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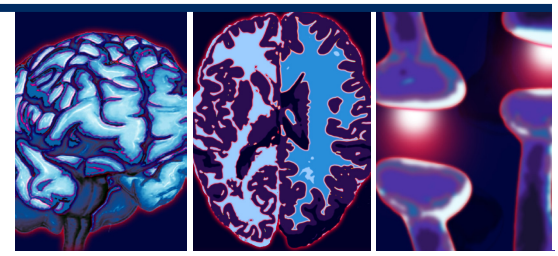

Recent approaches to pharmacotherapy of personality disorders

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Practice points

- Pharmacotherapy of personality disorders should be considered a symptom-focused treatment, targeting dimensions of affective dysregulation, impulsive-behavioral dyscontrol and cognitive-perceptual symptoms.
- To date, randomized controlled trials have been performed in samples of patients with antisocial personality disorder, schizotypal personality disorder and borderline personality disorder (BPD). However, the great majority of these trials have been conducted in samples with BPD.
- There is some evidence that mood stabilizers (topiramate, valproate and lamotrigine), second-generation antipychotics (olanzapine, aripiprazole), and omega-3 fatty acids can be useful for the treatment of affective symptoms and impulsive-behavioral dyscontrol in BPD patients.
- Antipsychotics produced an improvement of psychotic-like symptoms both in patients with BPD and schizotypal personality disorder.
- Selective serotonin reuptake inhibitors were found to be effective in decreasing depressed mood, anxiety, and anger in BPD patients, mainly with a comorbid major depressive episode. However, recent evidence no longer supports their use as first-line treatment of affective symptoms and impulsive-behavioral dyscontrol in BPD.
- Present studies suffer from important methodological limitations. Thus, further investigations are needed to confirm available findings.

SUMMARY A growing number of studies on pharmacotherapy of personality disorders have been performed. This article considers controlled trials conducted between 1990 and 2010, and is directed toward the treatment of personality disorders. Data on borderline personality disorder (BPD), antisocial personality disorder and schizotypal personality disorder (STPD) were collected and discussed, in order to provide indications for clinical practice. Concerning antisocial personality disorder and STPD, available evidence is too sparse to propose treatment recommendations. As for BPD, there is some evidence that mood stabilizers (topiramate, valproate, and lamotrigine), second-generation antipsychotics (olanzapine, aripiprazole), and omega-3 fatty acids can be useful to treat affective symptoms

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and impulsive-behavioral dyscontrol. Antipsychotics showed positive effects on cognitive symptoms both in patients with BPD and STPD. Selective serotonin reuptake inhibitors were found effective in decreasing depressed mood, anxiety and anger in BPD patients, mainly in subjects with a concomitant affective disorder. Effects of antidepressants on impulsive behaviors are uncertain. Further studies are needed to improve methods of trials and confirm these findings.

Personality disorders (PDs) are defined as enduring patterns of inner experience and behavior causing distress, which lead to maladaptive functioning in the areas of emotion, cognition, interpersonal relationships and impulse control [1]. Since the 1980s there has been increasing recognition that PDs can be considered as syndromes of interacting dimensional traits that arise from psychosocial development and/or biological vulnerability [2]. Personality dimensions acquired through social and cultural learning are termed character, whereas those believed to have a biological origin, genetically determined or acquired from overt injury to the CNS, are traditionally referred to as temperament. Temperament involves the biological regulation of cognition, perception, information processing, affect, and impulse, which is carried out by neurotransmitter systems. A pharmacological approach to treatment of PDs is based on the ability of medications to modify neurotransmitter functions that mediate expression of state symptoms and trait vulnerabilities related to personality dimensions.

According to Soloff's model [3,4], adopted by American Psychiatric Association (APA) guidelines for the treatment of borderline personality disorder (BPD) [1], pharmacotherapy of PDs may be reframed as symptom-specific treatment, focused on a few target dimensions, such as affective dysregulation, cognitive-perceptual symptoms and impulsive-behavioral dyscontrol.

Pharmacotherapy is an important adjunctive treatment in the overall management of patients with severe PDs, but is not a primary treatment for problems of character or maladaptive interpersonal relationships, which are the main focus of psychotherapy. Thus, medication should only be part of a comprehensive treatment plan including psychotherapy and social work, which should be developed considering the individual psychopathology, severity of illness and functioning.

Pharmacotherapy of PDs is still a relatively new and evolving clinical practice. It is important to note that the US FDA has not approved any medication for the treatment of PDs yet.

Randomized controlled trials (RCTs) on treatment of PDs are limited and the great majority of these trials have been conducted in patients with borderline PD. Nevertheless, these results have made possible the development of treatment guidelines that provide detailed recommendations for clinicians dealing with PD patients. Before presenting and discussing contents of available treatment guidelines, we will review double-blind randomized comparisons of drug versus placebo or drug versus drug published between 1990 and 2010 and directed at the treatment of PDs. Available controlled studies are focused on BPD, antisocial personality disorder (ASPD) and schizotypal personality disorder (STPD). Results of studies on each cluster of PDs are separately described.

Treatment of STPD

Schizotypal PD is generally considered a schizophrenia spectrum disorder [5,6]. Similarities between STPD and schizophrenia in phenomenology and biological correlates have provided the rationale for testing the efficacy of classical neuroleptics (flupentixol, thiothixene and haloperidol) in patients with STPD since 1980 [7–9]. Patients in these studies gained modest improvement after treatment with low doses of neuroleptics, with the greatest effects on psychotic-like symptoms and anxiety.

Concerning second-generation antipsychotics, few data are available [10,11] and only two RCTs on risperidone have been published [12,13].

