Bipolar Disorder with Comorbid Substance Use Disorder in a Young Male not Responding to Combination Therapy: Endoxifen Use for 2 Years

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Abstract**—** *Impulsivity is common to both bipolar disorder (BD) and substance use disorder (SUD). Bipolar disorder is in fact a risk factor for SUD, wherein substances may be used to achieve symptom relief. Impulsivity is associated with excessive protein kinase C (PKC) activity, and is implicated in the development of BD. This case report describes the use of endoxifen, a direct PKC inhibitor, for the management of a young male with BD and SUD who was not responsive to combination therapy with pharmacotherapies including lithium, haloperidol, and risperidone. The inclusion of endoxifen in the treatment regimen while discontinuing haloperidol and tapering of the dose of lithium led to reduced substance use and improvement of the symptoms of bipolar I mania within 3 weeks. The patient tolerated the treatment well, including long-term use for 2 years. Therefore, the utility of endoxifen in the management of SUD could be explored in larger studies.*

Keywords— bipolar disorder, endoxifen, impulsivity, protein kinase C, substance use disorder.

I. INTRODUCTION

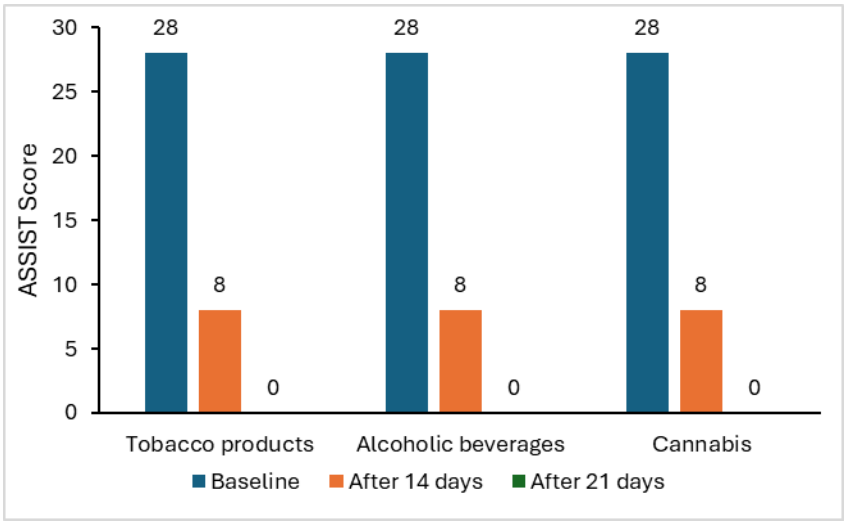
Impulsivity is a phenomenon that is common to bipolar disorder (BD) as well as substance use disorder (SUD). Excessive protein kinase C (PKC) activity is associated with prefrontal cortex deficits, and dysregulation in this brain region is associated with impulsivity.[1,2] Inhibition of PKC may help alleviate impulsivity in both BD and SUD patients. BD is a risk factor for addictions to alcohol, tobacco, opiates, cannabis, etc.[3] Comorbid addictions in BD could be mediated by shared neurobiology or involvement of neurotransmitter mechanisms. Furthermore, individuals with BD may "self-medicate" with substances to alleviate symptoms.[4]

This case report describes the management of a young male with BD and SUD (alcohol, tobacco, and cannabis), who was not responsive to combination therapy despite adherence to therapy. The inclusion of endoxifen in the treatment regimen led to a favorable response for mania, SUD and overall impulsivity. A full recovery was noted within 3 weeks of initiating endoxifen usage. Long-term treatment with endoxifen for 2 years did not lead to adverse effects and the patient did not consume substances during the treatment. Being a direct PKC inhibitor, endoxifen treatment leads to a faster response in reducing impulsivity in both SUD and BD.

