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Original Research Article

Endoxifen versus Divalproex sodium in Bipolar Disorder (Manic episode): A 6 week Randomised Controlled Study

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Abstract

Background: Bipolar Disorder (BD) is a chronic psychiatric condition characterized by recurrent manic and depressive episodes, significantly impairing daily functioning and quality of life. Conventional treatments such as divalproex have efficacy in managing acute mania but are often limited by side effects, affecting adherence.

Objective: This study aimed to compare the efficacy and tolerability of Endoxifen, a selective Protein Kinase C (PKC) inhibitor, with Divalproex in patients experiencing acute manic episodes of bipolar disorder.

Methods: In a prospective, randomized, open-label parallel-group design, 48 patients diagnosed with BD manic episodes were randomized to receive either divalproex sodium (1,000 mg/day) or endoxifen (8 mg/day) over six weeks. Primary efficacy was measured by change in Young Mania Rating Scale (YMRS) scores, and tolerability was assessed via the UKU Side Effect Rating Scale at baseline and follow-ups at 2, 4, and 6 weeks.

Results: Both groups demonstrated significant reductions in YMRS scores from baseline to week 6 (Divalproex: 32.57 ± 1.42 to 5.12 ± 0.68; Endoxifen: 32.67 ± 1.53 to 5.12 ± 0.94), with no statistically significant difference between groups ($p > 0.05$). However, the Endoxifen group exhibited significantly fewer and milder adverse effects, reflected by lower UKU scores at all follow-ups (Week 2: 4.22 ± 2.50 vs 2.09 ± 1.69; $p = 0.001$). Treatment adherence was high and comparable across groups.

Conclusions: Endoxifen offers comparable efficacy to divalproex in the treatment of acute mania but with a superior tolerability profile, suggesting it as a promising alternative for BD management. Its targeted PKC inhibition mechanism may underlie this clinical advantage, potentially improving patient adherence and outcomes. Larger, blinded trials with extended follow-up are warranted to confirm these findings and explore Endoxifen's role in maintenance therapy and personalized treatment strategies.

Keywords: Bipolar disorder, Endoxifen, Divalproex, Mania, Protein Kinase C, Mood stabilizers.

Introduction

Bipolar Disorder (BD) is a complex psychiatric illness typified by significant mood swings, including emotional highs of mania or hypomania and lows of depression [1]. These mood episodes may last from days to weeks, with the disorder's chronic, recurrent nature leading to persistent challenges in daily functioning.

Patients typically experience repeated episodes throughout their lives, with mood shifts that can substantially disrupt personal relationships and professional activities [2]. Globally, BD has an estimated prevalence of about 1%, transcending cultural and ethnic boundaries [3]. The World Health Organization ranks BD as the sixth leading cause of disability due to its early onset and long-lasting effects [4]. Mortality from suicide is alarmingly high; people with BD are 20–30 times more likely to attempt suicide compared to the general population, with risks spiking during severe depressive phases and mixed affective states [5].

BD most often presents in late adolescence or early adulthood, typically between ages 15 and 25, though later-onset and even childhood presentations are possible [6]. A pronounced genetic element is evident, with heritability estimates between 60% and 80%. First-degree

relatives of people with BD face a markedly increased risk, corroborated by genetic studies highlighting susceptibility genes involved in neurotransmission, intracellular signaling, and circadian rhythms [7,8,9]. The neurobiological foundation of BD centers on the dysregulation of key neurotransmitters—norepinephrine, dopamine, and serotonin—crucial for mood, reward, and emotional regulation [10]. During manic episodes, norepinephrine and dopamine levels rise, accounting for increased energy, euphoria, and impulsivity. In contrast, depressive episodes generally correspond to reduced levels, manifested as lethargy, anhedonia, and low mood [11]. Serotonin, a stabilizing influence on mood and emotion, tends to be suppressed across both poles of the disorder, compounding mood instability [12]. The finely tuned interplay among these neurotransmitters, when disturbed, lies at the heart of BD's symptomatic fluctuations. Recent attention has focused on protein kinase C (PKC), a family of intracellular enzymes deeply involved in neuronal signaling. PKC is believed to play a central role in BD's pathophysiology, particularly during manic states [13]. Elevations in PKC activity, especially during mania, disrupt both pre- and post-synaptic neurotransmission, leading to heightened neuronal excitability and impulsivity [Fig 1] [14]. This significance is underlined by findings that PKC inhibitors, including tamoxifen and its potent metabolite endoxifen, can alleviate manic symptoms and offer a novel treatment avenue targeting these molecular disturbances [15]. Disruptions in PKC-linked intracellular signaling pathways extend to gene regulation and synaptic stability. Aberrant PKC activity influences phosphoinositide pathways that control calcium signaling and neurotransmitter release; these disruptions contribute to excessive excitation and compromised synaptic balance [16]. PKC's involvement in activating nuclear factors such as NF-κB translates to enduring changes in neural plasticity and function, further implicating it in mood instability [17].

