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Pharmacotherapy of Borderline Personality Disorder: A Systematic Review

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Abstract: Borderline Personality Disorder (BPD) is a common disorder in psychiatric practice and drugs are widely used in its treatment, targeting symptom clusters, such as affective dysregulation, impulsive-behavioural dyscontrol, and cognitive-perceptual symptoms. In last period, a growing number of studies on pharmacological treatment of BPD have been performed, but different proposals of treatment guidelines are not completely in accordance on drug indications for BPD patients. This article reviews double-blind randomized controlled trials comparing active drugs versus placebo and drugs versus drugs, published between 1990 and 2010 and focused on the treatment of borderline personality disorder. Different classes of psychoactive agents, such as antipsychotics, mood stabilizers, antidepressants, and dietary supplementation were tested in BPD patients. More recent evidences suggest that mood stabilizers (topiramate, valproate and lamotrigine), second generation antipsychotics (olanzapine and aripiprazole) and omega-3 fatty acids can be useful to treat affective symptoms and impulsive-behavioural dyscontrol in BPD patients. Moreover, antipsychotics significantly improve cognitive symptoms in patients with BPD. SSRIs were found effective in decreasing severity of depressed mood, anxiety and anger, mainly in subjects with a concomitant affective disorder. Effects of antidepressants on impulsive behaviours are uncertain. Further studies are needed to improve methods of trials and confirm these findings.

Keywords: Borderline personality disorder, pharmacotherapy, antidepressants, antipsychotics, mood stabilizers, omega-3 fatty acids, randomized controlled trials, efficacy, adverse effects, treatment guidelines.
INTRODUCTION

Borderline personality disorder (BPD) is a common disorder in clinical practice, with an estimated prevalence of 0.7-5.9% in the community samples [1,2]. Patients with BPD are characterised by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self image [3]. Although psychotherapy is needed to attain lasting improvements in patients’ personality and overall functioning, pharmacotherapy is widely used to manage state symptoms and trait vulnerability factors.

According to Soloff’s model [4,5], adopted by APA guidelines for the treatment of BPD [3], pharmacotherapy may be reframed as a symptom-specific treatment, focused on dimensions mediated by alterations in neurotransmitter systems, such as affective dysregulation, cognitive-impulsive-behavioural dyscontrol, and perceptual symptoms. APA guidelines recommended antidepressants as first line treatment of affective dysregulation and impulsive-behaviours, while mood stabilizers and antipsychotics were considered as second or third choices. Antipsychotics were also recommended to control cognitive-perceptual symptoms.

Despite common use of medications in the treatment of BPD patients, there are still conflicting opinions regarding their effectiveness. Guidelines from the National Institute for Health and Clinical Excellence (NICE) [6] on management of BPD do not recommend drug therapy other than for treatment of mental disorders in comorbidity. Moreover, the US FDA (Food and Drug Administration) has not approved any medication for the treatment of borderline personality disorders, yet.
Nevertheless, in last years a growing number of studies on pharmacological treatment of BPD have been performed with encouraging results, and recent reviews on this topic [7-12] indicate some evidences of effectiveness.

The aim of this study is to review double-blind randomized controlled trials (RCTs) of medications for the treatment of borderline personality disorder published between 1990 and 2010. Data from RCTs are reported and commented for each class of drugs, in order to make clear the different level of evidence.

**ANTIDEPRESSANTS**

Disturbances in central serotonin function have been implicated in mood symptoms and impulsive-aggressive behaviours [13,14]. On the basis of this pathogenetic hypothesis, the following groups of antidepressants have been evaluated in the treatment of affective dysregulation, impulsivity and aggressiveness in BPD samples: tricyclic antidepressants (TCAs), monoamino-oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).

Concerning TCAs and MAOIs, data provided from studies before 1990 [15-17] indicated that the efficacy of these drugs in patients with BPD is limited. Although the efficacy of IMAOs on anger, anxiety, and depression was supported by a more recent study of phenelzine [18], the risk of potentially fatal hypertensive crisis or serotonin syndrome is considerable and induces to prefer other antidepressants.
SSRIs

SSRIs are antidepressant agents with a selective action on serotonin dysregulation. The lack of direct effects on other neurotransmitter systems is responsible for their better tolerability profile and lower risk of toxicity, compared to older antidepressants. These characteristics have rapidly increased their use in clinical practice.

Five RCTs testing the efficacy of SSRIs in borderline patients have been conducted so far: four studies on fluoxetine [19-22] and one on fluvoxamine [23] (Table 1).

