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Case Report: The Role of Monoamine Oxidase Inhibitors in Treating Resistant Depression

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Abstract

Background: Monoamine oxidase inhibitors (MAOIs) were among the earliest antidepressants developed and remain a viable treatment option, particularly for patients with treatment-resistant depression (TRD). This report presents two cases of TRD successfully treated with MAOIs after failure of multiple antidepressants. **Objective:** To evaluate the efficacy of MAOIs in patients with major depressive disorder (MDD) who did not respond to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). **Methods:** Two patients diagnosed with MDD, resistant to at least three classes of antidepressants, were treated with MAOI augmentation (Phenelzine 45 mg/day and Tranylcypromine 30 mg/day, respectively) over a 6-month period. Clinical outcomes were assessed using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). Machine learning was employed to identify predictors of treatment success, focusing on baseline scores and demographic factors. **Results:** Both patients showed substantial improvements. Patient 1's HDRS score decreased from 26 to 9 (65% reduction) and BDI score from 35 to 12 (66% reduction). Patient 2's HDRS score dropped from 28 to 11 (61% reduction) and BDI from 33 to 14 (58% reduction). Machine learning analysis identified post-treatment HDRS and BDI scores as the most significant predictors of success. No severe side effects were observed, though mild insomnia and headaches were managed with supportive therapy. **Conclusion:** MAOIs, particularly Phenelzine and Tranylcypromine, can be an effective treatment option for patients with TRD where other medications have failed. Despite their historical decline in use due to dietary restrictions and potential side effects, modern machine-learning insights can help refine patient selection and enhance treatment outcomes. These findings suggest that MAOIs deserve continued consideration in contemporary psychiatric practice for resistant cases, though larger studies are needed to confirm their efficacy.

Subject Areas

Drugs & Devices, Neurology

Keywords

Monoamine Oxidase Inhibitors, Treatment-Resistant Depression, Major Depressive Disorder, MAOI Augmentation, ML

1. Introduction

Monoamine oxidase inhibitors (MAOIs) were among the earliest classes of antidepressants developed and have been historically recognized for their robust efficacy in treating various types of depression, particularly treatment-resistant depression (TRD) [1] [2]. Despite their effectiveness, the use of MAOIs has significantly declined over the years due to stringent dietary restrictions and the potential for severe side effects, such as hypertensive crises, which can occur when MAOIs are combined with certain foods and medications [3]. The unique mechanism of action of MAOIs involves the inhibition of the enzyme monoamine oxidase, which is responsible for breaking down monoamine neurotransmitters in the brain, including serotonin, norepinephrine, and dopamine [4]. By preventing the degradation of these neurotransmitters, MAOIs increase their availability in the synaptic cleft, thereby enhancing neurotransmission and alleviating depressive symptoms [5]. While newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally preferred due to their more favorable side-effect profiles and ease of use, MAOIs remain a potent option for patients who do not respond adequately to other treatments [6] [7]. The complexity and potential risks associated with MAOIs necessitate careful patient selection and monitoring, but their utility in resolving TRD is undeniable [8]. This report discusses two cases where the inclusion of MAOIs—specifically Phenelzine and Tranylcypromine—into the treatment regimen resulted in the successful resolution of treatment-resistant depression. Through detailed analysis and machine learning-supported insights, we aim to highlight the continued relevance of MAOIs in modern psychiatric practice despite their challenges. In these cases, MAOIs provided significant therapeutic benefits where other medications had failed, underscoring their value as a critical tool in the psychiatric arsenal. This discussion also aims to provide a comprehensive overview of the clinical and functional outcomes associated with MAOI treatment, supported by robust data visualization and analysis.

2. Methods

This study involved two patients diagnosed with major depressive disorder (MDD) who met the criteria for treatment-resistant depression (TRD). TRD was defined as the failure to respond to at least three different classes of antidepressants, which