Koenigsberg *et al.* performed a 9-week RCT on 25 STPD patients (five subjects had comorbid BPD), randomly assigned to risperidone (0.25–2.00 mg/day) or placebo [12]. Patients in the risperidone group showed a significant decline in the Positive and Negative Syndrome Scale (PANSS) total, negative, positive, and general scores, compared with placebo. Significant differences were not found with the Schizotypal Personality Disorder Questionnaire (SPQ), the Hamilton Depression Rating Scale (HAMD) and the Clinical Global Impression (CGI). Moreover, seven of the 15 patients in the risperidone group dropped out because of side effects. In

recent years, there has been growing interest for treatment of cognitive performances measured by neuropsychological tests in schizophrenia spectrum disorders, such as STPD. McClure *et al.* enrolled 31 STPD patients, randomly assigned to risperidone (0.25–2.00 mg/day) or placebo, in order to evaluate the effects of risperidone on their cognitive performance [13]. Several patients in both groups dropped out and only 20 subjects completed all 12 weeks of the trial. There were no significant differences between the two treatment groups in improvement of neuropsychological functions (spatial and verbal working memory, vigilance, spatial memory, work list learning) from baseline. More encouraging results on these outcome measures were obtained by the same research group [14,15] using dopamine and adrenaline agonists. McClure *et al.* performed a double-blind, placebo-controlled trial of guanfacine on 29 STPD patients, supporting its efficacy in improving context processing [14]. In another RCT, they administered pergolide to 25 patients with STPD and found a significant improvement in visual spatial working memory, executive functioning, verbal learning and memory [15].

In conclusion, preliminary studies performed in STPD patients **(Table 1)** suggest a reduction of psychotic-like symptoms with antipsychotics and an improvement of cognitive performances measured by neuropsychological tests with dopamine and adrenaline agonists. Nevertheless, most studies suffer from high drop-out rates because of considerable sensitivity to side effects in this population. Moreover, some patients in these studies had concomitant BPD [8–10,12]. So, it remains unclear whether the reported improvements were due to the medications' effects on BPD-related symptoms.

Pharmacotherapy of cluster B PDs

Newer therapies for ASPD have received preliminary testing. Nevertheless most studies of patients with cluster B PDs are focused on treatment of BPD.

Results of controlled studies on the efficacy of each class of drugs are separately reviewed, in order to make clear the different level of evidence.

Treatment of BPD

■ Antidepressants

A considerable number of open-label trials and RCTs have been performed to assess the efficacy of antidepressants in the treatment of affective lability, impulsivity and aggressiveness in BPD samples. The following groups of antidepressants have been evaluated: tricyclic antidepressants, monoamino-oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). Concerning tricyclic antidepressants and MAOIs, available data [16–19] suggest that the efficacy of these drugs in patients with BPD is limited, with main effects on symptoms of depression. The risk of behavioral toxicity and the potential lethality support the preferential use of SSRIs or SNRIs to treat these patients.

Selective serotonin reuptake inhibitors

Six RCTs testing the efficacy of SSRIs have been conducted so far: five studies on fluoxetine [20–24], one study on fluvoxamine **(Table 2)** [25].

Salzmann and colleagues published a 12-week double-blind trial of fluoxetine (20–60 mg/day) in 27 patients with BPD or bipolar traits,

Table 1. Double-blind randomized trials in the treatment of schizotypal personality disorder.

Study (year)	Agents	Study design	Subjects	Results (primary outcome)	Ref.
Koenigsberg *et al.* (2003)	Risperidone (0.25–2.00 mg/day) versus placebo	RCT 9 weeks	25 STPD patients (5 BPD)	↓ PANSS total, negative, positive and general scores	[12]
McClure *et al.* (2009)	Risperidone (0.25–2.00 mg/day) versus placebo	RCT 12 weeks	20 STPD patients	No effects on cognitive performance	[13]
McClure *et al.* (2007)	Guanfacine (≤2 mg/day) versus placebo	RCT 4 weeks	29 STPD patients	↑ context processing ability	[14]
McClure *et al.* (2010)	Pergolide (≤3 mg/day) versus placebo	RCT 4 weeks	25 STPD patients	↑ visual spatial working memory, executive functioning, and verbal learning and memory	[15]

↓: Decrease of; ↑: Increase of; BPD: Borderline personality disorder; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; STPD: Schizotypal personality disorder.

Table 2. Double-blind randomized trials of selective serotonin reuptake inhibitors in the treatment of borderline personality disorder.

Study (year)	Agents	Study design	Subjects	Results (primary outcome)	Ref.
Markovitz (1995)	Fluoxetine (20–80 mg/day) versus placebo	RCT 14 weeks	17 BPD patients with concomitant Axis I affective and anxiety disorders	↓ anxiety and depression ↓ global symptoms	[20]
Salzmann *et al.* (1995)	Fluoxetine (20–60 mg/day) versus placebo	RCT 12 weeks	27 BPD patients with a good level of functioning, no Axis I or II comorbidity	↓ anger ↑ global functioning	[21]
Coccaro and Kavoussi (1997)	Fluoxetine (20–60 mg/day) versus placebo	RCT 12 weeks	40 patients with PDs (33% BPD, 25% female), impulsive-aggressive behaviors and comorbidity with dysthymic disorder, anxiety disorders or substance abuse	↓ irritability ↓ impulsive-aggression ↑ global functioning	[22]
Simpson *et al.* (2004)	Fluoxetine (40 mg/day) + DBT versus DBT + placebo	RCT 12 weeks	25 female BPD patients, no bipolar disorder	No significant effects on depression, anxiety, anger, dissociation and global functioning	[23]
Zanarini *et al.* (2004)	Fluoxetine (15 mg/day) versus olanzapine (2.5 mg/day) versus OFC	RCT 8 weeks	45 female BPD patients, no affective disorder	Olanzapine and OFC greater than fluoxetine on impulsive-aggression and depression	[24]
Rinne *et al.* (2002)	Fluvoxamine (150–250 mg/day) versus placebo	RCT 6 weeks Crossover	38 female BPD patients, comorbidity with mood and anxiety disorders	↓ rapid mood shift No effects on aggression and impulsivity	[25]

