Case report

Real world experience of Endoxifen augmentation therapy in a case of resistant OCD

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ABSTRACT

About 40%–60% of obsessive-compulsive disorder patients do not achieve full remission even when treated with selective serotonin reuptake inhibitor and cognitive behavioural therapy. Here, we describe a case of a 30-year-old female suffering from OCD, who was not improved even after fluoxetine 80 mg per day and behavioural therapy and was successfully treated with low dose fluoxetine (60 mg/day) and Endoxifen (8 mg/day).

Keywords: Endoxifen; Obsessive compulsive disorder; OCD.

INTRODUCTION

Obsessive compulsive disorder (OCD) is a psychiatric disorder presenting with intrusive thoughts (obsessions) which are recurrent and may or may not be followed by compensatory actions (compulsions), which decrease the anxiety arising out of the obsession (1). The lifetime prevalence of OCD has been reported to be 1–3% (2). Therapy options for OCD include pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and psychological interventions like cognitive behavioural therapy (CBT) (1,2). Only about 40-60% patients respond to these therapies. Almost one tenth of the non-responders have persistent and severe clinical symptoms, leading to profoundly impaired functioning and quality of life (2). The pathophysiology of OCD is not yet completely understood, however, the abnormal functioning in medial and orbital frontal-basal ganglia–thalamic circuits have been reported in published literature (2).

The mechanisms by which SSRIs extend benefit to the OCD patients is not absolutely known. The evidence related to effects of treatment with relatively high doses of SSRIs point towards the possible deficiency of serotonin in OCD patients. It might be possible that serotonin acts by modulating some fronto-executive functions like cognitive flexibility. Though full remission is not achieved even after treatment with SSRIs; with only around 40-60% patients responding to them (3). Severe functional decline is one of the challenging tasks among the treatment-resistant OCD cases. Previously, such patients were managed by selective ablation of neuronal pathways involved in pathophysiology of OCD (4). During the nineties, research on augmentation strategies started taking shape. Evidence started emerging which pointed towards the benefits of adding antidopaminergic agents (e.g., haloperidol, risperidone, etc.) to SSRIs. Over 2 decades, the potential role of many antidopaminergic agents as augmentation strategy was further strengthened as evident from recently published meta-analysis concluding that antidopaminergic agents are superior to placebo when combined with SSRIs in resistant OCD patients. Though, only about a third of the treatment resistant patients respond to it. Hence, there is tremendous need for the development of new treatment options beyond current guidelines (5). Keeping with this, we present a case report of a patient with treatment resistant OCD who was successfully treated with augmentation of Endoxifen to treatment per usual.

Endoxifen is an innovative treatment option currently being researched for patients with Bipolar I disorder. Endoxifen is a Protein Kinase C (PKC) inhibitor which is known to act rapidly and well tolerated (6,7). PKC is an enzyme belonging to the family of serine/threonine kinases, which play an important role in intracellular signal transduction pathways (6). It is implicated in regulating multiple neuronal processes related to mood regulation (8). As per the available data, drugs like antidepressants and mood stabilizers act by modulating the PKC pathway. Endoxifen has been reported to be four times more potent in inhibiting the PKC activity in comparison to tamoxifen (6). Endoxifen, is an active metabolite of tamoxifen, with an additional advantage that its metabolism is independent of CYP450 enzymes; especially major polymorphic isozyme CYP2D6 (9).

Drugs like lithium, valproate and some antidepressants are known to inhibit the PKC signalling pathway, though, indirectly (11). Hence, the recent introduction of Endoxifen, a direct inhibitor of PKC has opened up many gateways in the treatment of psychiatric disorders. Available evidence shows decreased functionality of the serotonin (5-HT) transporter in OCD which may be caused by impaired regulation of these transporters at intracellular level. PKC has shown to decrease the number of these 5-HT transporter proteins (11).

A study by Maraziti *et al.*, on OCD patients versus healthy controls explored if OCD patients were different from control subjects in terms of change in 5-HT transporters after stimulation of PKC with 4β-12-tetradecanoylphorbol 13-acetate. The results of the study concluded that there is PKC hyperactivity in OCD and that it is a potential therapeutic target (12).