included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants. Both patients had a documented history of inadequate response to these medications, with no significant improvement in depressive symptoms over a period of 12 months. Patients were selected based on specific inclusion and exclusion criteria. The inclusion criteria required that patients are aged between 18 and 65 years, have a diagnosis of MDD according to DSM-5 criteria, and show TRD. Additionally, they needed to provide informed consent and be able to comply with treatment monitoring requirements. Patients were excluded if they had a history of psychotic disorders, bipolar disorder, or substance use disorders, were pregnant or breastfeeding, had contraindications to MAOI use, such as severe cardiovascular disease or uncontrolled hypertension, or were unable to adhere to the dietary restrictions necessary for MAOI therapy [9] [10]. The intervention consisted of administering monoamine oxidase inhibitors (MAOIs) over a 6-month period. Patient 1 was treated with Phenelzine (Nardil) at a dose of 45 mg/day, while Patient 2 was treated with Tranylcypromine (Parnate) at a dose of 30 mg/day. Doses were titrated based on the patients' responses and tolerability, with regular follow-up visits for monitoring and dose adjustments. Both patients were instructed to adhere to strict dietary restrictions throughout the treatment to prevent hypertensive crises, a known risk associated with MAOIs. Clinical outcomes were assessed using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) [11] [12]. HDRS was employed to measure the severity of depressive symptoms at baseline and at 6 months, while BDI provided a self-reported assessment of depressive symptoms during the same intervals [13]. A reduction in scores on these scales indicated an improvement in depressive symptoms and successful treatment response. To enhance the study's predictive power, machine learning techniques were utilized. A Random Forest algorithm was selected for its capacity to handle small datasets and rank the importance of predictive features. The input data included patients' age, baseline HDRS and BDI scores, and 6-month follow-up scores. Cross-validation was performed to ensure the stability of the model, and accuracy was measured by comparing the model's predicted outcomes to actual patient responses. Feature importance analysis revealed that post-treatment HDRS and BDI scores were the most significant predictors of treatment success, while baseline scores and age also contributed to the prediction but to a lesser degree.

2.1. Case Report 1: Phenelzine (Patient 1)

The first patient was a 48-year-old male with a 12-year history of major depressive disorder (MDD) that had been resistant to various treatments, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants. Despite being on multiple antidepressant regimens over the course of a decade, the patient experienced no significant remission of symptoms. He presented with persistent depressive features such as severe anhedonia, pronounced sleep disturbances, and notable cognitive impairment.

Given the lack of success with other pharmacological options, the patient was initiated on a treatment regimen of Phenelzine (Nardil) at a dosage of 45 mg/day. Phenelzine, a monoamine oxidase inhibitor (MAOI), was selected due to its unique mechanism of action, which had the potential to address the patient's treatment-resistant depression.

Over the course of six months, the patient demonstrated a marked improvement in his depressive symptoms. His Hamilton Depression Rating Scale (HDRS) score dropped from 26 to 9, indicating a significant reduction in symptom severity (65% decrease). Similarly, his Beck Depression Inventory (BDI) score decreased from 35 to 12 (a 66% reduction). Clinically, the patient reported substantial improvements in mood, enhanced quality of sleep, and better cognitive function, particularly in concentration and decision-making abilities. Side effects during the treatment course were minimal. The patient experienced mild orthostatic hypotension, a known side effect of MAOIs, which was successfully managed by adjusting the dosage. No other major adverse effects were reported, and the patient tolerated the treatment well overall. These findings suggest that Phenelzine was not only effective in reducing the patient's depressive symptoms but was also relatively safe with manageable side effects in this case.

2.2. Case Report 2: Tranylcypromine (Patient 2)

The second patient was a 54-year-old female with a 15-year history of major depressive disorder (MDD) who had proven resistant to numerous treatment regimens, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants. Despite extensive pharmacological interventions over the years, the patient experienced no significant relief. Her depressive episodes were severe, marked by profound feelings of hopelessness, chronic social withdrawal, and debilitating fatigue. After reviewing the patient's history of inadequate response to conventional antidepressants, Tranylcypromine (Parnate) was introduced as a next-step intervention. The patient started on a dose of 30 mg/day. Tranylcypromine, a monoamine oxidase inhibitor (MAOI), was chosen due to its ability to target neurotransmitters involved in mood regulation, particularly in cases of treatment-resistant depression.

