Pharmacotherapy of Borderline Personality Disorder: A Systematic Review

(Article begins on next page)

24 April 2024

Pharmacotherapy of Borderline Personality Disorder: A Systematic Review

S. Bellino*, C. Rinaldi, P. Bozzatello and F. Bogetto

Centre for Personality Disorders, Unit of Psychiatry 1, Department of Neurosciences, University of Turin, Italy

*Address correspondence to this author at the Centre for Personality Disorders, Unit of

Psychiatry 1, Department of Neurosciences, University of Turin, via Cherasco 11,

10126 Turin, Italy; Tel: 0039-011-6634848; Fax: 0039-011-673473;

E-mail: silvio.bellino@unito.it

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 impulsiveaggressive

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 ⍺-adrenergic (⍺1) 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 ⍺1 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) versusr

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 psychotics 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 >

14

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 eicosepentaenoic 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 impulsivebehavioural 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-todate

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, forecoming 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-todrug

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.

REFERENCES

[1] Torgensen, S.; Kringlen, E.; Cramer, V. The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry*, **2001**, *58*, 590-596.

[2] Grant, B.F.; Chou, S.P.; Goldstein, R.B.; Huang, B.; Stinson, F.S.; Saha, T.D.; Smith, S.M.; Dawson, D.A.; Pulay, A.J.; Pickering, R.P.; Ruan, W.J. Prevalence, correlates, disability and comorbidity of, DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry*, **2008**, *69*, 533-545.

[3] American Psychiatric Association. Practice guideline for the treatment of patients with borderline personality disorder. *Am. J. Psychiatry*, **2001**, *158*, 1-52.

[4] Soloff, P.H. Algorithms for pharmacological treatment of personality dimensions: symptom-specific treatments for cognitive-perceptual, affective, and impulsive-behavioral dysregulation. *Bull. Menninger. Clin*., **1998**, *62*(2), 195-214.

[5] Soloff, P.H. Psychopharmacology of borderline personality disorder. Psychiatr. *Clin. North. Am.,* **2000**, *23*, 169-192.

[6] National Institute for Health and Clinical Excellence (NICE). Borderline personality disorder: treatment and management. Clinical Guideline 78. National Collaborating Centre for Mental Health: London, UK, **2009**.

[7] Nosè, M.; Cipriani, A.; Biancosino, B.; Grassi, L.; Barbui, C. Efficacy of pharmacotherapy against core traits of borderline personality disorder: metaanalysis of randomized controlled trials. *Int. Clin. Psychopharmacol*., **2006**, *21*(6), 345-353.

[8] Abraham, P.F.; Calabrese, J.R. Evidenced-based pharmacologic treatment of borderline personality disorder: a shift from SSRIs to anticonvulsants and atypical antipsychotics? *J. Affect. Disord*., **2008**, *111*(1), 21-30.

[9] Mercer, D.; Douglass, A.B.; Links, P.S. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. *J. Pers. Disord.,* **2009**, *23*(2), 156-174.

[10] Saunders, E.F.H.; Silk, K.R. Personality trait dimensions and the pharmacological treatment of borderline personality disorder. *J. Clin. Psychopharmacol*., **2009**, *29*(5), 461-467.

[11] Ingenhoven, T.; Lafay, P.; Rinne, T.; Passchier, J.; Duivenvoorden, H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. *J. Clin. Psychiatry*, **2010**, *71*(1), 14-25.

[12] Stoffers, J.; Völlm, B.A.; Rücker, G.; Timmer, A.; Huband, N.; Lieb, K. Pharmacological interventions for borderline personality disorder. *Cochrane Database Syst. Rev*., **2010**, *16*(6), CD005653.

[13] Coccaro, E.F.; Siever, L.J.; Klar, H.; Maurer, G.; Cochrane, K.; Cooper, T.B.; Mohs, R.C.; Davis, K.L. Serotonergic studies in affective and personality disorders patients: correlates with suicidal and impulsive aggressive behaviour. *Arch. Gen. Psychiatry*, **1989**, *46*, 587-599.

