Endoxifen Response in Schizoaffective Disorder: A Case Series

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Abstract— *Schizoaffective disorder has symptoms of both bipolar disorder and schizophrenia. Protein kinase C (PKC) activation is identified as to play a key role in both illnesses. Endoxifen, a potent inhibitor of the PKC signaling pathway, is effective in controlling acute bipolar mania at a dosage strength of 8 mg. Considering the PKC inhibitory activity of Endoxifen, we are presenting two patients with schizoaffective disorder who were administered with Endoxifen 8 mg to explore its role in providing better responses in patients.*

Keywords— Schizoaffective disorder, Protein kinase, Endoxifen, bipolar mania.

I. INTRODUCTION

Schizoaffective disorder is a chronic illness with a prevalence of around 0.3%[(1)]. Schizoaffective patients have features of either manic or depressive type, or in some cases, both. As per the DSM 5 diagnostic criteria, to be diagnosed with schizoaffective disorder at least two psychotic symptoms must be present as well as mood symptoms for a specific duration.

The symptoms of psychosis, which are identical to the primary criteria for schizophrenia, include [(2)]:

- Hallucinations
- Delusions
- Disorganized thinking or behavior
- Disorganized speech
- Negative symptoms

The mood symptoms that must be present include:

- Mania: decreased need for sleep, high energy
- Racing thoughts
- Rapid speech
- Bizarre or risk-taking behavior
- Depression: feelings of sadness and worthlessness

For diagnosing a patient with schizoaffective disorder, at least two weeks of schizophrenic symptoms should be present without any mood symptoms.[2] It has been evident from molecular studies that protein kinase C (PKC) plays a major role in pathogenesis of bipolar disorder as well as schizophrenia.[3,4] Below, we are presenting two patients with schizoaffective disorder who were treated with tab Endoxifen, which works through PKC inhibition.[5]

II. CASE REPORTS

2.1 Case 1

Mr. A, a 36-year-old married male with class 12 education was brought to our clinic in October 2020 by his family members with complaints of hearing voices, suspiciousness, aggressive behavior, irritability, not able to sit at one place, and not able to maintain focused attention. The patient was diagnosed with schizoaffective disorder as per DSM 5 diagnostic criteria.

Young Mania Rating Scale (YMRS) and Brief Psychiatric Rating Scale (BPRS) were applied on the patient in October 2020. The patient scored 42 and 50, respectively on these scales and was initiated on tab Divalproex Sodium 1000 mg twice a day along with Haloperidol long-acting injection (200 mg), which was given deep intramuscular every 2 weeks. The patient came for follow-up after 1 month; both the scales were applied again but no improvement was reported in scores of YMRS and BPRS, which were 44 and 51, respectively. The dose of Divalproex sodium was increased with an additional 750mg added in the night. The patient came for follow-up after 2 months in January 2021 and his condition was deteriorating; he was not cordial, was aggressive, showed poor self-care with symptoms of hallucinatory voices and suicidal intent. YMRS and BPRS of the patient was 41 and 53, respectively and thus an additional 25 mg of tab Lamotrigine was prescribed to the patient. The patient was asked to follow-up after two months. During the follow-up visit in March 2021, no significant improvement was reported and thus the dosage of tab Lamotrigine was increased up to 100 mg and the patient was asked to follow-up in 10 days. During the follow-up visit, the condition of the patient had deteriorated and thus after taking consent from patient as well as family members, tab Endoxifen 8 mg was started once a day. Follow-up visit was scheduled after 15 days. At the time of initiation, YMRS and BPRS scores of the patient were evaluated at baseline, which was 40 and 54, respectively. He came back to the clinic after 15 days; he showed a mild improvement in aggressive behavior and hearing voices; YMRS and BPRS scores were 35 and 47, respectively and thus the patient was asked to come back for follow-up after 2 months. The patient returned for follow-up in the month of June 2021 and was found to be stable on these medications; his YMRS and BPRS were 26 and 35, respectively. The patient was advised to come after 3 months. He came back in the month of October 2021 and as he was doing well on medication, tab Lamotrigine was stopped; his YMRS and BPRS were 16 and 28, respectively. On his next follow-up in December 2021, Haloperidol long-acting injections were reduced from 200 mg to 150 mg once in two weeks; all other medications were asked to be continued. During this visit, his YMRS and BPRS scores were 10 and 19, respectively.