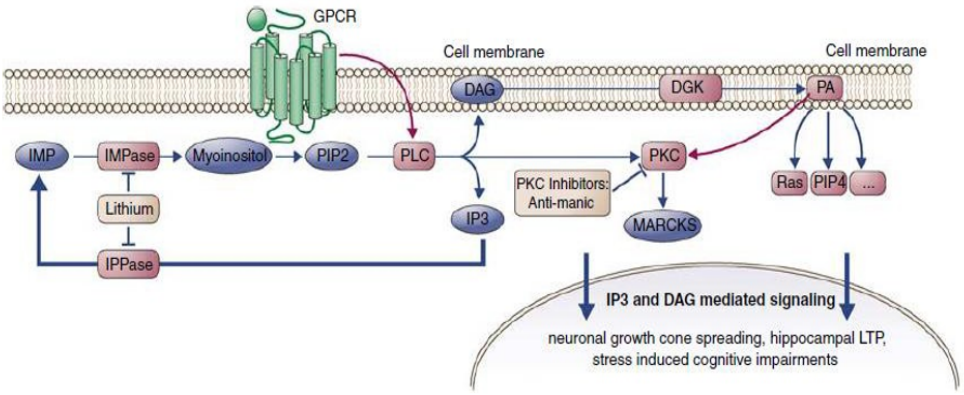

Figure 1: Hawse JR, Subramaniam M, Cicek M, Wu X, Gingery A, Grygo SB, et al. Endoxifen's molecular mechanisms of action are concentration dependent and different than that of other anti-estrogens. PLoS One. 2013;8(1):e54613.

Current BD management draws heavily on pharmacotherapy, supplemented by psychotherapy and lifestyle measures. The foundation remains pharmacological: mood stabilizers and antipsychotics designed to dampen acute symptoms, stabilize mood, and prevent relapse [18]. Lithium is a benchmark mood stabilizer, especially effective for mania and relapse prevention, chiefly by modulating neurotransmitter release and conferring neuroprotection [19]. Divalproex, an anticonvulsant, stabilizes mood by enhancing GABAergic activity and restricting abnormal neuronal firing [20]. Second-generation antipsychotics like olanzapine, quetiapine, and risperidone offer effective acute symptom control via dopamine receptor antagonism and are used for both manic and depressive states [21]. Despite their benefits, existing treatments are limited by significant tolerability issues such as weight gain, gastrointestinal complaints, sedation, and cognitive blunting—especially with second-generation antipsychotics and lithium [22]. Responses to treatment also vary substantially between individuals; many patients obtain only partial relief or struggle with adherence due to side effects, resulting in frequent relapses and hospitalizations [23]. Divalproex, while effective for acute mania and maintenance, brings its own adverse effects, primarily gastrointestinal symptoms, weight gain, hair loss, and the potential for liver toxicity, necessitating careful monitoring [24,25,26].The search for more targeted and tolerable treatments has led to renewed interest in endoxifen, an active metabolite of tamoxifen known for selectively inhibiting PKC [27]. By specifically targeting the dysregulated intracellular signaling central to BD, endoxifen represents a mechanistic advance over conventional mood stabilizers. Preclinical research demonstrates its capacity to reduce manic-like behaviors in animal models, and early clinical trials

suggest it is effective in controlling mania in humans. Ongoing studies seek to further clarify its therapeutic potential [28].

Bipolar disorder remains a significant public health challenge with profound consequences for quality of life, family dynamics, and broader societal productivity. Persistent limitations in the efficacy, tolerability, and adherence associated with current pharmacotherapies underscore the urgent need for novel and mechanism-based treatments. The present study therefore holds particular importance. It evaluates endoxifen—a selective PKC inhibitor—in direct comparison to divalproex, aiming to fill critical knowledge gaps regarding their efficacy and safety in acute mania. By investigating an agent with a novel mechanism, the research has the potential not only to improve therapeutic outcomes and patient adherence, but also to inform future clinical guidelines and enhance our understanding of BD pathophysiology.

The present study aims to assess the comparative efficacy and adverse effects of Endoxifen versus Divalproex in patients diagnosed with bipolar disorder experiencing a manic episode [1]. Specifically, the objectives are to evaluate the improvement in clinical status as measured by the Young Mania Rating Scale Score (YMRS) in patients receiving Endoxifen compared to those receiving Divalproex, and to systematically compare the adverse effect profiles of both medications in this patient population [2,3]. By directly measuring changes in YMRS and carefully monitoring and contrasting the incidence and type of side effects, this study seeks to provide evidence on the relative therapeutic benefits and tolerability of Endoxifen and Divalproex in acute mania, thereby informing the selection of optimal treatment strategies for bipolar disorder.

Material and Methods

This prospective, randomized, open-label, parallel-group clinical study was conducted over ten months, from May 2024 to February 2025, in the Department of Pharmacology in collaboration with the Department of Psychiatry at King George's Medical University (KGMU), Lucknow, India. Each participant was involved in the study for six weeks. Eligibility screening and recruitment took place in the Adult Psychiatry Outpatient Department, where patients with a clinical diagnosis of bipolar disorder in a manic episode, confirmed by consultant psychiatrists, were considered for participation. The study protocol was approved by the Institutional Ethics Committee (IEC: XXI-PGTSC-IIA/P29), and written informed consent was obtained from all participants or their legally acceptable representatives [1]. The sample size was calculated based on the assumption that there would be a 35% difference in efficacy as measured by the change in Young Mania Rating Scale (YMRS) scores between treatment groups. Setting a significance level (α) at 10% and a power of 80%, a minimum of 22 subjects were required per group. To allow for a 10% attrition rate, the target total enrolment was set at 48. The primary endpoint was defined as the proportion of responders at Day 21, indicated by a 50% or greater reduction in baseline YMRS scores [2].