↓: Decrease of; ↑: Increase of; BPD: Borderline personality disorder; DBT: Dialectical behavior therapy; OFC: Combination of olanzapine and fluoxetine; PD: Personality disorder; RCT: Randomized controlled trial.

evaluating effects on global functioning, anger and depression [21]. Patients had a good level of functioning (baseline Global Assessment of Symptoms [GAS] scores in the 70s) and did not present comorbidity with Axis I or II disorders. In a primary analysis, only the anger subscale of the Profile of Mood States (POMS) and the GAS yielded a statistical improvement over placebo in the 22 patients completing the trial. In a *post hoc* analysis with correction for the strong placebo effect, statistically significant differences between treatment conditions were obtained with respect to anger and aggression, which appeared to be independent of depression.

Markovitz conducted a 14-week RCT of fluoxetine (20–80 mg/day) in a group of 17 patients with BPD and high co-occurrence of affective/anxiety disorders and somatic symptoms [20]. Patients receiving fluoxetine improved significantly more than those receiving placebo on measures of depression, anxiety and global symptoms. Measures of impulsive-aggression were not included in this study. Comorbidity with affective and anxiety disorders limits interpretation of results, because SSRIs are effective for these disorders independently of BPD.

A double-blind placebo-controlled study by Coccaro and Kavoussi focused attention on impulsive-aggression as a dimensional construct, found across PD categories, but especially characteristic of BPD and other cluster B PDs [22]. They enrolled a mixed sample of 40 PD patients (approximately a third with a Diagnostic and Statistical Manual of Mental Disorders [DSM]-III-R diagnosis of BPD), all with impulsive-aggressive behavior and irritability (the female group constituted only a quarter of the total sample). Comorbid major depression or bipolar disorder were excluded, but dysthymic disorder, anxiety disorders, alcohol and substance abuse were common. Subjects were randomly assigned to fluoxetine (20–60 mg/day) or placebo in a ratio 2:1 for a 12-week trial. A significant improvement with respect to impulsive-aggressive behavior was seen in favor of fluoxetine after 10 weeks of treatment, but global improvement was already significant at week 4 and irritability decreased at week 6.

Rinne *et al.* tested the efficacy of fluvoxamine (mean dose 166 mg/day) versus placebo in 38 female patients with BPD [25]. The study was a double-blind controlled trial of 6 weeks, followed by a 6-week crossover. Significant improvement was found in the scale scores for rapid mood shifts, with the most improvement in the first 6 weeks. By contrast, no difference between the fluvoxamine and placebo group was observed with regard to the effect on impulsivity and aggression scores. The authors suggested that effects on anger and impulsivity may be related to gender.

Simpson *et al.* studied the effect of 12 weeks fluoxetine (40 mg/day) in a placebo-controlled trial in 25 females with BPD during dialectical behavior therapy (DBT) [23]. Combining fluoxetine did not show any additional benefit on self-report measures of depression, anxiety, anger, dissociation and global functioning.

Zanarini *et al.* compared fluoxetine (mean dose 15 mg/day) with olanzapine and a combination treatment of both drugs with respect to mood symptoms and impulsive-aggressive behavior in 45 female BPD patients [24]. There was no placebo control group. Olanzapine monotherapy and the combination were found to be superior to fluoxetine monotherapy. It is important to note that, for severe PD, an unusually low dose of fluoxetine was used, which might explain the lack of efficacy of fluoxetine.

In summary, there is some evidence that SSRIs are effective in decreasing affective symptoms [25], specifically depressed mood [20,21], anxiety [20], and anger [21,22] in BPD patients. Effects on impulsive-aggression appear independent of effects on affective symptoms and may be related to male gender.

■ Mood stabilizers

Several RCTs have investigated the efficacy of mood stabilizers in treatment of affective dysregulation and behavioral dyscontrol of BPD patients **(Table 3)**.

Lithium

The only RCT of lithium in BPD is reported by Links *et al.* [19]. In a crossover study, the effects of lithium and desipramine were compared in 17 patients. A significant improvement of anger and suicidality, but not of mood symptoms, was found in favor of the lithium therapy. Although this evidence is not sufficient to support the indication of lithium for these patients, the risk of toxicity and the need for regular blood level controls are significant limitations to the use of this drug in the BPD population.

Carbamazepine

De la Fuente and Lotstra conducted a RCT of carbamazepine in 20 BPD outpatients without any Axis I comorbidity [26]. Treatment lasted for 31 days. Carbamazepine doses were adjusted to yield plasma levels in the low therapeutic range. There were no significant differences between carbamazepine and placebo on measures of affective symptoms, behavioral dyscontrol or global assessment. Moreover, two patients receiving carbamazepine dropped out because of acting out behaviors. Considering the limited efficacy on BPD symptoms shown so far by this drug and the risk of severe adverse effects (e.g., exacerbation of behavioral dyscontrol and agranulocitosis), it should be considered a questionable treatment option.

Valproate

Hollander *et al.* performed a preliminary double-blind trial of valproate sodium (medium plasma concentration 80 µg/ml) in 16 BPD patients, finding marked improvement in global symptomatology, social functioning and BPD features such as depressive symptoms, aggressiveness, irritability and suicidal behavior [27]. The study suffered from a high drop-out rate (ten patients), which accounted for nonsignificant results in the intention to treat analysis.

The same authors [28] tested valproate treatment on a sample of 246 patients with a high degree of aggression (including BPD and other cluster B PDs), confirming its efficacy for treating impulsive-aggressive behavior. More recently, they reported that the effect of valproate in 52 BPD patients from the previous study, was higher among those with high trait impulsivity [29].

