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Safety and effectiveness of divalproex sodium extended release containing regimen in Indian patients with bipolar I disorder in continuation phase: Results of EASED registry

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ABSTRACT

The study was conducted to evaluate the safety and effectiveness of divalproex sodium XR containing regimen in patients with bipolar disorder (BPD) who are in continuation phase. It was an open-label, prospective, observational study conducted from July 2010 to December 2011 at 48 sites across India. Adult patients with bipolar I disorder of manic or mixed type fulfilling the DSM-IV criteria and who were in the continuation phase were included. Safety (primary outcome) was assessed by incidence of treatment emergent adverse events (AEs). Effectiveness (secondary outcome), was evaluated by proportion of patients who did not have a relapse, change in Clinical Global Impression Score-BP version-Severity of Illness (CGI-BP) and Young's Mania Rating Scale (YMRS) score. Data was recorded at three visits: visit-1 (baseline), visit-2 (end of 2 months ± 7 days) and visit-3 (end of 4 months ± 14 days), and summarised using descriptive statistics. $p < 0.05$ was considered statistically significant. A total of 489 and 468 patients were included in the safety and effectiveness analyses, respectively. Of the 66 AEs reported, 57 (89.0%) were mild and 7 (10.9%) were moderate (data missing for 2 events). In total, 75.0% (48/64) of the AEs were related to the study drug. No serious AEs reported ($N = 64$). No relapse observed in 93.3% of patients. There was a significant ($p < 0.0001$) reduction in the YMRS and CGI-BP scores from baseline to visit-3. Our study confirms the results of earlier studies in terms of good tolerability and effectiveness of divalproex sodium XR containing regimen in this study population.

1. Introduction

Bipolar disorder (BPD) causes unusual shifts in mood and is characterised by transition between depression and mania that affects one's ability to function (Hirschfeld et al., 2000). The National Comorbidity Study reported a lifetime prevalence of nearly 4.0% for BPD patients worldwide (Andreasen and Black, 2006). Prevalence of 12-month and lifetime Diagnostic and Statistical Manual of Mental Disorder (DSM)—IV bipolar I disorder in U.S. population was 2.0% (95% confidence interval [CI] = 1.82 to 2.18) and 3.3% (95% CI = 2.76 to 3.84), respectively (Grant et al., 2005). The WHO World Mental Health survey data shows a 0.1% lifetime as well as 12-month prevalence of Bipolar Spectrum in India (Merikangas et al., 2011). However, BPDs, including both bipolar disorder I and II, are frequently not recognised, and thus remain undiagnosed and untreated (Hirschfeld et al., 2000).

BPD imposes a significant economic burden on patients, their families and society as a whole (Dilsaver, 2011). Although there is lack of data on economic burden of BPD in India in published literature, it is likely to be significant. Additionally, patients and their families face significant social and interpersonal burden due to BPD. In a survey conducted in India, more than 90% of family members of patients with BPD reported care-related burden in the absence of clinical interventions (Maji et al., 2012). Similarly, half of the BPD patients showed negative outcomes with difficulties in inter-personal relationships (Chopra et al., 2010).

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Several therapeutic modalities have been recommended for the treatment of BPD. Mood stabilisers, namely, lithium and divalproex are useful in preventing relapse in BPD (Bowden, 2000). Divalproex sodium, an anticonvulsant and mood stabiliser, is widely prescribed to treat BPD as well. Current guidelines recommend valproate (either divalproex or other formulations) as monotherapy or combination therapy with other agents as first-line or second-line treatment for bipolar depression (Goodwin, 2009; Grunze et al., 2010; Yatham et al., 2009). In fact, along with lithium, divalproex sodium or valproic acid is the most commonly prescribed medication for patients with Bipolar Disorder (2012). Lithium and valproate have also been used for the maintenance therapy in BPD (Hirschfeld et al., 2002). A randomised placebo-controlled multicentre study of divalproex sodium extended release (XR) in patients hospitalised for acute mania showed that it was safe and well-tolerated for the treatment of manic episodes (Bowden et al., 2006). A study which compared the efficacy of divalproex, lithium, and placebo in patients with bipolar I disorder demonstrated that divalproex improved several dimensions of depressive morbidity and reduced the probability of depressive relapse, particularly in patients with manic episodes (Gyulai et al., 2003). Similarly, higher response rates (Bowden et al., 2010) and greater remission rates (Bowden et al., 2008) have been seen with sodium valproate when compared to lithium in BPD patients suffering from manic episodes. A 12-week randomised, double-blind, parallel group study on BPD patients showed that divalproex sodium was associated with a better adverse event (AE) profile and significantly less weight gain when compared to olanzapine (Zajecka et al., 2002). In a recent review by Cochrane group that included 6 randomised controlled trials comparing valproate with placebo, lithium, olazapine and lithium plus valproate combination, no difference in efficacy was found between valproate and lithium (Relative risk [RR] 1.02, 95% CI 0.87 to 1.20) though valproate group had fewer participants dropping out of treatment for any cause when compared with placebo or lithium (RR 0.82, 95% CI 0.71 to 0.95 and RR 0.87, 95% CI 0.77 to 0.98, respectively) (Cipriani et al., 2013).

