Current Clinical Psychopharmacology in Borderline Personality Disorder

Antonio Del Casale1,*, Luca Bonanni2, Paride Bargagna2, Francesco Novelli2, Federica Fiasche2, Marco Paolini2, Francesca Forcina2, Gaia Anibaldi2, Francesca Natalia Cortese2, Alessia Iannuccelli2, Barbara Adriani2, Roberto Brugnoli2, Paolo Girardi1, Joel Paris3 and Maurizio Pompili2

1Department of Dynamic and Clinical Psychology, and Health Studies, Faculty of Medicine and Psychology, Sapienza University, Rome, “Sant’Andrea” University Hospital, Rome, Italy; 2Department of Neuroscience, Mental Health, and Sensory Organs, Faculty of Medicine and Psychology, Sapienza University, Rome, “Sant’Andrea” University Hospital, Rome, Italy; 3McGill University, SMBD–Jewish General Hospital, Institute of Community and Family Psychiatry, Montreal, Canada

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.

Keywords: Borderline personality disorder, affective instability, drug treatment, impulsiveness, anger, atypical antipsychotics, mood stabilizers, antidepressants.

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
(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 (STEPSS) [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.

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.

| BPD Diagnostic Criteria (DSM-5) | Current Neuropharmacology, 2021, Vol. 19, No. 10 1761 |
|-------------------------------|---------------------------------------------------|
| Frantic efforts to avoid real or imagined abandonment, reflecting intolerance to be alone; | |
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 |
|-------|----------------|--------------------------|--------------------------------|---------------|---------------|---------------|----------------|-------------------------------------|
| 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 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) | no | 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, SS1 | 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 | 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      | 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-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 (13, 49)                    | 29.1 (5.96)   | no            | no            | CGI; BPRS; HAM-D; HAM-A; SO-FAS; 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. |
| 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, DB, 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; STA; 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. |
| Bellino et al., 2014 [119]               | VLP + Ω3; VLP  | Randomized Controlled Trial   | 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     | 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   | 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   | 18 (8, 10)                     | 35.3 (10.57)  | 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, somatof orm 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) | Comorbidities                                                                 | Psychotherapy | 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, amphetamine, 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, BDL, 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 Disorders. | no            | CGI-I, GAF, AQ, AIM, ALA, OAS-M, OAS-M, DES, SCL 90                            | Significant improvement on general psychopathology and anger symptoms. |
| 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 (8)         | 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 (patient- 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. |
| 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, SO-FAS, 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, dysthmic 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. |
| Domes et al., 2019 [115]    | OXY (24 UI)     | Randomized Controlled Trial (24) | 51 (0, 51)                      | 29.4 (7.9)    | N/A           | no            | M DBF, STAL, 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   | 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 | 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 | 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   | 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   | 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.                                                                       |
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 5HT₂A and dopamine D₃ receptors. It is not correlated to extrapyramidal symptoms because of the low affinity with D₂ receptors but can be a sedative agent because of the strong antagonist properties at M₁-muscarinic, H₁-histaminic, and α₁-adrenergic receptors. Olanzapine also has 5HT₂C antagonist properties and weaker 5HT₃ and α₂ 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 5HT₂A and dopamine D₃ 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

