IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Current and emerging medications for borderline personality disorder: is pharmacotherapy alone enough?

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1715115 since 2022-01-18T14:08:52Z

Published version:

DOI:10.1080/14656566.2019.1686482

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

16 September 2026

Current and emerging medications for borderline personality disorder: is pharmacotherapy alone enough?

Highlights

- Many psychotropic agents have been tested for the treatment of BPD symptom domains.
- In most cases, the studies are open-label trials or affected by severe limitations. There is little evidence of efficacy.
- Evidence supports the use of mood stabilizers, second-generation antipsychotics, and omega-3 fatty acids to treat BPD.
- Combining drugs with psychotherapy demonstrates better results than single therapies on several core symptoms of BPD.
- Data on the tolerability of psychotropic agents in BPD are scarce. Specific examinations of each drug's adverse effects are needed.

Information Classification: General

Abstract

Introduction

The treatment of borderline personality disorder (BPD) remains an open question for clinicians. There is scarce evidence available. The guidelines' conclusions diverge. Together with these factors, the complexity of BPD generates uncertainty in day-to-day practice. This narrative review aims to provide an overview of advances in BPD treatment and posit a critical opinion based on clinical evidence and practice.

Areas covered

We reviewed clinical trials of the efficacy of the main class of drugs in BPD: antidepressants, mood stabilizers, first-, second-, and third-generation antipsychotics, and other agents (opiate antagonists, clonidine, oxytocin, omega-3 fatty acids). We also included in this review studies on combinations of drugs and psychotherapies.

Expert Opinion

An individualized, tailored pharmacotherapy for BPD that targets the prominent symptom clusters can improve relevant aspects of the clinical picture. However, no medication is indicated to treat the global psychopathology of BPD. Polypharmacy should be avoided or strictly limited. To date, pharmacotherapy alone does not suffice to manage the complexity BPD. Combining medication with psychotherapy may improve specific BPD symptom dimensions. In particular, it may help those aspects that respond slowly or not at all to monotherapy.

Keywords

Borderline personality disorder; pharmacotherapy; psychotherapy; combined therapy; antidepressants, mood stabilizers; antipsychotics

Information Classification: General

1. Borderline Personality Disorder (BPD): common recommendations for the complex clinical entity

Borderline personality disorder (BPD) is a severe and heterogeneous mental disorder. It is characterized by a pattern of identity diffusion, impulsive behaviors, and chronic instability in affectivity and relationships [1]. Self-injuries and suicidal conduct may occur during critical phases of the disorder. Patients with BPD exhibit impairment in a wide range of functions [2], to a greater extent than patients with other psychiatric disorders [3]. They have long-term difficulties over their lifespans [4,5]. BPD does not suddenly emerge in adulthood. In fact, early precursors, prodromal signs, and processes that confer vulnerability to later personality pathology appear in youth [6,7,8]. A full diagnosis of BPD is as valid in adolescence as it is in adulthood. Borderline personality disorder is the most common personality disorder in clinical populations [9,10]. The lifetime prevalence of BPD has been estimated at around 1.4% in the community [11] and 25% in psychiatric inpatient settings [12]. Two studies based on data from the National Epidemiologic Survey on Alcohol and Related Conditions found higher rates, at 2.7 % [13] and 5.9 %, respectively [14]. The high prevalence significantly impacts mental health services [15,16]. The complexity of borderline personality disorder requires particular care in diagnostic processes and early therapeutic interventions.

Although several sets of guidelines for the treatment of BPD have been published in the last eighteen years, no medication has obtained an official indication for this mental disorder.

The American Psychiatric Association (APA) [17,18] guidelines supported the role of pharmacotherapy that is oriented at specific symptom domains to treat stated symptoms during periods of acute decompensation and trait vulnerabilities. It identified three symptom dimensions as the targets of drugs: affective dysregulation (including depressed mood, anxiety, anger, and mood lability), impulsive–behavioral dyscontrol, and cognitive-perceptual symptoms. Antidepressants and mood stabilizers were recommended as first- and second-line interventions for affective dysregulation and impulsive behavioral dyscontrol. Antipsychotics (first- and second-generation

Information Classification: General

antipsychotics) represented the first-line of treatment for cognitive-perceptual symptoms and the third choice for impulsive–behavioral dyscontrol symptoms. Similarly, in the practical and biological guidelines published by the World Federation of Societies of Biological Psychiatry (2007) [19], the main symptomatic targets of pharmacotherapy with different evidence levels were affective dysregulation, cognitive-perceptual symptoms, impulsivity, and anger. Moreover, the authors stated that the effects of pharmacotherapy in these patients may have increased responses in combination with psychosocial interventions. The guidelines from the National Institute for Health and Clinical Excellence (NICE) [20,21] reached rather different conclusions from the preceding guidelines. They stated that drug therapy was not recommended other than to treat mental disorders in comorbidity or to control specific acute symptoms during a crisis and with a short-term prescription [22]. NICE supported the central role of psychotherapy in treating BPD. The Australian National Health and Medical Research Council guidelines (2012) [23] took an intermediate approach. It recognized the role of medications as second-line or adjunctive treatment and confirmed psychotherapy as the first-line treatment. In substantial accordance with the treatment guidelines, two Cochrane systematic reviews [24,25] underlined the importance of combining psychotherapy and medications. Among pharmacotherapy, some evidence focused on second-generation antipsychotics, mood stabilizers, and omega-3 fatty acids. The data did not support the role of antidepressants.

This review aims to provide an overview of the advances in pharmacotherapy and combined therapy for BPD and express a critical opinion based on clinical evidence and practice.

1.1 Antidepressants

In recent years, antidepressants have been widely prescribed in patients affected by BPD, despite a lack of high-quality evidence of their efficacy in the scientific literature [26]. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been prescribed progressively less for all psychiatric indications. They have significant side effects, and there is a

Information Classification: General

high risk of a potentially fatal overdose. These medications have been replaced by selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). The overall usage of antidepressants in BPD has decreased recently, and now the prescription of these agents is recommended only for comorbid affective disorder [25].

To our knowledge, no placebo-controlled trials on the efficacy of antidepressants in BPD have been performed since 2010. In general, we observed a decrease in the number of investigations on medications in patients with a diagnosis of BPD in the last nine years. The existing studies often showed significant methodological limitations [27].

Among SSRIs, most RCTs investigated the efficacy of fluoxetine (5 trials) [28-32]. Three studies compared fluoxetine with placebo [28-30]. One study compared fluoxetine with dialectical behavioral therapy (DBT) [31], and one trial compared fluoxetine with the antipsychotic olanzapine and a combination of fluoxetine and olanzapine [32]. A more recent study evaluated the efficacy of fluoxetine in monotherapy in comparison with a combined therapy of fluoxetine and interpersonal psychotherapy adapted to BPD (IPT-BPD) [33]. The results of this study will be discussed in the paragraph on combining drugs and psychotherapy. In the initial trials, fluoxetine was found efficacious in decreasing anger, irritability, and impulsive aggression and in improving global functioning. Unexpectedly, the effect on depression was controversial and questionable. Two studies did not find any effect on depression [28,31], while one study [29] stated a beneficial effect of fluoxetine on depression and anxiety. This discrepancy may be due to a difference in the dose of fluoxetine used in the three samples. In the two studies published by Salzmann et al. and Simpson et al., the maximum dose was 60 mg/day, while in Markovitz's study, the maximum dose was 80 mg/day. The only RCT on fluvoxamine showed a significant effect on affective instability with a decrease in rapid mood shifts but not on aggressiveness and impulsivity [34]. More recently, sertraline was compared with olanzapine in one RCT [35]. The authors observed that sertraline decreased depression, obsessive symptoms, and hypersensitivity in interpersonal relationships,

Information Classification: General

while olanzapine was more effective on aggression, paranoid ideation, and self-mutilating behaviors.

There have been only two open trials of SNRIs in the treatment of BPD. The first evaluated the efficacy of venlafaxine [36], and the second investigated the effects of duloxetine [37]. Both drugs showed a reduction of somatic symptoms in BPD [36,37], and duloxetine improved depressive symptoms, impulsivity, outbursts of anger, and affective instability [37].

In summary, the findings of controlled studies of the efficacy of antidepressants in BPD are outdated as they have not been replicated after 2010. The main results were that SSRIs positively impacted affective symptoms. In particular, they helped a depressed mood, anxiety, anger, and impulsive behaviors in BPD patients. Nevertheless, the available evidence is weak on whether to support or exclude the use of SSRIs. Controlled trials of SNRIs are lacking, and there have been no new studies of new antidepressants, like vortioxetine.

The results of RCTs are displayed in Table 1.

1.2 Mood stabilizers

Clinicians have considered mood stabilizers an efficient therapeutic option in treating BPD patients since the 1990s. This class of medications has been found particularly useful in the short-term control of anger and impulsivity in BPD [38]. Although a Cochrane review (2010) [24] found some evidence of the efficacy of mood stabilizers (valproate and lamotrigine) in BPD, since 2010, few trials have been conducted to consolidate the data and reinforce their use in clinical practice [27,22].

Lithium was studied in only one RCT [39] that compared it with desipramine and placebo in BPD patients receiving concomitant psychotherapy. Although lithium showed a major efficacy in improving anger, irritability, and self-injuries, the risk of toxicity and the need for regular blood level controls represented significant limitations to its prescription in BPD. Nowadays, no more evidence is available about lithium carbonate, and there has been no study of lithium sulfate in BPD.

Information Classification: General

Carbamazepine was tested in one RCT [40] and found not to be significantly superior to placebo on measures of affective symptoms, behavioral dyscontrol, and global assessment. Due to the limited evidence of therapeutic benefits and the risk of adverse effects, carbamazepine is a questionable treatment option for this disorder.

Over the years, the most widely studied mood stabilizer in BPD patients has been valproate. Four double-blind placebo-controlled trials and one unblinded controlled study have been published. Two studies [41,42] reported the efficacy of valproate in reducing impulsive and aggressive behaviors of BPD patients. One study [43] showed the superiority of valproate on interpersonal sensitivity, anger, hostility, and aggressiveness in a sample of BPD patients with comorbid bipolar disorder. A more recent study [44] evaluated the effects of extended-release divalproex in BPD patients treated with four weeks of dialectical behavioral therapy (DBT). The results of this trial are less encouraging because no significant differences between the two groups were observed in the global assessment. The unblinded controlled trial [45] compared valproate with the association of valproate and omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid). The combined therapy was found superior to the single therapy for impulsivity, self-harm, and outbursts of anger.