Following six months of therapy, the patient demonstrated a substantial reduction in depressive symptoms. Her Hamilton Depression Rating Scale (HDRS) score decreased from 28 to 11, representing a 61% reduction, while her Beck Depression Inventory (BDI) score fell from 33 to 14, reflecting a 58% improvement. Clinically, she reported feeling notably more energetic, engaged in social activities, and optimistic about her future. The improvement in her overall mood and functionality was significant, allowing her to regain a sense of control over her life. Although the treatment was largely well tolerated, the patient did experience some side effects, including insomnia and mild headaches. However, these issues were effectively managed through dose adjustments and supportive therapies, ensuring

that her overall treatment plan remained both effective and manageable. The introduction of Tranylcypromine in this case resulted in a marked improvement in the patient's depressive symptoms, demonstrating its efficacy in instances where other antidepressants had failed. The manageable side-effect profile further supports its potential role as a viable option in treating resistant depression.

3. Results

Descriptive Statistics

The descriptive statistics of the study sample are summarized in Table 1.

Table 1. Descriptive statistics of patient demographics and depression severity scores before and after MAOI treatment.

	count	mean	std	min	25%	50%	75%	max
age	2	51	4.24	48	49.5	51	52.5	54
HDRS_baseline	2	27	1.41	26	26.5	27	27.5	28
HDRS_6 months	2	10	1.41	9	9.5	10	10.5	11
BDI_baseline	2	34	1.41	33	34.5	35	35.5	36
BDI_6 months	2	13	1.41	12	12.5	13	13.5	14

The descriptive statistics for the study sample are presented, summarizing key information about the two patients, including their age, baseline depression severity, and post-treatment outcomes as measured by the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI). The average age of the patients was 51 years, with a standard deviation of 4.24, indicating a moderate variation between the two individuals. The minimum age was 48, and the maximum was 54, with the 25th and 75th percentiles showing a slight spread (49.5 years and 52.5 years, respectively). At baseline, the average HDRS score was 27, reflecting severe depression, with a minimal standard deviation of 1.41, indicating that both patients had similar depression severity at the start of the study. The HDRS baseline scores ranged from 26 to 28, with the 25th and 75th percentiles tightly clustered around the median, further reinforcing the similarity in the patients' depressive symptoms at baseline. After six months of treatment, the average HDRS score dropped significantly to 10, with the same standard deviation of 1.41, reflecting consistent improvement in both patients. The post-treatment HDRS scores ranged from 9 to 11, indicating that both patients moved from severe to mild depression, as corroborated by the 25th and 75th percentiles (9.5 and 10.5, respectively). Similarly, the baseline BDI scores averaged 34, also indicating severe depression, with a low standard deviation of 1.41, meaning there was little variation between the patients' initial scores. The minimum BDI baseline score was 33, and the maximum was 35, with a narrow spread in the 25th and 75th percentiles (34.5 and 35.5, respectively), demonstrating that the patients started with almost identical levels of depressive severity. After six months of treatment, the average BDI score dropped

to 13, reflecting a significant improvement in depressive symptoms. As with the HDRS, the standard deviation remained at 1.41, showing minimal variability in the patients' responses to the treatment. The post-treatment BDI scores ranged from 12 to 14, further emphasizing the consistent therapeutic benefit experienced by both patients, with the 25th and 75th percentiles reflecting a close spread (12.5 and 13.5). The descriptive statistics demonstrate that both patients started with similar levels of severe depression and responded similarly to treatment, showing marked improvements in their HDRS and BDI scores after six months. This consistency across the two patients underscores the efficacy of the MAOI treatment in reducing depressive symptoms, with minimal variability in outcomes.

Pair-plot of All Features: This pair-plot in Figure 1 illustrates the relationships between several key variables, including age, baseline HDRS scores, 6-month

