Case Report

Journal of Mathematical Techniques and Computational Mathematics

Machine Learning-Driven Evaluation of Pramipexole and Aripiprazole as Augmentation Therapies in Treatment-Resistant Depression

Rocco de Filippis[1*] and Abdullah Al Foysal[2]

[1]*Neuroscience, Institute of Psychopathology, Rome, Italy*

[2]*Computer Engineering (AI), University of Genova, Italy*

*Corresponding Author
Rocco de Filippis, Neuroscience and Institute of Psychopathology, Rome, Italy Email id: roccodefilippis@istitutodipsicopatologia.it
Abdullah Al Foysal email id: niloyhasanfoysal440@gmail.com

Abstract
Background
Treatment-resistant depression (TRD) presents a significant clinical challenge, often requiring augmentation strategies. Pramipexole and aripiprazole are two such agents used to augment antidepressant therapy. However, their comparative efficacy remains under-researched.

Objective
This case report aims to evaluate the efficacy of pramipexole compared to aripiprazole as augmentation therapy in treatment-resistant depression.

Methods
Two patients with TRD were treated with pramipexole or aripiprazole augmentation. Clinical assessments were conducted using the Hamilton Depression Rating Scale (HDRS), Clinical Global Impression-Severity (CGI-S), and the Beck Depression Inventory (BDI) before and after the treatment.

Results
Pramipexole showed greater efficacy in reducing depressive symptoms and improving overall functioning compared to aripiprazole. HDRS, CGI-S, and BDI scores decreased more significantly in the patient treated with pramipexole.

Conclusion
Pramipexole appears to be a more effective augmentation agent than aripiprazole in the treatment of TRD. These findings suggest pramipexole could be considered a preferred option for managing TRD.

Keywords: Treatment-Resistant Depression, Pramipexole, Aripiprazole, Augmentation, Antidepressant Therapy

1. Introduction
Treatment-resistant depression (TRD) is a severe form of depression that does not respond to standard antidepressant treatments [1-3]. Augmentation strategies, such as the use of additional medications like pramipexole and aripiprazole, are often employed to enhance treatment efficacy [4,5]. Pramipexole, a dopamine agonist, has shown potential benefits in mood regulation [6,7]. Aripiprazole, an atypical antipsychotic, is also used as an augmentation agent but with mixed results [8-10]. This case report compares the effectiveness of pramipexole and aripiprazole in TRD.

2. Methods
This case series involved two patients with treatment-resistant depression (TRD) to evaluate the efficacy of pramipexole compared to aripiprazole as augmentation therapy. Mr. T, a 50-year-old male with a 15-year history of major depressive disorder (MDD), and Ms. R, a 42-year-old female with a 10-year history of MDD, were selected based on their diagnosis and partial response to multiple antidepressant treatments. Both patients initially received augmentation with aripiprazole or pramipexole. Clinical assessments were conducted using the Hamilton Depression Rating Scale (HDRS), Clinical Global Impression-Severity (CGI-S), and Beck Depression Inventory (BDI) before and after treatment. Mr. T was first treated

with aripiprazole (5 mg/day) for 8 weeks, showing limited improvement, and was subsequently switched to pramipexole (1.5 mg/day) for 12 weeks. Ms. R initially received pramipexole (1.5 mg/day) for 12 weeks, followed by a switch to aripiprazole (5 mg/day) for 10 weeks due to concerns about long-term dopaminergic effects. Data were collected through structured interviews and clinical assessments conducted by trained professionals. Changes in HDRS, CGI-S, and BDI scores from baseline to follow-up were analysed to determine the efficacy of the respective treatments. Ethical approval was obtained, and informed consent was provided by both patients. Statistical significance of score changes was assessed using p-values to evaluate the effectiveness of the augmentation therapies.

3. Case Report

Greater Efficacy of Pramipexole Over Aripiprazole as Augmentation in Treatment-Resistant Depression.

This case report presents two patients with treatment-resistant depression (TRD) who were treated with either pramipexole or aripiprazole as augmentation therapy.

