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SYSTEMATIC REVIEW ARTICLE

Current Clinical Psychopharmacology in Borderline Personality Disorder

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Abstract: ***Background*:** Patients with Borderline Personality Disorder (BPD) manifest affective and behavioral symptoms causing personal distress, relationship difficulties, and reduced quality of life with global functioning impairment, mainly when the disease takes an unfavorable course. A substantial amount of healthcare costs is dedicated to addressing these issues. Many BPD patients receive medications, mostly those who do not respond to psychological interventions.

***Objective*:** Our aim was to assess the efficacy of the most used strategies of pharmacological interventions in BPD with a comprehensive overview of the field.

***Methods*:** We searched the PubMed database for papers focused on the most used psychotropic drugs for BPD. We included randomized controlled trials and open studies in adult patients with BPD, focusing on the efficacy and tolerability of single classes of drugs with respect to specific clinical presentations that may occur during the course of BPD.

***Results*:** Specific second-generation antipsychotics (SGAs) or serotonergic antidepressants can be effective for different core symptoms of BPD, mainly including mood symptoms, anxiety, and impulse dyscontrol. Some atypical antipsychotics can also be effective for psychotic and dissociative symptoms. Specific antiepileptics can be useful in some cases in treating different BPD symptoms, mainly including mood instability, impulsiveness, and anger.

***Conclusion*:** No medication is currently approved for BPD, and clinicians should carefully assess the benefits and risks of drug treatment. Further studies are needed to identify specific personalized treatment strategies, also considering the clinical heterogeneity and possible comorbidities of BPD.

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1. INTRODUCTION

Borderline pathology was first described by Stern [1] as lying on a "borderland" between psychosis and neurosis. This construct had no direct implications for personality problems. Subsequently, it was increasingly viewed as a personality disorder. Linehan's [2] model has been the most influential in viewing the core symptom of borderline personality disorder (BPD) as emotion dysregulation. BPD is the most studied personality area because it is clinically common [3] and affects society significantly [4]. Its response to pharmacological interventions is limited to certain symptoms [5]. Although most patients improve with time [6], BPD can have a chronic course, with symptoms of marked impulsivity, instability of mood, problems in interpersonal relationships, and suicidality, which can have a negative impact on both clinical outcomes and effectiveness of treatments. One of the major clinical challenges is the management of chronic suicidality [7]. Making the diagnosis is crucial for planning treatment.

The prevalence of BPD in the community is estimated at about 2% of the adult population [8], but it is present in 9% of psychiatry outpatients [9] and is also common among inpatients [10]. It is predominantly diagnosed in women

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Table 1. BPD Diagnostic Criteria (DSM-5).

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), Borderline Personality Disorder is characterized by a pervasive instability of social relationships, self-image, and emotions; marked impulsivity beginning in early adulthood and present in at least five of the following contexts:

- Frantic efforts to avoid real or imagined abandonment, reflecting intolerance to be alone;
- Unstable and intense relationships marked by abrupt and extreme shifts between idealization and devaluation;
- Identity disturbance, seen in an unstable self-image or sense of self;
- Impulsivity that is potentially self-damaging in at least two of the following areas—spending, sex, substance abuse, reckless driving, binge eating;
- Recurrent suicidal gestures or threats, or self-mutilation;
- Affective instability with marked mood reactivity;
- Chronic feelings of emptiness;
- Frequent displays of inappropriate or intense anger or difficult control of anger;
- Transient and stress-related paranoid ideation or severe dissociative symptoms

(75%). It is important to diagnose BPD in adolescents, as most cases begin at that stage of development [11].

We have summarized the diagnostic criteria of BPD indicated by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [12] in Table **1**.

BPD often coexists with many other disorders, most commonly with mood disorders, substance use, eating disorders, post-traumatic stress disorder (PTSD), as well as other personality disorders. The most common comorbid condition is major depression [13], although this overlap can also be seen as an artifact of the DSM criteria [6]. BPD patients have high rates of self-harm [14] and suicide attempts [15]. There is now a large empirical literature on the psychotherapeutic treatment of BPD. A range of treatments deriving from both cognitive-behavioral and psychodynamic traditions have shown efficacy in randomized controlled trials (RCTs). The results of these studies suggest that BPD is a treatable disorder in most cases. The best known and most widely tested of these treatments is dialectical behavior therapy [2], which is derived from a cognitive-behavioral tradition. From the same tradition, there is evidence for schema-focused therapy (SFT) [16, 17] and for a briefer treatment called Systems Training for Emotional Predictability and Problem Solving (STEPPS) [18]. Other BPD-specific psychotherapies are derived from the psychoanalytic/psychodynamic tradition. The best known among these are mentalization-based therapy (MBT) [19] and transference-focused psychotherapy (TFP) [20]. In contrast to these specialty treatments, good psychiatric management (GPM) is a generalist approach to psychotherapy and treatment of BPD [21]. Although there have been few direct comparisons, enough data now exist from RCTs and meta-analyses to suggest that no approach has been consistently found superior to another, as supported by a recent Cochrane report [5], which also notes that the literature on long-term outcome remains sparse.

All psychotherapeutic treatments share many similarities; there is a common focus on emotion regulation, views of self and others, and unintegrated mental states. Furthermore, treatments for BPD generally include a focus on self-observation, controlling intense emotions, reducing impulsivity, and improving interpersonal relationships [6]. With regard to drug treatment, there are numerous studies in the literature focused on the pharmacological treatment of BPD, without conclusive evidence in support of therapeutic indications nor an existing consensus regarding the most appropriate duration of psychopharmacological treatment. It should also be noted that most published studies have relatively small samples, and their results have not been consistently replicated. Finally, we need to consider sociocultural factors that may have influenced published guidelines [22].

Some guidelines are highly conservative about psychopharmacology for BPD. Unfortunately, the last Cochrane report is already old [23], although a revision is being prepared. The National Institute for Health and Care Excellence (NICE) [24] guidelines state that antipsychotic drugs should not be used for the medium- and long-term treatment of BPD. They advise clinicians to consider drug treatments in the event of a crisis, but these should be prescribed for no longer than 1 week. The same guidelines stated that, when considering drug treatment for any reason for a person with BPD, clinicians should consider the existing evidence of the efficacy of target drugs and inform patients. While it can be important to treat comorbid disorders, one needs to recognize that medications that are effective in patients without personality disorders are less useful in those who have these diagnoses [25]. The relationship between BPD and depression is problematic because most patients meet the criteria for both but with very different psychopathological characteristics and treatment responses. Differential diagnosis is most important in distinguishing BPD from bipolar spectrum disorders, attention-deficit/hyperactivity disorder, and post-traumatic stress disorder [26,27].

The American Psychiatric Association guidelines recommended a symptom-targeted pharmacotherapy, consistent with the conclusion that pharmacology does not change the overall severity of the disorder [28,29]. However, since patients are heterogeneous, they may need personalized treatments.

This paper aims to review the scientific evidence of the efficacy of the main drugs used for treating its symptoms.

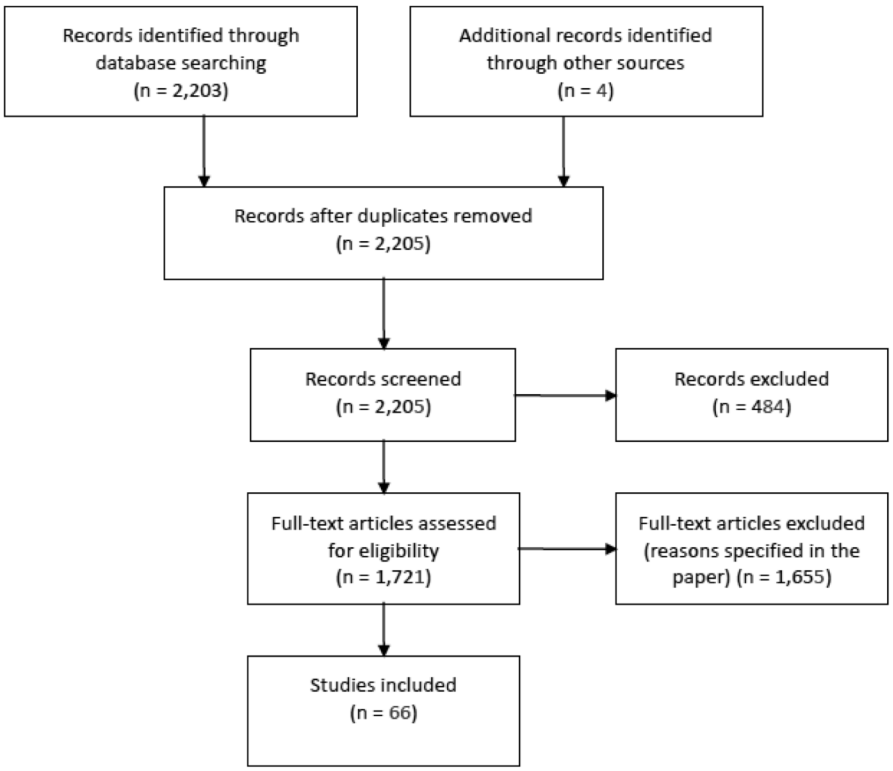

Fig. (1). PRISMA flow diagram showing search and inclusion strategy.

