Prescribing Trends in Bipolar I Disorder and Usage of Endoxifen: An Indian Perspective

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Abstract—

Objective: *Bipolar I disorder (BD-I) is a psychiatric illness characterized by erratic moods and impulsive behaviors. This survey assesses the prescription preferences among Indian psychiatrists for BD-I, current unmet needs, and benefits of endoxifen (a direct protein kinase C inhibitor) as a mood stabilizing agent in BD-I patients.*

Methods: *A literature review was carried out based on data from the PubMed Database to identify relevant articles (published between January 1980 and May 2022) using specific keywords. Twenty clinically relevant questions belonging to six major domains were drafted: (i) key attributes in the selection of psychotropic medications as front-line therapy; (ii) preference for mania and mixed episodes in front-line therapy; (iii) key attributes for the selection of maintenance therapy; (iv) preference for maintenance therapy; (v) role and positioning of endoxifen in front-line and maintenance settings; and (vi) determination of patient subgroups who can experience benefits from endoxifen. A total of 77 psychiatrists with significant experience in managing patients with bipolar disorder were identified across different cities in India. An electronic survey link to the questionnaire was sent to all the participants to record their views.*

Results: *For BD-I mania, a combination of mood stabilizers and an atypical antipsychotic was preferred. Typical side effects noted in Indian BD-I patients on lithium, valproate, or carbamazepine therapy include drug-induced tremors, hepatic failure, and metabolic disturbances. Experts suggested endoxifen in patients with acute and severe BD-I mania due to its good efficacy and tolerability profile. For the management of mixed episodes of BD-I, experts preferred endoxifen in combination with an antipsychotic therapy or selective serotonin reuptake inhibitor. Maintenance therapy was suggested in patients with more relapse tendencies and after a severe manic episode that warrants hospitalization.*

Conclusion: *The good tolerability profile of endoxifen encourages its use in patients whose current treatment options for BD-I bring challenging side effects.*

Keywords— Bipolar I disorder, prescribing practices, management, endoxifen, India.

I. INTRODUCTION

Bipolar disorder (BD) is a chronic recurrent psychiatric illness associated with significant disability and high suicide risk [1]. It is characterized by mood instability (mania, depression, or both) and impulsive behaviors [2-4]. Bipolar disorder encompasses the following subtypes [5,6]:

- Bipolar I disorder (BD-I) is defined by manic episodes that last at least 1 week (most of the day, nearly every day) or by severe manic symptoms that require immediate hospitalization. Manic episodes may be preceded by and may be followed by hypomanic or major depressive episodes (**Figure 1**).
- Bipolar II disorder (BD-II) is defined by a pattern of hypomanic episodes lasting at least 4 consecutive days (most of the day, nearly every day) and major depressive episodes typically lasting at least 2 weeks.
- Cyclothymic disorder is defined by recurrent hypomanic and depressive episodes for 2 years or longer.

