A Systematic Review: Pharmacological Treatment of Borderline Personality Disorder

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

Signature of the Students

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Approval

The thesis titled “Pharmacological Treatment of Borderline Personality Disorder: A Systematic Review” submitted by Md. Arafat Rahman (22346060) of Spring, 2026, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on June 11, 2026 .

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Ethics Statement

There is no involvement of animal or human trials in this project.

Abstract

Borderline personality disorder (BPD) is characterised by marked instability of mood, recurrent impulsive acts, a poorly consolidated sense of self, and chronic interpersonal dysfunction. Evidence-based psychotherapies, mainly dialectical behaviour therapy (DBT) and mentalization-based treatment (MBT) form the backbone of treatment, yet pharmacological agents are frequently co-prescribed to target affective dysregulation, impulsivity, and aggression. No single agent holds regulatory approval for BPD, and the evidence base underpinning current prescribing is limited and inconsistent. This review consolidates findings from 14 controlled trials conducted between 2011 and 2026, encompassing four pharmacological categories: second-generation antipsychotics, opioid receptor antagonists, mood-stabilising compounds, and a miscellaneous group comprising ketamine, psilocybin, omega-3 fatty acids, inhaled loxapine, oxytocin, and citalopram. Methodological rigour was assessed using the Cochrane Risk of Bias framework. Trial quality was predominantly low to moderate. Brexpiprazole and low-dose quetiapine yielded the most encouraging efficacy signals for core BPD pathology, whereas lamotrigine conferred no detectable benefit in the best-powered trial identified. Opioid antagonists showed preliminary signal for attenuating dissociative symptoms, and investigational agents such as ketamine and psilocybin warrant evaluation in larger, more rigorous studies. Well-powered, prospectively registered trials with harmonised outcome measures are urgently needed.

Keywords: borderline personality disorder, pharmacotherapy, systematic review, antipsychotics, mood stabilisers, opioid antagonists, randomised controlled trial, risk of bias.

Dedication

“Dedicated to my parents”

Acknowledgement

First and foremost, I would like to express my gratitude to the Almighty for his endless gifts and blessings, which have provided me with the strength and determination to complete this project.

It is my genuine pleasure to offer my heartfelt appreciation to my academic supervisor, Luluel Maknun Fariha (Senior Lecturer, School of Pharmacy, BRAC University), for her invaluable guidance and encouragement throughout this project. She has been a true source of advice and support, and her constructive comments and ideas were instrumental in completing this work in a timely manner.

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Chapter 1: Introduction

Borderline personality disorder (BPD) carries a rich and intricate clinical history. The term "borderline" entered the psychiatric vocabulary in the early twentieth century, attributed most notably to Adolf Stern (1938), who used it to describe patients whose presentations fell outside the established boundaries of neurosis and psychosis — occupying, in effect, a clinical no-man's land between (Stern, 1938).Earlier psychoanalytic writers had noted comparable presentations, though Stern's account is broadly credited as the first formal systematic conceptualisation. Otto Kernberg subsequently deepened the theoretical picture in the 1960s and 1970s, describing a distinctive borderline personality organisation anchored in identity diffusion, reliance on primitive defences, and persistently turbulent interpersonal relationships.

Formal diagnostic recognition came in 1980, when BPD was incorporated into the personality disorders chapter of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) (American Psychiatric Association, 2013). This represented a decisive transition from a purely psychoanalytic construct to an operationalised psychiatric diagnosis with explicit, empirically derived criteria (American Psychiatric Association, 2013). Subsequent revisions through DSM-IV and DSM-5 have refined but preserved the core diagnostic framework (American Psychiatric Association, 2013).

As of now, BPD is considered a known clinical mental disorder in the DSM-5-TR and the ICD-11 (Gunderson et al., 2018)It is categorized as a personality disorder with a dimensional approach to severity (Gunderson et al., 2018). Contemporary scholarship increasingly situates BPD within a biopsychosocial framework, highlighting the interplay of genetic vulnerability, neurobiological factors, and early adverse environments. The prognostic outlook for the condition has shifted markedly: rather than being viewed as intractable, BPD is now understood as a disorder amenable to intervention through evidence-based approaches such as DBT and MBT (Gunderson et al., 2018)

The aetiology of BPD is multifactorial, reflecting an interplay of genetic, neurobiological, and environmental influences(Gunderson et al., 2018). Twin and family studies suggest a substantial heritable component, with estimates commonly ranging from 40 to 60 percent, pointing to

inherited predispositions toward emotional dysregulation, impulsive behaviour, and interpersonal aggression (Gunderson et al., 2018)

Neurobiological abnormalities have also been seen, including dysfunction of the parts of the brain related to emotion regulation and impulse control like the amygdala, the prefrontal cortex and the hippocampus, alongside dysregulation of serotonergic neurotransmission — a system closely linked to impulse control and affective stability (Leichsenring et al., 2011)

Environmental factors such as childhood negative experiences, physical, sexual, and emotional abuse, neglect, parental loss, and poor attachment have been associated with the development of BPD (Ball & Links, 2009).Childhood trauma has been considered one of the most important risk factors of BPD because it interferes with the development of emotion regulation and social interactions(Ball & Links, 2009). Beyond discrete trauma, growing up in a context that systematically invalidates the child's emotional experience is associated with maladaptive coping and difficulty consolidating a stable sense of self(Crowell et al., 2009). This combination of biological vulnerability and environmental stressors constitutes the widely accepted model of BPD (Gunderson et al., 2018).

Population-based estimates place the lifetime prevalence of BPD at approximately 1.6%, though figures as high as 5.9% have been reported depending on the assessment method and sampling frame (American Psychiatric Association, 2013). Within clinical settings the disorder is substantially overrepresented: roughly one in ten psychiatric outpatients and approaching one in five inpatients meet diagnostic criteria, reflecting the burden of severe emotional dysregulation and the intensive service use that characterise the condition (Leichsenring et al., 2011).

Although there are many more diagnoses among women — nearly 75% of all clinical diagnoses are in women — research from the community suggests that the rate may be similar among men and women, which indicates a possible case of diagnostic bias in favour of women as well as treatment bias against men (Gunderson et al., 2018). It generally occurs during adolescence or early adulthood and significantly impacts the individual's social, occupational, and interpersonal functioning.

There are several psychotherapy methods used for the treatment of BPD focusing on improvement of emotion regulation, interpersonal skills, impulsivity, and decrease in self-harm behaviours (Gunderson et al., 2018) DBT, originally developed by Linehan, integrates cognitive-behavioural

techniques with mindfulness and acceptance-oriented principles to target the pervasive emotional dysregulation central to BPD (Linehan, 2015). Controlled trial evidence supports its effectiveness in curtailing suicidal acts, non-suicidal self-injurious behaviour, and rates of psychiatric admission among individuals with BPD (Linehan, 2015). Another approach widely used is Mentalization-Based Therapy (MBT), which assists patients to become more capable of comprehending their mental states and those of others (Bateman & Fonagy, 2019). Transference-Focused Psychotherapy (TFP) and Schema Therapy (ST) have similarly gained recognition for their durable benefits in restructuring dysfunctional personality patterns (Clarkin et al., 2007); Young et al., 2003).

Drug treatment in BPD serves an adjunctive rather than a primary role: no approved pharmacological agent exists for the core features of the disorder (Gunderson et al., 2018). Prevailing guidelines designate psychotherapy as the primary treatment modality, with medications reserved as targeted adjuncts for particular symptomatic presentations — including emotional dysregulation, impulsive and aggressive behaviour, anxiety, or co-occurring depressive conditions (Gunderson et al., 2018). SSRIs are frequently prescribed for mood and anxiety symptoms, yet evidence that they modify the fundamental pathology of BPD remains weak (Stoffers-Winterling, 2022). Contemporary guidance increasingly advocates minimising polypharmacy and curtailing prolonged use of benzodiazepines, which carry a recognised risk of worsening impulsive behaviour and increasing suicidality in this population (Gunderson et al., 2018).

The overarching aim of this review is to critically appraise available evidence from controlled trials examining pharmacological interventions for BPD published between 2011 and 2026. Chapter 2 outlines the search strategy and the databases consulted. Chapter 3 describes the criteria governing study eligibility and presents a quality assessment of the 14 included trials via the Cochrane Risk of Bias framework, together with an account of the outcome instruments used across studies; drug class-specific findings are reported in Sections 3.4 through 3.7. Chapter 4 integrates and contextualises these findings within a broader discussion, and Chapter 5 presents conclusions alongside their implications for clinical practice and future research directions.

Chapter 2: Methodology

2.1 Search Strategy

Searches were constructed using the following MeSH headings and free-text keywords:

Population (Borderline Personality Disorder): ("Borderline Personality Disorder"[MeSH] OR "borderline personality disorder" OR BPD OR "emotionally unstable personality disorder")

Intervention (Pharmacological Treatment / Drug Therapy): ("Drug Therapy"[MeSH] OR "Pharmacotherapy"[MeSH] OR "Pharmaceutical Preparations"[MeSH] OR drug OR drugs OR pharmacotherapy OR pharmacological OR pharmacologic* OR medication)

Study Design (Clinical Trials / Randomized Controlled Trials): ("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR randomized controlled trial OR RCT OR clinical trial OR treatment OR intervention)

Systematic searches were run in MEDLINE via PubMed and the Cochrane Central Register of Controlled Trials; ClinicalTrials.gov was also queried to identify registered and unpublished trial data. Filters restricting results to human studies and English-language publications were applied in all databases.

