ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2022; 8(8): 09-13
www.allresearchjournal.com
Received: 27-05-2022
Accepted: 30-06-2022

Mahesh Gowda
Spandana Nursing Home, Bangalore, Karnataka, India

Khushboo Dewani
Spandana Nursing Home, Bangalore, Karnataka, India

Corresponding Author:
Khushboo Dewani
Spandana Nursing Home, Bangalore, Karnataka, India

Cost-effectiveness of endoxifen therapy in severe psychotic bipolar I disorder: A case report

Mahesh Gowda and Khushboo Dewani

Abstract
Hyperactivation of protein kinase C (PKC) signaling is seen among patients with bipolar I disorder (BPD-I). Direct PKC inhibition can help in the faster remission of symptoms and reduce the chances of hospitalizations. Endoxifen, a direct inhibitor of the PKC signaling pathway, is safe and effective in controlling acute mania and mixed episodes of BPD-I at a dosage strength of 8 mg. Here we present the case of a patient with severe BPD-I mania with moderate psychotic features treated with endoxifen at a daily dose of 8 mg and paliperidone adjunctive therapy for 4 months. Treatment with endoxifen was efficacious in controlling manic and psychotic symptoms with no incidences of drug-induced tremors, weight gain, and metabolic disturbances. Endoxifen plus paliperidone antipsychotic therapy was economical as compared to lithium–olanzapine combination therapy due to no serious inpatient hospitalization. Endoxifen was well tolerated, and the patient resumed work at the end of 4 months. This case showed the safety and cost-effectiveness of endoxifen therapy in managing severe psychotic BPD-I disease.

Keywords: Bipolar I disorder, endoxifen, severe mania, protein kinase C, safety, healthcare costs

Introduction
Bipolar disorder (BPD) is a recurrent psychiatric illness characterized by unstable moods (manic or depressive), unstable personal relationships, and impulsive behaviors [1, 2]. Bipolar disorder includes different diagnoses: (i) BPD-I (manic episodes with or without depression); (ii) BPD-II (hypomania and periods of severe depression); (iii) cyclothymic disorder (both hypomanic and depressive episodes for 2 years or longer); (iv) BPD with mixed features (opposite mood polarities); and (v) rapid cycling BPD [2–5]. Patients with BPD experience functional decline, have higher rates of substance use disorders, and have reduced quality of life [1, 2, 6]. The evidence-based guidelines recommend second-generation antipsychotics, mood stabilizers, and anticonvulsant therapy as first-line monotherapy for the management of acute BPD mania in adults [7–10]. Conversely, in real-world clinical practice, patients with acute BPD are prescribed combinations of mood stabilizers, anticonvulsants, antipsychotics, and/or antidepressants, which increases the pill burden [10, 11]. In patients who experience severe episodes of mania, a combination of mood stabilizers (lithium or valproate) and second-generation antipsychotics in the first-line can hasten the process of recovery [7, 10, 12, 13]. However, treatment discontinuation is more frequent with combination therapy than with monotherapy due to tolerability issues, extrapyramidal symptoms, sedation, and weight gain [13]. Treatment of BPD incurs significant direct healthcare costs (medication, investigation, and hospitalization costs) and indirect costs (unemployment, caregiving, and excessive spending during mania/depression) to the patient [14]. These challenges highlight the need for more cost-effective and safe treatment options for managing patients with BPD.
Bipolar I disorder (BPD-I) is a chronic, disabling condition associated with overactive protein kinase C (PKC) intracellular signaling [15]. The approved treatments for the management of BPD-I are lithium and divalproex/valproate, which are indirect inhibitors of PKC [15, 16]. Depot atypical antipsychotics such as risperidone, paliperidone, and olanzapine may be given to patients who refuse medications and are unmanageable [10]. Recently, monotherapy with endoxifen, a direct PKC inhibitor, was found to be safe and effective (8 mg; once daily [OD]) in managing acute mania and mixed episodes of BPD-I disorder as compared to divalproex (1000 mg; OD) in a phase III randomized controlled trial [15].

Disease remission was achieved as early as on day 4 with endoxifen monotherapy as compared to day 7 with divalproex therapy, suggesting the faster onset of action [15]. We present the case of a patient with severe BPD-I mania with moderate psychotic features of suspicion and delusion who was successfully treated with a combination of endoxifen and paliperidone antipsychotic therapy.

