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Case Report

Long-Term Therapy With Endoxifen In Bipolar Disorder And Alcohol Abuse In A Real-World Setting: A Case Report.

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Running Title: Long-term use of endoxifen.

Abstract

Protein kinase C (PKC) signalling hyperactivity has been observed in bipolar disorder (BPD), and research indicates that inhibition of PKC may be useful in the treatment of mania. Endoxifen, a direct PKC inhibitor was shown to be well tolerated and effective in management of acute bipolar mania with or without mixed features. Herein, we present a case of a patient suffering from severe manic episode related to BPD with comorbid alcohol use who was treated with endoxifen 16 mg per day. Endoxifen at a high dose for an extended period of time was effective in managing manic episodes with no side effects. The patient also abstained from alcohol over the period of therapy. This case report demonstrates the long-term safety and efficacy of high-dose endoxifen in managing manic episodes in BPD patients.

Keywords: *Endoxifen, BPD, severe mania, Long-term use, Safety.*

INTRODUCTION

One of the most prevalent mental illnesses in the world, bipolar disorder, ranks 17th in terms of years lost to disability. Its global prevalence is estimated to be 2.4% throughout the lifetime.[1] With 25% of patients attempting suicide, high fatality rate is a serious concern. Remission of symptoms and reduction in frequency of mood episodes is the goal of treatment for mania.[2] Bipolar illness is undertreated despite a wealth of research and treatment options. Mania related to BPD is linked to overexpression of protein kinase C (PKC).[3,4] In this report, we present the case of a patient with BPD who had traits of impulsivity as well as alcohol abuse. The case demonstrates the effectiveness of endoxifen when used as combination therapy leading to rapid improvement in bipolar symptoms with no alcohol craving.

CASE PRESENTATION

A 25-year-old male presented to Synapse Mind Care outpatient unit with complaints of poor sleep and alcohol abuse accompanied by behavioural abnormalities such as anger, aggression, compulsive spending, and extravagant conversation regarding contesting elections. In addition, patient believed that some of his relatives, who were envious of him, were planning to attack him in collusion with his former classmates. Although his symptoms were severe and mandated hospitalization, his family did not give consent for the same. He was experiencing these symptoms for more than a year. He was consuming 360-400 mL of foreign whisky daily with no attempt to quit. Maximum period of abstinence reported was 3 months which was one year back. He also occasionally smoked 2-5 cigarettes in a day. Family

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history revealed that his mother was using escitalopram as self-medication to treat her anxiety for last two years.

The psychiatric interview based on 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was used to assess his emotional functioning, personality traits, and mental processes. He was diagnosed to have manic episode related to BPD. His Young Mania Rating Scale (YMRS) score was 51, suggestive of severe mania. On examination, no physical abnormalities were seen. However, as per the findings of laboratory test, the liver enzymes were slightly elevated, serum cholesterol level was around the higher normal upper limit, and glycosylated haemoglobin (HbA1c) was 5.5%.

Medical history revealed that he received sporadic treatment which included divalproex (750 mg BID), olanzapine 20 mg a day (5 mg tablet; 1 tablet in morning, 1 tablet in afternoon, and 2 tablets at night), a combination of risperidone + trihexyphenidyl (3 mg + 2 mg BID), and haloperidol (5 mg TID) for nearly a year.

At our clinic, the patient was initiated on olanzapine 15 mg BID, divalproex 1000 mg BID, and haloperidol 10 mg BID. The above treatment was continued for 10 days. On the 11th day, the YMRS score was still 48 without much improvement. Therefore, therapy with oral endoxifen 8 mg twice daily was added with changes in previous therapy of decrease in dose of divalproex 750 mg BID and haloperidol 5 mg BID. Endoxifen was initiated at a higher dose, considering the patient's acute agitated presentation, severity of illness, and comorbid substance use disorder. The dose of divalproex and haloperidol was reduced, as little benefit was observed with these treatments. After 8 days of endoxifen treatment, there was a noticeable reduction in his aggressive behaviour.

After 15 days, there was a discernible increase in sleep, with a duration of ten hours daily, an improvement in circadian rhythm and extravagant conversation. The dosage of olanzapine was lowered to 20 mg per day and haloperidol was gradually decreased to 5 mg at night by the end of the third week. Olanzapine dosage was lowered to 5 mg TID over the course of the following two weeks. At week 8, his YMRS score dropped to 18; his prescription included divalproex 1000 mg per day, endoxifen 8 mg in morning (decreased dose), olanzapine 10 mg per day, and propranolol 20 mg per day. Propranolol was added to the treatment regimen to address tremor and extrapyramidal symptoms, which were suspected to be related to divalproex. There were regular sessions of psychotherapy in addition to medications. Additionally, he received compliance and treatment adherence training. Over the next 4 weeks, divalproex and propranolol were discontinued. At 6 months, the YMRS score of 4 was noted and the patient remained on the same score until eight months. At 8 months follow-up, the patient was taking endoxifen 8 mg in the morning and olanzapine 10 mg daily which indicates a significant reduction in the overall pill burden and medication. No significant adverse event was reported by the patient till last visit. Additionally, the patient reported minimal alcohol and tobacco cravings and was abstinent from both substances. **Table 1** outlines the treatment timeline and corresponding clinical improvements over the course of Endoxifen therapy.