Most studies allowed the inclusion of patients with concurrent mood and anxiety disorders. This choice affects validity of findings, because SSRIs are effective to treat these disorders independently of BPD.

In two studies comparing fluoxetine to placebo, superior effects of antidepressant on depression, anxiety, and global functioning were reported [19,20]. Salzman and colleagues [20] in a double blind trial of fluoxetine (20-60 mg/day) in 27 symptomatic volunteers with BPD or traits, also evaluated effects on anger. Patients had a good level of functioning and did not present comorbidity with Axis I or II disorders. Statistical significant differences were obtained with respect to anger and aggression, which appeared to be independent of depression. In this study there was a robust placebo response. In fact, the treatment condition was significantly superior on only 2 of 5 measures.

Measures of impulsive aggression were evaluated in three RCTs [21-23]. In a placebo controlled study by Coccaro and Kavoussi [21], a mixed sample of 40 outpatients with various personality
disorders and impulsive-aggressive behaviour was enrolled
(approximately one-third with a DSM-III-R diagnosis of BPD).
Comorbid major depression or bipolar disorder were excluded, but
dystimic disorder, anxiety disorders, or substance abuse were common.
A significant improvement with respect to impulsive-aggressive
behaviour was reported after 10 weeks of fluoxetine
treatment, but global improvement was already significant at week
4 and irritability decreased at week 6. In contrast, no effects on
scales for impulsivity and aggression was observed in the only RCT
of fluvoxamine [23], performed on a group of female BPD patients.
Simpson et al. [22] presented data from a study combining
fluoxetine and psychotherapy. They studied the effects of the antidepressant
in a placebo controlled trial of 25 BPD women recruited
from patients hospitalized with comorbid Axis I pathology. Patients
received dialectical-behavioural therapy (DBT). Addition of
fluoxetine did not show any benefit on measures of depression,
anxiety, anger, dissociation and global functioning.
In summary, there is some evidence that SSRIs are effective in
decreasing affective symptoms [23], in particular depressed mood
[19,20], anxiety [19], and anger [20] in BPD patients. Efficacy on
impulsive aggression is discussed. It seems independent of effects
on affective symptoms and may be limited to male gender with high
levels of impulsivity [21,23].
Concerning tolerability of these antidepressants, adverse events
are not reported in most studies of BPD patients. In general, the
treatment group had significantly more complaints than the placebo
group (nausea, fatigue, sleep disturbance, anorexia, agitation, anxiety,
sexual dysfunction), although a significant difference between groups was reported in a single study and only for nausea [23].

**MOOD STABILIZERS**

Some Authors have proposed that a common pathogenetic mechanism underlying both BPD affective instability and bipolar disorder rapid mood cycling could be a rationale for using mood stabilizers in the treatment of BPD [24,25]. Moreover, it is supposed that antiepileptic drugs used to reduce the frequency of aggressive behaviours in patients with brain injury could be useful to control subclinical epileptic seizures underlying BPD outburst of anger [26,27]. According to these hypotheses, the efficacy of several mood stabilizers on affective dysregulation and behavioural dyscontrol has been investigated in RCTs of BPD patients (Table 2).

Concerning lithium and carbamazepine, two reviews published in the 1990s [28,29] on the treatment of personality disorders, suggested the efficacy of both agents on behavioural dyscontrol and aggressiveness. However, available evidences are not sufficient to support this indication. Only one RCT evaluated lithium in comparison with desipramine [30] in 17 BPD patients and reported a significant improvement of anger and suicidality (not of mood symptoms) in the group treated with lithium. De la Fuente and Lotstra [31] tested carbamazepine, an anticonvulsant blocking voltagegated sodium channels, in 20 BPD outpatients with no Axis I comorbidity. Authors did not find any significant differences with placebo on measures of affective symptoms, behavioural dyscontrol
or global assessment. So, considering the risk of toxicity and severe adverse effects, such as agranulocitosis (concentration of granulocytes below 100 cells/mm3 of blood), the use of this drug should not be indicated in the treatment of BPD.

On the contrary, a good amount of encouraging data have been collected on the efficacy of valproic acid, that is now one of the more extensively investigated mood stabilizer in BPD.

Sodium valproate is an antiepileptic drug that exerts its actions on dopamine, GABA and glutamate neurotransmission and on intracellular signalling. Hollander and colleagues conducted three randomized placebo-controlled trials to test the effects of valproate in borderline personality disorder [32-34].