[14] Carver, C.S.; Miller, C.J. Relations of serotonin function to personality: current views and a key methodological issue. *Psychiatry Res*., **2006**, *144*(1), 1-15.

[15] Montgomery, S.A.; Montgomery, D. Pharmacological prevention of suicidal behaviour. *J. Affect. Disord.,* **1982**, *4*, 291-298.

[16] Cowdry, R.W.; Gardner, D.L. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch. Gen. Psychiatry*, **1988**, *45*, 111-119.

[17] Soloff, P.H.; George, A.; Nathan, S.; Schulz, P.M.; Cornelius, J.R.; Herring,

J.; Ulrich, R.F. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J. Clin. Psychopharmacol*., **1989**, *9*, 238-

246.

[18] 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*, 377-385.

[19] Markovitz, P. In: Impulsivity and Aggression; Hollander, E.; Stein, D.J.; Ed,;

John Wiley & Sons: New York, **1995**; pp. 263-287.

[20] Salzman 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*, 23-29.

[21] Coccaro E.F.; Kavoussi, R.J. Fluoxetine and impulsive aggressive behaviour

in personality disordered subjects. *Arch. Gen. Psychiatry,* **1997**, *54*, 1081-

1088.

[22] Simpson, E.B.; Yen, S.; Costello, E.; Rosen, K.; Begin, A.; Pistorello, J.;

Pearlstein, T. Combined dialectical behavior therapy and fluoxetine in the

treatment of borderline personality disorder. *J. Clin. Psychiatry*, **2004**, *65*(3),

379-385.

[23] 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.

[24] Akiskal, H.S. Demystifying borderline personality: critique of the concept

and unorthodox reflections on its natural kinship with the bipolar spectrum.

Acta Psychiatr. Scand., **2004**, *110*, 401-407.

[25] Gunderson, J.G.; Weinberg, I.; Daversa, M.T.; Kueppenbender, K.D.;

Zanarini M.C.; Shea, M.T.; Skodol, A.E., Sanislow, C.A.; Yen, S.; Morey,

L.C.; Grilo, C.M.; McGlashan, T.H.; Stout, R.L.; Dyck, I. Descriptive and

longitudinal observations on the relationship of borderline personality disorder

and bipolar disorder. *Am. J. Psychiatry*, **2006**, *163*, 1173-1178.

[26] Mark, V.H.; Ervin, F.R. Violence and the Brain; Harper, and Brown: New

York, **1970**.

[27] Varghese, B.S.; Rajeev, A.; Norrish, M.; Khusaiby, S.B.M.A. Topiramate for

anger control: a systematic review. *Indian J. Pharmacol.*, **2010**, *42*(3), 135-

141.

[28] Stein, D.J. Drug treatment of the personality disorders. *Br. J. Psychiatry*,

1992, *161*, 167-184.

[29] Hori, A. Pharmacotherapy for personality disorders. *Psychiatry Clin. Neurosci.*,

1998, *52*, 13-19.

[30] Links, P.; Steiner, M.; Boiago, I.; Irwin, D. Lithium therapy for borderline

patients: preliminary findings. *J. Personal. Disord*., **1990**, *4*, 173-181.

[31] De la Fuente, J.; Lotstra, F. A trial of carbamazepine in borderline personality

disorder. *Eur. Neuropsychopharmacol.* **1994**, *4*, 479-486.

[32] Hollander, E.; Allen, A.; Lopez, R.P.; Bienstock, C.A.; Grossman, R.;

Siever, L.J.; Merkatz, L.; Stein, D.J. A preliminary double-blind, placebocontrolled

trial of divalproex sodium in borderline personality disorder. *J.

Clin. Psychiatry*, **2001**, *62*(3), 199-203.