Inclusion criteria for study participation were: diagnosis of bipolar disorder in a current manic phase according to ICD-10 DCR (F31.1), baseline YMRS score greater than 20, age between 18 and 50 years, willingness to provide informed consent or assent, no use of bipolar disorder medications in the preceding five days, and commitment to avoid non-permitted medications throughout the study period. Exclusion criteria comprised co-morbid psychiatric disorders, substance abuse or dependence, the need for additional psychotropic drugs or electroconvulsive therapy, significant medical or surgical illness, abnormal baseline laboratory investigations, the presence of psychotic symptoms, any risk of harm to self or others, and pregnancy or lactation.

Eligible participants were randomized by a computer-generated randomization schedule into two groups. Group A received divalproex sodium 500 mg twice daily (1,000 mg/day, orally), while Group B received endoxifen 8 mg once daily (orally). Both drugs were dispensed from a single-batch, commercially available source: Divalcad (divalproex sodium, Cadila Pharmaceuticals) and Zonalta (endoxifen, Intas Pharmaceuticals). Permitted rescue medications included lorazepam (up to 6 mg/day) for agitation and zolpidem (up to 10 mg/day) for insomnia. Adherence to the assigned medication regimens was monitored through pill counts and reports from caregivers at each clinical visit.

Upon entering the study, participants' socio-demographic and clinical data were recorded. Clinical evaluation and follow-up assessments took place at baseline, Week 2, Week 4, and Week 6. At each visit, the severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS), while adverse effects were systematically documented using the UKU

Side Effect Rating Scale. Drug adherence, occurrence of adverse effects, rescue medication use, and any protocol deviations were recorded meticulously throughout the study duration. Data were initially entered into Microsoft Excel and subsequently analyzed using appropriate statistical software. The diagnostic criteria for inclusion adhered to ICD-10 DCR standards for bipolar disorder, current manic episode (F31.1), ensuring a reproducible and internationally recognized

classification. The YMRS, comprising eleven clinician-rated items, was used to gauge manic symptom severity; a score reduction of 50% or more from baseline was considered a meaningful response. Four items (irritability, speech, thought content, and disruptive/aggressive behavior) were scored 0–8, and the remainder on a 0–4 scale, with a maximum possible score of 60. The UKU Side Effect Rating Scale, employed at each follow-up, covered psychiatric, neurologic, autonomic, and somatic domains to facilitate comprehensive adverse event documentation and to assist with causality assessments. Sociodemographic and clinical information were captured on a structured proforma, and baseline investigations including complete blood count (CBC), random blood sugar (RBS), serum urea, serum creatinine, and liver function tests (LFTs) were performed using automated analyzers (Sysmex XP-100 and Transasia XL-200).

All assessments were scheduled at baseline, Week 2, Week 4, and Week 6, with the same recording procedure for both groups. Each assessment included YMRS and UKU scoring, tracking of adherence and use of rescue medication, and was administered by trained clinicians to ensure consistency and reliability.

Data analysis was performed in SPSS version 21.0 after initial entry into Excel 2022. Categorical variables were described as frequencies and percentages, while continuous data were presented as mean ± standard deviation (SD) or standard error of mean (SEM). The Independent Samples t-test was used to compare YMRS scores at each time point, and categorical data such as adverse event rates and response rates were analyzed by Chi-square or Fisher's exact test. For tracking changes over time and interactions between time and treatment group, repeated measures ANOVA was applied, with adjustments for violations of sphericity as indicated. A p-value less than 0.05 was considered statistically significant, and findings were illustrated using bar charts and line graphs where appropriate. The primary outcome measure was the reduction in YMRS score from baseline to Week 6, where a 50% or greater reduction indicated treatment response. Secondary outcomes included the frequency and severity of adverse effects based on UKU scoring. By integrating measures of both clinical efficacy and tolerability, the study aimed to provide a comprehensive comparison of the outcomes with divalproex and endoxifen in the acute management of manic episodes in bipolar disorder [3,4].

Results

A total of 70 patients were screened for the study. Following application of inclusion and exclusion criteria, 22 patients were excluded—12 due to not meeting inclusion parameters (such as YMRS score below 20 or age outside 18–50 years), 5 with comorbid psychiatric illnesses (including schizophrenia and OCD), 3 with significant medical conditions (CVA, CKD, stroke, hepatic failure), and 2 lost prematurely due to non-adherence before randomization. No patient withdrew consent prior to randomization. Consequently, 48 patients were randomized equally into two groups: 24 received divalproex (Group A) and 24 received endoxifen (Group B).

During the study, three participants dropped out—one from Group A and two from Group B—due to treatment non-compliance or personal reasons. Ultimately, 45 patients (23 in Group A and 22 in Group B) completed all scheduled visits through week six and were included in the final analysis.

Sociodemographic and baseline clinical variables were comparable between groups, as summarized in Table 1. Age distribution showed no significant difference; most participants were aged 21–40 years in both groups. Residency status was largely urban (approximately two-thirds in both groups), with no significant association to treatment allocation. Educational attainment and occupational status were also evenly distributed, with the predominant education levels being secondary school or higher and occupations ranging from homemakers and unemployed to professionals and students. Marital status showed a majority being married (~60%), without significant difference between groups. Body mass index (BMI) categories were similarly balanced, with no statistically significant differences. Clinical history parameters—including past psychiatric history, family history of psychiatric illness, and personal history—were also similarly distributed across groups ($p > 0.05$). The only significant difference observed was in gender distribution; Group A had a higher proportion of males (73.9%) compared to Group B (36.4%) ($p = 0.025$).

