First Report of Endoxifen Treatment for 1 Year: A Case Report of Bipolar Disorder

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Abstract— *Bipolar disorder is a common chronic psychiatric condition, with treatment aimed at remission of symptoms and prevention of mood episodes. The pathophysiology of bipolar disorder I involves over expression of protein kinase C, which is thus considered a therapeutic target. Endoxifen, the metabolite of tamoxifen, has enhanced inhibitory action against protein kinase C, with a good safety profile. Endoxifen has shown promise in phase II and III clinical trials, with notable reduction in several symptom scale scores. This report describes the case of a woman with bipolar disorder diagnosed ten years prior, who was experiencing relapses. A change in medication to include endoxifen was effective. This is the first report of endoxifen use for duration of one year.*

Keywords— Bipolar disorder, Endoxifen, Protein kinase.

I. INTRODUCTION

Bipolar disorders are one of the most common psychiatric conditions, and are the seventeenth leading cause of disability across the world. The estimated lifetime prevalence of bipolar disorders is 2.4%.[(1)] A significant concern is the high mortality rate, with a quarter of patients attempting suicide.[(2)] The aim of treatment for acute manic episodes is symptom reduction and full remission, and that of acute depressive episodes is remission of symptoms and reduction of hypomanic and manic episodes. Maintenance treatment is aimed to prevent mood episodes.[(3)] Despite the extensive research and wide range of therapeutics, bipolar disorder remains undertreated.[(2)]

Bipolar disorder I is the manic-depressive type, associated with overexpression of protein kinase C (PKC). Endoxifen is a metabolite of tamoxifen with enhanced inhibitory action against PKC, being four times more potent than tamoxifen. The antimanic activity has been demonstrated in phase II and III trials, with promise for use as monotherapy.[(4)] In this report, we highlight the use of endoxifen for management of bipolar disorder, wherein it was used for the period of one year, making this the first report of its kind.

II. CASE REPORT

A 49-year-old woman with a history of hypothyroidism and thalassemia minor was diagnosed with bipolar disorder more than 10 years prior. Four years prior, she presented with a manic episode. She had a past history of multiple depressive episodes and couple of manic episodes. There was always a problem in achieving stability of mood which affected her functioning. The woman was a homemaker, and did not have a history of alcohol or substance abuse, and suicidal tendencies were not reported. The patient had received treatment with multiple drugs including olanzapine, desvenlafaxine, fluoxetine, risperidone, and aripiprazole. The patient had experienced side effects with olanzapine (weight gain, sedation), risperidone (irregular menstruation) and aripiprazole (agitation). The patient had been unable to function as a home maker causing a lot of distress to her. Her family had given up hope due to her repeated relapses and lack of stability on medications.

In April 2021, she presented with elated mood, over activity, social disinhibition and decreased sleep for a period of 6–8 weeks. She also complained of heaviness of head and burning sensation throughout her body which she found very distressing. Family reported her as being agitated and aggressive. Unlike before, she was not able to do her household chores. At this point, the Short Form 36 Health Survey (SF-36) score was 79 (maximum 100; lower score indicate more disability,

higher scores indicate less disability). The Young Mania Rating Scale (YMRS) score was 25, the Montgomery-Asberg Depression Rating Scale (MADRS) score was 11, the CGI BP score was 4, 6, 6 and the BPRS score was 72. Routine investigations including complete blood count, liver function tests, urea, creatinine, thyroid-stimulating hormone, and fasting plasma glucose were normal.

At the time of presentation, the patient was on treatment with olanzapine 10 mg once-daily, fluoxetine 20 mg per day and desvenlafaxine 100 mg per day. Both fluoxetine and desvenlafaxine were stopped immediately. The patient was started on endoxifen 8 mg once-daily. The dose of olanzapine was reduced to 5 mg once-daily and gradually stopped over a period of one month.

After three months, the patient showed an improvement in symptoms severity assessment scales (Table 1). The patient was able to undertake household chores. Specifically, with respect to question 4 of the SF-36, "During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?" and question 10, "During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?" the patient showed an improvement, with answers indicating the lack of interference of physical or emotional problems on daily activities and social activities. The details are presented in Table 2.

The treatment has continued for 1 year, and there have been no major relapses during this period. Minor mood fluctuations were managed by her family without the need for medical intervention. There were no side effects reported by the patient. She reported no changes in her menstrual cycle, and no sexual side effects.