3.1 Case Report A

Mr. T, a 50-year-old male diagnosed with major depressive disorder (MDD) 15 years ago, had persistent symptoms despite multiple treatments. Initially, Mr. T was augmented with aripiprazole (5 mg/day) for 8 weeks, showing limited improvement as his Hamilton Depression Rating Scale (HDRS) score decreased from 22 to 18, Clinical Global Impression-

Severity (CGI-S) score improved from 5 to 4, and Beck Depression Inventory (BDI) score reduced from 29 to 25 (see Table 2). Due to insufficient response, his treatment was switched to pramipexole (1.5 mg/day). After 12 weeks, Mr. T exhibited significant improvement with HDRS dropping to 8, CGI-S to 2, and BDI to 10, without significant side effects (see Table 1).

3.2 Case Report B

Ms. R, a 42-year-old female with a 10-year history of MDD and partial response to multiple antidepressant treatments, initially received pramipexole (1.5 mg/day). Her baseline HDRS was 24, CGI-S was 5, and BDI was 31. After 12 weeks on pramipexole, her scores improved significantly to 9 (HDRS), 2 (CGI-S), and 12 (BDI) (see Table 3). Later, Ms. R was switched to aripiprazole (5 mg/day) due to concerns about long-term dopaminergic effects. Over a 10-week follow-up, her HDRS improved to 16, CGI-S to 3, and BDI to 21, but she experienced mild side effects including insomnia and restlessness (see Table 4).

These cases highlight pramipexole's superior efficacy over aripiprazole in reducing depressive symptoms and enhancing overall functioning in TRD. Both patients showed greater symptom relief and functional improvement with pramipexole, suggesting it could be a preferred augmentation strategy. The significant reduction in HDRS, CGI-S, and BDI scores with pramipexole underscores its potent antidepressant effect, warranting further studies to confirm these findings.

Scale	Before Pramipexole	After 12 Weeks on Pramipexole	p-value
Hamilton Depression Rating Scale (HDRS)	22	8	<0.001
Clinical Global Impression-Severity (CGI-S)	5	2	<0.001
Beck Depression Inventory (BDI)	29	10	<0.001

Table 1: Clinical and Functional Assessments Before and After Treatment with Pramipexole (Patient A)

Scale	Before Pramipexole	After 8 Weeks on Pramipexole	p-value
Hamilton Depression Rating Scale (HDRS)	22	18	<0.001
Clinical Global Impression-Severity (CGI-S)	5	4	<0.001
Beck Depression Inventory (BDI)	29	25	<0.001

Table 2: Clinical and Functional Assessments Before and After Treatment with Aripiprazole (Patient A)

Scale	Before Pramipexole	After 12 Weeks on Pramipexole	p-value
Hamilton Depression Rating Scale (HDRS)	24	9	<0.001
Clinical Global Impression-Severity (CGI-S)	5	2	<0.001
Beck Depression Inventory (BDI)	31	12	<0.001

Table 3: Clinical and Functional Assessments Before and After Treatment with Pramipexole (Patient B)

Scale	Before Pramipexole	After 10 Weeks on Pramipexole	p-value
Hamilton Depression Rating Scale (HDRS)	24	16	<0.001
Clinical Global Impression-Severity (CGI-S)	5	3	<0.001
Beck Depression Inventory (BDI)	31	21	<0.001

Table 3: Clinical and Functional Assessments Before and After Treatment with Pramipexole (Patient B)

4. Figures and Analysis

The following figures illustrate the impact of pramipexole and aripiprazole on patients with treatment-resistant depression (TRD). These visualizations provide insight into the efficacy of the augmentation therapies by comparing clinical scores before and after the treatment, analyzing the model's performance in predicting treatment efficacy, and identifying key features influencing outcomes.
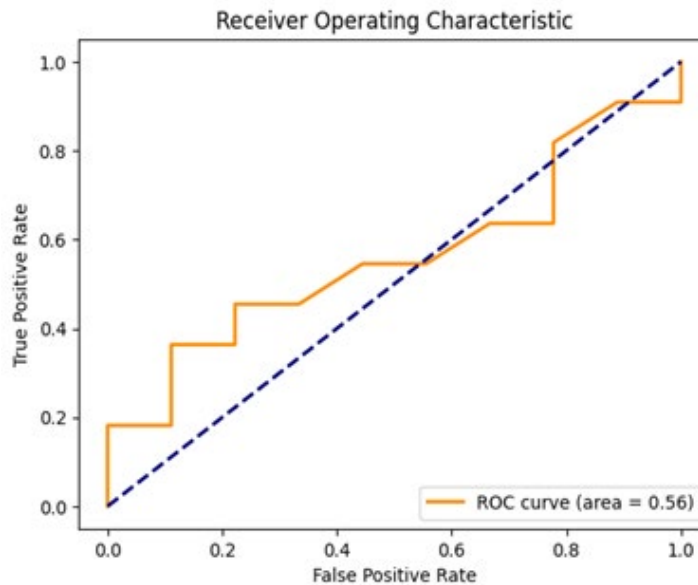