Another mood stabilizer that was tested in BPD patients was topiramate. Five RCTs were performed on this medication [46-51]. Two short-term [46,47] and two follow-up [48-50] studies showed that topiramate significantly reduced irritability and anger. One study [51] reported the improvement of global functioning, hostility, interpersonal sensitivity, and somatization symptoms in patients affected by BPD and comorbid mood disorders.

The efficacy of lamotrigine was evaluated in four RCTs [52-55]. The findings revealed significant effects on the outcomes of anger, impulsivity, affective instability, and interpersonal dysfunctions [52-54]. However, one study performed by Crawford and colleagues [55] showed that adding lamotrigine to usual care did not result in symptomatic relief and cost-effectiveness balance.

Information Classification: General

To our knowledge, oxcarbazepine has been tested in only one BPD open-label study [56]. This study reported improvements in anxiety, interpersonal relationships, impulsivity, affective fluctuations, and anger.

In our opinion, more studies on this class of drugs are needed to draw more reliable conclusions. Large-scale double-blind placebo trials should be conducted. Drug-drug comparison trials between different mood stabilizers would clarify their effects on symptom domains and establish whether there are significant differences in efficacy between the drugs. Nonetheless, the available evidence suggests that valproate, topiramate, and lamotrigine are a therapeutic option in treating impulsivity, anger, and affective instability in BPD patients.

The results of RCTs are displayed in Table 2.

1.3 Antipsychotics

Cognitive-perceptual symptoms represent a psychopathological dimension of BPD. In particular, stress-related transient psychotic-like symptoms (paranoid ideation and dissociative symptoms) can frequently occur over the course of the disorder.

Individuals with BPD have increased plasma and cerebrospinal fluid levels of dopamine metabolites, which could explain the transient psychotic and dissociative symptoms.

Before 1990, several studies on the use of first-generation antipsychotics in BPD resulted in controversial findings. These studies concerned flupentixol decanoate [57], loxapine versus chlorpromazine [58], thiothixene [59], and trifluoperazine [60]. After 1990, two RCTs were performed to evaluate the efficacy of haloperidol versus placebo [61] and phenelzine [62]. The results showed that haloperidol promoted the reduction of hostility, irritability, and impulsive-aggressive behaviors in BPD, but it failed to improve global severity and psychoticism. Moreover, haloperidol seemed to be responsible for the onset of depressive symptoms during prolonged treatment.

Information Classification: General

More recently, more investigations have been published on second (clozapine, risperidone, olanzapine, paliperidone, and ziprasidone) and third generation (aripiprazole) antipsychotics in the treatment of BPD. The use of newer antipsychotics has been preferred in clinical practice because of these medications are better tolerated than first-generation drugs. In fact, new antipsychotics are associated with fewer and milder extrapyramidal adverse effects, a lower risk of tardive dyskinesia, and a considerable improvement in cognitive functions [63]. This class of drugs showed a moderate effect on negative affectivity, disinhibition, and interpersonal dysfunction by improving dorsolateral and orbital frontal cortex activation [64,65].

Among new antipsychotics, clozapine was tested in four open-label studies of patients with BPD [66-69]. All the studies concluded that this medication was useful in reducing impulsivity, affective instability, self-mutilating behaviors, and cognitive-perceptual symptoms. However, these trials had a diagnostic bias due to the inclusion of patients with psychotic symptoms or disorders, which significantly affected the results. In a 2-year observational study that was recently published [70], clozapine was associated with a significant decrease in psychiatric admissions of patients with BPD without cases of serious adverse effects. However, generally, the risk of adverse effects, such as agranulocytosis, is considerable with clozapine. It is particularly dangerous in BPD patients because of their low adherence to treatment prescriptions and blood chemistry tests.

Four open-label studies [71-74] and one double-blind controlled trial [75] evaluated the efficacy of risperidone. The findings from the uncontrolled trials suggested an effect of this drug on impulsivity, aggressiveness, affective instability, and anxiety. The results of the only RCT highlighted the efficacy on psychoticism, paranoid ideation, phobic anxiety, and interpersonal sensitivity [22,75]. Two open-label studies were performed on the active metabolite of risperidone, paliperidone: One concerned the extended-release oral formulation [76], and one was on the long-acting intramuscular formulation [77]. Although their data need to be replicated, they showed that paliperidone improved global and specific BPD symptoms, such as impulsive behavioral dyscontrol and cognitive-perceptual disturbance.

Information Classification: General

Olanzapine was studied in nine RCTs and one open-label trial. In fact, it is the most thoroughly studied second-generation antipsychotic in BPD. Among RCTs, four trials evaluated the efficacy of this drug versus placebo [78-81]. Two studies compared olanzapine plus DBT psychotherapy versus placebo plus DBT [82,83]. Three drug-to-drug studies investigated the efficacy of olanzapine to sertraline [84], haloperidol [85], and asenapine, respectively [86]. The studies generally agreed that olanzapine improves global functioning, affective instability, anxiety and anger, interpersonal sensitivity, and impulsive-aggressive behaviors in BPD patients. The comparison of olanzapine with asenapine showed olanzapine had a superior effect on paranoid ideation [86]. The comparison with haloperidol did not find a difference between the two drugs on generic behavioral symptoms [85]. However, Shafti and Shahveisi administered olanzapine at a low mean dose (7 mg/day) and haloperidol at a relatively high mean dose (7mg/day). In the open-label randomized trial [87], olanzapine was compared with aripiprazole. Both medications were found effective in reducing global symptoms. Olanzapine did not show any superior effect on symptoms of hostility. It must be noted that a Cochrane systematic review (2010) [24] identified an increase in self-harming behavior when using olanzapine in BPD [24]. In contrast, BPD patients were found less likely to engage in self-mutilating acts when treated with aripiprazole [88-90].

Aripiprazole was found useful in the management of affective dysregulation, depression, impulse control, and paranoid symptoms in three RCTs of BPD patients [87-89] and one open-label trial [91], which tested the efficacy of the drug in augmentation of sertraline in a group of non-responders. The recent protocol for the "Verbal Experiences Response in Borderline Personality Disorder to Aripiprazole Trial Medication – Verbatim" randomized controlled trial [92] aims to inform BPD treatment decisions when the patients present with auditory verbal hallucinations.

Several studies on quetiapine mostly agreed and shared promising findings. Unfortunately, most of these studies were open-label [93-99], and only two RCTs were published more recently [100,101]. Quetiapine showed effects on a wide range of BPD symptoms, including impulsive-aggressive behaviors, anger, and affective instability, and it had positive effects on anxious-depressive

Information Classification: General

symptoms and general psychopathology [22,25]. The recently approved antipsychotic asenapine was studied in one open-label study [102] and one controlled trial, which compared asenapine with olanzapine [86]. Asenapine was found effective in improving affective instability, impulsivity, and cognitive symptoms, and it was superior to olanzapine on affective instability [86].

Ziprasidone was tested in one open-label and one controlled study [103,104]. Neither investigation found any evidence of the efficacy of this antipsychotic on symptoms of BPD.

Concerning inhaled loxapine, there were only case reports [105,106] and one retrospective analysis [107] available. The results suggested that inhaled loxapine may be useful for the emergency treatment of agitated patients with BPD and other personality disorders [108]. To date, we have no data on the newest antipsychotics, lurasidone, brexpiprazole, and cariprazine, in BPD sample.

In conclusion, first-generation antipsychotics can be administered to BPD patients during acute states with impulsive-aggressive behaviors and psychotic-like symptoms. However, there is little evidence of the efficacy. The treatment should be prescribed in low doses and for short periods because of its remarkable side effects and elevated dropout rate [109,22]. Among second-generation antipsychotics, there was evidence to support the therapeutic effect of olanzapine on cognitive symptoms, aggressiveness, outbursts of anger, and anxiety in BPD patients. Further controlled investigations are needed to confirm the preliminary, promising data on aripiprazole and quetiapine. Data on the newest medications have not been collected yet.

The results of RCTs are displayed in Table 3.

1.4 Other psychotropic agents

In recent years, opiate antagonists, oxytocin, clonidine, and omega-3 fatty acids have garnered growing attention as treatments for BPD symptoms.

Among opiate antagonists, naloxone and naltrexone were not found to be superior to placebo in treating acute dissociative states in patients with BPD in two small placebo-controlled studies [110,111]. An open-label trial reported the efficacy of nalmefene in reducing BPD global

Information Classification: General

symptomatology, self-injurious behavior, binge eating, and alcohol consumption in a group of BPD patients with alcohol use disorder [112].

The effects of intranasal oxytocin on social cognition in BPD were observed in one open-label study [113] and five randomized placebo-controlled trials [114-118]. The findings showed an improvement in interpersonal hypersensitivity, social behavior, and dysphoric emotional response to stress, with better regulation of abnormal behavioral and neural patterns in response to social context. The studies of oxytocin mainly examined laboratory outcomes related to prosocial behaviors instead of providing measures of clinical outcomes.

The α2 adrenergic agonist clonidine, usually administered to reduce blood pressure, was studied in two RCTs on its potential effect on BPD symptoms. The first study [119] compared two dosages of clonidine (75 or 150 mcg/day) and found that both resulted in a significant decrease in aversive inner tension, dissociative symptoms, the urge to commit self-injurious behaviors, and suicidal ideation. In the second placebo-controlled trial among BPD patients with or without post-traumatic stress disorder (PTSD) [120], BPD-related psychopathology (self-destruction and self-perception) improved selectively in the PTSD-positive subgroup.

In recent decades, omega-3 fatty acids have received increasing interest for their effects on psychiatric disorders, particularly depression. In BPD, three placebo-controlled studies compared the efficacy of omega-3 fatty acids with placebo [121-123], and one RCT compared the association of omega-3 fatty acids and valproate with single valproate [45]. The association of eicosapentaenoic acid and docosahexaenoic acid was found efficacious in treating depressive symptoms, aggressive behaviors, impulsivity, anger, and self-injury. The only study that evaluated the long-term efficacy of these agents in BPD (six months after discontinuation of omega-3 fatty acids with ongoing valproate) [124] suggested a long-lasting effect in terms of anger control.