Table 1: Combined Sociodemographic and Baseline Clinical Characteristics of Study Participants

Variable	Category	Group A (Divalproex) n (%)	Group B (Endoxifen) n (%)	p-value
Age	11–20	3 (13.04)	2 (9.09)	
	21–30	7 (30.43)	8 (36.36)	0.953
	31–40	7 (30.43)	7 (31.82)	
	41–50	6 (26.08)	5 (22.27)	
Gender	Male	17 (73.91)	8 (36.36)	0.025
	Female	6 (26.09)	14 (63.64)	
Residency	Urban	16 (69.56)	14 (63.64)	0.673
	Rural	7 (30.43)	8 (36.36)	
Education	Illiterate	3 (13.04)	2 (9.09)	0.907
	Primary School	5 (21.74)	6 (27.27)	
	Secondary School	6 (26.09)	7 (31.82)	
	Higher Secondary	5 (21.74)	5 (22.73)	
	Graduate & Above	4 (17.39)	2 (9.09)	
Occupation	Unemployed	6 (26.09)	5 (22.73)	0.914
	Homemaker	5 (21.74)	6 (27.27)	
	Student	4 (17.39)	2 (9.09)	
	Skilled Worker	3 (13.04)	4 (18.18)	
	Professional	3 (13.04)	3 (13.64)	
	Retired	2 (8.70)	2 (9.09)	
Marital Status	Married	15 (62.50)	14 (58.33)	0.939
	Unmarried	5 (29.17)	6 (32.13)	
	Divorced/Separated	3 (8.33)	2 (8.33)	
BMI	Normal	6 (26.09)	6 (27.27)	0.769
	Overweight	8 (34.78)	8 (36.36)	
	Obese	9 (39.13)	8 (36.36)	
Past Psychiatric History	Yes	12 (52.17)	12 (54.55)	0.873
	No	11 (47.83)	10 (45.45)	
Family History	Yes	8 (34.78)	7 (31.82)	0.832
	No	15 (65.22)	15 (68.18)	
Personal History	Yes	5 (21.74)	5 (22.73)	0.936
	No	18 (78.26)	17 (77.27)	

Assessment of manic symptom severity using the Young Mania Rating Scale (YMRS) demonstrated a marked decline over time in both treatment groups. Group A (divalproex) mean YMRS scores decreased from 32.57 ± 1.42 at baseline to 19.16 ± 1.19 at 2 weeks, 10.82 ± 0.90 at 4 weeks, and further to 5.12 ± 0.68 at 6 weeks. Similarly, Group B (endoxifen) showed reductions from 32.67 ± 1.53 at baseline to 19.18 ± 1.26 at 2 weeks, 10.82 ± 0.96 at 4 weeks, and 5.12 ± 0.94 by 6 weeks (Table 2, Figure 2).

The steady decline in scores reflected significant and comparable improvements in manic symptoms in both groups, with a consistent reduction in inter-subject variability as indicated by decreasing standard deviations.

Table 2: Young Mania Rating Scale (YMRS) Scores over Time in Patients Treated with Divalproex (Group A) and Endoxifen (Group B)

Time Point	Group A (Divalproex)	Group B (Endoxifen)	Sig
Baseline	32.57 ± 1.42	32.67 ± 1.53	0.818
2 weeks	19.16 ± 1.19	19.18 ± 1.26	0.963
4 weeks	10.82 ± 0.89	10.82 ± 0.96	0.999
6 weeks	5.12 ± 0.68	5.12 ± 0.94	0.996

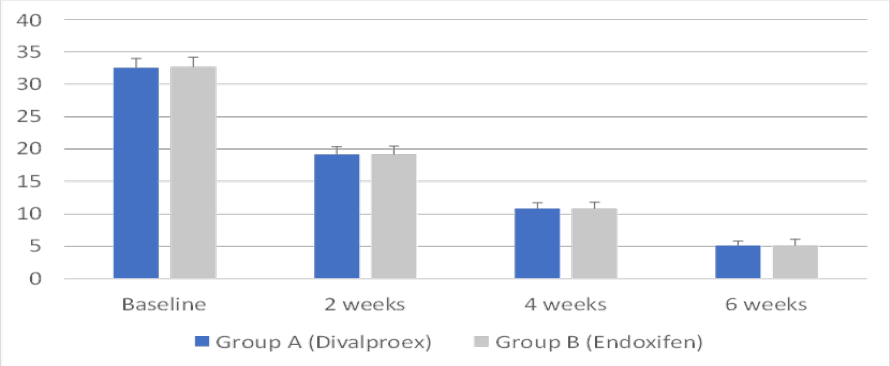

Figure 2: Young Mania Rating Scale (YMRS) Scores over Time in Patients Treated with Divalproex (Group A) and Endoxifen (Group B)

Analysis of adverse effects using the UKU Side Effect Rating Scale revealed a gradual decline in mean side effect scores over time in both groups. Group A's mean UKU score was 4.43 ± 2.50 at baseline, with slight decreases to 4.22 ± 2.50 at 2 weeks, 4.22 ± 2.52 at 4 weeks, and 4.04 ± 2.55 at 6 weeks, indicating relatively stable but mild side effects over the study duration. In contrast, Group B's scores showed a more pronounced reduction from 4.36 ± 3.42 at baseline to 2.09 ± 1.69 at 2 weeks, stabilizing near 2.0 at weeks 4 and 6 (Table 3, Figure 3). This suggests that participants receiving endoxifen experienced fewer or less severe side effects as treatment progressed.