2.2 Inclusion Criteria

To qualify for inclusion, a study was required to fulfil each of the following conditions. With regard to design, only controlled trial formats were acceptable, covering double-blind, single-blind, open-label, crossover, and active-comparator configurations. For the study population, all participants had to carry a formally established BPD diagnosis verified against a recognised classificatory system — DSM-III, DSM-IV, DSM-5, ICD-10, or ICD-11; trials that also enrolled patients with additional psychiatric conditions remained eligible where BPD constituted the primary diagnosis or a clearly delineated subgroup. Only studies recruiting adults aged 18 or older were considered; trials limited exclusively to children or adolescents were not eligible. On the intervention side, studies had to evaluate a pharmacological agent whose primary purpose was the treatment of BPD or associated symptom domains such as affective dysregulation, impulsivity, dissociation, self-harm, aggression, or comorbid depressive and anxiety features; pharmacological

agents assessed as augmentation strategies in combination with an established psychotherapy or a concurrent pharmacological regimen were also eligible. No restriction was applied with respect to drug class, dosage, route of administration, or duration of treatment. Studies were required to report at least one pre-specified quantitative outcome measure, whether a validated clinician-rated scale, a self-report instrument, or a neuroimaging or biological endpoint, assessed at baseline and at one or more post-baseline time points. To ensure currency and relevance to contemporary clinical practice, studies were required to have been completed between the years 2011 and 2026. Only studies published in the English language were considered eligible for inclusion.

2.3 Exclusion Criteria

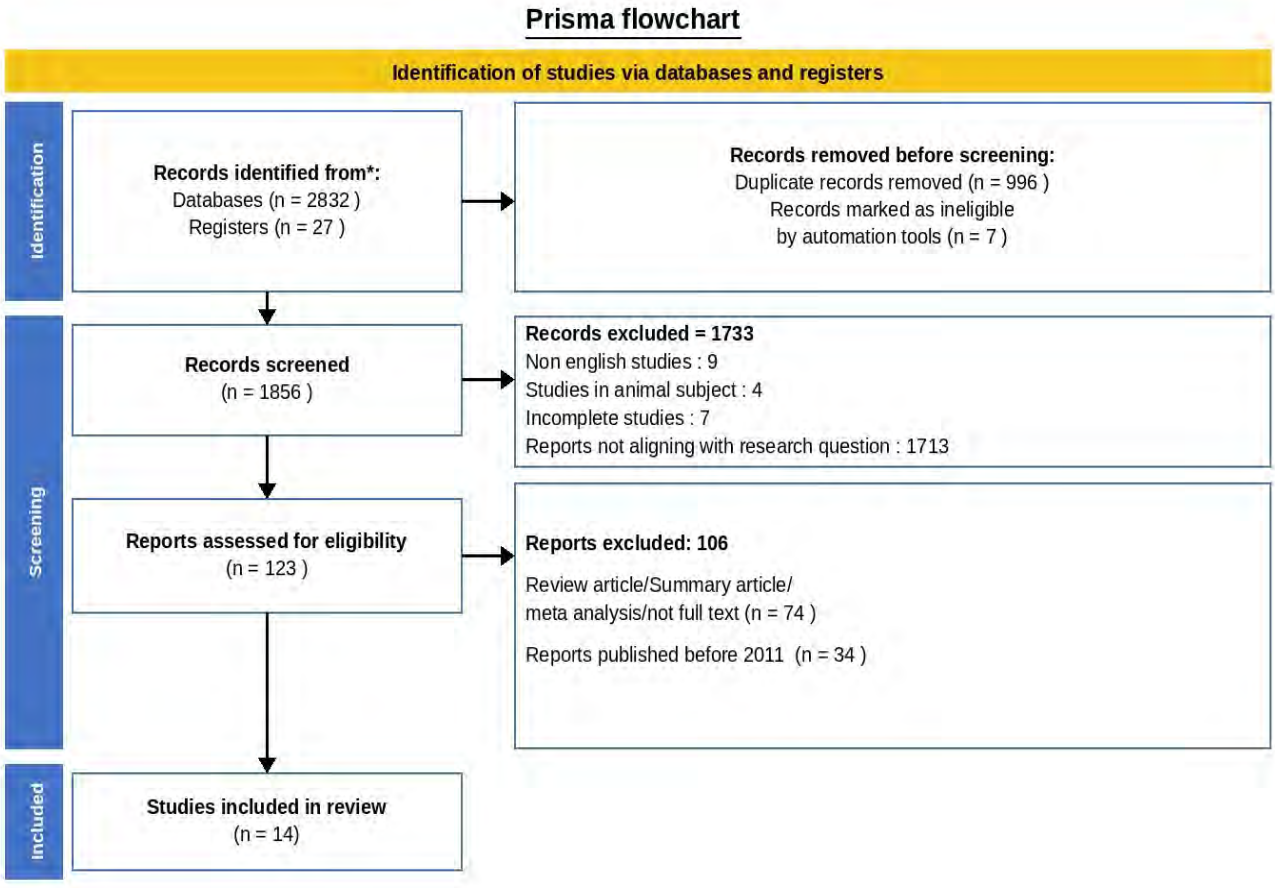
Any study that did not meet the inclusion requirements set out in Section 2.2 was excluded. In terms of design, non-randomised and observational approaches — comprising prospective cohorts, case-control studies, cross-sectional surveys, individual case reports, and case series — fell outside the review's scope. Evidence syntheses such as systematic reviews, meta-analyses, and scoping reviews were likewise excluded to avoid double-counting primary data. Publication formats that preclude adequate methodological appraisal — including editorials, letters, conference abstracts, poster presentations, and grey literature lacking accessible datasets — were also ineligible, as were studies conducted solely in non-human subjects. Regarding participant characteristics, trials in which BPD was neither the primary nor a co-primary diagnosis were excluded, along with those from which a clearly delineated BPD-specific subgroup could not be extracted; studies enrolling only individuals under 18 years of age were similarly ineligible. Trials in which the BPD diagnosis was not anchored to a recognised classificatory system (DSM-III, DSM-IV, DSM-5, ICD-10, or ICD-11) were also excluded. On the intervention side, studies in which pharmacotherapy was not the central experimental focus — including those where a drug formed only an incidental or uncontrolled component of a broader psychosocial programme — were not included; studies testing exclusively non-pharmacological approaches were excluded, as were trials evaluating benzodiazepines as a stand-alone BPD treatment, in view of both the lack of a credible evidence base and the documented hazard of worsening impulsivity and suicidal risk in this group. With respect to outcomes, studies that failed to report at least one quantitative efficacy measure assessed both at baseline and at a subsequent time point were excluded, as were those providing only pharmacokinetic or tolerability data in the absence of a validated clinical, self-report, or

neuroimaging outcome. Trials for which group-level summary statistics were unavailable were also not eligible. Finally, studies completed before 2011 or after 2026 were excluded, and only English-language publications were considered.

Chapter 3: Results

3.1 Figure 1: PRISMA Flowchart

Figure 1 displays the PRISMA 2020 flowchart illustrating how studies progressed through each selection stage. Initial searches across MEDLINE, the Cochrane Library, and ClinicalTrials.gov returned a combined total of 2,859 records. Following removal of 996 duplicate entries and a further 7 records flagged as ineligible by automated tools, 1,856 records advanced to title-and-abstract screening. After 1,733 of these were excluded, 123 reports underwent full-text review. A subsequent exclusion of 106 reports left 14 studies for inclusion in the final synthesis.



3.2 Risk of Bias Assessment

The methodological rigour of all 14 included studies was evaluated with the Cochrane Risk of Bias tool (versions RoB 1 and RoB 2 applied as appropriate to each design). Overall study quality ranged from low to moderate; not a single trial achieved unambiguously low risk across every assessed domain.

The LABILE lamotrigine trial (Crawford, 2018) was the only study rated overall low risk of bias. It employed web-based randomisation, robust allocation concealment, double-blinding with matched placebo, pre-registration, and an adequately powered sample (N=276). Its finding — that lamotrigine is ineffective for BPD — can therefore be interpreted with reasonable confidence. The quetiapine XR trial (Black et al., 2014) brexpiprazole trial (Grant et al., 2022) ketamine pilot (Fineberg et al., 2023), and citalopram fMRI study (Paret et al., 2021) were each rated some concerns, reflecting generally sound designs tempered by issues such as incomplete outcome data, potential rater unblinding, or small sample sizes.

Most of the remaining studies were judged to carry a high overall risk of bias. The divalproex ER pilot (Moen et al., 2012) was severely underpowered (N=15), had 40% attrition, and was commercially funded by the drug manufacturer. The oxytocin study (Maoz, 2024) was a non-pre-specified secondary subgroup analysis with non-randomised group comparisons and very small cell sizes, limiting its findings to hypothesis generation only. The retrospective naltrexone chart review (Timäus et al., 2021) lacked randomisation and blinding entirely, rendering its dramatically high odds ratios unreliable. The clozapine CALMED trial (Crawford, 2022) recruited only 13% of its target sample and experienced near-complete unblinding due to clozapine's distinctive side-effect profile. The psilocybin (Rosenblat, 2024), omega-3 (Bellino et al., 2014), and inhaled loxapine (Ferrer et al., 2022) studies were all open-label, making their clinician-rated outcomes particularly susceptible to expectancy bias.

Several methodological challenges recurred across studies. Large placebo responses were observed consistently, reflecting the well-documented sensitivity of BPD symptoms to structured clinical contact. Blinding was particularly difficult to maintain for agents with recognisable side-effect profiles, such as clozapine, quetiapine, and the psychedelic agents. Many trials were disrupted by COVID-19, further compromising recruitment and follow-up. Industry funding was

present in two trials (brexpiprazole — Otsuka; quetiapine — AstraZeneca), introducing an additional source of potential reporting bias.