Tonic glutamate overactivity due to chronic stress was found in subjects affected by BPD [125]. Therefore, recent investigations have focused on the role of N-methyl-D-aspartate (NMDA) receptor activity in sustaining BPD symptoms. Excessive stimulation of glutamate receptors

Information Classification: General

(NMDA) causes excitotoxicity. Memantine is an NMDA antagonist and a potential neuroprotective agent. The only RCT available [126] compared the effect of memantine with usual treatment in a group of BPD patients. Memantine was found useful in improving delusions, aggression, disinhibition, irritability, and depressed mood. Furthermore, memantine presented minimal abuse potential and was demonstrated to inhibit the abuse of addictive drugs [127].

The results of RCTs are displayed in Table 4.

1.5 Side effects

The real effects of psychotropic agents in the treatment of BPD symptoms are strongly affected by several issues concerning patient adherence to the prescription of medications and their sensitivity to the risk of side effects. Inadequate compliance with pharmacotherapy, sudden spontaneous changes of drugs and doses, weak and unstable therapeutic alliance, phenomena of pharmacophobia, or exaggerated intolerance to even mild adverse effects are all relevant problems that clinicians must deal with when treating BPD.

Concerning the tolerability of medications, adverse events have not been assessed in most studies of BPD patients. Only about 30% of the studies included in this review reported data on adverse effects. The adverse effects of antidepressants, mild sedation, akathisia, headache, nausea, and insomnia were found with fluoxetine [32,33]. Nausea was observed with fluvoxamine [34]. Headache and nausea were found with duloxetine [37].

Among mood stabilizers, the most common adverse effects were: tremors, diarrhea, nausea, dyspepsia, and transient hepatic transaminases increase with valproic acid [43,45]. Weight loss, fatigue, dizziness, paresthesia, and subjective cognitive impairment were found with topiramate [47,49,51]. Rash, pruritus, irritability, confusion, headache, and dizziness were found with lamotrigine [53-55]. Sedation, dizziness, headache, and nausea were found with oxcarbazepine [56]. Concerning first-generation antipsychotics, studies reported the incidence of extrapyramidal effects, in particular, with haloperidol [61,62,85]. Investigations that assessed the side effects of

Information Classification: General

second-generation antipsychotics revealed that clozapine may induce granulocytopenia and agranulocytosis (a concentration of granulocytes below 100 cells/mm^3 of blood) in about 1% of treated patients. Other common adverse effects are excessive salivation and weight gain [66,67]. Sleepiness, fatigue, hyperprolactinemia, and significant weight gain were observed with both risperidone [71-73] and olanzapine [32,81,82,85,86]. One Cochrane systematic review highlighted an increased risk of suicidal ideation and self-mutilating behaviors with olanzapine. The main adverse effects of aripiprazole were headache, nausea, insomnia, anxiety, and inner restlessness [87-89,91]. Quetiapine was responsible for sedation, dry mouth, and dizziness [96-100]. Patients treated with asenapine reported akathisia, restlessness, anxiety, and irritability [86,102]. Paliperidone was associated with insomnia [76], while ziprasidone was linked to gastrointestinal adverse effects [104].

The only data available among other therapeutic agents stated that omega-3 fatty acids were well-tolerated in BPD patients. Nalmefene was associated with dizziness, nausea, low appetite, and unsteady movement [112]. Oxytocin may cause headache, whereas clonidine induces xerostomia and orthostatic reactions (Ziegenhorn et al., 2009).

1.6 Combination of medications and psychotherapy

The conclusions of recent systematic reviews [128,25] and guidelines [20,129] underlined the role of psychotherapy as a first-line treatment of patients with BPD and confirmed the importance of combining psychotherapy and medications.

Several psychotherapeutic approaches were developed or adapted specifically for BPD patients. Most investigated models of psychotherapy were dialectical behavior therapy (DBT) [130] among cognitive-behavioral therapies and mentalization-based therapy [131] among psychodynamic treatments. An increasing amount of evidence has been obtained about the adaptation of interpersonal psychotherapy to BPD (IPT-BPD) [132-137].

Information Classification: General

In this review, we included only the trials that compared the combination of psychotherapy and medication with single psychotherapy or single medication to answer to our initial question: “is pharmacotherapy alone enough?”

Three RCTs evaluated the advantages of combining DBT and pharmacotherapy in comparison with DBT and placebo [31,82,83].

The association of fluoxetine with DBT did not provide additional benefits over single DBT [31]. The combined therapy of olanzapine and DBT showed a significant advantage over DBT plus placebo in treating depression, anxiety, and impulsive-aggressive behaviors [82]. In addition, olanzapine with DBT promoted a faster decrease in irritability and aggression than did DBT plus placebo [83].

Three other controlled trials investigated whether a combined treatment of IPT adapted to BPD (IPT-BPD) and fluoxetine was superior to single pharmacotherapy with fluoxetine [33,136,137]. The combination of pharmacotherapy and psychotherapy was found more efficacious than pharmacotherapy alone to treat three BPD core symptoms: disturbed interpersonal relationships, affective instability, and impulsivity. It was also more effective in reducing anxiety and improving the subjective perception of the quality of life [33]. The addition of IPT-BPD to the antidepressant showed advantages on impulsivity, interpersonal dysfunctions, and quality of life obtained that were maintained during two years of follow-up after the termination of psychotherapy [137]. One study of predictive factors of response to the addition of psychotherapy indicated that patients who presented more severe BPD psychopathology and a higher degree of fear of abandonment, affective instability, and identity disturbance had a higher chance of responding to combined therapy [136]. These symptoms, particularly identity disturbance, should be considered with particular care, as they are often refractory to usual BPD treatment.

In summary, there is insufficient data on the combination of pharmaco- and psychotherapy to draw any conclusions. However, most of the studies suggested that a combined approach may be useful

Information Classification: General

for improving specific BPD symptom dimensions, in particular those that respond slowly or not at all to monotherapy.

The results of RCTs are displayed in Table 5.

2. Meta-analytic studies

Several meta-analyses on BPD treatment have been published in recent years.

A meta-analytic study performed by Nosè et al. [138] suggested that antidepressants and mood stabilizers are useful on affective instability and anger, whereas antipsychotics show significant effects on impulsive–aggressive behaviors. In a meta-analysis of anger and depression in BPD, Mercer et al. [38] found that mood stabilizers are more beneficial than SSRIs in treating affective symptoms (both depressed mood and anger), while antipsychotics show a moderate effect on anger, but not depression. Ingenhoven and collaborators published two meta-analyses [139,140] with a symptom dimensions approach. In the first study [139], the authors concluded that impulsive–behavioral dyscontrol, anger, and anxiety show more improvement with mood stabilizers, and cognitive-perceptual symptoms and anger show a moderate response with antipsychotics. None of the dimensions or mood symptoms improve with antidepressants. In the second meta-analysis [140], the authors focused on the efficacy of antipsychotic drugs (including both classic neuroleptics and atypical antipsychotics). The antipsychotics showed weak effectiveness on cognitive-perceptual symptoms and mood lability (with a more pronounced effect on anger), and they were entirely ineffective on impulsive behavioral dyscontrol [22,140]. These findings contrast with another meta-analysis that included RCTs and open trials [141]. In the latter study, mood stabilizers and antipsychotics are found to be useful for treating affective dysregulation and impulsive behavioral dyscontrol. These two classes of drugs and antidepressants prove effective for treating affective dysregulation, while only antipsychotics improve cognitive-perceptual symptoms. Saunders and Silk [142] analyzed data from placebo-controlled trials on the efficacy of antipsychotics on the following symptom dimensions: affective instability, anxiety, inhibition,

Information Classification: General

cognitive-perceptual disturbance, and impulsivity aggression. All these dimensions benefit from treatment with antipsychotics.

Cochrane Systematic Reviews [24,25] of pharmacological interventions for BPD found evidence that supported the efficacy of mood stabilizers, second-generation antipsychotics, and omega-3 fatty acids on BPD symptoms. Nevertheless, the authors emphasized the need for higher quality evidence as most of the current recommendations are based on single study effect estimates [22].

3. Conclusions

We can conclude that a careful examination of trials published in recent years provides only limited evidence of the efficacy of some mood stabilizers (valproic acid), new generation antipsychotic (olanzapine and, to lesser degree, aripiprazole), and omega-3 fatty acids.

The small number of controlled studies, the heterogeneity of the results, and the methodological shortcomings in methods impede reaching any reliable conclusion on the utility of these drugs in clinical practice. Even less is known about specific adverse effects in BPD. Therefore, we suggest using these psychotropic agents only when a comorbid condition is present, or an acute crisis has to be addressed.

4. Expert opinion

Drugs are routinely prescribed in clinical practice for the treatment of BPD, although no psychotropic medication has been licensed for this disorder. Why are medications so frequently used, often in polypharmacy, for this clinical condition? Data from the literature shows that the percentage of BPD patients who have been treated with medications ranges between 90 and 99% [143], and multiple drugs were used in 67-84% of those cases [144]. Low-quality evidence, divergent guidelines recommendations, and differences between experimental settings and real-world clinical practice contributed to confusion and contrasting findings. At the moment, there is a generally low level of evidence to support the efficacy of psychotropic agents in BPD patients.

Information Classification: General

There are four evidence levels (from strongest to weakest). Level A signals that at least three RCTs are available. Level B means that at least two RCTs or one RCT and ≥1 prospective, large, open-label study have been published. Level C connotes that one RCT and one prospective, open-label study/case series or at least two prospective, open-label study/case series have been found. Level D means that the efficacy of the medication is only supported by expert opinions. In the guidelines of the WFSBP International Task Force [19], the evidence on patients with BPD was systematically estimated. Antidepressants and mood stabilizers showed Level B evidence of efficacy (fair), while second-generation antipsychotics had Level C evidence (minimal).

Although more controlled studies on these medications in BPD have become available in recent years, there is general agreement among the reviews in this field that the evidence is weak because of the severe methodological limitations of most studies. Small sample sizes, different gender proportions, heterogeneous selection criteria and assessment instruments, and high rates of dropouts were the most relevant limitations. In addition, the mean duration of the trials is too short (32 days-to 24 weeks) and insufficient to draw conclusions about the long-term efficacy and tolerability of medications in a long-lasting disorder such as BPD. For many drugs, most studies were open-label trials, which had limited clinical meaning, because there is significant evidence of spontaneous changes in BPD symptoms over time [145,146].