Case report

A 30-year-old female, a doctor by profession reported to the psychiatric OPD with 6 months duration of illness characterized by compulsions of repeated hand washing (>30x/day), cleaning the house (>10x/day), showering (>5x/day) including cleaning and washing rituals. She also had a compulsion to check locks, stove and kitchen appliances. In addition, she suffered from obsessions like contamination, aggressive obsessions like fear that she might harm self, magical thinking and symmetry. She was spending more than 8 hours in a day doing her compulsions which was interfering in her life with respect to interpersonal, social and occupational domains. Patient was having multiple interpersonal issues with her husband because she insisted him to bath/wash hands repeatedly too. Patient would limit the visit of guests to her house fearing contamination. She was often judged by her family members for her compulsion of cleaning the house every time they visited her house. Patients stopped attending family functions as a result of this. Patient also limited herself to her home, and stopped going to the clinic where she was practising, owing to her fear of infecting her child. Patient reported that she would sanitise her arms for at least 5 times every time she consulted a patient. Patient had developed contact dermatitis due to excessive sanitiser usage which was being treated by a dermatologist. In the first visit, the patient scored 38 on Y-BOCS (Yale-Brown Obsessive Compulsive Scale). Patient was diagnosed as F42.2 Obsessive-Compulsive disorder-Mixed obsessional thoughts and acted according to ICD-10 and was started on Fluoxetine 20 mg per day. Then it was gradually increased to 80 mg per day in a time span of 2 weeks. Patient was also subjected to Exposure and Response Prevention (ERP) Therapy. Patient did not improve with the maximum dose of Fluoxetine and ERP therapy even after 12 weeks. Her compulsions reduced, but her functioning was still impaired. She had not started going to the clinic. Patient also was non-compliant to medications due to gastric side effects. In later visits, the dosage of fluoxetine was reduced to 60 mg per day and Endoxifen 8 mg per day was added. The patient was serially followed up on a weekly basis for the next 4 weeks. Slowly the patient could be rehabilitated into her workplace. Her interpersonal relationship with her husband and family improved. She started interacting more with them. Her cleaning/washing compulsions reduced drastically after the introduction of Endoxifen. Her husband reported that she has stopped persuading him to perform cleaning/washing too. She had started going to the clinic regularly and used sanitiser optimally after each consultation. The contact dermatitis she had was also successfully treated. There was improvement in Y-BOCS from 32 in the first week of Endoxifen augmentation to 10 in the fourth week. Patient reported satisfaction with her improvement and was motivated to continue treatment. In short, the patient achieved remission.

Fig.1: Patient Journey: treatment timelines and improvement in Y-BOCS (Yale-Brown Obsessive Compulsive Scale)

CONCLUSION

There is a successful treatment of resistant OCD with Endoxifen augmentation in our case. One should keep in mind that this is an isolated scenario and more research is needed in this area. Randomised controlled trials establishing the role of PKC and thus Endoxifen in the treatment of OCD are needed to conclusively prove the effectiveness of the drug.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

REFERENCES

1. Klimke, A., Nitsche, M.A., Maurer, K., Voss, U. Case report: Successful treatment of therapy-resistant OCD with application of transcranial alternating current stimulation (tACS). Brain Stimul. 2016; 9(3):463-465.
2. Zhang, C., Zhang, Y., Li, D., Deng, Z., Nuttin, B., Voon, V., *et al.*, Habenular stimulation for neurosurgery resistant obsessive-compulsive disorder: A case report. Front Psychiatry. 2020; 11:29.
3. Robbins, T.W., Vaghi, M.M., Banca, P. Obsessive-Compulsive Disorder: Puzzles and Prospects. Neuron. 2019; 102(1):27-47.
4. Eitan, R., Arkadir, D., Linetsky, E., Bick, A.S., Gilad, M., Freedman, S., *et al.*, deep brain stimulation for obsessive compulsive disorder: case report of the first OCD patient in Israel. Harefuah. 2019;158 (7):418-422.
5. Grassi, G., Cecchelli, C., Vignozzi, L., Pacini, S. Investigational and experimental drugs to treat obsessive-compulsive disorder. J Exp Pharmacol. 2021; 12:695-706.
6. Ahmad, A., Sheikh, S., Shah, T., Reddy, M.S., Prasad, B., Verma, K.K., *et al.*, Endoxifen, a new treatment option for mania: A double-blind, active-controlled trial demonstrates the antimanic efficacy of Endoxifen. Clin Transl Sci. 2016; 9(5): 252-259.
7. Ahmad, A., Sheikh, S., Khan, M.A., Chaturvedi, A., Patel, P., Patel, R., *et al.*, Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. Bipolar Disord. 2021;23(6):595-603
8. Abrial, E., Bétourné, A., Etiévant, A., Lucas, G., Scarna, H., Lambás-Señas, L., *et al.*, Protein kinase C inhibition rescues manic-like behaviours and hippocampal cell proliferation deficits in the sleep deprivation model of mania. Int J Neuropsychopharmacol. 2014 ; 18(2):pyu031.
9. Ali, S.M., Ahmad, A., Shahabuddin, S., Ahmad, M.U., Sheikh, S., Ahmad, I. Endoxifen is a new potent inhibitor of PKC: a potential therapeutic agent for bipolar disorder. Bioorg. Med Chem Lett. 2010;20(8):2665-2667.
10. Battaini, F. Protein kinase C isoforms as therapeutic targets in nervous system disease states. Pharmacol Res. 2001; 44(5): 353-361.
11. Harwood, A.J. Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. Mol Psychiatry. 2005; 10(1):117-126.
12. Marazziti, D., Masala, I., Rossi, A., Hollander, E., Presta, S., Giannaccini, G., *et al.*, Increased inhibitory activity of protein kinase C on the serotonin transporter in OCD. Neuropsychobiology. 2000;41(4):171-177.