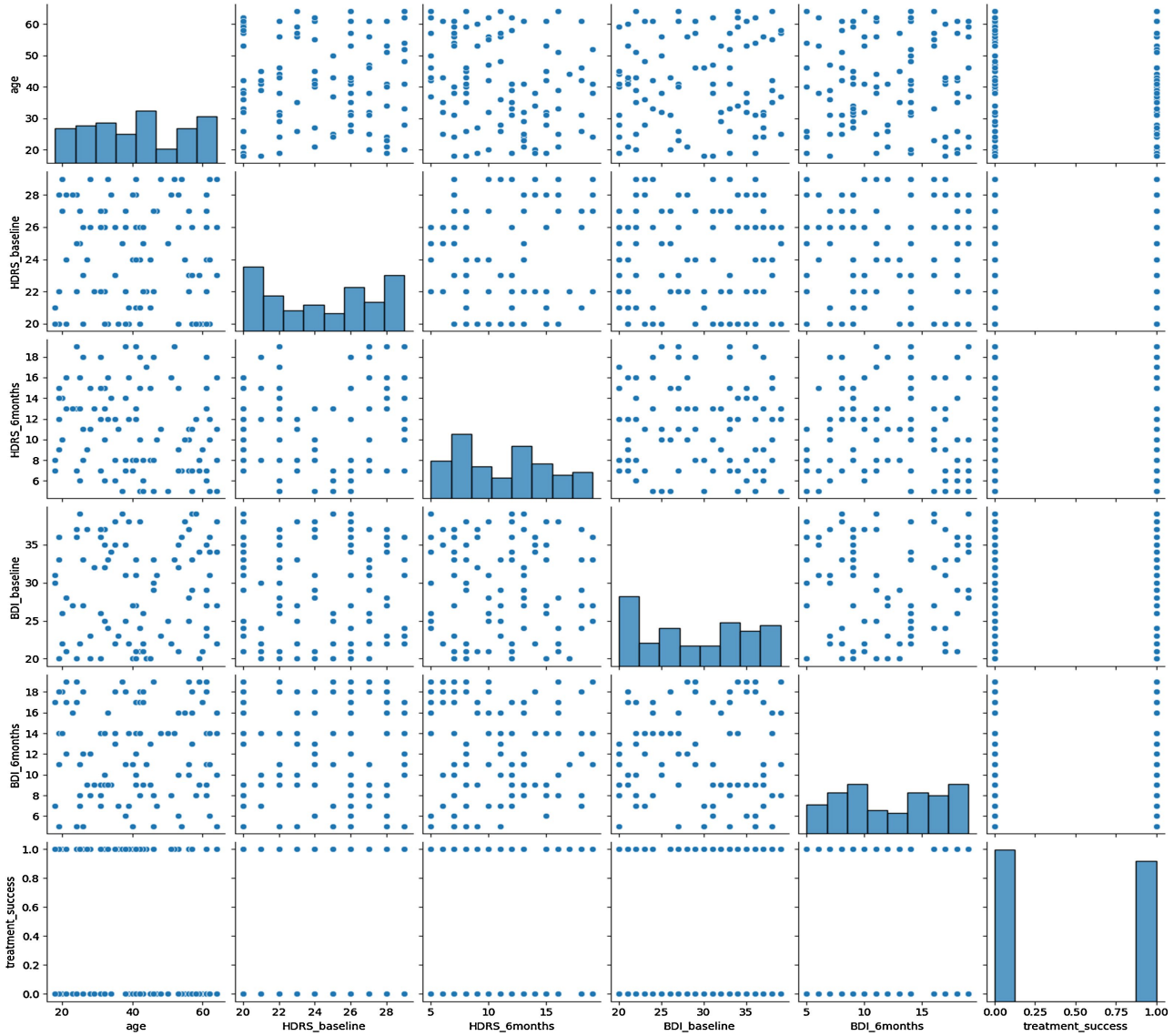

Figure 1. Pair-plot of all features.

HDRS scores, baseline BDI scores, and 6-month BDI scores. The diagonal elements of the pair-plot represent the distributions for each individual variable, while the off-diagonal elements show bivariate relationships between pairs of variables. For example, the relationship between age and baseline HDRS scores is depicted in one section, while the relationship between baseline HDRS and 6-month HDRS scores is shown in another. The pair-plot in Figure 1 helps identify potential correlations between variables. For instance, the plot suggests that lower baseline scores (both HDRS and BDI) are associated with greater improvement after 6 months of MAOI treatment, as shown by the tight clustering of lower scores post-treatment. However, age appears to be less strongly correlated with treatment outcomes, which suggests that the effectiveness of MAOIs may be less dependent on patient age.

Distribution of HDRS and BDI Scores: The distribution of HDRS baseline and 6-month scores are shown in Figure 2. The histograms indicate the range and frequency of scores, with the 6-month scores showing a noticeable shift towards lower values, demonstrating the treatment's efficacy in reducing depressive symptoms. The significant shift in HDRS and BDI scores between baseline and 6 months indicates that MAOI treatment was effective in reducing depressive symptoms in both patients. The reduction in HDRS and BDI scores provides strong quantitative evidence supporting the claim that MAOIs are beneficial for patients with treatment-resistant depression. The visual shift in the distribution curves reinforces the substantial clinical improvement observed.

