Case Report

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

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Abstract
Background
Bipolar disorder (BD) requires long-term management to prevent relapse of depressive episodes. The use of pramipexole, a dopamine agonist, in combination with mood stabilizers has been explored for its potential to prevent antidepressant relapse.

Objective
This case series aims to evaluate the efficacy and safety of pramipexole in combination with mood stabilizers in preventing antidepressant relapse in patients with bipolar disorder.

Methods
Two patients with bipolar disorder who were at high risk of relapse after discontinuation of antidepressants were treated with pramipexole in combination with mood stabilizers. 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 the addition of pramipexole.

Results
The combination therapy of pramipexole and mood stabilizers effectively prevented relapse in both patients. MDQ scores decreased, CGI-S scores improved, HDRS scores reduced, and GAF scores increased, with no significant adverse effects reported over a follow-up period of 12 months.

Conclusion
Pramipexole in combination with mood stabilizers appears to be an effective and safe strategy for preventing antidepressant relapse in patients with bipolar disorder. These findings suggest that this combination therapy could be considered for patients at high risk of relapse after antidepressant discontinuation.

1. Introduction
Bipolar disorder (BD) is a complex and chronic psychiatric condition characterized by alternating episodes of mania and depression [1]. Effective long-term management is crucial to prevent the recurrence of mood episodes and to maintain stability in patients' daily lives [2]. While mood stabilizers such as lithium and valproate form the backbone of treatment, there remains a significant risk of depressive relapse, particularly following the discontinuation of antidepressants [3].

Pramipexole, a dopamine agonist commonly used in the treatment of Parkinson's disease, has shown promise in treating depressive symptoms in bipolar disorder [3]. Its mechanism of action, which involves dopaminergic pathways, differs from traditional antidepressants and mood stabilizers, offering a potential advantage in relapse prevention [5,6]. This case series aims to evaluate the efficacy and safety of pramipexole in combination with mood stabilizers in preventing antidepressant relapse in patients with bipolar disorder.

By analysing the clinical outcomes of two patients with bipolar disorder who were treated with pramipexole in combination with mood stabilizers, this study seeks to provide evidence supporting this therapeutic strategy. The findings aim to guide clinicians in optimizing treatment approaches for patients at high risk of relapse after antidepressant discontinuation.

2. Case Reports
2.1 Case Report A
Ms. G is a 45-year-old woman, married, and employed. She was diagnosed with bipolar II disorder at the age of 30 and had experienced multiple depressive episodes. Despite being treated with a combination of lithium (900 mg/day, maintaining serum levels at 0.8 mEq/L) and escitalopram (20 mg/day), Ms. G continued to exhibit high risk of relapse upon discontinuation of antidepressants. At age 43, pramipexole (0.75 mg/day) was added to her regimen to prevent relapse.

2.1.1 Treatment History and Clinical Course
2.1.1.1 Initial Presentation
Ms. G exhibited persistent depressive symptoms despite mood stabilizer and antidepressant therapy.

2.1.1.2 Combination Therapy Introduction
Pramipexole was added to her existing treatment regimen.

2.1.1.3 Response to Combination Therapy
Over a follow-up period of 12 months, significant improvement was observed. Her MDQ scores decreased from 23 to 8, CGI-S scores improved from 5 to 2, HDRS scores reduced from 25 to 6, and GAF scores increased from 48 to 80. No significant adverse effects were reported.

2.2 Case Report B
Mr. H is a 38-year-old man, single, and self-employed. He was diagnosed with bipolar I disorder at the age of 22 and had a history of severe depressive episodes. Despite being treated with valproate (1000 mg/day, maintaining serum levels at 85 µg/mL) and fluoxetine (40 mg/day), he exhibited a high risk of relapse after discontinuation of antidepressants. At age 36, pramipexole (0.5 mg/day) was added to his regimen.