2. METHODS

We performed a PubMed search to identify peer-reviewed studies focused on psychopharmacological treatment in adult patients with BPD. We followed a stepwise method to identify relevant experimental articles.

First, on 10 July 2020, we identified studies through a standard search with the title/abstract specification in PubMed (http://www.pubmed.gov), using the terms "borderline personality disorder," "pharmacol*," "treatment," "therapy," "psychopharmacology," and excluding the terms "magnetic," "stimulation," "electroconvulsive," "ECT," "schizophrenia," "schizoaffective," "post-traumatic stress disorder," and "PTSD." We retrieved 2,203 papers.

Second, we included pharmacological trials, systematic reviews, and meta-analyses. We excluded articles with samples of BPD patients of fewer than 5 and studies that included patients with schizophrenia spectrum and obsessive-compulsive spectrum disorders, attention deficit and hyperactivity disorder (ADHD), case reports, bipolar disorders, head trauma, and neurological illnesses. We also excluded studies focused on psychotherapy not combined with pharmacological treatments, and neural stimulation, transcranial magnetic stimulations, and neurosurgery studies, as well as neuroimaging studies and animal studies.

Third, we searched for studies prior to the considered period in article references and on PubMed through the function "Similar articles," further considering another four studies.

On these bases, we considered 2,205 studies. Of these, 484 were not focused on BPD or not related to the topic; 49 were case reports or case series or had insufficient samples; 620 specifically focused on psychotherapy or psychosocial treatments; 217 were reviews; 705 mainly focused on clinical or psychopathological aspects; 7 were neuroimaging studies; 43 focused on other aspects of biological psychiatry; 2 were letters to the editor; 2 were duplicates; 10 were treatment guidelines.

Fourth, we finally included 66 papers focusing on the psychopharmacological treatment of BPD symptoms (see PRISMA flow-chart, Fig. **1**).

3. RESULTS

We summarized the results of this systematic review in Table **2**.

4. DISCUSSION

It has been evident since the end of the twentieth century that pharmacotherapy coupled with psychotherapy can produce a clinically significant improvement in mood and behavioral symptoms of patients with BPD [30]. Based on their specific mechanisms of action, different psychotropic drugs can act positively on different types of BPD symptoms. Here we summarize, for each drug within the main psychopharmacological classes (*i.e.*, antipsychotics, antidepressants, antiepileptics, and other drugs), the evidence of efficacy on some symptom dimensions of BPD.

4.1. Antipsychotics

Antipsychotic drugs are indicated in the treatment of schizophrenia and psychotic manifestations of mood disorders.

Table 2. Summary of included studies on drug treatment in BPD.