The first study [32] included 16 BPD outpatients (medium plasma concentration of valproate 80 μg/mL) and showed marked improvement in global symptomatology, social functioning and BPD features such as depressive symptoms, aggression, irritability and suicidal behaviour. A high dropout rate (10 patients) precluded finding significant differences between the treatment groups in the intent-to-treat analyses. The second study [33] tested valproate (serum level between 80-120 μg/mL) on a sample of 246 outpatients (BPD and other cluster B disorders) with impulsive aggressive symptoms, confirming its efficacy in reducing impulsive aggression. Valproate response (77%) was comparable in cluster B disorders, but the placebo response was only 54% (power study: 80 and 90% to detect effect sizes of 0.36 and 0.42). In the third [34] study the authors reported that the effect of valproate in a sample of 52 outpatients derived from the previous study was higher among
those with high trait of impulsivity. Only the first of these studies [32] excluded any concomitant Axis I and II disorders, while the second and the third trials included patients with other cluster B disorders, post-traumatic stress disorder and intermittent explosive disorder. Valproate showed benefits on impulsive aggression in all the three investigations. In a study of 30 volunteers women with comorbidity of BPD and bipolar II disorder, Frankenburg and Zanarini [35] reported effects of valproate (serum level between 50-100 μg/mL) also on other symptoms: interpersonal hostility, irritability and anger. Symptom levels declined 30% to 40% for patients treated with the active drug and 15% for those treated with placebo. Concerning adverse events, tremor, transaminase elevations (hepatic dysfunction), gastrointestinal symptoms, weight gain, depression, asthenia, and menstrual irregularities are reported. Periodic monitoring of drug blood level, cell count and hepatic function should be provided during valproate treatment.

Recently topiramate and lamotrigine have also been investigated to test their ability to control aggressive behaviours in BPD patients. Topiramate is an anticonvulsant that specifically blocks AMPA/Kainate-gated ion channels and sodium channels and positively modulates gamma-butyric acid receptors. At the moment, three RCTs of topiramate in BPD outpatients have been published. In the first of these studies, Nickel et al. [36] examined a group of 31 women with BPD and found that topiramate (50-250 mg/day) was superior to placebo with respect to most of the State-Trait Anger Expression Inventory (STAXI) scale. The difference in score
between the two groups for state-anger, trait-anger and anger-out ranged from 21% to 24% and the improvement of anger control was 13%. The second RCT was performed by the same Authors [37], included 42 male patients and obtained similar results. Follow-up studies on these two populations of BPD patients [38,39] found that topiramate was a safe agent with long-lasting effects in reducing aggression. A third RCT of topiramate (25-200 mg/day) was conducted by Loew et al. [40] in 56 females with BPD and concurrent mood disorders and showed a significant decrease of somatisation symptoms, interpersonal sensitivity, hostility, and an improvement of global functioning. Topiramate is associated with a variety of adverse effects (acute myopia, angle closure glaucoma, urinary tract stones, cognition difficulties) when used for treating epilepsy, probably at higher doses [27]. No serious side effects were recorded in the three trials on BPD patients. Weight loss was observed in all studies. In a few cases, paresthesia (skin sensation of tingling, pricking, or numbness), fatigue, dizziness, and headache were reported. Loew et al. [40] cited also menstrual pain, memory deficits, and troubles in concentrating.

Another mood stabilizer that has been evaluated in the treatment of BPD is lamotrigine, a widely prescribed anticonvulsant that has demonstrated its efficacy in a variety of neuropsychiatric disorders. The mechanism of action of lamotrigine depends on voltage sensitive sodium channels, that stabilize the neuronal membrane and inhibit the release of excitatory neurotransmitters. To date, two placebo controlled trials of lamotrigine in BPD are available. In the first study, Tritt and colleagues [41] tested the efficacy of
lamotrigine (200 mg/day) in a sample of 24 female outpatients and found a significant improvement of anger. This result was maintained in the follow-up observation [42]. In the second investigation, Reich and colleagues [43] treated 28 outpatients with a flexible dose of lamotrigine (25-275 mg/day) and evaluated BPD core symptoms with a specific scale (Zanarini Rating Scale for BPD). Results indicated a significant reduction of affective instability and impulsivity.

