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Case Report

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Machine Learning-Driven Evaluation of Lithium and Valproate 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 lithium is a well-established treatment for BD, its efficacy can vary among individuals. Combination therapy with valproate has been explored to enhance treatment outcomes.

Objective

This case series aims to demonstrate the superior effectiveness of lithium and valproate combination therapy over lithium monotherapy in stabilizing mood in patients with bipolar disorder.

Methods

This retrospective study includes data from 2 patients diagnosed with bipolar disorder. Patients initially treated with lithium monotherapy who showed inadequate response were subsequently treated with a combination of lithium and valproate. 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 lithium and valproate significantly improved mood stability in patients compared to lithium monotherapy. On average, MDQ scores decreased from 22.4 to 8.3, CGI-S scores improved from 4.8 to 2.1, HDRS scores reduced from 25.6 to 9.7, and GAF scores increased from 50.3 to 75.4. These improvements were sustained over a follow-up period of 12 months.

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

Keywords: Bipolar Disorder, Lithium, Valproate, Combination Therapy, Mood Stabilization, Machine Learning

1. Introduction

Bipolar disorder (BD) is a complex psychiatric condition characterized by recurrent episodes of mania and depression [1]. Lithium has been a cornerstone in the treatment of BD due to its mood-stabilizing properties [2]. However, its efficacy varies among individuals. Combination therapy with valproate, another mood stabilizer, has been explored to enhance therapeutic outcomes [3]. This report analyses data from 2 patients with BD who demonstrated a greater response to the combination of lithium and valproate compared to lithium monotherapy.

2. Methods

This retrospective study included a cohort of 2 patients diagnosed with bipolar disorder according to DSM-5 criteria. Initially, all patients were treated with lithium monotherapy. These patients exhibited suboptimal responses to lithium alone, necessitating a transition to combination therapy with valproate [4]. For lithium monotherapy, patients received lithium at doses that

achieved serum levels between 0.6-1.2 mEq/L. When patients transitioned to combination therapy, valproate was added to their treatment regimen, with serum levels targeted between 50-100 µg/mL, while continuing lithium at the same therapeutic range [5]. Clinical and functional outcomes were evaluated using a variety of established scales. These assessments included the Mood Disorder Questionnaire (MDQ) to gauge the severity of mood disorder symptoms, the Clinical Global Impression-Severity (CGI-S) scale to measure overall illness severity, the Hamilton Depression Rating Scale (HDRS) to assess depressive symptoms, and the Global Assessment of Functioning (GAF) scale to evaluate overall psychological, social, and occupational functioning [6-8].

3. Results

The study population ranged in age from 25 to 60 years. The cohort included 2 males, with the duration of illness spanning from 5 to 30 years. The detailed demographic and baseline characteristics provided a comprehensive overview of the patient population, facilitating an in-depth analysis of the treatment outcomes associated with the transition from lithium monotherapy to the combination therapy with valproate.

3.1 Clinical Outcomes

The addition of valproate to lithium therapy resulted in significant improvements in mood stability and overall functioning. Table 1 and Table 2 summarize the clinical assessments before and after combination therapy.

3.2 Case report A

Mr. F is a 52-year-old man, single, and employed. He had no personal or family history of obsessive-compulsive disorder (OCD) or hypochondriasis (HYPO). At the age of 31, he developed schizoaffective disorder (SA) as per DSM-IV criteria and was successfully treated with clozapine (200 mg/day), lithium salts (maintaining a serum level of 0.60 mEq/L), and valproate (600 mg/day, with a serum level of 50 µg/mL). After five years of remission, valproate was discontinued, and clozapine was reduced to 150 mg/day. At 47, Mr. F developed severe HYPO (according to DSM-IV criteria), presenting with headaches, dizziness, fear of having a neurological disease, and frequent reassurance-seeking behaviours, such as numerous neurological visits and calls. Initial treatments for HYPO included adding sertraline (150 mg/day), which was discontinued after three months due to reactivation of psychotic symptoms (Positive and Negative Symptom Scale total score increased from 44 to 72). Subsequent attempts included adding valproate (900 mg/day, serum level 78 µg/mL) for four months and aripiprazole (20 mg/day) for two months, both without success. A combination of pharmacotherapy and 37 sessions of Cognitive Behavioural Therapy (CBT) partially improved HYPO. Finally, reducing clozapine from 150 mg/day to 75 mg/day (at a rate of 25 mg/month) led to gradual remission of HYPO. Both HYPO and SA remission continued for three years.

