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Endoxifen Approval for Bipolar Disorder in India

A Premature or a Pragmatic Decision?

Rishab Gupta, MD,¹ and Swarndeep Singh, MD²

Abstract: In this commentary, we critique the Indian government's decision to approve endoxifen for the treatment of acute mania among adults.

Key Words: Endoxifen, Tamoxifen, Bipolar Disorder, Drug approval

Endoxifen is an active metabolite of tamoxifen, which is a nonsteroidal selective estrogen receptor modulator.¹ Tamoxifen is a well-known, FDA-approved (the United States Food & Drug Administration) drug for treating hormone-sensitive metastatic breast cancer and preventing breast cancer in high-risk women.² Both tamoxifen and endoxifen have been investigated for their role in treating manic episodes.^{3,4} This newfound research interest in these two molecules is mainly because of their ability to inhibit protein kinase C (PKC), an enzyme implicated in the pathogenesis of bipolar disorder (BD).⁵ Endoxifen has been found to be four times more potent in inhibiting PKC compared to tamoxifen in preclinical research.⁶ That said, neither tamoxifen nor endoxifen are FDA-approved. In fact, endoxifen has not yet been approved by the FDA for any clinical indication. Endoxifen has not been endorsed by any treatment guidelines for managing BD till date, while tamoxifen remains a third-line option in the CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines,⁷ and a fourth-line option in the CINP (The International College of Neuropsychopharmacology) guidelines for the treatment of acute mania.⁸ To the best of our knowledge, no other major psychiatric organization guidelines endorse tamoxifen for BD management. With the exception of India, no other country has approved endoxifen for treating any illness yet.

A quick search on the website ClinicalTrials.gov, a drug trial registry maintained by National Institutes of Health, USA shows only one trial of endoxifen, posted in March 2020, that has unknown recruitment status currently.⁹ This trial has been sponsored by Jina Pharmaceuticals, the same company that conducted Phase I, II, and III trials in India (in collaboration with Intas Pharmaceuticals, a major Indian pharmaceutical company and two other pharmaceutical companies with Indian roots, Novum Pharmaceuticals and Lambda Pharmaceuticals) that prepared the ground for subsequent approval of endoxifen for the treatment of acute mania by the drug regulatory body in India.¹⁰ In this commentary, we discuss whether the decision to approve endoxifen for the treatment of mania is premature or pragmatic considering the available scientific literature on this topic.

The Central Drugs Standard Control Organization (CDSCO) of the Government of India (the Indian equivalent of the FDA) headed by the Drugs Controller General of India (DGCI) approved endoxifen for acute treatment of manic episodes (with or without mixed features) among patients with bipolar disorder type 1 (BD-1) in December 2019.¹¹ The agency approved endoxifen on the heels of a single, multicenter, non-inferiority Phase III trial conducted at 18 different centers under the pharma-academia partnership by Ahmad et al.¹² Unfortunately, this trial suffers from serious shortcomings, including short study duration (three weeks), an unclear sample size calculation ($n = 228$), use of fixed-dose divalproex sodium extended-release (1000 mg/day) as a comparator, and strict selection criteria.¹³ However, to contextualize, several previous drug trials in acute mania have been of 3-12 weeks duration.^{14,15} Valproate has well-established serum levels for its anti-seizure (50-100 mcg/mL) and anti-manic (80-125 mcg/mL) effects.¹⁶ Moreover, it has been suggested that a serum valproate level above 94 mcg/mL is necessary for robust anti-manic effects.¹⁷ Additionally, there can be significant interindividual variations in plasma levels of valproate at similar doses due to unpredictable valproate autoinduction, genetic variability in cytochrome P450 enzymes involved in its metabolism, and/or plasma protein displacement reactions.^{18,19} Thus, valproate dose optimization is typically required with therapeutic drug monitoring. Thus, the lack of same in the above study¹² is a major limitation. The use of fixed-dose divalproex sodium without checking serum valproate levels in the study participants (in contrast to the standard practice in the

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clinical settings) might have led to erroneous results due to decreased efficacy of valproate, thereby affecting the statistical margin to demonstrate non-inferiority.²⁰ These deficiencies are likely to jeopardize the internal and external validity of the trial findings. Additionally, the data regarding the number of patients having mania with psychotic symptoms were not provided in the above trial.¹² This is an important omission because two patients had developed delusions in the endoxifen arm of a previous randomized controlled trial (RCT) conducted by the same group of researchers.²¹ Thus, there is a lack of clarity regarding endoxifen's use in acute mania with psychotic symptoms. This is another area of potential concern given that a significant proportion of patients experience psychotic symptoms during a manic episode.²² That said, in some patients accompanying psychotic symptoms may subside spontaneously after manic symptoms remit, obviating the need for antipsychotics.