Table 3: UKU Scores over Time in Patients Treated with Divalproex (Group A) and Endoxifen (Group B)

Time Point	Group A (Divalproex)	Group B (Endoxifen)	Sig.
Baseline	4.43 ± 2.50	4.36 ± 3.42	0.937
Week 2	4.22 ± 2.50	2.09 ± 1.69	**0.001**
Week 4	4.22 ± 2.52	2.05 ± 1.65	**0.001**
Week 6	4.04 ± 2.55	2.00 ± 1.69	**0.002**

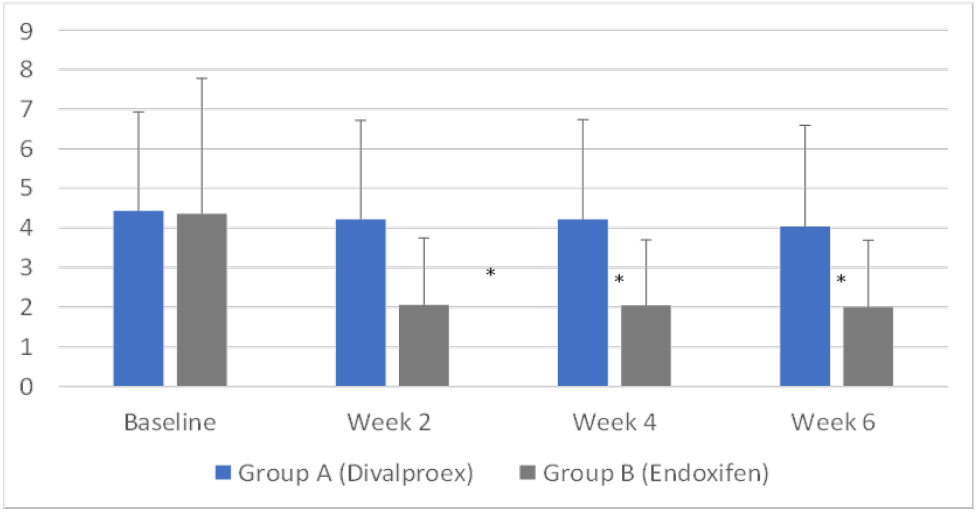

Figure 3: UKU Scores over Time in Patients Treated with Divalproex (Group A) and Endoxifen (Group B)

Adverse drug reactions (ADRs) were nearly universal, occurring in 100% (23/23) of Group A and 90.9% (20/22) of Group B participants.

Across all subjects, 95.6% reported one or more ADRs, with 42 events documented in total—22 in the divalproex group and 20 in the endoxifen group. The majority of ADRs were neurological in nature, comprising 40.9% of ADRs in Group A and 40.0% in Group B.

Psychic ADRs accounted for 27.3% and 25.0%, respectively, while autonomic and other ADRs made up the remainder (Figure 4).

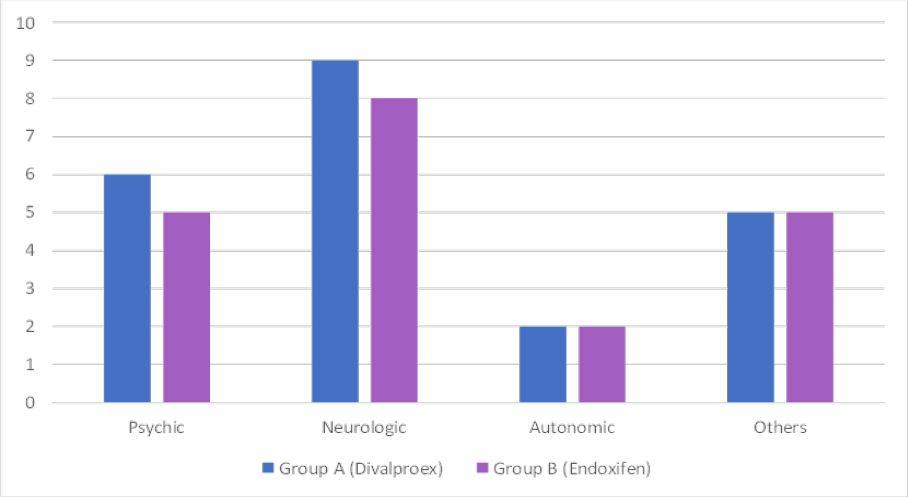

Figure 4: Number of Adverse Drug Reactions Reported by Treatment Group

Specific ADRs with similar incidence across groups included tremor (approximately 17–18%), sedation (~13%), akathisia and extrapyramidal symptoms (9–13%), and other symptoms such as weight gain, headache, and dry mouth (8–9%). Notably, none of the patients in Group A were free of ADRs, whereas two patients (9.1%) in Group B reported no adverse effects during the study period (Figure 5).