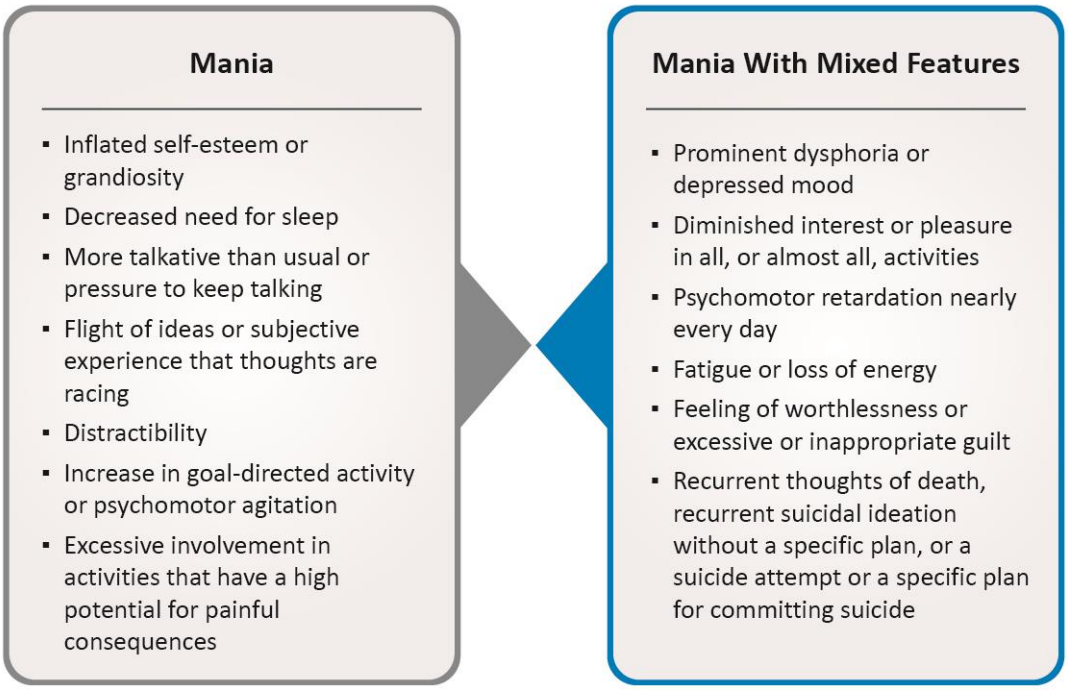

FIGURE 1: Symptoms of mania and mania with mixed features

Adapted from: DSM-5 (Fifth edition) [5], National Institute of Mental Health: Bipolar Disorder [6], and Hu J et al. 2014 [7].

Bipolar disorder is common in clinical psychiatric practice. A large-scale cross-sectional survey across 11 countries in the USA, Europe, and Asia (World Mental Health Initiative) indicated that the lifetime prevalence of bipolar spectrum disorders was 2.4%, with a prevalence of 0.6% for BD-I and 0.4% for BD-II [8]. In India, the prevalence of bipolar spectrum disorder is 0.1%, of which BD-I accounts for roughly 20% of the patient population [9]. Studies from India suggest a substantially higher incidence of mania than major depressive episodes in the course of BD-I [9,10]. Drugs typically used for the treatment of BD-I mania include mood stabilizers (MS) and antipsychotics as monotherapy or a combination of both in patients with severe illness and those requiring hospitalization [11]. For the management of BD-I depression, initial treatment options include antipsychotics, MS, and antidepressants [11]. A systematic review by Vázquez GH highlighted a disease recurrence risk in BD patients (96.0% BD-I; mean onset age: 23.1 years; follow-up: 1.9 years) during treatment with an MS or antipsychotic drug as 39.3% (21.9%/year) [12]. Combination therapy is more likely than monotherapy to result in treatment discontinuation because of problems with tolerability, extrapyramidal symptoms, sedation, and weight gain [13]. Since the last decade, studies have recognized the major role of overactive protein kinase C (PKC) intracellular signaling in psychiatric disorders such as BD and schizophrenia [14-19]. Endoxifen (4-OH-N-desmethyltamoxifen), a direct PKC inhibitor, was found to be safe and effective

in managing acute mania, severe mania with psychotic features, and mixed episodes of BD-I [20-23]. In this article, we aim to capture prescribing preferences among Indian psychiatrists for BD-I and current unmet needs in the medical management of BD-I. We also aim to gather insights from experts on their experience and benefits of endoxifen as a mood-stabilizing agent in patients with BD-I.

II. METHODOLOGY

2.1 Literature Review and Development of the Questionnaire

An extensive literature review was carried out based on data from the PubMed Database to identify relevant articles published between January 1980 and May 2022 using keywords such as "bipolar," "bipolar 1 disorder," "mania," "hypomania," "depression," "mixed state," "mood stabilizers," "antipsychotics," "anticonvulsants," "antidepressants," "protein kinase C," "mixed episodes," "treatment," "maintenance," "endoxifen," "guidelines," and "management." Various combinations of keywords were used. Twenty clinically relevant questions were drafted (**Figure 2**). The content of the questionnaire was prepared keeping in mind the practice environment in India (**Supplementary file**).