Table 1. Treatment timelines.

Time Point	Medication Regimen	Clinical Notes	YMRS Score
Before presentation	Divalproex 750 mg BID; Risperidone 3 mg + trihexyphenidyl 2 mg BID; Olanzapine 5 mg TID; Haloperidol 5 mg TID	-	-
At presentation	Olanzapine 15 mg BID Divalproex 1000 mg BID Haloperidol 10 mg BID	Initial presentation	51
Day 11 (Endoxifen initiated), day 1 of Endoxifen initiation	Endoxifen 8 mg BID Divalproex 750 mg BID Haloperidol 5 mg BID	Endoxifen added	48
Day 8–21 (ongoing)	Gradual reduction: Haloperidol 5 mg HS, plan to stop Olanzapine 5 mg TID	Aggression subsided (Day 8); Sleep, circadian rhythm and extravagant conversation improved (Day 15)	-
Week 8	Divalproex 500 mg BID, Endoxifen 8 mg in morning (decreased dose), Olanzapine 5 mg BID, Propranolol 20 mg OD	Stabilization phase	18
Month 6–8	Endoxifen 8 mg (morning); Olanzapine 5 mg BID	Maintenance phase No craving for substance Stopped substance use	4

DISCUSSION

BPD 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. BPD is more likely to occur with alcohol dependence than with alcohol abuse.[6,7] Alcohol intake might aggravate the clinical course of BPD, making treatment more difficult. The case described above demonstrates how addition of endoxifen leads to a reduction in the dosages of other drugs and rapid improvement of symptoms. The treatment with endoxifen was well-tolerated, and the patient was also able to stop alcohol consumption. Earlier, endoxifen has been shown to be a useful part of combination treatment regimen in a case of a young male with comorbid BPD and alcohol abuse.[5]

Evidence shows that ethanol exposure causes changes in the expression and promotes intracellular translocation of PKCε, an isoform of PKC. Selective inhibitors of PKCε catalytic activity might be effective in reducing ethanol consumption.[8,9] Hence, it is hypothesised that PKC inhibitor like endoxifen may be useful for management of substance abuse.

Endoxifen is a direct PKC inhibitor with proven safety and efficacy in treatment of bipolar disorder as evident in two major clinical studies. Endoxifen (4 mg/day or 8 mg/day) or divalproex (2:1) was given to 84 patients with BPD I in a double blind, randomised, active-controlled trial. A notable improvement in YMRS score was observed with 8 mg of endoxifen daily which is similar to 1000 mg daily dose of endoxifen.[1] In another multicenter, double-blind, active-controlled research, patients with BPD I acute manic episodes with or without mixed characteristics were treated with either 8 mg of endoxifen or 1000 mg of divalproex. Significantly, endoxifen (n=116) decreased the overall YMRS score from 33.1 to 17.8 with early remission and better tolerability profile.[2]

Additionally, there are few post-marketing case studies which establish the efficacy of endoxifen 8 mg in successfully reducing the severe symptoms of BPD. In a study reported by Dubey (2022)10, a 52-year-old patient with severe mania symptoms was treated with endoxifen for 3 months and the YMRS score of 36 was reduced to 13 on day 6. The treatment was well-tolerated by patient as there were no adverse events reported. Also, he did not consume alcohol during this period. In another case report, an adult male was diagnosed with severe BPD (YMRS=49) for over a year and exhibited violent conduct, grandiosity, psychostimulant addiction, and a significant family history of mental health issues. He was administered endoxifen 8mg in the treatment regimen and after six months, the prescription was reduced to just endoxifen and risperidone due to its efficacy and no adverse effects were reported, also, there was a notable reduction in YMRS score to 4.[11]

In this care report, treatment with endoxifen for 6 months was effective in reducing the high YMRS score of 51 to 4 without hampering the safety of patient. We also observed a significant reduction in pill burden. Also, the patient was an alcohol addict and after completing the treatment regimen his alcohol craving was reduced. Hence, it may be concluded that PKC inhibitor like endoxifen can also be useful for management of substance abuse along with reduction in the symptoms of bipolar disorder.

CONCLUSION

This case demonstrates the long-term effectiveness and safety of endoxifen to control mania in a patient with severe symptoms of bipolar disorder through improvement in YMRS score along with a reduction in the craving for alcohol and dose of concomitant antipsychotic medications.

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Conflicts of Interest

No conflict of interest

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