| Study                        | Drug (Dose, mg) | Design (Duration, Weeks) | Treatment Sample, Number (m, f) | Mean Age (SD) | Comorbidities | Psychotherapy | Assessment Tools | BPD Symptoms Improved after Treatment |
|------------------------------|-----------------|--------------------------|--------------------------------|---------------|---------------|---------------|-----------------|---------------------------------------|
| Simeone et al., 2011 [114]   | OXY (40 U)      | Prospective Study        | 14 (8, 6)                      | 35.1 (8.0)    | no            | no            | RQ, TSST, PMC, RSES, PMS, CTQ       | Attention of stress-induced dysphoria. |
| Zanarini & Frankenburg, 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 Voluntary Movement Scale; ALC: Affective Lability Scale; ALP: alprazolam; AMO: amoxapine; AQ: aggression questionnaire; ASN: asparagine; AWAC: average weekly alcohol consumption; AY3: ayahuasca; BAFDG: Brodmann area FDG uptake quantification; BAS: Barnes Akathisia Scale; BCF: baclofen; BDH: Bus-Parkinson Hostility inventory; BDI: Borderline distress index; BDII–BDI: Beck Depression Inventory II–Beck Depression Inventory; BPD: borderline personality disorder; BPS: 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: chloridone; CLZ: clozapine; CRB: carbamazepine; CTQ: Childhood Trauma Questionnaire; DERS: Difficulties in Emotion Regulation Scale; DEX: Dissociation-Tension Scale acute; DBD: Gunderson diagnostic interview for Borderline Personality Disorder; DIPDIV: Diagnostic Interview for DSM-IV Personality Disorders; DLX: duloxetine; DOTES: Dosage Record Treatment Emergent Symptom Scale; DSMIV: Structured Interview for DSM-IV Personality Disorders; DTS: dissociative tension scale; EQ: Short Form and Experiences Questionnaire; EQ-SD-3L: Health-related quality of life; ER: extended release; FFMQ: mindfulness traits; Facet Mindfulness Questionnaire; FLP: papitoxol; FLV: fluvoxamine; FLX: fluoxetine; GAS: Global Assessment of Functioning; GBP: gabapentin; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HDP: heavy drinking days test; HLP: haloperidol; HPI: Hyler Personality inventory; HS: SF-36 Health Survey; IP-64: Inventory of Interpersonal Problems; IMPS: Inpatient Multidimensional Psychiatric Scale; KSAS: Kiddie Schedule for Affective Disorder and Schizophrenia; LAI: long-acting injection; LMT: lamotrigine; MADRS: Montgomery–Åsberg Depression Rating Scale; MDDF: Multimodal Mood Questionnaire; MET: Multifaceted Empathy Test; MEIE: Module for Intermittent Explosive Disorder—revised; MNN: mementine; MOAS: Modified Overt Aggression Scale; MPH: methylphenidate; MMI-BP: McLean Screening Instrument for Borderline Personality Disorder; NLM: nalmefene; NLT: naltrexone; NNX: naloxone; OAM-M: Overt Aggression Scale Modified; OLA: olanzapine; OXY: oxotremorine; 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; RRQ: Relationship Questionnaire; RSA: rates of serious AEs; RSES: Rosenberg Self-Esteem Scale; RSP: risperidone; SAR: Symptoms Angius 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; SSE: Schizophrenia Symptom Inventory; STAIE: State- Trait Anger Expression Inventory; STAI: State-Trait Anxiety-Inventory; STAI He: State-Trait Anger Expression Inventory; STAXI: State-Trait Anger Expression Inventory; TFL: trifluoperazine; THR: thiadiazide; 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: zonisamide; Ω3: omega-3 fatty acid.
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 5HT2A, 5HT2C, H1, and α2 antagonism, and D2 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 5HT2C 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 D2 receptors, reducing positive symptoms of psychoses and possibly aggressive, explosive, and hyperactive behaviors. By blocking D2 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 5HT2A and dopamine D2 receptors (serotonin-dopamine antagonist) (SDA). It has a complex profile of affinity since it can bind several receptors, including the H1, α1, M1, 5HT2B, 5HT2C, 5HT6, and 5HT7. 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 D2 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 improvement 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 D2 and serotonin 5HT2A receptors and has affinities with H1, α1, and α2 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 (SNaRIs) 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 serotonergic 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 very 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-HT_{2A} receptors and interacts with 5-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 procyclidine 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 over-activity. 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; EPA 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 pre-treatment 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.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

In the last three years, Paolo Girardi has received consultation fees from Angelini, Janssen, Lundbeck, and Otsuka, which did not influence the content of this article; Maurizio Pompili has received lecture or advisory board honoraria or engaged in clinical trial activities with Angelini, Lundbeck, Janssen, Otsuka, Italfarmaco, and Allergan, which did not influence the content of this article; Antonio Del Casale has received lecture or advisory board honoraria or engaged in clinical trial activities with Imagine/Edra, GlaxoSmithKline, and Fidia, which did not influence the content of this article.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Stern, A. Psychoanalytic investigation of and therapy in the border line group of neuroses. Psychoanal. Q., 1938, 7, 467-489. http://dx.doi.org/10.1080/21674086.1938.11925367

[2] Linehan, M.M. Cognitive Behavioural Therapy of Borderline Personality Disorder; Guilford: New York, NY, USA, 1993.