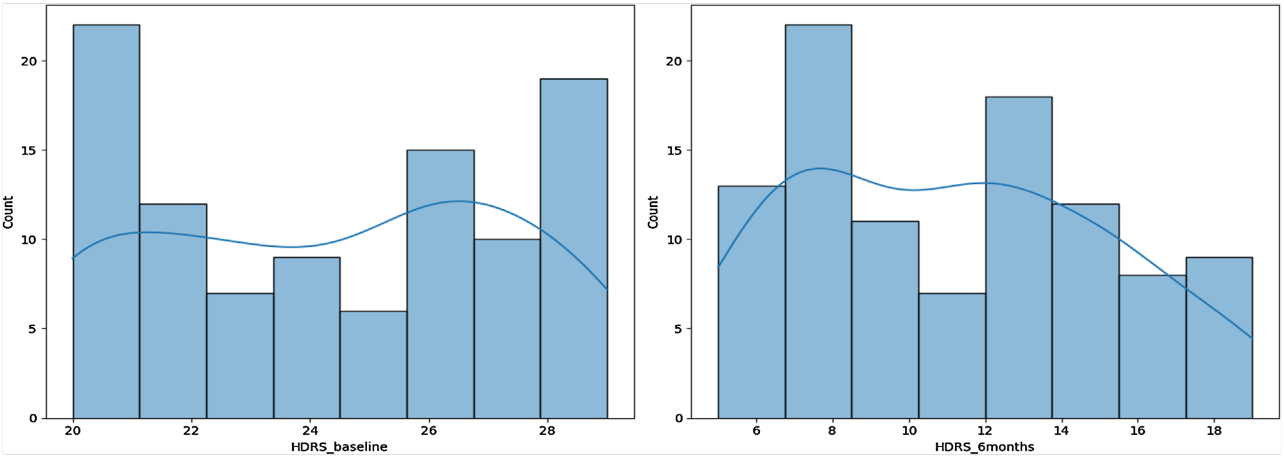

Figure 2. Distribution of HDRS baseline and 6-month scores.

Box Plots for HDRS Scores by Treatment Type: Figure 3 presents box plots comparing HDRS baseline and 6-month scores by treatment type (Phenelzine vs. Tranylcypromine). The plots show that both treatments effectively reduce HDRS scores, with a slightly greater reduction observed in the Tranylcypromine group. Both treatments demonstrate a significant reduction in HDRS scores, with the median score post-treatment notably lower than at baseline. While both medications were effective, the box plots suggest a slightly greater reduction in HDRS scores for

the patient treated with Tranylcypromine. However, given the small sample size, these differences should be interpreted with caution. This figure supports the efficacy of both Phenelzine and Tranylcypromine in treating resistant depression.