Case Report

Case Presentation

A 45-year–old married woman with a long history of BPD-I was brought to the outpatient unit with complaints of agitation, loquaciousness, delusion, and disturbed sleep. The patient is a healthcare professional. She reported a familial transition of bipolar affective disorder from her mother and experienced the first episode of bipolar mania at the age of 22 years. She had a history of similar episodes (N=8) of poor sleep, loquaciousness, hyperactivity, restlessness, and irritability, which lasted for hours, days, or a couple of weeks. Since then, she tried multiple treatments for the management of mania, such as mood stabilizer lithium, atypical antipsychotics (olanzapine, amisulpride), and anticonvulsants (Encorate Chrono) for 2–3 months, but later discontinued therapy due to side effects such as lithium toxicity, weight gain, tremors, hyperprolactinemia, and hyperammonemia. Considering the occupation of the patient, which involved performing surgery, drug-induced tremors led to significant productivity loss. During the lockdown phase of COVID-19 in March 2020, she experienced severe symptoms of BPD-I mania, notably intense emotions, delusions, unusual talkativeness, and impaired judgment. Conditions such as social isolation and economic fallout during COVID-19 caused unprecedented stress and affected her activities of daily living. In addition, she experienced paranoid or persecutory delusions, psychomotor agitation, and delusion of infidelity and expressed distrust over family members, which affected her personal life.

Case Evaluation

No abnormalities were found on physical examination. Blood investigation showed the following findings: (i) serum creatinine—0.90 mg/dL; (ii) serum urea—26.3 mg/dL; (iii) serum sodium—139 mEq/L; (iv) serum potassium—3.6 mEq/L; (v) serum chloride—100 mEq/L; and (vi) ammonia—116 µmol/L. The patient had no preexisting medical condition or lifestyle-related comorbidity. Hemoglobin, bilirubin, thyroxin, and thyroid-stimulating hormone levels were all normal. The Young Mania Rating Scale (YMRS) was used to assess the severity of manic symptoms. A YMRS score of ≤12 was defined as remission, 13–19 as minimal symptoms, 20–25 as mildly manic, 26–37 as moderately manic, and 38–60 as severely manic [17, 18]. At the time of presentation, the total YMRS score was 41 of 60, indicating severe mania (elevated mood: 2, increased motor activity/energy levels: 3, sexual interest: 2, sleep: 2, irritability: 6, rate and amount of speech: 4, language–thought disorder: 2, content: 8, disruptive–aggressive behavior: 6, appearance: 3, and insight into the current presentation: 3). In addition, the Brief Psychiatric Rating Scale (BPRS) was used to measure psychiatric symptoms such as anxiety, suspiciousness, hallucination, and psychoses (mildly ill: 18–31; moderately ill: 32–53; and severely ill: 54–126) [19, 20]. At the time of presentation, the total BPRS score was 44, indicating a moderate level of anxiety, suspiciousness, hallucination, and psychoses.

Case Management

After the initial case evaluation, she was prescribed tab lithium 1 g and tab olanzapine 20 mg for the management of bipolar mania (treatment I). However, after 4 months, she discontinued this treatment due to weight gain and frequent tremors indicative of mild-to-moderate lithium toxicity. During the second visit, she was prescribed tab Encorate Chrono 500 mg twice daily (BID), tab endoxifen 8 mg OD, and paliperidone 150 mg intramuscular (IM) (on day 1 and day 8) as adjunctive therapy (treatment II). Monitoring liver function and ammonia levels was recommended. Endoxifen was advised for this patient as it does not cause weight gain and tremors, which are important to avoid productivity loss. After 20 days of treatment, hyperammonemia was reported in the absence of overt hepatic failure due to anticonvulsant Encorate Chrono therapy, which was managed with tab Rifagut 400 mg and Duphalac oral solution BID. She was advised to continue endoxifen 8 mg OD and paliperidone 150 mg IM once monthly as adjunctive therapy for 3 months (treatment III). Her symptoms of irritability and delusion decreased, and the total YMRS reduced to 6 at the third follow-up, indicating disease remission. In addition, the BPRS score was reduced to 22, indicating improvement in the patient's condition (low level of anxiety, suspiciousness, hallucination, and psychoses). Figure 1 summarizes the patient's treatment chart, reasons for treatment discontinuation, and changes in YMRS score over time. The patient's condition improved further during the fourth follow-up (YMRS: 0 and BPRS: 18). During the last follow-up after 3 months, the patient expressed treatment satisfaction with endoxifen therapy in terms of efficacy and safety (treatment III). The endoxifen therapy was well tolerated with no adverse effects. The patient's condition returned to normal, and she resumed her work. Table 1 provides a comparative overview of direct healthcare costs and indirect expenditure with three different treatment regimens.

