26 weeks in the past (as recorded in their medical records), and be receiving Li/ QTP+DVP treatment.

Regardless of whether a patient had a mixed, manic, or depressive index episode, they could still be included. A DSM-IV diagnosis of an anxiety disorder, known intolerance to active treatments, pregnancy or lactation, substance or alcohol abuse or dependence, concurrent medications that could adversely affect quetiapine levels, and unstable or inadequately treated medical illness were among the exclusion criteria for the precategorisation phase.

Procedures

Participants in the study were to be outpatients between the ages of 18 and 65 with a DSM-IV diagnosis of bipolar I disorder and be suffering hypomania or mania with a Young Mania Rating Scale (YMRS) score of ≥15. For the first four weeks of the 12-week study, participants were assessed weekly; after that, they were assessed every two weeks. Bipolar disorder (BDI) was confirmed at screening using the Structured Clinical Interview for DSM-IV (SCID) [7]. Confirmation of the inclusion and exclusion criteria, laboratory testing, a physical examination that included an eye exam, and an EKG (if the person was older than 50) were also included in the screening visit. Study medication was administered concurrently with other psychiatric drugs recommended to participants at study entrance. At every evaluation, the frequency and seriousness of adverse events (both general and medication- related) as well as withdrawals brought on by AEs were noted.

Medications

Lithium was started at 600 mg/day where as DVP was initiated as 500 mg/day and QTP was initiated a 100mg/day. An unblinded physician encouraged these targets to be maintained with real-world application, but slower titration or declines were permitted for tolerance.

Statistical Analysis

SPSS software, version 17, was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). The Student's t test was utilized for continuous variables and the chi- square test or Fisher's exact test for categorical variables in order to compare the baseline characteristics between the two groups.

At the conclusion of follow-up, the recurrence rates of any mood episodes between the two groups were compared using the chi-square test. Time-to-recurrence curves were created using the Kaplan-Meier method, and the log-rank test was performed to examine the differences between the two groups.

Results

Patient disposition and characteristics

Table 1 shows the baseline clinical and demographic information for the patients. Age, sex, education, family history of BD, and prior hospitalizations did not significantly differ between the two groups. A total Patients in the Li and QTP+DVP groups shared comparable demographic traits and baseline disease severity.

Table 1: Comparing the lithium and divalproate sodium groups' sociodemographic characteristics and

confounding variables

Parameters	Lithium Group (N=150)	Quetiapine and Divalproex sodium Group (N=163)	P Value
Age (mean year)	41.8 ±12.8	42.1±11.9	0.572
Weight (mean	80.8 ±18.6	80.3±17.9	0.372
Gender			
Male (N%)	66 (44%)	70 (43%)	0.362
Female (N%)	84 (56%)	93 (57%)	0.583
Education (Years)	14.9±7.2	15.6±8.1	0.629
DSM-IV diagnosis of bipolar I disorder, most recent episode, n (%)			
Mania	73	78	0.238
Depression	44	48	0.374
Mixed	33	37	0.295
Positive family History of BD(%)	57(38%)	59 (36%)	0.297
Rating scale, mean (SD)			
MADRS	3.4 ±3.5	3.7 ±3.8	0.673
YMRS	2.5 ±3.1	2.2 ±2.8	0.721
Comorbid alcohol abuse/ dependence (N%)			

MDRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale.

"Recurrence" was defined as starting an antipsychotic, antidepressant, mood-stabilizing medication (other than lithium or divalproex), an anxiolytic (other than lorazepam), or any other medication to treat mania, depression, or a mixed event; being hospitalized for mania, depression, or a mixed event; having YMRS or MADRS total scores of at least 20 at two consecutive assessments, or at the final assessment if the patient stops taking the medication; or withdrawing from the study by the patient if the researcher believes the discontinuation was caused by an event (mania, depression, or mixed). The number of events that took place is represented by the data.

Recurrent rates of any mood episode: Table 2 displays the study's main findings. In terms of pole-specific recurrence, the groups of quetiapine and divalproex outperformed the lithium group statistically in preventing the recurrence of depressive episodes ($\chi 2 = 6.62$, $p = .001$). According to our definition, the Quetiapine and Divalproex sodium Group outperformed the Lithium Group in terms of the rates of symptomatic recurrence and syndromic recurrence of manic or depressive episodes, and the groups differed significantly from one another (Table 2). In this investigation, no recurrence of mixed episodes was seen.

Table 2: Key findings from the 24 week follow-up

Recurrence definition	Lithium Group (N=150)	Quetiapine and Divalproex sodium Group (N=163)	P value
Mania	22 (14.6%)	5 (3.06%)	0.001
Symptomatic recurrence [a]	7 (4.6%)	1 (0.6%)	0.006
Syndromic recurrence [b]	15 (10%)	4 (2.5%)	0.005
Depression	30 (20%)	12 (7.4%)	0.001
Symptomatic recurrence [a]	22 (14.6%)	7 (10.4%)	0.006
Syndromic recurrence [b]	7 (4.6%)	2 (1.2%)	0.002
Any mood episode	52 (34.6%)	21 (12.9%)	0.001
Symptomatic recurrence [a]	30 (20%)	12 (7.4%)	0.005
Syndromic recurrence [b]	22 (14.6%)	8 (4.9%)	0.001

[a]Score ≥ 12 on Young's Mania Rating Scale or ≥ 7 on Hamilton Depression Rating Scale, or if the patient's condition required an increase in the dosage of olanzapine or lamotrigine.