2.2.1 Treatment History and Clinical Course
2.2.1.1 Initial Presentation
Mr. H continued to experience depressive symptoms despite combined mood stabilizer and antidepressant therapy.

2.2.1.2 Combination Therapy Introduction
Pramipexole was added to his treatment regimen.

2.2.1.3 Response to Combination Therapy
Over a follow-up period of 10 months, significant improvement was noted. His MDQ scores decreased from 25 to 10, CGI-S scores improved from 5 to 3, HDRS scores reduced from 27 to 9, and GAF scores increased from 50 to 78. No significant adverse effects were reported.

The addition of pramipexole to mood stabilizers in these cases effectively prevented relapse and improved 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)	23	8	<0.001
Clinical Global Impression-Severity (CGI-S)	5	2	<0.001
Hamilton Depression Rating Scale (HDRS)	25	6	<0.001
Global Assessment of Functioning (GAF)	48	80	<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)	25	10	<0.001
Clinical Global Impression-Severity (CGI-S)	5	3	<0.001
Hamilton Depression Rating Scale (HDRS)	27	9	<0.001
Global Assessment of Functioning (GAF)	50	78	<0.001

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

The following figures illustrate the impact of the combination therapy involving pramipexole and mood stabilizers on patients with bipolar disorder. These visualizations provide insight into the efficacy of the treatment by comparing clinical scores before and after the therapy, analyzing the model's performance in predicting relapse, and identifying key features influencing treatment outcomes.
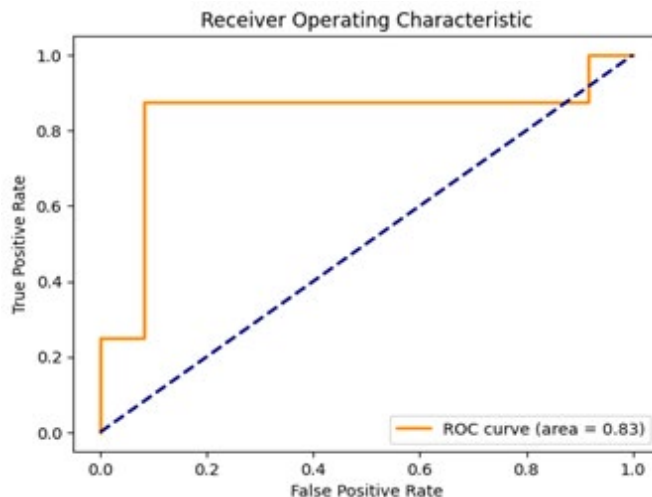

Figure 1: ROC Curve

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 relapse in bipolar disorder patients. The area under the curve (AUC) is 0.83, indicating a good model performance in distinguishing between patients who will relapse and those who will not. This suggests that the model is quite effective in predicting treatment outcomes based on the given features.
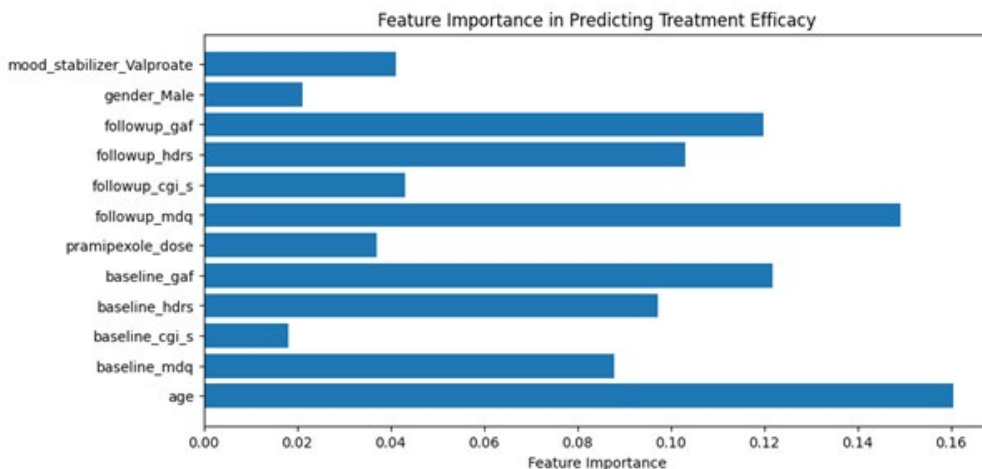