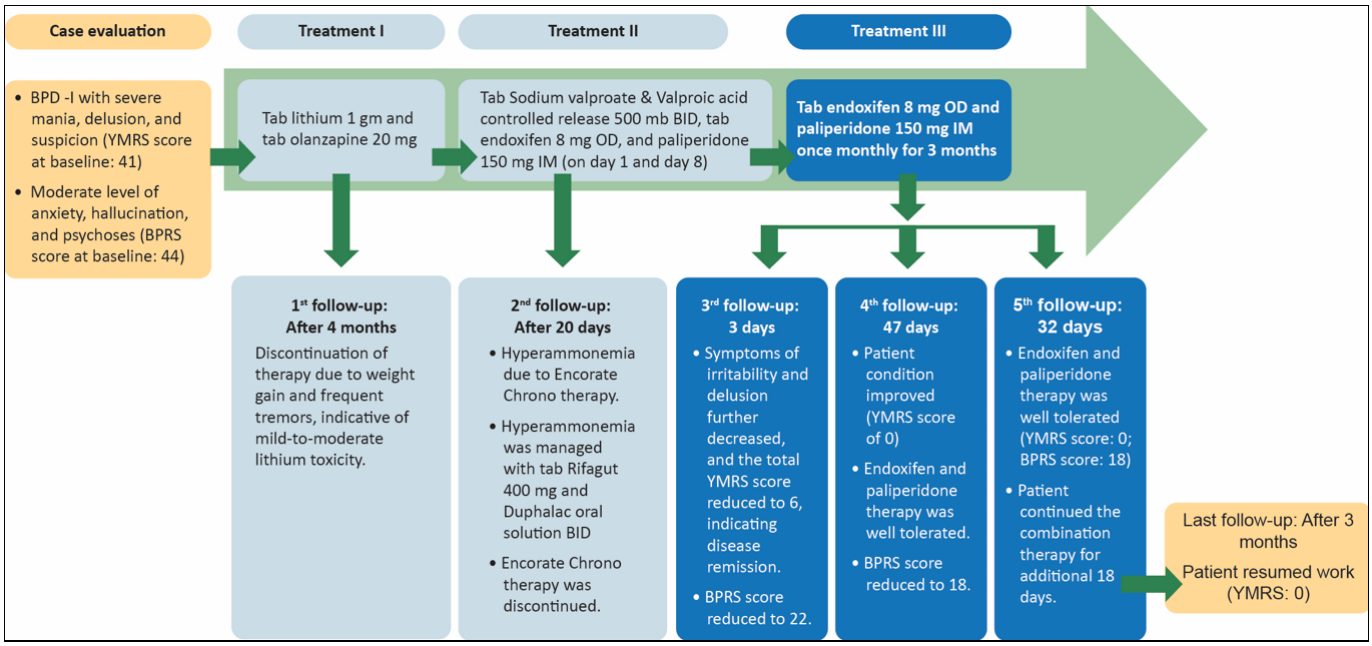

Fig 1: Patient's treatment chart, reasons for treatment discontinuation, and change in YMRS score over time. BPD-I: Bipolar I disorder; YMRS: Young Mania Rating Scale; OD: Once daily; BID: Twice daily; IM: Intramuscular; Tab: Tablet; BPRS: Brief Psychiatric Rating Scale

Table 1: Direct medical and nonmedical costs during the study period

Description	Treatment I: Lithium 1 g + olanzapine 20 mg	Treatment II: Sodium valproate and valproic acid 500 mg BID + endoxifen 8 mg OD + paliperidone 150 mg IM	Treatment III: Endoxifen 8 mg OD + paliperidone 150 mg IM
	Duration: 4 months	Duration: 20 days	Duration: 4 months
Direct healthcare costs			
Medication cost	INR 1950	INR 26,526	INR 51,280
Outpatient cost	INR 2500	–	INR 2400
Inpatient hospitalization (if any)	INR 46,300	INR 42,600	–
Investigation cost	INR 2000	INR 2740	–
Indirect costs			
Excessive spending pattern (if any)	INR 1,35,000	–	–
Total	INR 1,87,750	INR 71,866	INR 53,680