Frankenburg and Zanarini conducted a 6-month placebo-controlled study of valproate sodium (plasma concentration 50–100 µg/ml) in 30 women with comorbidity of BPD and bipolar II disorder [30]. A significant improvement of interpersonal sensitivity, anger, hostility and aggressiveness was found in the valproate group.

In conclusion, valproate is one of the more extensively investigated drugs for treatment of impulsive-aggressive behaviors in BPD.

Table 3. Double-blind randomized trials of mood stabilizers in the treatment of borderline personality disorder.

Study (year)	Agents	Study design	Subjects	Results (primary outcome)	Ref.
Links *et al.* (1990)	Lithium (986 mg/day) versus desipramine versus placebo	RCT 6 weeks Crossover	17 BPD patients, all receving concomitant psychotherapy	↓ irritability and anger ↓ self-mutilation in favor of lithium No effects on mood symptoms High rate of drop-out (10 patients)	[19]
De la Fuente and Lotstra (1994)	Carbamazepine (plasma level) versus placebo	RCT 4.5 weeks	20 BPD outpatients, no Axis I comorbidity	No effects on affective symptoms, behavioral dyscontrol and global assessment	[26]
Hollander *et al.* (2001)	Valproate sodium (plasma level) versus placebo	RCT 10 weeks	16 BPD patients, no psychotic and affective disorders	No significant differences because of high rate of drop-out (10 patients)	[27]
Hollander *et al.* (2003)	Valproate sodium (plasma level) versus placebo	RCT 12 weeks	96 cluster B PDs with impulsive-aggression (52 BPD), no affective disorders	↓ irritability ↓ impulsive-aggression ↓ global severity	[28]
Frankenburg and Zanarini (2002)	Valproate sodium (plasma level) versus placebo	RCT 6 months	30 female BPD patients with concomitant bipolar II disorder	↓ interpersonal sensitivity ↓ anger and hostility ↓ aggressiveness	[30]
Nickel *et al.* (2004)	Topiramate (50–250 mg/day) versus placebo	RCT 8 weeks	31 female BPD patients	↓ irritability and anger	[31]
Nickel *et al.* (2005)	Topiramate (50–250 mg/day) versus placebo	RCT 8 weeks	42 male BPD patients	↓ irritability and anger	[32]
Loew *et al.* (2008)	Topiramate (25–200 mg/day) versus placebo	RCT 10 weeks	56 female BPD and mood disorder patients	↓ somatization symptoms ↓ interpersonal sensitivity ↓ hostility ↑ global functioning	[36]
Tritt *et al.* (2005)	Lamotrigine (50–200 mg/day) versus placebo	RCT 8 weeks	24 female BPD patients	↓ anger	[38]
Reich *et al.* (2009)	Lamotrigine (25–275 mg/day) versus placebo	RCT 12 weeks	28 BPD patients with major depression and anxiety disorders	↓ impulsivity ↓ affective instability	[40]

↓: Decrease of; ↑: Increase of; BPD: Borderline personality disorder; PD: Personality disorder; RCT: Randomized controlled trial.

Topiramate

Topiramate has also been investigated to test its ability to control aggressive behaviors in BPD patients.

In the first RCT by Nickel *et al.* [31], 31 women with BPD were treated with topiramate (50–250 mg/day) or placebo for 8 weeks. Topiramate was superior to placebo with respect to most of the State-Trait Anger Expression Inventory (STAXI) scales. The second topiramate RCT by the same group [32] included 42 male patients and obtained approximately the same results.

Follow-up studies performed by these authors [33–36] found that topiramate was a safe agent with long-lasting effects in reducing aggression in BPD.

A third RCT on topiramate (25–200 mg/day for 10 weeks) was performed by Loew *et al.* in 56 females with BPD and concurrent mood disorders, finding a significant decrease of somatization symptoms, interpersonal sensitivity, and hostility and an improvement of global functioning [37].

Lamotrigine

To date, only two double-blind trials of lamotrigine in BPD are available. In 2005, Tritt *et al.* assessed the efficacy of lamotrigine (titrated to a dose of 200 mg/day) versus placebo in the treatment of aggression in 24 female BPD outpatients [38]. The study found a significant improvement of anger after 8 weeks of treatment. Moreover, during the 18-month follow-up observation, significant changes of all the scales of the STAXI were reported in the lamotrigine-treated subjects [39].

Reich *et al.* performed a 12-week double-blind placebo-controlled study of 28 BPD patients,

in order to evaluate the efficacy of lamotrigine in the treatment of affective instability [40]. A significantly greater reduction of affective instability and impulsivity was found in the group with lamotrigine.

In conclusion, available studies provide initial evidence that the mood stabilizers topiramate, valproate and lamotrigine can be useful for the treatment of affective symptoms related to anger and impulsive-aggression in BPD patients.

■ Antipsychotics

Antipsychotics are widely used in clinical practice for treatment of BPD patients. RCTs have been performed both for classical neuroleptics and new generation antipsychotics, considering effects not only on psychotic or psychotic-like symptoms, but also on different dimensions of BPD psychopathology **(Table 4)**.

Classical neuroleptics

Since the 1980s, many RCTs have been conducted to test the efficacy of neuroleptics such as flupentixol decanoate [41], loxapine, chlorpromazine [42], thiothixene [8], trifluoperazine [16], and haloperidol [17,43] in BPD patients.