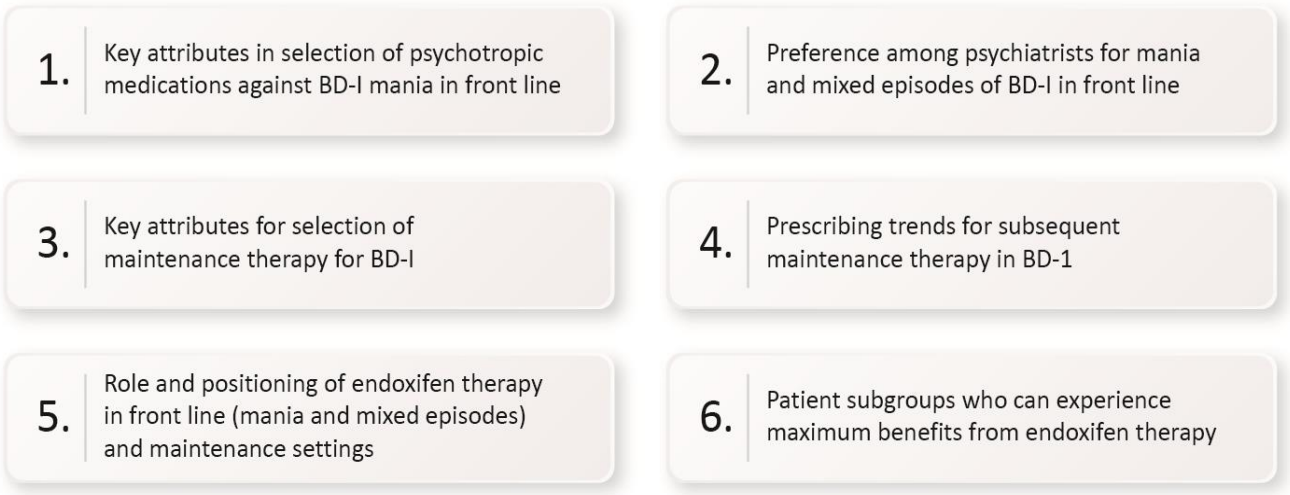

FIGURE 2: Major domains of the survey questionnaire

BD-I: Bipolar I disorder.

2.2 Study Design

For the phase I survey, psychiatrists (N=77) with at least 10 years of clinical experience in managing BD patients across 56 locations in India were identified. Around 64 psychiatrists started endoxifen therapy in BD-I patients at various time points in a 2-year study duration (2021–2022). The questionnaire was rolled out to the participants through an online survey platform. One-to–one online discussions were held with each of the participants and preferences were captured. Respondents were expected to fill in their preferences for a given indication from the options provided. Certain open-ended questions were included in the survey to seek experts' opinions based on clinical practice.

2.3 Data Analysis

Descriptive statistics using the frequency counts of the responses to each question were generated. For data analysis, no formal statistical modeling was done. Here, we report interim results of the phase I survey (n=77). The survey will be extended further (phases II and III; 2023 onward) to include opinions from psychiatrists across different cities in India.

III. RESULTS

3.1 Clinician's Perspective on the Current Burden of BD-I in India

Based on the clinical practice, experts agreed that around 5%–29% of their patient population are diagnosed with BD (84%; N=64 experts). More than 50% of BD patients are diagnosed to have BD-I (45%; N=34 experts).

3.2 Current Challenges in the Medical Management of BD-I and the Role of Endoxifen in Front-Line Settings

3.2.1 BD-I Mania

Experts opined that the selection of psychotropic medications against mania in patients with BD-I is dependent on efficacy (faster onset of action and reduced rate of relapse) and safety profile (minimal metabolic disturbances, no weight gain, and no change in blood glucose or thyroid hormone levels). Consideration of age and gender and minimal need for drug monitoring were rated as the least preferred criteria for medication selection. For the treatment of BD-I mania, a combination of an MS (lithium, valproate, or carbamazepine) and an atypical antipsychotic was the preferred first choice for the majority of experts (67%; N=51 experts), followed by an MS (lithium, valproate, or carbamazepine) with a typical antipsychotic (33%; N=25), whereas valproate with benzodiazepine was the third preference (30%; N=23 experts) (**Table 1**). Lithium, endoxifen, olanzapine, endoxifen with atypical antipsychotics, and valproate were the preferred choice of therapy in women of reproductive age (15–49 years). In women of the nonreproductive age group, endoxifen, lithium, and valproate were suggested. Nonadherence to the treatment regimen is more frequent with combination therapy due to tolerability issues and pill burden than with monotherapy. Typical side effects noted in Indian BD-I patients on MS therapy (lithium, valproate, or carbamazepine) include drug-induced tremors, hepatic failure, and metabolic disturbances (**Table 2**). Adherence to the treatment is affected due to sedation and weight gain.

TABLE 1
PREFERENCE FOR MANAGEMENT OF BD-I MANIA (N=77)

	First preference (%)	Second preference (%)	Third preference (%)
Lithium monotherapy	11	9	11
Antipsychotic monotherapy	3	9	13
Divalproex/valproate monotherapy	7	14	12
Lithium with benzodiazepine	1	12	18
Valproate with benzodiazepine	5	9	30
Carbamazepine/oxcarbamazepine with and without benzodiazepine	1	1	8
MS (lithium, valproate, carbamazepine/oxcarbamazepine) in combination with atypical antipsychotic	67	12	3
MS (lithium, valproate, carbamazepine/oxcarbamazepine) in combination with typical antipsychotic	5	33	5

MS: Mood stabilizer.