[3] Widiger, T.A.; Frances, A.J. Epidemiology, diagnosis, and comorbidity of borderline personality disorder. American Psychiatric Press Review of Psychiatry; Tasman, A.; Hales, R.E.; Frances, A.J., Eds.; American Psychiatric Press: Washington, DC, USA, 1989, Vol. 8, pp. 8-24.

[4] Bender, D.S.; Dolan, R.T.; Skodol, A.E.; Sanislow, C.A.; Dyck, I.R.; McGlashan, T.H.; Shea, M.T.; Zanarini, M.C.; Oldham, J.M.; Gunderson, J.G. Treatment utilization by patients with personality disorders. Am. J. Psychiatry, 2001, 158(2), 295-302. http://dx.doi.org/10.1176/appi.apj.158.2.295 PMID: 1156814

[5] Storebo, O.J.; Stoffers-Winterling, J.M.; Vollm, B.A.; Kongerslev, M.T.; Mattivi, J.T.; Jørgensen, M.S.; Faltinsen, E.; Todorovac, A.; Sales, C.P.; Callesen, H.E.; Lieb, K.; Simonsen, E. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst. Rev., 2020, 5(5), CD012955. PMID: 32368793

[6] Paris, J. Treatment of borderline personality disorder: A guide to evidence-based practice. 2020, Guilford Press, pp.316.

[7] Paris, J. Borderline personality disorder. CMAJ, 2005, 172(12), 1579-1583. http://dx.doi.org/10.1503/cmaj.045281 PMID: 15939918

[8] Trull, T.J.; Jahng, S.; Tomko, R.L.; Wood, P.K.; Sher, K.J. Revised NESARC personality disorder diagnoses: gender, prevalence, and comorbidity with substance dependence disorders. J. Pers. Disord., 2010, 24(4), 412-426. http://dx.doi.org/10.1521/pedi.2010.24.4.412 PMID: 20695803

[9] Zimmerman, M.; Rothschild, L.; Chelminski, I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. Am. J. Psychiatry, 2005, 162(10), 1911-1918. http://dx.doi.org/10.1176/appi.ajp.162.10.1911 PMID: 16199838

[10] Comtois, K.A.; Russo, J.; Snowden, M.; Srebnik, D.; Ries, R.; Roy-Byrne, P. Factors associated with high use of public mental health services by persons with borderline personality disorder. Psychiatr. Serv., 2003, 54(8), 1149-1154. http://dx.doi.org/10.1176/appi.ps.54.8.1149 PMID: 12883144

[11] Chanen, A.M.; McCutcheon, L. Prevention and early intervention for borderline personality disorder: current status and recent evidence. Br. J. Psychiatry Suppl., 2013, 54, e24-e29. http://dx.doi.org/10.1192/bjp.bp.112.119180 PMID: 23288497 Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed; American Psychiatric Association: Washington, DC, USA, 2013.

[12] Lahmeyer, H.W.; Reynolds, C.F., III; Kupfer, D.J.; King, R. Biologic markers in borderline personality disorder: a review. J. Clin. Psychiatry, 1989, 50(6), 217-225. PMID: 2492895

[13] Clarkin, J.F.; Widiger, T.A.; Frances, A.; Hurt, S.W.; Gilmore, M. Prototypic typology and the borderline personality disorder. J. Abnorm. Psychol., 1983, 92(3), 263-275. http://dx.doi.org/10.1037/0021-843X.92.3.263 PMID: 6619404

[14] McGlashan, T.H. The Chestnut Lodge follow-up study. III. Long-term outcome of borderline personalities. Arch. Gen. Psychiatry, 1986, 43(1), 20-30. http://dx.doi.org/10.1001/archpsyc.1986.01800010220003 PMID: 3942471

[15] Kellogg, S.H.; Young, J.E. Schema therapy for borderline personality disorder. J. Clin. Psychol., 2006, 62(4), 445-458. http://dx.doi.org/10.1002/jclp.20240 PMID: 16470629

[16] Giesen-Bloo, J.; van Dyck, R.; Spinhoff, P.; van Tilburg, W.; Dirksen, C.; van Asselt, T.; Kremer, I.; Nadot, M.; Arntz, A. Outpatient psychotherapy for borderline personality disorder: Randomized trial of schema-focused therapy vs transference-focused psychotherapy. Arch. Gen. Psychiatry, 2006, 63(6), 649-658. http://dx.doi.org/10.1001/archpsyc.63.6.649 PMID: 16754838