Based on this risk-of-bias analysis, no pharmacological agent currently has unequivocal high-quality evidence supporting its use in BPD. Findings across the majority of trials must be regarded as exploratory or hypothesis-generating. Adequately powered, double-blind, active-comparator, pre-registered RCTs with standardised outcome measures are urgently needed before any agent can reliably inform clinical practice.

Table 1: Risk of Bias Summary Table

Study (Year)	D1 Rand.	D2 Alloc.	D3 Blind (Pt)	D4 Blind (Out)	D5 Inc. Data	D6 Sel. Rep.	D7 Other	Overall	Quality (%)
Moen et al. (2012)	?	?	?	?	−	?	−	−	36%
Crawford et al. (2018)	+	+	+	+	?	+	+	+	93%
Maoz et al. (2024)	+	?	+	?	−	?	−	−	50%
Timäus et al. (2021)	−	−	−	−	+	−	−	−	14%
Schmahl et al. (2012)	+	+	+	+	+	+	−	?	86%
Grant et al. (2022)	+	+	+	?	?	+	N/A	?	83%
Crawford et al. (2022)	+	+	+	−	−	+	N/A	−	67%
Shafti and Kaviani (2015)	?	N/A	−	−	+	?	N/A	−	40%
Black et al. (2014)	+	+	+	+	?	?	N/A	?	83%
Paret et al. (2021)	+	+	+	?	?	?	N/A	?	75%
Fineberg et al. (2023)	+	+	+	?	?	+	N/A	?	83%
Ferrer et al. (2022)	−	−	−	−	+	?	N/A	−	25%
Bellino et al. (2014)	?	−	−	−	?	?	N/A	−	25%
Rosenblat et al. (2024)	+	−	−	−	?	+	N/A	−	42%

Abbreviations: D1 Rand. = Domain 1: Randomisation Process; D2 Alloc. = Domain 2: Allocation Concealment; D3 Blind (Pt) = Domain 3: Blinding of Participants; D4 Blind (Out) = Domain 4: Blinding of Outcome Assessors; D5 Inc. Data = Domain 5: Incomplete Outcome Data; D6 Sel. Rep. = Domain 6: Selective Reporting; D7 Other = Domain 7: Other Sources of Bias; + = Low Risk; ? = Some Concerns; − = High Risk; N/A = Not Applicable.

3.3 Outcome Measures and Rating Scales

A heterogeneous array of validated instruments was used across the 14 included studies to quantify pharmacological efficacy in BPD. Familiarity with these tools is necessary for accurate interpretation of the evidence tables and for gauging the degree to which results from different trials can meaningfully be compared. The instruments described in this section served as primary or secondary outcome measures in at least one of the reviewed studies.

ZAN-BPD Scale : Administered by a trained clinician, the ZAN-BPD comprises nine items that quantify the severity of cardinal BPD features across four domains — affective, cognitive, impulsive, and interpersonal (Zanarini et al., 2003). Possible scores span from 0 to 36, where higher values denote more severe symptomatology. It was used as the primary outcome in the brexpiprazole trial(Grant et al., 2022), the clozapine CALMED trial (Crawford, 2022) the lamotrigine LABILE trial (Crawford, 2018), and as a secondary measure in the quetiapine study (Black et al., 2014)

BPRS Scale : The Brief Psychiatric Rating Scale **(** is a broadly applied, clinician-administered rating instrument covering a wide range of psychiatric symptoms — including anxiety, tension, hostility, depressed affect, and thought disturbances (Overall & Gorham, 1962). It was employed as the primary outcome measure in the comparative olanzapine versus aripiprazole study (Shafti & Kaviani, 2015)

CGI-S. : The CGI-S is a one-item, clinician-rated global measure of illness severity using a seven-point scale anchored at 1 (not ill) and 7 (among the most severely ill patients) (Guy, 1976). In the olanzapine versus aripiprazole trial (Shafti & Kaviani, 2015) mean CGI-S scores were used to compare overall clinical improvement between treatment arms.

PANSS-EC : The **Positive and Negative Syndrome Scale – Excited Component** is a five-item subscale evaluating acute agitation across domains of impulse dyscontrol, tension, hostility, uncooperativeness, and psychomotor excitement (Kay et al., 1987). Items are individually scored on a 1-to-7 scale, yielding an aggregate score between 5 and 35. It served as the primary outcome in the inhaled loxapine study (Ferrer et al., 2022).

DSS : The Dissociative States Scale captures the severity and temporal extent of dissociative episodes and served as the primary outcome in both crossover trials conducted by Schmahl et al. (2012). In Study 1, baseline DSS scores were 3.11 ± 1.55 for intensity and 21.1 ± 11.7 for duration; in Study 2, corresponding values were 2.91 ± 1.51 and 18.4 ± 12.4.

SCL-90 : The Symptom Checklist-90 is a 90-item patient-completed questionnaire that quantifies psychological distress across nine distinct symptomatic dimensions (Derogatis, 1977). It was used as the primary outcome in the divalproex ER trial by Moen et al. (2012), in which no significant time-by-group interaction was found [$F(8, 56) = 1.09$; $p = .38$].

BIS-11 : The Barratt Impulsivity Scale is a 30-item self-report measure quantifying impulsivity across attentional, motor, and non-planning subscales (Patton et al., 1995). It was employed in the divalproex ER pilot (Moen et al., 2012) and the omega-3 fatty acids combination trial (Bellino et al., 2014), in which combination therapy produced significantly greater reductions in impulsivity ($p = 0.031$).

BSS : The Beck Scale for Suicide Ideation is a 21-item instrument assessing the current intensity of suicidal ideation (Beck et al., 1979). It served as the primary outcome in the ketamine versus midazolam pilot by (Fineberg et al., 2023)

MADRS : The Montgomery–Åsberg Depression Rating Scale is a 10-item clinician-rated scale measuring depressive symptom severity (Montgomery & Åsberg, 1979). It was the primary outcome in the psilocybin-assisted psychotherapy trial (Rosenblat et al., 2024), in which the treatment group showed a mean between-group reduction of 6.6 points (Hedge's $g = 1.07$, $p = 0.005$).

Outcome Questionnaire-45 (OQ-45) and Hopkins Symptom Checklist-11 (HSCL-11). Both were used in the intranasal oxytocin trial (Maoz, 2024), where a significant interaction between BPD diagnosis and treatment allocation was observed on the OQ-45 ($B = 8.93$, $p = .007$) and HSCL-11 ($B = 0.25$, $p = .02$).

Statistical Values: p, D, and Related Metrics. The p-value expresses the probability that a result at least as extreme as that observed would arise by chance alone, assuming the null hypothesis to be true; a threshold of $p < 0.05$ is conventionally adopted to denote statistical significance (Fisher, 1925). Cohen's d is a standardised index of effect magnitude, with approximate benchmarks of 0.2, 0.5, and 0.8 representing small, medium, and large effects respectively (Cohen, 1988). Hedge's g is a closely related effect size statistic that incorporates a correction for small-sample bias. Odds ratios (OR) are reported in the naltrexone retrospective analysis (Timäus et al., 2021). Hazard ratios (HR) are reported in the quetiapine study (Black et al., 2014), with HR = 2.54 for the low-dose group indicating approximately 2.5 times faster time to clinical response than placebo.

3.4 Second-Generation Antipsychotics

Four studies evaluated the efficacy and safety of second-generation antipsychotic agents in borderline personality disorder and its associated symptoms. These studies collectively provided data on 195 participants. The agents assessed include olanzapine and aripiprazole as a direct comparator pair, brexpiprazole, clozapine, and quetiapine administered at two dosage levels. Follow-up durations ranged from 8 weeks to 6 months.

Table 2: Second-Generation Antipsychotics

Drug Name	Study Design	Key Findings	Reference
Olanzapine / Aripiprazole	Randomized, open-label, parallel (8 weeks)	BPRS: −25.7% vs −18.8%; OLZ superior on CGI-S; notable reductions across anxiety, tension, depressed mood, and hostility domains	(Shafti and Kaviani, 2015)
Brexpiprazole	Randomized, double-blind, placebo-controlled (12 weeks)	ZAN-BPD: 14.9→3.1 vs 14.9→8.4 (placebo); significant improvement in BPD symptoms	(Grant et al., 2022)
Clozapine	Randomized, double-blind, placebo-controlled (CALMED; 6 months)	No significant benefit (ZAN-BPD: 9.68 vs 13.54 placebo, NS); trial terminated early (COVID-19)	(Crawford et al., 2022)
Quetiapine	Randomized, double-blind, placebo-controlled (8 weeks)	Low-dose (150 mg/day): significant improvement on Zanarini scale (p=0.031); moderate dose (300 mg/day): NS	(Black et al., 2014)

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; NS = Not Significant; OLZ = Olanzapine; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder

3.4.1 Efficacy in Borderline Personality Disorder

A randomised, open-label, parallel-group trial by Shafti and Kaviani comprising 24 participants (12 in each arm) directly compared olanzapine and aripiprazole over an 8-week treatment period in patients meeting diagnostic criteria for BPD (Shafti & Kaviani, 2015). The primary endpoint was the percentage reduction in total Brief Psychiatric Rating Scale (BPRS) score; this fell by approximately 25.7% in the olanzapine group and 18.8% in those treated with aripiprazole (Shafti & Kaviani, 2015). The Buss-Durkee Hostility Inventory (BDHI) total score also improved in both groups, with olanzapine producing a reduction of approximately 15% and aripiprazole of 12.2% (Shafti & Kaviani, 2015). A reduction in the mean total Clinical Global Impression-Severity (CGI-