BPD patients tolerated lamotrigine relatively well. The most considerable adverse event was rash, that required drug discontinuation. Other adverse events included pruritus, sedation, confusion, headache, dizziness, and irritability [43]. A recent review [44] collecting all safety and tolerability information on lamotrigine in patients with bipolar disorder reported that the most common adverse event was headache, followed by nausea. Other common side effects included insomnia, somnolence, back pain, fatigue, rash, rhinitis, and abdominal pain. Serious rash was found not to be related to the use of lamotrigine, although it has been estimated at 0.8% in epilepsy clinical trials.

In conclusion, available controlled studies provide initial evidence that mood stabilizers topiramate, valproate, and lamotrigine can be considered useful and well tolerated treatments of 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 second generation antipsychotics (Table 3).

**CLASSICAL NEUROLEPTICS**

Since the 1980s, one RCT on flupentixol decanoate [45], one on loxapine vs chlorpromazine [46], one on thiotixene [47], one on trifluoperazine [16] were performed in BPD psychopathology. Two trials [18,48] have been conducted on efficacy of haloperidol, a butyrophenone derivative with strong D2 receptors central antagonism. Soloff and colleagues [18] performed a 5-week RCT and evaluated the efficacy of haloperidol (4 mg/day) versus phenelzine (60 mg/day) and placebo in a group of 108 BPD inpatients with no comorbidity. Data showed that the improvements with haloperidol was limited to hostility and impulsive-aggressive behaviours. In a 16 week continuation trial [48], haloperidol treatment (≤ 6 mg/day) did not obtain significant effects in 54 responders of these 108 patients. It induced an increase of depression severity and only a modest improvement of irritability.

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: movement disorders such as acute dystonic reactions, pseudoparkinsonism, inability to initiate movement, and inability to remain motionless).
SECOND GENERATION ANTIPSYCHOTICS

The new generation antipsychotics present a double mechanism of action, characterized by the antagonism of both dopamine and serotonin-2 (5-HT2) receptors, that has been associated not only with antipsychotic properties, but also with antimanic and antidepressant effects [49]. 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 randomized controlled trials.

Olanzapine is a thienobenzodiazepine with high affinity for dopamine (D2 through D4) and serotonin receptors (5-HT2A), and a lower affinity for histamine (H1), muscarinic (M1 through M5), and ß-adrenergic (ß1) receptors. The therapeutic efficacy seems to be due to antagonism at D2 through D4 and 5-HT2A receptors, while antagonism at H1, M1-M5, and ß1 receptors is probably responsible for adverse effects [50].

Three RCTs have been performed on olanzapine compared to placebo in BPD treatment. Zanarini and Frankenburg [51] conducted a 6-month RCT of olanzapine (mean dose 5.33 mg/day) in 28 BPD females, reporting the efficacy of olanzapine over placebo in interpersonal sensitivity, anxiety, anger, hostility, paranoia, psychoticism, and global functioning. Bogenschutz and Nurnberg [52] evaluated 40 BPD subjects and outlined an improvement in overall borderline psychopathology significantly superior with olanzapine (5-10 mg/day) than placebo. This finding was not confirmed by Schulz et al. [53] in another
RCT on 314 outpatients receiving olanzapine (2.5-20 mg/day) versus placebo. These Authors only observed that the time to response was shorter for olanzapine (effect size: 0.03).

All the above described RCTs of olanzapine had restrictive inclusion criteria excluding comorbidity. This choice was responsible for sample characteristics quite different from common clinical population. Nevertheless, it could be useful to evaluate effects of therapy on core BPD symptoms.

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

According to a study by Zanarini et al. [54] comparing the efficacy of olanzapine, fluoxetine, and their combination in female BPD patients, olanzapine monotherapy and the combination were found to be superior to fluoxetine alone respect to mood symptoms and impulsive-aggressive behaviour. Two RCTs [55,56] compared olanzapine to placebo in a combined treatment with dialectical behavioural therapy (DBT). The first [55] reported that olanzapine (mean dose 8.83 mg/day) led to a significant reduction of anxiety, depressive symptoms and impulsive-aggressive behaviours in a sample of 60 BPD outpatients with no comorbid Axis I disorders. The second trial [56], including 24 BPD women outpatients, showed a considerable improvement of irritability (effect size: 0.8), aggression (effect size: 0.5), depressive symptoms (effect size: 0.2), and self-injury (effect size: 1.5) in both groups (olanzapine plus DBT versus placebo plus DBT). Irritability and aggression scores decreased more quickly in the olanzapine group. This trial is relatively
unspecific for borderline pathology because of multiple Axis I and II comorbidities.