[33] Hollander, E.; Tracy, K.A.; Swann, A.C.; Coccaro, E.F.; McElroy, S.L.;

Wozniak, P.; Sommerville, K.W.; Nemeroff, C.B. Divalproex in the treatment

of impulsive aggression: efficacy in cluster B personality disorders.

Neuropsychopharmacology, **2003**, *28*(6), 1186-1197.

[34] Hollander, E; Swann, A.C.; Coccaro, E.F.; Jiang, P.; Smith, T.B. Impact of

trait impulsivity and state aggression on divalproex versus placebo response

in borderline personality disorder. *Am. J. Psychiatry.* **2005**, *162*, 621-624.

[35] Frankenburg, FR;, Zanarini, M.C. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J. Clin. Psychiatry,* **2002**, *63*(5), 442-446.

[36] Nickel, M.K.; Nickel, C.; Mitterlehner, F.O.; Lahmann, C.; Leiberich, P.K.; Rother, W.K.; Loew, T.H. Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. *J. Clin. Psychiatry,* **2004**, *65*(11), 1515-1519.

[37] Nickel, M.K.; Nickel, C.; Kaplan, P.; Lahmann, C.; Mühlbacher, M.; Tritt, K.; Krawczyk, J.; Leiberich, P.K.; Rother, W.K.; Loew, T.H. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol. Psychiatry,* **2005**, *57*(5), 495-499.

[38] Nickel, M.K.; Loew, T.H. Treatment of aggression with topiramate in male borderline patients, part II: 18-month follow-up. *Eur. Psychiatry,* **2008**, *23*(2), 115-117.

[39] Loew, T.H.; Nickel, M.K. Topiramate treatment of women with borderline personality disorder, part II: an open 18-month follow-up. *J. Clin. Psychopharmacol*., **2008**, *28*(3), 355-357.

[40] Loew, T.H.; Nickel, M.K.; Muehlbacher, M.; Kaplan, P.; Nickel, C.; Kettler, C.; Fartacek, R.; Lahmann, C.; Buschmann, W.; Tritt, K.; Bachler, E.; Mitterlehner, F.; Pedrosa, G.F.; Leiberich, P.; Rother, W.K.; Egger, C. Topiramate treatment for women with borderline personality disorder: a doubleblind, placebo-controlled study. *J. Clin. Psychopharmacol.,* **2006**, *26*(1), 61-66.

[41] Tritt, K;, Nickel C.; Lahmann, C.; Leiberich, P.K.; Rother, W.K.; Loew, T.H.; Nickel, M.K. Lamotrigine treatment of aggression in female borderline-patients: a randomized, double-blind, placebo-controlled study. *J. Psychopharmacol.,*

2005, *19*, 287-291.

[42] Leiberich, P.; Nickel, M.K.; Tritt, K.; Pedrosa, G.F. Lamotrigine treatment of

aggression in female borderline patients, Part II: an 18-month follow-up. *J.*

Psychopharmacol., **2008**, *22*(7), 805-808.

[43] Reich, D.B.; Zanarini, M.C.; Bieri, K.A. A preliminary study of lamotrigine

in the treatment of affective instability in borderline personality disorder. *Int.*

Clin. Psychopharmacol., **2009**, *24*(5), 270-275.

[44] Seo, H.J.; Chiesa, A.; Lee, S.J.; Patkar, A.A.; Han, C.; Masand, P.S.; Serretti,

A.; Pae, C.U. Safety and tolerability of lamotrigine: results from 12 placebocontrolled

clinical trials and clinical implications. *Clin. Neuropharmacol.,*

2011, *34*(1), 39-47.

[45] Montgomery, S.A.; Montgomery, D.B.; Janyanthi, Rani S.; Roy, DH;Shaw

P.J.; McAuley, R. In: Maintenance therapy in repeat suicidal behaviour: a

placebo controlled trial. Proceedings of the 10th International Congress for

Suicide Prevention and Crisis Intervention: Ottawa, **1979**, pp. 227-229.