TABLE 2
LIST OF SIDE EFFECTS AND ADVERSE EVENTS EXPERIENCED WITH THE USAGE OF LITHIUM, CARBAMAZEPINE, AND DIVALPROEX/VALPROATE IN INDIAN PATIENTS WITH BD-I MANIA

	Lithium	Divalproex/valproate	Carbamazepine
Side effects	• Tremor • Nausea • Diarrhea • Weight gain • Acne • Impaired memory • Hypothyroidism • Delirium • Excessive urination • Increased serum creatinine levels • Metallic taste	• Alopecia • Weight gain • Tremor • Hepatotoxicity • Gastrointestinal disturbances • Liver dysfunction • Menstrual irregularities • Hyperammonemia • Hyponatremia	• Agranulocytosis • Ataxia • Skin rash • Weight gain • Nausea • Withdrawal seizures • Elevations in liver enzymes • Hepatotoxicity
Caution	Therapeutic drug monitoring required	• Monitoring liver function and ammonia levels required • Therapeutic drug monitoring required	Therapeutic drug monitoring required

Experts mentioned that mania is associated with an overactive PKC intracellular signaling, and direct PKC inhibition with endoxifen can help in faster remission of symptoms with no incidence of treatment-emergent depression, tremors, weight gain, or metabolic disturbances. There was no need for therapeutic drug monitoring during endoxifen therapy, unlike lithium, valproate, and carbamazepine therapy. **Table 3** lists key attributes of endoxifen that stood out to experts during the phase I survey. For acute manic episodes, experts preferred endoxifen (**Table 4**) in combination with an MS (66%; N=50 experts) or atypical antipsychotic (62%; N=47 experts). Few respondents preferred to use endoxifen alone in the treatment of mild-to–moderate BD-I mania (37%; N=28 experts).

TABLE 3
KEY ATTRIBUTES OF ENDOXIFEN THAT STOOD OUT TO EXPERTS (N=77)

	Response (%)
Fast response	82
No need for therapeutic drug monitoring unlike lithium and divalproex	79
No adverse effects such as a decrease in platelet count, hair loss, and tremors	79
Convenience (one pill a day)	78
Lesser/no impact on metabolic parameters, such as thyroid hormone levels, blood glucose levels, and weight	78
Reduction in pill burden	74
No incidence of treatment-emergent depression	70

TABLE 4
PREFERENCE FOR THE USE OF ENDOXIFEN IN BD-I MANIA (N=77)

	Preference (%)
In combination with an MS	66
In combination with atypical antipsychotics	62
As monotherapy in mild-to–moderate mania	37
In combination with an MS and atypical antipsychotic	34
In combination with a benzodiazepine	28
In combination with typical antipsychotics	12

BD-I: Bipolar I disorder; MS: Mood stabilizer.

3.2.2 Mixed Episodes of BD-I

Around 57% of experts (N=43) mentioned that they were "very concerned" about the incidence of treatment-emergent mania due to antidepressant therapy in patients with BD-I and would not prescribe it. Some experts (37%; N=28) were "somewhat concerned" about the incidence of treatment-emergent mania due to antidepressant therapy in BD-I and would prescribe it if the benefits outweighed the risk. For the treatment of BD-I patients with acute depression, a combination of MS and antipsychotic was the first preferred choice (**Table 5**) for the majority (43%; N=33 experts), followed by an MS and a selective serotonin reuptake inhibitor (SSRI; 34%; N=26 experts), whereas MS in combination with a tricyclic antidepressant (TCA) was the third preference (28%; N=21 experts). For the management of mixed episodes of BD-I, experts preferred endoxifen in combination with an antipsychotic therapy (68%; N=52 experts) or SSRIs (32%; N=24 experts). Few respondents preferred to use endoxifen alone (41%; N=31 experts) or in combination with a TCA (4%; N=3 experts) for the treatment of mixed episodes of BD-I.

TABLE 5
PREFERENCE FOR MANAGEMENT OF BD-I PATIENTS WITH ACUTE DEPRESSION (N=77)

	First preference (%)	Second preference (%)	Third preference (%)
MS in combination with an SSRI	37	34	26
MS in combination with a TCA	–	16	28
MS in combination with an antipsychotic	43	28	22
MS monotherapy	20	22	24

BD-I: Bipolar I disorder; MS: Mood stabilizer; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant.