In a double blind study comparing olanzapine (mean dose 7 mg/day) to haloperidol (mean dose 7 mg/day) in 28 female inpatients with BPD, Shafti and Shahveisi [57] did not find significant differences between drugs in reducing severity of mental or behavioural symptoms (a large effect size > 0.8 was calculated for both drugs). It must be noticed that this trial did not consider a control group with placebo.

The available RCT about aripiprazole, a quinolone derivative with partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, was performed by Nickel et al. [58]. The Authors found significant improvements on psychotic symptoms, depression, anxiety, and hostility in 57 BPD, that were confirmed in an 18 month follow-up observation [59]. Aripirazole was administered at the dose of 15 mg/day.

One RCT has been published on ziprasidone [60], a benzisoxazole derivative that mainly exerts dopamine type 2 (D2) and serotonin type 2 (5-HT2) receptor antagonist activity. This study evaluated the efficacy of ziprasidone (mean dose 84 mg/day) in 60 BPD patients selected from clinical services (outpatients and psychiatric emergency services). Symptoms of psychoticism, depression, anxiety, impulsivity, and hostility were assessed, but the study failed to show any significant effects on these measures of psychopathology.

As for the adverse effects of second generation antipsychotics in trials of BPD, main symptoms were represented by weight gain [51-57], hyperprolactinaemia (elevation of prolactin level >
25ng/ml in women of childbearing age and > 20ng/ml in men and post-menopausal women) [53], dizziness, somnolence, and tremor [57] in patients treated with olanzapine; headache, insomnia, nausea, constipation and anxiety with aripirazole [58]; dizziness and gastrointestinal symptoms with ziprasidone [60].

**OPIATE ANTAGONISTS AND OMEGA-3 FATTY ACIDS**

Other psychotropic agents, such as opiate antagonists and omega-3 fatty acids, have been investigated for their efficacy on symptoms of BPD (Table 4).

One small double-blind study [61] did not show any effect of i.v. administration of naloxone in the treatment of acute dissociative states. Better results have been found in two randomized controlled trials on the addition of omega-3 fatty acids to standard psychiatric care. Ethyl-eicosapentaenoic acid (1g/day) was more effective than placebo on depressive symptoms and aggressive behaviors in a group of 30 female outpatients [62]. The other study [63] included both BPD patients and subjects with self-harm behaviours. It showed significantly greater improvements in scales for depression, suicidality and reaction to daily stresses in the group using eicosapentaenoic acid (1.2 g) plus docosahexaenoic acid (0.9g). In conclusion, the results of the two studies of omega-3 fatty acids are promising for treatment of mood symptoms and aggressive behaviors in BPD patients, in particular considering the good tolerability of these agents.
TREATMENT GUIDELINES AND CONCLUSIVE REMARKS

In the last two decades a growing number of studies on pharmacological treatment of BPD have been performed. Reviewing the literature on this topic, we identified twenty-nine RCTs testing the efficacy of drugs belonging to the classes of antidepressants, mood stabilizers, antipsychotics, opiate antagonists and omega-3 fatty acids. Although many open-label investigations with promising results have been published, we chose to include only double-blind controlled studies, in order to report data collected with the most reliable methods.

Our findings suggest that certain medications may be effective to treat specific symptoms of borderline personality disorders.

There is some evidence that SSRIs are effective in decreasing depressed mood, anxiety, and anger in BPD patients, in particular when an affective disorders is present. Effects of SSRIs on impulsive aggression have less support and may be limited to male gender [10]. 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-behavioural dyscontrol in BPD. These agents appear to have significant effects also on global functioning. As for second generation antipsychotics, there is growing evidence 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 also dietary supplementation by omega-3
fatty acids could be considered as an option to treat mood symptoms and impulsive aggressive behaviours.

In conclusion, a pharmacotherapy targeted on well-defined symptom domains of BPD can be effective to improve some features of clinical picture, but no medication is indicated at the moment to obtain a global treatment of the disorder itself. In particular, no drugs were found efficacious to treat core domains of BPD, such as “avoidance of abandonment”, “chronic feelings of emptiness”, “identity disturbance”, “dissociation”, that perhaps could be considered the main focus of psychotherapy.

An overall consensus about drug indications in the treatment of BPD is still lacking, but it is useful to consider our finding in comparison with the available guidelines and recent reviews on this issue.