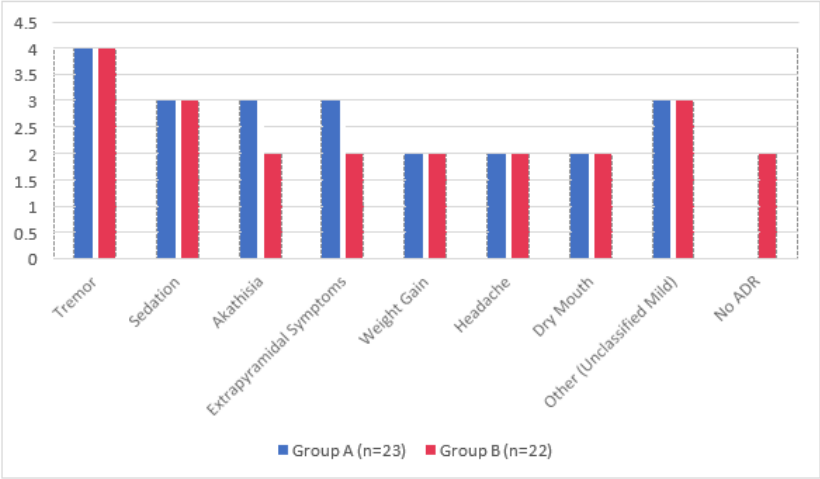

Figure 5: Comparative Distribution of Specific ADR Symptom Types

Discussion

The present study compared the efficacy and tolerability of Endoxifen and Divalproex in treating acute manic episodes in Bipolar Disorder, using the Young Mania Rating Scale (YMRS) and the UKU Side Effect Rating Scale at baseline and follow-ups over six weeks. Both treatments produced significant improvements in manic symptoms, with mean YMRS scores declining similarly from approximately 32.6 to around 5 by week six in both groups. No statistically significant differences in symptom reduction were found between treatments, indicating comparable efficacy. In contrast, tolerability differed markedly: Endoxifen was associated with significantly lower UKU side effect scores at all follow-up points, suggesting a better side effect profile.

The clinical benefits of Endoxifen may be attributed to its targeted inhibition of Protein Kinase C (PKC), a key intracellular enzyme implicated in manic pathophysiology. This mechanism offers a more focused modulation of neuronal signaling pathways compared to Divalproex's broader enhancement of GABAergic neurotransmission and sodium channel blockade. Notably, Endoxifen demonstrated a rapid onset of action with greater symptom reduction early in treatment sustained throughout the study period, while Divalproex's effects showed a more gradual improvement. The improved tolerability of Endoxifen was reflected in fewer reports of sedation, gastrointestinal discomfort, and cognitive impairment—side effects commonly associated with valproate-type agents. This reduced adverse effect burden is likely related to Endoxifen's selective pharmacologic action and may translate

into better patient satisfaction and adherence. Remarkably, no participants in either group discontinued treatment during the trial, suggesting excellent engagement and medication adherence. Pill counts and caregiver reports confirmed compliance, with Endoxifen recipients reporting fewer subjective side effect complaints and greater willingness to continue therapy. These findings support Endoxifen's feasibility for routine outpatient use, in addition to demonstrating its clinical efficacy.

These results are consistent with prior research: Zarate et al. (2007) showed significant mania score reductions with tamoxifen, and Ahmad et al. (2016) reported a comparable six-week YMRS decline with Endoxifen. Similarly, the Divalproex efficacy observed aligns with pooled data from Cipriani et al. (2011). The better tolerability of Endoxifen echoes Ahmad et al.'s (2017) findings of fewer discontinuations compared to valproate, and contrasts with some tamoxifen studies where moderate side effects were noted (Kulkarni et al., 2008). The exceptionally low dropout rate in this study contrasts with the 10–30% attrition typically seen in bipolar mania trials (Velligan et al., 2009), which may reflect rigorous screening, close monitoring, and structured follow-up. Clinically, these findings underscore Endoxifen as a promising first-line or adjunctive option for mania management.

Its rapid symptom control combined with a superior safety profile suggests utility especially for patients vulnerable to side effects of conventional mood stabilizers. Endoxifen's unique dual role as a selective estrogen receptor modulator and PKC inhibitor may be particularly advantageous for women experiencing hormone-related mood fluctuations, such as perimenopausal or premenstrual exacerbations, further personalizing treatment approaches. Future exploration of dosing optimization and combination strategies with other psychotropics could maximize therapeutic outcomes. Methodologically, the randomized controlled design and use of validated scales strengthen the study's findings. Direct head-to-head comparison provides clinicians with clear guidance when choosing between these agents. Regular and systematic follow-ups enhanced safety monitoring and data reliability.

Limitations include a modest sample size and short duration, which limit detection of rare adverse events and long-term efficacy data. The open-label design introduces potential bias despite employing standardized assessments. Lack of extended follow-up precludes

conclusions about maintenance or relapse prevention, and the single-center outpatient setting may limit generalizability to other populations, such as inpatients or community-based samples.To further validate these promising results, larger, multi-center, double-blind randomized trials with longer follow-up are needed. Investigating Endoxifen's role in maintenance therapy, its effectiveness in mixed or rapid-cycling bipolar subtypes, and its pharmacogenomic interactions—particularly CYP2D6 polymorphisms affecting metabolism—will enable more precise, personalized bipolar disorder treatments.

Conclusion

This study contributes significantly to the evolving treatment landscape of bipolar disorder (BD) by providing direct comparative data on the efficacy and tolerability of Endoxifen versus Divalproex in managing acute manic episodes. The results demonstrate that Endoxifen is equally effective in reducing manic symptoms compared to Divalproex, while offering a notably better side effect profile. This improved tolerability, evidenced by fewer and milder adverse events, translates into enhanced patient comfort and potentially greater adherence to treatment regimens—an essential factor for long-term management of BD. The rapid onset of symptom control observed with Endoxifen further strengthens its clinical appeal, as promptstabilization of mood is critical during acute episodes. Unlike conventional mood stabilizers, which may be burdened by sedation, cognitive dulling, and metabolic effects, Endoxifen's targeted mechanism as a Protein Kinase C (PKC) inhibitor may provide therapeutic benefits with fewer systemic side effects. These advantages suggest that Endoxifen could serve as a valuable addition to existing pharmacological options, addressing unmet needs related to tolerability and patient compliance. Importantly, the study highlights Endoxifen's potential as a novel and effective alternative without compromising safety. While these findings are promising, larger-scale studies with longer follow-up periods are warranted to validate and extend the applicability of these results across diverse patient populations and different phases of bipolar illness, including maintenance therapy and relapse prevention. In summary, Endoxifen emerges as a promising pharmacological option in the treatment of manic episodes in BD, offering both efficacy and improved tolerability. Its introduction into clinical practice could represent a meaningful advance in mood disorder therapeutics, enhancing patient outcomes through better symptom control and increased treatment acceptability.