In 1993, Soloff *et al.* performed a 5-week RCT of haloperidol (4 mg/day) versus the MAOI phenelzine (60 mg/day) and placebo in a large sample of BPD inpatients (n = 108), finding that haloperidol efficacy was limited to hostility and impulsive-aggressive behaviors [18]. Cornelius *et al.* followed the 54 responders of these 108 patients in a continuation study lasting 16 weeks [44]. Haloperidol was prescribed up to a maximum of 6 mg/day, but failed to obtain significant effects. During prolonged haloperidol treatment, depression significantly increased in severity and global clinical improvement was modest, limited to irritability. Moreover, 64% of patients in the haloperidol group dropped out during follow-up.

In conclusion, classical neuroleptics might be administered to BPD patients during acute states with anger and psychotic-like symptoms, but evidence of efficacy is poor, and treatment should be administrated in low doses and for short periods because of common and remarkable adverse effects (extrapyramidal symptoms).

New generation antipsychotics

Several open-label studies with risperidone, clozapine, and quetiapine have shown considerable effects on cognitive-perceptual symptoms, anger, and impulsivity in BPD patients. However, only olanzapine, aripiprazole and ziprazidone have been tested in RCTs.

Olanzapine

Olanzapine has been the most thoroughly studied atypical antipsychotic in the treatment of BPD. Three studies investigated the effects of olanzapine compared with placebo.

Zanarini and Frankenburg performed a 6-month RCT of olanzapine (mean dose 5.33 mg/day) in 28 women with BPD [45]. A significant improvement over placebo was reported in a wide range of symptoms, including interpersonal sensitivity, anxiety, anger, hostility, paranoia, psychoticism and global functioning.

Bogenschutz and Nurnberg investigated the efficacy of olanzapine (5–10 mg/day) in 40 BPD subjects during a 12-week RCT [46]. They observed a significant improvement with the CGI scale modified for BPD, but not with the Symptom Checklist-90 subscales.

In another RCT performed by Schulz *et al.*, 314 patients were randomly assigned to olanzapine (2.5–20 mg/day) or placebo for 12 weeks [47]. Both groups showed a significant improvement of BPD symptomatology (Zanarini Rating Scale for BPD) and did not differ at end point. However, time to response was significantly shorter for olanzapine.

In recent years, studies comparing olanzapine with other active drugs, psychotherapy, or their combination have been published.

The study by Zanarini *et al.* comparing the efficacy of olanzapine (mean dose 3.3 mg/day), fluoxetine, and their combination has already been described [24].

Soler *et al.* [48] reported a 12-week trial of olanzapine (mean dose 8.83 mg/day) versus placebo in 60 BPD outpatients, who received a concomitant psychotherapy with DBT. Olanzapine was superior to placebo in reducing anxiety, depressive symptoms and impulsive-aggressive behaviors. In a following study with a similar design, Linehan *et al.* included 24 women with BPD, who were randomly assigned to receive olanzapine (mean dosage 5 mg/day) plus DBT or placebo plus DBT for 21 weeks [49]. Both groups of patients showed a considerable improvement of irritability, aggression, depressive symptoms, and self-injury, but irritability and aggression scores decreased more quickly in the olanzapine group.

Table 4. Double-blind randomized trials of antipsychotics in the treatment of borderline personality disorder.

Study (year)	Agents	Study design	Subjects	Results (primary outcome)	Ref.
Soloff *et al.* (1993)	Haloperidol (4 mg/day) versus phenelzine (60 mg/day) versus placebo	RCT 5 weeks	108 BPD inpatients with concomitant major depression	↓ hostility ↓ impulsive-aggression	[18]
Cornelius *et al.* (1993)	Haloperidol (≤6 mg/day) versus placebo	RCT 16 weeks	54 BPD outpatients, responders from the study by Soloff *et al.*	↓ irritability	[44]
Zanarini and Frankenburg (2001)	Olanzapine (5.33 mg/day) versus placebo	RCT 6 months	28 female BPD patients	↓ anger ↓ interpersonal sensitivity ↓ anxiety ↓ paranoid ideation ↑ global functioning	[45]
Bogenschutz and Nurnberg (2004)	Olanzapine (5–10 mg/day) versus placebo	RCT 12 weeks	40 BPD outpatients	↓ anger ↓ global symptoms	[46]
Schulz *et al.* (2008)	Olanzapine (2.5–20.0 mg/day) versus placebo	RCT 12 weeks	314 BPD patients	No significant differences of BPD symptoms Faster ↓ BPD severity in olanzapine group	[47]
Soler *et al.* (2005)	Olanzapine (5–20 mg/day) + DBT versus DBT + placebo	RCT 12 weeks	60 BPD patients	↓ anxiety ↓ depression ↓ impulsive-aggression	[48]
Linehan *et al.* (2008)	Olanzapine (5 mg/day) + DBT versus DBT + placebo	RCT 21 weeks	24 female BPD patients	No significant differences of general symptoms Faster ↓ irritability and aggression in the olanzapine group	[49]
Shafti and Shahveisi (2010)	Olanzapine (7 mg/day) versus haloperidol (7 mg/day)	RCT 8 weeks	28 female BPD inpatients	No significant differences of generic behavioral symptoms	[50]
Nickel *et al.* (2006)	Aripiprazole (15 mg/day) versus placebo	RCT 8 weeks	57 BPD patients	↓ depression and anxiety ↓ anger ↓ aggressiveness ↓ paranoia ↑ global functioning	[51]
Pascual *et al.* (2008)	Ziprasidone (84 mg/day) versus placebo	RCT 12 weeks	60 BPD patients	No effects on psychoticism, depression, anxiety, impulsivity and hostility	[53]

↓: Decrease of; ↑: Increase of; BPD: Borderline personality disorder; DBT: Dialectical behavior therapy; RCT: Randomized controlled trial.

In a recent 8-week double-blind study comparing olanzapine (mean dose 7 mg/day) with haloperidol (mean dose 7 mg/day) in 28 female inpatients with BPD, Shafti and Shahveisi did not find significant differences between drugs in reducing the severity of generic behavioral symptoms (anxiety, depressive mood and hostility subscales of the Brief Psychiatric Rating Scale) [50]. It must be noted that this trial did not use a control group with placebo.

