A Systematic Review on Pharmacological Interventions in Borderline Personality Disorder: Efficacy, Safety, and Management Challenges

Abstract

Background: Borderline Personality Disorder (BPD) is a complex psychiatric condition characterized by emotional instability, impulsivity, and interpersonal difficulties. Pharmacotherapy is commonly used in addition to psychotherapy to manage specific symptom domains of BPD. This systematic review aims to evaluate the safety and efficacy of pharmacological interventions in BPD.

Methods: A systematic literature search was conducted using Ovid Medline. The initial search identified 1,689 papers, which were screened based on relevance to the topic, resulting in 12 studies that met the inclusion criteria. The final 12 articles were grouped into three overarching themes: the efficacy of antipsychotics, the effectiveness of non-antipsychotic treatments, and challenges in pharmacological management.

Results: The review revealed mixed outcomes for pharmacotherapy in BPD. Antipsychotics showed some efficacy in reducing emotional dysregulation and impulsivity, though side effects were noted. Non-antipsychotic treatments, including lamotrigine, showed limited efficacy, while ketamine showed potential effectiveness

for refractory cases. Challenges in pharmacological management were prominent.

Discussion: Pharmacotherapy can play a role in symptom management for BPD, especially for severe cases unresponsive to psychotherapy alone. However, the evidence remains inconsistent, and no medication has demonstrated comprehensive efficacy across all symptom domains.

Conclusion: Pharmacological interventions for BPD offer symptom relief for certain patients, particularly with antipsychotics. However, due to the inconsistent evidence and concerns about long-term safety, pharmacotherapy should be carefully individualized and combined with psychotherapy.

Keywords: Pharmacotherapy; BPD; Efficacy; Psychiatry; Management

Introduction

Borderline Personality Disorder (BPD) is a pervasive psychiatric condition, characterized by emotional dysregulation, impulsivity, unstable relationships, and identity disturbance. It affects approximately 1-2% of the general population, with estimates as high as 10-20% in psychiatric inpatient settings, representing a significant public health concern [1,2]. BPD is associated with elevated rates of comorbidity, particularly with mood disorders, substance use disorders, and other personality disorders, and is a leading cause of suicide, with up to 10% of affected individuals dying by suicide [3,4].

While psychotherapy, particularly Dialectical Behavior Therapy (DBT), remains the cornerstone of treatment for BPD [5], pharmacotherapy is often used adjunctively to manage specific symptom domains such as affective instability, impulsivity, and cognitive-perceptual disturbances [6]. Commonly prescribed medications include antidepressants, mood stabilizers, and antipsychotics, although none are specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of BPD [7]. Recent systematic reviews highlight the ongoing debate regarding the efficacy of these pharmacological interventions, noting variable outcomes and the lack of robust evidence supporting a universal pharmacological approach to BPD management [8, 9]. Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to target mood instability, while atypical antipsychotics and mood stabilizers are often used for impulsivity and aggression [10].

Despite the widespread use of pharmacological treatments in BPD, the evidence for their efficacy remains inconclusive [11,12,13]. Meta-analyses and updated systematic reviews continue to emphasize the importance of targeting specific symptoms rather than seeking global efficacy in pharmacotherapy for BPD [8, 14]. A systematic review by Stoffers et al. (2010) found that while second-generation antipsychotics, mood stabilizers, and omega-3 fatty acids may reduce some BPD symptoms, the overall effect sizes were small, and the benefits were primarily seen in individual symptom domains rather than in global functioning [10]. Furthermore, concerns about the long-term safety of these medications, particularly considering potential adverse effects such as metabolic syndrome, weight gain, and sedation, have raised questions about their appropriate use [2,7]. These concerns are echoed in recent studies, which have identified both emerging treatment trends and challenges in balancing efficacy with tolerability [15, 16].

Given these limitations, this systematic review aims to evaluate the current literature on the safety and efficacy of pharmacological treatments for BPD. By synthesizing available evidence, we hope to provide clearer guidance for clinicians on which pharmacological interventions offer the most benefit in symptom management while considering the risks associated with long-term medication use.

Methods

The search was conducted using the Ovid Medline and the search words were created using boolean operators. The search words used were “Borderline Personality Disorder/ or (borderline adj2 personalit*),” “Drug Therapy/ or (drug* or pharmacotherap* or pharmacologic* or medication*).” The Ovid Medline resulted in 1689 papers. All subsequent literature was collected, and a total of 45 duplicates was removed, resulting in 1644 articles eligible to be screened. The initial screen was based on the papers’ relevance to the topic. Papers were removed if they were not about the topic we were researching, efficacy of pharmacotherapy of patients with BPD. After the initial review, 387 papers were left for review, 18 of which were not retrieved. The remaining 369 articles were reviewed and assessed based on our inclusion and exclusion criteria. Our inclusion criteria included any studies exploring the efficacy and safety of pharmacotherapy to treat BPD and conducted within the United States, 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. Exclusion criteria included papers that were from 2010 or earlier (63 articles excluded), did not focus on pharmacotherapy (79 papers excluded), focused solely on side effects (5 papers excluded), were gender specific (23 papers excluded), were not in English (2 papers excluded), were not conducted in the United States (144), were a review or meta-analysis (17 papers excluded), were not BPD specific (9 papers excluded), or included comorbidities such as suicidality, medical conditions (Ehlers Danlos), and psychiatric, mood, and other personality