TABLE 1
SYMPTOMS ASSESSMENT SCALE SCORES AT BASELINE VISIT AND FOLLOW-UP VISITS

Scale	Baseline	3 months	12 months
YMRS	25	5	5
MADRS	11	1	1
CGI BP	4, 6, 6	2, 2, 2	1, 2, 2
BPRS	72	32	32
SF-36	79	-	98

BPRS: Brief Psychiatric Rating Scale; CGI BP: Clinical Global Impressions – Bipolar Version; MADRS: Montgomery–Åsberg Depression Rating Scale; YMRS: Young Mania Rating Scale; SF-36: Short Form 36 Health Survey

TABLE 2
SPECIFIC IMPROVEMENT IN RESPONSES TO QUESTION 4 AND QUESTION 10 OF THE SF-36

Question	SF-36 (Baseline)	SF-36 (12 months)
Q4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?		
a. Cut down the amount of time you spent on work or other activities	Yes	No
b. Accomplished less than you would like	Yes	No
c. Were limited in the kind of work or other activities	Yes	No
d. Had difficulty performing the work or other activities (for example, it took extra effort)	Yes	No
Q10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	None of the time

III. DISCUSSION

The case described highlights the utility of endoxifen in the management of bipolar disorder in a patient with repeated relapses, as well as depressive episodes and manic episodes. The treatment was safe and effective over the course of a year, which makes it the first report on long-term use of endoxifen for one year in a patient with bipolar disorder. The treatment had a benefit of good tolerability, which helped to stabilize the patients' condition.

Endoxifen is an inhibitor of PKC, and PKC is known to be involved in regulation of presynaptic and postsynaptic neurotransmission. Tamoxifen was studied for its utility in targeting PKC in patients with bipolar disorder. Though it possesses antimanic properties, the bioavailability and function vary considerably among populations, likely due to genetic polymorphism of CYP2D6. To circumvent this, endoxifen, a metabolite of tamoxifen which is independent of CYP2D6 metabolism, is promising for the management of bipolar disorder. Endoxifen inhibits PKC to a greater extent than tamoxifen (78% vs. 25%).[5] Steady-state levels are achieved within 14 days, with dose-dependent pharmacokinetics. It has a mean terminal elimination half-life of 52.05 h (single dose of 4 mg).[6]

Since endoxifen is not metabolized in the liver, drug interactions with other antipsychotics is unlikely, as these are commonly metabolized by cytochrome P450 enzymes. This lends endoxifen an advantage over other drugs. Safety data indicates it is well-tolerated and safe compared with divalproex. Most adverse effects are mild or moderate, and usually resolve within the same day.[4,6] Interestingly, the risk of weight gain is not present for endoxifen. This is of benefit as weight gain is a risk in patients with bipolar disorders, and antipsychotics usually add to this risk. Endoxifen also does not alter thyroid function, unlike valproic acid and divalproex. The expected benefit of this tolerability profile is improved adherence to therapy.[4] This was reflected in the case presented, as the patient was adherent to treatment for one year, and did not report adverse effects. Furthermore, the patient did not report any menstrual irregularities, unlike with previous treatment with risperidone. This indicates that endoxifen 8 mg is a very low dose to limit estrogen-related activity, even when used over the long term (one year).

In a phase II trial, endoxifen at doses of 4 mg/day and 8 mg/day led to improvement of mania, as reported by the YMRS within 4 days of treatment initiation. A response rate of 64.29% was achieved after 21 days of treatment with 8 mg/day of endoxifen.[6] These findings were confirmed in a phase III study among adult patients with bipolar disorder. Treatment with endoxifen 8 mg per day improved multiple measures of mania, including YMRS, MADRS and CGI-BP. Furthermore, remission was achieved faster with endoxifen (at 4 days) than with divalproex.[4]

In this case, the patient showed improvement in multiple measures of symptoms, with tremendous improvement noted at three months, which was maintained until one year of therapy. Specifically, the patient was able to undertake regular daily activities, and social activities, which was unlike when she presented for treatment. At the end of one year, the patient reported that her emotional and physical condition interfered with social activities "none of the time", and that her physical condition did not interfere with her regular daily activities. This was even felt by her family, as they noted her being unable to function as a home maker at the time of presentation. In fact, the emergent trends in psychiatry indicate not just symptom recovery, but also a return to normal functioning and a meaningful life is of importance.[7] This outcome of treatment with endoxifen, leading to a restoration of daily functioning, is a key indicator of its efficiency, and also indicates that endoxifen is useful in preserving functioning and improving quality of life in patients with bipolar disorder.

IV. CONCLUSION

The management of bipolar disorder requires treating manic and depressive episodes, as well as maintenance therapy to ensure long-term therapy to mood stability. This case reports highlights the role of endoxifen, which is a novel PKC inhibitor with enhanced inhibitory effect, which is independent of metabolic enzymes, has few adverse effects, rapid action and improves manic symptoms in patients with bipolar disorder. The clinical data was supported by our observations of improved symptoms, with no major relapses noted for the period of one year. Improvement over YMRS, MADRS, BPRS and CGI BP were observed. The patient had good quality of life within a year of endoxifen treatment and started doing household chores unlike before, with improved SF36 score. Endoxifen has the potential to be an effective therapeutic for bipolar disorder, with potential for safe long-term use.

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