S) score was additionally observed, with olanzapine achieving a decrease of approximately 20% and aripiprazole of approximately 19%, indicating comparable global symptomatic improvement across both treatment arms (Shafti & Kaviani, 2015)

A randomised, double-blind, placebo-controlled trial by Grant et al. comprising 80 participants examined the efficacy of brexpiprazole over a 12-week treatment period in patients with BPD (Grant et al., 2022). The treatment group showed a reduction in mean ZAN-BPD score from 14.9 (SD = 4.4) at baseline to 3.1 (SD = 3.9) at week 12, compared with a change from 14.9 (SD = 4.5) to 8.4 (SD = 5.5) in the placebo group over the same period (Grant et al., 2022)

The CALMED (Clozapine and Mood Effects) randomised, double-blind, placebo-controlled trial by Crawford et al. comprising 29 participants examined the efficacy of clozapine over a 6-month treatment period in patients with treatment-refractory BPD (Crawford, 2022). On the primary outcome, no statistically significant difference emerged between the two groups; endpoint mean ZAN-BPD scores were 9.68 (SD = 2.38) in the clozapine arm and 13.54 (SD = 2.92) in the placebo group (Crawford, 2022). The trial was terminated early due to recruitment difficulties arising from the COVID-19 pandemic, substantially limiting the interpretability of the null finding (Crawford, 2022)

A randomised, double-blind, placebo-controlled trial by Black et al. comprising 95 participants examined the efficacy of quetiapine extended release at two dosage levels — low-dose (150 mg/day; n = 33) and moderate-dose (300 mg/day; n = 33) — compared with placebo (n = 29) over an 8-week treatment period in patients with BPD (Black et al., 2014). Low-dose quetiapine produced a statistically significant improvement relative to placebo (d = 0.79, p = 0.031), whereas the difference between the moderate-dose group and placebo did not reach statistical significance (d = 0.41, p = 0.265) (Black et al., 2014). Time to treatment response was significantly faster in both quetiapine groups compared to placebo, with hazard ratios of 2.54 (p = 0.007) for the low-dose group and 2.37 (p = 0.011) for the moderate-dose group (Black et al., 2014)

3.4.2 Efficacy in Symptoms Associated with Borderline Personality Disorder

In the Shafti and Kaviani trial, both olanzapine and aripiprazole produced significant improvements across multiple symptom domains assessed using the BPRS subscales (Shafti & Kaviani, 2015). Reductions were observed in anxiety (olanzapine: 12.1%; aripiprazole: 11.6%), tension (olanzapine: 15.3%; aripiprazole: 13.3%), depressive mood (olanzapine: 12.8%;

aripiprazole: 19.65%), and hostility (olanzapine: 32.5%; aripiprazole: 31.4%) (Shafti & Kaviani, 2015). A differential pattern of symptom response was also observed between the two agents: olanzapine demonstrated comparatively greater improvements in uncooperativeness and excitement, while aripiprazole produced relatively larger effects on suspiciousness and unusual thought content (Shafti & Kaviani, 2015)

In the brexpiprazole trial by Grant et al., no significant between-group differences were observed on secondary symptom outcomes, including measures of anxiety and tension (Grant et al., 2022) Similarly, in the CALMED clozapine trial by Crawford et al., no statistically significant effects were observed on any secondary outcomes assessing associated symptoms of BPD (Crawford, 2022) In the Black et al. quetiapine trial, meaningful gains relative to placebo were observed in both the low-dose and moderate-dose arms across a range of secondary outcome measures assessing BPD-associated symptoms, including the MADRS (Black et al., 2014)

3.4.3 Side Effects

In the Shafti and Kaviani trial, adverse events were recorded for both treatment arms across the 8-week follow-up period (Shafti & Kaviani, 2015). In the olanzapine group, the most commonly reported adverse effects were weight gain (n = 3), somnolence (n = 4), dizziness (n = 2), and tremor (n = 1) (Shafti & Kaviani, 2015). In the aripiprazole group, reported adverse events included tremor (n = 1), inner restlessness (n = 2), headache (n = 1), and insomnia (n = 10), with insomnia constituting a notably more frequent adverse effect in the aripiprazole arm relative to olanzapine (Shafti & Kaviani, 2015).

In the brexpiprazole trial by Grant et al., among the 37 participants who completed the study in the placebo group, 19 reported at least one adverse event, with the most common being nausea (n = 6), fatigue (n = 4), restlessness (n = 3), headaches (n = 2), hallucinations (n = 2), sleep problems (n = 2), tremor (n = 1), sweating (n = 1), and increased appetite (n = 1) (Grant et al., 2022). Among the 40 participants assigned to brexpiprazole, 11 (27.5%) reported at least one adverse event, with the most frequently reported events being restlessness (n = 3), dry mouth (n = 3), nausea (n = 2), fatigue (n = 2), headache (n = 1), and increased appetite (n = 1) (Grant et al., 2022).

In the quetiapine trial by Black et al., cardiovascular and metabolic adverse effects were monitored across all three arms throughout the 8-week study period (Black et al., 2014). The moderate-dose quetiapine group experienced a statistically significant increase in heart rate (1.03 bpm/week),

while the low-dose quetiapine group showed a statistically significant decrease in systolic blood pressure (0.53 mmHg/week) (Black et al., 2014). Mean weight gained between the first and final visit was 1.0 lb (SD = 4.4) in the placebo group, 1.0 lb (SD = 7.2) in the low-dose quetiapine group, and 3.0 lb (SD = 9.2) in the moderate-dose quetiapine group (Black et al., 2014).

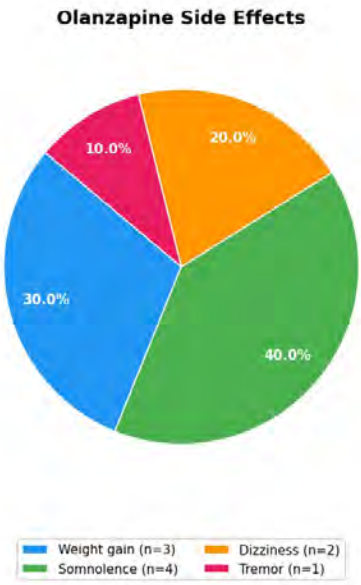


Figure 2. Olanzapine adverse events by type

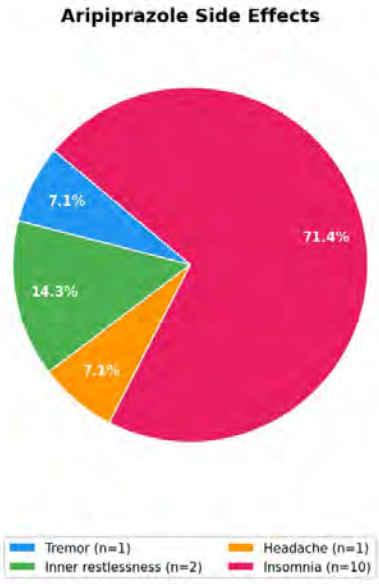


Figure 3. Aripiprazole adverse events by type

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Figure 4. Brexpiprazole adverse events – placebo arm

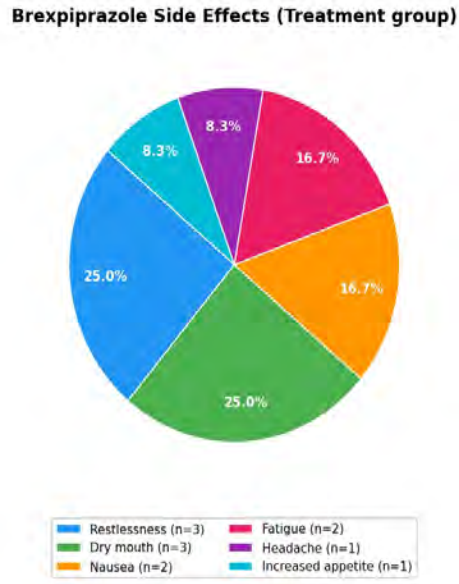

Figure 5. Brexpiprazole adverse events – treatment arm

3.5 Opioid Antagonists

Two studies evaluated the data on opioid antagonists' effectiveness on borderline personality disorder and its related symptoms. These studies collectively provided data on 190 participants. Both trials assessed naltrexone. Follow-up duration ranged from 8 weeks to approximately 3.5 years.

Table 3: Opioid Antagonists

Drug Name	Study Design	Key Findings	Reference
Naltrexone	Retrospective chart analysis (~31 days)	OR 43.2 (p≤0.0001) for symptom response; high-dose OR 791.8; naltrexone only drug with significant contribution	(Timäus et al., 2021)
Naltrexone	Randomized, double-blind, placebo-controlled crossover (6 weeks)	Numerical improvement in dissociative symptoms; Cohen's d ~0.2 (NS); no significant effect on secondary outcomes	(Schmahl et al., 2012)

Abbreviations:OR=Odds Ratio;NS=Not Significant

3.5.1 Efficacy in Borderline Personality Disorder

A retrospective chart analysis by Timäus et al. comprising 161 BPD inpatients examined the relative contribution of naltrexone and other psychotropic drugs to overall symptom improvement (Timäus et al., 2021). A treatment responder was defined as any patient who demonstrated clinically meaningful gains in at least four of a pre-specified list of symptom domains — encompassing mood and drive disturbances, suicidal ideation, impulsivity, insufficient adherence to therapy, and self-injurious behaviour (Timäus et al., 2021). Patients who received naltrexone were significantly more likely to be classified as treatment responders than those who did not (OR 11.4, $p \leq 0.0001$) (Timäus et al., 2021). Stepwise logistic regression analysis confirmed that naltrexone was the only medication that significantly contributed to symptom improvement during the treatment period (OR 43.2, $p \leq 0.0001$) (Timäus et al., 2021). A dose-dependent effect was observed: high-dose naltrexone (>50–150 mg/day) yielded an odds ratio of 791.8 ($p \leq 0.0001$), while low-dose naltrexone (25–50 mg/day) yielded an odds ratio of 26.6 ($p \leq 0.0001$) (Timäus et al., 2021). None of the other drug classes — including antipsychotics, antidepressants, mood stabilizers, or benzodiazepines — showed a statistically significant contribution to overall improvement (Timäus et al., 2021).