disorders (Attention-deficit/hyperactivity disorder (ADHD), Bipolar Disorder, Generalize Anxiety Disorder (GAD), Post Traumatic Stress Disorder (PTSD), Dysthymia, Narcissistic Personality Disorder, and Depression, 16 papers excluded). This review led to a final number of n=11 papers that fit both the inclusion and exclusion criteria. The articles were consolidated, and limitations and potential future research were assessed, discussed, and recorded. Figure 1 shows a visual representation of the paper and data collection discussed here, using the PRISMA model.

Results

A total of 12 papers were included in the systematic review that fit the inclusion criteria. The studies all discussed the safety and efficacy of pharmacotherapy for use in BPD. The research highlights the challenges of managing BPD symptoms such as emotional instability, impulsivity, and self-harming behaviors, and explores a variety of pharmacological approaches ranging from antipsychotics to mood stabilizers and emerging treatments. While medications play a role in symptom control, many studies emphasize the need for individualized treatment plans and the integration of psychotherapy to optimize outcomes.

Below, the 12 articles are categorized into three themes, each representing the primary

focus of the included studies. Theme 1: Efficacy of Antipsychotics for BPD includes six articles that discuss the efficacy and safety of antipsychotics. Theme 2: Effectiveness of Non-Antipsychotic Pharmacological Treatments includes two articles that investigate effectiveness of specific pharmacological options. Theme 3: Pharmacological Management and Treatment Challenges consists of four articles examining the prescribing trends, challenges, and the common practice of treating BPD.

Theme 1: Efficacy of Antipsychotics for BPD

Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial

The study by Black et al. (2014) examines the effectiveness of both low and moderate doses of extended-release quetiapine in the treatment of borderline personality disorder (BPD). This randomized, double-blind, placebo-controlled trial targeted the efficacy of quetiapine, an atypical antipsychotic, in dealing with the emotional dysregulation, impulsivity, and interpersonal difficulties characteristics of BPD. Ninety-five adult participants that were diagnosed with BPD were randomly assigned to receive either a low dose (150mg/day) or a moderate dose of (300mg/day) of extended-release quetiapine, or a placebo for eight weeks. The main outcome measured was a change in the severity of BPD symptoms utilizing the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). Secondary outcomes included assessments of mood, anxiety, and overall functioning. 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. However, the moderate dose of extended-release quetiapine was associated with a slight increase in side effects such as sedation and weight gain. The study concludes that extended-release quetiapine, particularly at a low dose, may be an applicable treatment option for BPD, offering symptom relief with a tolerable side effect profile. However, the authors caution that further research is needed to confirm these findings within longer-term studies and larger populations [17].

A case series of clozapine for borderline personality disorder

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.[18].

Quetiapine's effect on the SCL-90-R domains in patients with borderline personality disorder

The study by Lee et al. (2016) investigates the effect of quetiapine on the Symptom Checklist-90-revised (SCL-90—R) domains in patients diagnosed with borderline personality disorder (BPD). Quetiapine, an atypical antipsychotic, was administered to assess its impact on multiple psychological symptoms associated with BPD, such

as interpersonal sensitivity, depression, as well as anxiety. Findings show that quetiapine significantly reduce scores across multiple SCL-90-R domains, showing improvements in mood anxiety, and general psychopathology. The study indicated that quetiapine may be beneficial in relieving core symptoms of BPD [19].

Randomized controlled trials of olanzapine treatment of borderline personality disorder: two similar studies with different results

The article by H. George Nurnberg (2011) covers two randomized controlled trials evaluating the usage of olanzapine for treating borderline personality disorder (BPD), which produced conflicting results. While one study showed significant symptom improvement in BPD patients treated with olanzapine, the other demonstrated no meaningful differences between olanzapine and placebo groups. The commentary searches for potential reasons for these discrepancies, such as variations in the study design, dosing, and patient populations, and highlight the complexities of using antipsychotic like olanzapine in bpd treatment [20].

Open-label treatment with olanzapine for patients with borderline personality disorder

The study by Zanarini et al. (2012) investigates the effects of open-label olanzapine treatment in patients with borderline personality disorder (BPD). The research focused on the safety and efficacy of olanzapine throughout a twelve-week period for reducing BPD symptoms such as affective instability, impulsivity, and interpersonal issues. Results showed a significant improvement in symptom severity, with patients

responding well to olanzapine. However, weight gain was noted as a side effect, warranting careful monitoring. The study suggest that olanzapine may be a viable option for BPD symptom management [21].

Theme 2: Effectiveness of Non-Antipsychotic Pharmacological Treatments

The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial.

This randomized placebo-controlled study investigated the clinical and cost-effectiveness of lamotrigine for borderline personality disorder (BPD). Despite the theoretical interest of mood stabilizers such as lamotrigine for managing mood dysregulation in BPD, the study found no significant differences between the lamotrigine and the placebo groups in reduced symptoms or life quality improvement over the course of fifty-two weeks. These results suggest that lamotrigine may not be an effective treatment for BPD [22].