[17] Black, D.W.; Blum, N.S. Systems Training for Emotional Predictability and Problem Solving for Borderline Personality Disorder: Implementing STEPPS around the Globe; Oxford University Press: New York, NY, USA, 2017. http://dx.doi.org/10.1093/med:psych/9780199384426.001.0001

[18] Bateman, A.; Fonagy, P. Psychotherapy for Borderline Personality Disorder: Mentalization-based Treatment; Oxford University Press: Oxford, UK, 2004. http://dx.doi.org/10.1093/med:psych/9780198527664.001.0001

[19] Levy, K.N.; Meehan, K.B.; Kelly, K.M.; Reynoso, J.S.; Weber, M.; Clarkin, J.F.; Kernberg, O.F. Change in attachment patterns and reflective function in a randomized control trial of transference-focused psychotherapy for borderline personality disorder. J. Consult. Clin. Psychol., 2006, 74(6), 1027-1040. http://dx.doi.org/10.1037/0022-006X.74.6.1027 PMID: 17154733

[20] Gunderson, J.G.; Links, P.R. Handbook of Good Psychiatric Management for Borderline Personality Disorder; American Psychiatric Publishing: Washington, DC, 2014.
line-fluoxetine combination in women with borderline personality disorder. J. Clin. Psychiatry, 2004, 65(7), 903-907. http://dx.doi.org/10.4088/JCP.v65n0704 PMID: 15291677

[39] Soler, J.; Pascual, J.C.; Campins, J.; Barrachina, J.; Puigdemont, D.; Alvarez, E.; Perez, V. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. Am. J. Psychiatry, 2005, 162(6), 1221-1224. http://dx.doi.org/10.1176/appi.ajp.162.6.1221 PMID: 15930077

[40] Black, D.W.; Zanarini, M.C.; Romine, A.; Shaw, M.; Allen, J.; Schulz, S.C. 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, 171(11), 1174-1182. http://dx.doi.org/10.1176/appi.ajp.2014.13101348 PMID: 24968985

[41] Villeneuve, E.; Lemelin, S. Open-label study of atypical neuroleptic quetiapine for treatment of borderline personality disorder: impulsivity as main target. J. Clin. Psychiatry, 2005, 66(10), 1298-1303. http://dx.doi.org/10.4088/JCP.v66n1013 PMID: 16259544

[42] Van den Eynde, F.; Senturk, V.; Nauds, K.; Vogels, C.; Bernage, K.; Thas, O.; van Heeringen, C.; Audenaert, K. Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. J. Clin. Psychopharmacol, 2008, 28(2), 147-155. http://dx.doi.org/10.1097/JCP.0b013e3181664bf4 PMID: 18344724

[43] 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, 67(7), 1044-1046. http://dx.doi.org/10.4088/JCP.v67n0705 PMID: 16898446

[44] Lee, S.S.; Allen, J.; Black, D.W.; Zanarini, M.C.; Schulz, S.C. Quetiapine’s effect on the SCL-90-R domains in patients with borderline personality disorder. Ann. Clin. Psychiatry, 2016, 28(1), 4-10. PMID: 26855980

[45] 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, 31(1), 158-163. http://dx.doi.org/10.1016/j.pnpbp.2006.08.012 PMID: 17045720

[46] Gruettet, T.; Friege, L. Quetiapine in patients with borderline personality disorder and psychosis: a case series. Int. J. Psychiatry Clin. Pract., 2005, 9(3), 180-186. http://dx.doi.org/10.1080/13651500510029048 PMID: 24937788

[47] Van den Eynde, F.; De Saedeleer, S.; Nauds, K.; Day, J.; Vogels, C.; van Heeringen, C.; Audenaert, K. Quetiapine treatment and improved cognitive functioning in borderline personality disorder. Hum. Psychopharmacol., 2009, 24(8), 646-649. http://dx.doi.org/10.1002/hup.1075 PMID: 19946934

[48] Bozzatello, P.; Rocca, P.; Uscinska, M.; Bellino, S. Efficacy and tolerability of aripiprazole compared with olanzapine in borderline personality disorder: An open-label randomized controlled trial. CNS Drugs, 2017, 31(9), 809-819. http://dx.doi.org/10.1007/s40263-017-0458-4 PMID: 28741044