Although recent guidelines from the National Institute for Health and Clinical Excellence (NICE) on management of borderline personality disorder [6] do not recommend drug therapy other than for treatment of mental disorders in comorbidity, both treatment guidelines by the American Psychiatric Association (APA) [3,64] and the guidelines proposed by the World Federation of Societies of Biological Psychiatry (WFSBP) [65] provide more encouraging indications about the use several drugs in BPD treatment.

APA guidelines recommend to choose antidepressant agents as first-line interventions for affective dysregulation and impulsive-behavioural dyscontrol, while antipsychotics represent a first-line therapy for cognitive-perceptual symptoms. Mood stabilizers and second generation antipsychotics are considered by APA task force
only as second or third choices for affective instability and impulsive behaviours. The more recent WFSBP guidelines conclude that the off-label use of psychotropic agents may help individuals with BPD to improve affective symptoms (depressed mood, anxiety, mood swings) and impulsivity. A pharmacotherapy might also be indicated in severe conditions to support psychosocial interventions, although there is not much of an evidence-base on when or how to combine pharmacotherapy and psychotherapy. In the last period, results of meta-analyses and conclusions of systematic reviews have supported a noticeable shift from the choice of antidepressants to the use of mood stabilizers and second generation antipsychotics in the treatment of BPD [8]. Despite the wide use of SSRIs in clinical practice, antidepressants cannot further be recommended as first choice treatment in BPD on the basis of up-to-date empirical evidences [10]. Many authors retain that prescription of SSRIs should be reserved to treatment of concomitant depressive disorders, rather than BPD affective dysregulation itself [11,12].

In a meta-analysis concerning efficacy of medications on anger and depression in BPD patients, Mercer et al. [9] suggested that mood stabilizers should be considered as first-line therapy for these symptoms, taking the place of SSRIs. Second generation antipsychotics have been found to have a medium effect on symptoms of anger and no effects on depression. A single review by Saunders and Silk [10] presented more favourable conclusions for this class and stated that the use of antipsychotics is supported by substantial evidence to treat all dimensions of BPD.

Ingenhoven et al. [11] evaluated and summarized the efficacy
of pharmacotherapy on specific symptom domains of borderline and schizotypal PDs. Mood stabilizers had positive effects on global functioning, impulsive-behavioural dyscontrol, anger, and anxiety. Antipsychotics had a moderate effect on cognitive symptoms and anger. On the contrary, antidepressants were not found effective on impulsive-behavioural dyscontrol and mood symptoms. According to the Cochrane Systematic Review of pharmacological interventions for BPD [12], the available evidences indicate 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 major depression.

Findings from these studies raise considerable questions on the decisional algorithm proposed by the 2001 APA guidelines. In particular, the recommendation to administer SSRIs or related antidepressants as first-line agents to treat affective dysregulation and impulsive-behavioural dyscontrol and low doses antipsychotics only in case of predominant cognitive perceptual symptoms should be reconsidered on the basis of data from more recent trials.

All reviews are in accordance on the overall weakness of available evidences, as studies suffer of considerable methodological limitations. In fact, they are affected by small sample sizes (most of the studies have fewer than 50 participants), different gender proportions, heterogeneous selection criteria and assessment instruments, high rates of drop-outs. The mean duration of trials is about 12 weeks (it ranges from 32 days to 24 weeks) and is not enough to draw conclusions on the long-term efficacy and tolerability of
medications in these patients. Moreover, it should be noticed that a publication bias is possible, considering that only few studies reported negative or non-significant findings. Concerning the applicability of data from RCTs to clinical practice, we should not underestimate the differences between study samples and clinical populations, in which the presence of comorbidity with Axis I disorders is the rule and not an exclusion criterion. Another remarkable difference of trials from clinical practice is that patients included in a study sample are treated with a selected dose of a single therapeutic agent, while those observed in the usual clinical settings are commonly treated with multiple medications and combined psychotherapy at the same time. So, further investigations focused on association of drugs and combination of psychosocial interventions are required to collect data that can be more easily and reliably applied to the everyday patients.