3.2.3 Determination of Patient Pool That Can Reap Maximum Benefits from Endoxifen Therapy in Front-Line Setting

The experts opined that a good tolerability profile of endoxifen encourages its use in patients (**Table 6**) where current treatment options for BD-I bring challenging side effects, such as lithium toxicity, sedation, and tremors (75%; N=57 experts). Other patient subgroups in whom endoxifen has a promising role include: (i) female patients with BD-I (71%; N=54 experts); (ii) working-class BD-I patients as endoxifen has no sedative effect (71%; N=54 experts); and (iii) patients seeking for reduced pill burden (67%; N=51 experts).

TABLE 6
PATIENT PROFILES WHO CAN BENEFIT FROM ENDOXIFEN THERAPY IN FRONT-LINE SETTINGS (N=77)

	Preference (%)
Patients facing challenges with other treatment options	75
Female patients with BD-I	71
Working-class BD-I patients	71
Patients seeking reduced pill burden	67
Patients with mild-to–moderate mania	61
Patients with mixed episode	51
Patients with severe mania, who are frequently hospitalized	50
Elderly patients with BD-I	47

BD-I: Bipolar I disorder; MS: Mood stabilizer.

3.2.4 Duration of Endoxifen Therapy in Front-Line Settings

In the phase I survey, the maximum duration of endoxifen therapy studied in patients with BD-I varied from 1 month to 12 months (**Figure 3).** This is because the experts (N=64) did not initiate endoxifen treatment in the same month.

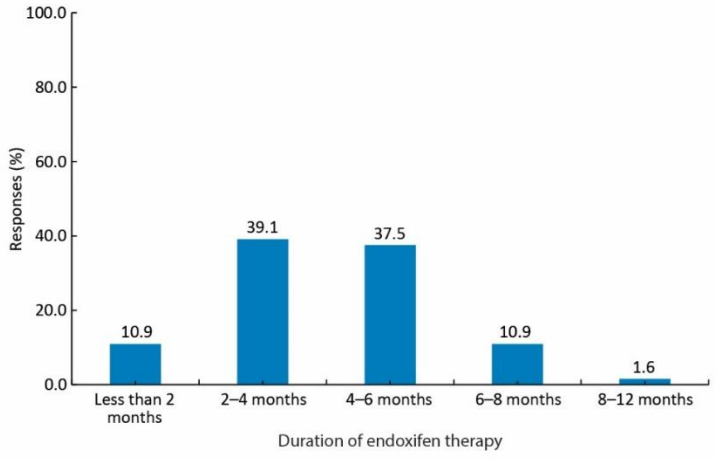

FIGURE 3: Maximum duration of endoxifen therapy studied in patients with BD-I (N=64)
BD-I: Bipolar I disorder

3.3 Current Challenges in the Medical Management of BD-I in Maintenance Settings and the Role of Endoxifen

Experts agreed that the selection of psychotropic medications for maintenance in patients with BD-I is strongly dependent on the efficacy and safety profile (minimal metabolic disturbances and thyroid hormone levels). Experts indicated maintenance therapy in the following patient types of BD-I:

- After the first episode of acute BD-I mania (63%; N=48 experts)
- After the first mixed episode of BD-I (70%; N=53 experts)
- In patients with bipolar depression (63%; N=48 experts)
- After subsequent episodes (71%; N=54 experts)
- After any episode severe enough to warrant hospitalization (82%; N=62)
- In patients with more relapse tendency (86%; N=65)

Lithium (34%; N=26 experts) monotherapy was the preferred treatment option in the maintenance settings, followed by valproate (29%; N=22 experts) and carbamazepine/oxcarbazepine (32%; 24 experts) monotherapy (**Table 7**). The most frequently reported reasons for treatment discontinuation during maintenance therapy in Indian patients with BD-I were metabolic disturbances (weight gain and change in glucose and cholesterol levels), sedation, and risk of extrapyramidal symptoms. Experts (100%; N=77) mentioned that they were interested to try endoxifen in maintenance settings of BD-I. As per the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines, medications that have been found to be effective in the acute phase should be continued during the maintenance phase [24]. Thus, endoxifen has the potential to be an effective therapeutic for BD for long-term use. With such an encouraging experience, the experts unanimously agreed to try endoxifen in the maintenance settings of BD-I. The key attributes of endoxifen that make it a preferred choice of therapy under maintenance settings are an encouraging real-world experience (good efficacy and safety profile), convenient dosing, and no therapeutic drug monitoring (86%; N=65 experts).