A pair of double-blind placebo-controlled randomised crossover trials by Schmahl et al. with a combined total of 29 participants specifically examined naltrexone's efficacy on dissociative symptoms in BPD (Schmahl, 2012). Across both trials, dissociative symptom scores were numerically lower during the naltrexone phase than during placebo; however, these differences did not attain statistical significance (Schmahl, 2012). Effect sizes for both studies were small (Cohen's d of around 0.2) (Schmahl et al., 2012). The dose of naltrexone (50 vs. 200 mg/day) did not predict treatment effects in Study 2 (Schmahl, 2012).

3.5.2 Efficacy in Symptoms Associated with Borderline Personality Disorder

In the retrospective study by Timäus et al., female gender and comorbid substance-related disorders were associated with a lower likelihood of improvement, while having first-degree relatives with major depression (F33) was associated with a significantly higher probability of a better clinical outcome across all three logistic regression models (OR ranging from 4.94 to 14.84, $p \leq 0.05$) (Timäus et al., 2021). In the Schmahl et al. trials, secondary outcome measures in Study 2 — including the number and duration of flashbacks, BPD-specific symptomatology (Borderline Symptom List-95), depression (Beck Depression Inventory and Hamilton Depression Scale), anxiety (Hamilton Anxiety Scale), and anger (State-Trait Anger Inventory) — did not yield significant differences or trends between naltrexone and placebo conditions (Schmahl, 2012)

3.5.3 Side Effects

In the retrospective analysis by Timäus et al., the study was limited by the absence of systematic side effect data, as information on adverse events was not consistently recorded in the patient charts (Timäus et al., 2021). In the Schmahl et al. crossover trials, no serious adverse events were observed in either study (Schmahl, 2012). Under naltrexone, one patient in Study 2 developed obstipation, while another reported mild-to-moderate headache, difficulties concentrating, nausea, and sedation (Schmahl, 2012). The overall adverse event profile of naltrexone was mild and comparable to that of placebo across both trials (Schmahl, 2012).

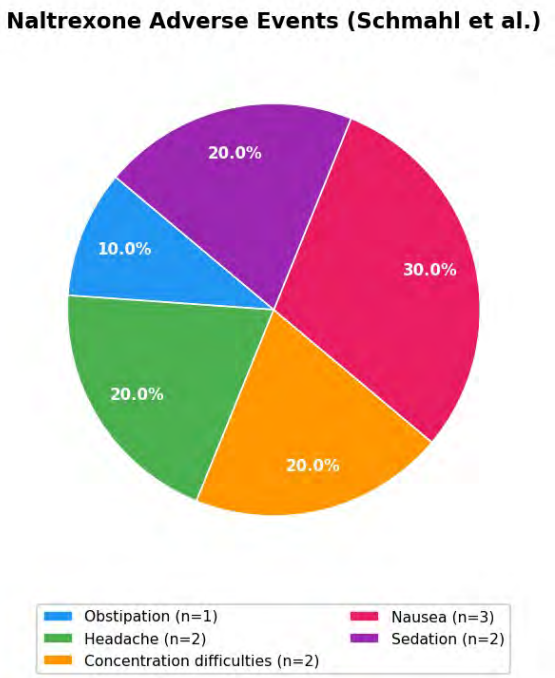

Figure 6. Naltrexone adverse events (Schmahl et al.)

3.6 Mood Stabilisers

Three studies examined the efficacy and tolerability of anticonvulsant or mood-stabilising agents — along with one agent possessing neuromodulatory properties (intranasal oxytocin) — in patients with BPD and associated symptoms, collectively contributing data from 349 participants. The agents under evaluation comprised divalproex extended release (ER) in combination with dialectical behaviour therapy (DBT), lamotrigine, and intranasal oxytocin (IN-OT) used as an add-on treatment in patients with concurrent major depressive disorder (MDD). Observation periods across these studies ranged from 4 to 52 weeks.

Table 4: Mood Stabilisers

Drug Name	Study Design	Key Findings	Reference
Divalproex ER + DBT	Randomized, single-blind, placebo-controlled (12 weeks)	No significant difference vs placebo on SCL-90 or impulsivity; significant improvement in both groups (p=0.001)	(Moen et al., 2012)
Intranasal Oxytocin	Randomized controlled trial (12 months)	Significant improvement in MDD patients without BPD comorbidity (p=.001); NS in those with BPD (p=.76)	(Maoz et al., 2024)
Lamotrigine	Multicenter, double-blind, placebo-controlled RCT (LABILE; 52 weeks)	ZAN-BPD: 11.3 vs 11.5; adj. diff. 0.1 (95% CI −1.8, 2.0; p=0.906); no benefit on any secondary outcome	(Crawford et al., 2018)

Abbreviations: NS = Not Significant; OR = Odds Ratio;SCL-90=The Symptom Checklist-90;MDD=Major depressive disorder

3.6.1 Efficacy in Borderline Personality Disorder

A double-blind, placebo-controlled pilot trial by Moen et al. (2012) examined the efficacy of divalproex ER in 15 BPD patients who had not responded to a 4-week condensed DBT run-in phase (Moen et al., 2012). Neither the SCL-90 [$F(8,56) = 1.09$; $p = .38$] nor the Barratt Impulsivity Scale Motor subscale [$F(6,39) = 0.21$; $p = .97$], indicating no significant advantage of divalproex ER over placebo (Moen et al., 2012). Notably, both groups showed significant improvement from baseline to endpoint ($p = .001$), suggesting that the improvement was primarily driven by the condensed DBT component rather than the pharmacological agent (Moen et al., 2012). An additional finding of clinical interest was that approximately 12% of participants (2 of 17)

improved sufficiently during the 4-week condensed DBT run-in alone and did not require randomisation (Moen et al., 2012)

The LABILE trial by Crawford et al. (2018) was a multicentre, double-blind, placebo-controlled RCT — the largest pharmacological RCT specifically designed for BPD to date. 276 adults were randomly allocated 1:1 to receive either up to 400 mg/day of lamotrigine or an inert placebo (Crawford, 2018). The mean ZAN-BPD score at 52 weeks was 11.3 (SD = 6.6) in the lamotrigine group and 11.5 (SD = 7.7) in the placebo group (adjusted difference = 0.1, 95% CI = -1.8, 2.0; p = 0.906) (Crawford et al., 2018). There was no evidence of any treatment effect at 12, 24, or 52 weeks, and sensitivity analyses produced consistent null results (Crawford, 2018)

A secondary analysis of a randomised controlled trial by Maoz et al. (2024) examined intranasal oxytocin (IN-OT; 32 IU twice daily) as an adjunct treatment in 58 inpatients with severe MDD, of whom 60.3% (n = 35) had comorbid BPD (Maoz, 2024). Among patients without comorbid BPD, oxytocin administration was associated with markedly greater symptomatic gains (B = -8.32, p = .001), whereas those with concurrent BPD showed no meaningful response (B = 0.61, p = .76) (Maoz et al., 2024). An equivalent pattern emerged on the HSCL-11 (B = 0.25, p = .02) (Maoz, 2024)

3.6.2 Efficacy in Symptoms Associated with Borderline Personality Disorder

In the divalproex ER trial, no significant difference was found between treatment groups on the Borderline Evaluation of Severity over Time (BEST Parts A+B) at any timepoint, and both arms showed comparable, gradual reductions in symptom severity (Moen et al., 2012). Within the LABILE trial, a broad range of secondary endpoints — depressive symptoms, deliberate self-harm, social and occupational functioning, alcohol and substance use, and health-related quality of life similarly revealed no between-group differences (Crawford, 2018). In the intranasal oxytocin study, no significant interaction effects were found on measures of anxiety or depression for either patients with or without comorbid BPD (Maoz, 2024)

3.6.3 Side Effects

In the divalproex ER trial, participants assigned to active treatment documented a range of adverse events including weight gain, sedation, confusion, heightened appetite, yawning, vivid dreams, tremor, peripheral oedema, and tinnitus (Moen et al., 2012). Mean weight gain was markedly

higher in the divalproex ER group (mean +13.43 lbs) compared to placebo (mean -0.2 lbs) (Moen et al., 2012). One participant was withdrawn due to elevated liver enzymes (Moen et al., 2012). In the LABILE trial, 246 adverse events were documented in the lamotrigine arm versus 285 in the placebo arm; serious adverse events were recorded in 26 participants (19%) receiving lamotrigine and 32 (23%) in the placebo group (Crawford, 2018) The trial authors specifically noted the importance of avoiding lamotrigine in women of childbearing age given its known teratogenic risk profile (Crawford, 2018). In the intranasal oxytocin study, no harmful effects of IN-OT administration were observed in patients with comorbid BPD, and the adverse event profile was comparable to that of placebo across both patient groups (Maoz, 2024)