While there are international guidelines about appropriate therapeutic management of BPD, they are predominantly based on evidence gathered from large studies based in Western countries. The rational management of BPD in Indian patients is possible only in light of evidence gathered from contemporary clinical practice in India. There is a scarcity of data supporting the effectiveness and safety of divalproex sodium XR during the continuation phase of BPD patients in India.

The current study was proposed to evaluate the safety and effectiveness of divalproex sodium XR (Depakote XR®) in patients with BPD and is the first of its kind in India. Primary objective of the study was to evaluate the safety of divalproex sodium XR containing regimen in patients with BPD in continuation phase. Secondary objective of the study was to evaluate the effectiveness of divalproex sodium XR containing regimen in patients with BPD in the continuation phase.

2. Materials and methods

The present study was an open-label, single-arm, multicentre, prospective observational study, conducted from July 2010 to December 2011 at 48 sites across India by 48 investigators. The study was conducted according to the guidelines for Good Epidemiology Practice, the principles of Declaration of Helsinki of 1975, as revised in 2000, and in accordance with the local regulations of institutional review board/institutional ethics committee. Written, signed informed consent was obtained from each patient enrolled in the study.

Adult patients with bipolar I disorder of manic or mixed type (as per DSM-IV-TR criteria), who were treated for an acute episode and were in the continuation phase (defined as commencing once euthymia and resolution of psychosis have been achieved), (Sharma et al., 1997) and who were, prescribed divalproex sodium XR containing regimen by the investigator, were included in the study. Patients having any other clinically significant psychiatric disorder, cardiovascular, hepatic, neurological, endocrine or other major systemic disease were excluded from the study.

Case report forms were used to collect data from source documents (patient file, prescription letters or any other relevant document) at three visits: visit 1 (baseline), visit 2 (end of 2 months ± 7 days) and visit 3 (end of 4 months ± 14 days). Demographic features, dose and duration for which divalproex sodium XR was taken, duration of BPD, concomitant medication use, relapse of mania associated with BPD and Clinical Global Impression Score-BP version-Severity of Illness (CGI-BP) and Young's Mania Rating Scale (YMRS) score were recorded in the case report forms.

The total number of AEs reported by patients and the severity, seriousness, and relationship of the AE to the study medication were analysed. Proportion of patients who discontinued study drug at visit 2 and visit 3 and the reasons for discontinuation were documented. Effectiveness of the drug was assessed by measuring the change in CGI-BP and YMRS at visit 2 (end of 2 months ± 7 days) and visit 3 (end of 4 months ± 14 days) compared to baseline (visit 1). Proportion of patients experiencing relapse were also recorded.

2.1. Statistical analysis

Assuming that 23% of the patients would have shown treatment-emergent AEs, with confidence interval of 90% and precision of 3%, it was estimated that 529 patients would be required for the study. A sample size of 635 was determined for the study assuming a drop out of 20%. All categorical variables were presented as proportions and percentages. Continuous variables were reported as mean with standard deviation. A p-value <0.05 was considered statistically significant. All statistical analyses were carried out using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient disposition and demographics

Out of the total 578 patients screened, 489 were included in the safety analyses and 468 were included in the effectiveness analyses; 474 patients completed the study. Patient disposition and the reasons for discontinuation have been summarised in Fig. 1. In the safety analyses set, 345 patients (70.6%) were male and 144 (29.4%, $N = 489$) were female, with a mean age of 35.6 ± 11.1years. In the effectiveness analysis set, 331 (70.7%, $N = 468$) patients were male and 137 (29.3%, $N = 468$) patients were female, with a mean age 35.6 ± 11.0 years. The mean duration of BPD was 69.2 ± 82.2 months and the mean duration of acute episodes was 31 ± 23.7 days. The mean dose of divalproex sodium XR taken was 907.9 ± 316.1 mg/day and 883.5 ± 300.8 mg/day during visit 2 and 3, respectively. Divalproex sodium XR was taken for a mean duration of 65.1 ± 16.0 and 104.5 ± 28.1 days for visit 2 and visit 3, respectively. Olanzapine was the most commonly used concomitant medication at visit 2 [$n = 149$ (44.6%)] and visit 3 [$n = 119$ (39.8%)] (Table 1).

3.2. Safety outcomes

A total of 66 AEs were observed in 56 patients (11.5%, $N = 489$) during the study. Most frequently observed AEs were alopecia (2.5%, 12 events in 12 patients) and tremor (1.4%, 8 events in 7