[49] Soloff, P.H.; Cornelius, J.; George, A.; Nathan, S.; Perel, J.M.; Ulrich, R.F. Efficacy of phenelzine and haloperidol in borderline personality disorder. Arch. Gen. Psychiatry, 1993, 50(5), 377-385. http://dx.doi.org/10.1001/archpsyc.1993.01820170055007 PMID: 8489326

[50] Cornelius, J.R.; Soloff, P.H.; George, A.; Ulrich, R.F.; Perel, J.M. Haloperidol vs. phenelzine in continuation therapy of borderline disorder. Psychopharmacol. Bull., 1993, 29(2), 333-337. PMID: 8290683

[51] Cornelius, J.R.; Soloff, P.H.; Perel, J.M.; Ulrich, R.F. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. Am. J. Psychiatry, 1993, 150(12), 1843-1848. http://dx.doi.org/10.1176/ajp.150.12.1843 PMID: 8238640

[52] Benedetti, F.; Sforzin, L.; Colombo, C.; Maffei, C.; Smeraldi, E. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. J. Clin. Psychiatry, 1998, 59(3), 103-107. http://dx.doi.org/10.4088/JCP.v59n0302 PMID: 9541151

[53] Frankenburg, F.R.; Zanarini, M.C. Clozapine treatment of borderline patients: a preliminary study. Compr. Psychiatry, 1993, 34(6), 402-405.
Drug Treatments in Borderline Personality Disorder

Bellino, S.; Paradiso, E.; Bogetto, F. Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am. J. Psychiatry, 2006, 163*(5), 833-838.

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, 2011680194* http://dx.doi.org/10.1155/2011/680194 PMID: 21826264

Palomares, N.; Montes, A.; Díaz-Már, M.; Carrasco, J.L. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. *Int. Clin. Psychopharmacol., 2015, 30*(6), 338-341. http://dx.doi.org/10.1097/YIC.000000000000095 PMID: 26230268

Rotca, P.; Marchiaro, L.; Cocuzza, E.; Bogetto, F. Treatment of borderline personality disorder with risperidone. *J. Clin. Psychiatry, 2002, 63*(3), 241-244.

Teicher, M.H.; Gled, C.A.; Aaronson, S.T.; Gunter, P.A.; Schatzberg, A.F.; Cole, J.O. Open assessment of the safety and efficacy of thoridiazine in the treatment of patients with borderline personality disorder. *Psychopharmacol. Bull., 1989, 25*(4), 535-549. PMID: 2631134

Pascual, J.C.; Soler, J.; Puigdemont, D.; Pérez-Egea, R.; Tiana, T.; Alvarez, E.; Pérez, V. Ziprasidone in the acute treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J. Clin. Psychiatry, 2008, 69*(4), 603-608. http://dx.doi.org/10.4088/JCP.v69n0412 PMID: 18251623

Pascual, J.C.; Olfer, S.; Soler, J.; Barrachina, J.; Alvarez, E.; Pérez, V. Ziprasidone in the acute treatment of borderline personality disorder in inpatient emergency services. *J. Clin. Psychiatry, 2004, 65*(9), 1281-1282. http://dx.doi.org/10.4088/JCP.v65n0918b PMID: 15367057

Knudler, M.P.; Lobo, E.; Chappell, J.; Bergstrom, R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin. Pharmacokinet., 2011, 50*(5), 281-294. http://dx.doi.org/10.2165/11539240-00000000-00000 PMID: 21366359

Muscatal, M.R.A.; Zocchi, R.A.; Pandolfi, G.; Mangano, P.; Lorusso, S.; Cedro, C.; Battaglia, F.; Spina, E.; Bruno, A. Duloxetine in psychiatric disorders: Expansions beyond major depression and generalized anxiety disorder. *Front. Psychiatry, 2019, 10*, 772. http://dx.doi.org/10.3389/fpsyg.2019.00772 PMID: 31749717

Bellino, S.; Paradiso, E.; Bozzatello, P.; Bogetto, F. Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study. *J. Psychopharmacol., 2010, 24*(3), 333-339. http://dx.doi.org/10.1177/0269881108095715 PMID: 18719047

Benfield, P.; Heel, R.C.; Lewis, S.P. Fluoxetine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs, 1986, 32*(6), 481-508. http://dx.doi.org/10.2165/00003495-19863206-00002 PMID: 2878798