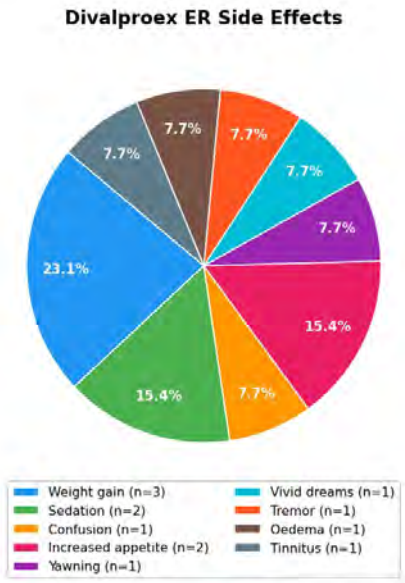

Figure 7. Divalproex ER adverse events

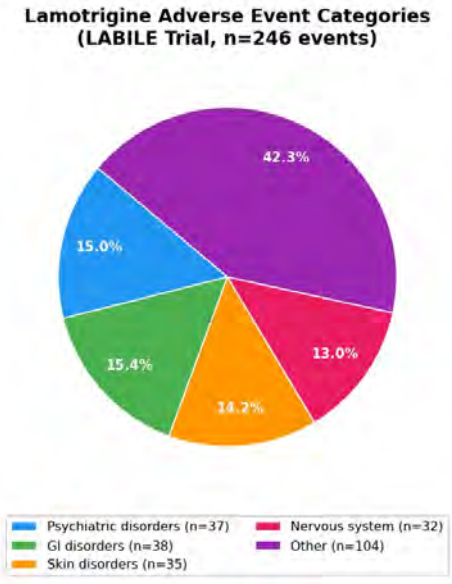

Figure 8. Lamotrigine adverse event categories (LABILE trial)

3.7 Miscellaneous Pharmacological Agents

Five studies examined a diverse set of pharmacological agents in patients with BPD, together contributing data from 175 participants. The compounds under investigation comprised citalopram, ketamine, inhaled loxapine, omega-3 fatty acids combined with valproic acid, and psilocybin administered alongside structured psychotherapy. Duration of follow-up varied from a single acute-dose assessment to six months.

Table 5: Miscellaneous Pharmacological Agents

Drug Name	Study Design	Key Findings	Reference
Citalopram	Randomized, double-blind, crossover (single dose)	Reduced amygdala response to negative faces ($p<0.05$); no significant effect on scenes or other brain regions	(Paret et al., 2021)
Psilocybin	Randomized, waitlist-controlled (6 months)	MADRS reduction; Hedge's $g=1.07$ ($p<0.01$); mild-moderate adverse events, transient worsening of suicidality in 2 participants	(Rosenblat et al., 2024)
Inhaled Loxapine	Prospective naturalistic (acute, 60 min)	PANSS-EC: $21.5 \rightarrow 5$ ($p<0.000002$); rapid agitation reduction; no serious adverse effects	(Ferrer et al., 2022)
Ketamine vs Midazolam	Randomized, double-blind, active-comparator (4 weeks)	No group difference in suicidal ideation (BSS); socio-occupational functioning improved in ketamine group at Day 14 ($p=0.03$)	(Fineberg et al., 2023)
Omega-3 + Valproate	Randomized controlled trial (12 weeks)	Combination superior to monotherapy: impulsivity (BIS-11, $p=0.031$), self-harm (SHI, $p=0.042$), anger ($p=0.001$)	(Bellino et al., 2014)

Abbreviations: BIS-11 = Barratt Impulsiveness Scale, Version 11; CI = Confidence Interval; DBT = Dialectical Behaviour Therapy; MDD = Major Depressive Disorder; NS = Not Significant; RCT = Randomised Controlled Trial; SCL-90 = Symptom Checklist-90; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

3.7.1 Efficacy in Borderline Personality Disorder

A placebo-controlled, double-blind, randomised crossover trial by Paret et al. comprising 30 female participants examined the effect of a single 20 mg oral dose of citalopram on neural responses to affective stimuli in BPD using functional magnetic resonance imaging (fMRI) (Paret et al., 2021). A single 20 mg dose of citalopram produced a statistically significant attenuation of

bilateral amygdala activation in response to negatively valenced facial stimuli (n = 25; treatment difference left hemisphere: -0.06 ± 0.16, $p < 0.05$; right hemisphere: -0.06 ± 0.17, $p < 0.05$) (Paret et al., 2021) Neural responses to negative affective scenes were not significantly altered (Paret et al., 2021)

A double-blind, randomised controlled pilot study by Fineberg et al. comprising 22 participants with BPD and current suicidal ideation examined the effects of a single intravenous infusion of ketamine (0.5 mg/kg, n = 10) versus the psychoactive comparator midazolam (0.04 mg/kg, n = 12) (Fineberg et al., 2023). Both arms exhibited substantial within-group reductions in suicidal ideation across the post-infusion period ($p < 0.001$); however, the between-group comparison did not reach statistical significance ($F(6, 116.46) = 0.65$, $p = 0.69$) (Fineberg et al., 2023). A significant group x timepoint effect was observed for socio-occupational functioning at Day 14 ($F(1, 20.12) = 5.16$, $p = 0.03$) (Fineberg et al., 2023).

A prospective naturalistic study by Ferrer et al. comprising 30 patients with personality disorders (of whom 23, or 76.7%, were diagnosed with BPD) examined the efficacy of inhaled loxapine (IL) at 9.1 mg for the management of acute agitation (Ferrer et al., 2022). PANSS-EC scores decreased significantly from a median of 21.50 at baseline to 5 at T3 ($z = -4.787$, $p = 2 \times 10^{-6}$) (Ferrer et al., 2022) No additional medication was required for any patient during the follow-up (Ferrer et al., 2022)

A 12-week randomised controlled trial by Bellino et al. comprising 43 BPD outpatients compared the efficacy of omega-3 fatty acids (EPA 1.2 g/day + DHA 0.8 g/day) in combination with valproic acid against valproic acid monotherapy (Bellino et al., 2014). Combination treatment conferred statistically superior outcomes over valproic acid alone on measures of impulsivity (BIS-11, $p = 0.031$), self-injurious behaviour (SHI, $p = 0.042$), and the BPDSI subscales for impulsivity ($p = 0.031$) and anger outbursts ($p = 0.001$) (Bellino et al., 2014)

A randomised, waitlist-controlled, open-label feasibility trial by Rosenblat et al. comprising 30 participants examined psilocybin-assisted psychotherapy (PAP) with a fixed 25 mg dose (Rosenblat, 2024). At the two-week primary endpoint, the immediate treatment group showed greater reductions in MADRS scores compared to the waitlist period, with a mean between-group difference of 6.6 points and a large effect size (Hedge's $g = 1.07$, 95% CI: 0.3–1.8, $p = 0.005$) (Rosenblat, 2024)

3.7.2 Efficacy in Symptoms Associated with Borderline Personality Disorder

In the citalopram trial by Paret et al., the finding of a significant amygdala response reduction was restricted to the faces task and was not replicated in the scenes task, suggesting that the neural modulation of citalopram in BPD is specific to certain types of affective stimuli (Paret et al., 2021) In the ketamine trial by Fineberg et al., anxiety symptoms and core BPD symptoms measured by the ZAN-BPD-SRV did not show group or group x timepoint differences (Fineberg et al., 2023) Self-reported anxiety in the psilocybin trial by Rosenblat et al. similarly showed only minimal and short-lived improvement (Rosenblat, 2024). In the omega-3 study by Bellino et al., both treatment arms showed comparable improvements in anxiety and depressive symptoms and social functioning, with no significant between-group differences in these domains (Bellino et al., 2014). For inhaled loxapine, all subscales of the PANSS-EC demonstrated significant score reductions across all assessment time points (Ferrer et al., 2022)

3.7.3 Side Effects

In the citalopram trial by Paret et al., adverse events were infrequent; headaches were the most commonly reported event (n = 11) and were observed at similar frequencies in both treatment arms (Paret et al., 2021) In the ketamine trial by Fineberg et al., infusions were well tolerated in both groups with no serious adverse events on the day of infusion or in the two weeks following (Fineberg et al., 2023). Dissociative symptoms during infusion were significantly greater in the ketamine group at the 20-minute timepoint ($t(12.3) = 3.61$, $p = 0.01$), but resolved by 40 minutes after infusion in both groups (Fineberg et al., 2023). Two participants in the ketamine group experienced acute psychiatric distress and suicidal ideation in the fourth week after infusion (Fineberg et al., 2023). In the inhaled loxapine study, no significant adverse effects were registered; a physiologically significant but clinically unremarkable decrease in arterial tension and cardiac frequency was observed ($p < 0.001$) (Ferrer et al., 2022). In the omega-3 fatty acids trial, adverse effects were mild in both groups, with the most common being gastrointestinal disturbances such as nausea and dyspepsia, and a modest weight gain of less than 2 kg (Bellino et al., 2014). In the psilocybin trial, the safety profile was generally mild to moderate and consistent with what is anticipated from this class of agent; no serious adverse events were documented. Two participants experienced a short-lived intensification of suicidal thoughts in the 24 to 48 hours following a dosing session, though neither required additional clinical intervention (Rosenblat, 2024).

