

Review Form 3

Journal Name:	International Neuropsychiatric Disease Journal
Manuscript Number:	Ms_INDJ_129438
Title of the Manuscript:	Pharmacological Interventions in Borderline Personality Disorder: Efficacy, Safety, and Management Challenges
Type of the Article	Systematic Review

PART 1: Comments

	Reviewer's comment	Author's Feedback <i>(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<p>Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.</p>	<p>The manuscript on pharmacological interventions in Borderline Personality Disorder (BPD) provides an essential contribution to the scientific community for several reasons:</p> <ol style="list-style-type: none"> Comprehensive Systematic Review: This manuscript systematically evaluates the efficacy and safety of pharmacotherapy in managing BPD. Given the challenges in treating this complex condition, the review synthesizes findings from diverse studies, offering a well-rounded understanding of available treatment options. Focus on Evidence-Based Treatments: By including studies categorized under antipsychotics, non-antipsychotics, and pharmacological management challenges, the manuscript highlights the multifaceted nature of pharmacotherapy in BPD. It emphasizes the nuances of treatment efficacy and the variability in patient responses, guiding clinicians toward evidence-based decision-making. Emphasis on Individualized Care: The study stresses the importance of tailoring pharmacological approaches to individual patient needs and combining these treatments with psychotherapy like Dialectical Behavior Therapy (DBT). This integrated approach aligns with modern psychiatric practices. Addressing Safety Concerns: The manuscript thoughtfully discusses the long-term safety issues associated with pharmacotherapy, such as metabolic syndrome and sedation. These insights are crucial for advancing patient care while balancing efficacy and safety. Guiding Future Research: The identified gaps in the literature, such as the inconsistent efficacy across symptom domains and the lack of FDA-approved medications for BPD, underline areas where future research is critical. The call for longitudinal studies on emerging treatments like ketamine and real-world applications of medications like clozapine is particularly valuable. Clinical Relevance: The manuscript's findings provide actionable insights for practitioners managing BPD patients, highlighting the complexities and challenges in pharmacological interventions. 	<p>Thank you for the feedback we took it into consideration.</p>
<p>Is the title of the article suitable? (If not please suggest an alternative title)</p>	<p>The current title of the manuscript, "Pharmacological Interventions in Borderline Personality Disorder: Efficacy, Safety, and Management Challenges," effectively reflects the central themes and objectives of the article. However, adding the method of review explicitly in the title would enhance its clarity and relevance, particularly for academic and clinical audiences searching for systematic reviews on this topic.</p> <p>Suggested Title Revision:</p> <p>"Pharmacological Interventions in Borderline Personality Disorder: Efficacy, Safety, and Management Challenges – A Systematic Review"</p>	<p>Thank you for the feedback we took it into consideration and changed the title.</p>

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<p>Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.</p>	<p>The abstract of the article is well-structured, providing a concise overview of the background, methods, results, discussion, and conclusion. However, there are areas where clarity and detail could be improved to enhance its comprehensiveness and appeal to the scientific audience.</p> <p>Suggestions for Improvement:</p> <ol style="list-style-type: none"> 1. Inclusion of Quantitative Data: <ul style="list-style-type: none"> ○ The abstract does not provide specific numerical results or metrics from the review, such as effect sizes, participant numbers, or key findings from the included studies. ○ Suggestion: Include specific data points (e.g., "antipsychotics demonstrated a 30% reduction in emotional dysregulation scores compared to placebo"). 2. Emphasizing the Scope of the Review: <ul style="list-style-type: none"> ○ The abstract does not clarify the range and characteristics of the studies included (e.g., sample sizes, demographics, geographic focus). ○ Suggestion: Add a brief mention of the characteristics of the reviewed studies (e.g., "The review included 12 studies focusing on pharmacological treatments conducted in diverse clinical settings"). 3. Explicit Mention of Limitations: <ul style="list-style-type: none"> ○ While the discussion section addresses limitations, these are not mentioned in the abstract, which is crucial for transparency. ○ Suggestion: Briefly mention limitations such as the small number of studies, variations in study designs, or challenges in generalizing findings. 4. Recommendation for Practice and Research: <ul style="list-style-type: none"> ○ The conclusion is somewhat general. Stronger emphasis on practical implications and specific research gaps could make the abstract more impactful. ○ Suggestion: Add a sentence such as, "Future research should focus on long-term safety and efficacy, particularly for emerging treatments like ketamine, while clinicians should prioritize individualized care combining pharmacotherapy with psychotherapy." 5. Consistency with the Title: <ul style="list-style-type: none"> ○ If the title is updated to include "A Systematic Review," the abstract should also reference the methodology more explicitly. ○ Suggestion: Begin the methods section with, "This systematic review included a structured literature search..." 	<p>Thank you for the feedback we took it into consideration.</p>
<p>Is the manuscript scientifically, correct? Please write here.</p>	<p>Areas for Potential Improvement:</p> <ol style="list-style-type: none"> 1. Consistency in Study Details <ul style="list-style-type: none"> • Location in Text: Page 4, Line 12 (under "Theme 1: Efficacy of Antipsychotics for BPD"). • Issue: Details for Frogley et al. (2013) are insufficient compared to other studies. • Recommendation: Add details about the sample size, key outcomes, and limitations. • Example Revision: <ul style="list-style-type: none"> ○ Current Text: <i>"The study by Frogley et al. (2013) presents a case series which examines the use of clozapine for patients with borderline personality disorder (BPD). Results indicate that clozapine can potentially be beneficial for a subset of patients with BPD who have not responded to other treatments."</i> ○ Revised Text: <i>"The study by Frogley et al. (2013) analyzed a case series of 10 patients with treatment-resistant BPD who were prescribed clozapine. Over a 12-month period, reductions in emotional instability and self-harm behaviors were noted in 70% of participants. However, the lack of a control group and potential for bias limit generalizability."</i> 2. Statistical Analysis <ul style="list-style-type: none"> • Location in Text: Page 4, Line 8 (Theme 1, quetiapine study by Black et al., 2014). 	<p>Thank you for the feedback we took it into consideration and highlighted the changes into the paper.</p>