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Antipsychotics								
Bellino *et al.*, 2011 [58]	PAL (ER) (4.8)	Observational Study	14 (4, 10)	25.2 (4.9)	N/A	no	CGI-S, HAM-D, HAM-A, SOFAS, BPRS, BPDSI, DOTES	Overall symptoms, impulsivity, outbursts of anger, dissociative symptoms, paranoid ideation.
Bellino *et al.*, 2006 [43]	QTP	Clinical Trial	14 (7, 7)	29.64 (5.5)	no	no	CGI; BPRS; HAM-D; HAM-A; SOFAS; BPDSI; BIS-11	Excluding depressive symptoms, overall improvement of BPD symptoms, mostly functioning, anxiety, anger and impulsivity.
Bellino *et al.*, 2008 [57]	ARI (10-15); SRT	Comparative Study (12)	21 (12, 9)	26.32 ± 4.6	no	no	BPRS, CGI, HAM-D, HAM-A, SOFAS, BPDSI, BIS-11	Severity of symptoms, impulsivity, dissociation, and paranoid ideation. Improvement in global functioning.
Benedetti *et al.*, 1998 [52]	CLZ (25-100)	Clinical Trial	12 (2, 10)	29.8 (5.5)	N/A	no	BPRS, CGI, HAM-D, GAF	Increase of social and global functioning; improvements in depressive and anxiety symptoms
Black *et al.*, 2014 [40]	QTP (150-300)	Randomized Controlled Trial	95 (28, 67)	QTP 150 = 28.2 (8.0) QTP 300 = 30.2 (8.1)	Mood disorders, Anxiety disorders, Substance use disorders (Any axis I disorder in 76 patients)	no	DSMIVI, YMRS, ZAN-BPD, MADRS, OAS, YMRS, GAF, BDI, BIS-11, SCL-90, SDS, SAR, BAS, AIMS	Improvements in overall symptoms, mainly impulsivity, aggressive behaviour, and work/school functioning. Slightly effective on impulsivity and somatic symptoms.
Bozzatello *et al.*, 2017 [48]	ASN; OLA (5-10)	Comparative Study	40 (24, 26)	24.7 (5.3)	N/A	no	CGI-S, HAM-D, HAM-A, SOFAS, BPDSI, BIS-11, MOAS, SHI, DOTES	Overall symptoms, mostly affective instability, and dissociation/paranoid ideation.
Cornelius *et al.*, 1993 [50]	HLP (6); PHN (90)	Double-Blind, Placebo-Controlled Continuation Study (5)	54 (14, 40)	27.6 (8)	no	no	GAS, BDI, ADI, BDHI, HAM-D, IMPS, SSI	Modest improvements in irritability and depressive symptoms.
Cornelius *et al.*, 1993 [51]	HLP; PHN	Double-Blind, Placebo-Controlled Continuation Study	54	N/A	Atypical depression	no	GAS, SCL-90, HAM-D, BDI	Limited efficacy of continuation therapy.
Frankenburg & Zanarini, 1993 [53]	CLZ (75-550)	Preliminary Study	15 (6, 9)	29.1 (8.6)	Psychotic disorder	no	BPRS, CGI, GAF	Significant improvement of social and global functioning.
Jensen & Andersen, 1989 [54]	AMO (150-300)	Clinical Trial (4)	5 (2, 3)	32	N/A	no	BPRS, HAM-D, CGI	No effect could be shown.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Kutcher *et al.*, 1995 [76]	FLP	Open Prospective Study	13 (2, 11)	17.2	no	no	DIB, KSAS, HPI, WSI, Life Stressors Subscale of the WSI, AIMS, BDI, SCL-90	Improvements in impulsivity, depression/dysphoria, general psychopathology and global functioning.
Lee *et al.*, 2016 [44]	QTP (150 or 300)	Placebo-Controlled Randomized Controlled Trial (9)	66 (18, 48)	29.5 (8.3)	No current comorbidities	no	SCL-90-R, ZAN-BPD	Quetiapine 150: improvements in interpersonal sensitivity, depression, and hostility. Quetiapine 300: improvements in interpersonal sensitivity, depression, hostility, phobic anxiety, and overall symptoms.
Linehan *et al.*, 2008 [35]	OLA	Randomized Controlled Trial	24 (0, 24)	18-60	no	yes (DBT)	DAS-M; HAM-D	Anger and impulsivity.
Nickel *et al.*, 2006 [56]	ARI (15)	Randomized Controlled Trial (8)	26 (4, 22)	22.1 (3.4)	Depressive disorders, anxiety disorders, obsessive-compulsive disorders, somatoform disorders.	TS: 18; PBS: 19	SCL-90-R, CGI, HAM-D, HAM-A, STAXI	Overall symptoms, depression, anxiety, and anger.
Nickel *et al.*, 2007 [55]	ARI	Randomized Controlled Trial (52)	26 (4, 22)	N/A	no	no	SCL-90-R; HAM-D; HAM-A; STAXI; CGI	Overall symptoms.
Palomares *et al.*, 2015 [59]	PAL (LAI) (50 - 150 per month)	Observational Study	16 (4, 12)	32.6 (8)	N/A	no	CGI-BPD, HAM-A, MADRS, BIS-11, STAXI-2	Significant improvement of psychopathological status and increase of psychosocial functioning. Improvements of impulsive-disruptive behaviours and general functioning.
Pascual *et al.*, 2004 [63]	ZPR (20 - 160)	Clinical Trial	12 (2, 10)	26.2 (5.7)	N/A	no	CGI-S, HAM-D, HAM-A, BPRS, BIS, SCL-90-R	Improvement in global psychopathology, depression, anxiety, global functioning, and impulsivity.
Pascual *et al.*, 2008 [62]	ZPR	Randomized Controlled Trial	60 (11, 49)	29.1 (5.96)	no	no	CGI; BPRS; HAM-D; HAM-A; SOFAS; BPDSI; BIS-11	No effect could be shown.
Perrella *et al.*, 2007 [45]	QTP	Prospective Study	23 (9, 14)	29.7 (4.86)	History of alcohol and/or substance abuse (N = 13)	no	CGI; BPRS; GAF; AGGRESSION QUESTIONNAIRE; HAM-D	Depression, hostility, suspiciousness, aggression, and functioning.
Rocca *et al.*, 2002 [60]	RSP (3.27)	Open-Label Trial (8)	13	N/A	Antisocial personality disorder (N=4)	no	CGI; BPRS; HAM-D; OAS	Reduction of aggressive behaviour, coupled with an overall improvement of symptoms, including depressive symptoms. Increase in energy and global functioning.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Schulz *et al.*, 1999 [37]	OLA (7.73)	Clinical Trial	11 (2, 9)	37	Dysthymia	no	SCL-90, BPRS, SIB, BDHI, BIS11, GAF	Reduction of BPD severity, somatic symptoms, aggressive behaviour, and improved social functioning.
Schulz *et al.*, 2008 [33]	OLA	Randomized Controlled Trial	314 (89, 223)	18-65	no	14	ZAN-BPD; SCL-90-R; GAF; SFDS; MOAS; MADRS	Decrease of suicidality and self-harm ideation, anger, irritability; increase of social interactions.
Soler *et al.*, 2005 [39]	OLA (8.83)	Randomized Controlled Trial (12)	60 (13, 47)	27.57	no	weekly 150-minute group psychotherapy sessions	CGI; HAM-D; HAM-A	Depressive symptoms, clinical anxiety. The olanzapine plus dialectical behaviour therapy group experienced a significantly greater decrease in the frequency of impulsivity/aggressive behaviour.
Soloff *et al.*, 1993 [49]	HLP (4); PHN (60)	Randomized Controlled Trial	108 (26, 82)	26.7 (7.2)	Schizotypal personality disorder, Major Depressive Disorder	no	HAM-D, BDHI, GAS, SCL-90, SSI, BIS	Depressive and somatic symptoms.
Teicher *et al.*, 1989 [61]	THR (92)	Open Label Study (12)	11 (3, 8)	N/A	no	no	BPRS, SCL-90, DIB, PDE	Global psychopathology; improvements on the impulse action patterns, affects, and psychosis; interpersonal relations, hostility and depressive features. Subjects completing the entire study showed significant improvement in paranoid ideation, interpersonal sensitivity, and anxiety.
Van Den Eynde *et al.*, 2009 [47]	QTP	Prospective Study	41 (7, 34)	27 (9)	no	yes	TMTA; TMTB; Tower of London task	Executive functions improved.
Van Den Eynde *et al.*, 2008 [42]	QTP	Prospective Study	41 (7, 34)	N/A	no	yes	BIS; BDHI; BDI; STAXI; STAI; CGI; SCWT; IGT	Overall symptoms.
Villeneuve & Lemelin, 2005 [41]	QTP (50-400)	Clinical Trial	34 (9, 25)	33.65 (6.36)	DSM-IV axis I and axis II	no	BIS, BDHI, HS, HAM-D, HAM-A, BPRS, GAF	Global psychopathology, anxiety, and depression.
Zanarini & Frankenburg, 2001 [34]	OLA (2.5)	Randomized Controlled Trial	28 (0, 28)	27.6	N/A	yes	SCL-90, HDI, DES, PANSS, GAF	Amelioration of anxiety, depression, somatic symptoms, interpersonal sensitivity, anger and paranoia.
Zanarini *et al.*, 2011 [36]	OLA	Randomized Controlled Trial	451 (119, 332)	18-65	no	no	ZAN-BPD; OAS; SDSS; SCL-90; MADRS	Improvement of global psychopathology and symptoms severity except for depression. In addition, there were significant reductions in inappropriate anger, emotional instability, paranoid dissociation, suicidality and self-harm.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Zanarini *et al.*, 2012 [32]	OLA	Randomized Controlled Trial	472 double-blind; 444 open label (165, 307)	double blind 32.3 (9.3); open label 34.3 (11.1)	no	no	DIPDIV, ZAN-BPD, STAEI	Global psychopathology, with the exception of suicidal or self-mutilating behaviour for the study 2 OLZ 2.5 group.
Antiepileptics								
Bellino *et al.*, 2014 [119]	VLP + Ω3; VLP	Randomized Controlled Trial (12)	34 (8, 26)	25.2 (6.4)	no	no	CGI, HAM-D, HAM-A, SOFAS, BPDSI, BIS-11, MOAS, SHI, DOTES	Impulsiveness, self-harm, and outbursts of anger.
Bozzatello *et al.*, 2018 [89]	VLP, Ω3 + VLP previous group = 860.2 ± 50.3; VLP previous group = 880.2 ± 45.4	Retrospective Study (24)	Ω3 + VLP = 16; VLP = 15 (6, 25)	25 (6.4)	no	no	BPDSI, BIS11, SHI	Effects on impulsive-behavioural dyscontrol, outbursts of anger, and self-injuries, but after 24 weeks of follow-up the difference was maintained only for outbursts of anger.
Crawford *et al.*, 2018 [94]	LMT → 200 (in women taking oral contraceptives → 400)	Randomized Controlled Trial (52)	137 (34, 103)	36.1 (11)	no	N/A	ZAN-BPD, BDI, ADA, SFQ, EQ-5D-3L	At 52 weeks, effective on general psychopathology of BPD.
Crawford *et al.*, 2018 [95]	LMT (400)	Randomized Controlled Trial (52)	49	36.1 (11)	no	N/A	ZAN-BPD, BDI, ADA, SFQ, EQ-5D-3L	General psychopathology, depression, social functioning, alcohol use, substance abuse, quality of life.
De la Fuente & Lotstra, 1994 [102]	CRB (6.44-7.07 ug/ml	Randomized Controlled Trial (4)	10 (4, 6)	33.8	no	N/A	DIB, HAM-D, BPRS, GAS, SCL-90	No effect could be shown.
Frankenburg & Zanarini, 2002 [86]	VLP (serum level 50-100 mg/l)	Randomized Controlled Trial (24)	20 (7, 13)	27.3 (7.4)	Bipolar disorder, type 2	N/A	MOAS	Interpersonal sensitivity, anger/hostility, and overall aggression.
Hollander *et al.*, 2005 [87]	VLP (500-2250)	Randomized Controlled Trial (12)	18 (8, 10)	35.3 (10.57)	History of Major Depressive Disorder, alcohol abuse/dependence	N/A	BIS-11, MOAS	Impulsive aggression.
Leiberich *et al.*, 2008 [93]	LMT (200)	Retrospective Study (52)	18 (0, 18)	29.2	no	no	STAXI	Aggression (intensity and threshold of the perceived feeling of anger).
Loew & Nickel, 2008 [100]	TPR (200)	Observational Study (52)	23 (0, 23)	N/A	Depressive disorders, anxiety disorders, obsessive-compulsive disorders, somatoform disorders	no	SCL-90, HS, IIP	Overall symptoms, except psychoticism.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbid-ities	Psycho-therapy	Assessment Tools	BPD Symptoms Improved after Treatment
Loew *et al.*, 2006 [99]	TPR (25-200)	Randomized Controlled Trial (10)	28 (0, 28)	24.9 (5.3)	Depressive disorders, anxiety disorders, obsessive-compulsive disorders, somatoform disorders	no	SCL 90, HS, IIP	Somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, interpersonal problems, perception of health, and global severity of illness.
Nickel & Loew, 2008 [97]	TPR	Randomized Controlled Trial (18)	22 (22, 0)	29.5	N/A	N/A	STAXI	Aggressive behaviour.
Nickel *et al.*, 2005 [96]	TPR (25-250)	Randomized Controlled Trial (8)	22 (22, 0)	29.5	Mood disorders, somatoform disorders, anxiety disorders, eating disorders. Current occasional misuse of alcohol, ampheta-mine, or cannabis.	TG n 6 (27.3%), PG n 4 (20%)	STAXI	Improvement in anger (traits and state).
Nickel *et al.*, 2004 [98]	TPR (25-250)	Randomized Controlled Trial (8)	21 (0, 21)	25.5	N/A	N/A	STAXI	Improvements in anger.
Peris *et al.*, 2007 [101]	GBP (1200-3200)	Clinical Trial (24)	48 (19; 29)	32.5 (7.7)	no	no	HAM-A, YMRS, BDI, BIS-11, CGI	Anxiety, affective instability, and depressive symptoms.
Reich *et al.*, 2009 [92]	LMT (25-275)	Randomized Controlled Trial (12)	15 (4, 11)	28.4 (9.5)	Major Depressive Disorder, PTSD, OCD, GAD, Panic disorder, Social phobia, specific phobia)	no	ALA, ZAN-BPD	Affective instability and impulsivity.
Simeon *et al.*, 2007 [88]	VLP	Clinical Trial (12)	20 (13, 7)	37.0 (11.3)	Mood Disorders, Anxiety Disorders, Personality disorders other than BPD, Binge eating disorder, Body dysmorphic disorder, Lifetime Substance Use Disor-ders.	no	CGI-I; GAF, AQ, AIM, ALA, 0AS-M, 0AS-M, DES, SCL 90	Significant improvement on general psychopathology and anger symptoms.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Stein *et al.*, 1995 [84]	VLP	Clinical Trial (8)	11 (5, 6)	34.8 (6.7)	no	yes	HAM-D, HAM-A, SCL 90, MOAS	Overall symptoms, and subjective irritability.
Tritt *et al.*, 2005 [91]	LMT (200)	Randomized Controlled Trial (8)	18 (0, 18)	29.4	no	no	STAXI	Improvements in anger symptoms.
Cowdry & Gardner, 1988 [30]	ALP (4.7); CRB (820); TFL (7.8); TRY (40) added on to psychotherapy	Cohort Study (6)	16 (0, 16)	31.6	no	yes	Modified Bunney-Hamburg rating scale	Effectiveness of CRB (physician-rated) and TRY (patients- and physician-rated). Patients who tolerated a full trial of TFL showed improvement. CRB reduced the severity of behavioural dyscontrol; ALP increased the severity of the episodes of serious dyscontrol.
Antidepressants								
Bellino *et al.*, 2010 [66]	DLX (60)	Randomized Controlled Trial (12)	18 (7, 11)	29.6 (2.33)	no	no	CGI, BPRS, HAM-D, HAM-A, SOFAS, BPDSI, SCL-90-Somatization Subscale	Overall psychopathology, functioning, depression, impulsivity, outbursts of anger, and affective instability.
Cornelius *et al.*, 1990 [72]	FLX (20-40)	Clinical Trial (8)	5 (1, 4)	31.8	Major Depressive Disorder, dysthymic disorder, adjustment disorder.	no	GAS, GSI, PSDI, PTS, SCL-90, HAM-D, BDHI, SSI	Overall psychopathology, distress, psychotic symptoms / paranoid ideation, impulsivity.
Markovitz & Wagner, 1995 [83]	VNL (75-200)	Clinical Trial (12)	39 (15, 24)	31 (10.5)	no	no	DIB, SCL-90 and subscale for somatic symptoms	Somatic symptoms, self-injurious behaviour.
New *et al.*, 2004 [69]	FLX (20)	Randomized Controlled Trial (12)	13 (7, 6)	32.8 (9.2)	no	no	DSM IVI, MIE, BDHI, OAS, HAM-D, BAFDG	Improvements in aggressive symptoms.
Rinne *et al.*, 2002 [80]	FLV (20-60)	Randomized Controlled Trial (18)	21 (0, 21)	29.2 (7.6)	N/A	no	BPDI	Improvement in short-term and long-term rapid mood shifts. No effect on impulsivity and aggression.
Salzman *et al.*, 1995 [68]	FLX (60)	Randomized Controlled Trial (12)	13 (3, 10)	37.0	no	no	PMS, GAF, PDRS	Improvement of anger and depression.
Simpson *et al.*, 2004 [71]	FLX (20-40)	Randomized Controlled Trial (12)	9 (4, 5)	39.78 (9.71)	Major depressive disorder, PTSD	DBT	STAIT, BDI, MOAS, DES, GAF, SSAI	Increase of social and psychopathological functioning. Improvements in overall symptoms.
Other Drugs								
Domes *et al.*, 2019 [115]	OXY (24 UI)	Randomized Controlled Trial (24)	51 (0, 51)	29.4 (7.9)	N/A	no	MDBF, STAI, STAXI, VAS, MET	Affective empathy and approach motivation.
Kulkarni *et al.*, 2018 [104]	MMN (20)	Randomized Controlled Trial	17 (2, 15)	35.6 (10.8)	no	no	ZAN-BPD	Overall symptoms

