Case Series

# Endoxifen in Depressive Phases of Bipolar Disorder: a case series

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## ABSTRACT

The Central Drugs Standard Control Organization (CDSCO) has approved Endoxifen in the trearment of acute manic episode with or without mixed features in Bipolar 1 disorder in adults in 2019. The role of the molecule in the management of depressive phases of illness has still been debated especially in Bipolar II disorder where major depressive episode is a core features. The 4 case reports in this case series reflect the improvement of MADRS scoring from baseline to the end of six weeks along with the improved scorings in YMRS and CGI scales. A detailed long term prospective longitudinal study is required to find out the safety, efficacy, tolerability and effectiveness of Endoxifen in depressive phases of illness in Unipolar as well as Bipolar disorder as adjunct as well as monotherapy.

**Keywords:** Endoxifen, case series, depressive phase, MADRS score, Bipolar II disorder.

## Introduction:

Endoxifen, 4 hydroxytamoxifen, has received FDA (Food and Drug Administration) approval for the management of manic and mixed episodes of bipolar disorder. It doesn't per se get approval for the depressive phases of the illness of bipolar affective disorder. On the contrary, tamoxifen has been attributed to causing iatrogenic depression. Four cases are presented here, which comprise this case series. In all the cases, Endoxifen (8 mg/day) was administered orally. Endoxifen is a direct PKC (protein kinase C) inhibitor. [1]

**Case discussions:** The four cases in this case series were recruited during the depressive phases of illnesses who have been diagnosed with bipolar affective disorder as per ICD 10. All the cases were monitored at baseline (Day 3, Day 7, Day 14, Day 28, and Day 42) to check the improvement of symptoms and the emergence of adverse effects, if any. All the cases described here belong to the age range of 20–28 years, and all subjects were male.

**Case vignette 1**: Mr. AB, a 28-year-old male hailing from a rural background, presented with a low mood, a lack of interest in pleasurable activities, decreased sleep and appetite, mild tremulousness, and anxiety without any suicidal ideation. He had been diagnosed initially with a manic episode four years ago. He had been treated with Tab Olanzapine, Endoxifen, Quetiapine, and Lithium Carbonate sustained release 400 mg/day; Divalproex sodium 500 mg/day; Clonazepam 0.5 mg/day. His routine blood tests were within normal limits.

**Case vignette 2**: Mr. AP, also hailing from a rural background, presented with depressive symptomatology. He was treated with the antipsychotic drug Olanzapine (5 mg), mood stabilizers Lithium carbonate (900 mg/day), Divalproex sodium (500 mg/day), and Clonazepam (0.5 mg/day) alongwith Tab Endoxifen 8 mg/day for 6 weeks. There were no known medical comorbidities or co-dependence to any psychoactive substances.

**Case vignette 3**: Mr. AM presented in the depressive phase of bipolar affective disorder with comorbid substance abuse, alcohol dependence, and cannabis abuse. He was treated with Tab Endoxifen (8 mg/d), Risperidone (3 mg/d), Divalproex sodium (500 mg/d), Lithium carbonate (800 mg/d), and Clonazepam (1 mg/day). The case was very challenging because of high AUDIT score (Alcohol Use Disorder Identification Test) 10 and high score (7/10 Yes responses) in Marijuana Dependence Checklist (MDC).

**Case vignette 4**: Mr FH, 22 years engineering student presented with dysphoria, irritability, low mood, lack of interest in pleasurable activities for the last 8 months. He had attempted to commit suicide by hanging following up in relationship . He had made past deliberate self-harm attempts on two occasions by hanging two years back (attempted once with moderate risk, lethality and low rescue ) and, has a family history of suicide among first-degree relatives.

Table 1 summarizes age, gender, illness variables and responses following treatment of Endoxifen. All the subjects were male and belonged to the younger age group (range 20-28 years). The duration of illness is ranging from 6-48 months. The case 1 had hypothyroidism as medical comorbidity. The case 3 had cannabis abuse and alcohol dependence meeting the criteria as per ICD 10. The case 4 had one deliberate self harm attempt and family history of completed suicide in first degree relative.