Current treatment guidelines diverge on the role of medications in BPD, which produces uncertainty among clinicians. APA guidelines [17,18] and WFSBP guidelines [19] support the use of drugs with psychotherapy, when possible, to treat symptoms of BPD. In fact, the APA concluded that BPD is a complex condition that can be effectively treated with a targeted pharmacological approach and suggested that single classes of drugs may affect specific symptom domains. Taking a rather similar approach, WFSBP guidelines concluded that the off-label use of psychotropic agents may help individuals with BPD to improve the cluster of affective symptoms, including depressed mood, anxiety, mood swings, and impulsivity. Despite considering approximately the same evidence as the previous guidelines, the NICE and ANHMRC [20,23] expressed substantially

Information Classification: General

divergent opinions and were strongly in favor of psychotherapy with much more limited use of medications. In fact, neither source recommended drug therapy other than to treat mental disorders in comorbidity (depression) or control specific acute symptoms during a crisis and with a short-term administration. One reason for this discordance is that the English and Australian expert groups considered more parameters to draw clinical recommendations, such as evidence of cost-effectiveness, not only for medications but also for clinical management and psychological therapies. In addition, these guidelines were developed in light of the peculiar care pathway for personality disorders in Britain and Australia.

However, a series of clinical factors must be considered to decide the most appropriate treatment approach for these patients. BPD is a challenging and often treatment-resistant clinical condition [144] with a high risk of suicidal behaviors. Patients frequently present an acute exacerbation of symptoms with impulsive and self-harming conduct, agitation, and depressive or transient psychotic symptoms. Adequate psychotherapy for BPD is not always available, and patients may refuse or discontinue it. These problematic situations lead clinicians to prescribe medications. There is a high risk of administering too many drugs for too long to manage different domains of impairing and refractory symptoms. Clinicians should choose the fewest possible medications based on the predominant psychopathological factors and design pharmacotherapy in terms of individualized, tailored intervention rather than applying unspecific polypharmacy.

Among pharmacotherapies from the last decade, we observed a shift from a high predominance of prescribing antidepressants to the present-day preference for mood stabilizers and second-generation antipsychotics. Since 2010 there have been no trials among BPD patients to assess the efficacy and tolerability of antidepressants (except for one follow-up study). Recent systematic reviews stated that there is insufficient evidence to prescribe these drugs to BPD patients, except in the case of comorbidity with depression or anxiety disorders. In contrast, more recent controlled trials indicated that mood stabilizers (valproate, topiramate, and lamotrigine) and second- and third-generation antipsychotics (olanzapine and quetiapine, and aripiprazole, respectively) can

Information Classification: General

significantly affect core symptoms of the disorder, such as impulsive-behavioral dyscontrol, affective instability, and cognitive-perceptual symptoms. Nevertheless, the only antipsychotic for which there is sizable positive evidence is olanzapine. Classical neuroleptics have failed to demonstrate effects on BPD symptoms, except for reducing impulsive-aggressive behaviors during acute states, and adverse effects strongly limit their use. Dietary omega-3 supplementation and oxytocin have garnered growing interest among researchers due to promising findings in terms of beneficial effects, particularly on the symptom domain of anger. They may represent two interesting therapeutic options. Omega-3 fatty acids have a high level of tolerability with very mild or absent side effects. Oxytocin seems to address the domain of social cognition, which tends to respond poorly to other pharmacological treatments.

In our opinion, an individualized, tailored pharmacotherapy for BPD, with the fewest medications needed to target the prominent symptom clusters could improve relevant aspects of the clinical picture. However, no medication is actually indicated to treat the global psychopathology of this personality disorder. Polypharmacy is still common in clinical practice. It is not supported by data and should be avoided or strongly limited. We conclude that at the moment, chemical pharmacotherapy alone cannot manage a complex, severe, impairing condition such as BPD. Several core symptom domains, such as fears of abandonment, chronic feelings of emptiness, and identity disturbances, are refractory to pharmacotherapy. They could be the focus of specific psychotherapies or combined therapies. As we have reported in this review, the initial data appear in favor of the efficacy of these interventions on resistant BPD symptoms. The number of controlled, well-designed trials to test medications in BPD has generally decreased over the last few years probably because preceding investigations had fewerencouraging results than expected. Based on available findings, psychotherapy appropriately adapted for severe personality disorders or associated with select mood stabilizers or new antipsychotics appears to be the most promising therapeutic tool for treating BPD patients.

Information Classification: General

Further issues about pharmacotherapy have resulted from new diagnostic categories proposed by ICD 11 [147]. In particular, there has been a debate over whether the new ICD-11 diagnostic category of complex PTSD (CPTSD) can be interpreted as substantially equivalent to PTSD comorbid with Borderline Personality Disorder (BPD). It is likely that a group of patients receiving a diagnosis of BPD with DSM-5 criteria develop their symptoms on a post-traumatic basis and present both symptoms of PTSD and symptoms of disturbances in self-organization, which overlap with several core symptoms of BPD [148]. The ICD-11 diagnostic criteria for CPTSD reflect a structure model consisting of two higher-order factors. The first factor includes typical symptoms of PTSD, such as prolonged feelings of terror, marked preoccupation with a relationship with a perpetrator, isolation, and disruption in intimate relationships, and search for a rescuer. The second factor includes disturbances in self-organization, such as problems in affect regulation, feelings of shame, guilt, or failure, and difficulties in sustaining relationships. Of course, these two factors' structure is not recognizable in the majority of BPD patients. Moreover, a history of trauma is not necessary for a diagnosis of BPD, while it is an essential requirement for the diagnosis of CPTSD [149]. Nevertheless, there is abundant evidence of the trauma of early life for BPD patients, and a subgroup of patients may have been misdiagnosed as BPD. They might be better classified in the new category of CPTSD. The crossover between CPTSD and BPD opens up the field's consideration of trauma therapies and medications. At the moment, no controlled trials of pharmacotherapy are available in samples of CPTSD patients. A recent systematic review and meta-analysis of available trials in this clinical population considered psychosocial interventions, such as cognitive-behavioral therapy, exposure alone, and eye movement desensitization and reprocessing. It found initial evidence of partial efficacy [150]. Determining whether to use medication as a single or combined therapy is interesting, and the topic needs to be explored in its entirety.

Information Classification: General

References

1. American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders (5th ed.) (DSM-5). American Psychiatric Publishing (2013).
2. Frankenburg FR, Zanarini MC. The association between borderline personality disorder and chronic medical illnesses, poor health-related lifestyle choices, and costly forms of health care utilization. J Clin Psychiatry. 2004 Dec;65(12):1660-5.
3. Ansell EB, Sanislow CA, McGlashan TH, Grilo CM. Psychosocial impairment and treatment utilization by patients with borderline personality disorder, other personality disorders, mood and anxiety disorders, and a healthy comparison group. Compr Psychiatry. 2007 Jul-Aug;48(4):329-36. Epub 2007 Apr 6.
4. Skodol AE, Pagano ME, Bender DS et al. Stability of functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder over two years. Psychol Med. 2005 Mar;35(3):443-51.
5. Tomko RL, Trull TJ, Wood PK, Sher KJ. Characteristics of borderline personality disorder in a community sample: comorbidity, treatment utilization, and general functioning. J Pers Disord. 2014 Oct;28(5):734-50. doi: 10.1521/pedi_2012_26_093.
6. Miller AL, Muehlenkamp JJ, Jacobson CM. Fact or fiction: diagnosing borderline personality disorder in adolescents. Clin Psychol Rev. 2008 Jul;28(6):969-81. doi: 10.1016/j.cpr.2008.02.004. Epub 2008 Mar 10.
7. Kaess M, Brunner R, Chanen A. Borderline personality disorder in adolescence. Pediatrics. 2014 Oct;134(4):782-93. doi: 10.1542/peds.2013-3677. Epub 2014 Sep 22.
8. Bozzatello P. Early detection and outcome in borderline personality disorder. Frontiers in Psychiatry. 2019, submitted.
9. Leichsenring F, Leibing E, Kruse J et al. Borderline personality disorder. Lancet. 2011 Jan 1;377(9759):74-84. doi: 10.1016/S0140-6736(10)61422-5.
10. Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. Am J Psychiatry. 2009 May;166(5):530-9. doi: 10.1176/appi.ajp.2009.08121825.
11. Lenzenweger MF, Pastore RE. On determining sensitivity to pain in borderline personality disorder. Arch Gen Psychiatry. 2007 Jun;64(6):747-8; author reply 748-9.
12. Gunderson JG, Links PS. Borderline Personality Disorder: A Clinical Guide. Amer Psychiatric Pub Inc, 2008.
13. Tomko RL, Brown WC, Tragesser SL et al. Social context of anger in borderline personality disorder and depressive disorders: findings from a naturalistic observation study. J Pers Disord. 2014 Jun;28(3):434-48. doi: 10.1521/pedi_2012_26_064. Epub 2012 Sep 17.
14. Grant BF, Goldstein RB, Chou SP et al. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Mol Psychiatry. 2009 Nov;14(11):1051-66. doi: 10.1038/mp.2008.41. Epub 2008 Apr 22.
15. Zanarini MC, Frankenburg FR, Hennen J, Silk KR. Mental health service utilization by borderline personality disorder patients and Axis II comparison subjects followed prospectively for 6 years. J Clin Psychiatry. 2004 Jan;65(1):28-36
16. Cristea IA, Gentili C, Cotet CD et al. Efficacy of Psychotherapies for Borderline Personality Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017 Apr 1;74(4):319-328. doi: 10.1001/jamapsychiatry.2016.4287.