Salzmann, C.; Wolfson, A.N.; Schatzberg, A.; Looper, J.; Henke, R.; Albanese, M.; Schwartz, J; Miyawaki, E. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J. Clin. Psychopharmacol., 1995, 15*(1), 23-29. http://dx.doi.org/10.1097/00003474-199502000-00005 PMID: 7714224

New, A.S.; Buchsbaum, M.S.; Hazlett, E.A.; Goodman, M.; Koenigsberg, H.W.; Lo, J.; Iskander, L.; Newmark, R.; Brand, J.; Olfenb, K.; Siever, L.I. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacol. (Berl.), 2004, 176*(3-4), 451-458. http://dx.doi.org/10.1007/s00213-004-1913-8 PMID: 15160265

Norden, M.J. Fluoxetine in borderline personality disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry, 1989, 13*(6), 885-893. http://dx.doi.org/10.1016/0027-5840(89)90040-7 PMID: 2813806

Simpson, E.B.; Yen, S.; Costello, E.; Rosen, K.; Begin, A.; Pistorelli, J.; Pearlstein, T. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J. Clin. Psychiatry, 2004, 65*(3), 379-385. http://dx.doi.org/10.4088/JCP.v65n0314 PMID: 15096078

Cornelius, J.R.; Soloff, P.H.; Perel, J.M.; Ulrich, R.F. Fluoxetine trial in borderline personality disorder. *Psychopharmacol. Bull., 1999, 36*(1), 151-154. PMID: 23731370

Reimold, M.; Solbach, C.; Noda, S.; Schaefer, J.E.; Bartels, M.; Beneke, M.; Machulla, H.J.; Bares, R.; Glaser, T.; Wormstall, H. Occupancy of dopamine D1, D2 and serotonin (2A) receptors in schizophrenic patients treated with flupentixol in comparison with risperidone and haloperidol. *Psychopharmacology (Berl.), 2007, 190*(2), 241-249. http://dx.doi.org/10.1007/s00213-006-0611-0 PMID: 17111172

Ghaneian, H.; Centini, A.K.; Kennedy, S.H. Fatigue in patients with major depressive disorder: Prevalence, burden and pharmacological approaches to management. *CNS Drugs, 2018, 32*(1), 65-74. http://dx.doi.org/10.1007/s40263-018-0490-z PMID: 29338573

Zhang, Y.; Becker, T.; Kösters, M. Preliminary study of patterns of medication use for depression treatment in China. *Asia-Pac. Psychiatry, 2013, 5*(4), 336-341. http://dx.doi.org/10.1080/19434916.2013.834286 PMID: 24161362

Kutcher, S.; Papadodemou, G.; Reiter, S.; Gardner, D. The successful pharmacological treatment of adolescents and young adults with borderline personality disorder: a preliminary open trial of fluphenoxil. *J. Psychiatry Neurosci., 1995, 20*(2), 113-118. PMID: 7703220

Wilde, M.J.; Plesker, G.L.; Benfield, P. Fluvoxamine. An updated review of its pharmacology, and therapeutic use in depressive illness. *Drugs, 1993, 46*(5), 895-924. http://dx.doi.org/10.2165/00003495-19934605-00008 PMID: 7507038

Burton, S. W. A review of fluvoxamine and its uses in depression, 1991. http://dx.doi.org/10.1007/0-395-94076-6_203 PMID: 15092605

Rinne, T.; van den Brink, W.; Wouters, L.; van Dyck, R. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am. J. Psychiatry, 2002, 159*(12), 2048-2054. http://dx.doi.org/10.1176/appi.ajp.159.12.2048 PMID: 12450955

Feighner, J.P. Mechanism of action of antidepressant medications. *J. Clin. Psychiatry, 1999, 60*(Suppl. 4), 9-11. PMID: 10086478

Iastrebov, D.V. Treatment-resistant depressions in borderline psychiatry. *Zh. Nevrol. Psikhiatr. Im. S. S. Korsakova, 2011, 111*(4), 47-50. PMID: 21525015

Markovitz, P.J.; Wagner, S.C. Venlafaxine in the treatment of borderline personality disorder. *Psychopharmacol. Bull., 1995, 31*(4), 773-777. PMID: 8851652

