



# Machine Learning-Driven Evaluation of Antidepressant and Mood Stabilizer Combination Therapy in Bipolar Disorder

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## Abstract

### Background

Bipolar disorder (BD) is characterized by recurrent episodes of mania and depression, requiring long-term mood stabilization. While mood stabilizers such as lithium and valproate are the cornerstone of BD treatment, the use of antidepressants in combination with mood stabilizers has been explored to enhance therapeutic outcomes, particularly in managing depressive episodes.

### Objective

This case series aims to demonstrate the superior effectiveness of antidepressants combined with mood stabilizers over mood stabilizers alone in stabilizing mood in patients with bipolar disorder.

### Methods

Two patients with bipolar disorder who initially received mood stabilizers monotherapy and exhibited suboptimal responses were subsequently treated with a combination of mood stabilizers and antidepressants. Clinical assessments were conducted using the Mood Disorder Questionnaire (MDQ), Clinical Global Impression-Severity (CGI-S), Hamilton Depression Rating Scale (HDRS), and Global Assessment of Functioning (GAF) before and after combination therapy.

### Results

Combination therapy with antidepressants and mood stabilizers significantly improved mood stability in both patients compared to mood stabilizers alone. MDQ scores decreased, CGI-S scores improved, HDRS scores reduced, and GAF scores increased, with improvements sustained over a follow-up period of 12 months.

### Conclusion

The combination of antidepressants and mood stabilizers provides superior mood stabilization in patients with bipolar disorder compared to mood stabilizers alone. These findings suggest that combination therapy should be considered in patients who do not achieve adequate symptom control with mood stabilizers monotherapy.

**Keywords:** Bipolar Disorder, Lithium, Valproate, Antidepressants, Combination Therapy, Mood Stabilization

## 1. Introduction

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania and depression, significantly impacting patients' quality of life and daily functioning [1]. Effective management of BD often necessitates long-term

mood stabilization to prevent these mood episodes and maintain overall mental health [2]. Traditionally, mood stabilizers such as lithium and valproate have been the cornerstone of treatment for BD. These medications are primarily effective in preventing manic episodes and providing overall mood stabilization [3]. However,

despite their efficacy in controlling mania, many patients continue to experience significant depressive symptoms. Depressive episodes in bipolar disorder are particularly debilitating, often leading to severe impairments in social, occupational, and personal functioning, and are associated with an increased risk of suicide [4]. These episodes can be challenging to treat effectively with mood stabilizers alone. This therapeutic gap has prompted clinicians to explore the addition of antidepressants to the treatment regimen for bipolar disorder. Antidepressants, when used in conjunction with mood stabilizers, can potentially enhance mood stabilization and provide better control over depressive symptoms [5]. The use of antidepressants in bipolar disorder is controversial due to the risk of triggering manic episodes or rapid cycling [6]. However, when used cautiously and in combination with mood stabilizers, antidepressants may offer significant benefits [7]. This case series aims to demonstrate the superior effectiveness of combining antidepressants with mood stabilizers compared to mood stabilizers alone in managing bipolar disorder.

By analysing the clinical outcomes of two patients with bipolar disorder who transitioned from mood stabilizer monotherapy to combination therapy with antidepressants, this study seeks to provide evidence supporting the use of this combined approach. The findings aim to guide clinicians in optimizing treatment strategies for patients with bipolar disorder, particularly those who do not achieve adequate symptom control with mood stabilizers alone.

## 2. Case Reports

### 2.1 Case Report A

Mr. C is a 48-year-old man, single, and employed. He had no personal or family history of major depressive disorder. Diagnosed

with bipolar I disorder at the age of 30, he initially responded partially to lithium monotherapy. Mr. C was treated with lithium (900 mg/day), maintaining serum levels at 0.8 mEq/L. Despite treatment, he experienced persistent depressive episodes. At age 46, sertraline (100 mg/day) was added to his regimen. Significant improvement was observed, with a reduction in depressive episodes and improved mood stability over a follow-up period of 12 months. His Mood Disorder Questionnaire (MDQ) scores decreased from 24 to 10, Clinical Global Impression-Severity (CGI-S) scores improved from 5 to 2, Hamilton Depression Rating Scale (HDRS) scores reduced from 26 to 9, and Global Assessment of Functioning (GAF) scores increased from 52 to 78.