TABLE 7

PREFERENCE FOR MAINTENANCE TREATMENT OF BD-I (N=77)

	First Preference (%)	Second preference (%)	Third preference (%)
Lithium monotherapy	34	16	13
Valproate monotherapy	25	29	13
Carbamazepine/oxcarbazepine monotherapy	–	13	32
Combination of lithium and an atypical antipsychotic	8	17	14
Combination of valproate and an atypical antipsychotic	21	17	14
Combination of lithium/valproate with an extended-release atypical antipsychotic	12	8	13

BD-I: Bipolar I disorder

IV. DISCUSSION

The main findings of this survey of prescribing practices of Indian psychiatrists for the treatment of BD-I are as follows:

- A combination of an MS and atypical antipsychotic is the preferred treatment option for BD-I mania.
- For the management of BD-I patients with acute depression, experts preferred MS in combination with antipsychotic therapy or an SSRI. Experts were concerned about the incidence of treatment-emergent mania due to antidepressant therapy in patients with BD-I.
- Maintenance therapy was suggested in patients with more relapse tendencies and after a severe manic episode that warrants hospitalization.

The current mainstays for the management of BD-I mania are lithium and divalproex/valproate, which are indirect inhibitors of PKC [25]. Endoxifen is a direct PKC inhibitor with proven efficacy independent of CYP2D6-mediated metabolism in patients with BD-I [20]. Direct PKC inhibition with endoxifen can help in the faster remission of symptoms and reduce the chances of inpatient hospitalizations [22]. Experts suggested endoxifen in patients with acute and severe BD-I mania due to

the good efficacy and tolerability profile of endoxifen. Endoxifen was preferred in patients with mixed features of BD-I in combination with an antipsychotic therapy or an SSRI. **Figure 4** lists the BD-I patient pool who can reap maximum benefits from endoxifen therapy in front-line settings (mania and mixed episodes).

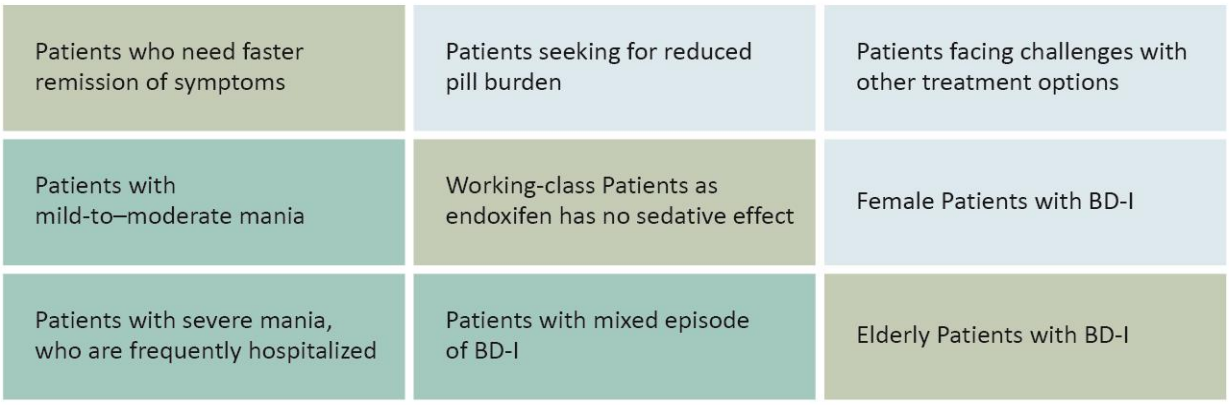

FIGURE 4: Role and positioning of endoxifen in the medical management of BD-I in front-line settings
BD-I: Bipolar I disorder

Strengths: The psychiatrists were selected to best represent the breadth of knowledge and clinical expertise in the field from all over India. There was no selection bias.

Limitation: The patient's voice was not included in the consensus process. Endoxifen is a comparatively new drug and its usage and duration captured are still limited as compared to standard-of–care treatment for BD-I.

V. CONCLUSION

BD-I is a psychiatric illness characterized by unstable moods, impulsive behaviors, and reduced quality of life. The selection of psychotropic medications against BD-I is strongly dependent on drug efficacy (faster onset of action and reduced relapse rate) and safety profile (minimal metabolic disturbances, no weight gain, and no change in blood glucose or thyroid hormone levels). Treatment with endoxifen is efficacious in controlling mania and mixed episodes of BD-I, with no adverse effects. The major usage of endoxifen was in combination, except in mild-to–moderate mania. Key attributes of endoxifen that stand out to experts were faster remission of symptoms, reduced pill burden, and no incidences of drug-induced tremors, weight gain, and metabolic disturbances, unlike lithium and valproate therapy. The good tolerability profile of endoxifen encourages its use in a wide spectrum of BD-I patients. As per CANMAT guidelines, medications that have been found to be effective in the acute phase should be continued during the maintenance phase. Thus, endoxifen has the potential to be an effective therapeutic for BD-I for long-term use. With such an encouraging experience, experts unanimously agreed to try endoxifen in the maintenance settings of BD-I.