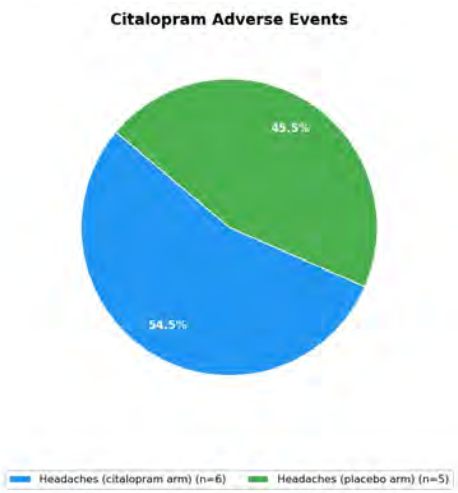

Figure 9. Citalopram adverse events

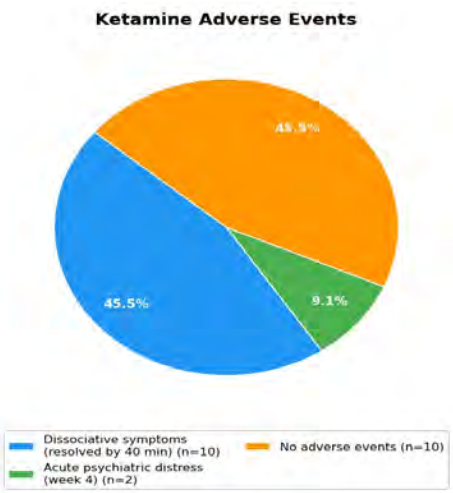

Figure 10. Ketamine adverse events

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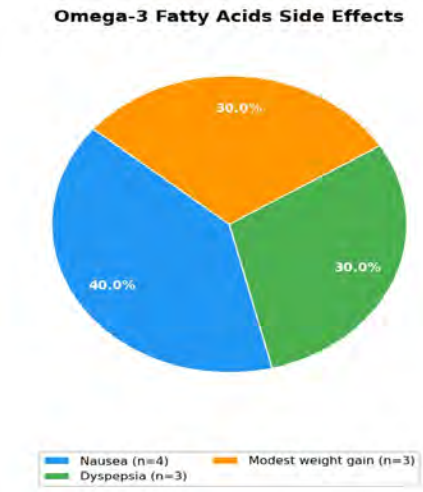

Figure 11. Omega-3 fatty acids adverse events

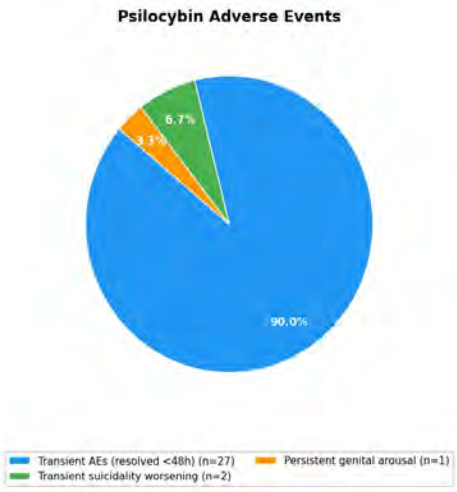

Figure 12. Psilocybin adverse events

Chapter 4: Discussion

This synthesis integrated findings from 14 controlled trials — randomised and non-randomised — that collectively evaluated pharmacological interventions across four therapeutic categories in BPD: second-generation antipsychotics, opioid antagonists, mood-stabilising agents, and a heterogeneous miscellaneous group. Data were drawn from a combined total of 909 participants. The available evidence base remains constrained in both volume and methodological quality, and no drug class currently holds regulatory approval for BPD; as a result, no individual agent can at present be endorsed for routine clinical use with any degree of confidence. Nevertheless, several findings merit careful consideration, particularly when contextualised against the rating instruments and statistical parameters detailed in Chapter 3.3. A comprehensive appraisal of each trial's quality using the Cochrane Risk of Bias framework is presented in the Risk of Bias Summary Table (Section 3.2).

Among second-generation antipsychotics, brexpiprazole produced the largest numerical change on the primary outcome (see Table 2). In the Grant et al. (2022) trial, mean ZAN-BPD scores fell from 14.9 at baseline to 3.1 at week 12 in the brexpiprazole arm, compared with a reduction from 14.9 to 8.4 in the placebo arm. The ZAN-BPD is scored from 0 to 36, where scores above approximately 10 represent clinically significant symptom burden and scores of 15 or above typically correspond to severe, pervasive disruption across relationships, emotional regulation, and identity stability. A baseline score of 14.9 therefore indicates that, on average, enrolled participants were experiencing near-severe BPD pathology at study entry. The reduction to 3.1 in the brexpiprazole arm corresponds to a score in the range associated with minimal or subclinical symptom presence. The placebo group nonetheless showed a marked improvement across the trial period, consistent with the documented sensitivity of BPD symptomatology to structured clinical contact and non-specific therapeutic factors (Paris, 2010)

Low-dose quetiapine (150 mg/day) achieved statistical significance on the ZAN-BPD in the Black et al. (2014) trial (Cohen's $d = 0.79$; $p = 0.031$), representing a large effect size by conventional benchmarks. The time-to-response hazard ratio of 2.54 ($p = 0.007$) indicates that patients in the low-dose group reached clinical response approximately 2.5 times faster than those on placebo. The 300 mg/day condition did not reach statistical significance ($d = 0.41$; $p = 0.265$), and the moderate-dose group showed a greater trend toward weight gain (3.0 lbs versus 1.0 lbs for

placebo). The CALMED clozapine trial (Crawford, 2022) returned a mean endpoint ZAN-BPD difference of approximately 3.86 points in favour of clozapine, but this did not reach statistical significance given that only 29 of a planned 212 participants were recruited. The trial was terminated early owing to COVID-19 disruption and should be considered inconclusive rather than negative. The olanzapine versus aripiprazole trial (Shafti & Kaviani, 2015) reported BPRS reductions of 25.7% and 18.8%, respectively, with differential patterns across symptom domains, though the open-label design limits the interpretability of these differences.

The naltrexone evidence base is inconsistent across study designs and demands cautious interpretation (see Table 3). In the retrospective chart analysis by Timäus et al. (2021), the odds ratio for overall treatment response reached 43.2, with an OR of 791.8 for high-dose naltrexone (>50 mg/day). Values of this magnitude are a well-recognised consequence of unmeasured confounding in non-randomised, retrospective work — most notably confounding by indication, whereby prescribers selectively assign a drug to patients who are already predisposed to respond (Rothman et al., 2008). The Timäus study was not randomised, had no pre-specified allocation, and collected no systematic adverse event data. Its findings are best regarded as hypothesis-generating. The Schmahl et al. (2012) crossover trials, by contrast, were genuinely double-blind and randomised. Although naltrexone yielded numerically lower dissociative symptom scores than placebo across both studies, the magnitude of the differences was modest (Cohen's d ≈ 0.2) and statistical significance was not achieved. A prospective, adequately powered, and pre-registered RCT is required to clarify the true discrepancy between retrospective and controlled trial findings.

The LABILE trial (Crawford, 2018) provides the strongest evidence of any included study, and its findings are negative (see Table 4). With an adjusted mean difference of 0.1 ZAN-BPD points (95% CI: −1.8 to 2.0; p = 0.906) at 52 weeks in a sample of 276 participants, the null result was consistent across all four ZAN-BPD subscales, across all follow-up timepoints (12, 24, and 52 weeks), and across multiple sensitivity analyses. The upper bound of +2.0 ZAN-BPD points represents less than 6% of the scale's 36-point range — a difference so small as to be imperceptible in everyday clinical contact. Taken together, the trial effectively rules out any meaningful effect of lamotrigine on BPD symptomatology. The known teratogenic risk of lamotrigine is also relevant given that the majority of clinical BPD diagnoses are in women of reproductive age (Crawford, 2018).

The divalproex ER pilot (Moen et al., 2012) was too underpowered for independent interpretation, yet the absence of significant differences on both the SCL-90 [$F(8,56) = 1.09$; $p = .38$] and the BIS-11 motor subscale [$F(6,39) = 0.21$; $p = .97$] aligns with the interpretation that pre-to-post gains observed in both arms ($p = 0.001$) were attributable to the condensed DBT component rather than to the pharmacological agent. The contrast between a mean weight increase of 13.43 lbs in the divalproex group and a mean weight reduction of 0.2 lbs in the placebo group highlights that, for an agent producing no pharmacological benefit, divalproex imposed a clinically meaningful metabolic burden on participants. The intranasal oxytocin finding (Maoz, 2024) is of theoretical interest: the OQ-45 interaction coefficient ($B = 8.93$, $p = .007$) indicated that BPD diagnosis was associated with a significantly attenuated response to oxytocin relative to MDD patients without BPD comorbidity, consistent with neurobiological evidence of oxytocin system dysregulation in BPD possibly related to early trauma exposure (Bertsch et al., 2013)

Among the miscellaneous agents, the omega-3 plus valproate combination (Bellino et al., 2014) yielded the most clinically meaningful findings among the miscellaneous agents (see Table 5). The combined regimen outperformed valproic acid alone in attenuating impulsivity on the BIS-11 ($p = 0.031$), with a mean between-group difference of approximately 11 points on a scale spanning 30 to 120. Anger, as quantified by the BPDSI, also showed a statistically significant between-group advantage in favour of the combination ($p = 0.001$). A plausible synergistic mechanism has been proposed, whereby EPA and DHA augment serotonergic transmission through phospholipid membrane remodelling, potentially acting in concert with the GABAergic effects of valproate (Sublette et al., 2011) Inhaled loxapine produced a swift and statistically robust reduction in acute agitation, with PANSS-EC scores declining from a median of 21.5 at baseline to 5 within 60 minutes ($p < 0.000002$); no participant required rescue medication throughout the observation window (Ferrer et al., 2022). The non-injectable route of administration may be of particular practical relevance in emergency settings where patient cooperation is limited. The psilocybin-assisted psychotherapy trial (Rosenblat, 2024) demonstrated a between-group MADRS reduction of 6.6 points at the two-week endpoint, with a large effect size (Hedge's $g = 1.07$; $p = 0.005$). Two participants experienced a brief exacerbation of suicidal ideation lasting 24–48 hours post-dose, a safety signal that demands careful monitoring given the already elevated baseline suicidality characteristic of BPD. The citalopram fMRI study (Paret et al., 2021) found a significant reduction in amygdala BOLD response to negative facial expressions following a single 20 mg dose,

providing mechanistic support for serotonergic modulation of the neural circuits driving emotional hyperreactivity, though the specificity of this finding to one stimulus type and its reliance on a neuroimaging rather than clinical outcome limit its direct clinical implications.

