



# Endoxifen Usage in Bipolar Disorders Patients: My Experiential Journey

Prasad R Gundugurti<sup>1\*</sup>, Shivangini Singh<sup>2</sup>, Simhachalam Gurugubelli<sup>3</sup>, Sri R Vemulakonda<sup>4</sup>

<sup>1</sup>Department of Schizophrenia and Psychopharmacology, Asha Hospital, Hyderabad, Telangana, India.

<sup>2</sup>Department of Psychiatry, King George Medical College, Lucknow, Uttar Pradesh, India.

<sup>3</sup>Mississippi, United States of America.

<sup>4</sup>Senior Research Officer, Chicago, Illinois

## INTRODUCTION

Bipolar affective disorder is a severe mental illness that affects 0.3% of the Indian population, as estimated in the National Mental Health Survey 2016.<sup>1</sup> Antipsychotic drugs and mood stabilizers have both been used as first-line agents in the treatment of the manic phase of bipolar I disorder, either singly or in combination. Tamoxifen, a protein kinase C (PKC) inhibitor, has shown efficacy in the treatment of the manic phase of bipolar I disorder. Tamoxifen is recommended as a third-line agent in the treatment of bipolar mania, as per CANMAT and ISBD 2019 treatment guidelines on bipolar disorder.<sup>2</sup>

Endoxifen is the active metabolite of tamoxifen and is a more potent inhibitor of the PKC signaling pathway.<sup>3</sup> In two randomized controlled trials, endoxifen has been shown to be efficacious in the control of acute bipolar mania at two doses of 4 and 8 mg.<sup>4,5</sup> However, endoxifen at a dose of 8 mg is recommended in patients with bipolar I disorder acute manic episodes.<sup>5</sup> The knowledge and experience with the use of endoxifen at present are limited. We present a case demonstrating the efficacy of endoxifen in the management of acute bipolar mania, in which treatment was given for 9 weeks. To the best of our knowledge, this is the first reported case where treatment with endoxifen was successfully given for such a duration.

Bipolar disorder is associated with the overexpression of protein kinase C (PKC).<sup>6</sup> 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 a promise for use as monotherapy. Our journey with endoxifen started during the COVID time. While in the outpatient department, I saw patients, and suddenly out of nowhere, we were introduced to this molecule, endoxifen. It was a surprise to see this molecule get launched, and it was something unexpected. The next week, it was reading and assimilating the data about PKC and its relevance. The interesting connection of PKC is also associated with both lithium and divalproate gave us some quiet satisfaction. I started looking at the data. Tamoxifen was tested

## ARTICLE INFO

### \*Correspondence:

Prasad R Gundugurti  
prasad40@gmail.com  
Department of  
Schizophrenia and  
Psychopharmacology,  
Asha Hospital,  
Hyderabad, Telangana,  
India

### Dates:

Received: 09-03-2024

Accepted: 25-04-2024

Published: 05-06-2024

### How to Cite:

Gundugurti PR, Singh S,  
Gurugubelli S,  
Vemulakonda SR.  
Endoxifen Usage in  
Bipolar Disorders  
Patients: My Experiential  
Journey. Indian Journal  
of Clinical Psychiatry.  
2024;4(1): 14-16.  
doi: 10.54169/ijocp.v4i01.113

© IJOCP, 2024. Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License, which allows users to download and share the article for non-commercial purposes, so long as the article is reproduced in the whole without changes, and the original authorship is acknowledged. If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. If your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <https://creativecommons.org/licenses/by-nc-sa/4.0/>

in patients with bipolar disorder and our research showed that endoxifen was indeed a metabolite of tamoxifen.

Reading further, what grasped our focus was the endoxifen trials, both being done in India, and as we worked through multicentric studies, it gave us confidence in its usability in our practice. However, it was not clear which patients with bipolar disorder should be used.