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AUTHOR CONTRIBUTIONS

All the authors have contributed to Concepts, Design, definition of intellectual content, data acquisition, data analysis, statistical analysis, and manuscript preparation. Dr. MS Reddy has also contributed to manuscript editing and review.

CONFLICT OF INTEREST

None

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None

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SUPPLEMENTARY MATERIAL

PRESCRIBING TRENDS IN BIPOLAR I DISORDER AND USAGE OF ENDOXIFEN: AN INDIAN PERSPECTIVE

Major domains	Questions
Clinician's perspective on the current burden of BD-I in India	**1.** In your clinical practice, what percentage of patient population are diagnosed with BD? a) Less than 5% b) 5%–14% c) 15%–29% d) 30%–49% e) 50%–69% f) More than 70% **2.** In your clinical practice, what percentage of BD patients are diagnosed with BD-I? a) Less than 5% b) 5%–9% c) 10%–29% d) 30%–49% e) 50%–69% f) More than 70% g) Not sure
Key attributes in selection of psychotropic medications against mania in patients with BD-I	**3.** In your expert opinion, what are the key attributes in selection of psychotropic medications against mania in patients with BD-I? (Rank in order: 1—most preferred and 6—least preferred) a) Predominantly efficacy b) Avoidance of treatment-emergent mania and depression c) Both efficacy and safety (minimal metabolic disturbances- no weight gain, no change in blood glucose or thyroid hormone levels) d) Minimal need for drug monitoring e) Faster onset of action and reduced rate of relapse f) Age and gender
Prescribing trends among psychiatrists for BD-I mania Note: Endoxifen is not mentioned in the following options There is a separate section which captures the role and benefits of endoxifen in BD-I mania.	**4.** What is your preference in management of BD-I mania? (Rank in order of efficacy: 1— most preferred and 8—least preferred) a) Lithium monotherapy b) Antipsychotics monotherapy c) Divalproex/valproate monotherapy d) Lithium with benzodiazepine e) Valproate with benzodiazepine f) Carbamazepine/oxcarbamazepine with and without benzodiazepine g) Mood stabilizer (lithium, valproate, carbamazepine/oxcarbamazepine) in combination with atypical antipsychotic h) Mood stabilizer (lithium, valproate, carbamazepine/oxcarbamazepine) in combination with typical antipsychotic **5.** Open-ended: What is your preferred treatment choice for BD-I mania in female patients? a) In reproductive age group b) In non-reproductive age group
Current challenges in medical management of BD-I mania	**6.** Open-ended: What are the most frequent adverse events experienced, with usage of below drugs in BD-1 mania? a) Lithium b) Divalproex/valproate c) Carbamazepine d) Atypical antipsychotic (risperidone, olanzapine)
Role and positioning of endoxifen in BD-I mania	**7.** Mania is associated with overactive protein kinase C intracellular signaling. Would you consider direct PKC inhibitor as a treatment option for mania management in your clinical practice? a) Yes b) No