**Table 1:** Summary of cases with demographic, illness variables and response following treatment.

| Variables/Parameters | Case 1 (Mr AB) | Case 2 (Mr AP) | Case 3 (Mr AM) | Case 4 (Mr FH) |
|---|---|---|---|---|
| Age (years) | 28 | 20 | 24 | 22 |
| Gender | Male | Male | Male | Male |
| Duration of illness (months) | 48 | 12 | 6 | 8 |
| Comorbidities/Live Events | Subclinical Hypothyroidism | Nil | Cannabis abuse & Alcohol dependence | H/o DSH (Deliberate Self Harm) attempt. |

| Variables/Parameters | Case 1 (Mr AB) | Case 2 (Mr AP) | Case 3 (Mr AM) | Case 4 (Mr FH) |
|---|---|---|---|---|
| Dose & duration of Endoxifen therapy | Endoxifen 8 mg/d for 6 weeks | Endoxifen 8 mg/d for 6 weeks | Endoxifen 8 mg/d for 6 weeks | Endoxifen 8 mg/d for 6 weeks |
| Co-prescribing drugs (total dose/day) | Quetiapine (300 mg/d), Lithium (450 mg/d), Divalproex Sod (500 mg/d), Clonazepam (0.25 mg) | Olanzapine (5 mg), Lithium (900 mg), Divalproex Sodium (500mg), Clonazepam (0.5 mg) | Risperidone (3 mg), Divalproex Sod (500mg), Lithium SR (400 mg), Clonazepam (1mg) | Olanzapine (15 mg), Lithium (600 mg), Clonazepam (2mg) |
| YMRS (Baseline, 42 days) | 46, 12 | 52, 10 | 44,8 | 41, 6 |
| MADRS (Baseline, 42 days) | 17, 7 | 15,6 | 18, 7 | 20, 5 |
| CGI (Baseline, 42 days) | 5,1 | 5,2 | 5,1 | 5,1 |