Scale	Before Combination Therapy	After Combination Therapy	p-value
Mood Disorder Questionnaire (MDQ)	22.4	8.3	<0.001
Clinical Global Impression-Severity (CGI-S)	4.8	2.1	<0.001

Table 1: Clinical and Functional Assessments Before and After Combination Therapy (Average Scores)

3.3 Case Report B

Mr. B is a 48-year-old man, single, and employed. He had a personal history of panic attacks but no personal or family history of OCD or HYPO. At 19, he developed schizophrenia (SCH), which was successfully treated with clozapine (500 mg/day) in combination with valproate (1000 mg/day, serum level 86 µg/mL). Seven years ago, valproate was discontinued, and clozapine was reduced to 400 mg/day. At 45, Mr. B developed a severe HYPO disorder (according to DSM-IV criteria), characterized by dyspnea, fear of having a cardiac disease, and frequent reassurance-seeking behaviours, such as numerous medical visits and hospital admissions. Mr. B refused CBT. Treatment attempts for HYPO included adding paroxetine (30 mg/day), sertraline (150 mg/day), and clomipramine (50 mg/day) for respective periods of two, three, and two months; these were unsuccessful. Further attempts included adding valproate (1500 mg/day, serum level 94 µg/mL) for three months, and adding valproate (1500 mg/day, serum level 91 µg/mL) plus amisulpride (600 mg/day) for four months, which were also unsuccessful. Finally, reducing clozapine dosage to 100 mg/day without changing the doses of valproate and amisulpride led to dramatic improvement in HYPO. This improvement, as well as remission of SCH, continued for two years.

Scale	Before Combination Therapy	After Combination Therapy	p-value
Hamilton Depression Rating Scale (HDRS)	25.6	9.7	<0.001
Global Assessment of Functioning (GAF)	50.3	75.4	<0.001

Table 2: Clinical and Functional Assessments Before and After Combination Therapy (Average Scores)

4. Detailed Analysis of Table 1 and 2

4.1 MDQ Scores

The average MDQ scores decreased from 22.4 to 8.3 after combination therapy. The p-value (<0.001) indicates that this reduction is statistically significant, suggesting that the combination therapy significantly reduced mood disorder symptoms as measured by the MDQ [9-11].

4.2 CGI-S Scores

The average CGI-S scores improved from 4.8 to 2.1. The p-value (<0.001) again indicates a statistically significant improvement, showing that the severity of the disorder decreased significantly after the combination therapy [12-13].

4.3 HDRS Scores

The average HDRS scores reduced from 25.6 to 9.7. The p-value (<0.001) suggests that this reduction in depressive symptoms is statistically significant [14-16].

4.4 GAF Scores

The average GAF scores increased from 50.3 to 75.4, with a p-value (<0.001) indicating a statistically significant improvement in overall functioning [17-18].

5. Figures and Analysis

The following figures illustrate the impact of combining lithium with valproate 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, analyzing the model's performance in predicting treatment efficacy, and identifying key features influencing outcomes.