[46] Leone, N.F.: Response of borderline patients to loxapine and chlorpromazine.

J. Clin. Psychiatry, **1982**, *43*(4), 148-150.

[47] Goldberg, S.C.; Shulz, S.C.; Shulz, P.M.; Reisnick, R.J.; Hamer, R.M. Borderline

and schizotypal personality disorders treated with low dose thiothixene

vs placebo. *Arch. Gen. Psychiatry,* **1986**, *43*(7), 680-686.

[48] 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*, 1843-1848.

[49] Vieta, E.; Goikolea, J.M. Atypical antipsychotics: newer options for mania

and maintenance therapy. *Bipolar Disord*, **2005**, *7*(4), 21-23.

[50] Bhana, N.; Foster, R.H.; Olney, R. Olanzapine: an updates review of its use

in the management of schizophrenia. *Drugs*, **2001**, *61*, 111-161.

[51] Zanarini, M.C.; Frankenburg, F.R. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. *J. Clin. Psichiatry,* **2001**, *62*(11), 849-854.

[52] Bogenschutz, M.P.; Nurnberg, G.H. Olanzapine versus placebo in the treatment of borderline personality disorder. *J. Clin. Psychiatry*, **2004**, *65*, 104-109.

[53] Schulz, S.C.; Zanarini, M.C.; Bateman, A.; Bohus, M.; Detke, H.C.; Trzaskoma, Q.; Tanaka, Y.; Lin, D.; Deberdt, W.; Corya, S. Olanzapine for the treatment of borderline personality disorder: variable dose, 12-week, randomised double blind placebo-controlled study. *Br. J. Psychiatry,* **2008**, *193*, 485–492.

[54] Zanarini, M.C.; Frankenburg, F.R.; Parachini, E.A. A preliminary randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J. Clin. Psichiatry,* **2004**, *65*, 903-907.

[55] Soler, J.; Pascual, J.C.; Campins, J.; Barrachina, J.; Puigdemont, D.; Alvarez, E.; Pérez, V. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am. J. Psychiatry,* **2005**, *162*, 1221-1224.

[56] Linehan, M.M.; McDavid, J.D.; Brown, M.Z.; Sayrs, J.H.R.; Gallop, R.J. Olanzapine plus dialectical behavior therapy for women with high irritability who meet criteria for borderline personality disorder: a double-blind, placebo-controlled pilot study. *J. Clin. Psychiatry*, **2008**, *69*(9), 999-1005.

[57] Shafti, S.S.; Shahveisi, B. Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double-blind trial. *J. Clin. Psychopharmacol*., **2010**, *30*(1), 44-47.

[58] Nickel, M.K.; Muehlbacher, M.; Nickel, C.; Kettler, C.; Pedrosa Gil, F.;

Bachler, E.; Buschmann, W.; Rother, N.; Fartacek, R.; Egger, C.; Anvar, J.; Rother, W.K.; Loew, T.H.; Kaplan, P. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebocontrolled study. *Am. J. Psychiatry,* **2006**, *163*(5), 833-838.

[59] Nickel, M.K.; Loew, T.H.; Pedrosa, F. Aripiprazole in treatment of borderline patients, part II: an 18-month follow-up. *Psychopharmacol.*, **2007**, *191*, 1023-1026.

[60] Pascual, J.C.; Soler, J.; Puigdemont, D.; Pérez-Egea, R.; Tiana, T.; Alvarez, E.; Pérez, V. Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. *J. Clin. Psychiatry*, **2008**, *69*(4), 603-608.

[61] Philipsen, A.; Schmahl, C.; Lieb, K. Naloxone in the treatment of acute dissociative states in female patients with borderline personality disorder. *Pharmacopsychiatry*, **2004**, *37*(5), 196-199.

[62] 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*, 167-169.