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbidities	Psychotherapy	Assessment Tools	BPD Symptoms Improved after Treatment
Miyaoka *et al.*, 2008 [123]	YGS (6400)	Controlled Clinical Trial	20 (0, 20)	32.5 (6.8)	Alcohol or drug abuse	no	AQ, CGI, BPRS, HAM-D, GAF	Global psychopathology, somatic concern, anxiety, tension, depressive mood, hostility, suspiciousness, motor retardation, uncooperativeness, excitement, aggressive behaviour, and functioning.
Philipsen *et al.*, 2004 [110]	CLN (75-150 mcg)	Interventional Study (1 Day)	14 (0, 14)	28.7 (6.9)	Major depressive disorder, trichotillomania, bulimia, alcohol abuse, agoraphobia, obsessive-compulsive disorder	no	DES, heart rate, blood pressure	Aversive inner tension, dissociative symptoms, urge to commit self-injurious behaviour, and suicidal ideations significantly decreased. The strongest effects were seen between 30 and 60 minutes after drug intake.
Philipsen *et al.*, 2004 [107]	NLX (0.4)	Controlled Clinical Trial	9 (0, 9)	34.9 (6.7)	Post-traumatic stress disorder, binge-eating disorder, obsessive-compulsive disorder, major depressive disorder, social phobia, specific phobia	no	DES, CADES, SDS, DTS	No effect could be shown.
Rolland *et al.*, 2015 [109]	BCL (102.2 vs 94.6)	Prospective Cohort Study (52)	23 (13, 10)	45(11.2)	Alcohol use disorder, benzodiazepine use and abuse, axis I comorbidities	no	HD, RSA, AWAC	The mean rate of heavy drinking days, the rate of serious AEs, and the rate of treatment discontinuation after AEs were significantly higher in BPD.
Schmahl *et al.*, 2012 [105]	NLT (50 - 200)	Randomized Controlled Trial (12)	29 (0, 29)	Study 1: 28.3 (8.0); Study 2: 29.2 (8.9)	no	no	DES, DSS, HAM-A, STAI, BDI, HAM-D, STAXI, BS-23, naltrexone plasma levels	No significant effect could be shown.

(Table 2) contd….

