Pharmacotherapy of personality disorders: what we know and what we have to search for

(Article begins on next page)

19 December 2024

iris - AperTO

Pharmacotherapy of personality disorders: what we know and what we have to search for

Running head: Pharmacotherapy of personality disorders

Paola Bozzatello, MD, PhD

Camilla Ghirardini., MD

Maria Uscinska., PhD

Paola Rocca, MD

Silvio Bellino, MD

Centre for Personality Disorders, Department of Neuroscience, University of Turin,

via Cherasco 11, 10126, Turin, Italy,

tel./fax : 00390116335425, e-mail: silvio.bellino@unito.it

Abstract

Pharmacotherapy for personality disorders is in the early stage of development because the evidence base for effective drug treatment is insufficient, biased toward borderline personality disorder and rampant with methodological issues. In this paper, we reviewed randomized, placebo-controlled trials of drugs efficacy in patients with personality disorders published between 1990 and 2016. Overwhelming majority of studies focused on borderline personality disorder (BPD), and the accumulation of evidence resulted in 7 meta-analyses, which are interpreted into better strategies for evidence-based practice. Little research attention was given to schizotypal (SPTD) and antisocial (ASPD) personality disorders, with only indirect treatment efficacy evidence for the obsessive-compulsive (OCPD) and avoidant (AvPD) personality disorders. Some avenues for future efficacy research are indicated.

2

Introduction

Traditionally, drug treatment for personality disorders was considered ineffective and even contraindicated. To date, personality disorders are deemed to reflect biologically determined temperaments with underlying neurobiological vulnerabilities that could be amenable to treatment with medication [2-5]. While psychotherapy remains to be the primary modality in the overall treatment of personality disorders, pharmacotherapy can be an important adjunct used to treat well-defined target symptoms of the disorder [6].

When borderline personality disorder (BPD) first entered the DSM-III as a 'behavioural pattern resistant to traditional psychotherapy' (American Psychiatric Association, 1980), treatment approach for this disorder shifted toward pharmacotherapy [7]. The notion that other personality disorders may be amenable to treatment with medications was pioneered by Kraepelin [8], who observed that relatives of patients with schizophrenia evidenced attenuated cognitive and interpersonal symptoms of the disorder, which appeared to endure as personality traits.

Growing enthusiasm for the potential benefits of drugs in the treatment of personality disorders led to relevant efficacy studies, and a number of recent systematic reviews lend some support to the use of pharmacotherapy. Majority of research attention has focused on BPD and the accumulation of evidence base led to the official treatment guidelines which state that pharmacotherapy is an important adjunct used to treat well-defined target symptoms of the disorder which often fall within three behavioral dimensions — affective dysregulation, impulsive-behavioral dyscontrol, and cognitive-perceptual distortion [6, 130]. Nevertheless, our knowledge of how pharmacology can be best applied to personality disorder is limited due to the systematic evidence base being scarce, biased toward BPD, confounded by comorbid psychopathology, limited by small sample sizes, short follow- up, and lack of consensus on core outcome measures [9-11]. Consequently, despite the growing evidences to support the use of pharmacotherapy in personality disorders, there are no Food and Drug Administration (FDA) or European Medicines Agency (EMA) - approved medications for treating this disorder and therefore pharmacotherapy for personality disorders remains off-label.

In this paper, we reviewed placebo-controlled randomized trials for the efficacy of pharmacotherapy in treating personality disorders published between the year 1990 and 2016. In the light of the evidence gathered, a discussion of clinical recommendations will follow.

Treatment of Cluster A personality disorders

To our best knowledge, four placebo-controlled studies for the drug treatment of Schizotypal Personality Disorder (STPD) have been published within the given time frame. No RCTs exist for other cluster A personality disorders. However they are deemed to fall on a continuum with the psychotic disorders, and therefore candidates to treatment with antipsychotics [12, 13].

Thus, in recent years there was a growing interest of clinical research in treating STPD because it is considered a precursor to schizophrenia [14]. Given the evidence of increased dopamine activity in STPD that is also characteristic of schizophrenia, the focus of pharmacotherapy for schizotypal traits is the regulation of dopamine pathways [15]. Early open-label studies reported improvement in psychotic symptoms with haloperidol [16], thiothixene [17] and olanzapine, which was also found to improve depressive symptoms [18]. Moreover, thiothixene was found to be superior to haloperidol in improving derealisation, anxiety, and depression [19].