Information Classification: General

17. American Psychiatric Association. Practice guideline for the treatment of patients with borderline personality disorder. Am. J. Psychiatry 158, 1–52 (2001).
18. Oldham JM, Bender DS, Skodol AE et al. Testing an APA practice guideline: symptom-targeted medication utilization for patients with borderline personality disorder. J Psychiatr Pract. 2004 May;10(3):156-61.
19. *Herpertz SC, Zanarini M, Schulz CS et al.; WFSBP Task Force on Personality Disorders; World Federation of Societies of Biological Psychiatry (WFSBP). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders. World J Biol Psychiatry. 2007;8(4):212-44.
20. NHS National Institute for Health and Clinical Excellence (NICE): Borderline personality disorder: treatment and management. Recent guidelines on general management of borderline personality disorder. www.guidance.nice.org.uk/CG78. 2009.
21. NHS National Institute for Health and Clinical Excellence (NICE): Personality disorders: borderline and antisocial. www.nice.org.uk/guidance/qs88. 2015.
22. *Bozzatello P, Ghirardini C, Uscinska M et al. Pharmacotherapy of personality disorders: what we know and what we have to search for. Future Neurol. 2017. (0) 12(4), 199–222
23. National Health and Medical Research Council (NHMRC) – Australian Government - Clinical Practice Guideline for the Management of Borderline Personality Disorder (2012). www.nhmrc.gov.au/guidelines-publications/mh25.
24. **Stoffers JM, Völlm BA, Rücker G et al. Pharmacological interventions for borderline personality disorder. Cochrane Database Syst. Rev. 16(6), CD005653 (2010).
25. **Stoffers JM, Lieb K. Pharmacotherapy for borderline personality disorder--current evidence and recent trends. Curr Psychiatry Rep. 2015 Jan;17(1):534. doi: 10.1007/s11920-014-0534-0.
26. Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. Psychiatry Res. 1997 Dec 5;73(3):147-57.
27. Hancock-Johnson E, Griffiths C, Picchioni M. A Focused Systematic Review of Pharmacological Treatment for Borderline Personality Disorder. CNS Drugs. 2017 May;31(5):345-356. doi: 10.1007/s40263-017-0425-0.
28. Salzman C, Wolfson AN, Schatzberg A et al. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. J Clin Psychopharmacol. 1995 Feb;15(1):23-9.
29. Markovitz P. Pharmacotherapy of impulsivity, aggression, and related disorders. In: Impulsivity and Aggression. Hollander E, Stein DJ (Eds). John Wiley & Sons, NY, USA, 263–287 (1995)
30. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry. 1997 Dec;54(12):1081-8.
31. Simpson EB, Yen S, Costello E et al. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. J Clin Psychiatry. 2004 Mar;65(3):379-85.
32. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. J Clin Psychiatry. 2004 Jul;65(7):903-7.

Information Classification: General

33. Bellino S, Rinaldi C, Bogetto F. Adaptation of interpersonal psychotherapy to borderline personality disorder: a comparison of combined therapy and single pharmacotherapy. Can J Psychiatry. 2010 Feb;55(2):74-81.
34. Rinne T, van den Brink W, Wouters L et al. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. Am J Psychiatry. 2002 Dec;159(12):2048-54.
35. Jariani M, Saaki M, Nazari H et al. The effect of Olanzapine and Sertraline on personality disorder in patients with methadone maintenance therapy. Psychiatr Danub. 2010 Dec;22(4):544-7.
36. Markovitz PJ, Wagner SC. Venlafaxine in the treatment of borderline personality disorder. Psychopharmacol Bull. 1995;31(4):773-7.
37. Bellino S, Paradiso E, Bozzatello P et al. Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study. J Psychopharmacol. 2010 Mar;24(3):333-9. doi: 10.1177/0269881108095715. Epub 2008 Aug 21.
38. Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J Pers Disord. 2009 Apr;23(2):156-74. doi: 10.1521/pedi.2009.23.2.156.
39. Links, P.; Steiner, M.; Boiago, I.; Irwin, D. Lithium therapy for borderline patients: preliminary findings. J. Personal. Disord., 1990, 4, 173-181.
40. de la Fuente JM, Lotstra F. A trial of carbamazepine in borderline personality disorder. Eur Neuropsychopharmacol. 1994 Dec;4(4):479-86.
41. Hollander E, Allen A, Lopez RP et al. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. J Clin Psychiatry. 2001 Mar;62(3):199-203.
42. Hollander E1, Swann AC, Coccaro EF et al. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. Am J Psychiatry. 2005 Mar;162(3):621-4.
43. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry. 2002 May;63(5):442-6.
44. Moen R, Freitag M, Miller M et al. Efficacy of extended-release divalproex combined with "condensed" dialectical behavior therapy for individuals with borderline personality disorder. Ann Clin Psychiatry. 2012 Nov;24(4):255-60.
45. Bellino S, Bozzatello P, Rocca G et al. Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of the association with valproic acid. J Psychopharmacol. 2014 Feb;28(2):125-32. doi: 10.1177/0269881113510072. Epub 2013 Nov 5.
46. Nickel MK, Nickel C, Mitterlehner FO et al. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. J Clin Psychiatry. 2004 Nov;65(11):1515-9.
47. Nickel MK, Nickel C, Kaplan P et al. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. Biol Psychiatry. 2005 Mar 1;57(5):495-9.

Information Classification: General

48. Nickel MK. Topiramate treatment of aggression in male borderline patients. Aust N Z J Psychiatry. 2007 May;41(5):461-2.
49. Nickel M. Topiramate reduced aggression in female patients with borderline personality disorder. Eur Arch Psychiatry Clin Neurosci. 2007 Oct;257(7):432-3.
50. Nickel MK, Loew TH. Treatment of aggression with topiramate in male borderline patients, part II: 18-month follow-up. Eur Psychiatry. 2008 Mar;23(2):115-7. Epub 2007 Nov 19.
51. Loew TH, Nickel MK. Topiramate treatment of women with borderline personality disorder, part II: an open 18-month follow-up. J Clin Psychopharmacol. 2008 Jun;28(3):355-7. doi: 10.1097/JCP.0b013e318173a8fb.
52. Tritt K, Nickel C, Lahmann C et al. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. J Psychopharmacol. 2005 May;19(3):287-91.
53. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. Int Clin Psychopharmacol. 2009 Sep;24(5):270-5. doi: 10.1097/YIC.0b013e32832d6c2f.
54. Leiberich P, Nickel MK, Tritt K et al. Lamotrigine treatment of aggression in female borderline patients, Part II: an 18-month follow-up. J Psychopharmacol. 2008 Sep;22(7):805-8. doi: 10.1177/0269881107084004. Epub 2008 Feb 28.
55. Crawford MJ, Sanatinia R, Barrett B et al. The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial. Am J Psychiatry. 2018 Aug 1;175(8):756-764. doi: 10.1176/appi.ajp.2018.17091006.
56. Bellino S, Paradiso E, Bogetto F. Oxcarbazepine in the treatment of borderline personality disorder: a pilot study. J Clin Psychiatry. 2005 Sep;66(9):1111-5.
57. Montgomery SA. The psychopharmacology of borderline personality disorders. Acta Psychiatr Belg. 1987 May-Jun;87(3):260-6.
58. Leone NF. Response of borderline patients to loxapine and chlorpromazine. J Clin Psychiatry. 1982 Apr;43(4):148-50.
59. Goldberg SC, Schulz SC, Schulz PM et al. Borderline and schizotypal personality disorders treated with low-dose thiothixene vs placebo. Arch Gen Psychiatry. 1986 Jul;43(7):680-6.
60. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry. 1988 Feb;45(2):111-9.
61. Cornelius JR, Soloff PH, Perel JM et al. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. Am J Psychiatry. 1993 Dec;150(12):1843-8.
62. Soloff PH, Cornelius J, George A et al. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch Gen Psychiatry. 1993 May;50(5):377-85.
63. Bellino S, Bozzatello P, Brignolo E et al. New Antipsychotics in Treatment of Mood Instability and Cognitive Perceptual Symptoms in Borderline Personality Disorder. Current Psychopharmacology. 2012 Volume 1, Issue 1. doi: 10.2174/2211556011201010086.
64. Ripoll LH. Clinical psychopharmacology of borderline personality disorder: an update on the available evidence in light of the Diagnostic and Statistical Manual of Mental Disorders - 5. Curr Opin Psychiatry. 2012 Jan;25(1):52-8. doi: 10.1097/YCO.0b013e32834c3f19.

Information Classification: General

65. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge Medicine (Paperback), 2013.
66. Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. Compr Psychiatry. 1993 Nov-Dec;34(6):402-5.
67. Benedetti F, Sforzini L, Colombo C et al. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. J Clin Psychiatry. 1998 Mar;59(3):103-7.
68. Chengappa KN, Ebeling T, Kang JS et al. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. J Clin Psychiatry. 1999 Jul;60(7):477-84.
69. Parker GF. Clozapine and borderline personality disorder. Psychiatr Serv. 2002 Mar;53(3):348-9.
70. Rohde C, Polcwiartek C, Correll CU et al. Real-World Effectiveness of Clozapine for Borderline Personality Disorder: Results From a 2-Year Mirror-Image Study. J Pers Disord. 2018 Dec;32(6):823-837. doi: 10.1521/pedi_2017_31_328. Epub 2017 Nov 9.
71. Rocca P, Marchiaro L, Cocuzza E et al. Treatment of borderline personality disorder with risperidone. J Clin Psychiatry. 2002 Mar;63(3):241-4.
72. Friedel RO, Jackson WT, Huston CS et al. Risperidone treatment of borderline personality disorder assessed by a borderline personality disorder-specific outcome measure: a pilot study. J Clin Psychopharmacol. 2008 Jun;28(3):345-7. doi: 10.1097/JCP.0b013e318173083e.
73. Díaz-Marsá M, Galian M, Montes A et al. Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report. Actas Esp Psiquiatr. 2008 Mar-Apr;36(2):70-4.
74. Carrasco JL, Palomares N, Marsá MD. Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. Psychopharmacology (Berl). 2012 Nov;224(2):347-8. doi: 10.1007/s00213-012-2880-0. Epub 2012 Oct 11.
75. Szigethy EM, Schulz SC. Risperidone in comorbid borderline personality disorder and dysthymia. J Clin Psychopharmacol. 1997 Aug;17(4):326-7.
76. Bellino S, Bozzatello P, Rinaldi C, Bogetto F. Paliperidone ER in the Treatment of Borderline Personality Disorder: A Pilot Study of Efficacy and Tolerability. Depress Res Treat. 2011; 2011:680194. doi: 10.1155/2011/680194. Epub 2011 Aug 4.
77. Palomares N, Montes A, Díaz-Marsá M, Carrasco JL. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. Int Clin Psychopharmacol. 2015 Nov;30(6):338-41. doi: 10.1097/YIC.0000000000000095.
78. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2001 Nov;62(11):849-54.
79. Bogenschutz MP, Nurnberg GH. Olanzapine versus placebo in the treatment of borderline personality disorder. J Clin Psychiatry. 2004 Jan;65(1):104-9.
80. Schulz SC, Zanarini MC, Bateman A, et al. Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. Br J Psychiatry. 2008 Dec;193(6):485-92. doi: 10.1192/bjp.bp.107.037903.