[63] Hallahan, B.; Hibblen, J.R.; Davis, J.M.; Garland, M.R. Omega-3 fatty acid supplementation in patients with recurrent self-harm: single centre doubleblind randomized controlled trial. *Br. J. Psychiatry,* **2007**, *190*, 118-122.

[64] Oldham, J.M. Guideline watch: practice guideline for the treatment of patients with borderline personality disorder; American Psychiatric Association: Arlington, **2005**.

[65] Herpertz, S.C.; Zanarini, M.; Schulz, C.S.; Siever, L.; Lieb, K.; Möller H.J. World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for biological treatment of personality disorders. *World J. Biol. Psychiatry,* **2007**, *8*(4), 212-244.

Table 1. Double Blind Randomized Trials of Antidepressants (SSRIs) in the Treatment of Borderline Personality Disorder

Drug and Study	Dosage	Study design (comparator drugs)	Treatment duration	Sample	Findings
FLUOXETINE					
Markovitz, 1995 [19]	20-80 mg/day	db, pc	14 w	17 BPD patients with affective and anxiety disorders	↓anxiety/depression, ↓global symptomatology
Salzman et al,1995 [20]	20-60 mg/day	db, pc	12 w	27 BPD or trait with good functioning, no Axis I or II comorbidity	↓ anger, ↓ depression
Coccaro and Kavoussi, 1997 [21]	20-60 mg/day	db, pc	12 w	40 PDs (33% BPD, 25% ♀) with dysthymic disorder, anxiety disorders, substance abuse	↓irritability, ↓impulsive-aggression
Simpson et al, 2004 [22]	40 mg/day	db, pc	12 w	25 ♀ BPD in treatment with DBT, no bipolar disorders	no significant effects
FLUVOXAMINE					
Rinne et al, 2002 [23]	150-250 mg/day	db, pc cross-over	6 w	38 ♀ BPD with affective and anxiety disorders	lower incidence of rapid mood shift, no significant effects on impulsive-aggression

Abbreviations: db = double-blind; pc = placebo controlled; w = week; ♀ = female; ↓ = decrease of.

Table 2.   Double Blind Randomized Trials of Mood-Stabilizers in the Treatment of Borderline Personality Disorder

Drug and Study	Dosage	Study design (comparator drugs)	Treatment duration	Sample	Findings
LITHIUM					
Links *et al*, 1990 [30]	986 mg/day	db, pc (desipramine) cross-over	6w	10 BPD	↓ irritability/anger, ↓ self mutilation
CARBAMAZEPINE					
De la Fuente and Lotstra, 1994 [31]	plasma level	db, pc	4.5 w	20 BPD outpatients, no Axis I comorbidity	no significant effects
VALPROATE					
Hollander *et al*, 2001[32]	plasma level	db, pc	10 w	16 BPD no psychotic and affective disorders	↓irritability/aggressiveness, ↓depression, improved global functioning, high dropout rate (10 patients)
Hollander *et al*, 2003 [33]	plasma level	db, pc	12 w	96 PDs (52 BPD) no affective disorders	↓irritability, ↓impulsive-aggression, ↓global severity effect sizes: 0.36-0.42
Frankenburg and Zanarini, 2002 [35]	plasma level	db, pc	24 w	30 ♀ BPD with bipolar II disorder	↓interpersonal sensitivity, ↓anger, ↓aggressiveness
TOPIRAMATE					
Nickel *et al*, 2004[36]	50-250 mg/day	db, pc	8 w	31 ♀ BPD	↓ irritability/anger (reduction of anger: 21-24%; improvement of anger control: 13%)
Nickel *et al*, 2005[37]	50-250 mg/day	db, pc	8 w	42 ♂ BPD	↓ irritability/anger
Loew *et al*, 2006[40]	25-200 mg/day	db, pc	10 w	56 ♀ BPD and mood disorders	↓somatization symptoms, ↓interpersonal sensitivity, ↓hostility, improved global functioning.
LAMOTRIGINE					
Tritt *et al*, 2005[41]	50- 200 mg/day	db, pc	8 w	27 ♀ BPD	↓ anger
Reich *et al*, 2009[43]	25-275 mg/day	db, pc	12 w	28 BPD with major depression and anxiety disorders	↓impulsivity, ↓affective instability

Abbreviations: db = double-blind; pc = placebo controlled; w = week; ♂ = male; ♀ = female; ↓ = decrease of.