In the first placebo-controlled study risperidone (0.25–2.00 mg/day) was administered to 25 STPD patients over 9 weeks, and a decrease in positive and negative symptoms was reported as measured by the Positive and Negative Symptoms Scale (PANSS) [20]. However, no significant improvements were found with the Schizotypal Personality Disorder Questionnaire (SPQ), the Hamilton Depression Rating Scale (HAMD), and the Clinical Global Impression (CGI). Furthermore, seven out of 15 patients in the risperidone condition had dropped out due to side effects.

More recently a line of research focused on the treatment of the cognitive deficit associated with schizophrenia spectrum disorders. The effect of risperidone (0.25–2.00 mg/day) on cognitive performance was compared to placebo in 31 STPD patients over 12 weeks [21]. No significant treatment effect was found with regard to neuropsychological functions such as spatial and verbal

working memory, spatial memory, vigilance, and work list learning. Furthermore, there was a high drop out with just 20 subjects completing the trial.

Other two placebo-controlled studies focused on the potential benefits of dopamine agonists in improving the cognitive deficit associated with STPD. Guanfacine was shown to improve context processing in 29 STPD patients [22], and pergolide led to a significant improvement in visual spatial working memory, executive functioning, verbal learning and memory in 25 STPD patients [23]. It should be noticed that the pergolide trial was halted because of evidence of heart problems related to use.

Results of RTCs are summarized in Table 1.

Treatment of Cluster B personality disorders

Among the Cluster B personality disorders the majority of studies were focused on the treatment of borderline personality disorder (BPD). Some preliminary evidences are available for antisocial personality disorder (ASPD), but the findings are still sparse and inconclusive. No studies have been published on other cluster B personality disorders.

Pharmacotherapy for borderline personality disorder

1) Antidepressants

Several antidepressants have been studied in treating specific BPD symptoms in the past years. In particular research attention focused on selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), rather than tricyclic antidepressants and monoamino-oxidase inhibitors (MAOIs), due to better tolerability and low risk of potential fatal overdose. Nevertheless, the preference for antidepressants in BPD treatment has decreased in recent years and their use is currently recommended only in the presence of a comorbid affective disorder [24].

Whilst fluoxetine received the greatest research attention out of SSRIs tested, [25-31], only one report of the efficacy of fluvoxamine and one of treatment with sertraline have been published to date [32,33]. The three RCTs that compared fluoxetine with placebo reported a significant efficacy of this drug on

anger, aggression, and anxiuos-depressive symptoms. In particular, Salzmann and colleagues [26] performed a 12-week placebo-controlled trial to evaluate the efficacy of fluoxetine (20-60 mg/day) in 27 patients with BPD without psychiatric comorbidity. In a post hoc analysis with correction for the strong placebo effect, statistically significant differences between treatment conditions were obtained with respect to anger and aggression, which appeared to be independent of depression. Efficacy of fluoxetine (20-60 mg/day) compared with placebo on impulsive-aggressive behaviours and irritability was also reported in a 12 week trial including a mixed sample of 40 PD patients (one-third BPD patients) with comorbid dysthymic disorder, anxiety disorder, alcohol and substance abuse [27]. Markovitz and colleagues [25] in a 14 week-RCT comparing fluoxetine (20-80 mg/day) and placebo in a group of 17 BPD patients with high co-occurrence of affective/anxiety disorders and somatic symptoms found that fluoxetine improved significantly depression, anxiety, and global symptoms, while impulsiveness and aggression were not measured in this study. Given the well-established efficacy of SSRIs in treating affective and anxiety disorders, insufficient control for comorbidity of these disorders in the Markovitz's study hampers interpretation of the results, as it is difficult to distinguish symptomatic improvement of a comorbid disorder from true change of underlying personality.