Aripiprazole

The only RCT of aripiprazole (15 mg/day) was performed by Nickel *et al.* in 57 BPD patients, and found significant effects on psychotic symptoms, depression, anxiety and hostility after 8 weeks [51]. Improvements were confirmed in an 18-month follow-up observation study [52].

Ziprasidone

Pascual *et al.* included 60 BPD patients in a 12-week placebo-controlled trial to test efficacy of ziprasidone (mean dose 84 mg/day) on psychoticism, depression, anxiety, impulsivity and hostility [53]. The study failed to show any significant effect of ziprasidone in this sample.

In conclusion, there is growing evidence that the atypical antipsychotic olanzapine significantly improves cognitive symptoms, aggressiveness, anxiety and depression in BPD samples. Further studies are required to test the efficacy of newer drugs, such as aripiprazole.

Other agents

Other psychotropic agents, such as opiate antagonists and omega-3 fatty acids, have been tested for their efficacy regarding symptoms of BPD **(Table 5)**.

One small double-blind study, including nine BPD patients, failed to show efficacy of intravenous administration of naloxone (0.4 mg) in the treatment of acute dissociative states [54].

Zanarini and Frankenberg investigated the effects of omega-3 fatty acids in the treatment of 30 female BPD patients [55]. They reported significant improvements in depressive symptoms and aggressive behaviors in response to ethyl-eicosapentaenoic acid (1 g/day) compared with placebo in an 8-week RCT. Hallahan *et al.* performed a second study evaluating 49 subjects with self-harm behaviors (35 with a diagnosis of BPD) in a 12-week RCT [56]. Patients were randomized to receive eicosapentaenoic acid (1.2 g) plus docosahexaenoic acid (0.9 g) versus placebo, in addition to standard psychiatric care. The group receiving omega-3 fatty acids had significantly greater improvements in scales for depression, suicidality and reaction to daily stresses.

In conclusion, the results of these two studies are promising for treatment of mood symptoms and aggressive behaviors in BPD patients, in particular, considering the good tolerability of these agents.

Treatment of antisocial PD

Studies investigating the pharmacological treatment of ASPD are scarce and involve heterogeneous samples **(Table 6)**. Eight trials have been performed, but none of them included patients only on the basis of having ASPD. Most studies are oriented around the treatment of drug or alcohol abuse in ASPD patients, while no study focused on the disorder itself.

Drugs compared with placebo belong to four categories:

- Antiepileptics: one investigation has been conducted using carbamazepine [57], at a dose of 450 mg/day for incarcerated men with aggression. No data were available for the ASPD subgroup in this trial. Three studies have been performed with phenytoin [57–59] at a dose of 300 mg/day. Barratt reported that phenytoin is more effective than placebo for reducing frequency and intensity of aggressive behaviors in 126 male prisoners with impulsive-aggression [58]. No separate results about symptoms of ASPD are provided by the other two studies [57,59]. Two controlled trials [57,60] compared efficacy of valproate with placebo in outpatients with aggression, but neither reported significant findings in the ASPD group.

- Antidepressants: two RCTs investigated the efficacy of desipramine. The first [61] included methadone-maintained inpatients with opioid and cocaine dependency, the other [62] involved methadone-maintained outpatients with sole cocaine dependence. Desipramine was not found superior to placebo in either study. The trial performed by Powell [63] in a sample of 20 men with alcohol dependence, reported the efficacy of nortriptyline (25–75 mg/day) in reducing mean number of drinking days, level of anxiety, and alcohol dependence, but not the severity of alcohol misuse.

- Dopamine agonists: two controlled trials have been published on amantadine and bromocriptine. In the first study [61], amantadine was not found superior to placebo in men with opioid and cocaine dependency. The study on bromocriptine [63] reported the efficacy of this drug at 15 mg/day on anxiety symptoms of 18 men with alcohol dependency.

Table 5. Double-blind randomized trials of opiate antagonists and omega-3 fatty acids in the treatment of borderline personality disorder.

Study (year)	Agents	Study design	Subjects	Results (primary outcome)	Ref.
Philipsen *et al.* (2004)	Naloxone iv. (0.4 mg) versus placebo	RCT	9 BPD patients	No different effects on dissociative symptoms	[54]
Zanarini and Frankenberg (2003)	Ethyl-eicosapentaenoic acid (1 g/day) versus placebo	RCT 8 weeks	30 female BPD patients	↓ depressive symptoms ↓ aggressive behaviors	[55]
Hallahan *et al.* (2007)	Eicosapentaenoic acid (1.2 g/day) plus docosahexaenoic acid (0.9 g/day) versus placebo	RCT 12 weeks	49 subjects with self-harm behaviors (35 BPD patients)	↓ depression and suicidality ↓ reaction to daily stresses	[56]

↓: Decrease of; BPD: Borderline personality disorder; iv.: Intravenous; RCT: Randomized controlled trial.

Table 6. Double-blind randomized trials in the treatment of antisocial personality disorder.

Study (year)	Agents	Study design	Subjects	Results	Ref.
Barratt *et al.* (1997)	Phenytoin (300 mg/day) versus placebo	RCT 9 weeks	126 male prisoners with impulsive-aggression	↓ aggressive behaviors	[58]
Powell *et al.* (1995)	Nortriptyline (25–75 mg/day) versus bromocriptine (15 mg/day) versus placebo	RCT 4 weeks	38 male ASPD with alcohol dependence	↓ drinking days, level of anxiety and alcohol dependence in the nortriptyline group ↓ anxiety symptoms in the bromocriptine group	[63]

↓: Decrease of; ASPD: Antisocial personality disorder; RCT: Randomized controlled trial.