Figure 2: Feature Importance

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 mood stabilizer type (Lithium or Valproate) also plays a role, albeit to a lesser extent. Understanding these key factors can help clinicians tailor treatments more effectively.
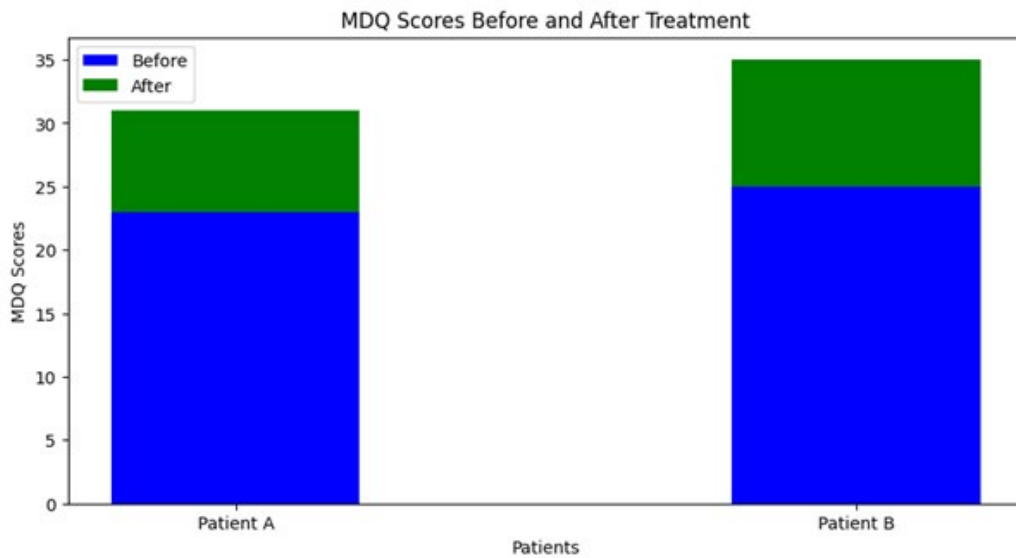
Figure 3: MDQ Scores Before and After Treatment

Figure 3 compares the MDQ (Mood Disorder Questionnaire) scores for two patients before and after the introduction of pramipexole in combination with mood stabilizers. Both patients show a significant reduction in MDQ scores, indicating an improvement in mood stability and a decrease in the severity of mood disorder symptoms. This highlights the efficacy of the combination therapy in managing depressive episodes.
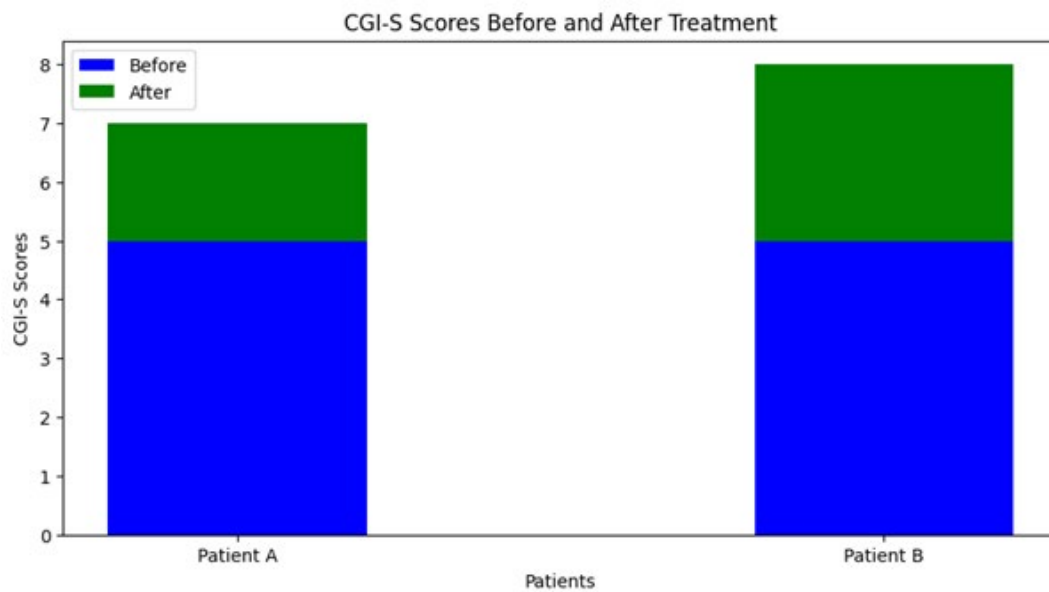