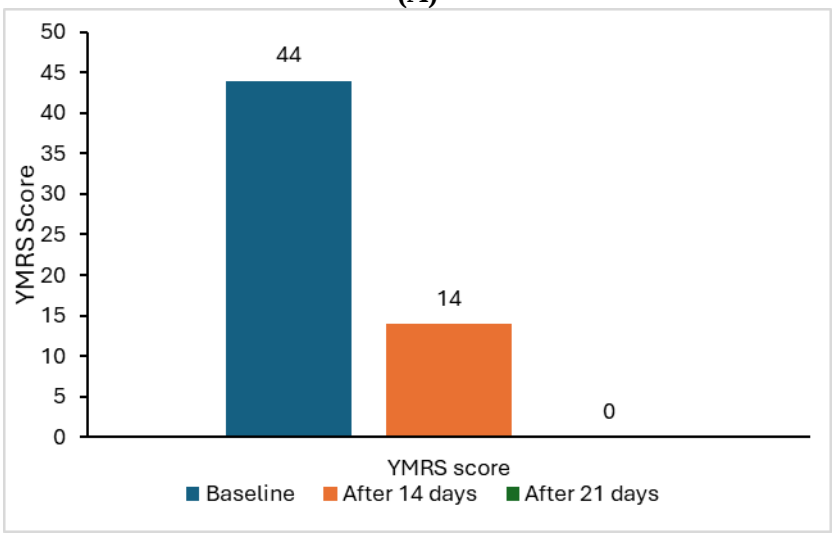
II. CASE REPORT

A 25-year-old male diagnosed with BD 2 years and 2 months prior presented with an increase in symptoms for 3-4 weeks. The patient had a history of polysubstance use (alcohol, tobacco, and cannabis) which was absent before the diagnosis of BD. He consumed 350 mL of alcohol, 30 cigarettes and two joints of cannabis daily.

This patient was an engineer who used to work from home. He lived with his family and was unmarried. The patient presented with grandiosity, overactivity, over-talkativeness, substance use and decreased sleep. There was a high impulsivity to consume alcohol, tobacco and cannabis. The Young Mania Rating Scale (YMRS) score was 44 out of 60, and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) score was 28 out of 36 for tobacco products, 28 out of 36 for alcoholic beverages, and 28 out of 36 for cannabis, indicating the need for more intensive treatment (Figures 1A and 1B).



(A)



(B)

FIGURE 1. (A) Change in ASSIST scores with endoxifen treatment (B) Change in YMRS score with endoxifen treatment.

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; YMRS: Young Mania Rating Scale. Maximum ASSIST score: 36 for each substance; maximum YMRS score: 60.

Based on the diagnosis of BD and SUD, the patient was initiated on lithium (450 mg twice-daily), haloperidol (15 mg daily) and risperidone (4 mg twice-daily) for 1 month. This treatment was targeted to mania, substance use, and impulsivity, since it was likely that SUD was linked to BD. The patient was adherent to the therapy and no side effects occurred; however, there was no improvement noted in the symptoms.

The patient was hospitalized and the treatment regimen was altered. Haloperidol was discontinued. Endoxifen 8 mg was prescribed for 2 days, after which the dose was increased to 8 mg twice-daily. Lithium was tapered off over 15 days, as endoxifen was included in the treatment regimen as a mood stabilizer. Risperidone was continued at a dose of 4 mg daily. The patient was discharged after 7 days. At the first follow-up visit (7 days after discharge) it was noted that alcohol consumption had reduced by 60-70% while the consumption of tobacco and cannabis had ceased. At this point the ASSIST score was 8 out of 36 for each of tobacco products, alcoholic beverages and cannabis, and the YMRS score was 14 out of 60 (Fig. 1A and 1B).

Full recovery was noted within 3 weeks of initiating endoxifen treatment, at which time the patient did not consume alcohol, tobacco and cannabis. In addition, symptoms of bipolar I mania, such as grandiosity, overactivity, over-talkativeness and decreased sleep had diminished. Overall impulsivity had reduced as well. The ASSIST score and the YMRS score were both 0 (Fig. 1A and 1B). The patient was stable on endoxifen 8 mg once-daily and risperidone 4 mg daily with no recurrent symptoms. The patient has been on endoxifen monotherapy for 2 years with no adverse events and no substance consumption.