Study	Drug (Dose, mg)	Design (Duration, Weeks)	Treatment Sample, Number (m, f)	Mean Age (SD)	Comorbid-ities	Psycho-therapy	Assessment Tools	BPD Symptoms Improved after Treatment
Simeon *et al.*, 2011 [114]	OXY (40 UI)	Prospective Study	14 (8, 6)	35.1 (8.0)	no	no	RQ, TSST, PMC, RSES, PMS, CTQ	Attenuation of stress-induced dysphoria.
Zanarini & Franken-burg, 2003 [120]	Ω3	Randomized Controlled Trial	51 (0, 51)	29.4 (7.9)	N/A	no	MDBF, STAI, STAXI, VAS, MET	Improvements of aggressive behaviour and depressive symptoms.

Legend. ADA: Acts of Deliberate Self-Harm Inventory; **ADHD RS**: ADHD Rating Scale; **AEs**: adverse events; **AIM**: Affective Intensity Measure; **AIMS**: Abnormal Involuntary Movement Scale; **ALA**: Affective Lability Scale; **ALP**: alprazolam; **AMO**: amoxapine; **AQ**: aggression questionnaire; **ASN**: asenapine; **AWAC**: average weekly alcohol consumption; **AYA**: ayahuasca; **BAFDG**: Brodmann area FDG uptake quantification; **BAS**: Barnes Akathisia Scale; **BCF**: baclofen; **BDHI**: Buss-Durkee Hostility inventory; **BDI**: Borderline distress index; **BDI-II**: Beck Depression Inventory-II; **BIS-11**: Barratt Impulsiveness Scale; **BPD**: borderline personality disorder; **BPDI**: BPD Severity Index; **BPDSI**: borderline personality disorder severity index; **BPRS**: Brief Psychiatric Rating Scale; **BS-23**: Borderline Symptom List-23 (short version); **CADES**: clinician administered dissociative states scale; **CGI**: Clinical Global Impression scale; **CLN**: clonidine; **CLZ**: clozapine; **CRB**: carbamazepine; **CTQ**: Childhood Trauma Questionnaire; **DERS**: Difficulties in Emotion Regulation Scale; **DES**: Dissociation-Tension-Scale acute; **DIB**: Gunderson diagnostic interview for Borderline Personality Disorder; **DIPDIV**: Diagnostic Interview for DSM-IV Personality Disorders; **DLX**: duloxetine; **DOTES**;: Dosage Record Treatment Emergent Symptom Scale; **DSMIVI**: Structured Interview for **DSM-IV** Personality Disorders; **DTS**: dissociative tension scale; **EQ**: Short Form and Experiences Questionnaire; **EQ-5D-3L**: Health-related quality of life; **ER**: extended release; **FFMQ**: mindfulness traits: Five Facet Mindfulness Questionnaire; **FLP**: flupentixol; **FLV**: fluvoxamine; **FLX**: fluoxetine; **GAS**: Global Assessment of Functioning; **GBP**: gabapentin; **HAM-A**: Hamilton Anxiety Rating Scale; **HAM-D**: Hamilton Depression Rating Scale; **HD**: Heavy drinking days test; **HLP**: haloperidol; **HPI**: Hyler Personality inventory; **HS**: SF-36 Health Survey; **IIP-64**: Inventory of Interpersonal Problems; **IMPS**: Inpatient Multidimensional Psychiatric Scale; **KSAS**: Kiddle Schedule for Affective Disorder and Schizophrenia; **LAI**: long-acting injection; **LMT**: lamotrigine; **MADRS**: Montgomery-Åsberg Depression Rating Scale; **MDBF**: Multimodal Mood Questionnaire; **MET**: Multifaceted Empathy Test; **MIE**: Module for Intermittent Explosive Disorder—revised; **MMN**: memantine; **MOAS**: Modified Overt Aggression Scale; **MPH**: methylphenidate; **MSI-BP**: McLean Screening Instrument for Borderline Personality Disorder; **NLM**: nalmefene; **NLT**: naltrexone; **NLX**: naloxone; **OAS-M**: Overt Aggression Scale-Modified; **OLA**: olanzapine; **OXY**: oxytocin; **PBS**: placebo sample; **PDRS**: Personality Disorder Rating Scale; **PHN**: phenelzine; **PMC**: Profile of Mood Changes; **PMS**: Profile of Mood State; **PSDI**: Positive Symptoms distress index; **PTS**: Positive total symptoms; **QOL**: quality of life; **QTP**: quetiapine; **RQ**: Relationship Questionnaire; **RSA**: rates of serious AEs; **RSES**: Rosenberg Self-Esteem Scale; **RSP**: risperidone; **SAR**: Symptoms Angus Rating Scale; **SAT-P**: Satisfaction Profile; **SCL-90**: Symptom Check List 90 items; **SDS**: Sheenan Disability scale; **SFDS**: somatoform dissociation questionnaire; **SDSS**: Social Desirability Scale; **SFQ**: Social Functioning Questionnaire ; **SHI**: Self-Harm Inventory; **SOFAS**: Social and Occupational Functioning Assessment Scale; **SSI**: Schizotypal Symptom Inventory; **STAEI**: State-Trait Anger Expression Inventory; **STAI**: State-Trait-Anxiety-Inventory; **STAIT**: State-Trait Anger Expression Inventory; **STAXI**: State-Trait Anger Expression Inventory; **TFL**: trifluoperazine; **THR**: thioridazine; **TMTAB**: Trail Making Test A and B; **TPR**: topiramate; **TRY**: tranylcypromine; **TS**: treatment sample; **TSST**: Trier Social Stress Test; **VAS**: visual analogue scale; **VLP**: valproate; **VNL**: venlafaxine; **YGS**: yi-gan san; **YMRS**: Young Mania Rating Scale; **ZAN-BPD**: Zanarini Rating Scale for Borderline Personality Disorder; **ZPR**: ziprasidone; **Ω3**: omega-3 fatty acid.

These drugs can contribute to mood stabilization in the long-term treatment of the major depressive and bipolar disorders. These drugs are widely used for the treatment of various symptoms that may occur in patients with BPD.

Olanzapine. Olanzapine is an antagonist at both serotonin $5HT_{2A}$ and dopamine D_2 receptors. It is not correlated to extrapyramidal symptoms because of the low affinity with D_2 receptors but can be a sedative agent because of the strong antagonist properties at M_1-muscarinic, H_1-histaminic, and α_1-adrenergic receptors. Olanzapine also has $5HT_{2C}$ antagonist properties and weaker $5HT_7$ and α_2 antagonist properties, which have been linked to its antidepressant activity [31]. There is strong evidence of olanzapine's effectiveness in treating most BPD symptoms. A 12 weeks' placebo-control double-blind study showed improvement of BPD symptoms with olanzapine at a daily dose of 2.5–5 mg, except for suicidality and self-harming [32]. Specific BPD symptoms that significantly improved with olanzapine use are intense anger, affective instability, chronic feelings of emptiness, identity disturbance, impulsivity, frantic efforts to avoid abandonment, and unstable personal relationships [33–35]. The BPD treatment with olanzapine at a dose of 5–10 mg correlated with improvements in different symptoms, including paranoid ideation, dissociation, as well as irritability, and suicidal behaviors [36]. Other evidence noted the improvement in both the overall BPD and depressive symptoms using olanzapine in this kind of patient [37]. Further research demonstrated that the association of olanzapine with fluoxetine could be more effective than olanzapine monotherapy on depressive symptoms in BPD [38]. Other data showed a significant decrease in depressive symptoms and clinical anxiety. The added-on dialectical behavior therapy correlated with significantly greater improvement in the frequency of impulsivity/aggressive episodes [39]. Olanzapine proved to be effective in women with BPD to treat the anxiety symptoms and episodes of anguish [34]. Beyond the therapeutic effects of olanzapine, the tolerability profile should be assessed, especially in relation to the issues of weight gain and metabolic syndrome [32,37].