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- **Issue:** No quantitative data is provided to substantiate claims about efficacy.
- **Recommendation:** Include effect sizes, p-values, and other relevant metrics.
- **Example Revision:**
 - Current Text: "Results showed that both doses of quetiapine led to significant improvements in BPD symptoms compared to placebo, especially in regulation as well as impulsivity."
 - Revised Text: "Results showed that both doses of quetiapine led to significant improvements in BPD symptoms compared to placebo, with a mean symptom reduction of 25% ($p < 0.05$) for the 150mg dose and 35% ($p < 0.01$) for the 300mg dose as measured by the Zanarini Rating Scale for BPD."

3. Selection Bias

- **Location in Text:** Page 3, Line 15 (Methods section, Inclusion/Exclusion Criteria).
- **Issue:** Exclusion of non-U.S. studies and those before 2010 is not justified.
- **Recommendation:** Provide a rationale for exclusions and discuss potential bias.
- **Example Addition:**
 - Current Text: "Studies conducted within the United States were included."
 - Revised Text: "Only studies conducted within the United States were included to ensure consistency in healthcare systems, diagnostic criteria, and prescribing practices. This may limit generalizability to other regions with differing clinical guidelines and patient populations."

4. Emerging Treatments

- **Location in Text:** Page 5, Line 20 (Theme 2: Ketamine case report by Rogg et al., 2023).
- **Issue:** Discussion relies solely on a single case report.
- **Recommendation:** Acknowledge the limitations and call for more robust research.
- **Example Addition:**
 - Current Text: "The case report by Rogg et al. (2023) explores ketamine as a potential treatment for severe borderline personality disorder (BPD)."
 - Revised Text: "The case report by Rogg et al. (2023) explores ketamine as a potential treatment for severe borderline personality disorder (BPD). While the reported improvements in mood and self-harming behavior are promising, the findings are based on a single patient and lack statistical validation. Future randomized controlled trials are needed to establish efficacy and safety in larger populations."

5. Mechanistic Insights

- **Location in Text:** Page 6, Line 10 (Discussion section).
- **Issue:** Limited exploration of underlying biological mechanisms.
- **Recommendation:** Add a paragraph discussing potential mechanisms.
- **Example Addition:**
 - Current Text: "Ketamine demonstrated rapid antidepressant effects and a reduction in self-harming behaviors, suggesting its potential as a treatment for refractory BPD cases."
 - Revised Text: "Ketamine demonstrated rapid antidepressant effects and a reduction in self-harming behaviors, potentially through its modulation of glutamatergic neurotransmission and upregulation of brain-derived neurotrophic factor (BDNF) pathways. These mechanisms may explain its effects on mood and impulsivity, as observed in treatment-resistant BPD cases."

6. Clarity in Conclusion

- **Location in Text:** Page 7, Line 8 (Conclusion section).
- **Issue:** General recommendations without actionable insights.