TABLE 1
REDUCTION IN YMRS AND BPRS SCORES AFTER INITIATION OF TAB ENDOXIFEN (8 MG) (CASE 1)

S.No.	Time since initiation of Endoxifen	YMRS	BPRS
1.	April 2021 (0 month 0 day)	40	54
2.	15 days	35	47
3.	2 months (June 2021)	26	35
4.	6 months (October 2021)	16	28
5.	8 months (December 2021)	10	19

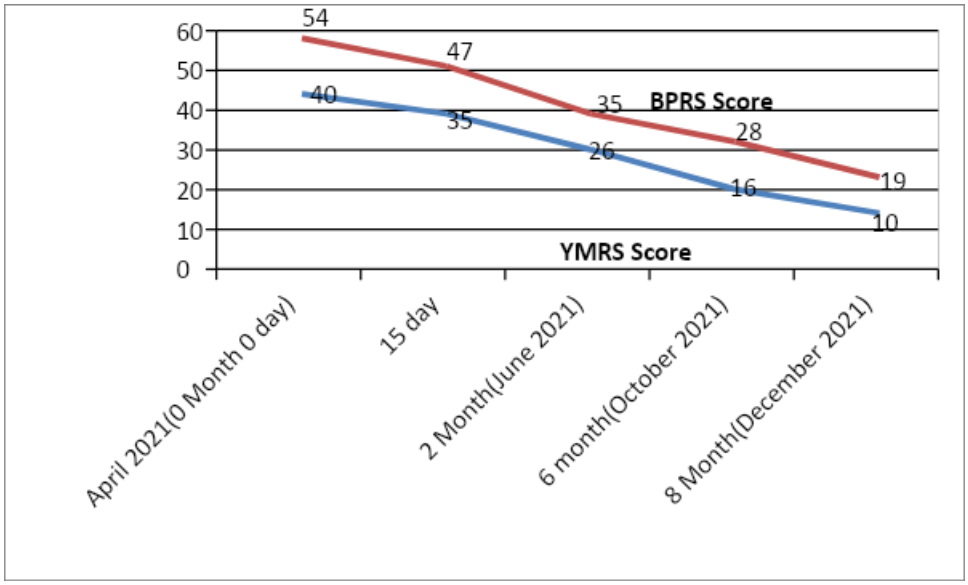

FIGURE 1: Reduction in YMRS and BPRS scores after initiation of tab Endoxifen (8 mg) (Case 1)

2.2 Case 2:

Mrs. B, a 41-year-old married female with a Bachelor's degree in Arts came to our clinic in June 2020 with complaints of hearing voices, suspiciousness, poor self-care, irritability, distractibility, reckless behavior, and over-familiarity. The patient was previously under treatment from another psychiatrist for 4 years and upon enquiring with family members it was revealed that the patient was having similar complaints in the past too. On further enquiry, they mentioned that the patient showed aggressive behavior, over-familiarity and disturbed sleep for some time, but for the past 15-20 days, she showed psychotic symptoms with complaints of suspiciousness, hearing voices, disorganized speech and poor self-care. The patient was diagnosed with schizoaffective disorder as per DSM 5 diagnostic criteria. The patient was on tab Lithium 300 mg BID along with tab Olanzapine 10 mg twice a day and was on the same treatment for the past 6 months from another psychiatrist. In June 2020, when the patient was brought to our clinic, her YMRS and BPRS scores were 38 and 49, respectively. Doses of tab Lithium were titrated to 400 mg twice a day and all other medicines were asked to be continued. The patient returned for follow-up after one month in July 2020; she did not show any improvement while being on these medications and her YMRS and BPRS scores were 37 and 47, respectively. Along with these tablets, tab Risperidone 2 mg BID and THP 2 mg were added and the patient was asked to come for a follow-up visit after 3 months. The patient came for follow-up in November with a mild improvement on her YMRS and BPRS scores of 34 and 43, respectively. The patient was called for follow-up again after 3 months in February 2021; her condition had worsened and she complained of hearing voices, irritability, and reckless behavior. Her dosage of Lithium was titrated to 450 mg twice a day and she was called for follow-up in the month of April 2021. During the visit, the patient complained of suspiciousness, hearing voices, over-familiarity to unknown people, increase in energy and a decreased need for sleep, and restlessness. Akathisia was suspected and tab Risperidone was stopped; after taking consent from patient and her family members, tab Endoxifen 8 mg half-tablet was prescribed to be taken at night. At the time of initiation of Endoxifen, YMRS and BPRS scores of the patient were 37 and 45, respectively. The patient was called for follow-up after one month in May and during the visit, a slight improvement was observed with her YMRS and BPRS scores at 33 and 42, respectively. The dosage of Endoxifen was increased to 8 mg and she was called for follow-up in June 2021. The patient was responding well to this medication and akathisia was resolved on stopping Risperidone. The patient was called after two months in August 2021; during the visit, she showed improvement on these medications and her YMRS and BPRS scores were 28 and 37, respectively. The next follow-up was scheduled after 3 months in November 2021, and she was found to be stable on medication; her YMRS and BPRS scores also reduced to 19 and 26, respectively.