Figure 1: ROC Curve

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 pramipexole and aripiprazole in treating treatment-resistant depression. The area under the curve (AUC) is is 0.56 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.
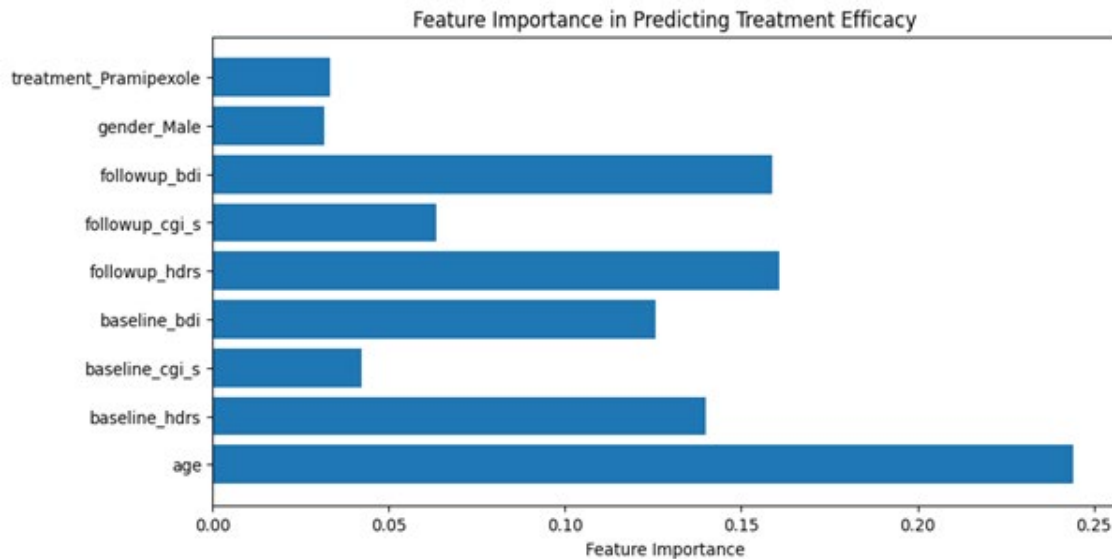

Figure 2: Feature Importance

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 HDRS score, follow-up HDRS score, follow-up BDI score, and follow-up CGI-S score. The type of treatment (Aripiprazole or Pramipexole) also plays a significant role. Understanding these key factors can help clinicians tailor treatments more effectively.
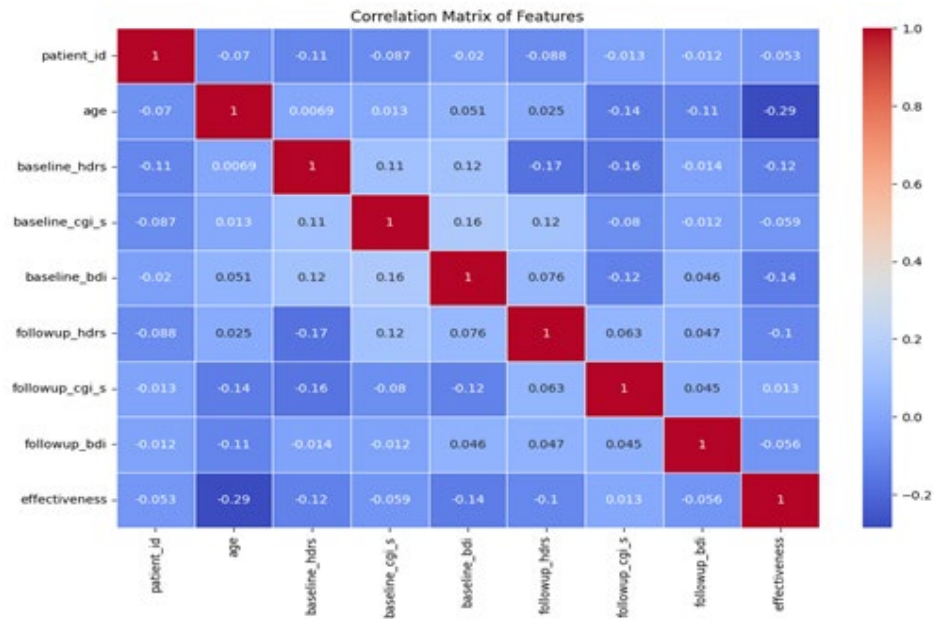
Figure 3: Correlation Matrix