- Opioid antagonists: only one study on naltrexone is available in this category [64]. The authors compared subgroups of alcohol dependents with and without ASPD or BPD and concluded that "diagnosis of PD did not adversely affect alcohol outcomes, and patients with ASPD or BPD did not have a poorer response to medication" [64].

In summary, it is difficult to draw any conclusion about ASPD treatment from the data available in the literature. Only three drugs (nortriptyline, bromocriptine and phenytoin) were found superior to placebo. There is some evidence that nortriptyline could be useful in decreasing alcohol abuse of ASPD patients and both nortriptyline and bromocriptine are effective on anxiety symptoms in individuals with ASPD and alcohol dependency. There is also some evidence that phenytoin controls impulsive-aggressive behaviors in ASPD subjects. However, it remains unclear whether any drugs are effective in the treatment of core features of this PD.

Pharmacotherapy of cluster C PDs

Treatment of avoidant PD

To date, no RCTs on pharmacological treatment of patients with cluster C PDs have been published. Nevertheless, the treatment guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) [65] indicated the efficacy of antidepressants (SSRIs, SNRIs and MAOIs) for anxious/avoidant PD, on the basis of data concerning Axis I anxiety disorders like social phobia.

Treatment guidelines & meta-analyses

In 2001, the APA published the first set of guidelines for the treatment of borderline PD, proposing a pharmacotherapy targeted at three symptom dimensions: affective dysregulation, impulsive-behavioral dyscontrol and cognitive-perceptual symptoms. APA guidelines and following updates [1,66] recommended to choose antidepressant agents (SSRIs and MAOIs) and mood stabilizers as first- and second-line interventions for affective dysregulation, SSRIs and mood stabilizers for impulsive-behavioral dyscontrol, and antipsychotics as first-line therapy for cognitive-perceptual symptoms.

In 2007, an International Task Force of the WFSBP [65] developed practical guidelines for the biological treatment of three PDs: borderline, schizotypal and anxious/avoidant. The authors considered the evidence levels of each class of medications: level A, good research-based evidence (at least three RCTs); level B, fair research-based evidence (at least two RCTs or one RCT and ≥1 prospective, large, open-label study); level C, minimal research-based evidence (one RCT and one prospective, open-label study/case series or at least two prospective, open-label studies/case series); level D, expert opinion based. The WFSBP Task Force recommended atypical antipsychotics for STPD (evidence level C) and antidepressants for anxious/avoidant PD (evidence level A), basing these indications only on data concerning Axis I anxiety disorders, like social phobia.

Concerning BPD treatment, only evidence level C is achieved for antidepressants and mood stabilizers, while the efficacy of second-generation antipsychotics is indicated on a fair research-based evidence level (level B).

Guidelines from NICE on management of borderline and antisocial PDs [101,102] have a more prudent position and do not recommend drug therapy other than for treatment of mental disorders in comorbidity. So, they reach different conclusions from other guidelines, despite considering approximately the same evidence. A reason for this discordance is that the NICE group graded available evidence as 'low quality'.

Moreover, the NICE guidelines have been developed looking at the care pathway within the NHS in England and Wales, considering evidence of cost–effectiveness (including evidence of harm) not only for medications, but also for the whole range of treatments (clinical management and psychological therapies) [67].

Recently, following the growing number of pharmacological trials in patients with BPD, a few meta-analyses on BPD treatment have been published. One was performed by the Cochrane Collaboration [68] and included ten RCTs published between 1980 and 2001, predominantly on classical antipsychotics and antidepressants. These authors did not find a good level of evidence for medication efficacy in BPD. In the same year, a meta-analysis by Nosè *et al.* on 22 RCTs concluded that antidepressants and mood stabilizers are effective against affective instability and anger, while antipsychotics have positive effects on impulsive-aggressive behaviors and global functioning [69]. In the systematic review by Duggan *et al.* on the pharmacological treatment of PDs, efficacy of atypical antipsychotics and mood stabilizers in improving cognitive-perceptual symptoms and impulsivity aggression, respectively, was reported [70]. Recently, results of meta-analyses and conclusions of systematic reviews have indicated a noticeable shift from the choice of antidepressants to mood stabilizers and second-generation antipsychotics in the treatment of BPD [71]. Few reviews tried to summarize available data providing indications focused on APA or similar dimensions of BPD psychopathology.

In a meta-analysis concerning efficacy of medications on anger and depression in BPD patients, Mercer *et al.* suggested that mood stabilizers should be considered as first-line therapy for anger and affective symptoms, rather than SSRIs [72]. Antipsychotics were found to have a medium effect on symptoms of anger and no effects on depression. Ingenhoven *et al.* evaluated the efficacy of pharmacotherapy for borderline and schizotypal PDs on specific target domains: cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, affective dysregulation (depressed mood, anxiety, anger and mood lability) and global functioning [73]. Mood stabilizers had positive effects on global functioning, impulsive-behavioral dyscontrol, anger and anxiety. Antipsychotics had a moderate effect on cognitive symptoms and anger. Antidepressants were not found to be effective on impulsive-behavioral dyscontrol and mood symptoms, but they had a small effect on anxiety and anger. Saunders and Silk collected and analyzed data from placebo-controlled trials on treatment of BPD, sorting target symptoms into the trait dimensions of affective instability, anxiety inhibition, cognitive-perceptual disturbances and impulsivity aggression [74]. They found that antipsychotics had the strongest evidence for all dimensions.

According to the Cochrane Systematic Review of pharmacological interventions for BPD [75], the available evidence indicates that mood stabilizers, second-generation antipsychotics, and omega-3 fatty acids may be effective for treating specific BPD symptoms. The use of antidepressants is supported by data only in patients with concomitant depression.