	8. In your expert opinion, which attributes of the endoxifen treatment stand out to you? (Please select all that apply) a) Only direct PKC inhibitor b) Fast response c) Convenience (one pill a day) d) Reduces pill burden e) No incidence of treatment-emergent depression f) No need for therapeutic drug monitoring unlike lithium and divalproex g) No adverse effects such as decrease in platelet count, hair loss, and tremor h) Lesser/No impact on metabolic parameters such as thyroid hormone levels, blood glucose levels and weight **9.** Endoxifen at a daily dose of 8 mg was found to be efficacious and safe in BD-I patients with acute manic episodes as compared to 1000 mg divalproex. Would you prefer to prescribe endoxifen as monotherapy or in combination with other therapies? (Please select all that apply) a) As monotherapy in mild to moderate mania b) In combination with benzodiazepine c) In combination with atypical antipsychotics d) In combination with typical antipsychotics e) In combination with mood stabilizer f) In combination with mood stabilizer and atypical antipsychotic
Current challenges in medical management of BD-I depression	**10.** Are you concerned about incidence of treatment-emergent mania due to antidepressant therapy in patients with BD-I disorder? a) Very concerned, I would not prescribe it b) Somewhat concerned, I would prescribe if benefits outweighed the risk c) Not really concerned as it is a rare event d) Unsure
Prescribing trends among psychiatrists for mixed episodes of BD-I Note: Endoxifen is not in the following options. There is a separate section on role and benefits of endoxifen in management of mixed episodes of BD-I	**11.** Based on your clinical practice, how would you rate the clinical applicability of the following treatments in BD-I patients and acute depression? (Rank in order of efficacy: 1— most preferred and 4—least preferred) a) Mood stabilizer and a selective serotonin reuptake inhibitor b) Mood stabilizer and tricyclic antidepressant c) Mood stabilizer in combination with an antipsychotic therapy d) Mood stabilizer monotherapy
Role and positioning of endoxifen in mixed episodes of BD-I	**12.** Based on the available efficacy and safety data of endoxifen (in phase III clinical trial, endoxifen significantly improved YMRS and MADRS scores in treatment of acute mania with or without mixed features in BD-I), how would you recommend endoxifen therapy for the management of mixed episodes of BD-I? (Please select all that applies) a) Endoxifen monotherapy b) Endoxifen in combination with a selective serotonin reuptake inhibitor (SSRI) c) Endoxifen in combination with a tricyclic antidepressant d) Endoxifen in combination with an antipsychotic therapy
Determination of patient pool that can reap maximum benefits from endoxifen therapy in front-line	**13.** In your opinion, which patient pool would benefit maximum from endoxifen therapy? (Please select all that apply) a) Patients who need faster response b) Patients seeking for reduced pill burden c) Patients with mild-to–moderate mania d) Patients with severe mania, who are frequently hospitalized e) Patients facing challenges with other treatment options f) Female patients with BD-I g) Elderly patients with BD-I h) Patients with mixed episode i) Working-class patients as endoxifen has no sedative effect

Duration of endoxifen therapy in front-line	**14.** Open-ended: In your clinical practice, what is the maximum duration of endoxifen therapy you have tried in patients with BD-I?
Key attributes in selection of maintenance therapy for BD-I	**15.** In your expert opinion, what are the key attributes for your selection of maintenance therapy for BD-I? (Rank in order: 1—most preferred and 7—least preferred) a) Predominantly safety b) Predominantly efficacy c) Avoidance of treatment-emergent mania and depression d) Both efficacy and safety (minimal metabolic changes, thyroid hormone levels) e) Minimal need for drug monitoring f) Faster onset of action and reduced rate of relapse g) Age and gender
Prescribing trends among psychiatrists for maintenance therapy in BD-I Note: Endoxifen is not in the following options.	**16.** In which of the following patient types would you suggest/recommend maintenance therapy in BD-I? (Please select all that apply) a) After the first episode of acute mania b) After subsequent episodes c) After the first mixed episode of BD-I d) After any episode severe enough to warrant hospitalization e) In patients with more relapse tendency f) In patients with bipolar depression **17.** How would you rate the clinical applicability of the following maintenance therapies in patients with BD-I? (Rank in order of efficacy: 1—most preferred and 6—least preferred) a) Lithium monotherapy b) Valproate monotherapy c) Carbamazepine/oxcarbazepine monotherapy d) Combination of lithium and an atypical antipsychotic e) Combination of valproate and an atypical antipsychotic f) Combination of lithium/valproate with an extended-release atypical antipsychotic g) None of the above
Current challenges in medical management of BD-I in maintenance settings	**18.** In your clinical practice, what are the most frequently reported reasons for discontinuation during maintenance treatment of BD-1? (Rank in order: 1—most reported and 6— least reported) a) Pill burden b) Alopecia, tremors c) Risk of extrapyramidal symptoms d) Metabolic disturbances (weight gain, change in glucose and cholesterol levels) e) Drug titrations and drug monitoring f) Sedation
Role and benefits of endoxifen in maintenance settings of BD-I	**19.** In real world settings, endoxifen has > 20,000 Rx in Indian setting (Ref: IMS ORG MAT Feb`22) and the duration of endoxifen treatment is also on increasing trend due to good safety and efficacy profile. With such encouraging experience, would you try using endoxifen in maintenance setting of BD-I? a) Yes b) No **20.** According to you, which of the following attributes of endoxifen can make it a preferred choice for maintenance in BD-I? a) Good safety profile b) Convenient dosing and no therapeutic drug monitoring required c) Encouraging real world experience d) Efficacy observed so far in trials may be expected over longer durations of treatment e) All the above