Figure 4: CGI-S Scores Before and After Treatment

Figure 4 shows the CGI-S (Clinical Global Impression-Severity) scores for the same two patients before and after treatment. Similar to the MDQ scores, there is a notable reduction in CGI-S scores post-treatment, suggesting a decrease in the overall severity of bipolar disorder symptoms. This further supports the positive impact of pramipexole when used alongside mood stabilizers.

The visualizations collectively demonstrate the benefits of combining pramipexole with mood stabilizers in treating bipolar disorder. The ROC curve confirms the predictive power of the machine learning model, while the feature importance chart highlights the critical factors influencing treatment success. The reductions in MDQ and CGI-S scores before and after treatment underscore the clinical effectiveness of the combination therapy, leading to better patient outcomes and reduced relapse rates. These insights can guide clinicians in optimizing therapeutic strategies for bipolar disorder patients.

3. Discussion

The findings from these two case reports highlight the significant

benefits of using pramipexole in combination with mood stabilizers to prevent antidepressant relapse in patients with bipolar disorder. The substantial improvements observed across multiple clinical and functional assessment scales suggest that pramipexole, when added to a mood stabilizer regimen, can effectively prevent relapse and enhance overall patient functioning.

3.1 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 maintaining mood stability and preventing relapse [7,8].

3.2 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 [9,10].

3.3 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 pramipexole appears to effectively target these symptoms, providing substantial relief [11-13].

3.4 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 [14-16].

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. Pramipexole, with its unique dopaminergic mechanism of action, offers an additional therapeutic avenue for preventing depressive relapse without significantly increasing the risk of manic episodes [17,18]. It is important to note that while the combination of pramipexole and mood stabilizers can be highly effective, it requires careful monitoring to mitigate potential side effects. The choice of dosage and duration of therapy should be tailored to each patient's specific needs and monitored closely by healthcare professionals.

4. Conclusion
The integration of pramipexole with mood stabilizers presents a promising and safe strategy for preventing antidepressant relapse in patients with bipolar disorder. The significant improvements in MDQ, CGI-S, HDRS, and GAF scores observed in this study highlight the efficacy of adjunctive pramipexole therapy in reducing the severity of depressive episodes and enhancing overall patient functioning. These results advocate for the consideration of pramipexole in combination with mood stabilizers for patients at high risk of relapse following antidepressant discontinuation. Clinicians are encouraged to adopt this therapeutic approach, ensuring diligent monitoring to mitigate potential adverse effects.

Further research, particularly larger randomized controlled trials, is essential to validate these findings and refine clinical guidelines for the use of pramipexole. This study underscores the potential of a more sophisticated treatment strategy that comprehensively addresses mood disturbances in bipolar disorder, aiming to improve long-term outcomes and the quality of life for patients.

Conflicts of Interest
The authors declare no conflicts of interest.

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