Information Classification: General

81. Zanarini MC, Schulz SC, Detke HC et al. A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2011 Oct;72(10):1353-62. doi: 10.4088/JCP.08m04138yel.
82. Soler J, Pascual JC, Campins J et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. Am J Psychiatry. 2005 Jun;162(6):1221-4.
83. Linehan MM, McDavid JD, Brown MZ et al. Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder: a double-blind, placebo-controlled pilot study. J Clin Psychiatry. 2008 Jun;69(6):999-1005.
84. Jariani M, Saaki M, Nazari H, Birjandi M. The effect of Olanzapine and Sertraline on personality disorder in patients with methadone maintenance therapy. Psychiatr Danub. 2010 Dec;22(4):544-7.
85. Shafti SS, Shahveisi B. Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double-blind trial. J Clin Psychopharmacol. 2010 Feb;30(1):44-7. doi: 10.1097/JCP.0b013e3181c826ff.
86. Bozzatello P, Rocca P, Uscinska M, Bellino S. Efficacy and Tolerability of Asenapine Compared with Olanzapine in Borderline Personality Disorder: An Open-Label Randomized Controlled Trial. CNS Drugs. 2017 Sep;31(9):809-819. doi: 10.1007/s40263-017-0458-4.
87. Shafti SS, Kaviani H. A comparative study between olanzapine and aripiprazole for management of female borderline personality symptoms. Bulletin of Clinical Psychopharmacology 25(1):1 · March 2015. doi: 10.5455/bcp.20140923100030.
88. Nickel MK, Muehlbacher M, Nickel C et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. Am J Psychiatry. 2006 May;163(5):833-8.
89. Nickel MK, Loew TH, Pedrosa GF. Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. Psychopharmacology (Berl). 2007 May;191(4):1023-6. Epub 2007 Feb 23.
90. Bellino S, Bozzatello P, Brignolo E, Bogetto F. Antipsychotics in the Treatment of Impulsivity in Personality Disorders and Impulse Control Disorders. Current Psychopharmacology, 2013, 2, 5-17. 2211-5579/13 $58.00+.00
91. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of aripiprazole augmentation in sertraline-resistant patients with borderline personality disorder. Psychiatry Res. 161(2), 206–212 (2008).
92. Chanen AM, Betts J, Jackson H et al. Aripiprazole compared with placebo for auditory verbal hallucinations in youth with borderline personality disorder: Protocol for the VERBATIM randomized controlled trial. Early Interv Psychiatry. 2019 Jan 28. doi: 10.1111/eip.12774.
93. Adityanjee, Schulz SC. Clinical use of quetiapine in disease states other than schizophrenia. J Clin Psychiatry. 2002;63 Suppl 13:32-8.
94. Adityanjee, Romine A, Brown E et al. Quetiapine in patients with borderline personality disorder: an open-label trial. Ann Clin Psychiatry. 2008 Oct-Dec;20(4):219-26. doi: 10.1080/10401230802467545.

Information Classification: General

95. Villeneuve E, Lemeline S. Open-label study of atypical neuroleptic quetiapine for treatment of borderline personality disorder: impulsivity as main target. J Clin Psychiatry. 2005 Oct;66(10):1298-303.
96. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of quetiapine in the treatment of borderline personality disorder: A pilot study. J Clin Psychiatry. 2006 Jul;67(7):1042-6.
97. Perrella C, Carrus D, Costa E, Schifano F. Quetiapine for the treatment of borderline personality disorder; an open-label study. Prog Neuropsychopharmacol Biol Psychiatry. 2007 Jan 30;31(1):158-63. Epub 2006 Oct 11.
98. Roepke S, Merkl A, Dams A et al. Preliminary evidence of improvement of depressive symptoms but not impulsivity in cluster B personality disorder patients treated with quetiapine: an open label trial. Pharmacopsychiatry. 2008 Sep;41(5):176-81. doi: 10.1055/s-2008-1076730. Epub 2008 Sep 1.
99. Van den Eynde F, Senturk V, Naudts K et al. Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. J Clin Psychopharmacol. 2008 Apr;28(2):147-55. doi: 10.1097/JCP.0b013e318166c4bf.
100. Black DW, Zanarini MC, Romine A et al. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2014 Nov 1;171(11):1174-82. doi: 10.1176/appi.ajp.2014.13101348.
101. Lee SS, Allen J, Black DW et al. Quetiapine's effect on the SCL-90-R domains in patients with borderline personality disorder. Ann Clin Psychiatry. 2016 Feb;28(1):4-10.
102. Martín-Blanco A, Patrizi B, Villalta L et al. Asenapine in the treatment of borderline personality disorder: an atypical antipsychotic alternative. Int Clin Psychopharmacol. 2014 Mar;29(2):120-3. doi: 10.1097/YIC.0000000000000004.
103. Pascual JC, Oller S, Soler J et al. Ziprasidone in the acute treatment of borderline personality disorder in psychiatric emergency services. J Clin Psychiatry. 2004 Sep;65(9):1281-2.
104. Pascual JC1, Soler J, Puigdemont D et al. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. J Clin Psychiatry. 2008 Apr;69(4):603-8.
105. Kahl KG, Negt P, Wollmer A et al. Inhaled Loxapine for Acute Treatment of Agitation in Patients With Borderline Personality Disorder: A Case Series. J Clin Psychopharmacol. 2015 Dec;35(6):741-3. doi: 10.1097/JCP.0000000000000402.
106. Krüger TH, Wollmer MA, Negt P et al. Inhaled loxapine for emergency treatment of agitated patients with borderline personality disorder : A series of five cases. Nervenarzt. 2016 Nov;87(11):1222-1226.
107. Patrizi B, Navarro-Haro MV, Gasol M. Inhaled loxapine for agitation in patients with personality disorder: an initial approach. Eur Neuropsychopharmacol. 2019 Jan;29(1):122-126. doi: 10.1016/j.euroneuro.2018.10.009. Epub 2018 Nov 26.
108. de Berardis D, Fornaro M, Orsolini L et al. The Role of Inhaled Loxapine in the Treatment of Acute Agitation in Patients with Psychiatric Disorders: A Clinical Review. Int J Mol Sci. 2017 Feb 8;18(2). pii: E349. doi: 10.3390/ijms18020349.
109. Bellino S, Rinaldi C, Bozzatello P et al. Recent approaches to pharmacotherapy of personality disorders. Neuropsych. 1(3), 259–273 (2011).

Information Classification: General

110. Philipsen A, Schmahl C, Lieb K. Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. Pharmacopsychiatry. 2004 Sep;37(5):196-9.
111. Schmahl C, Kleindienst N, Limberger M et al. Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. Int Clin Psychopharmacol. 2012 Jan;27(1):61-8. doi: 10.1097/YIC.0b013e32834d0e50.
112. Martín-Blanco A, Patrizi B, Soler J et al. Use of nalmefene in patients with comorbid borderline personality disorder and alcohol use disorder: a preliminary report. Int Clin Psychopharmacol. 2017 Jul;32(4):231-234. doi: 10.1097/YIC.0000000000000170.
113. Bartz J, Simeon D, Hamilton H et al. Oxytocin can hinder trust and cooperation in borderline personality disorder. Soc Cogn Affect Neurosci. 2011 Oct;6(5):556-63. doi: 10.1093/scan/nsq085. Epub 2010 Nov 29.
114. Simeon D, Bartz J, Hamilton H et al. Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. Psychoneuroendocrinology. 2011 Oct;36(9):1418-21. doi: 10.1016/j.psyneuen.2011.03.013. Epub 2011 May 4.
115. Bertsch K, Gamer M, Schmidt B et al. Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. Am J Psychiatry. 2013 Oct;170(10):1169-77. doi: 10.1176/appi.ajp.2013.13020263.
116. Brüne M, Ebert A, Kolb M et al. Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder. Hum Psychopharmacol. 2013 Nov;28(6):552-61.
117. Brüne M, Kolb M, Ebert A et al. Nonverbal communication of patients with borderline personality disorder during clinical interviews: a double-blind placebo-controlled study using intranasal oxytocin. J Nerv Ment Dis. 2015 Feb;203(2):107-11. doi : 10.1097/NMD.0000000000000240.
118. Ebert A, Kolb M, Heller J et al. Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. Soc Neurosci. 2013;8(4):305-13. doi: 10.1080/17470919.2013.807301.
119. Philipsen A, Richter H, Schmahl C et al. Clonidine in acute aversive inner tension and self-injurious behavior in female patients with borderline personality disorder. J Clin Psychiatry. 2004 Oct;65(10):1414-9.
120. Ziegenhorn AA, Roepke S, Schommer NC et al. Clonidine improves hyperarousal in borderline personality disorder with or without comorbid posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2009 Apr;29(2):170-3. doi: 10.1097/JCP.0b013e31819a4bae.
121. Zanarini MC, Frankenburg FR. omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry. 2003 Jan;160(1):167-9.
122. Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. Br J Psychiatry. 2007 Feb;190:118-22.
123. Amminger GP, Chanen AM, Ohmann S et al. Omega-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: a post hoc subgroup analysis of a double-blind, randomized controlled trial. Can J Psychiatry. 2013 Jul;58(7):402-8.