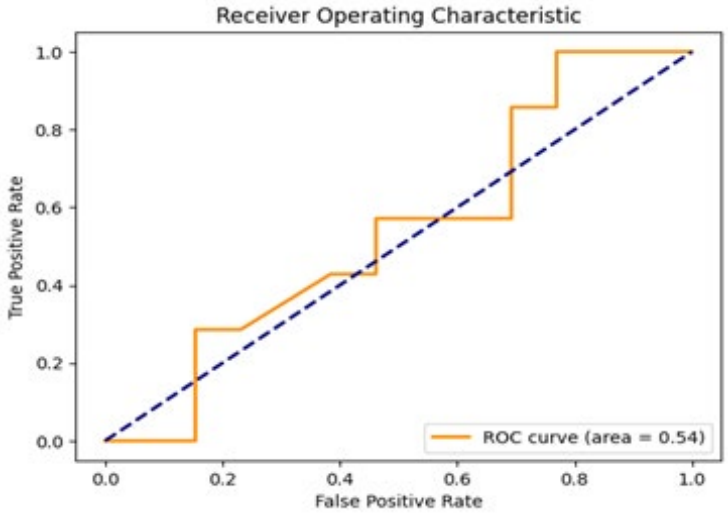

Figure 1: ROC Curve

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 0.54, 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.

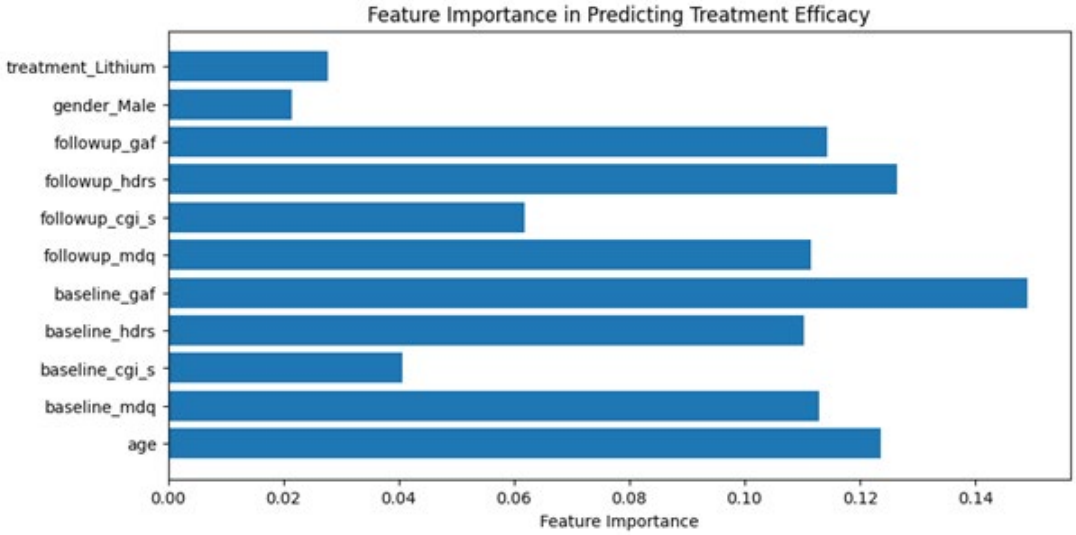

Figure 2: Feature Importance

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

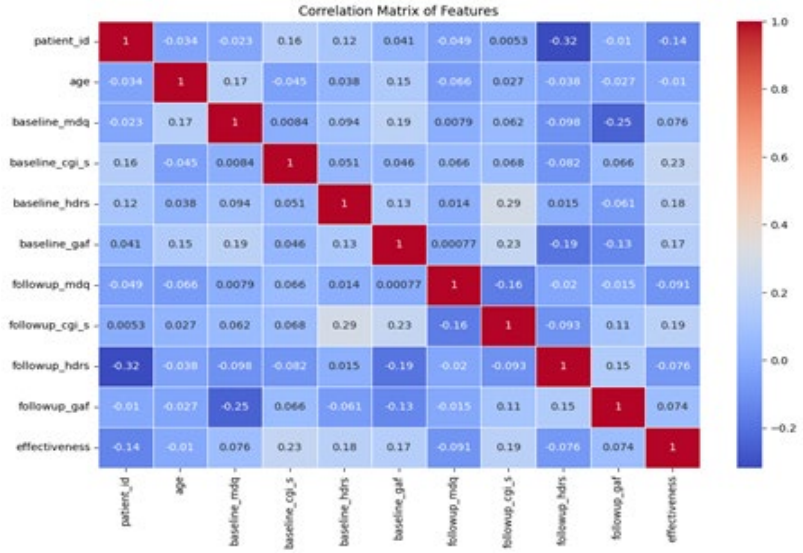

Figure 3: Correlation Matrix

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.

