Tackling Bipolar Disease with Impulsivity: The Role of Endoxifen

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Abstract**—** *Bipolar disorder (BD) is characterized by mood changes, and traits of impulsivity are often reported in these patients. Alcohol use disorder is also reported among patients with BD. Protein kinase C is known to be involved in the pathogenesis of BD, and there are reports on its link to impulsivity as well as alcohol use disorder. Thus, the use of a protein kinase C inhibitor, such as endoxifen, could address all three conditions. We present a case of a male patient with BD who displayed impulsivity and alcohol abuse. Initial management with combination therapy was not successful in reducing symptoms. The addition of endoxifen to the treatment allowed the reduction of dosage of sodium valproate and lithium and led to a rapid improvement in symptoms. This report showcases the utility of endoxifen in the management of bipolar disorder.*

Keywords— Endoxifen, bipolar disorder, impulsivity, protein kinase C.

I. INTRODUCTION

Bipolar disorder is a chronic mental health disorder characterized by drastic mood changes. Bipolar mania is linked to overactive protein kinase C (PKC) signaling. Patients experience acute manic or mixed episodes, with changes in mood, energy, and activities.[1] Impulsivity is also noted in patients with bipolar disorder during periods of acute mania. This behavior encompasses uncontrolled expenditure and suicide attempts.[2] Furthermore, there are reports that patients with comorbid bipolar disorder and alcohol use disorders demonstrate greater impulsivity compared with bipolar disorder patients without alcohol misuse. Conversely, impulsivity associated with bipolar disorder may increase the risk for impulsivity-related disorders such as alcohol use disorder.[3]

We present in this report, a case of a patient with bipolar disorder who showed traits of impulsivity as well as alcohol abuse. The case describes the use of combination therapy and the introduction of endoxifen in the regimen, which led to rapid improvement in bipolar symptoms.

II. CASE REPORT

A 38-year-old male (weight 86 kg) was admitted to the hospital for a sudden-onset seizure. Blood tests were normal, and the patient underwent magnetic resonance imaging (MRI) of the brain with epilepsy protocol, as well as electroencephalography (EEG). On the bases of these tests, the patient was diagnosed with mesial temporal sclerosis (MTS). He was treated with oxcarbazepine 600 mg, brivaracetam 100 mg, and clobazam 10 mg. The patient initially improved with this treatment, but then began feeling low and lost interest in activities he previously found pleasurable. The patient stopped going to work (he was a crane operator at a shipping port) and began drinking alcohol daily (8-10 pegs of whiskey or rum).

Due to his chronic alcoholism, he underwent a major accident and was admitted to the neurosurgical department once again. The patient had suffered undisplaced facial bone fractures and subdural hemorrhage. The neurosurgeon started the patient on antidepressants. The patient showed improvement within 4 weeks. Subsequently, the patient started talking grandiosely and started purchasing unnecessarily and spending money on buying products that were of no use. The patient had purchased a tractor and spent 50,000 rupees in trading.

At this point, the patient was brought to a neuropsychiatrist for further management. During the assessment of history, it was discovered that the patient had been suffering from bipolar mood disorder type 2 for several years. The Young Mania Rating

Scale (YMRS) score was 47. His uncle also suffered the same illness and committed suicide due to defaulting on treatment. The patient was initiated on lithium 900 mg, sodium valproate 2 g, olanzapine 10 mg HS, trifluoperazine 10 mg, oxcarbazepine 600 mg, and brivaracetam 100 mg.

The patient stabilized with these medications, but suffered side effects of sexual dysfunction, hair loss, and mild tremors. Therefore, sodium valproate was tapered to 1,500 mg and lithium was tapered to 600 mg. However, the patient continued to report tremors and irritability, and was hypomanic even with polypharmacy. The patient's wife reported that the manic episode was 17 days old, and the patient was hypomanic for the last 3 months, with a YMRS score of 35. The patient was initiated on endoxifen 8 mg once daily, and responded well to this treatment, with an improvement in the YMRS score from 35 to 29 in just four days of treatment with endoxifen. The patient's relatives reported that he was calm and composed. After 20 days of treatment with endoxifen, the YMRS score reduced to 13, and therefore, dosages of sodium valproate and lithium were tapered; after 6 weeks, the score was 8; and after 3 months, the score was 3 (Figure 1). At this point, the patient was on endoxifen 8 mg, lithium 400 mg, oxcarbazepine 450 mg for MTS, brivaracetam 50 mg, and clonazepam 1 mg. The patient did not have any manic or depressive symptoms, or impulsivity. Endoxifen treatment led to reduced impulsivity and alcoholism, Furthermore, the patient completely stopped alcohol consumption after 3 months, and resumed his job.

