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Case Report

Long-term effectiveness and safety of endoxifen in the treatment of bipolar mania: a case report

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ABSTRACT

Bipolar disorder (BD) displays abnormalities in protein kinase C (PKC) signaling, and evidence suggests that inhibiting PKC may help treat mania. Endoxifen a potent inhibitor of the PKC signaling pathway, is effective in controlling acute bipolar mania, at doses of 8 mg OD, for a period of 3-weeks. Here we present the case of a patient with severe mania, increased alcohol consumption administered endoxifen 8 mg BID for a period of 3-months, to achieve a better response. High-dose, long-term treatment with endoxifen was efficacious in controlling manic symptoms, with no adverse effects. Additionally, the patient didn't consume alcohol during the course of treatment. This case showed the long-term effectiveness and safety of high-dose endoxifen to control mania in a patient with BD.

Keywords: Endoxifen, Bipolar mania, Severe mania, Long-term use, Safety, Effectiveness

INTRODUCTION

Bipolar disorder (BD) is a severe chronic mood disorder with a worldwide prevalence of approximately 1%. It is characterized by episodes of mania or hypomania, which alternate or occur concomitantly with episodes of depression. Acute bipolar mania can be a medical emergency and might require hospitalization to prevent individuals from inflicting self-injury through hyperactive and impulsive activity.[1] Recent evidence-based guidelines recommend second-generation antipsychotics, mood stabilizer lithium, and anticonvulsant valproate as first-line monotherapy for adults with acute mania.[2-4] However, only 50-60% of patients respond to available therapies, amid data from clinical trials suggesting that 20% more patients respond to combination therapy as compared to monotherapy with mood stabilizers.[2,5]

Studies on the pathophysiology of BD indicate abnormalities in protein kinase C (PKC) signaling, and evidence suggests that inhibition of PKC can help treat mania.[6] Hence, PKC inhibitors are being explored for the treatment of mania associated with BD.[7] We present the case of a patient with BD presenting with acute mania who was successfully treated with an 8 mg BID dose of endoxifen, a direct PKC inhibitor.

CASE REPORT

A 52-year-old male was brought to our outpatient unit with complaints of disturbed sleep, and behavioral changes like irritability, aggression, extravagance, loquaciousness, wandering away from home, and increased alcohol consumption for 2-months. No abnormalities were found on physical examination. His young mania rating scale (YMRS) score was 36. The patient had a history of similar episodes of disturbed sleep, loquaciousness, hyperactivity, nymphomania, extravagance, irritability, and masquerading in 2001, 2003, 2007, 2009, 2011, 2014, and 2017, each lasting 5-6 months. Additionally, there was also a history of episodes of lack of interest, sleepiness, decreased communication, and hyposexuality, each lasting 2 to 3-weeks.

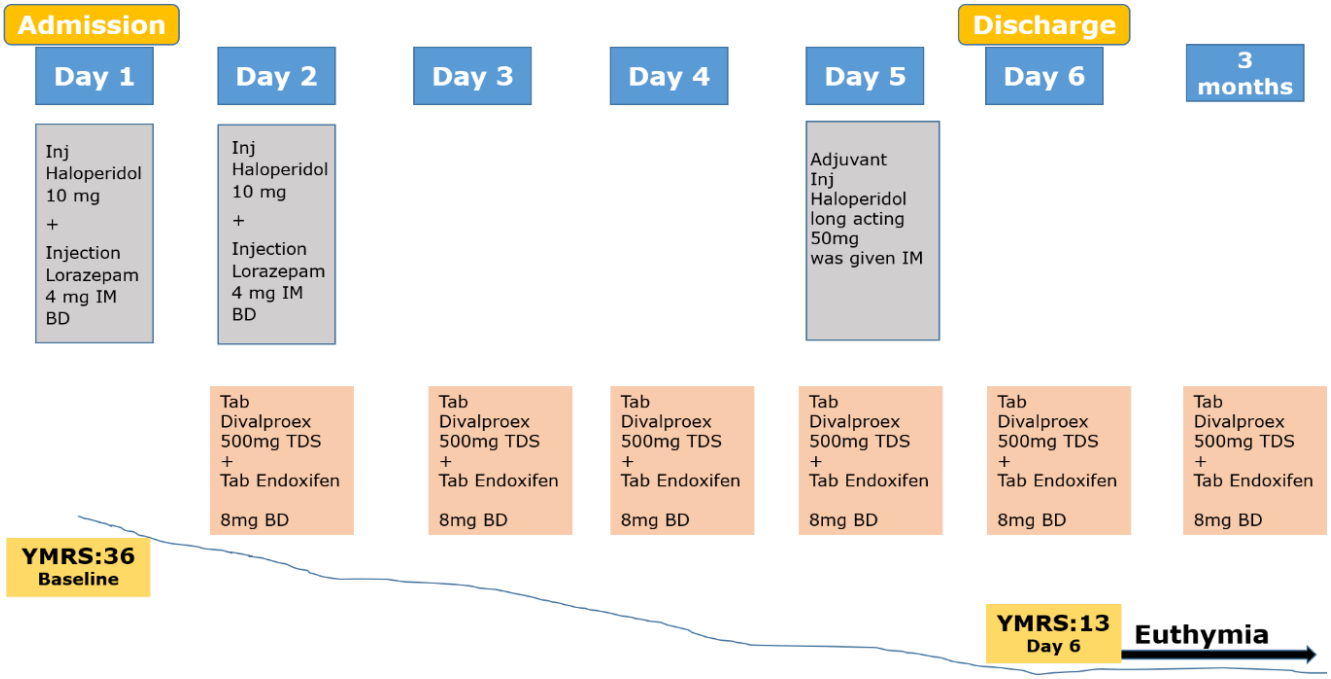

Figure 1: Patient's treatment chart.