[b]The patient's condition met the DSM-IV-TR criteria for manic or depressive episode or the patient had active suicide ideation.

Table 3 shows the average changes in weight, BMI, glucose, HbA1c, insulin, and lipid parameters from the time of enrolment to the conclusion period and from the time of categorization until the study's conclusion. During the study phase, the Li group experienced higher increases in triglycerides and glucose levels than the QTP+DVP group. The two medications' prevalent adverse effects, such as sleepiness and weight gain, were tolerable to all other participants. There were no serious drug-related side effects or suicides among the study's patients.

Table 3: Adverse events

AEs (≥5%), n (%)	Lithium Group (N=150)	Quetiapine and Divalproex sodium Group (N=163)	P Value
Metabolic parameters			
Glucose (mg/dL)	4.0	−0.4	0.22
HbA1c (%)	0.2	0.0	0.34
TC (mg/dL)	−0.5	−8.0	0.64
LDL-C (mg/dL)	−2.8	−6.3	0.43
HDL-C (mg/dL)	0.4	1.0	0.48
Triglycerides (mg/dL)	14.1	−21.0	0.33
Weight and BMI parameters			
Weight change (kg)	+0.5	−1.9	0.29
BMI change (kg/m2)	0.2	−0.7	0.32

Discussion

With a one-year follow-up period, this is the first naturalistic observational study to assess the effectiveness of lithium, divalproex sodium and quetiapine in treating bipolar depression. The direct comparison of these two drugs as maintenance treatments for bipolar disorder was made possible by the naturalistic approach, which is similar to actual practice. According to our findings, compared to lithium, quetiapine and divalproex sodium had a longer duration to recurrence of a depressive episode and a lower recurrence rate.

The ultimate goal of treatment for bipolar disorder patients is to prevent recurrence or relapse in order to lessen the overall burden of their lives, particularly that which is brought on by depressed symptoms [18]. Bipolar illness patients experience depressed symptoms for the majority of their lives [19], therefore drugs that can stop both manic and depressive episodes will be very helpful. However, only quetiapine has been shown to be comparatively effective in preventing both manic and depressive episodes among atypical antipsychotics [20,21]. According to our findings, quetiapine and divalproex sodium were superior to lithium as preventative measures against depression recurrence.

In addition to the prevention of depressive episodes, we also found that patients treated with quetiapine and divalproex sodium had a longer duration to recurrence of depression than those treated with Lithium. To control the covariates for the prevention of bipolar recurrence, further analysis of our results revealed that patients with more residual symptoms but no different bipolar subtypes or concurrent antidepressants had a higher risk for recurrence of depression. This suggests that quetiapine and divalproex sodium are effective maintenance treatment for bipolar disorder.

When treating adult patients with an acute manic or mixed episode, direct head-to-head comparisons of lithium and quetiapine have produced conflicting findings. One study found no difference between the two drugs [22], while another found quetiapine to be somewhat better than lithium [23]. Compared to participants receiving lithium, a higher percentage of subjects in our study who received quetiapine and divalproex saw a response to treatment.

The current study has the advantage of employing a continuation study design, which has not been frequently used in prior research on the effectiveness of olanzapine maintenance medication [24]. Previous research findings showed that olanzapine was effective in preventing manic and depressive episodes when it was continued to be administered after the acute phase in patients who responded well to the medication and were tolerable.

Given that lithium does not always demonstrate positive efficacy in maintenance treatment, it is plausible that quetiapine and divalproex were more effective than lithium in preventing bipolar depression in the current observational study [25]. Bipolar disorder patients are typically advised to receive long-term prophylactic treatment in order to avoid experiencing another mood episode [26]. The effectiveness of the recommended agent should be weighed against its safety and tolerability, which are also linked to non-adherence in bipolar disorder patients, as these patients are likely to require medication for the rest of their life [27]. Lithium and quetiapine with divalproex sodium were both usually well tolerated in our study. Nonetheless, there were some variations in the laboratory variables and adverse effects. The mean glucose change in our study varied by treatment group, with larger rates observed in lithium-treated groups. In the quetiapine plus divalproex group, the incidence and incidence density of a single emergent fasting blood glucose reading of ≥126 mg/dL were higher than in the lithium group. Patients included in this study cannot have their incidence and risk for diabetes reliably and accurately determined because the study's design does not include conclusive diagnostic tests. Furthermore, this study revealed that individuals getting lithium treatment saw an average increase in body weight and BMI that was higher than that of patients receiving quetiapine with divalproex. It was also confirmed in one 18-month

trial that receiving lithium therapy was linked to a weight gain of 5-8 kg during the study (3.8 kg during the acute phase and 2.0 kg during the relapse prevention phase) [28].

The current study has a number of limitations. First, the study's naturalistic design permitted the prescription of either drug based on clinical judgment based on the bipolar subtypes and symptom profiles of the patients. Additional restrictions include the short follow-up time, which limits the generalizability of the results to 24 weeks, and the small sample size of both study arms, which results in insufficient power.

Conclusion

According to this prospective naturalistic study, quetiapine and divalproex are more effective than lithium in preventing both mania and depression episodes in bipolar disorder patients. There is no significant difference in the safety profile of lithium in comparison to quetiapine and divalproex sodium. Large-scale randomized trials are necessary in the future to confirm our findings.

Article information

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Author contributions

Sharat Ranjan: Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection.

Barun Kumar Sinha: Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection.

Jeetendra Kumar: Conceptualization; Formal analysis; Methodology; Writing—original draft; data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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