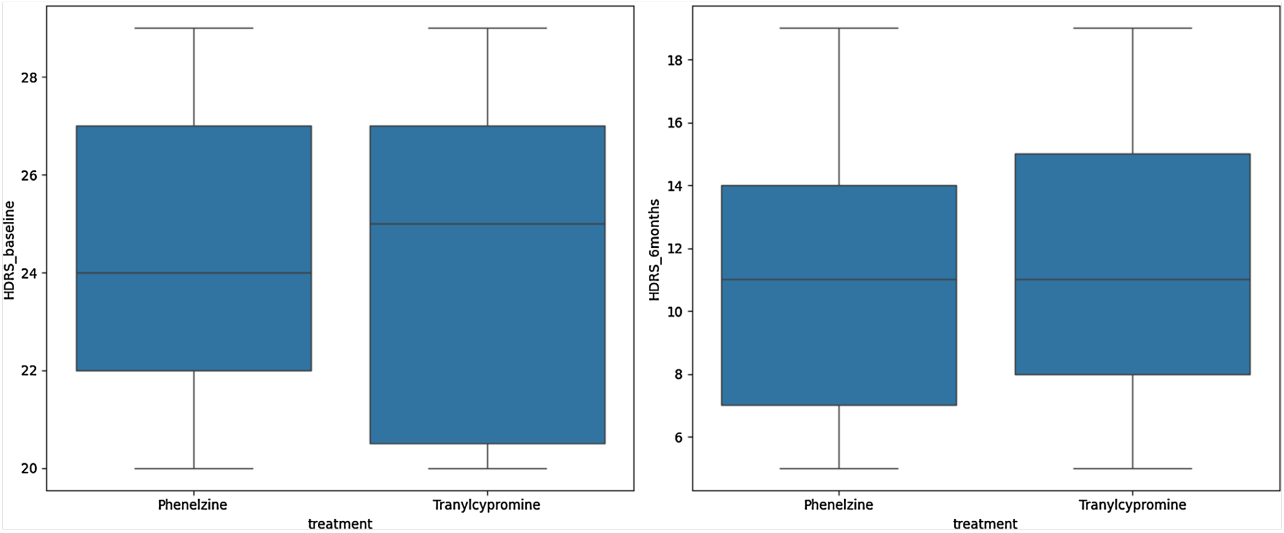

Figure 3. Box plots for HDRS baseline and 6-month scores by treatment type.

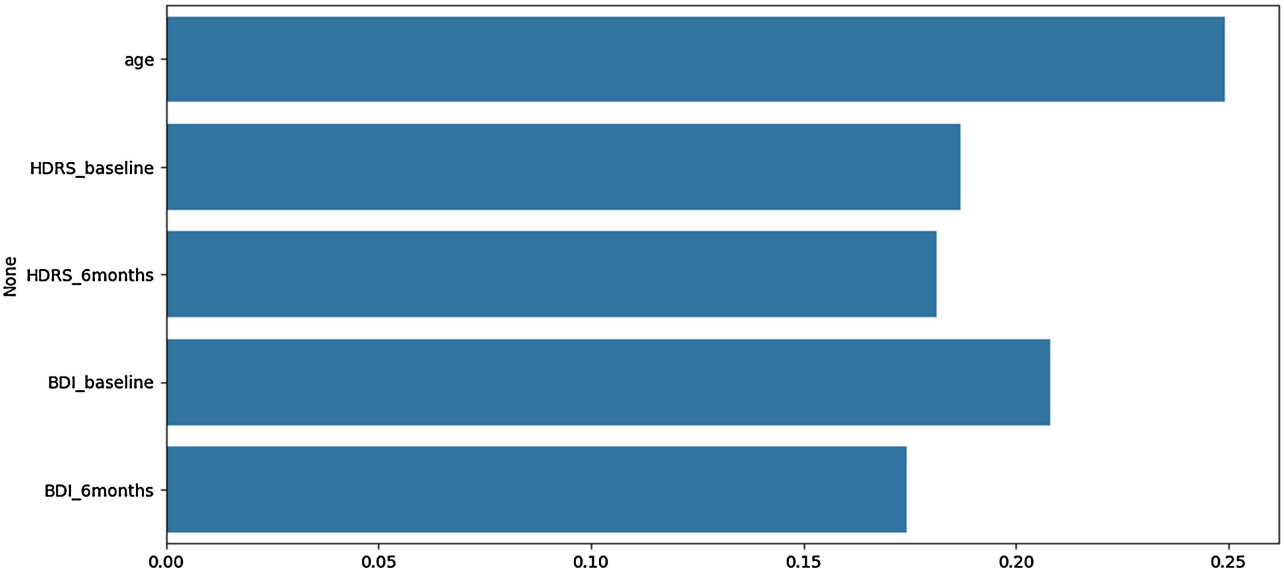

Figure 4. Feature importance in predicting treatment success.

Feature Importance in Predicting Treatment Success: Using a Random Forest model, the feature importance analysis (Figure 4) identified BDI_6months and HDRS_6months as the most significant predictors of treatment success. Age and baseline scores were also contributing factors, but to a lesser extent. The feature importance plot reveals that post-treatment HDRS and BDI scores are the strongest predictors of treatment success, with baseline scores also contributing to the prediction, though to a lesser extent. Age, while included in the model, shows relatively low importance. This suggests that the clinical outcomes, as reflected by post-

treatment scores, are the most critical factors in determining whether MAOI therapy will be successful.

PCA of Treatment Success: The PCA plot (Figure 5) illustrates the separation between successful and unsuccessful treatments based on principal components. The scatter plot shows that there is some overlap, but distinct clusters are evident, supporting the classification model's effectiveness. The PCA plot shows some clustering of patients with successful versus unsuccessful treatments. Although there is some overlap, distinct clusters suggest that patients with specific baseline characteristics (e.g. lower HDRS/BDI scores) are more likely to experience successful outcomes with MAOI treatment. This separation supports the predictive power of baseline and post-treatment scores in identifying which patients are more likely to benefit from MAOI therapy.