Information Classification: General

124. Bozzatello P, Rocca P, Bellino S. Combination of Omega-3 Fatty Acids and Valproic Acid in Treatment of Borderline Personality Disorder: A Follow-Up Study. Clin Drug Investig. 2018 Apr;38(4):367-372. doi: 10.1007/s40261-017-0617-x.
125. Grosjean B, Tsai GE. NMDA neurotransmission as a critical mediator of borderline personality disorder. J Psychiatry Neurosci. 2007 Mar;32(2):103-15.
126. Kulkarni J, Thomas N, Hudaib AR, et al. Effect of the Glutamate NMDA Receptor Antagonist Memantine as Adjunctive Treatment in Borderline Personality Disorder: An Exploratory, Randomised, Double-Blind, Placebo-Controlled Trial. CNS Drugs. 2018 Feb;32(2):179-187. doi: 10.1007/s40263-018-0506-8.
127. Rammes G, Danysz W, Parsons CG. Pharmacodynamics of memantine: an update. Curr Neuropharmacol. 2008 Mar;6(1):55-78. doi: 10.2174/157015908783769671.
128. Borschmann R, Henderson C, Hogg J et al. Crisis interventions for people with borderline personality disorder. Cochrane Database Syst Rev. 2012 Jun 13;(6):CD009353. doi: 10.1002/14651858.CD009353.pub2.
129. Boyce P, Carter G, Penrose-Wall J. Summary Australian and New Zealand Clinical Practice Guideline for the Management of Adult Deliberate Self-Harm (2003). Australasian Psychiatry, 11(2), 150–155. https://doi.org/10.1046/j.1039-8562.2003.00541.x
130. Linehan MM. Dialectical behavior therapy for treatment of borderline personality disorder: implications for the treatment of substance abuse. NIDA Res Monogr. 1993;137:201-16.
131. Bateman AW, Fonagy P. Mentalization-based treatment of BPD. J Pers Disord. 2004 Feb;18(1):36-51.
132. Angus L, Gillies LA. Counselling the Borderline Client: An Interpersonal Approach. Canadian Journal of Counselling and Psychotherapy. g/1994, Vol. 28 (69-82).
133. Markowitz JC, Skodol AE, Bleiberg K. Interpersonal psychotherapy for borderline personality disorder: possible mechanisms of change. J Clin Psychol. 2006 Apr;62(4):431-44.
134. Bateman AW. Interpersonal psychotherapy for borderline personality disorder. Clin Psychol Psychother. 2012 Mar-Apr;19(2):124-33. doi: 10.1002/cpp.1777. Epub 2012 Feb 20.
135. Bellino S, Bozzatello P, De Grandi E, Bogetto F. Interpersonal psychotherapy: a model of intervention for borderline personality disorder. Riv Psichiatr. 2014 Jul-Aug;49(4):158-63. doi: 10.1708/1600.17450.
136. **Bellino S, Bozzatello P, Bogetto F. Combined treatment of borderline personality disorder with interpersonal psychotherapy and pharmacotherapy: predictors of response. Psychiatry Res. 2015 Mar 30;226(1):284-8. doi: 10.1016/j.psychres.2014.12.064. Epub 2015 Jan 13.
137. **Bozzatello P, Bellino S. Combined therapy with interpersonal psychotherapy adapted for borderline personality disorder: A two-years follow-up. Psychiatry Res. 2016 Jun 30;240:151-156. doi: 10.1016/j.psychres.2016.04.014. Epub 2016 Apr 13.
138. Nosè M, Cipriani A, Biancosino B et al. Efficacy of pharmacotherapy against core traits of borderline personality disorder: meta-analysis of randomized controlled trials. Int Clin Psychopharmacol. 2006 Nov;21(6):345-53.
139. **Ingenhoven T, Lafay P, Rinne T, Passchier J, Duivenvoorden H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. J Clin Psychiatry. 2010 Jan;71(1):14-25.
140. Ingenhoven TJ, Duivenvoorden HJ. Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on

Information Classification: General

symptomatic outcome domains. J Clin Psychopharmacol. 2011 Aug;31(4):489-96. doi: 10.1097/JCP.0b013e3182217a69.
141. Vita A, De Peri L, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. J Clin Psychopharmacol. 2011 Oct;31(5):613-24. doi: 10.1097/JCP.0b013e31822c1636.
142. Saunders EF, Silk KR. Personality trait dimensions and the pharmacological treatment of borderline personality disorder. J Clin Psychopharmacol. 2009 Oct;29(5):461-7. doi: 10.1097/JCP.0b013e3181b2b9f3.
143. Paolini E, Mezzetti FA, Pierri F, Moretti P. Pharmacological treatment of borderline personality disorder: a retrospective observational study at inpatient unit in Italy. Int J Psychiatry Clin Pract. 2017 Mar;21(1):75-79. doi: 10.1080/13651501.2016.1235202. Epub 2016 Sep 27.
144. Starcevic V, Janca A. Pharmacotherapy of borderline personality disorder: replacing confusion with prudent pragmatism. Curr Opin Psychiatry. 2018 Jan;31(1):69-73. doi: 10.1097/YCO.0000000000000373.
145. Arens EA, Stopsack M, Spitzer C, et al. Borderline personality disorder in four different age groups: a cross-sectional study of community residents in Germany. J Pers Disord. 2013 Apr;27(2):196-207. doi: 10.1521/pedi.2013.27.2.196.
146. Chanen AM, Kaess M. Developmental pathways to borderline personality disorder. Curr Psychiatry Rep. 2012 Feb;14(1):45-53. doi: 10.1007/s11920-011-0242-y
147. World Health Organization. International statistical classification of diseases and related health problems (11th Revision) 2018.
148. Brewin CR, Cloitre M, Hyland P, Shevlin M, et al. A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. Clinical Psychology Review 58 (2017) 1–15..
149. Haravuori H, Kiviruusu O, Suomalainen L, Marttunen M. An evaluation of ICD-11 posttraumatic stress disorder criteria in two samples of adolescents and young adults exposed to mass shootings: factor analysis and comparisons to ICD-10 and DSM-IV. BMC Psychiatry. 2016 May 12;16:140. doi: 10.1186/s12888-016-0849-y.
150. Karatzias T, Murphy P, Cloitre M, Bisson J, et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol Med. 2019 Aug;49(11):1761-1775. doi: 10.1017/S0033291719000436.

** These studies provide important data in promiment fields of research: an accurate review and a meta-analysis of available evidences of efficacy of pharmacotherapy and the first findings about clinical predictors of response and long-term efficacy of combined therapy in BPD.

* These studies are also of particular interest for the topic of this review: the first is not so recent, but is the only available set of treatment guidelines for BPD provided by the Federation of Societies of Biological Psychiatry with a special focus on the use of drugs; the second is a narrative review of literature on BPD pharmacotherapy with an attempt to address some core issues and open questions.

Information Classification: General

Table 1: Randomized controlled trials of antidepressants for borderline personality disorder.

Study (year) [Ref.]	Interventional arm(s)	Comparison arm(s)	Sample	Treatment duration	Results
Salzamann et al. (1995) [28]	Fluoxetine (20–60 mg/day)	Placebo	27 BPD patients	12 weeks	Decrease in anger, improvement in global functioning. No effect on depression
Markovitz (1995) [29]	Fluoxetine (20–80 mg/day)	Placebo	17 BPD patients with concomitant affective and anxiety disorders	14 weeks	Decrease of all symptoms
Coccaro and Kavoussi (1997) [30]	Fluoxetine (20–60 mg/day)	Placebo	40 patients with PDs (33% BPD) and comorbidity with dysthymia, anxiety disorders or substance abuse	12 weeks	Improving of irritability, impulsive-aggression, and global functioning
Simpson et al. (2004) [31]	Fluoxetine (40 mg/day) + DBT	Placebo + DBT	25 female BPD patients	12 weeks	No effects
Zanarini et al. (2004)[32]	Fluoxetine (15 mg/day)	Fluoxetine (15 mg/day) + olanzapine (2.5 mg/day) and olanzapine (2.5 mg/day)	45 female BPD patients	8 weeks	Both the comparison arms resulted to be superior to fluoxetine monotherapy to decrease all symptoms
Rinne et al. (2002) [34]	Fluvoxamine (150–250 mg/day)	Placebo	38 female BPD patients, comorbidity with mood and anxiety disorders	6 weeks	Decrease of rapid mood shifts. No effects on aggression and impulsivity
Jariani et al. (2010) [35]	Sertraline (50–100 mg/day)	Olanzapine (5–10 mg/day)	120 BPD patients on methadone therapy	12 weeks	Sertraline > olanzapine in decreasing depression, hypersensitivity in interpersonal relationship, and obsessions. Olanzapine > sertraline in decreasing anxiety, aggression, paranoia, and self-harming Sertraline = olanzapine in decreasing Somatization symptoms
Markovitz et al. (1995) [36]	Venlafaxine				Effective in reducing somatic symptoms
Bellino et al. (2010)[37]	Duloxetine (60 mg/day)		18 BPD patients	12 weeks	Improvement of depressive symptoms, impulsivity, outbursts of anger, and affective instability

Ref.: reference; BPD: borderline personality disorder; DBT: dialectical behavioral therapy

Information Classification: General

Table 2: Randomized controlled trials of mood stabilizers for borderline personality disorder.

Study (year) [Ref.]	Interventional arm(s)	Comparison arm(s)	Sample	Treatment duration	Results
Links et al. (1990) [39]	Lithium (986 mg/day)	Desipramine and placebo	17 BPD patients receiving concomitant psychotherapy	6 weeks	Lithium was superior to ecrease anger, irritability and self-mutilation. No effects on mood symptoms
De la Fuente and Lotstra (1994) [40]	Carbamazepine (plasma level)	Placebo	20 BPD outpatients	4.5 weeks	No effects
Hollander et al. (2001) [41]	Valproate sodium (plasma level)	Placebo	16 BPD patients	10 weeks	No effects (probably because of high drop-out rate)
Hollander et al. (2005) [42]	Valproate sodium (plasma level)	Placebo	96 cluster B PDs (52 BPD) with impulsive-aggression	12 weeks	Improvement of global symptopathology, impulsive-aggression, and irritability
Frankenburg and Zanarini (2002) [43]	Valproate sodium (plasma level)	Placebo	30 female BPD patients with comorbid bipolar II disorder	6 months	Improvement of interpersonal sensitivity, anger, hostility, and aggressiveness
Moen et al. (2012) [44]	Divalproex ER (plasma level)	Placebo	15 BPD patients after 4 weeks of "condensed" DBT	4 weeks	No differences between the two arms
Bellino et al. (2014) [45]	EPA and DHA with valproic acid (plasma level)	Valproic acid only (plasma level)	43 BPD outpatients	12 weeks	Combined therapy > single therapy for impulsivity, self-harm, and outbursts of anger
Nickel et al. (2004) [46]	Topiramate (50–250 mg/day)	Placebo	31 female BPD patients	8 weeks	Improvement of irritability and anger
Nickel et al. (2005) [47]	Topiramate (50–250 mg/day)	Placebo	42 male BPD patients	8 weeks	Improvement of irritability and anger
Loew et al. (2008) [51]	Topiramate (25–200 mg/day)	Placebo	56 female BPD patients with concomitant mood disorders	10 weeks	Improvement of somatization, interpersonal sensitivity, hostility and global functioning
Tritt et al. (2005) [52]	Lamotrigine (50–200 mg/day)	Placebo	24 female BPD patients	8 weeks	Improvement of anger
Reich et al. (2009) [53]	Lamotrigine (25–275 mg/day)	Placebo	28 BPD patients with major depression and anxiety disorders	12 weeks	Improvement of impulsivity and affective instability
Leiberich et al., (2008) [54]	Lamotrigine (50–200 mg/day)	Placebo	27 female BPD patients	18 months follow-up	Improvement of aggression in the long-term treatment
Crawford et al., (2015) [55]	Lamotrigine (25-400 mg/die)	Placebo	28 BPD patients	52 weeks	No effect in terms of symptomatic reliefs and cost-effectiveness balance.