Ketamine as a Treatment Option for Severe Borderline Personality Disorder: A Case Report

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. The study details the case of a

patient with BPD who demonstrated significant symptom improvement, specifically in mood and self-harming behavior, following ketamine administration. The authors talk through the possible mechanisms behind ketamine's rapid antidepressant effects and its potential role in treating refractory BPD symptoms. The need for further research is emphasized to evaluate efficacy and safety in a broader BDP population [23].

Theme 3: Pharmacological Management and Treatment Challenges

Case Study Application for Psychopharmacology With Borderline Personality Disorder

The article by Barbara J. Limandri (2018) presents a case study that focuses on psychopharmacological treatment of borderline personality disorder (BPD). It investigates the challenges clinicians encounter when prescribing medications for BPD, given the disorder's complex symptoms like emotional dysregulation and impulsivity. Individualized treatment plans may optimize outcomes, balancing the usage of mood stabilizers, antipsychotics, and antidepressants to target specific symptoms. The case study highlights the importance of comprehensive care, including psychotherapy, to enhance the efficacy of medication [24].

Changes over the last 15 years in the psychopharmacological management of persons with borderline personality disorder

The study by Martin-Blanco et al. (2017) examines changes in the

psychopharmacological management of borderline personality disorder (BPD) throughout the last fifteen years. Obtaining data from a cohort of BPD patients, researchers highlight trends in prescribing practices, indicating the increased usage of atypical antipsychotics and mood stabilizers, while the use of antidepressants declined. The study suggests that the increased of BPD's neurobiology has influenced these shifts in treatments, although it emphasizes the for continuous research to determine the most effective pharmacological interventions for BPD [25].

Psychotropic medication use in hospitalized patients with borderline personality disorder

The article by Moeller et al. (2016) examines the use of psychotropic medications in hospitalized patients that are diagnosed with borderline personality disorder (BPD). The study emphasizes the patterns of medication usage, including antipsychotics, mood stabilizers, antidepressants, and anxiolytics, and assess how these medications address the main symptoms of BPD, such as emotional instability impulsivity, and aggression. Findings suggest polypharmacy is common in this population with many patients receiving multiple psychotropic drugs, despite the limited amount of evidence supporting their efficacy for treatment of BPD [26].

Real-World Effectiveness of Clozapine for Borderline Personality Disorder: Results From a 2-Year Mirror-Image Study

The study by Rohde et al. (2018) examines the real-world effectiveness of clozapine

for patients with borderline personality disorder (BPD) utilizing a 2-year-mirror-image-design. Researchers compared clinical outcomes, including hospitalization rates and symptom severity, before and after beginning clozapine treatment. Results indicated significant improvements in lowering hospitalization and managing severe symptoms such as impulsivity as well as emotional dysregulation, indicating that clozapine can be a viable option for severe, treatment-resistant BPD cases. Although, the study calls for further research to solidify these findings [27].

Discussion

This systematic review provides a comprehensive overview of the current pharmacological approaches used in the management of BPD. The findings reinforce the view that pharmacotherapy, while commonly utilized in clinical practice, presents a mixed efficacy profile in treating the core symptoms of BPD. This observation aligns with meta-analytic evidence showing inconsistent results across studies, with certain pharmacological agents providing modest benefits in limited symptom domains [8, 9]. The articles included in the review showed evidence supporting the fact that the use of medications remains focused on individual symptom control rather than broad improvements in overall functioning.

The efficacy of atypical antipsychotics, such as clozapine, quetiapine, and olanzapine,

was demonstrated across multiple studies included in this review [17,18,19,20,21,22]. Low-dose clozapine and quetiapine were shown to offer some benefit, particularly in addressing emotional dysregulation and impulsivity. Concerns regarding side effects, such as weight gain, sedation, and the long-term safety profile of these medications present potential challenges [17,19]. However, systematic reviews emphasize that the efficacy of antipsychotics remains limited to individual symptom clusters rather than comprehensive symptom improvement [14, 15].

Lamotrigine showed no significant impact on BPD symptoms in a randomized controlled trial [23]. 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 [24]. However, despite some effectiveness, there is a need for more research into these pharmacotherapies for the treatment of BPD.

One of the most notable findings from this review is the challenge of managing BPD pharmacologically [27]. In addition, the emphasis on individualized treatment plans highlights the importance of combining pharmacotherapy with psychotherapy, especially Dialectical Behavior Therapy (DBT). The findings of our review are similar to earlier systematic reviews, which stressed the fragmented nature of

pharmacological evidence for BPD and the limited applicability of existing randomized trials to clinical practice [28]. Emerging evidence suggests that future research should prioritize integrated approaches combining pharmacological and psychotherapeutic interventions, particularly for addressing refractory symptoms and treatment-resistant cases [16, 29].

Conclusion

This review presents the limitations and benefits of pharmacological treatments for BPD. While this review showed that some pharmacological options may be effective, the evidence is limited, and no medication is universally effective. 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.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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Figure 1. PRISMA Model Data Collection