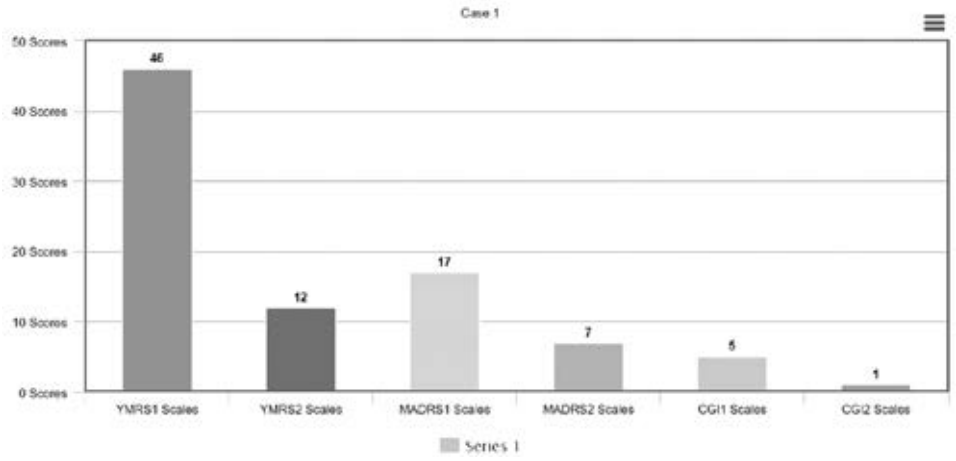


**Fig 1:** Reduction of YMRS & MADRS scores (Baseline and six weeks) of Case 1.

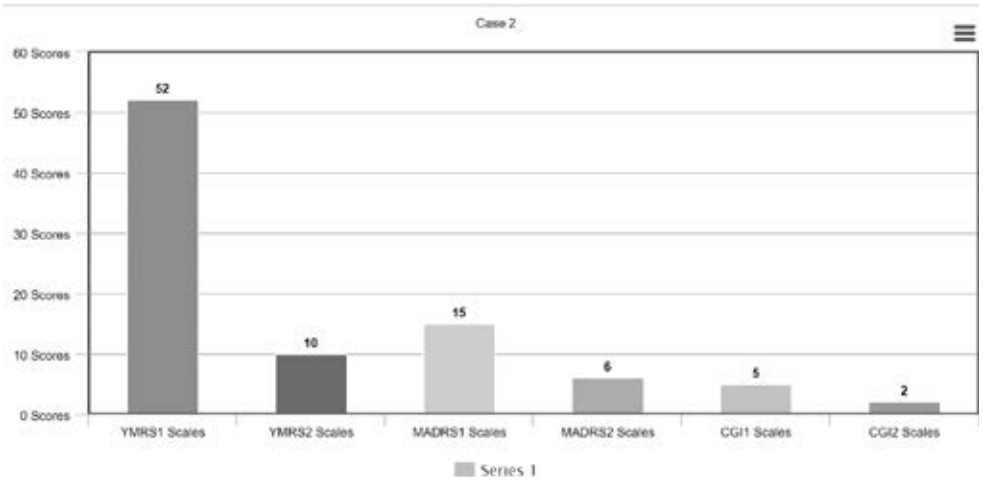


**Fig 2:** Reduction of YMRS & MADRS scores (Baseline and six weeks) of Case 2.

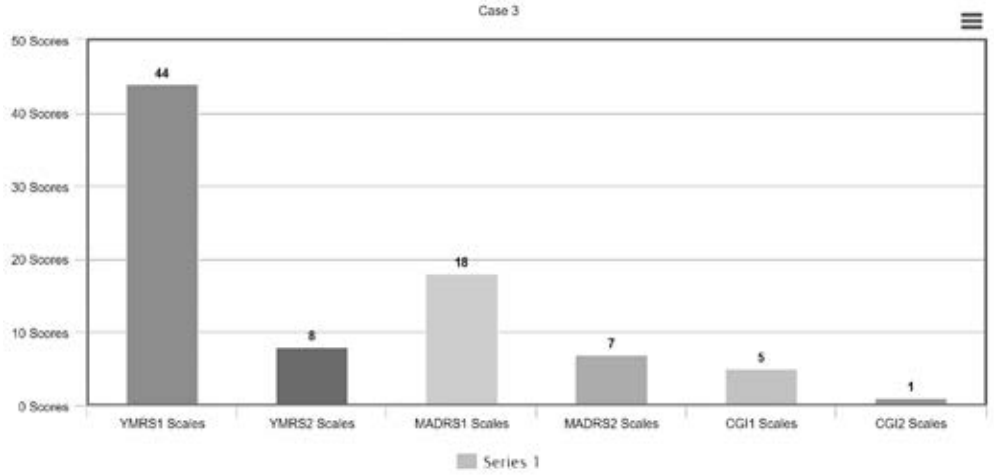


**Fig 3:** Reduction of YMRS & MADRS scores (Baseline and six weeks) of Case 3.

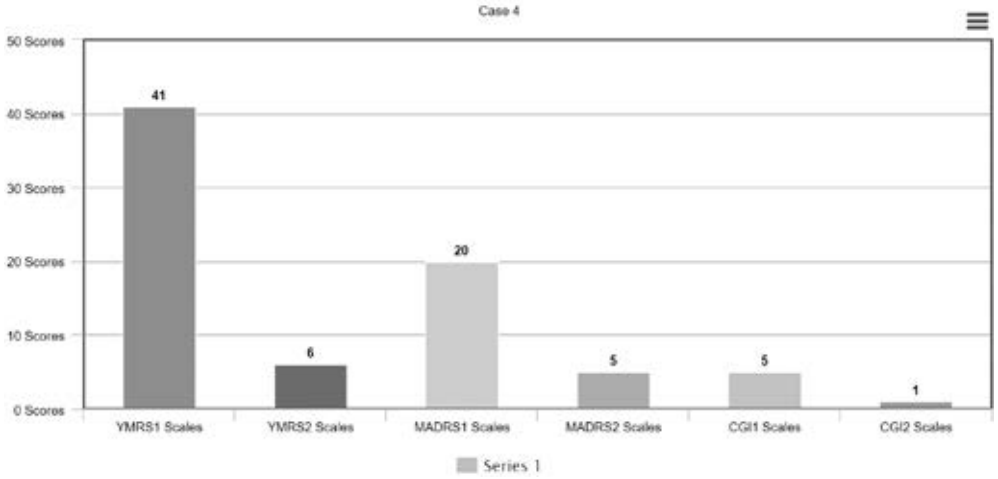


**Fig 4:** Reduction of YMRS & MADRS scores (Baseline and six weeks) of Case 4.

**Discussion:**

In all the above cases the patients were in depressive phases of Bipolar affective disorder. Patients were on antipsychotic drugs and/or Lithium carbonate and Divalproex sodium. None of the patients were put on any antidepressants. Still all the patients responded well with Endoxifen at a dose of 8 mg/day for 6 weeks and there had been improvement in the MADRS and CGI scales.

