The Cognitive Burden of Bipolar Disorder: A Case Report of A Patient Managed Successfully using Endoxifen

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Abstract— *Bipolar disorder carries a substantial long-term risk, and can lead to cognitive impairment. This can have far-reaching impacts on both social and professional realms of life, thus contributing to increased disability. This case report describes a patient with bipolar disorder who was treated with lithium and suffered worsening cognition. Switching to endoxifen led to an alleviation of symptoms and restoration of cognitive function. It also enabled the discontinuation of lithium therapy within 4 weeks of initiating endoxifen. The case highlights the potential of endoxifen to be used as a primary mood stabilizer in patients with bipolar disorder in the presence of cognitive function.*

Keywords— Endoxifen, bipolar disorder, lithium, cognitive dysfunction.

I. INTRODUCTION

Bipolar disorder is known to be a severe and debilitating condition, that affects 2.4% of people worldwide. The long-term psychological risk of bipolar disorder is substantial. Cognitive impairment is known to occur during mood states as well as during euthymia and leads to functional impairment.[1] Furthermore, it has been suggested that cognitive impairment is a marker of bipolar disorder at onset, and is detectable in the early years of bipolar disorder.[2] Apart from the direct impact of bipolar disorder on cognition, medications used for the management of bipolar disorder can also impact cognition. Lithium is one such mood stabilizer that is known to negatively impact cognition in the short term and in the long term.[1]

We present a case of a patient with bipolar disorder on treatment with lithium carbonate, who reported worsening cognition. Switching from lithium carbonate to endoxifen restored cognitive function, making endoxifen a useful option in the management of bipolar disorder.

II. CASE REPORT

A 38-year-old male with known bipolar disorder was on maintenance treatment with lithium 800 mg per day, and thyroxine (for hypothyroidism). He presented with complaints of inability to make business decisions. The patient was self-employed, and involved in running a family-owned packaging business. The patient worked for 2 to 3 days per week, instead of 6 days per week. Along with cognitive dysfunction, the patient then presented with sleeplessness, angry behaviour, and restlessness for two weeks. The recent changes in his behavior were not appreciated by some of the employees. The patient's wife helped with the business and business-related decisions when the patient was unable to cope.

The patient had a first manic episode six years prior, and the patient required injectables and brief hospitalization. At the time, the patient was discharged with lithium carbonate as the primary mood stabilizer. Another major episode occurred two years prior, when he developed hypothyroidism, likely due to treatment with lithium. The patient was subsequently initiated on 25 micrograms of thyroxine, while lithium treatment was continued. Following this, the patient was stable on treatment with lithium carbonate and thyroxine, with only mild depressive symptoms such as irritability and reluctance to participate in social events.

History-taking revealed significant disability in paying attention. The patient reported that he faced difficulty making effective business decisions and in holding meaningful conversations. His family members, including his wife, endorsed these difficulties in social situations, such as the inability to decide on a car parking arrangement for a birthday party. His indecisiveness appeared to be a form of cognitive problems and had become a challenge for his business. Evaluation of symptoms was carried out using the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) scale. This 16-item self-reported instrument measures subjective cognitive dysfunctions including executive function, processing speed, working memory, verbal learning and memory, attention/concentration, and mental tracking. A 4-point scale is used to rate each item (0=never, 1=sometimes, 2=often, and 3=always). The scores of each item are added to give the total score, and higher scores indicate more subjective complaints.[3] The assessment of symptoms revealed a score of 24, and the patients had severe functional impairment. The patient was very reluctant to try other medications, including anti-depressants.

The patient was started on endoxifen 8 mg, while lithium was slowly tapered and stopped within 4 weeks. Within 8 weeks, the patient was stable and manic symptoms resolved. He started managing his business better, and there were no complaints of disruptive behavior. After two months of follow-up, the patient seemed calmer and more cooperative, as well as more thoughtful. His ability to participate in therapeutic and social conversations improved. The COBRA score at follow-up was 6. The patient stated that he felt "a lot clearer in the head".