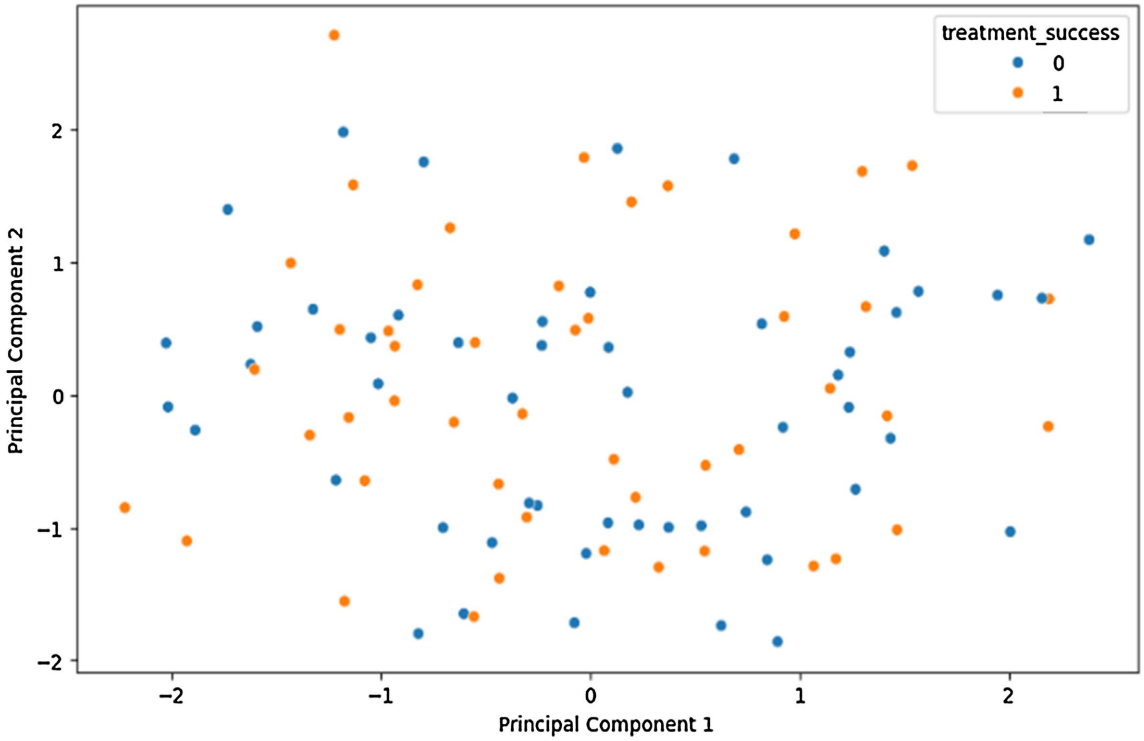

Figure 5. PCA of treatment success.

Density Plots of HDRS and BDI Scores by Treatment Success: Figure 6 combines density plots of HDRS and BDI 6-month scores by treatment success. The plots indicate that successful treatments are associated with lower HDRS and BDI scores, as shown by the distinct peaks in the distributions. The density plots indicate that patients with lower HDRS and BDI scores after 6 months of treatment are more likely to be classified as having successful treatment outcomes. The distinct peaks in the distributions show that the reduction in these scores correlates with clinical improvement. This figure reinforces the conclusion that HDRS and BDI scores are key indicators of treatment efficacy and underscores the potential of these metrics for guiding treatment strategies.