OD: Once daily; BID: Twice daily; IM: Intramuscular

Discussion

BPD-I is a chronic, recurrent, psychiatric illness characterized by unstable moods, unstable personal relationships, and impulsive behaviors. The management of severe mania in patients with BPD-I is directed at faster resolution of symptoms because of irritability, disruptive–aggressive behavior, agitation, and psychosis. The PKC signaling system plays an important role in psychiatric disorders such as BPD and schizophrenia [21–23]. Direct PKC inhibition can help in the faster remission of symptoms and reduce the chances of inpatient hospitalizations. Drugs typically used for the treatment of BPD-I include indirect PKC inhibitors (lithium, divalproex/valproate) and atypical antipsychotics (risperidone, paliperidone, olanzapine, cariprazine), which are associated with teratogenic risks, hepatic failure, extrapyramidal symptoms, and metabolic disturbances. Endoxifen (4-OH-N-desmethyltamoxifen) is a direct PKC inhibitor with proven efficacy independent of CYP2D6-mediated metabolism in patients with BPD-I [15]. In addition, endoxifen at a daily dose of 8 mg has been shown to reduce the severity of manic and psychotic symptoms in schizoaffective disorder [23]. Paliperidone is an active metabolite of risperidone (9-OH-risperidone) [24]. The once-monthly extended-release (ER) formulation of paliperidone has shown to significantly delay psychotic and/or manic relapses in patients with schizoaffective disorders [25]. The efficacy and safety of long-term use of ER formulation of paliperidone (150 mg) have also been established in severe psychotic bipolar patients [25, 26].

In this case study, the efficacy and safety of endoxifen 8 mg OD and paliperidone adjunctive therapy are studied in a patient with severe psychotic BPD-I. The use of endoxifen 8 mg OD and paliperidone adjunctive therapy was effective (YMRS at baseline: 41 vs. YMRS 25 days after initiation of treatment II: 6 vs. YMRS at the end of therapy: 0) and well tolerated in the treatment of severe manic episodes associated with BPD-I. The endoxifen plus paliperidone adjunctive therapy was cost-effective (total cost: INR 53,680 for 4 months) as compared to treatment I (lithium–olanzapine combination therapy [INR 1,87,750 for 4 months]) and treatment II (Encorate Chrono 500 mg BID, endoxifen 8 mg OD, and paliperidone adjunctive therapy [INR 71,866 for 20 days]) due to no serious inpatient hospitalizations. The patient did not experience any episode of treatment-emergent depression, impulsive behavior, excessive spending pattern, and/or delusion during

endoxifen therapy. Furthermore, the patient did not experience tremors, weight gain, or metabolic disturbances (change in blood glucose/thyroid hormone levels) during the study period and follow-up. There was no need for therapeutic drug monitoring during endoxifen therapy unlike lithium and anticonvulsant Encorate Chrono therapy. The patient expressed treatment satisfaction with endoxifen therapy and resumed work unlike previous treatment options.

Conclusion

Here we present the case of a patient with severe mania with moderate psychotic features of suspicion and delusion who was successfully treated with endoxifen 8 mg OD and paliperidone 150 mg adjunctive therapy for 4 months to achieve a better response. Treatment with endoxifen was efficacious in controlling manic and psychotic symptoms, with no adverse effects. The good tolerability profile of endoxifen encourages its use in patients where current treatment options for BPD-I bring challenging side effects, such as lithium toxicity, weight gain, tremors, hyperprolactinemia, and/or hyperammonemia. Even productivity loss was addressed with endoxifen due to a good safety profile as the patient resumed work at the end of 4 months unlike previous treatment options (lithium, olanzapine, and anticonvulsant Encorate Chrono therapy). Endoxifen plus paliperidone adjunctive therapy reduced the overall pill burden and was cost-effective as it avoided direct costs, such as hospitalization costs and investigation costs, and indirect costs, such as excessive spending. This case showed the long-term effectiveness and safety of endoxifen 8 mg OD to control severe mania and moderate psychotic symptoms in a patient with BPD-I.

Acknowledgments

We acknowledge the contribution of Dr. Imran Ahmad toward data analysis and case study writing. We thank BioQuest Solutions for its editorial support.

Funding: None

Authors' Contribution: Both authors have been involved in treatment decisions and management of the patient during the hospital stay.

The content has been contributed by both the authors.

Dr. Mahesh Gowda is the primary psychiatrist responsible for patient care during follow-up and outpatient management.