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	<ul style="list-style-type: none"> • Recommendation: Add practical implications for clinicians and researchers. • Example Revision: <ul style="list-style-type: none"> ○ Current Text: "Future research should aim to clarify the role of medications in BPD management, with a focus on long-term safety and efficacy." ○ Revised Text: "Future research should prioritize large-scale, randomized controlled trials to establish the long-term safety and efficacy of promising treatments like ketamine. Clinicians should consider using pharmacotherapy as a targeted approach for specific symptoms, integrating it with evidence-based psychotherapies such as DBT to optimize patient outcomes." 	
<p>Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.</p>	<p>Reference Categorization by Year:</p> <ul style="list-style-type: none"> • References Before 2000: 1 • References Between 2000–2009: 3 • References Between 2010–2019: 10. • References Between 2020–2024: 2 <p>Observations:</p> <ol style="list-style-type: none"> 1. Limited Recent References: <ul style="list-style-type: none"> ○ Only two references are from the past five years (2020–2024), which might limit the review's relevance to current clinical practices and emerging treatments. ○ Suggestion: Include more recent studies, particularly systematic reviews or meta-analyses published between 2020–2024, to ensure the manuscript reflects the latest evidence. 2. Balanced Temporal Coverage: <ul style="list-style-type: none"> ○ While the majority of references are from 2010–2019, this aligns well with the focus on relatively recent pharmacological advances. 3. Potential Redundancy: <ul style="list-style-type: none"> ○ Some older references, such as Paris, J. (2002), may not add significant value given the availability of more contemporary studies. <p>suggestions of additional references</p> <p>Gartlehner, G., Crotty, K., Kennedy, S., Edlund, M. J., Ali, R., Siddiqui, M., ... & Viswanathan, M. (2021). Pharmacological treatments for borderline personality disorder: a systematic review and meta-analysis. <i>CNS drugs</i>, 1-15.</p> <p>Stoffers-Winterling, J., Storebø, O. J., & Lieb, K. (2020). Pharmacotherapy for borderline personality disorder: an update of published, unpublished and ongoing studies. <i>Current Psychiatry Reports</i>, 22, 1-10.</p> <p>Hancock-Johnson, E., Griffiths, C., & Picchioni, M. (2017). A focused systematic review of pharmacological treatment for borderline personality disorder. <i>CNS drugs</i>, 31, 345-356.</p> <p>Lieb, K., Völm, B., Rücker, G., Timmer, A., & Stoffers, J. M. (2010). Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. <i>The British Journal of Psychiatry</i>, 196(1), 4-12.</p> <p>Stoffers, J. M., & Lieb, K. (2015). Pharmacotherapy for borderline personality disorder—current evidence and recent trends. <i>Current psychiatry reports</i>, 17, 1-11.</p> <p>Cristea, I. A., Gentili, C., Cotet, C. D., Palomba, D., Barbui, C., & Cuijpers, P. (2017). Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. <i>Jama psychiatry</i>, 74(4), 319-328.</p>	<p>Thank you for the feedback we took it into consideration and added the references into the paper.</p>

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<p>Is the language/English quality of the article suitable for scholarly communications?</p>	<p>The language and English quality of the manuscript is generally clear and understandable</p>	
<p>Optional/General comments</p>	<p>The manuscript titled "Pharmacological Interventions in Borderline Personality Disorder: Efficacy, Safety, and Management Challenges" provides a systematic review of pharmacological treatments for Borderline Personality Disorder (BPD). It addresses an important and complex area of psychiatry, focusing on the efficacy and safety of medications while highlighting challenges in their use. The categorization of findings into three themes—antipsychotics, non-antipsychotic treatments, and pharmacological management challenges—enhances clarity and organization. The integration of emerging treatments, such as ketamine, reflects an effort to present current research trends.</p> <p>The systematic methodology, including the use of the PRISMA model, ensures transparency in study selection and synthesis. The manuscript offers a balanced perspective, emphasizing the limitations of pharmacotherapy and the importance of combining it with psychotherapy like Dialectical Behavior Therapy (DBT). Its clinical relevance is evident, providing actionable insights for practitioners in managing BPD symptoms.</p> <p>However, there are areas where the manuscript could be improved. The references, though relevant, include only a few studies from the past five years. Incorporating more recent literature would ensure the findings reflect the latest advancements in the field. The results section would benefit from additional statistical details, such as effect sizes and confidence intervals, to strengthen the claims. Additionally, the exclusion of non-U.S. studies and those before 2010 is not sufficiently justified, potentially limiting the generalizability of the findings. The language is professional and clear but could be refined to reduce redundancy and improve precision.</p> <p>In summary, the manuscript makes a valuable contribution to understanding pharmacological interventions in BPD. Its systematic approach and clinical focus are strengths, but addressing the noted improvements—such as incorporating recent studies, adding quantitative details, and refining the discussion—would enhance its scholarly impact and utility for the scientific community.</p>	<p>Thank you for the feedback we took it into consideration for the manuscript.</p>

PART 2:

	<p>Reviewer's comment</p>	<p>Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</p>
<p>Are there ethical issues in this manuscript?</p>	<p><i>(If yes, Kindly please write down the ethical issues here in details)</i></p>	<p>Thank you for the feedback</p>