It is a common practice to continue the same agent for continuation or maintenance treatment (at least 6–9 months after remission of the manic episode) that was used to successfully control acute mania.^{7,23} However, there is no evidence-base supporting the efficacy of either tamoxifen or endoxifen for preventing recurrence of mood episodes in patients with BD-I unlike that for SGAs, valproate or lithium.²⁴ To date, the long-term safety of endoxifen, over a period of months to years, has not been evaluated. This is particularly worrisome because endoxifen is a selective estrogen receptor modulator and the key metabolite of tamoxifen, may share tamoxifen's side effect profile. Tamoxifen use has been associated with a two to three-fold higher risk of developing endometrial cancer among women as compared to an age-matched population cohort of women.²⁵ This risk is dose- and duration-dependent. Although no clear adverse effects were seen with either endoxifen or tamoxifen among male subjects included in the trials but none of those studies had lasted >6 weeks³; this duration may not be sufficient for the hormone-imbalance-related adverse effects to manifest. Although the demographic details and clinical factors among patients with BD-I are different than that of male patients with breast cancer but it is notable that long-term data from the latter group treated with tamoxifen showed a high discontinuation rate (20%) due to adverse effects (mainly thromboembolic events, loss of libido, bone pain, cognitive impairment).²⁶

Tamoxifen is associated with depressive symptoms, anxiety, hot flashes, sexual side effects, menstrual changes, osteoporosis, hepatotoxicity, blood dyscrasia, visual changes, increased risk of pulmonary thromboembolism, endometrial hyperplasia, uterine polyps, and teratogenicity.²⁷ Thus, tamoxifen and its related drug, endoxifen may not be a relatively safer option compared to conventionally used medications (mood stabilizers, atypical antipsychotics) to treat acute mania.

With the approval of endoxifen, there are some practical concerns too. Cost-effectiveness of the treatment is also an important consideration while choosing a drug, especially in low- and middle-income countries like India. The price at which endoxifen is being sold in India is almost five times higher than that of divalproex sodium, and about 10–20 times higher than that of commonly used SGAs (e.g., Aripiprazole, Olanzapine, etc.). This may translate into poor cost effectiveness in case of endoxifen.

We believe the decision to approve a new drug should not be solely based on the efficacy and safety data obtained from Phase III clinical trials. The approval process should also involve an assessment of the already available treatment options for the condition or indication that the new drug intends to target. This provides much needed context for weighing the risks and benefits of a new drug.

Also, for a new drug to be FDA-approved, ideally it should have a well-established clinical benefit that outweighs any conceivable risks or uncertainties with its use, and should also offer some advantage (in terms of its efficacy, tolerability or both) over the

existing standard treatment options for the target condition.²⁸ Clearly, the approval of endoxifen for acute treatment of mania in BD-I patients falls short of this well-established standard. Using this drug may put patients at unnecessary risk when well-tested and effective alternatives are available to treat BD. Endoxifen's safety and efficacy for preventing future mood episodes (which are inevitable in most patients)^{29,30} in BD-I are still unclear. The phase IV study (mandated by the DCGI) aimed at answering some of the above questions has still not been completed. Till then, it is not judicious to widely use endoxifen for the treatment of mania. Further, newer, innovative approaches aimed at improving the side effect profile of SGAs over long-term use for maintenance treatment among patients with BD should be explored. Pharmacological agents are being investigated to further improve the metabolic side effect profile of SGAs. For example, the recent FDA-approved combination of olanzapine and samidorphan for the treatment of schizophrenia and BD has been shown to mitigate antipsychotic-associated weight gain.³¹ It would have been ideal if the DCGI had waited for more evidence in favor of endoxifen before giving its approval for marketing of this drug in India.

Finally, it is not uncommon for doctors to prescribe and patients to “demand” newer drugs when they first hit the market anticipating dramatic results. Having trained and practiced in the Indian healthcare system, we have witnessed first-hand the practices of many pharmaceutical companies offering free drug samples to patients and providing incentives to clinicians to prescribe their drugs.³² The off-label use of psychotropic medications is also quite frequent.^{33,34} We are concerned that these factors might accelerate the penetration of endoxifen in the market prematurely before we have sufficient understanding of its risk/benefit ratio and cost/benefit ratio. We caution that endoxifen, being similar to tamoxifen, should be considered as an option to treat acute mania only after a careful consideration and discussion of risks/benefits with the patient and their family and after providing them with a list of alternative medications. We will consider our effort a success if even some patients, their families, and treating clinicians will make a well-informed decision while choosing endoxifen for BD.

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