31

Table 3.   Double Blind Randomized Trials of Antipsychotics in the Treatment of Borderline Personality Disorder.

Drug and Study	Dosage	Study design (comparator drugs)	Treatment duration	Sample	Findings
HALOPERIDOL					
Soloff et al, 1993	4 mg/day	db, pc (phenelzine)	5 w	108 BPD inpatients comorbid depression	↓hostility, ↓impulsive-aggression
Cornelius et al, 1993	≤6 mg/day	db, pc	16 w	54 BPD outpatients responders from Soloff study	↓irritability
OLANZAPINE					
Zanarini and Frankenburg, 2001 [51]	5.33 mg/day	db, pc	24 w	28 ♀ BPD	↓anger , ↓interpersonal sensitivity, ↓anxiety, ↓ paranoid ideation, improved global functioning effect size: 0.03
Zanarini et al, 2004 [54]	2.5 mg/day	db (fluoxetine, olanzapine + fluoxetine)	8 w	45 ♀ BPD no affective disorder	both olanzapine and olanzapine + fluoxetine > fluoxetine on impulsive aggression and depression
Bogenschutz and Nurnberg, 2004 [52]	5-10 mg/day	db, pc	12 w	40 BPD	↓anger, ↓global symptoms
Schulz et al, 2008 [53]	2.5-20 mg/day	db, pc	12 w	314 BPD	no significant differences for generic symptoms, ↓ BPD severity faster in the olanzapine group
Soler et al, 2005 [55]	5-20 mg/day	db, pc	12w	60 BPD treated with DBT	↓anxiety, ↓depression, ↓impulsive-aggression
Linehan et al, 2008 [56]	5 mg/day	db, pc	21w	24 ♀ BPD treated with DBT	no significant differences for generic symptoms ↓ irritability and aggression, faster in the olanzapine group, effect sizes: 0.5-0.8
Shafti and Shahveisi, 2010 [57]	7 mg/day	db (haloperidol)	8 w	28 ♀ BPD inpatients	no significant differences for generic behavioural symptoms, effect size > 0.8 for both drugs
ARIPIPRAZOLE					
Nickel et al, 2006 [58]	15 mg/day	db, pc	8 w	57 BPD	↓depression, anxiety ↓anger, ↓aggressiveness, ↓paranoia, improved global functioning
ZIPRAZIDONE					
Pascual et al, 2008 [60]	84 mg/day	db, pc	12w	16 BPD	no significant effects

Abbreviations: db = double-blind; pc = placebo controlled; w = week; ♀ =female; ↓ = decrease of; > = superior to.

Table 4. Double Blind Randomized Trials of other Drugs in the Treatment of Borderline Personality Disorder

Drug and Study	Dosage	Study design (comparator drugs)	Treatment duration	Sample	Results
NALOXONE					
Philipsen *et al*, 2004 [61]	0.4 mg i.v.	db, pc	-	9 BPD	no significant differences for dissociative symptoms
OMEGA-3 FATTY ACIDS					
Zanarini and Frankenberg, 2003 [62]	ethyl-eicosapentaenoic acid, 1 g/day	db, pc	8 w	30 ♀ BPD	↓depression, ↓aggression
Hallahan *et al*, 2007[63]	eicosapentaenoic acid 2.1 g/day + docosaex-aenoic acid 0.9 g/day	db, pc	12 w	49 subjects with self-harm behaviours (35 BPD)	↓depression, suicidality, milder reaction to daily stresses.

Abbreviations: db = double-blind; pc = placebo controlled; w = week; ♀ = female; ↓ = decrease of.