He had been diagnosed with bipolar affective disorder 15-years ago, and the current state indicated mania. He had been previously treated with valproate and olanzapine, with no response, and was currently not on any medication. The detailed history of compliance and discontinuation of treatment in the last 15-years was not available.

He was admitted to the hospital and administered intramuscular injections of haloperidol 10 mg and lorazepam 4 mg twice, on day one. On day 2, the injections were continued and tab divalproex 500 mg TID and tablet endoxifen 8 mg BID were added. On day 3, the injections were switched to pro re nata and oral medications were continued. On day 5, an adjuvant intramuscular injection of long-acting haloperidol 50 mg was administered. On day 6, the patient's YMRS score was 13. He was discharged within one week of admission, and the same dose of oral medications was continued for 3-months, during which the patient remained in euthymia. During the 3-months, the patient was followed up six times. His symptoms of irritability and aggression further decreased, and the YMRS sub-scores showed further improvement. He did not consume alcohol during this period. There were no adverse effects of therapy. The timeline of treatment is shown in Figure 1.

DISCUSSION

Bipolar I disorder (BPD I) also known as bipolar mania is associated with the overactive intracellular signaling of PKC. Several studies have demonstrated the significant role of PKC in the pathophysiology of the disease.[5,6] However, the exact causes of BD are still unknown and none of the agents approved for treatment are based on the understanding of its pathophysiology or the ability of the drugs to modify the pathophysiology. Drugs approved for the treatment of BPD I include lithium, valproate, carbamazepine, and some atypical antipsychotics.[8]

PKC is a structurally homologous group of proteins, with 10 isoforms identified until now. They are known to play a vital role in cell signaling pathways, and evidence suggests a possibility of imbalance in the PKC signaling system to be associated with mood disorders. Thus, PKC is a potential novel target for the development of new drugs to treat BD.[7] The approved treatments for BPD I such as lithium and valproate are known indirect inhibitors of PKC, having a slower onset of action.

Endoxifen, a direct PKC inhibitor is an active metabolite of tamoxifen and is four times more potent than tamoxifen.[9] There are few studies about the use of endoxifen for treating patients with BPD I. In a double-blind, randomized, active-controlled study, 84 subjects with BPD I were administered endoxifen (4 mg/day or 8 mg/day) or divalproex in a 2:1 ratio. Patients on 4 mg/day or 8 mg/day endoxifen showed significant early improvement in mania, as seen from the YMRS scores. At the study endpoint, response rates were 44.44% and 64.29% with 4 mg/day and 8 mg/day endoxifen, respectively, compared to 21% with divalproex.[7] Another multicenter, double-blind, active-controlled study compared the outcomes of 8 mg endoxifen with those of 1000 mg divalproex in patients with BPD I acute manic episodes with/without mixed features. Endoxifen (n=116) significantly ($p<0.0001$) reduced total YMRS score from 33.1 to 17.8 ($p<0.001$). Early time to remission of the disease was observed with endoxifen compared to divalproex.[10]

The recommended dose of endoxifen is 8 mg once daily and there are no studies about doses above 8 mg.[10] However, a study demonstrated dose proportionality in peak drug concentrations in plasma (C_{max}) and area under the concentration-time curve of endoxifen.[9] This is the first case in which a dose of 8 mg BID was administered, aiming at achieving a better response in a patient with severe mania, and the outcomes showed good efficacy with no adverse effects. Moreover, the amount of endoxifen required to control mania is 125-250 times less than divalproex (active control), a commonly used drug for the treatment of this disease.[7]

Psychostimulants, which can trigger manic episodes in susceptible persons, are known to activate PKC.[11] BD and alcoholism often co-occur; about 60.7% of people with BPD I were reported to have a lifetime diagnosis of substance abuse, such as alcohol or other drugs. BD is more likely to occur with alcohol dependence than with alcohol abuse. Alcohol intake might aggravate the clinical course of BD, making treatment more difficult.[12] Evidence shows that ethanol exposure causes changes in the expression and promotes intracellular translocation of PKCε, an isoform of PKC.[13] Selective inhibitors of PKCε catalytic activity might be effective in reducing ethanol consumption.[14] One of the important observations, in this case, was that the patient did not consume alcohol for 3 months while on combined endoxifen and divalproex therapy, while there was a history of increased alcohol consumption before treatment initiation. The role of PKC inhibition in reducing alcohol intake needs further exploration.

CONCLUSION

Currently, the clinical trials of endoxifen had been till 8mg dose and duration of 3-weeks in the acute setting. However, data about its long-term safety and efficacy is lacking. This case showed the long-term effectiveness and safety of high-dose endoxifen to control mania in a patient with BD. Further studies to generate evidence about the efficacy and safety of endoxifen over the long term in patients with BPD I are necessary to provide an alternative treatment option to the physicians and patients.

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