TABLE 2
YMRS AND BPRS SCORES AFTER THE INITIATION OF ENDOXIFEN IN PATIENT NO. 2

S.No.	Time since initiation of Endoxifen	YMRS	BPRS
1.	April 2021 (0 month)	37	45
2.	May 2021 (1 month)	33	42
3.	June 2021 (2 months)	30	39
4.	August 2021 (4 months)	28	37
5.	November 2021 (7 months)	19	26

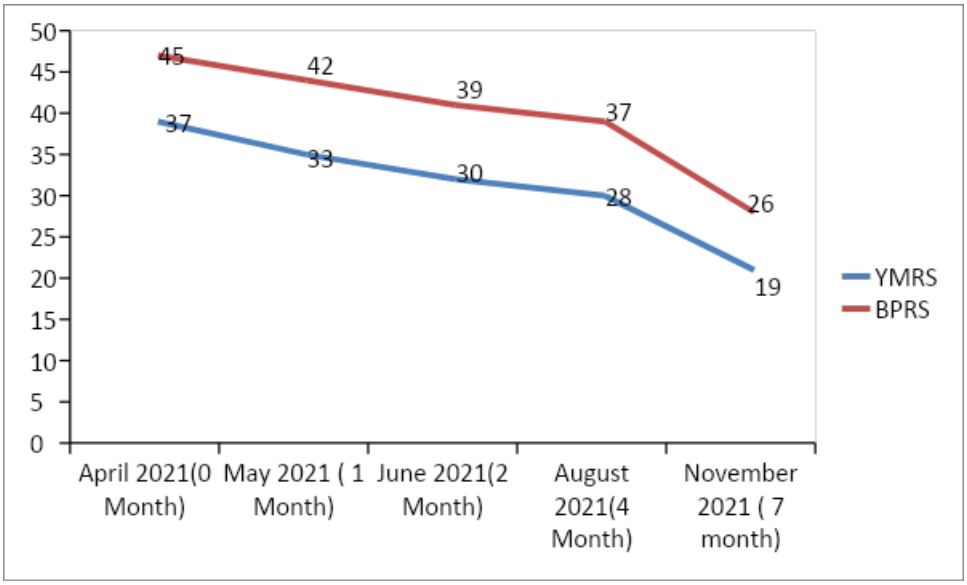

FIGURE 2: YMRS and BPRS scores after the initiation of Endoxifen in patient no. 2

III. DISCUSSION

Hyperactivation of PKC is seen among patients of both schizophrenia and bipolar disorders[3, 4] while looking at schizoaffective disorders, symptoms of both the illnesses are present. Hence, we tried tab Endoxifen in these patients as it works by inhibition of PKC.[6]

Psychostimulants like amphetamine and methamphetamine work through PKC activation, which is responsible for the pathogenesis of bipolar disorder as well as schizophrenia.[7,8] As Endoxifen works through PKC inhibition, it may be the reason Endoxifen is effective in the treatment of schizoaffective disorder.[6]

In a study conducted by Ahmad A et al., 49% bipolar patients showed improvement in their symptoms with Endoxifen over a duration of 3 weeks.[6] Though long-term studies are lacking on Endoxifen, its tolerability profile encourages its use especially in patients where current treatment options bring challenging side effects. In the female patient's case presented above, akathisia was suspected and tab Respiridone was stopped. Later on, Endoxifen was added not just because of its efficacy due to PKC inhibition but also because extrapyramidal symptoms have not been reported with this molecule till now. Further, Endoxifen is also a selective estrogen receptor and parent molecule of Tamoxifen, which is well-known for its use in the treatment and prevention of breast cancer due to its anti-estrogen activity. Endoxifen is safe, considering studies conducted evaluating the long-term use of Tamoxifen for durations as long as 5–10 years (ATLAS STUDY with 12,894 women). In the case of the female patient mentioned above, it's worth noting that there were no sexual side effects observed with Endoxifen 8 mg over a duration of 8 months.

Endoxifen might also bring promising benefits of reducing overall pill burden and injectable usage, which needs to be evaluated further. In the male patient's case presented above, after the usage of Endoxifen over a longer period of time, along with improvement in symptoms, there was no longer a need to continue Lamotrigine and the dosage of Haloperidol had also eventually come down, which was a relief for the patient.

IV. LIMITATION

This is a case series, so the data generated from here cannot be generalized on the whole population, thus a cross-sectional or longitudinal study with longer durations and larger number of subjects will give a better insight on this topic.

V. CONCLUSION

Currently, no clinical trial has been done with Endoxifen on schizoaffective patients, and we prescribed Endoxifen to patients who were diagnosed with schizoaffective disorder and not getting better results with other medications. In our 2 patient cases with schizoaffective disorder, Endoxifen 8mg tablets reduced the severity of symptoms. YMRS score in patient 1 improved from 40 to 10 while in patient 2, it improved from 37 to 19.BPRS score too showed improvement from 54 to 19 in patient 1 and 45 to 26 in patient 2. Due to good tolerability profile and better efficacy, Endoxifen was continued beyond 6 months and both the patients have maintained well on treatment without any adverse events being reported.

Though large randomized trials with Endoxifen are lacking, it can be a worthy option to explore in schizophrenia as well. Further studies are required to generate evidence about efficacy and safety of Endoxifen for providing an alternative treatment for schizophrenic and schizoaffective disorder patients.

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