Findings from these studies raise considerable questions on the decisional trees proposed by APA guidelines [1]. In particular, the recommendation to administer SSRIs or related antidepressants to treat affective dysregulation and impulsive-behavioral dyscontrol should be reconsidered on the basis of more recent results.

Conclusion & future perspective

In recent years a growing number of trials on the pharmacological treatment of PDs, in particular of BPD, have been performed. Nevertheless, available studies from important methodological limitations, such as a small number of patients, samples made of only male or female gender, heterogeneous selection criteria and outcome measures, and high rates of drop-outs. Moreover, the duration of trials is usually short and no conclusions can be drawn on the long-term use of medications in these patients.

Despite these limitations, the review of the RCTs published from 1990 to 2010 provided some evidence of the efficacy of certain medications to treat specific symptoms of borderline PDs. Proposing indications on drug treatment of other PDs is more difficult and poorly reliable because available data are sparse.

Preliminary studies performed with antipsychotics in patients with schizotypal PD suggested a reduction of psychotic-like symptoms.

However, some subjects included in these trials had concomitant BPD and it remains unclear whether reported improvements were due to the effects of medications on BPD-related

symptoms. Furthermore, drugs were used at low doses to minimize considerable sensitivity to side effects in this population. Although antipsychotics may reduce clinical symptoms, they do not induce a substantial benefit for cognitive performance of individuals with STPD. Recent trials suggested an improvement of cognitive performance in these patients (e.g., working memory and context processing) using dopamine and adrenaline agonists, but these agents are not currently used in clinical practice.

Concerning treatment of antisocial PD, there is initial evidence that nortriptyline and bromocriptine could produce some effects in individuals with concurrent alcohol dependence, while phenytoin seems to reduce impulsive-aggressive behaviors. However, it is questionable whether any drug is effective in the treatment of core features of ASPD.

Investigations on psychotropic agents in the treatment of BPD have recently tested several drugs belonging to the classes of antidepressants, mood stabilizers and antipsychotics.

In summary, there is some evidence that SSRIs are effective in decreasing depressed mood, anxiety, and anger in BPD patients, in particular when comorbidity with affective disorders is present. Many authors retain that prescription of SSRIs should be reserved for treatment of a comorbid major depressive episode, rather than BPD affective dysregulation itself [65,73,75]. Effects of SSRIs on impulsive-aggression have less support and may be limited to male gender. Concerning mood stabilizers, available studies provide evidence that topiramate, valproate and lamotrigine can be useful for the treatment of affective symptoms related to anger and impulsive-behavioral dyscontrol in BPD patients. These agents also appear to have significant effects on global functioning. As for second-generation antipsychotics, there is growing evidence from RCTs that olanzapine significantly improves cognitive symptoms, anger, anxiety and depression in BPD. Further controlled studies are needed to confirm the efficacy of newer drugs, such as aripiprazole.

Balancing the evidence of efficacy against adverse effects, some authors retain that dietary supplementation by omega-3 fatty acids could also be considered as an option to treat mood symptoms and impulsive-aggressive behaviors.

In conclusion, a pharmacotherapy targeted on well-defined symptom domains of BPD can be effective in improving some features of the clinical picture, but no medication is indicated to perform a global treatment of the disorder itself.

Most clinical trials testing the efficacy of drugs in BPD patients provide results on change of single symptoms or clusters of symptoms. Even if APA guidelines recommend a dimensional treatment of BPD, dimensions are usually not considered in single trials, mainly because authors do not choose dimensional instruments to evaluate outcome. There is the need for a more clear distinction of the two concepts of symptoms and dimensions in both research and clinical application.

Concerning the applicability of data from RCTs to clinical practice, we should not underestimate the differences between study samples and clinical populations. In fact, patients in clinical populations are not selected on the basis of inclusion/exclusion criteria. So, the level of social dysfunction and the frequency of Axis I and II comorbidity (in particular with mood disorders) are likely higher in usual practice. Moreover, patients with PDs present impulsive-behavioral dyscontrol and poor compliance and adherence. Therefore, clinicians prescribing medications should carefully inform and monitor them, in order to minimize the risk of intoxication, abuse, self-poisoning and side effects. As stated in the NICE guidelines and reported in a previous review by our group [76], some of the drugs administered to PD patients are potentially harmful: for example, valproate semisodium is potentially dangerous for women of child-bearing age, who are the largest proportion of BPD patients in clinical practice and often do not adopt adequate birth control methods; and antipsychotics can induce serious neurological and metabolic side effects [67]. It should also be stressed that drugs potentially fatal in overdose must be used with great caution in PD patients at risk of suicide [1]. Thus, tolerability profile, characteristics of patients and evidence of efficacy should be carefully examined and balanced before prescribing medications to PD patients. Another remarkable difference between trials and clinical practice is that patients included in study samples are usually treated with selected doses of a single therapeutic agent, while those observed in the usual clinical settings are more commonly treated with multiple medications and psychotherapy at the same time. So, further investigations focused on associations of drugs

and combination of medications and psychosocial interventions are required to collect data that can be more easily and reliably applied to everyday patients.

As repeatedly suggested in this article and by others [70–74], future perspectives of research should focus on a series of core topics: large-scale multicenter RCTs of mood stabilizers and new antipsychotics in order to confirm preliminary evidence; drug-to-drug comparisons (e.g., atypical vs traditional antipsychotics, different mood stabilizers) to explore differential effects of medications; fixed-dosage and long-term studies in order to determine appropriate doses and duration of treatments; identification of biological, clinical and pharmacological factors that predict response to drug treatments; assessment of results of combined therapy in comparison with single pharmaco- and psychotherapy; and selection of a set of outcome measures that can be retained reliable and specific to test drug efficacy and safety in BPD populations.

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