The patient was compliant with the treatment and the patient's family was happy with the treatment. He continues his job as an engineer working from home without work distress and disability due to his psychiatric condition.

III. DISCUSSION

There is a strong association between BD and alcohol and nicotine dependence, as well as the use of illicit drugs.3 Individuals who consume illicit substances may be unable to quit or reduce consumption due to deficient impulse control.2 BD is characterized by dysregulation in the prefrontal cortical deficits, and lesions in this brain region are associated with impulsivity.1 Increased PKC activity can lead to impulsivity, and impulsivity is noted in both BD and SUD. Reducing PKC can reduce impulsivity and improve the patients of BD and SUD.[1,2,5]

In the case described, the patient was working from home, which could have led to increased stress due to the blurred boundaries of work-life balance. The paucity of face-to-face interactions and absence of workplace support can increase the likelihood of developing a mood disorder.[6] BD and the associated extreme mood states can damage social relationships, and patients with BD are less likely to be married.[7] Individuals with BD may consume illicit substances to improve mood, alleviate tension or boredom, increase energy, or to escape from reality. There are several consequences of comorbid SUD, including higher severity of BD with more relapses and poor response to pharmacotherapy. In addition, the risk of suicide and tendency to commit violent crimes is higher. Individuals with comorbid SUD and BD tend to have a higher lifetime risk of infection with hepatitis C virus and HIV. Therefore, effective pharmacotherapy is essential for the management of these comorbid conditions.[3] The complexity in the development of BD and the social impact of this condition underscores the need for an effective and safe therapeutic option which resolves both manic symptoms and substance use, and can be used for long-term treatment.

Both BD and SUD are characterized by impulsivity. Impulsivity involves the attenuation of control mechanisms that would otherwise suppress reward-driven responses. The resulting 'disinhibition' or predisposition towards can present as SUD.[2] Dysregulation in the prefrontal cortex are known to impulsivity and poor judgment. Individuals with BD have prefrontal cortical deficits, associated with altered PKC intracellular signaling. Excessive PKC activation can disrupt prefrontal cortical regulation, thus leading to signs of impulsivity.[1]

Endoxifen is a direct PKC inhibitor which reduces the signs of impulsivity in both mood disorder and substance use,[6,7] unlike lithium and valproate which are indirect inhibitors of PKC. Being independent of CYP2D6 genetic polymorphisms, endoxifen has predictable bioavailability and lacks drug-drug interactions unlike the parent molecule, tamoxifen. Endoxifen achieves early remission in patients with BD which could be attributed to the direct inhibition of PKC.[5]

In this case study, endoxifen was added to the treatment regimen as it is a direct PKC inhibitor. PKC can lead to impulsivity through its action in the prefrontal cortex, and endoxifen inhibits PKC, potentially alleviating symptoms of mania as well as impulsivity associated with substance abuse. This was needed as PKC inhibition is necessary to reduce impulsivity in BD and SUD. Endoxifen was well-tolerated and its rapid efficacy within 3 weeks permitted the reduction of other drugs and reduced the pill burden. Furthermore, long-term use of endoxifen for 2 years did not lead to adverse effects, and the patient did not consume substances throughout treatment and was maintained on remission. Phase II and III clinical trials have demonstrated that endoxifen has rapid antimanic effects compared with divalproex and reduces the YMRS score significantly.[5,8] There have been several recent case reports which highlight the efficacy of endoxifen in managing impulsivity in BD and SUD.[9-11] The current case report adds to the growing evidence base for the utility of endoxifen in mood disorders and the comorbid conditions thereof.

IV. CONCLUSION

Endoxifen is effective for the management of mania and comorbid SUD because it directly inhibits PKC and hence reduces impulsivity in both mania and SUD. This case study additionally demonstrates the safety of the 2 years of long-term use of endoxifen. It would be beneficial to explore the utility of endoxifen in the management of SUD based on its known tolerability profile and efficacy in reducing impulsivity.

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