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.
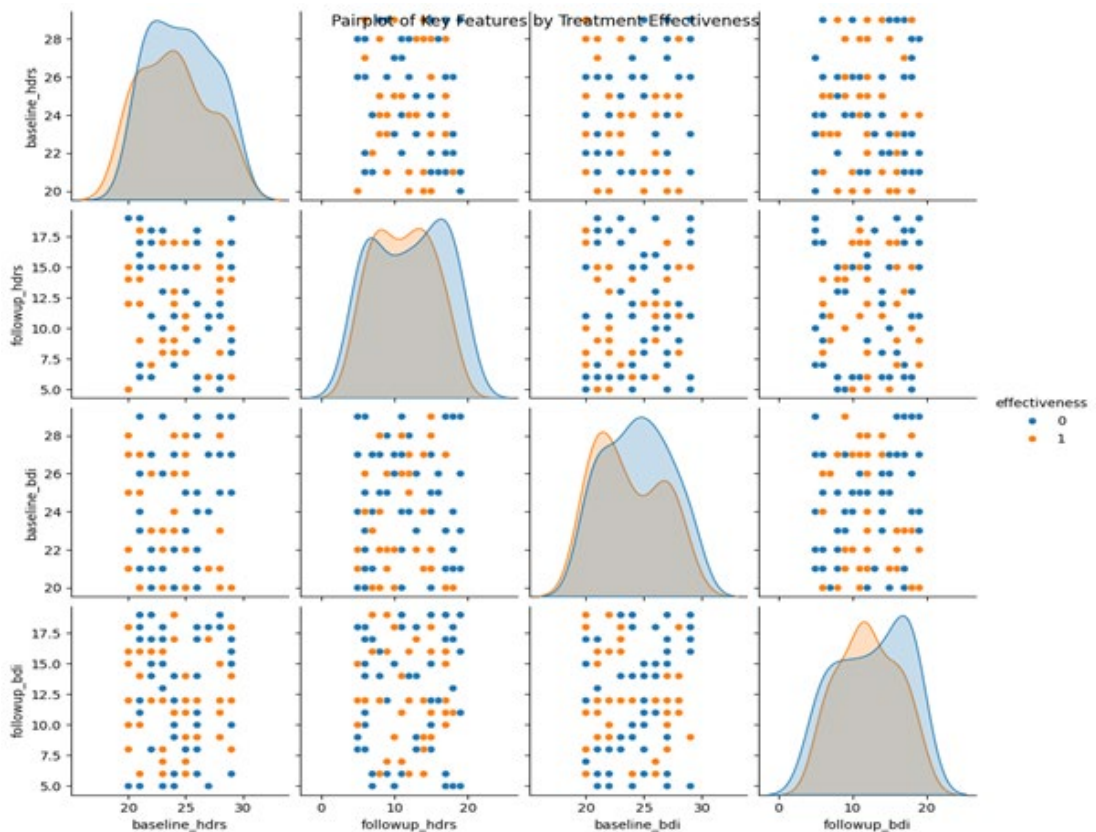