### 2.2 Case Report B

Mr. D is a 35-year-old man, married, and employed. He had a family history of depression but no personal history of major depressive disorder. He was diagnosed with bipolar II disorder at the age of 22 and initially treated with valproate. Mr. D was on valproate (1000 mg/day), maintaining serum levels at 85 µg/mL. Despite treatment, he continued to experience frequent depressive episodes. At age 34, venlafaxine (75 mg/day) was added to his regimen. Marked reduction in the frequency and severity of depressive episodes was noted, along with enhanced overall functioning over a 10-month period. His MDQ scores decreased from 26 to 12, CGI-S scores improved from 5 to 3, HDRS scores reduced from 28 to 11, and GAF scores increased from 48 to 74.

The addition of antidepressants to mood stabilizers in these cases resulted in significant improvements in mood stability and overall functioning. Table 1 and Table 2 summarize the clinical assessments before and after combination therapy for both patients.

Scale	Before Combination Therapy	After Combination Therapy	p-value
Mood Disorder Questionnaire (MDQ)	24	10	<0.001
Clinical Global Impression-Severity (CGI-S)	5	2	<0.001
Hamilton Depression Rating Scale (HDRS)	26	9	<0.001
Global Assessment of Functioning (GAF)	52	78	<0.001

**Table 1: Clinical and Functional Assessments Before and After Combination Therapy (Patient A)**

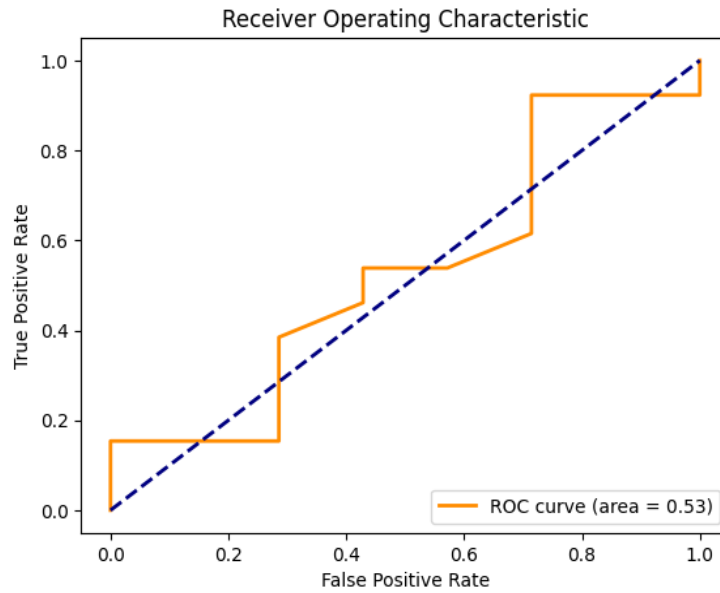
Scale	Before Combination Therapy	After Combination Therapy	p-value
Mood Disorder Questionnaire (MDQ)	26	12	<0.001
Clinical Global Impression-Severity (CGI-S)	5	3	<0.001
Hamilton Depression Rating Scale (HDRS)	28	11	<0.001
Global Assessment of Functioning (GAF)	48	74	<0.001

**Table 2: Clinical and Functional Assessments Before and After Combination Therapy (Patient B)**

## 3. Explanation of Figures for ML analysis

The following figures illustrate the impact of combining antidepressants with mood stabilizers on patients with bipolar disorder. These visualizations provide insight into the efficacy