Quetiapine. Quetiapine is an antagonist at both serotonin $5HT_{2A}$ and dopamine D_2 receptors but has several differentiating pharmacologic properties, especially at different doses and formulations. Quetiapine has an active metabolite, norquetiapine, which has many activities. Quetiapine can cause weight gain, and it can increase fasting triglyceride levels and insulin resistance. Quetiapine has proven to be effective in BPD at a daily dosage ranging from 150 mg to 300 mg for the treatment of intense anger, affective instability, chronic feelings of emptiness, identity disturbance, and frantic efforts to avoid abandonment, and unstable personal relationships. However, the side effects are more frequent in patients who used a dosage of 300 mg, without having a greater improvement than those who took 150 mg per day [40]. Treatment with a daily dose of 300 mg was correlated with a reduction of hypomanic and manic symptoms. However, it has not proved to be useful in controlling impulsivity [40]. In contrast, other studies showed a reduction of impulsivity in patients taking quetiapine at daily dosages ranging from 50 mg to 400 mg (up to a maximum of 800 mg/day). Substance abuse and gambling, which have been linked to impulsivity, can also improve. The use of quetiapine has proven to be effective in the treatment of depressive and anxiety symptoms and reducing the emotional instability and psychological distress in BPD [41-45], although with some

inconsistency in terms of improvement of depressive symptoms [43]. Some studies showed the effectiveness of quetiapine in the treatment of psychotic symptoms in BPD patients, especially at high dosages [43-46]. Other evidence underlined that quetiapine could improve cognitive symptoms [47] and overall social and work functioning [43-46] in BPD. From the included studies, there is insufficient evidence of the efficacy of quetiapine on suicidality and self-injurious behavior in BPD. The reported inconsistencies may be linked with different factors, including the heterogeneity of the study samples, comorbidities, other concomitant treatments, differences in the psychopathological state of included patients, genomic aspects, and other possible environmental and biological variables.

Asenapine. This atypical antipsychotic is characterized by $5HT_{2A}$, $5HT_{2C}$, H_1, and α_2 antagonism, and D_2 antagonism. Asenapine can be sedating, especially upon first dosing, but does not have a high propensity either for extrapyramidal symptoms or weight gain/dyslipidemia, despite its $5HT_{2C}$ antagonism added to weaker antihistaminic properties. Asenapine at a daily dose of 5-10 mg improved overall functioning, anxiety, aggression, and impulsivity in BPD patients. Like olanzapine, it was effective in improving emotional lability, dissociative symptoms, and paranoid ideation. There is a lack of evidence of its effectiveness on depressive symptoms, suicidal/self-injury behaviors, and identity disturbance in patients with BPD [48]. Given the presence of only a single open-label RCT, more studies are needed to assess the effectiveness of asenapine in treating BPD symptoms.

Haloperidol. This typical antipsychotic strongly blocks the dopamine D_2 receptors, reducing positive symptoms of psychoses and possibly aggressive, explosive, and hyperactive behaviors. By blocking D_2 receptors in the striatum, it can cause extrapyramidal symptoms [31]. Treatment with haloperidol at a daily dose of 4 mg proved to be effective in BPD patients for different symptoms, including depression, anger, hostility, impulsivity, and particularly for some schizotypal characteristics such as paranoid ideation illusions, and ideas of reference [49]. Other evidence underlined that a combination of haloperidol and phenelzine resulted in modest improvements of irritability and depressive symptoms in the short term of BPD treatment [50] and limited long-term efficacy of neuroleptics and Monoamine oxidase inhibitors (MAOIs) antidepressants [51].

Clozapine. This is an antagonist of both serotonin $5HT_{2A}$ and dopamine D_2 receptors (serotonin-dopamine antagonist) (SDA). It has a complex profile of affinity since it can bind several receptors, including the H_1, α_1, M_1, $5HT_{2B}$, $5HT_{2C}$, $5HT_6$, and $5HT_7$. Clozapine has been used only for treating severe cases of BPD because of the lack of indication and issues in tolerability (risk of agranulocytosis, cholinergic symptoms, and eosinophilic myocarditis) [31]. It was administered at a daily dosage ranging from 25 to 100 mg, followed by improvements in thought disturbance, alterations of perception, suspicion, illusions, dissociative symptoms, and strange beliefs in patients with severe BPD [52]. However, its efficacy has not been demonstrated in the treatment of psychomotor slowdown, depressed mood, guilt, emotional blunt, and megalomaniac tendencies in BPD [53].

Amoxapine. Short-term treatment with amoxapine at a daily dosage of 200 mg improved schizophrenic-like and depressive symptoms in patients with schizotypal personality disorders but did not show changes in BPD patients [54].

Aripiprazole. This is a partial agonist of the D_2 dopamine receptor and is theoretically an atypical antipsychotic with reduced extrapyramidal symptoms and hyperprolactinemia [31]. In BPD patients, aripiprazole proved to be effective in the treatment of obsessive-compulsive symptoms, insecurity in social relationships, depression, anxiety, aggressiveness/hostility, phobic symptoms, paranoid thinking, and other psychotic symptoms [55,56]. In the long-term treatment, it improved depressive and anxious symptoms, reducing the amount of anger in BPD patients [55]. Aripiprazole augmentation for 3 months in sertraline-resistant patients with borderline personality disorder improved the global clinical impression and proved to be effective in treating impulsivity, dissociation, and paranoid ideation. This add-on treatment did not show significant changes in anxiety and depression in these patients, with no improvements in abandonment feelings, interpersonal relationships, identity symptoms, parasuicidal behavior, affective instability, emptiness, and outbursts of anger [57]. More studies are needed on the effects of aripiprazole on different symptoms, including abandonment, interpersonal relationships, identity disturbance, parasuicidal behavior, affective instability, and emptiness.

Paliperidone. This drug is an antagonist of dopamine D_2 and serotonin $5HT_{2A}$ receptors and has affinities with H_1, $\alpha 1$, and $\alpha 2$ receptors [31]. Different studies showed its effectiveness in treating psychotic symptoms and impulsive dyscontrol in BPD. The oral drug (3–6 mg/die) or long-acting injection (50–150 mg/day) both led to an improvement in general functioning, impulsivity, anger, paranoid ideation, and dissociative symptoms [58,59]. The main tolerability issues could be a possible increase in prolactin serum levels and the manifestation of extrapyramidal symptoms, especially with the oral formulation [58]. Based on its metabolic profile, paliperidone palmitate could be more tolerable [59]. There is insufficient evidence of response to depressive symptoms, suicidal and self-injury behaviors, and affective instability in BPD treated with paliperidone.

Risperidone. A short-term (8 weeks) treatment with risperidone at low-to-moderate doses (mean daily dosage of 3.27 mg) in BPD with aggressive behavior proved to be effective in treating aggression. This treatment resulted in an overall improvement, especially in depressive symptoms, and correlated with an increase in energy and better global functioning [60]. This evidence underlined the need for further studies to explore the efficacy of risperidone in the treatment of BPD.

Thioridazine. A single 12-week open study showed that thioridazine might exert prominent effects on BPD patients, including improvements in impulsiveness, affective and psychotic symptoms, and interpersonal relations. However, sedation and erectile dysfunction were significant tolerability issues [61]. No further studies have followed this 1989 evidence.

Ziprasidone. This atypical antipsychotic has an affinity with serotonin $5HT_{2A}$, $5HT_{1B}$, and dopamine D_2 receptors [31]. Ziprasidone at a daily dose of 80 mg for the treatment of BPD patients proved to be effective in the control of anger, paranoid ideation, impulsivity, and emotional instability, but not for anxiety and depressive symptoms [62]. The use of ziprasidone (daily dose range of 40–160 mg) could be considered for managing acute cases of BPD, considering the reported improvements of suicidal and self-injurious risk, hostility and aggression, impulse control, and severe anxious depressive symptoms [63].

4.2. Antidepressants

Several studies have focused on the possible efficacy in the treatment of BPD symptoms of antidepressant drugs, including selective serotonin (SSRIs) and serotonin and norepinephrine (SNaRI) reuptake inhibitors, administered as monotherapy or added on to psychotherapy.

Duloxetine. This is a potent SNaRI mainly used for the treatment of the major depressive disorder, diabetic neuropathic pain, stress urinary incontinence, and generalized anxiety disorder [64]. It can be effective not only in the treatment of mood disorders, or panic disorder but also of several clusters of BPD symptoms [65]. In an open trial of 12 weeks, a total sample of 14 BPD patients was treated with duloxetine at a daily dose of 60 mg, with statistically significant improvements observed in clinical status, overall psychopathology, and depression. Duloxetine appeared to be selectively effective on impulsivity and affective dysregulation (outbursts of anger, affective instability). It could also be an effective treatment for its positive effects on BPD patients with somatic symptoms [66]. However, further studies focused on duloxetine treatment are needed in patients with BPD to better assess its efficacy and tolerability.