Information Classification: General

Ref.: reference; BPD: borderline personality disorder; DBT: dialectical behavioral therapy

Table 3: Randomized controlled trials and open trials of antipsychotics for borderline personality disorder.

Study (year) [Ref.]	Interventional arm(s)	Comparison arm(s)	Sample	Treatment Duration	Results
Cornelius et al. (1993) [61]	Haloperidol (≤6 mg/day)	Placebo	54 BPD outpatients from Soloff et al. (1993) study	16 weeks	Improvement of hostility and impulsive-aggression
Soloff et al. (1993) [62]	Haloperidol (4 mg/day)	Phenelzine (60 mg/day) and placebo	108 BPD inpatients with concomitant major depression	5 weeks	Improvement of irritability
Szigety &Schultz (1998) [75]	Risperidone (2.5 mg/day)	Placebo	27 BPD patients	8 weeks	No difference with regard to global functioning. Risperidone > placebo in reducing psychoticism, paranoid ideas, phobic anxiety and interpersonal sensitivity
Zanarini and Frankenburg (2001) [78]	Olanzapine (5.33 mg/day)	Placebo	28 female BPD patients	6 months	Improvement of anger, interpersonal sensitiv, anxiety, paranoid ideation and global functioning
Bogenschutz and Nurnberg (2004) [79]	Olanzapine (5–10 mg/day)	Placebo	40 BPD outpatients	12 weeks	Improvement of anger and global symptoms
Schulz et al. (1998) [80]	Olanzapine (2.5–20 mg/day)	Placebo	314 BPD patients	12 weeks	No differences between two groups. Faster amelioration in olanzapine group.
Zanarini et al. (2011) [81]	Olanzapine low doses (2.5 mg/day) and moderate doses (5–10 mg/day)	Placebo	451 BPD outpatients	12 weeks	Olanzapine moderate doses > placebo in global symptoms
Soler et al. (2005) [82]	Olanzapine (5–20 mg/day) + DBT	Placebo + DBT	60 BPD patients	12 weeks	Improvement of anxiety, depression and impulsive-aggression
Linehan et al. (2008) [83]	Olanzapine (5 mg/day) + DBT	Placebo + DBT	24 female BPD patients	21 weeks	No differences of general symptoms. Faster decrease of irritability and aggression in olanzapine group
Jariani et al. (2010) [84]	Olanzapine (5-10 mg/day)	Sertraline (50-100 mg/day)	120 BPD patients on methadone maintenance therapy	12 weeks	Both drugs improving depression, anxiety, aggression, sensitivity in interpersonal relationships, obsessive symptoms, pessimistic behaviors and somatization disorders
Shafti and Shahveisi (2010) [85]	Olanzapine (7 mg/day)	Haloperidol (7 mg/day)	28 female BPD inpatients	8 weeks	No differences
Bozzatello et al. (2017) [86]	Olanzapine (5-10 mg/day)	Asenapine (5-10 mg/day)	51 BPD patients between 18 and 50 years	12 weeks	Asenapine > Olanzapine in treating affective instability Olanzapine > Asenapine in treating paranoid ideation and dissociation

Information Classification: General

Shafti and Kaviani (2015) [87]	Olanzapine (6.4 mg/day)	Aripiprazole (7 mg/day)	24 female BPD inpatients	8 weeks	Olanzapine > Aripiprazole on uncooperativeness and excitement Aripiprazole > Olanzapine on suspiciousness and unusual thought content
Nickel et al. (2006) [88]	Aripiprazole (15 mg/day)	Placebo	57 BPD patients	8 weeks	Improvement of depression, anxiety, anger, aggressiveness, paranoia and global functioning
Nickel et al. (2007) [89]	Aripiprazole (15 mg/day)	Placebo	52 BPD patients	18 months	Effective and relatively safe agent in the long-term treatment
Chanen et al. (2018) [92]	Aripiprazole (2-30 mg/day)	Placebo	154 BPD patients	12 weeks + 27-week follow-up	Improvement of general psychopathology, borderline personality pathology, social and occupational functioning
Black et al. (2014) [100]	Quetiapine low (150 mg/day) and moderate doses (300 mg/day)	Placebo	95 BPD patients (70.5% female)	8 weeks	Quetiapine low doses > placebo in all the outcomes measures (in particular affective instability, cognitive-perceptual symptoms and aggressiveness). Faster response in both the treatment groups
Lee et al. (2016) [101]	Quetiapine low (150 mg/day) and moderate doses (300 mg/day)	Placebo	95 BPD patients (70.5% female)	8 weeks	Improvement of all the outcomes measures with both quetiapine doses
Pascual et al. (2008) [104]	Ziprasidone (84 mg/day)	Placebo	60 BPD patients	12 weeks	No effects
Bellino et al. (2009) [91]	Sertraline (50-100 mg/day) + Aripiprazole (10-15 mg/day)	Open label trial	21 BPD patients between 18 and 50 years	12 weeks	Improvement of impulsivity and dissociation/paranoid ideation
Perrella et al. (2007) [97]	Quetiapine (400-800 mg/day)	Open label trial	29 BPD outpatients	12 weeks	Improvement of mood symptoms and aggression
Bellino et al. (2011) [76]	Paliperidone ER (3-6 mg/day)	Open label trial	18 BPD outpatients	12 weeks	Improvement of impulsive dyscontrol, anger, and cognitive-perceptual disturbances
Rocca et al. (2002) [71]	Risperidone (3.27 mg/day)	Open label trial	15 BPD outpatients	8 weeks	Improvement of depressive symptoms, energy and global functioning

BPD: borderline personality disorder; DBT: dialectical behavioral therapy; >: superior of.

Information Classification: General

Table 4: Randomized controlled trials of other psychotropic agents and for borderline personality disorder.

Study (year) [Ref.]	Interventional arm(s)	Comparison arm(s)	Sample	Treatment Duration	Results
Philipsen et al. (2004) [110]	Naloxone (0,4 mg/day)	Placebo	9 BPD patients	15 min	No differences in dissociative symptoms
Schmahl et al. (2012) [111]	Naltrexone (50 or 200 mg/day)	Placebo	29 BPD patients	3 weeks	No differences in dissociative symptoms
Bertsch et al. (2013) [115]	Oxytocin (26 IU)	Placebo	40 female nonmedicated BPD patients	45 minutes	Improvement of social hypersensitivity, anger and aggressive behavior
Philipsen et al. (2004) [119]	Clonidine (75 µg/day)	Clonidine (150 µg/day)	14 female BPD patients	30,60 and 120 min	Decrease (maximum after 30-60 min) of all the symptoms with both doses of clonidine
Ziegenhorn et al. (2009) [120]	Clonidine (up to 0,3 mg/day)	Placebo	18 BPD patients, some of them with concomitant PTSD	6 weeks	Decrease of hyperarousal symptoms independently of PTSD comorbidity. Decrease of BPD specific and general symptoms mainly in the PTSD-positive subgroup
Zanarini and Frankenburg, (2003) [121]	EPA (1 g/day)	Placebo	30 female BPD patients	8 weeks	Improvement of Depressive symptoms and aggressive behaviors
Hallahan et al. (2007) [122]	EPA (1.2 g/day)+DHA (0,9 g/day)	Placebo	49 patients with self-harm behaviors (35 BPD)	12 weeks	Improvement of depression, suicidality and reaction to daily stress
Amminger et al. (2013) [123]	PUFAs (1,2 g/day)	Placebo	15 adolescent BPD patients with high risk of psychosis	12 weeks	Improvement of global functioning and schizophrenia-like symptoms
Bellino et al. (2014) [45]	EPA (1.2 g/day) + DHA (0,8 g/day) + valproate (800-1300 mg/day)	Valproate (800-1300 mg/day)	43 BPD outpatients	12 weeks	No differences with regard to global symptoms. Improvement of impulsivity, anger and self-mutilating conducts in omega-3 group
Bozzatello et al. (2018) [124]	EPA (1.2 g/day) + DHA (0,8 g/day) + valproate (800-1300 mg/day)	Valproate (800-1300 mg/day)	43 BPD outpatients	24 weeks follow-up	Combined therapy with omega-3 fatty acids showed long-lasting effects after discontinuation in terms of anger control.
Kulkarni et al. (2018) [126]	Memantine (20 mg/die)	Placebo	33 BPD outpatients	8 weeks	Memantine showed > improvement on aggression, disinhibition, irritability and depressed mood

BPD: borderline personality disorder; PTSD: Posttraumatic Stress Disorder; EPA: Eicosapentaenoic acid; PUFAs: Polyunsaturated fatty acid; >: superior of.

Information Classification: General

Table 5: Randomized controlled trials of combined therapy (pharmacotherapy + psychotherapy) for borderline personality disorder.

Study (year) [Ref.]	Interventional arm(s)	Comparison arm(s)	Sample	Treatment duration	Results
Simpson et al. (2004) [31]	Fluoxetine (40 mg/day) + DBT	Placebo + DBT	25 female BPD patients	12 weeks	No effects on depression, anxiety, anger, dissociation, and global functioning
Soler et al. (2005) [82]	Olanzapine (5–20 mg/day) + DBT	Placebo + DBT	60 BPD patients	12 weeks	Improvement of anxiety, depression, and impulsive-aggression
Linehan et al. (2008) [83]	Olanzapine (5 mg/day) + DBT	Placebo + DBT	24 female BPD patients	21 weeks	No differences in treatment of general symptoms. Faster decrease of irritability and aggression in the olanzapine group
Bellino et al. (2010) [33]	Fluoxetine (20-40 mg/day) + IPT-BPD	Fluoxetine (20-40 mg/day)	44 BPD patients	32 weeks	Combined therapy > fluoxetine in improving BPD core symptoms (interpersonal relationships, affective instability, and impulsivity), anxiety and QoL
Bellino et al. (2015) [136]	Fluoxetine (20-40 mg/day) + IPT-BPD	Fluoxetine (20-40 mg/day)	44 BPD patients	32 weeks	More severe BPD psychopathology and higher degree of fear of abandonment, affective instability, and identity disturbance predicted response to combined therapy
Bozzatello and Bellino (2016) [137]	Fluoxetine (20-40 mg/day) + IPT-BPD	Fluoxetine (20-40 mg/day)	44 BPD patients	24 months	Persistence of advantages of combined therapy on impulsivity, interpersonal dysfunctions, and QoL

Ref.: reference; BPD: borderline personality disorder; DBT: dialectical behavioral therapy; IPT-BPD: interpersonal psychotherapy adapted to BPD; QoL: quality of life; > : superior to

Information Classification: General