Endoxifen's potential role in bipolar disorder is an area of emerging research, though it is not currently a standard treatment for this condition. Here are a few points regarding its exploration in bipolar disorder:

1. **Mechanism of Action**: Endoxifen is primarily known for its activity as a metabolite of tamoxifen, a medication used in breast cancer treatment. Tamoxifen and its metabolites, including endoxifen, interact with estrogen receptors in the brain and other tissues. Estrogen receptors are known to play a role in mood regulation and may influence pathways implicated in bipolar disorder.

2. **Research Studies**: Some preliminary studies have investigated the potential use of tamoxifen or endoxifen in bipolar disorder. These studies are small-scale and exploratory, often focusing on understanding the mechanisms through which these compounds might affect mood stabilization.

3. **Potential Benefits**: Research suggests that endoxifen could modulate neurotransmitter systems involved in mood regulation, potentially offering a novel mechanism for treating bipolar disorder. However, more rigorous clinical trials are needed to establish its safety, efficacy, and optimal dosing regimen for this purpose.

4. **Challenges and Considerations**: Using endoxifen or tamoxifen in bipolar disorder presents several challenges, including potential side effects associated with long-term use, interactions with other medications, and variability in individual responses. Additionally, the safety profile and long-term effects of tamoxifen or endoxifen for bipolar disorder treatment are not yet well-established.

While there is interest in exploring endoxifen's potential role in bipolar disorder treatment, it remains investigational. Individuals considering or currently using medications like tamoxifen or endoxifen for other medical conditions should consult with healthcare providers to discuss potential risks, benefits, and alternative treatment options specifically tailored to bipolar disorder management.

Endoxifen, as a metabolite of tamoxifen, has been studied in the context of mood disorders, including bipolar depression, but research in this area is still in its early stages. [2] Here's a summary of the current understanding and research findings:

1. Mechanism of Action: Endoxifen, like tamoxifen, acts as a selective estrogen receptor modulator (SERM). Estrogen receptors are present in the brain and are involved in various processes related to mood regulation. It is hypothesized that endoxifen could potentially modulate these receptors and influence neurotransmitter systems implicated in bipolar depression.

2. Research Studies: There have been some preclinical studies and a few small clinical trials exploring the use of tamoxifen or endoxifen in bipolar disorder, particularly in bipolar depression. These studies have shown mixed results, with some indicating potential efficacy in reducing depressive symptoms. 3

3. Clinical Evidences: One small clinical trial conducted in patients with bipolar depression found that adjunctive treatment with tamoxifen, which increases endoxifen levels, led to significant improvements in depressive symptoms compared to placebo. However, larger and more robust clinical trials are needed to confirm these findings and establish the safety and efficacy of endoxifen specifically. 4,5

4. Considerations: Despite the promising initial findings, the use of tamoxifen or endoxifen in bipolar depression is not without challenges. Both substances can have significant side effects, including potential risks related to long-term use. Additionally, individual responses to these medications may vary, and they may interact with other medications commonly used in bipolar disorder treatment.

5. Future Directions: Further research is needed to elucidate the precise mechanisms of action of endoxifen in mood disorders and to establish its role in bipolar depression treatment. This includes larger clinical trials with well-defined patient populations, longer treatment durations, and comprehensive assessments of both efficacy and safety.

**Conclusion:** While there is preliminary evidence suggesting a potential benefit of endoxifen in bipolar depression, it remains an investigational treatment. Patients and healthcare providers should carefully weigh the potential benefits and risks before considering the use of tamoxifen or endoxifen for this indication, and decisions should be made based on the latest clinical evidence and individual patient factors.

**Conflicts of interest:** Nil

**Funding and Financial support:** Nil

Ethical approval: Written informed consent has been taken from the cases, IEC approval taken for the original trial.

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