Fluoxetine. This antidepressant can enhance serotoninergic neurotransmission through potent and selective inhibition of the neuronal reuptake of serotonin [67]. In the pharmacological treatment of BPD patients, fluoxetine has proven to be effective in impulsive lack of control, decreasing impulsivity, self-injury behaviors, and sensitivity to rejection [68]. It could reduce aggressive behaviors in BPD patients more effectively in men compared to women. Fluoxetine pharmacological effects were also assessed by fluorodeoxyglucose – positron emission tomography (FDG-PET) imaging. Changes in the right orbital frontal cortex regional cerebral blood flow (rCBF) correlated with aggression improvement, with an indirect correlation between the medial right temporal and orbital-frontal cortices rCBF [69]. Improvements in the general clinical status of BPD patients were also observed, with the administration of fluoxetine for 6 months and a daily dose ranging from 5 to 40 mg. The most responsive symptoms to the fluoxetine treatment appeared to be the sensitivity to rejection, anger, depressed mood, mood instability, irritability, anxiety, obsessive-compulsive symptoms, and impulsivity (including substance use and overeating) [70].

The efficacy of fluoxetine administered at a dosage of 40 mg per day has been further studied on BPD patients in a 12-week, randomized, double-blind study, added on to dialectical behavior therapy (DBT) as compared to placebo and DBT (a 4-month therapy was designed). In respect to baseline, this study suggested that fluoxetine added on to DBT does not correlate with any additional improvement as compared to placebo and DBT [71].

Treatment of BPD with fluoxetine administered for 8 weeks correlated with significant improvements in general severity of psychopathology, distress, and psychotic symptoms (*e.g.*, paranoid ideation). A decrease in impulsiveness may also occur [72]. Administered up to dosages of 60 mg, fluoxetine has proven to be effective on the general symptoms profile of the disorder, particularly on aggressiveness and mood symptoms, with ver big improvements in anger and depression. BPD patients receiving fluoxetine compared to those on placebo showed decreased anger and depression [68].

In brief, fluoxetine treatment can be effective for controlling anger, aggression, distress, paranoid ideation, mood, and global functioning in patients with BPD. Its effectiveness on aggressive behaviors might be because patients with BPD may exhibit aggression during states of deflected mood.

Flupentixol. This antidepressant drug has similar affinities with dopamine D_2, D_1 , and $5\text{-}HT_{2A}$ receptors and interacts with $5\text{-}HT_{2A}$ and D_1 receptors [73]. The dual dopaminergic-noradrenergic action can be most effective in improving depressed mood, fatigue, low energy, and other symptoms of major depressive disorder [74,75]. In a prospective, open study on subjects with BPD, 8 weeks of treatment with a low daily dose of flupentixol (3 mg) following a titration schedule with added-on procyciclidine for prevention of extrapyramidal side effects, there were significant improvements in general psychopathology and impulsivity symptoms [76]. These improvements could be ascribed to the neuroleptic effects and serotonergic affinities of flupentixol.

Fluvoxamine. This drug facilitates serotonergic transmission via potent and selective inhibition of serotonin reuptake into the presynaptic neurons. The overall antidepressant efficacy of fluvoxamine administered at a daily dosage of 100–300 mg for a period of 4–6 weeks has proven to be as effective as different tricyclic antidepressants, including imipramine, clomipramine, and desipramine [77]. Its effectiveness has been demonstrated in the treatment of depression in patients with obesity, obsessive-compulsive disorder, and bulimia nervosa, which in some cases can be comorbid with BPD [78], and its use has been suggested for treating BPD symptoms [79]. Fluvoxamine proved to be effective in treating rapid mood shifts in BPD, with the main effect arising in the first 6 weeks of treatment, but there was a lack of efficacy in the treatment of impulsivity and aggressive behaviors [80].

Venlafaxine. This SNaRI also interacted very weakly with dopamine receptors [81] and proved to be most effective for depressive episodes without psychotic features that showed resistance to the standard pharmacological treatment [82]. Considering its possible efficacy in the treatment of various BPD aspects, venlafaxine has been tested in patients with BPD who showed somatic symptoms and self-injurious behavior. It has been studied with an initial daily dosage of 75 mg divided into two administrations, with increases of 75

mg each 3-7 days for 12 weeks, showing a significant reduction of somatic symptoms and self-injurious behavior [83].

4.3. Antiepileptics

The most studied antiepileptic drugs in the treatment of BPD are valproic acid, lamotrigine, topiramate, gabapentin, and carbamazepine.

Valproate. This drug acts with the blockade of voltage-gated sodium channels and increases the brain levels of gamma-Aminobutyric acid (GABA), which contributes to its anti-manic effect. Several studies focused on its use in the treatment of BPD patients. Stein and colleagues performed one of the first studies in 1995. This 8-week open trial on BPD patients showed a significant decrease in overall symptoms as well as in irritability [84]. Another open-label trial showed that valproate could be an effective treatment for impulsive and aggressive symptoms in some patients who did not respond to other agents, including serotonergic antidepressants [85]. Similar results emerged from Frankenburg and Zanarini's double-blind 6-month RCT on 30 women, who showed valproate-related improvements in interpersonal sensitivity and anger/hostility, as well as overall aggression [86]. In addition, other studies demonstrated a reduction in impulsive aggression and irritability in BPD [87,88]. More recently, Bozzatello and colleagues conducted a 24-week follow-up study after a previous 12-week randomized trial, in which they compared the efficacy of omega-3 fatty acid added on to valproic acid *vs.* valproic acid monotherapy in BPD. The positive effects of combination therapy emerged, in particular, on some characteristic symptoms of BPD, such as impulsive-behavioral dyscontrol, explosions of anger, and self-harm. In the long term, the combined therapy has proven to be significantly effective in the treatment of outbursts of anger. This allows the observation that the choice of the combination of omega-3 fatty acids and valproic acid as an effective long-term therapy would be justified only when anger behaviors are the main feature of the disorder [89]. However, treatment with valproate in addition to DBT has not proved more effective than DBT alone [90], which emphasizes the importance of psychological interventions in BPD. In conclusion, the use of valproic acid in patients with BPD has demonstrated its effectiveness, especially in controlling the symptoms of irritability and aggression. There is a need for further controlled studies to determine which patients are most likely to benefit from this drug and open the way to personalized treatment strategies.

Lamotrigine. Lamotrigine is a sodium channel-blocking antiepileptic drug. The mechanism of action by which lamotrigine is able to treat bipolar disorder has not yet been fully clarified; however, the blocking of voltage-gated sodium channels is believed to be implicated in some way. Some studies investigated its use as a mood stabilizer in BPD. Tritt and colleagues [91] conducted an 8-week, double-blind RCT in 27 BPD women, showing significant improvements in symptoms of anger and anger traits. In the same direction are the results of another, albeit preliminary, 12-week, double-blind, placebo-controlled study of BPD patients with possible comorbid anxiety or major depressive disorders. Furthermore, lamotrigine was found to be effective in treating affective instability and general impulsivity [92]. Similarly, an 18-month follow-up study showed that lamotrigine was more effective than a placebo in treating the dimension of aggression, specifically regarding the intensity and threshold of the perceived feeling of anger [93]. However, a more recent 52-week, two-arm, double-blind, large-scale multicenter RCT comparison of lamotrigine versus placebo in BPD patients failed to show significant superiority of lamotrigine [94]. This evidence underlines that lamotrigine is not clinically or more costly effective than the usual care in BPD subjects [94,95]. In brief, although several studies showed that lamotrigine had shown evidence of efficacy in reducing aggressive symptoms, affective lability, and impulsivity in BPD, the most extensive study failed to find any effect at all. At this point, therefore, clinicians should hesitate to prescribe this agent while waiting for further studies to clarify its efficacy.