We decided to gather information on how to use it in patients with bipolar mania, preferably inpatients, to be the first lot for trials. My team in Asha enthusiastically worked with a few patients between January and February of 2021. They asked for collecting evidence as we used and felt satisfied with our initial experience with lithium/and divalproate and endoxifen was reasonably and satisfying. We sat together and thought a good trial with endoxifen alone with a mood stabilizer, though a short three-week trial with patients of bipolar disorder and an institutional ethics committee-approved open-label study might actually give a good insight. We have got the trial going in a double-blind study and; in one group received endoxifen at 8 to 16 mg per day and another group received mood stabilizers divalproate or lithium with olanzapine. We have done for 31 and 32 each group each in inpatients for acute mania.

We analyzed as one each in each group, dropped out for social reasons, and the YMRS scale and CGI-S were used along with a side-effects scale to assess the emergent side effects. Lorazepam injections were used to control the agitation. We had more or less similar effective scales booth responses were comparable. There are some significant changes, though, 57% in the endoxifen group and the other group 56% compared. So, we arrived at a reasonable comparison of efficacy and fewer side effects. Our results have shown modest efficacy and are comparable to the valproate group. The side effects reported were slightly high in another group compared to endoxifen. An initial 4<sup>th</sup> day improvement occurred in the endoxifen group a bit more.

Today, we are more knowledgeable and understand more about endoxifen and consider this molecule useful in patients with bipolar mania. Our experience in prophylaxis, both as a standalone molecule and with other known molecules, has

made us wiser, too. It gave us an impetus to plan further studies both for efficacy and other psychiatric conditions.

After two and a half years of the experiential use of endoxifen, we further gained experience to see the effectiveness in bipolar disorder patients with comorbid alcohol and cannabis-dependent use as comorbidities, specifically the manic aspect of it. We could see a significant reduction of dependent abuse in both alcoholic use patients and cannabis-dependent abuse in a significant number of patients. I considered the utility of endoxifen in mood disorder-associated pathological gambling in most of the cases of patients in online gambling/betting money patients. Well into over a year, the families were particularly happy in noticing that the reduction was great up to 85% times in time spent in pathological gambling, and over 250 to 300% improvement of on savings during endoxifen usage of over a year.

In summary, our confidence in endoxifen kept growing to the extent that we started an investigator-initiated multicentric open-label study and am sure in the near future will present data of 30 centers of the ICHGCP trial. Also, considering the experience, we found no metabolic side effects, no prolactin-related side effects, no hair loss as in valproate usage, and no polycystic ovary diseases in the above one-year follow-ups of a fairly large sample.

In summary, though we need much more robust evidence both in the efficacy and safety of endoxifen, the current experience, though limited, gives us sufficient confidence to further use this molecule in patients with bipolar mood disorder and in comorbid alcohol and substance use.

## REFERENCES

1. Murthy RS. National mental health survey of India 2015–2016. *Indian journal of psychiatry*. 2017 Jan 1;59(1):21-6.
2. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, Sharma V, Goldstein BI, Rej S, Beaulieu S, Alda M. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar disorders*. 2018 Mar;20(2):97-170.
3. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes TR, Cipriani A, Coghill DR, Fazel S, Geddes JR, Grunze

- H, Holmes EA. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*. 2016 Jun;30(6):495-553.
4. Ahmad A, Sheikh S, Khan MA, Chaturvedi A, Patel P, Patel R, Buch BC, Anand RS, Shah TC, Vora VN, Ramasubramanian V. Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. *Bipolar Disorders*. 2021 Sep;23(6):595-603.
  5. Ahmad A, Sheikh S, Shah T, Reddy MS, Prasad BS, Verma KK, Chandrakant BB, Paithankar M, Kale P, Solanki RV, Patel R. Endoxifen, a new treatment option for mania: a double-blind, active-controlled trial demonstrates the antimanic efficacy of endoxifen. *Clinical and Translational Science*. 2016 Oct;9(5):252-9.
  6. Saxena A, Scaini G, Bavaresco DV, Leite C, Valvassoria SS, Carvalho AF, Quevedo J. Role of protein kinase C in bipolar disorder: a review of the current literature. *Complex Psychiatry*. 2017 Oct 7;3(2):108-24.