Other controlled studies were performed to evaluate the efficacy of the combination of fluoxetine with psychotherapeutic interventions in comparison with psychotherapy plus placebo [28], or fluoxetine monotherapy [30,31]. One blind placebo-controlled trial tested the efficacy of the association of fluoxetine (40 mg/day) and Dialectical Behaviour Therapy (DBT) versus placebo plus DBT in a sample of 20 females with BPD. [28]. Results showed that patients treated with the combination of fluoxetine and DBP did not evidence any additional benefits over placebo + DBT treatment on self-report measures of depression, anxiety, anger, dissociation, and global functioning. Different findings were obtained by two controlled studies [30,31] aimed to evaluate the short and long-term efficacy of combined therapy with fluoxetine (20-40 mg/day) and Interpersonal Psychotherapy adapted to BPD (IPT-BPD) in a sample of 55 BPD outpatients. In particular, combined therapy with adapted IPT was found superior to single fluoxetine after 32 weeks of treatment, concerning core symptoms of the disorder (interpersonal relationships, affective instability, and impulsivity), anxiety, and quality of life [30]. Forty-four patients who completed the 32 weeks trial underwent 24 months of follow-up receiving all fluoxetine 20-40 mg/day. The most of the differences between combined therapy and

single pharmacotherapy were maintained after two years of follow-up [31]. Fluoxetine was also studied in comparison with an active drug [29], in a RCT aimed to evaluated the efficacy of three type of treatments: fluoxetine in monotherapy (15 mg/day), olanzapine in monotherapy (2.5 mg/day), and the association of both drugs. The study sample consisted of 45 female BPD patients. Olanzapine monotherapy and combined therapy were found to be superior to fluoxetine monotherapy on mood symptoms and impulsive-aggressive behaviours. However, the choice to administer an unusually low dose of fluoxetine might have accounted for the lower level of efficacy found for fluoxetine.

The only RCT on the efficacy of fluvoxamine included 38 women with BPD receiving a dose of 150-250 mg/day of the drug versus placebo over 6 weeks. This phase of treatment was followed by a 6 week crossover phase [32]. While significant improvement in rapid mood shifts was evidenced in the early phase of the treatment (week 1 to 6), no difference between the two groups was observed with regard to impulsivity and aggression scores. The lack of superiority of drug treatment on impulsivity and aggression might be related, according to authors' opinion, to the female gender of the sample, as these symptoms have usually a lower degree of severity in females.

Study concerning the efficacy of sertraline was conducted in 120 BPD patients on methadone maintenance therapy that were randomly assigned to two treatment groups: sertraline 50-100 mg/day or olanzapine 5-10 mg/day [37]. The outcomes taken into consideration included somatization, depression, anxiety, obsession, aggression, hypersensitivity in interpersonal relationship, paranoia, and self-mutilating behaviours. Following 12 weeks of treatment both drugs evidenced clinical efficacy in improving global psychopathology, nevertheless some differences were found in specific symptom domains. While anxiety and depression benefited from both treatments, olanzapine was more efficacious in treating anxiety, and sertraline evidenced greater positive effect on depression. Furthermore, both drugs demonstrated efficacy in decreasing hypersensitivity in interpersonal relationship (major effect with sertraline) and aggression (major effect with olanzapine). Although somatization and obsessive symptoms benefited from both treatment, sertraline evidenced greatest efficacy in improving obsession. In addition, olanzapine led to a stronger reduction of paranoia and self-mutilating behaviours.

Thus, the available evidence demonstrates the efficacy of SSRIs in decreasing affective symptoms, in particular depressed mood, anxiety, anger and impulsive behaviors in BPD patients. However, these

results have been obtained in rather old studies and have not been replicated after 2010, except for the follow-up study on efficacy of combined therapy with fluoxetine and IPT-BPD.

The two SNRIs venlafaxine and duloxetine have been studied in one open trial each [34,35], but more consistent evidences from controlled trials are missing.

Results of RTCs are displayed in Table 2.1.

2) Mood stabilizers

Mood stabilizers have been considered from clinicians a useful therapeutic option in the treatment of BPD patients. Several RCTs including lithium, carbamazepine, valproate, topiramate, and lamotrigine have been performed over the years to investigate the efficacy of these drugs in improving affective dysregulation and behavioural dyscontrol. In the only RCT on lithium efficacy in treating BPD symptoms, the drug was compared to desipramine and placebo in 17 patients receiving concomitant psychotherapy for 6 weeks [36]. While a significant improvement in anger and suicidality was reported in favour of the lithium therapy, no effect was evidenced with regard to change of mood symptoms. The risk of toxicity and the need for regular blood level controls are significant limitations to the use of this drug in BPD population, hence lithium has no longer been studied in these patients and there is insufficient evidence to support its therapeutic effects.