The patient's wife reported that he was managing the business better, and social engagement had improved. Furthermore, compared to before endoxifen treatment, the patient did not have more trouble remembering recent occurrences and recalling recent conversations, did not need more assistance with transport, and did not have more difficulty in finding the right words to speak.

III. DISCUSSION

The case described in this report showcases the role of endoxifen in the management of bipolar disorder, based on its favorable pharmacodynamics and safety profile. It was effective in replacing lithium as the main mood stabilizer, as it led to remission, and also improved cognitive function. Bipolar disorder is a leading cause of disability, with both patients and their families experiencing lower functional status, reduced quality of life, and stress on personal relationships, as well as loss of employment, difficulty in regaining employment, and absenteeism from work. These collectively contribute to the cost and disability of the disease.[4]

Cognitive dysfunction is linked to adverse psychosocial outcomes and unemployment outcomes.[5] Cognitive impairment is not just a characteristic of bipolar disorder but impacts disease outcomes as well. Patients with bipolar disorder experience defects in primary attention processing, executive function, and verbal memory.[6] It has been reported that 12–40% of patients with bipolar disorder have specific deficits in verbal learning, working memory, and executive function, while a similar proportion have impairments in all cognitive domains.[7] Studies indicate that impaired verbal memory is linked to the duration of illness, the number of manic episodes, and the number of psychiatric hospitalizations.[6] Since functional deficits persist beyond the manic stage, it increases the direct and indirect costs associated with bipolar disorder.[5] Health-related absenteeism is significantly higher among patients with bipolar disorder than those without (18.9 days vs. 7.4 days annually), and it also increases health benefit costs.[8]

Caregiver burden is another aspect of bipolar disease and involves the expenditure of time and money. It is also the cause for worry, tension, and grief. This caregiving strain has been reported for various psychiatric illnesses, affecting over 90% of caregivers of those with bipolar disorder when the patient is hospitalized, and persisting in 70% of caregivers at 15 months after hospitalization.[9]

One aspect of concern is the cognitive dysfunction arising from the use of lithium for the management of bipolar disorder. Lithium has displayed a potential for thyroid, renal and cognitive dysfunction.[10] As seen in this case, the patient developed hypothyroidism after long-term use of lithium and then reported cognitive dysfunction. A meta-analysis has reported that lithium treatment is associated with impairment of immediate verbal learning and memory, as well as creativity.[11] Impaired

cognitive function has clinical implications for the treatment of bipolar disorder, as these adverse effects are a leading cause of medication nonadherence.[12]

Endoxifen is a protein kinase C (PKC) inhibitor that has demonstrated anti-manic activity in patients with bipolar disorder I. It effectively reduces the Young Mania Rating Scale (YMRS) score and improves the Montgomery–Åsberg Depression Rating Scale (MADRS) score, leading to early remission from the disease.[13] The advantage of endoxifen is the safety profile, which is reflected in the low rate of treatment discontinuations due to adverse effects (0-0.9%),[13,14] in contrast with the high rate of treatment discontinuation with lithium (54% of patients report discontinuing lithium on at least one occasion, of which 62% cite adverse effects as the reason for discontinuation).[15] In addition, endoxifen does not negatively impact cognitive function.[13,14] The adverse effects of endoxifen are mild to moderate, and resolve within the same day.[14] Long-term use of endoxifen is well-tolerated, and it is a useful agent for preserving functioning and improving quality of life.[16]

IV. CONCLUSION

Neurocognitive difficulties in bipolar disorder are known to occur with lithium treatment. In this case, neurocognitive difficulties due to lithium therapy impacted the patient's ability to run his business as well as his profession. Treating the patient with endoxifen led to improvement in the patient's neurocognitive dysfunction, and improvement of manic symptoms. This case also described an additional benefit of endoxifen including increased work productivity and reduced absenteeism, better decision-making, and reduction of caregiver burden. Furthermore, the side effects noted with lithium (hypothyroidism) were not noted with endoxifen. Overall, the benefits of endoxifen indicate that it is a an ideal choice for the management of bipolar disorder.

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