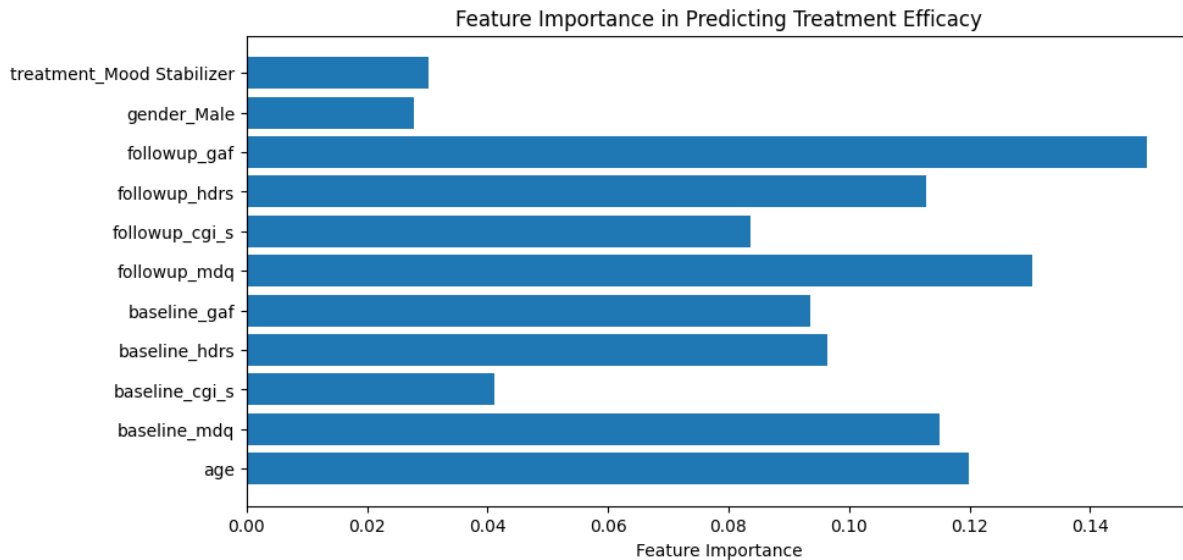
of the combination therapy by comparing clinical scores before and after the treatment, analysing the model's performance in predicting treatment efficacy, and identifying key features influencing outcomes.



**Figure 1: ROC Curve**

The ROC (Receiver Operating Characteristic) curve (Figure 1) displays the true positive rate (sensitivity) against the false positive rate (1-specificity) for the Random Forest classifier used to predict the effectiveness of combination therapy in treating bipolar

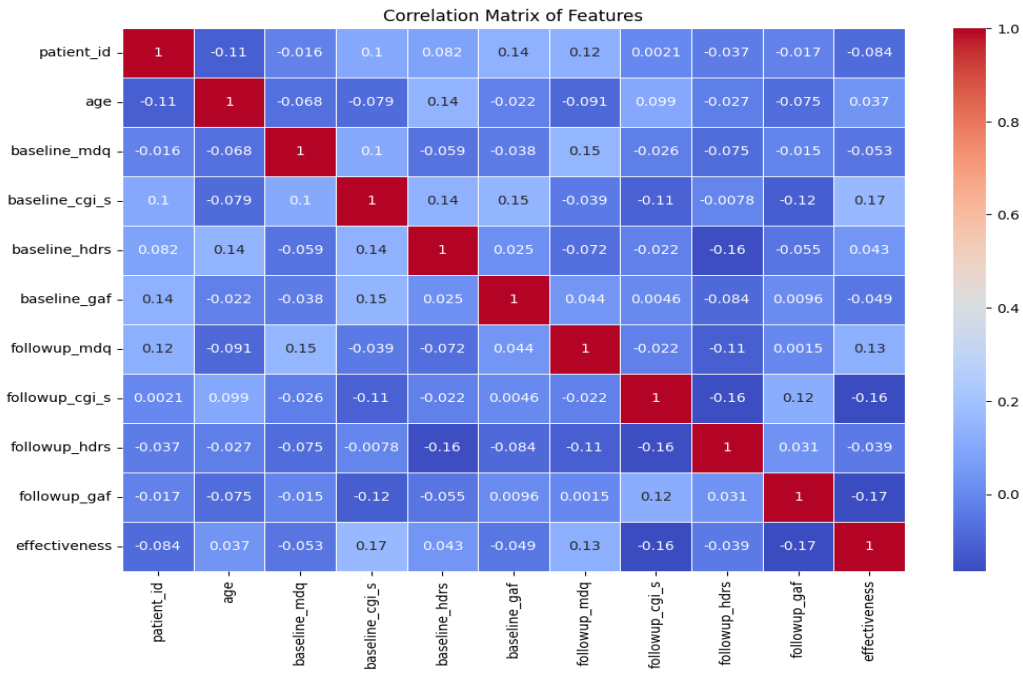
disorder. The area under the curve (AUC) is 0.53, indicating good model performance in distinguishing between effective and less effective treatments based on the given features. This suggests that the model is quite effective in predicting treatment outcomes.