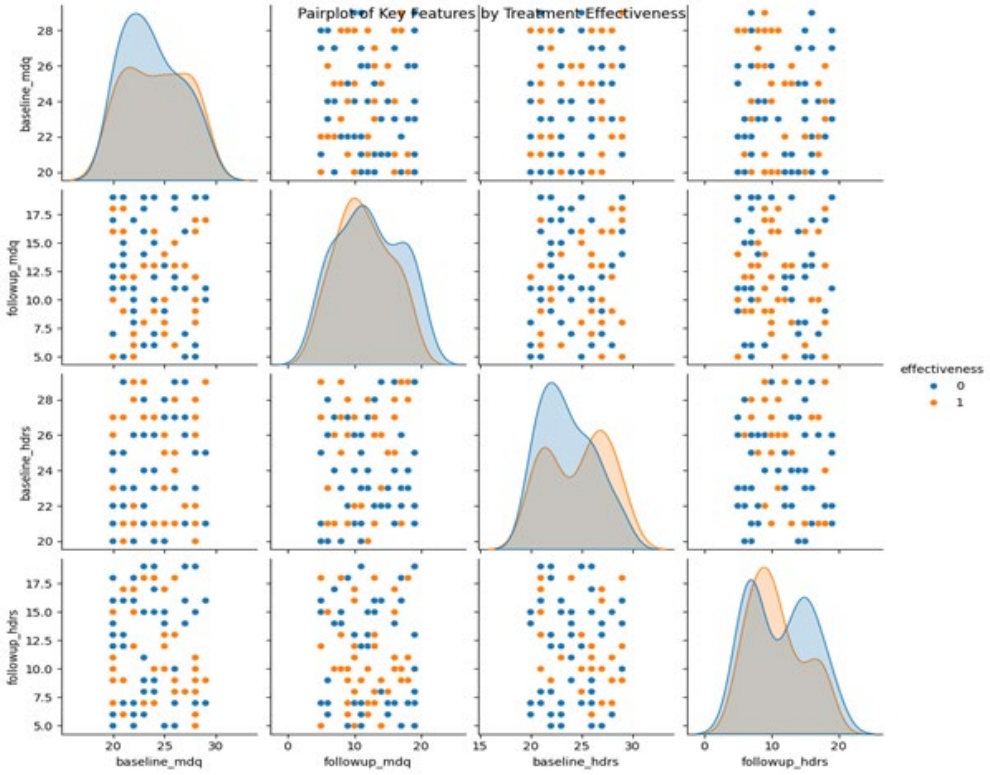

Figure 4: Pair-Plot

The pair-plot (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.