References

1. Craddock N, Sklar O. Genetics of bipolar disorder. Lancet. 13; 381(9878):1654-62.
2. Kupfer DJ, Frank E, Grochocinski VJ, Cluss PA, Houck PR, Stapf DA. Demographic and

clinical characteristics of individuals in a bipolar disorder case registry. J Clin Psychiatry. 2002; 63(2):120-5.
3. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011; 68(3):241-51.
4. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013; 382(9904):1575-86.
5. Schaffer A, Isometsä ET, Tondo L, Moreno DH, Turecki G, Reis C, et al. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord. 2015; 17(1):1-16.
6. Post RM, Leverich GS, Kupka RW, Keck PE Jr, McElroy SL, Altshuler LL, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry. 2010; 71(7):864-72.
7. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet. 2003; 123C(1):48-58.
8. Cardno AG, Gottesman II. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. Am J Med Genet. 2000; 97(1):12-7.
9. Nurnberger JI Jr, Berrettini WH, Tamarkin L, Hamovit J, Norton JA Jr, Gershon ES, et al.Suppression of melatonin secretion in some bipolar patients. Am J Psychiatry. 1988; 145(5):621-5.
10. Hirschfeld RM. The mood disorder questionnaire: a simple, patient-rated screening instrument for bipolar disorder. Prim Care Companion J Clin Psychiatry. 2002; 4(1):9-11.
11. Ashok AH, Marques TR, Jauhar S, Nour MM, Goodwin GM, Young AH, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry. 2017; 22(5):666-79.
12. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem. 1994; 40(2):288-95.
13. Manji HK, Lenox RH. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. Biol Psychiatry. 1999; 46(10):1328-51.
14. Zarate CA, Manji HK. Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. CNS Drugs. 2009; 23(7):569-82.
15. Ahmad A, Sheikh S, Shah T, Reddy MS, Prasad BSV, Verma KK, et al. Endoxifen, a new treatment option for mania: a double-blind, active-controlled trial demonstrates the antimanic efficacy of endoxifen. Clin Transl Sci. 2016; 9(5):252-9.
16. Newton AC. Protein kinase C: structure, function, and regulation. J Biol Chem.1995; 270(48):28495-8.
17. Grimes CA, Jope RS. CREB DNA binding activity is inhibited by glycogen synthase kinase-3 beta and facilitated by lithium. J Neurochem. 2001; 78(6):1219-32.
18. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord. 2016; 4:27.
19. Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. CNS Drugs. 2013; 27(2):135-153.
20. Bowden CL. Clinical correlates of therapeutic response in bipolar disorder. J Affect Disord.2001;67(1-3):257-265.
21. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry. 2015;14(2):119-136.
22. Vieta E, Suppes T. Bipolar disorders: effects of antipsychotics, antidepressants, and mood stabilizers on body weight and metabolism. Psychopharmacol Bull. 2008;41(4):15-25.
23. Vellingan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70 Suppl 4:1-46; quiz 47-8.
24. Pies R. How should efficacy be evaluated in randomized clinical trials of treatments for bipolar disorders? J Affect Disord. 2008;107(1-3):17-23.
25. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672-1682.
26. Thase ME. Antidepressant treatment of the depressed phase of bipolar disorder: a review. J Clin Psychiatry. 2010;71(9):1253-1265.
27. Manji HK, Quiroz JA, Payne JL, Singh J, Lopes BP, Viegas JS, Zarate CA. The underlying neurobiology of bipolar disorder. World Psychiatry. 2003;2(3):136-146.major depression. Arch Gen Psychiatry. 2006;63(8):856-864.
28. Einat H, Yuan P, Gould TD, Li J, Du J, Zhang L, Manji HK, Chen G. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. J Neurosci.