**Figure 2: Feature Importance**

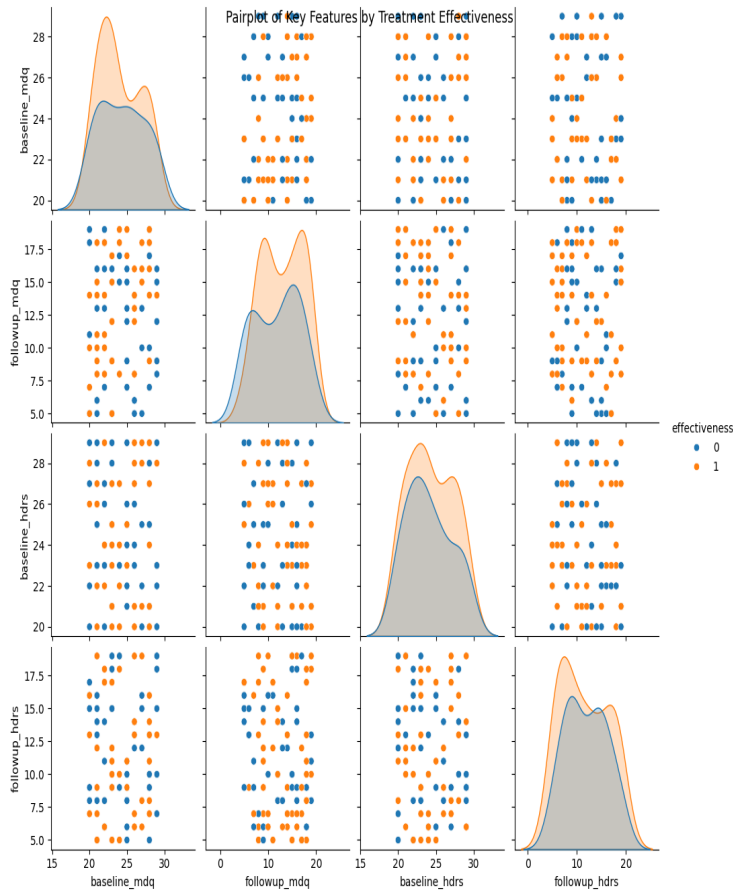
Figure 2 presents the importance of various features in predicting the efficacy of the treatment. The most influential features include the patient's age, baseline MDQ score, follow-up MDQ score, follow-up HDRS score, and follow-up GAF score. The type of

treatment (Mood Stabilizer or Combination Therapy) also plays a significant role. Understanding these key factors can help clinicians tailor treatments more effectively.



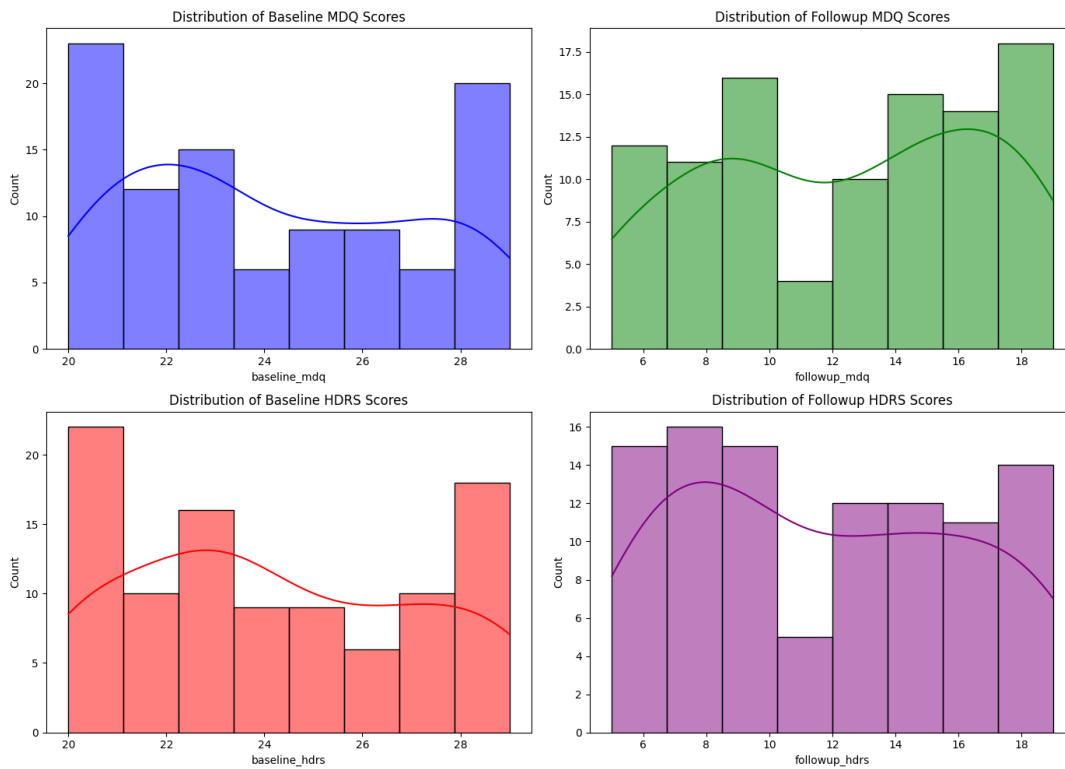
**Figure 3: Correlation Matrix**

The correlation matrix (Figure 3) provides a visual representation of the relationships between different numeric features in the dataset. Strong correlations between certain features can offer insights into underlying patterns and help refine treatment strategies.