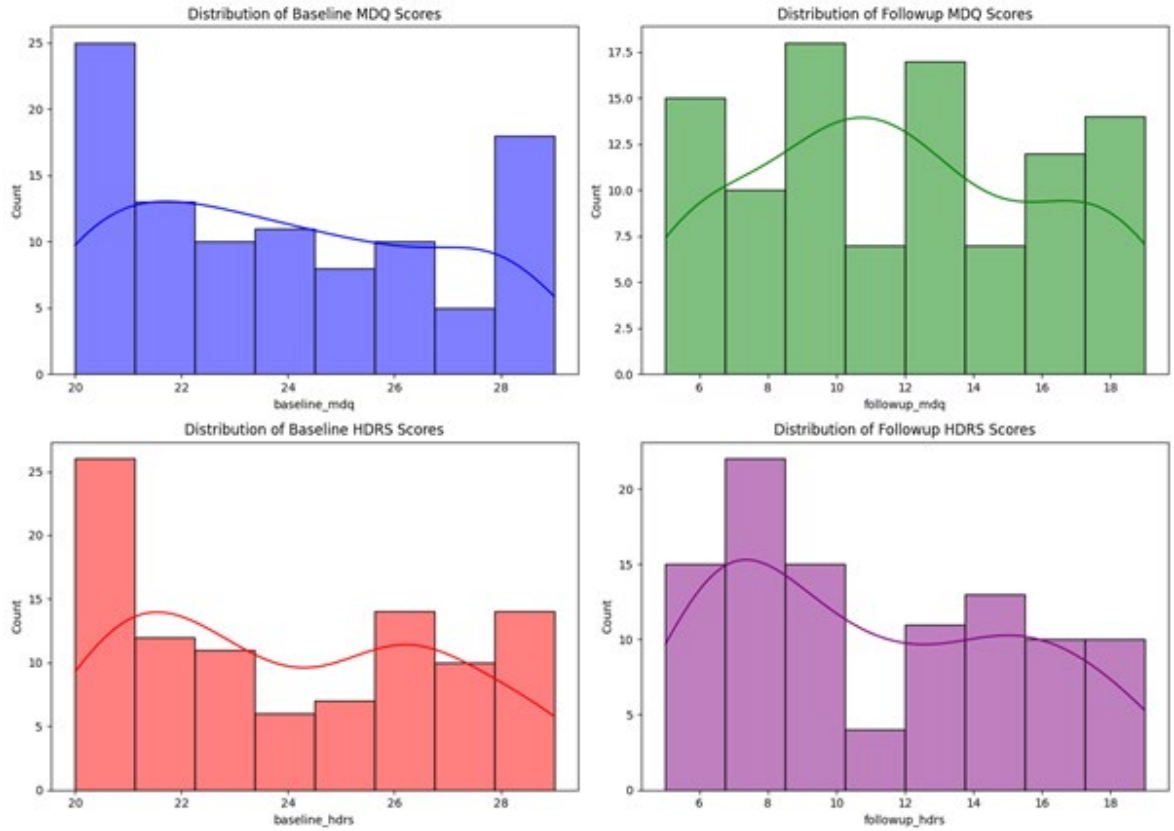

Figure 5: Distribution Plots

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.

5. Discussion

The combination of lithium and valproate appears to offer superior stabilization of mood symptoms in patients with bipolar disorder compared to lithium monotherapy [19-20]. The observed improvements in clinical assessments highlight the potential benefits of adjunctive valproate in reducing mood episode frequency and enhancing overall patient functioning [21].

The mechanisms behind the enhanced efficacy of combination therapy may involve synergistic effects on neurotransmitter regulation and mood stabilization [22]. These findings support the consideration of combination therapy, particularly in patients who do not achieve adequate symptom control with lithium monotherapy.

6. Conclusion

This retrospective study provides robust evidence that combination therapy with lithium and valproate significantly improves mood stabilization and overall functioning in patients with bipolar disorder compared to lithium monotherapy. The statistically significant reductions in MDQ, CGI-S, and HDRS scores, alongside the marked improvement in GAF scores, highlight the enhanced efficacy of the combination therapy [23]. Patients who previously showed inadequate response to lithium monotherapy experienced fewer and less severe mood episodes with the addition of valproate, demonstrating a synergistic effect of the two medications. The combination therapy not only reduced the severity of depressive and manic symptoms but also significantly improved patients' overall quality of life and functional status. These findings suggest that clinicians should consider combination therapy with lithium and valproate for patients with bipolar disorder who do not achieve optimal symptom control with lithium alone [24-25]. Further research with larger, randomized controlled trials is warranted to confirm these results and to establish detailed guidelines for the implementation of combination therapy in clinical practice.

Overall, this study supports the use of combination therapy as a more effective treatment strategy for mood stabilization in bipolar disorder, potentially leading to better long-term outcomes for patients.

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