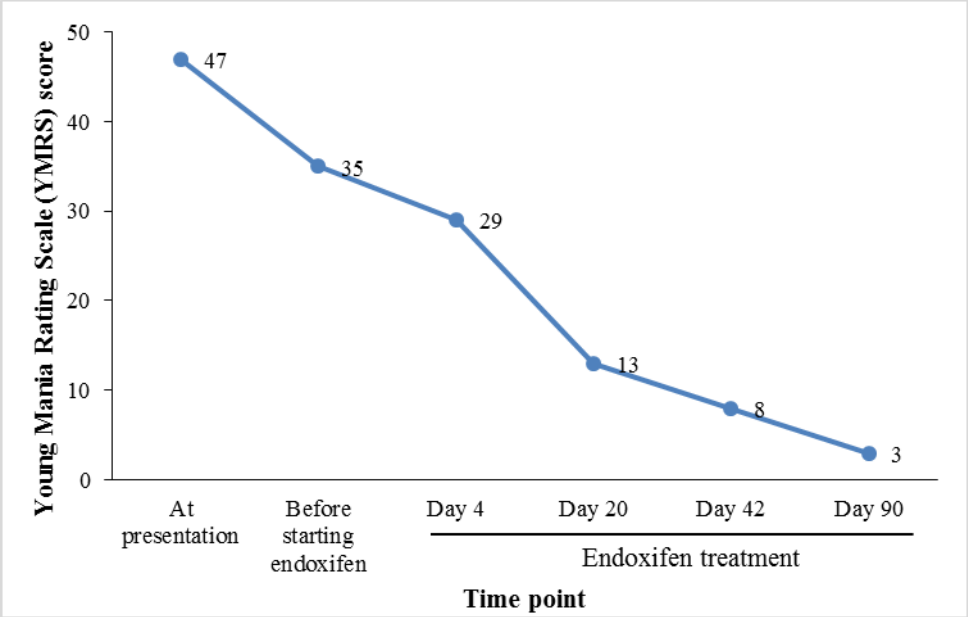

FIGURE 1: Change in Young Mania Rating Scale after initiating treatment with endoxifen

III. DISCUSSION

The case described above demonstrates how switching to endoxifen allowed a reduction of the dosages of other drugs (sodium valproate and lithium) and led to a rapid improvement of symptoms. The treatment with endoxifen was well-tolerated, and the patient was able to resume his job as well as stop alcohol consumption. Endoxifen proved to be a useful part of this combination treatment regimen in the case of a young male with comorbid bipolar disorder and alcohol abuse.

Endoxifen is a metabolite of tamoxifen and has a fourfold higher inhibitory action against PKC compared to the parent molecule. Endoxifen has a number of advantages, including its lipid-soluble nature and ability to cross the blood-brain barrier.[1] PKC plays a role in the pathogenesis of not just bipolar disorder, but also impulsivity and alcohol use disorder.[4-6] Patients with mood disorders have an imbalance in PKC signaling, which is required for the modulation of neuronal processes involved in mood regulation.[4] Studies have shown that elevated levels of PKC signaling can contribute to impulsivity, which is a sign of prefrontal cortical dysfunction leading to impulsivity.[5] Finally, PKC is involved in the response to ethanol exposure, wherein animal studies show that deletion of PKC produces a low ethanol consumption.[6] These studies indicate that targeting PKC may be a useful approach to treating these conditions.[4,6]

Clinical trials have demonstrated the safety and effectiveness of endoxifen, a PKC inhibitor, for the management of bipolar disorder. At a dose of 8 mg daily, endoxifen significantly reduced YMRS by 21 days of treatment (from 33.1 to 17.8).[1] In the case presented in this report as well, the YMRS score reduced from 35 to 13 after 20 days of treatment with endoxifen. Clinical

studies report no serious adverse effects of endoxifen.[1] Similarly, another study reported a reduction of YMRS score by 16.21 points after 21 days of treatment with endoxifen, while it has a safety comparable with that of divalproex.[4]

The patient in this case was a chronic alcoholic, and alcohol can aggravate the course of bipolar disorder, as well as change the expression of PKC. Endoxifen was useful in relieving bipolar disorder symptoms and could also have allowed the de-addiction from alcohol. Past case reports indicate that endoxifen may have a role to play in patients with bipolar disorder and comorbid alcohol abuse.[7]

Clinical trials have reported an early response after four days of treatment with endoxifen, with significant improvement in YMRS score.[1,4] Our case as well showed a reduction in YMRS score from 35 to 29 in four days. The rapid action of endoxifen is beneficial in providing relief to patients. The lower doses required and lack of interaction with other drugs gives endoxifen a unique advantage over other molecules.[1,4]

IV. CONCLUSION

In conclusion, endoxifen is an effective treatment option for bipolar disorder and impulsivity, and it reduces the overall burden of other medications that have to be prescribed to such patients. In this case, endoxifen treatment enabled rapid control of symptoms within 4 days, and the patient subsequently returned to work. The patient did not resume alcohol consumption while on endoxifen treatment. Endoxifen is effective as well as safe and can be part of a combination treatment regimen.

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