In addition, forthcoming research on pharmacotherapy of BPD should take into account a series of core topics: controlled trials of drugs already tested in open-label case series (for example, this is the case of the antipsychotic quetiapine), large-scale multi-centre RCTs of recent mood stabilizers and new generation antipsychotics in order to replicate preliminary findings in small samples; drug-to-drug comparisons to explore differential effects on symptom dimensions; selection of a set of outcome measures that can be retained reliable and specific for BPD populations; identification of biological, clinical and pharmacological factors that are predictive of treatment response.
FINANCIAL CONTRIBUTIONS AND POTENTIAL CONFLICTS OF INTEREST

The authors have no relevant involvement with any organization with a financial interest in or conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, grants received, or royalties.
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### Table 1. Double Blind Randomized Trials of Antidepressants (SSRIs) in the Treatment of Borderline Personality Disorder

<table>
<thead>
<tr>
<th>Drug and Study</th>
<th>Dosage</th>
<th>Study design (comparator drug)</th>
<th>Treatment duration</th>
<th>Sample</th>
<th>Findings</th>
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<td>FLUoxetine</td>
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<td>Markovitz, 1995 [19]</td>
<td>20-40 mg/day</td>
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<td>17 BPD patients with affective and anxiety disorders</td>
<td>Increased anxiety depression, global symptomatology</td>
</tr>
<tr>
<td>Salomon et al, 1997 [20]</td>
<td>20-40 mg/day</td>
<td>db, pc</td>
<td>12 w</td>
<td>27 BPD or trait with good functioning, no Axis I or II comorbidity</td>
<td>Increased depression</td>
</tr>
<tr>
<td>Coenraet and Launois, 1997 [21]</td>
<td>20-40 mg/day</td>
<td>db, pc</td>
<td>12 w</td>
<td>40 PDs (33% BPD, 21% AD) with dysthymic disorder, anxiety disorders, substance abuse</td>
<td>Increased irritability, impulsive aggression</td>
</tr>
<tr>
<td>Simpson et al, 2004 [22]</td>
<td>40 mg/day</td>
<td>db, pc</td>
<td>12 w</td>
<td>25 BPD in treatment with DBT, no bipolar disorder</td>
<td>No significant effects</td>
</tr>
<tr>
<td>FLUOXAMINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russo et al, 2002 [23]</td>
<td>150-250 mg/day</td>
<td>db, pc</td>
<td>6 w</td>
<td>38 BPD with affective and anxiety disorders</td>
<td>Lower incidence of rapid mood shift, no significant effects on impulsive aggression</td>
</tr>
</tbody>
</table>

Abbreviations: db = double-blind; pc = placebo controlled; w = week; f = female; m = male; decrease of.
<table>
<thead>
<tr>
<th>Drug and Study</th>
<th>Doses</th>
<th>Study design (comparator drugs)</th>
<th>Treatment duration</th>
<th>Sample</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>LITHIUM</td>
<td>960 mg/day</td>
<td>db, pc (placebo minus) cross-over</td>
<td>6w</td>
<td>10 BPD</td>
<td>↓ irritability, anger, self-mutilation</td>
</tr>
<tr>
<td>GABAPENTINE</td>
<td>plasme level</td>
<td>db, pc</td>
<td>4.5 w</td>
<td>20 BPD patients, no Axis I comorbidity</td>
<td>no significant effects</td>
</tr>
<tr>
<td>VALPROATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollander et al. 2001(32)</td>
<td>plasme level</td>
<td>db, pc</td>
<td>10 w</td>
<td>14 BPD</td>
<td>↓ irritability, aggression, depression, improved global functioning, high dropout rate (10 patients)</td>
</tr>
<tr>
<td>Hollander et al. 2003(33)</td>
<td>plasme level</td>
<td>db, pc</td>
<td>12 w</td>
<td>26 PD (12 BPD)</td>
<td>↓ irritability, impulse-aggression, global severity, affect case: 0.56-0.42</td>
</tr>
<tr>
<td>Frankenburg and Zornius, 2002 (33)</td>
<td>plasme level</td>
<td>db, pc</td>
<td>24 w</td>
<td>30 % BPD with bipolar II disorder</td>
<td>↓ interpersonal sensitivity, impulse, aggression, aggression</td>
</tr>
<tr>
<td>TOPIRAMATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel et al. 2004(36)</td>
<td>50-250 mg/day</td>
<td>db, pc</td>
<td>8 w</td>
<td>31 % BPD (reduction of impuls: 21-24%; improvement of anger control 13%)</td>
<td></td>
</tr>
<tr>
<td>Nickel et al. 2005(37)</td>
<td>50-250 mg/day</td>
<td>db, pc</td>
<td>8 w</td>
<td>43 % BPD</td>
<td>↓ irritability/anger</td>
</tr>
<tr>
<td>Lowes et al. 2006(39)</td>
<td>25-200 mg/day</td>
<td>db, pc</td>
<td>10 w</td>
<td>56 % BPD</td>
<td>↓ irritability, aggression, impulse, improved global functioning.</td>
</tr>
<tr>
<td>LAMOTRIGINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turet et al. 2005(41)</td>
<td>50-200 mg/day</td>
<td>db, pc</td>
<td>8 w</td>
<td>27 % BPD</td>
<td>↓ anger</td>
</tr>
<tr>
<td>Reisch et al. 2009(43)</td>
<td>25-275 mg/day</td>
<td>db, pc</td>
<td>12 w</td>
<td>28 % BPD</td>
<td>↓ impulsivity, effective irritability</td>
</tr>
</tbody>
</table>