Conflict of Interest: None

References

1. Marzani G, Price Neff A. Bipolar disorders: Evaluation and treatment. Am Fam Physician. 2021;103(4):227-239.
2. Gautam S, Jain A, Gautam M, Gautam A, Jagawat T. Clinical practice guidelines for bipolar affective disorder (BPAD) in children and adolescents. Indian J Psychiatry. 2019;61(Suppl 2):294-305.
3. Mind [Internet]. Bipolar disorder, 2022 Feb [cited 2022 March 09]. Available at: https://www.mind.org.uk/information-support/types-of-mental-health-problems/bipolar-disorder/types-of-bipolar/. Accessed on: 07 July 2022.
4. Muneer A. Mixed states in bipolar disorder: Etiology, pathogenesis and treatment. Chonnam Med J. 2017;53(1):1-13.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [Internet]. Washington DC: American Psychiatric Publishing; 2013 [cited 2022 March 21]. Available at: http://repository.poltekkes-kaltim.ac.id/657/1/Diagnostic%20and%20statistical%20manual%20of%20mental%20disorders%20_%20DSM-5%20%28%20PDFDrive.com%20%29.pdf. Accessed on: 07 July 2022.
6. Sylvia LG, Montana RE, Deckersbach T, Thase ME, Tohen M, Reilly-Harrington N, *et al.* Poor quality of life and functioning in bipolar disorder. Int J Bipolar Disord. 2017;5(1):10.
7. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170.
8. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, *et al.* Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495-553.
9. Fountoulakis KN, Yatham L, Grunze H, Vieta E, Young A, Blier P, *et al.* The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, grading of the evidence, and a precise algorithm. Int J Neuropsychopharmacol. 2017;20(2):121-179.
10. Shah N, Grover S, Rao GP. Clinical practice guidelines for management of bipolar disorder. Indian J Psychiatry. 2017;59(Suppl 1):S51-S66.
11. Reddy YJ, Jhanwar V, Nagpal R, Reddy MS, Shah N, Ghorpade S, *et al.* Prescribing practices of Indian psychiatrists in the treatment of bipolar disorder. Aust N Z J Psychiatry. 2019;53(5):458-469.
12. Goldberg JF. Complex combination pharmacotherapy for bipolar disorder: Knowing when less is more or more is better. Focus (Am Psychiatr Publ). 2019;17(3):218-231.
13. Geoffroy PA, Etain B, Henry C, Bellivier F. Combination therapy for manic phases: A critical review of a common practice. CNS Neurosci Ther. 2012;18(12):957-964.
14. Cloutier M, Greene M, Guerin A, Touya M, Wu E. The economic burden of bipolar I disorder in the United States in 2015. J Affect Disord. 2018;226:45-51.
15. Ahmad A, Sheikh S, Khan MA, Chaturvedi A, Patel P, Patel R, *et al.* Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. Bipolar Disord. 2021;23(6):595-603.
16. Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, *et al.* Treatment for bipolar disorder in adults: A systematic review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK532183/.

17. Hanssen I, Huijbers MJ, Lochmann-van Bennekom MWH, Regeer EJ, Stevens AWMM, Evers SMAA, *et al.* Study protocol of a multicenter randomized controlled trial of mindfulness-based cognitive therapy and treatment as usual in bipolar disorder. BMC Psychiatry. 2019;19(1):130.
18. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-435.
19. Zhou X, Wang X, Li R, Yan J, Xiao Y, Li W, *et al.* Neutrophil-to-lymphocyte ratio is independently associated with severe psychopathology in schizophrenia and is changed by antipsychotic administration: A large-scale cross-sectional retrospective study. Front Psychiatry. 2020;11:581061.
20. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R, *et al.* Clinical implications of brief psychiatric rating scale scores. Br J Psychiatry. 2005;187:366–371.
21. Saxena A, Scaini G, Bavaresco DV, Leite C, Valvassori SS, Carvalho AF, *et al.* Role of protein kinase C in bipolar disorder: A review of the current literature [published correction appears in Mol Neuropsychiatry. 2018;3(3):180. Valvassoria, Samira S [corrected to Valvassori, Samira S]]. Mol Neuropsychiatry. 2017;3(2):108-124.
22. Carroll LS, Williams NM, Moskvina V, Russell E, Norton N, Williams HJ, *et al.* Evidence for rare and common genetic risk variants for schizophrenia at protein kinase C, alpha. Mol Psychiatry. 2010;15(11):1101-1111.
23. Singh H. Endoxifen response in schizoaffective disorder: A case series. IMJ Health. 2022;8(2):1-5.
24. Marino J, English C, Caballero J, Harrington C. The role of paliperidone extended release for the treatment of bipolar disorder. Neuropsychiatr Dis Treat. 2012;8:181-189.
25. Li K, Liao Y, Yang Z, Yang C, Chen M, Wu X, *et al.* Case report: Paliperidone palmitate in the management of bipolar I disorder with non-compliance. Front Psychiatry. 2021;11:529672.
26. Buoli M, Ciappolino V, Altamura AC. Paliperidone palmitate depot in the long-term treatment of psychotic bipolar disorder: A case series. Clin Neuropharmacol. 2015;38(5):209-211.