Stein, D.J.; Simeon, D.; Frenkel, M.; Islam, M.N.; Hollander, E. An open trial of valproate in borderline personality disorder. *J. Clin. Psychiatry, 1995, 56*(11), 506-510. PMID: 75929502
Drug Treatments in Borderline Personality Disorder

Current Neuropharmacology, 2021, Vol. 19, No. 10

1779

science and pharmacotherapy. CNS Neurosci. Ther., 2010, 16(5), e138-e156.
http://dx.doi.org/10.1111/j.1755-5949.2010.00185.x PMID: 20626426

[113] Jones, C.; Barrera, I.; Brothers, S.; Ring, R.; Wahlestedt, C. Oxytocin and social functioning. Dialogues Clin. Neurosci., 2017, 19(2), 193-201.
http://dx.doi.org/10.31887/DCNS.2017.19.2/cjones PMID: 28867943

[114] Simeon, D.; Bartz, J.; Hamilton, H.; Crystal, S.; Braun, A.; Ketay, S.; Hollander, E. Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. Psychoneuroendocrinology, 2011, 36(9), 1418-1421.
http://dx.doi.org/10.1016/j.psyneuen.2011.03.013 PMID: 21546164

[115] Domès, G.; Ower, N.; von Dawans, B.; Spengler, F.B.; Dziobek, I.; Bohus, M.; Matthies, S.; Philipsen, A.; Heinrichs, M. Effects of intranasal oxytocin administration on empathy and approach motivation in women with borderline personality disorder: a randomized controlled trial. Transl. Psychiatry, 2019, 9(1), 328.
http://dx.doi.org/10.1038/s41388-019-0658-4 PMID: 31801937

[116] Shahidi, F.; Ambigaipalan, P. Omega-3 polyunsaturated fatty acids and their health benefits. Annu. Rev. Food Sci. Technol., 2018, 9, 345-381.
http://dx.doi.org/10.1146/annurev-food-111317-095850 PMID: 29350557

[117] Patrick, R.P.; Ames, B.N. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J., 2015, 29(6), 2207-2222.
http://dx.doi.org/10.1096/fj.14-268342 PMID: 25713056

[118] Freeman, M.P.; Hibbelin, J.R.; Wisner, K.L.; Davis, J.M.; Mischoulon, D.; Peet, M.; Keck, P.E.; Jr; Marangell, L.B.; Richardson, A.J.; Lake, J.; Stoll, A.L. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J. Clin. Psychiatry, 2006, 67(12), 1954-1967.
http://dx.doi.org/10.4088/JCP.v67n1217 PMID: 17194275

[119] Bellino, S.; Bozzatello, P.; Rocca, G.; Bogetto, F. Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of the association with valproic acid. J. Psychopharmacol., 2014, 28(2), 125-132.
http://dx.doi.org/10.1177/026988113510072 PMID: 24196948

[120] Zanarini, M.C.; Frankenburg, F.R. omega-3 Fatty acid treatment of women with borderline personality disorder: A double-blind, placebo-controlled pilot study. Am. J. Psychiatry, 2003, 160(1), 167-169.
http://dx.doi.org/10.1176/appi.ajp.160.1.167 PMID: 12505817

[121] Doo, A.R.; Kim, S.N.; Park, J.Y.; Cho, K.H.; Hong, J.; Eun-Kyung, K.; Moon, S.K.; Jung, W.S.; Lee, H.; Jung, J.H.; Park, H.J. Neuroprotective effects of an herbal medicine, Yi-Gan San on MPP+/MPTP-induced cytotoxicity in vitro and in vivo. J. Ethnopharmacol., 2010, 131(2), 433-442.
http://dx.doi.org/10.1016/j.jep.2010.07.008 PMID: 20633628

[122] Tateno, M.; Ukai, W.; Ono, T.; Saito, S.; Hashimoto, E.; Saito, T. Neuroprotective effects of Yi-Gan San against beta amyloid-induced cytotoxicity on rat cortical neurons. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2008, 32(7), 1704-1707.
http://dx.doi.org/10.1016/j.pnpbp.2008.07.006 PMID: 18675875

[123] Miyaoka, T.; Furuya, M.; Yasuda, H.; Hayashia, M.; Inagaki, T.; Horiguchi, J. Yi-gan san for the treatment of borderline personality disorder: an open-label study. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2008, 32(1), 150-154.
http://dx.doi.org/10.1016/j.pnpbp.2007.06.026 PMID: 17765378