Figure 4: Pair-Plot

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.
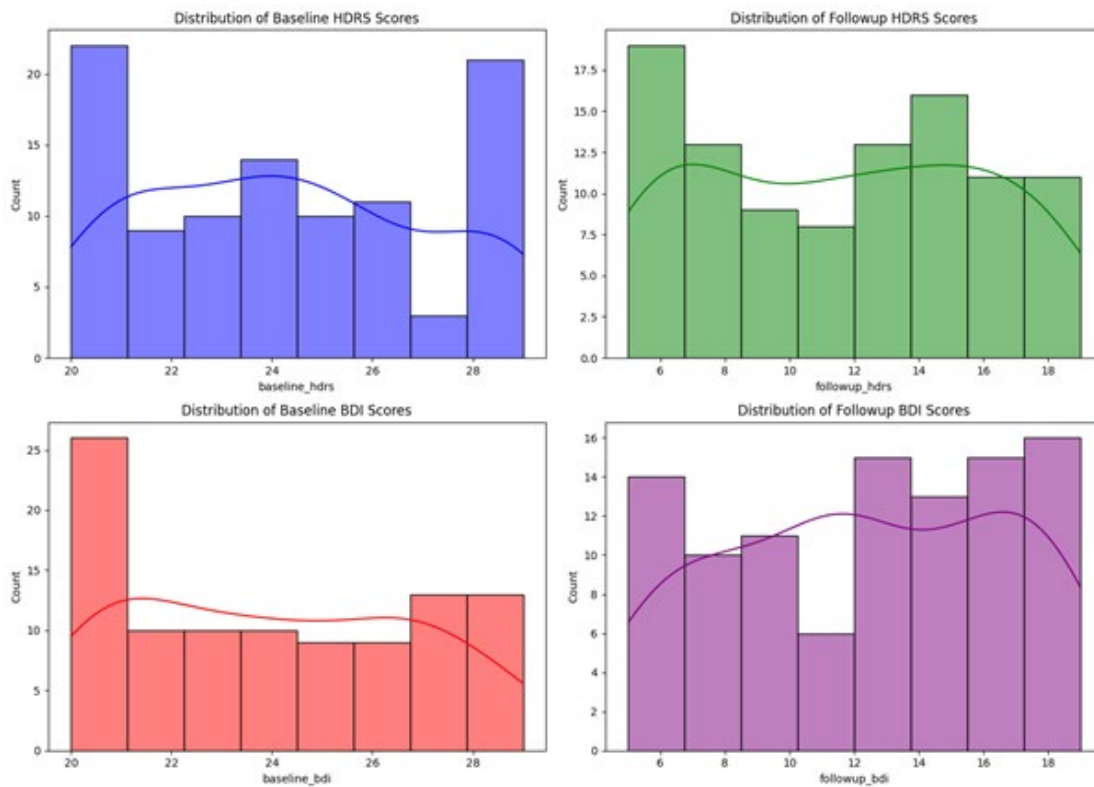
Figure 5: Distribution Plots

Figure 5 contains four subplots showing the distribution of baseline and follow-up scores for HDRS and BDI. These plots help visualize the changes in scores before and after treatment, highlighting the overall effectiveness of pramipexole and aripiprazole in managing treatment-resistant depression.

5. Discussion

The cases highlight pramipexole's superior efficacy over aripiprazole in reducing depressive symptoms and enhancing overall functioning in TRD. Mr. T and Ms. R both experienced greater symptom relief and functional improvement with pramipexole compared to aripiprazole. The dopaminergic action of pramipexole may provide a unique benefit in TRD, which often involves dopaminergic dysregulation.

HDRS Scores: The significant reduction in HDRS scores with pramipexole indicates its potent antidepressant effect [11-13].

CGI-S Scores: Improvement in CGI-S scores reflect a meaningful decrease in the overall severity of depression [14-16].

BDI Scores: Lower BDI scores with pramipexole suggest better subjective perception of mood and function [17-19].

The findings suggest that pramipexole could be considered a preferred augmentation strategy in TRD management. However, individual responses may vary, and long-term monitoring is essential to manage potential side effects.

6. Conclusion

This case series demonstrates the superior efficacy of pramipexole over aripiprazole as an augmentation therapy in treatment-resistant depression (TRD). Both patients, Mr. T and Ms. R, showed greater improvements in depressive symptoms and overall functioning with pramipexole. Significant reductions in Hamilton Depression Rating Scale (HDRS), Clinical Global Impression-Severity (CGI-S), and Beck Depression Inventory (BDI) scores underscore pramipexole's potent antidepressant effects. Mr. T experienced marked improvement after switching from aripiprazole to pramipexole, and Ms. R had substantial symptom relief and enhanced functioning during her initial pramipexole treatment compared to aripiprazole. These findings suggest pramipexole may be a more effective augmentation agent for managing TRD, providing significant benefits without notable adverse effects [20]. While individual responses can vary, and careful monitoring is essential, pramipexole could be considered a preferred option for patients who do not respond adequately to standard antidepressant therapies [21]. Further studies are needed to confirm these results and better understand the long-term efficacy and safety of pramipexole and aripiprazole in TRD.