Abbreviations: db = double-blind; pc = placebo controlled; w = week; % = male; % = female; ↓ = decrease of.
## Table 3. Double-Blind Randomized Trials of Antipsychotics in the Treatment of Borderline Personality Disorder:

<table>
<thead>
<tr>
<th>Drug and Study</th>
<th>Dose</th>
<th>Study design (comparator drugs)</th>
<th>Treatment duration</th>
<th>Sample</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>4 mg/day</td>
<td>db, pc (placebo)</td>
<td>5 w</td>
<td>100 BPD adolescent * connected depression</td>
<td>hostility, impulsivity, aggression</td>
</tr>
<tr>
<td></td>
<td>&lt;6 mg/day</td>
<td>db, pc</td>
<td>16 w</td>
<td>34 BPD outpatient response from Soeff study</td>
<td>irritability</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5.3 mg/day</td>
<td>db, pc</td>
<td>24 w</td>
<td>38 BPD</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2.5 mg/day</td>
<td>db (fluoxetine, olanzapine = fluoxetine)</td>
<td>8 w</td>
<td>45 BPD</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>5-10 mg/day</td>
<td>db, pe</td>
<td>12 w</td>
<td>40 BPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5-20 mg/day</td>
<td>db, pe</td>
<td>12 w</td>
<td>31 BPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-20 mg/day</td>
<td>db, pe</td>
<td>12 w</td>
<td>60 BPD treated with DBT</td>
<td>anxiety, impulsivity, aggression</td>
</tr>
<tr>
<td></td>
<td>5 mg/day</td>
<td>db, pe</td>
<td>21 w</td>
<td>34 BPD treated with DBT</td>
<td>no significant differences for generic symptoms</td>
</tr>
<tr>
<td></td>
<td>7 mg/day</td>
<td>db (haloperidol)</td>
<td>8 w</td>
<td>28 BPD untreated patients</td>
<td>no significant differences for generic behavioral symptoms, effect size = 0.8 for both drugs</td>
</tr>
<tr>
<td>Ariperazone</td>
<td>15 mg/day</td>
<td>db, pe</td>
<td>8 w</td>
<td>57 BPD</td>
<td></td>
</tr>
<tr>
<td>Ziprazidone</td>
<td>84 mg/day</td>
<td>db, pe</td>
<td>12 w</td>
<td>16 BPD</td>
<td></td>
</tr>
</tbody>
</table>

Abbrreviations: db = double-blind; pc = placebo controlled; w = weeks; 0 = equal; 1 = decrease of → = superior to.
Table 4.  Double Blind Randomized Trials of other Drugs in the Treatment of Borderline Personality Disorder

<table>
<thead>
<tr>
<th>Drug and Study</th>
<th>Dosage</th>
<th>Study design</th>
<th>Treatment duration</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NALOXONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philipson et al, 2004 [61]</td>
<td>0.4 mg i.v.</td>
<td>db, pc</td>
<td>-</td>
<td>9 BPD</td>
<td>no significant differences for dissociative symptoms</td>
</tr>
<tr>
<td>OMEGA-3 FATTY ACIDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanarini and Frankenburg, 2003 [62]</td>
<td>ethyl eicosapentaenoic acid, 1 g/day</td>
<td>db, pc</td>
<td>8 w</td>
<td>10 % BPD</td>
<td>Depression, agitation</td>
</tr>
<tr>
<td>Helligian et al, 2007 [63]</td>
<td>eicosapentaenoic acid 2.1 g/day + docosahexaenoic acid 0.9 g/day</td>
<td>db, pc</td>
<td>12 w</td>
<td>49 subjects with self-harm behaviors (35 BPD)</td>
<td>Depression, mortality, suicide attempts to daily preser.</td>
</tr>
</tbody>
</table>

Abbreviations: db = double-blind; pc = placebo controlled; w = week; f = female; m = female;