Topiramate. Topiramate is an antiepileptic drug that acts by blocking the voltage-sensitive sodium channels; this leads to an inhibition of glutamate release and to an increase of GABA neurotransmission. Furthermore, topiramate acts as a carbonic anhydrase inhibitor. Topiramate has proven to be effective in reducing BPD symptoms in the main studies included in this review. Nickel and colleagues conducted a double-blind RCT on 42 men with BPD, demonstrating that topiramate treatment induced an improvement of symptoms, as well as weight loss. Topiramate appeared to be an effective agent mainly in the treatment of anger in BPD [96]. A second paper by the same authors described a follow-up study on the same group of patients, who were assessed every 6 months for 18 months. The topiramate group showed an even greater improvement than the placebo group in BPD symptoms, and weight loss persisted even after 18 months [97]. Another placebo-controlled RCT on 29 women with BPD showed improvements in overall symptoms and weight loss [98]. A fourth placebo-controlled RCT was performed on 28 women with BPD treated with topiramate *vs*. 28 on placebo. This study demonstrated a significant improvement in somatization symptoms, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and global severity of symptoms. There was a lack of efficacy in treating obsessive-compulsive symptoms, depression, paranoid ideation, and psychoticism. With regard to interpersonal problems, there was an improvement in overly autocratic, competitive, introverted, and expressive symptoms. Weight loss was additionally observed [99]. The topiramate has proven to be effective in treating overall symptoms, except psychoticism, in a subsequent follow-up study [100]. All of these studies had relatively small samples but suggested that topiramate could be a valid option in the treatment of BPD. Large-scale studies are needed to reach a firm conclusion.

Gabapentin. Gabapentin is a leucine analog that binds to voltage-sensitive calcium channels, closing them and diminishing excessive neuronal activity and release of neurotransmitters. A 6-month open-label, multicenter trial demonstrated the safety and effectiveness of gabapentin on BPD symptoms at a daily dose of 1200–3200 mg. This drug proved to be effective in treating anxiety, affective instability, and depressive symptoms in BPD patients, although it was often combined with other concomitant treatments (47% anxiolytics; 27% antidepressant; 13% antipsychotics) [101]. Gabapentin may be a promising therapeutic approach for

treating some BPD symptoms, but there is a need for further studies to confirm these findings.

Carbamazepine. Carbamazepine is an antiepileptic drug that interacts with the open conformation of voltage-sensitive sodium channels by blocking them and inhibiting glutamate release. It is widely used in psychiatry, mainly in the treatment of bipolar disorder for its antimanic activity. However, a double-blind RCT of carbamazepine on BPD treated for 30 days showed a lack of efficacy in treating BPD symptoms [102].

4.4. Other Drugs

Memantine. This is a channel blocker of the N-methyl-D-aspartate (NMDA) receptor that can regulate glutamate overactivity. Its off-label use in the treatment of BPD is supported by the hypothesis of glutamate dysregulation and excitotoxicity of BPD core symptoms [103]. To date, only a double-blind placebo-controlled RCT showed that a dose of 20 mg of memantine per day added on to another usual drug treatment was well tolerated and improved BPD symptoms [104]. Given the existence of only one study, further research is needed to assess the efficacy of memantine compared to placebo and other treatments in patients with BPD.

Naloxone/naltrexone. Naloxone and naltrexone have proven some effectiveness in BPD. Dissociation was less severe under naltrexone than under placebo [105,106], which gives indirect support to the hypothesis that naltrexone might reduce dissociative symptoms in patients with BPD. With regard to naloxone, there is evidence of a lack of efficacy of naloxone in BPD. A single dosage of 0.4 mg was not superior to a placebo for the treatment of acute dissociation in BPD patients [107]. These inconsistencies could be ascribed to differences in study designs and small sample sizes.

Nalmefene. This is an antagonist of opioid μ and δ receptors and a partial agonist of κ receptors. An 8-week open study on patients with BPD and comorbid alcohol use disorder showed that the treatment with nalmefene was safe and effective in improving BPD global symptomatology, self-injurious behavior, symptoms of alcohol consumption, and binge eating [108].

Baclofen. Baclofen is a γ amino-butyric acid type B receptor agonist. It was used to treat spasticity and alcohol dependence. The only study focused on BPD suggested that the use of high doses of baclofen in patients with BPD and alcohol dependence is associated with enhanced neuropsychiatric concerns [109] so that alternative treatments should be considered.

Clonidine. A study on women with BPD and acute aversive inner tension with the urge to commit self-injury showed that clonidine at a dose of 75-150 mcg improved the symptoms, reducing inner tension, dissociative symptoms self-injurious behavior, and suicidal ideations [110]. To the best of our knowledge, this is the only study on this drug in the treatment of BPD, so there is a need for further placebo-controlled studies with larger populations.

Oxytocin. Oxytocin is a neuropeptide produced in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. It plays an important part in social cognition, social behaviors, and fear conditioning [111, 112]. It has a role in the pathophysiology of anxiety disorders through its involvement in social attention, positive social evaluation, prosocial behaviors, and anxiolytic effects [113]. Anxiety and problems in social functioning are key symptoms of BPD; thus, oxytocin has been considered a possible treatment. A pilot study demonstrated its effects on the dysphoric emotional response to stress, with a tendency toward a more dampened cortisol stress-related response [114]. Another recent study showed that intranasal oxytocin *vs.* placebo significantly improved affective empathy and approach motivation in BPD, indicating a favorable effect of a single dose in women with BPD, adjusting their social functioning similarly to healthy controls [115]. An interesting point of view is that dysfunction in social interactions can be a major issue of BPD. Treatment with oxytocin may be effective for this aspect and consequently on other BPD symptoms. However, there is still a paucity of evidence of efficacy, and further studies with larger samples are needed.

Omega-3 fatty acids. Omega-3 polyunsaturated fatty acids are α -linolenic acid (ALA; 18:3 ω-3), stearidonic acid (SDA; 18:4 ω -3), eicosapentaenoic acid (EPA; 20:5 ω -3), docosapentaenoic acid (DPA; 22:5 ω -3), and docosahexaenoic acid (DHA; 22:6 ω-3). Many studies showed psychological symptoms improvement with omega-3 fatty acids [116]. Polyunsaturated fatty acids like EPA might increase serotonin release from presynaptic neurons by reducing E2 prostaglandins; DPA might influence serotonin receptor action by increasing cell membrane fluidity in postsynaptic neurons; furthermore, marine omega-3 fatty acid intake may help prevent and modulate the severity of brain dysfunction [117]. Treatment with omega-3 correlated with significant benefits in patients with depressive episodes, both with major depressive and bipolar disorders [118]. Omega-3 polyunsaturated fatty acids were associated with valproate for treating patients with BPD, and this combination proved to be effective in treating impulsivity and hostility [119]. Furthermore, ethyl-EPA was safe and effective in 8-week monotherapy in women with moderately severe BPD. Patients treated with ethyl-EPA vs. placebo showed a significant improvement in overall aggressive and depressive symptoms [120]. Besides, there is a need for studies on BPD assessing the efficacy of omega-3 fatty acids in different kinds and doses, for longer periods of time and in larger samples.

Yi Gan San. Used to treat Parkinson's disease, Yi Gan San has been used in Asia to treat symptoms of neurodegenerative disorders and to detoxify the liver. Yi Gan San pretreatment protected dopaminergic neurons from the damage of various neurotoxins [121]. It might have neuroprotective effects by inhibiting beta amyloid-induced apoptosis in cortical neurons [122]. An open-label study on women with BPD showed significant clinical improvement that occurred over 12 weeks of treatment in both clinician-rated scales and self-reported questionnaires. Its effect was recognized at 2 weeks, with an improvement of overall psychopathology, depressive symptoms, aggressive behavior, and global functioning [123]. These effects may relate to possible neuroprotection of dopaminergic neurons, which could be a therapeutic alternative and needs further investigation. However, the efficacy of Yi Gan San on BPD symptoms needs to be confirmed in

further studies that replicate the results of the only study performed so far.

CONCLUSION

There are no medications currently approved for the treatment of BPD. Clinicians should carefully assess the benefits and risks of drug treatment in affected patients. Different core symptoms of BPD could respond to drug treatment in patients who did not manifest improvements through psychological interventions. Different serotonergic antidepressants and atypical antipsychotics can be safe and effective for the treatment of mood symptoms, anxiety, and impulse dyscontrol. Atypical antipsychotics can also be useful in the treatment of psychotic and dissociative symptoms. Specific antiepileptics can be useful in treating mood instability, impulsive symptoms, and anger in patients with BPD. The use of drugs belonging to other classes is not indicated in the treatment of BPD symptoms. Considering the heterogeneity of the clinical presentation, biological correlates, and possible comorbidities of BPD, and the different mechanisms of action of considered drugs, further studies are needed to identify specific personalized treatment strategies.

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