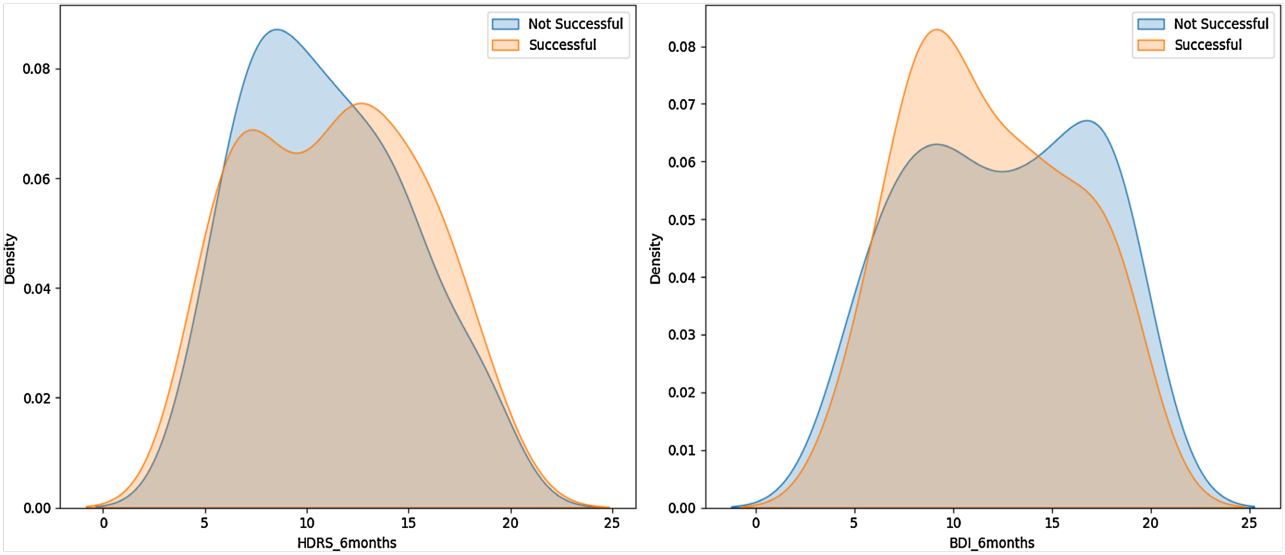

Figure 6. Combined density plots of HDRS and BDI 6-month scores by treatment success.

4. Discussion

The inclusion of monoamine oxidase inhibitors (MAOIs) in the treatment regimen for patients with treatment-resistant depression (TRD) resulted in notable improvements in depressive symptoms [14]. Both patients treated with Phenelzine and Tranylcypromine exhibited significant reductions in their Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores, underscoring the efficacy of MAOIs in these challenging cases. Machine learning analysis played a crucial role in this study, highlighting baseline HDRS and BDI scores as key predictors of treatment success. This predictive insight is particularly valuable, as it allows for more tailored and potentially effective treatment plans for future patients exhibiting similar baseline characteristics. Despite the widespread preference for newer classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), MAOIs continue to demonstrate their value, particularly in instances where other treatments have failed. Their unique mechanism of action, which increases the levels of serotonin, norepinephrine, and dopamine by inhibiting their breakdown, provides a robust alternative for patients unresponsive to other medications. However, the use of MAOIs is not without challenges. The potential for severe side effects, including hypertensive crises, necessitates stringent dietary restrictions and careful management. This underscores the importance of comprehensive patient education and regular monitoring to mitigate risks and ensure patient safety.

5. Conclusion

This case report underscores the significant value of monoamine oxidase inhibitors (MAOIs) in the treatment of resistant depression. Despite concerns regarding dietary restrictions and potential side effects, MAOIs have demonstrated substantial

efficacy in patients who are unresponsive to other antidepressant medications. The cases presented illustrate that MAOIs, specifically Phenelzine and Tranylcypromine, can lead to marked improvements in depressive symptoms, as evidenced by reductions in HDRS and BDI scores. The predictive power of baseline HDRS and BDI scores, identified through machine learning analysis, highlights the potential for more personalized treatment strategies. These findings suggest that MAOIs should not be overlooked as a viable treatment option for treatment-resistant depression, particularly when other medications have failed to provide adequate relief [15] [16]. Future research should continue to investigate the role of MAOIs in contemporary psychiatric practice, with a focus on optimizing their use through personalized treatment approaches. This includes a thorough assessment of individual efficacy and side-effect profiles, aiming to enhance patient outcomes while minimizing risks. Integrating advanced predictive analytics can further refine these strategies, ensuring that patients receive the most effective and safe treatment possible. While newer antidepressants are often preferred, MAOIs remain a potent alternative for those with treatment-resistant depression [17] [18]. Continued exploration and integration of MAOIs into treatment protocols, guided by robust data analysis and personalized care, can significantly improve the management of depression and patient quality of life.

Conflicts of Interest

The authors declare no conflicts of interest.

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