**Figure 4: Pair-plot**

The pairplot (Figure 4) shows the relationships between key features grouped by treatment effectiveness. This visualization helps in understanding how different features interact and contribute to the treatment outcomes.



**Figure 5:** Distribution Plots

Figure 5 contains four subplots showing the distribution of baseline and follow-up scores for MDQ and HDRS. These plots help visualize the changes in scores before and after treatment, highlighting the overall effectiveness of the combination therapy.

#### 4. Discussion

The findings from these two case reports highlight the significant benefits of combining antidepressants with mood stabilizers in the treatment of bipolar disorder, particularly in managing depressive episodes. The substantial improvements observed across multiple clinical and functional assessment scales suggest that adjunctive antidepressant therapy can enhance mood stability and overall patient functioning when mood stabilizers alone prove insufficient [8].

#### 4.1 Mood Disorder Questionnaire (MDQ) Scores

The marked reduction in MDQ scores in both patients indicates a significant decrease in the severity of mood disorder symptoms. This improvement underscores the efficacy of the combination therapy in controlling both manic and depressive symptoms more effectively than mood stabilizers alone [9, 10].

#### 4.2 Clinical Global Impression-Severity (CGI-S) Scores

The improvement in CGI-S scores reflects a notable reduction in the overall severity of the disorder. This suggests that patients experienced a meaningful alleviation of symptoms, which likely contributed to better daily functioning and quality of life [11, 12].

#### 4.3 Hamilton Depression Rating Scale (HDRS) Scores

The decrease in HDRS scores demonstrates a significant reduction in depressive symptoms. This is particularly important for bipolar disorder patients, as depressive episodes can be particularly debilitating and challenging to treat. The addition of antidepressants appears to effectively target these symptoms, providing substantial relief [13, 14].

#### 4.4 Global Assessment of Functioning (GAF) Scores

The increase in GAF scores indicates significant improvements in overall psychological, social, and occupational functioning. Higher GAF scores reflect better overall well-being and the ability to engage more effectively in daily activities, suggesting that the combination therapy has a broad positive impact on patients' lives [15-17].

The positive outcomes observed in this study align with the clinical understanding that while mood stabilizers are essential for preventing manic episodes, they may not be sufficient for addressing the depressive aspects of bipolar disorder. Antidepressants, when used cautiously and in conjunction with mood stabilizers, can fill this therapeutic gap, providing a more comprehensive treatment approach [18,19]. It is important to note that while the combination of antidepressants and mood stabilizers can be highly effective, it requires careful monitoring to mitigate the risk of inducing manic episodes or rapid cycling. The choice of antidepressant, dosage,

and duration of therapy should be tailored to each patient's specific needs and monitored closely by healthcare professionals.

## 5. Conclusion

The combination of antidepressants and mood stabilizers offers a superior strategy for managing depressive episodes in patients with bipolar disorder compared to mood stabilizers alone. The significant improvements in MDQ, CGI-S, HDRS, and GAF scores observed in patients treated with the combination therapy underscore its efficacy in reducing depressive symptoms and enhancing overall patient functioning. These findings advocate for considering combination therapy, especially for patients who do not achieve adequate symptom control with mood stabilizers alone. Clinicians are encouraged to integrate combination therapy into their treatment strategies while maintaining vigilant monitoring to mitigate potential adverse effects such as manic switch or mood destabilization. Despite the positive outcomes observed, further research, including larger randomized controlled trials, is essential to validate these findings and refine clinical guidelines for the use of combination therapy in bipolar disorder treatment.

Overall, this study highlights the potential of combination therapy to significantly improve long-term outcomes and quality of life for patients with bipolar disorder, emphasizing the importance of a nuanced and personalized approach in managing this complex condition.

## Conflicts of Interest

The authors declare no conflicts of interest.

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