2003;23(19):7311-7316.
29. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672–82.
30. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2016;387(10027):1561–72.
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington: APA; 2013.
32. Goodwin FK, Jamison KR. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. New York: Oxford University Press; 2007.
33. Vieta E, Salagre E, Grande I, et al. Early intervention in bipolar disorder. Am J Psychiatry.2018;175(5):411–26.
34. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170.
35. Malhi GS, Bell E, Boyce P, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2021;55(1):7–117.
36. Scott J, Pope M. Self-reported adherence to treatment with mood stabilisers, plasma levels, and psychiatric hospitalization in bipolar disorder. Bipolar Disord. 2002;4(4):217–22.
37. Fountoulakis KN, Yatham LN, Grunze H. Practical management of bipolar disorder: a worldwide perspective. Int J Neuropsychopharmacol. 2019;22(9):676–92.
38. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a network-based understanding of mood dysregulation. Am J Psychiatry. 2014;171(8):829–43.
39. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress, and neuroplasticity. Lancet Psychiatry. 2014;1(6):461–72.
40. Ashok AH, Marques TR, Jauhar S, et al. The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. Mol Psychiatry. 2017;22(5):666– 79.
41. Machado-Vieira R, Manji HK, Zarate CA Jr. The role of the glutamatergic system in mood disorders: neurobiology and treatment. Expert Rev Neurother. 2009;9(7):1003–14.
42. Munkholm K, Braüner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2013;144(1-2):16–27.
43. Khandaker GM, Dantzer R, Jones PB. Immunopsychiatry: essential facts. Psychol Med.2017;47(13):2229–37.
44. Grande I, Fries GR, Kunz M, Kapczinski F. The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatr Clin North Am. 2016;39(1):79–93.
45. Post RM. The impact of bipolar disorder on brain structure and function: Current issues and perspectives. Int J Neuropsychopharmacol. 2020;23(8):599–617.
46. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170.
47. Malhi GS, Bell E, Boyce P, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders.Aust N Z J Psychiatry. 2021;55(1):7–117.
48. Malhi GS, Tanious M, Das P, Berk M. The science and practice of lithium therapy. Int J Bipolar Disord. 2016;4(1):8.
49. Bowden CL. Valproate. Bipolar Disord. 2003;5(3):189–202.
50. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378(9799):1306–15.
51. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. Lancet. 2013;381(9878):1672–82.
52. Frye MA. Bipolar disorder—a focus on depression. N Engl J Med. 2011;364(1):51–9.
53. Maximov PY, Lee TM, Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. Curr Clin Pharmacol. 2013;8(2):135–55.
54. Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. Biol Psychiatry. 1998;44(9):839–50.
55. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of a protein kinase C inhibitor in treating acute mania. Mol Psychiatry. 2007;12(9):805–12.
56. Paoletti AM, Orrù M, Muggianu M, et al. Role of estrogens in the brain: Implications for neurodegenerative diseases. Front Aging Neurosci. 2020;12:243.
57. Balu DT, Coyle JT. Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. Neurosci Biobehav Rev. 2011;35(3):848–70.
58. Yildiz A, Sachs GS, Turgay A. Tamoxifen: A protein kinase C inhibitor for the treatment of mania: A review of the data. J Affect Disord. 2011;134(1–3):345–52.
59. Kulkarni J, de Castella AR, Fitzgerald PB, et al. Estrogen in severe mental illness: A potential new treatment approach. Arch Gen

Psychiatry. 2008;65(9):955–60.
60. Berk M, Dodd S, Kauer-Sant'Anna M, Malhi GS. Bipolar mood disorder: The PKC hypothesis of pathophysiology and pharmacotherapy. Clin Psychopharmacol Neurosci. 2007;5(1):1–8.
61. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. Psychol Med. 2017;47(3):373-9.
62. Bowden CL, Singh V, Thompson P, et al. Valproate: Mechanisms and clinical evidence.Bipolar Disord. 2010;12(6):654–62.
63. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: Can we see the forest for the trees? Cell Mol Life Sci. 2007;64(16):2090–103.
64. Einat H, Yuan P, Gould TD, et al. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. J Neurosci. 2003;23(19):7311–6.
65. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. Valproate in the treatment of acute mania: A placebo-controlled study. Arch Gen Psychiatry. 1991;48(1):62–8.
66. Swann AC, Bowden CL, Calabrese JR, et al. Differential effect of number of previous episodes of mania and depression on response to treatment in bipolar disorder. Am J Psychiatry. 1999;156(7):1053–4.
67. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: A multiple-treatments meta-analysis. Lancet. 2011;378(9799):1306–15.
68. Gentile S. Valproic acid in mood disorders: From clinical trials to clinical practice. Expert Opin Pharmacother. 2014;15(7):885–93.
69. Tomson T, Battino D. Teratogenic effects of antiepileptic medications. Neurol Clin.2009;27(4):993–1002.
70. McIntyre RS, Soczynska JK, Woldeyohannes HO, et al. Metabolic syndrome and bipolar disorder: An international perspective. J Affect Disord. 2010;126(3):366–87.
71. Jordan VC, Brodie AM. Development and evolution of therapies targeted to the estrogen receptor for the treatment and prevention of breast cancer. Steroids. 2007;72(1):7–25.
72. Rubinow DR, Schmidt PJ. Estrogen receptor function in mood disorders. Mol Psychiatry.2019;24(5):753–67.
73. Löscher W. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog Neurobiol. 1999;58(1):31–59.
74. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomised trial of a protein kinase C inhibitor in the treatment of acute mania. Mol Psychiatry. 2007;12(9):805–12.
75. Kulkarni J, de Castella AR, Fitzgerald PB, et al. Estrogen as a psychotropic agent: research findings and therapeutic implications. Arch Womens Ment Health. 2008;11(3):173–81.
76. Paoletti AM, Orrù M, Muggianu M, et al. Neuroprotective effects of selective estrogen receptor modulators in mental disorders. Front Aging Neurosci. 2020;12:243.
77. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of a protein kinase C inhibitor in the treatment of acute mania. Mol Psychiatry. 2007;12(9):805–812.
78. Ahmad A, Sheikh S, Shah T, et al. Endoxifen, a new treatment option for mania: a double-blind, active-controlled trial demonstrates the antimanic efficacy of endoxifen. Clin Transl Sci. 2016;9(5):252–259.
79. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378(9799):1306– 1315.
80. Kulkarni J, de Castella AR, Fitzgerald PB, et al. Estrogen in severe mental illness: A potential new treatment approach. Arch Gen Psychiatry. 2008;65(9):955–960.
81. Ahmad A, Verma KK, Sheikh S, et al. Clinical efficacy and tolerability of endoxifen in the treatment of bipolar mania: A randomized, double-blind comparison with sodium valproate. Indian J Psychol Med. 2017;39(2):144–150.
82. Velligan DI, Weiden PJ, Sajatovic M, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. J Clin Psychiatry. 2009;70 Suppl 4:1–46.