Considered alongside one another, the 14 included trials differ substantially in the confidence with which their findings can be interpreted, and these differences are consequential for the weight assigned to individual results. The LABILE trial (Crawford, 2018) occupies a distinct position in this regard. Its large, adequately powered sample, double-blind design with matched placebo, web-based randomisation, robust allocation concealment, and prospective pre-registration collectively produce a level of internal validity that no other included study approaches. The practical implication is that the null result for lamotrigine — consistent across all subscales, all follow-up timepoints, and all sensitivity analyses — can be regarded as a genuine finding rather than an artefact of methodological weakness. The brexpiprazole trial (Grant et al., 2022) and the quetiapine trial (Black et al., 2014) occupy an intermediate position. Both employed double-blind, placebo-controlled designs with samples of adequate size, and both were rated some concerns overall. In the brexpiprazole trial, the primary limitation is the potential for rater unblinding given the drug's recognisable side-effect profile, compounded by the involvement of an industry funder whose interests were aligned with a positive result. In the quetiapine trial, incomplete outcome data and the absence of prospective registration introduce analogous uncertainties, though the three-arm design and the consistency of the low-dose effect across primary and secondary outcomes lend the finding a degree of plausibility. The CALMED clozapine trial (Crawford, 2022) presents a different interpretive challenge: its design was sound, but recruitment reached only 13% of the planned sample before the trial was terminated owing to COVID-19 disruption, and near-complete unblinding arose from the distinctive adverse effect profile of clozapine. The null result should therefore be regarded as inconclusive rather than negative. The olanzapine versus aripiprazole comparison (Shafti & Kaviani, 2015) is the only head-to-head active-comparator trial in the review, which gives it a practical relevance that placebo-controlled designs lack; however, the open-label design and the small sample of 24 participants mean that the differential response patterns observed across symptom domains cannot be attributed to the drugs with any confidence. For the opioid antagonist evidence, the contrast between the two available studies is particularly instructive. The retrospective chart analysis by Timäus et al. (2021) was neither randomised nor blinded, and the odds ratios it reported — 43.2 for overall response and 791.8 for high-dose

naltrexone — are of a magnitude that is more consistent with unmeasured confounding than with a genuine pharmacological effect on that scale. The Schmahl et al. (2012) crossover trials, by contrast, were properly controlled and double-blind; their more modest, non-significant effect sizes (Cohen's d ≈ 0.2) carry correspondingly greater credibility, and the contrast with the retrospective findings illustrates how dramatically non-randomised designs can inflate apparent treatment effects in this population. The divalproex ER pilot (Moen et al., 2012) is similarly difficult to interpret in isolation. The pre-randomisation DBT run-in phase, which produced significant improvement in a subset of participants before any drug was administered, represents a confound that the subsequent randomised comparison could not disentangle from pharmacological effects; the null finding on both the SCL-90 and the BIS-11 is consistent with the drug having no specific effect, but the sample of 15 was far too small to conclude this with any reliability. The intranasal oxytocin study (Maoz, 2024) was not designed as a BPD pharmacotherapy trial; the BPD subgroup comparison emerged from a secondary analysis of a depression trial, the group assignment was determined by diagnosis rather than randomisation, and the subgroup was not pre-specified. Its contribution lies primarily in generating a hypothesis about oxytocin system dysregulation in BPD rather than in providing evidence of a treatment effect. Among the miscellaneous agents, the ketamine pilot (Fineberg et al., 2023) is the most rigorously designed, employing an active comparator, double-blinding, and prospective registration; its principal limitation is the small sample of 22 participants, which was insufficient to detect a between-group difference on the primary suicidal ideation outcome even if one existed. The omega-3 plus valproate (Bellino et al., 2014) benefited from an active-comparator design that avoids the ethical and methodological difficulties of placebo control in this population, but the open-label administration of both conditions means that expectancy effects cannot be excluded from the clinician-rated outcomes. A similar limitation applies to the inhaled loxapine study (Ferrer et al., 2022), which was an open-label naturalistic observation without a comparator arm; the marked reduction in PANSS-EC scores is consistent with the known trajectory of acute agitation over time and cannot be attributed to the drug alone on the basis of this design. The psilocybin trial (Rosenblat, 2024) was appropriately described by its authors as a feasibility study, and it should be read as such: the open-label design and the intensity of the accompanying psychotherapy make it impossible to isolate the pharmacological contribution to the MADRS improvement observed, and the large effect size is most plausibly an upper-bound estimate from an early-phase, unblinded trial. The citalopram fMRI

study (Paret et al., 2021) stands apart from all others in the review in using a neuroimaging endpoint as its primary outcome. Its double-blind, placebo-controlled crossover design is a methodological strength, and the amygdala finding provides mechanistic support for serotonergic involvement in BPD's characteristic emotional hyperreactivity; nevertheless, the absence of a validated clinical outcome measure means that the practical significance of the neural effect remains unclear. Considered in aggregate, the variation in study quality across the 14 trials is not a peripheral concern but a central feature of the evidence base, and it directly determines how far any individual finding can be taken as a basis for clinical inference.

This review was carried out in accordance with prospectively established eligibility criteria focused on randomised and controlled trial designs, with rigour evaluated using the Cochrane Risk of Bias 2 tool. Spanning four drug classes, 14 studies, and 909 participants, it represents a reasonably comprehensive and up-to-date appraisal of the controlled pharmacotherapy evidence in BPD. The primary limitations are the substantial heterogeneity across outcome measures — which rendered statistical pooling impractical and necessitated a narrative approach — and the predominance of trials with high or uncertain bias risk, constraining the confidence of any conclusions drawn. Restricting eligibility to English-language publications carries an inherent risk of language bias. Of particular concern is the near-total underrepresentation of male participants across many of the included trials, which considerably limits the applicability of these findings to men with BPD — a population already subject to systematic underdiagnosis.

Considered in totality, the evidence reviewed here supports a targeted, symptom-specific approach to adjunctive pharmacotherapy in BPD rather than any broadly applicable first-line drug strategy. Inhaled loxapine demonstrated rapid and clinically meaningful reductions in acute agitation and appears well suited to emergency settings. Omega-3 supplementation added to a mood stabiliser produced reproducible gains in impulsivity and anger management across two symptom-targeted outcome measures. Low-dose quetiapine may offer benefit for affective dysregulation in selected patients, contingent on ongoing metabolic monitoring. The body of evidence argues persuasively against lamotrigine in BPD, compounded by its teratogenic risk in women of reproductive age. Structured psychotherapy — DBT foremost — remains the cornerstone of treatment. Future trials should prioritise adequate statistical power, active-comparator arms, harmonised outcome instruments, and sufficiently long follow-up periods. A prospective, pre-registered RCT is needed for naltrexone to reconcile the divergent signals from retrospective and crossover evidence.

Psilocybin-assisted psychotherapy and ketamine both require larger, more rigorous trials before their risk-benefit profiles in BPD can be meaningfully characterised.

Chapter 5: Conclusion

Based on 14 controlled trials encompassing 909 participants, this review confirms that pharmacological treatment of BPD remains an area of genuine evidential uncertainty. No agent currently holds a licensed indication for BPD, and none of the interventions reviewed produced sufficiently robust or replicable evidence to underpin definitive practice recommendations. The strongest and most methodologically credible finding is the null result for lamotrigine from the LABILE trial, conducted across 276 participants over 52 weeks; the primary outcome confidence interval excludes any effect of clinical consequence. Within the second-generation antipsychotics, brexpiprazole and low-dose quetiapine generated the most promising efficacy signals, though independent replication in larger trials is essential before these findings can inform practice. Mood-stabilising agents as a class delivered limited therapeutic benefit relative to the adverse effects they imposed. Naltrexone retains potential as a treatment candidate, but the divergence between retrospective and controlled evidence means that prospective validation is a prerequisite for any clinical inference. Among the miscellaneous agents, omega-3 augmentation of valproic acid produced a consistent signal for reductions in impulsivity and anger, inhaled loxapine showed rapid effectiveness for acute agitation management, and psilocybin-assisted psychotherapy demonstrated preliminary antidepressant activity within a small-scale feasibility study. Across the full body of findings, pharmacotherapy in BPD should be conceptualised as a symptom-directed adjunct to psychotherapy, deployed in a time-limited and targeted manner wherever feasible. Advancing this field will require adequately powered, prospectively registered trials that incorporate active comparators, standardised outcome batteries, and observation periods long enough to capture durable treatment effects.

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