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Endoxifen: The diverse molecule- a case series

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Abstract
Endoxifen, a protein kinase C inhibitor (PKC), has been approved for use in bipolar affective disorder Recent literature depicts that it has been used in other disorders like impulsivity of borderline personality disorders, substance abuse and many more [2]. Here we upheld a series of cases showing multi-faceted use of the molecule in our daily clinical practice. There are documented evidences regarding efficacy of endoxifen in bipolar affective disorders and substantial data to suggest its benefit compared to the most commonly used mood stabilisers. But this molecule can give encouraging output in other major psychiatric illnesses if used effectively as depicted in our cases and its relatively safer side effect profile is an added cherry on the top of the cake. Further research and explorative studies are warranted to support the claim.

Keywords: Endoxifen, bipolar affective disorder, protein kinase C inhibitor (PKC), psychiatric illnesses, mood stabilizers

Introduction
Endoxifen, a protein kinase C inhibitor (PKC), has been approved for use in bipolar affective disorder [1]. Recent literature depicts that it has been used in other disorders like impulsivity of borderline personality disorders, substance abuse and many more [2]. Here we upheld a series of cases showing multi-faceted use of the molecule in our daily clinical practice.

Case 1
A 56 year old female presented with acute psychotic symptoms of irrelevant talk, reduced sleep, hallucinatory behaviour and paranoid ideations. She has had similar complaints of psychotic episode 2 years ago when she was diagnosed with psychotic depression. She was on escitaopram 10 mg, clonazepam 0.5 mg, risperidone 4mg with Quetiapine 50 mg. She stopped medicines on her own 10 days back leading to exacerbation along with diabetic ketoacidosis (DKA) as she had missed doses of her oral hypoglycemic medicines also. She was admitted under general medicine for management of DKA. Once stabilized, she was examined and diagnosed as Bipolar Affective Disorder in Mixed State. She was started on Endoxifen 8 mg twice a day, Divalproex 500mg once at night, Trifluoperazine 5 mg twice a day, Trihexyphenidyl 2 mg BD, Escitalopram 20mg and clonazepam 1mg both once at night. The patient was symptomatically better but had significant weight gain and hair loss leading to mood worsening. So the dose of divalproex was reduced to 250 mg OD and then stopped eventually. Currently she is well maintained on endoxifen 16 mg and other medications being in same dosage as the last time.

Case 2
A 46 year male diagnosed with Alcohol Use Disorder (AUD) presented with withdrawal symptoms. He was managed with benzodiazepines initially and then was started with naltrexone 50 mg at night, fluoxetine 40 mg OD, risperidone 6 mg and lithium 600 mg at night. He had 2-3 episodes of relapses in between and was having profuse sweating and ataxia presumably due to lithium. Since 3 months, he was started on endoxifen 8 mg OD in addition to the existing regimen. Lithium was slowly cross tapered to endoxifen 8 mg BD, currently on complete remission and is well maintained.

Case 3

A 33/M diagnosed with bipolar affective disorder with gambling addiction presented with features suggestive of mania like claiming himself to be the most powerful man in india, irritable behavior, aggression, reduced need for sleep with loss of 1 lakh rupees in gambling. He had 4 episodes of mania in the past with wanning and waxing course in gambling behavior. He was settled with antipsychotics and benzodiazepines initially and then started on Lithium 800 mg, Valproate 800 mg, aripirazole 15 mg, cyclotin 20 mg. and Naltrexone 50 mg. The manic features settled down though he had intermittent mood fluctuation and occasional relapses in the form of mixed episodes and excessive indulging into gambling. Sodium valproate was cross-tapered to Endoxifen 16 mg. Currently since 3 months he has no gambling replases, no mood fluctuations, working well, able to enjoy his family and work and also has started taking interest in hobbies.

Case 4

A 43/M diagnosed with schizophrenia for past 10 years tried on many antipsychotics in the past with partial remission presented with acute psychotic break with delusions of persecutions, auditory hallucination and violent behavior. After initial stabilisation, he was started on Tablet clozapine 100 mg, sodium valproate 500 mg and trifluoperazine 5 mg. The dosage was slowly increased to 200 mg clozapine keeping the rest two same. The patient improved significantly but still had occasional relapses of short duration. After 3 months of treatment he exhibited side effects like hypersalivation, nocturnal eneuresis with headache. Clozapine was reduced to 150 mg and endoxifen was added in a dose of 8 mg OD as augmentation initally and then increased to 16 mg a day. The side effects reduced and he is now in complete remission.

Discussion

Endoxifen has many advantages over traditional mood stabilisers like sodium valproate on being less sedative, better side effect profile and almost equally efficacious in bipolar illness [1]. Recent evidence advocates alteration in activity of intracellular PKC signalling cascade in the pathophysiology and treatment of the bipolar disorder [3] the approved treatments for BPAD include lithium and valproate that are indirect inhibitors of PKC but having a delayed onset of action [4]. Though available treatments are effective in a major proportion of subjects, still, 40-50% are not benefitted [5]. Many, preclinical and clinical studies have demonstrated satisfactory results of tamoxifen in mania which is a selective PKC inhibitor [6-16]. Endoxifen, an active metabolite of tamoxifen and a direct PKC inhibitor is fourfold potent than tamoxifen [1]. Results of a multicentric, double-blind study using a daily dose of 8 mg endoxifen in patients with BPD I showed that acute manic episodes with/without mixed features significantly reduced the total YMRS score and was well-tolerated for 3 weeks [1]. In another study the molecule was found to reduce impulsivity of borderline personality disorder [2]. The PKC inhibition in the frontal lobe was proposed to be the underlying mechanism responsible for the same [9, 10]. Coming to our cases, in the first case, the patient was switched to endoxifen owing to side effects and lack of full remission which was completely resolved after the switch. There are evidences on benefit of endoxifen on the depressive state of bipolar illnesses but this is one of the rare instances where it was successful in complete remission in a mixed state. PKC inhibition in anterior cingulate gyrus and orbitiofrontal cortex as well as restoring interhemispheric balance are the proposed mechanisms for the same [17]. In the second case, the molecule was successfully used in reducing craving and relapses in alcohol use disorder. An *in vitro* study conducted has also reported that there is increased PKC activity with naturally occurring cannabinoid, delta-9-tetrahydrocannabinol [18, 19]. In another case was it was found that patient's craving for hookah/shisha reduced with endoxifen treatment [17]. Also, extensive data have demonstrated reduction in behavioral and amphetamine stimulated activities by tamoxifen and other inhibitors of PKC pathway [20, 21, 22]. In the third case, endoxifen was introduced to the regimen by switching from valproate which helped the patient achieve remission. It goes in sync with the existing literature on its benefit in the mixed state as stated before [1]. In the fourth case we used the drug for schizophrenia by reducing clozapine and introducing the molecule leading to significant improvement. Though there are no existing literature to corroborate this but the possible mechanisms could be the PKC signal modulation in the mesocortical and mesolimbic dopaminergic pathways [23].

Conclusion

There are documented evidences regarding efficacy of endoxifen in bipolar affective disorders and substantial data to suggest its benefit compared to the most commonly used mood stabilisers. But this molecule can give encouraging output in other major psychiatric illnesses if used effectively as depicted in our cases and its relatively safer side effect profile is an added cherry on the top of the cake. Further research and explorative studies are warranted to support the claim

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