References

1. Souery, D., Papakostas, G. I., & Trivedi, M. H. (2006). Treatment-resistant depression. *Journal of Clinical Psychiatry, 67*, 16.
2. Gaynes, B. N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., ... & Lohr, K. N. (2020). Defining treatment-resistant depression. *Depression and anxiety, 37*(2), 134-145.
3. Fava, M. (2003). Diagnosis and definition of treatment-resistant depression. *Biological psychiatry, 53*(8), 649-659.
4. Cusin, C., Iovieno, N., Iosifescu, D. V., Nierenberg, A. A.,

Fava, M., Rush, A. J., & Perlis, R. H. (2013). A randomized, double-blind, placebo-controlled trial of pramipexole augmentation in treatment-resistant major depressive disorder. *The Journal of clinical psychiatry, 74*(7), 16792.

5. Barbee, J. G., Conrad, E. J., & J. JAMHOUR, N. O. W. A. L. (2004). Aripiprazole augmentation in treatment-resistant depression. *Annals of Clinical Psychiatry, 16*(4), 189-194.

6. Bennett Jr, J. P., & Piercey, M. F. (1999). Pramipexole—a new dopamine agonist for the treatment of Parkinson's disease. *Journal of the neurological sciences, 163*(1), 25-31.

7. Aiken, C. B. (2007). Pramipexole in psychiatry: a systematic review of the literature. *Journal of Clinical Psychiatry, 68*(8), 1230-1236.

8. Barbee, James G., Erich J. Conrad, and N. O. W. A. L. J. JAMHOUR. "Aripiprazole augmentation in treatment-resistant depression." Annals of Clinical Psychiatry 16, no. 4 (2004): 189-194.

9. Philip, N. S., Carpenter, L. L., Tyrka, A. R., & Price, L. H. (2008). Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. *Journal of Psychiatric Practice®, 14*(1), 34-44.

10. Srisurapanont, M., Suttajit, S., Maneeton, N., & Maneeton, B. (2015). Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: a systematic review and meta-analysis of randomized-controlled trials. *Journal of Psychiatric Research, 62*, 38-47.

11. Hori, H., & Kunugi, H. (2012). The efficacy of pramipexole, a dopamine receptor agonist, as an adjunctive treatment in treatment-resistant depression: an open-label trial. *The scientific world journal, 2012*(1), 372474.

12. Zarate Jr, C. A., Payne, J. L., Singh, J., Quiroz, J. A., Luckenbaugh, D. A., Denicoff, K. D., ... & Manji, H. K. (2004). Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biological psychiatry, 56*(1), 54-60.

13. Sporn, J., Ghaemi, S. N., Sambur, M. R., Rankin, M. A., Recht, J., Sachs, G. S., ... & Fava, M. (2000). Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Annals of Clinical Psychiatry, 12,* 137-140.

14. Berk, M., Ng, F., Dodd, S., Callaly, T., Campbell, S., Bernardo, M., & Trauer, T. (2008). The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. *Journal of evaluation in clinical practice, 14*(6), 979-983.

15. Rabinowitz, J., Mehnert, A., & Eerdekens, M. (2006). To what extent do the PANSS and CGI-S overlap?. *Journal of Clinical Psychopharmacology, 26*(3), 303-307.

16. Forkmann, T., Scherer, A., Boecker, M., Pawelzik, M., Jostes, R., & Gauggel, S. (2011). The clinical global impression scale and the influence of patient or staff perspective on outcome. *BMC psychiatry, 11,* 1-7.

17. Lemke, M. R. (2008). Dopamine agonists in the treatment of non-motor symptoms of Parkinson's disease: depression. *European Journal of Neurology, 15*, 9-14.

18. Lemke, M. R. (2008). Depressive symptoms in Parkinson's disease. *European Journal of neurology, 15*, 21-25.

19. Ataíde, M., Franco, C. M. R., & Lins, O. G. (2014). Daytime Sleepiness in Parkinson′s Disease: Perception, Influence of Drugs, and Mood Disorder. *Sleep disorders, 2014*(1), 939713.

20. Pae, C. U. (2014). Pramipexole augmentation in treatment-resistant major depressive disorder. *Expert review of neurotherapeutics, 14*(1), 5-8.

21. Tundo, A., Betro', S., de Filippis, R., Marchetti, F., Nacca, D., Necci, R., & Iommi, M. (2023). Pramipexole augmentation for treatment-resistant Unipolar and bipolar depression in the real world: A systematic review and meta-analysis. *Life, 13*(4), 1043.