De la Fuente and Lotstra [37] studied the efficacy of carbamazepine versus placebo on affective symptoms, behavioural dyscontrol or global assessment in 20 BPD outpatient for 5 weeks. Carbamazepine doses were adjusted to yield plasma levels in the low therapeutic range. No significant differences were found in clinical benefits between carbamazepine and placebo, maybe due to the very limited duration of the trial. However, the limited evidence of therapeutic benefits in treating BPD against the risk of severe adverse effects (e.g. agranulocytosis), carbamazepine is considered a questionable treatment option for these patients. A mood stabilizer that was extensively studied in BPD was valproate. Hollander et al. [38] tested valproate sodium (medium plasma concentration 80 µg/mL) versus placebo in a preliminary 10-week, double-blind designed trial on 16 BPD patients. Unfortunately, the study failed to demonstrate significant improvement in global symptomatology, affective dysregulation, and behavioral dyscontrol in favour of valproate, probably due to the high dropout rate (10 of 16 patients). The same authors [39] performed a second RCT on valproate with a similar design. A large sample of 246 patients with high level of aggression (including BPD and other

cluster B personality disorders) received valproate treatment for 12 weeks. The study provided an evidence for the efficacy of valproate in treating impulsive-aggressive behaviours. A later revision of the data [40] revealed a correlation between high trait impulsivity and effect of valproate.

The efficacy of valproate in treating BPD symptoms was further confirmed in a 6-month placebo controlled study conducted by Frankenburg and Zanarini [41] in 30 female BPD patients with comorbidity of bipolar II disorder. Valproate sodium (plasma concentration 50-100 µg/ml) demonstrated a significant decrease of interpersonal sensitivity, anger, hostility, and aggressiveness.

More recently, Moen et al. [42] tested divalproex ER in 15 BPD patients after 4 weeks of "condensed" Dialectical Behavioral Therapy. Although there were no significant differences in clinical benefits between participants in divalproex ER treatment versus placebo, a significant improvement was observed in both groups from baseline to endpoint.

The potential benefits of topiramate (50-250 mg/day) on the ability to control aggressive behaviours was tested against placebo over 8-week in 31 females and 42 males with BPD respectively [43,44]. Topiramate evidenced treatment efficacy in both studies with respect to irritability and anger. The follow-up studies by the same research group provided evidence to supports the long-lasting effects of topiramate in reducing aggression in BPD with a low side effects profile [45-47].

A third 10-week RCT on topiramate (25-200 mg/day) conducted by Loew et al. [48] in 56 females with BPD and concurrent mood disorders reported a significant reduction in somatization symptoms, interpersonal sensitivity, and hostility. Furthermore, an improvement of global functioning emerged from this set of data.

To date, two double blind trials [49,50], one follow-up study [51] and one study protocol [52] with regard to the efficacy of lamotrigine in BPD treatment are available.

The efficacy of lamotrigine (titrated to a dose of 200 mg/day) versus placebo was tested in 24 female BPD outpatients after 8 weeks of treatment [49] and during a 18-month of follow-up observation [51]. A significant improvement in anger was reported both after 8 weeks of treatment and during the follow-up period in the lamotrigine treated group. Reich et al. [50] tested the efficacy of lamotrigine in treating impulsivity and affective instability over 12 week in a double blind placebo controlled study of 28 BPD patients with major depression and anxiety disorders and reported a significantly greater reduction in the primary outcomes in the active treatment group.

In summary, the preliminary results suggested that the mood stabilizers valproate, topiramate, and lamotrigine can be considered promising treatment tools in the treatment of affective symptoms related to anger and impulsive aggression in BPD patients.

Results of RCTs are summarized in Table 2.2.

3) Antipsychotics

In the last years, the evidence of efficacy of antipsychotics in the treatment of BPD has continuously increased. Both classical neuroleptics and second generation antipsychotics have shown to be efficacious in targeting psychotic or psychotic-like symptoms, as well as different dimensions of BPD psychopathology. Second generation antipsychotics are widely considered preferable because of their better tolerability profile.

3.1) Classical neuroleptics

Since the 1980s, several RCTs have been conducted to test the efficacy of different neuroleptics (flupenthixol decanoate, loxapine, chlorpromazine, thiothixene, trifluoperazine, and haloperidol) in BPD treatment [53-59]. Unfortunately, among these studies, the only two that can be considered acceptable in terms of inclusion criteria, trial duration, and relevant findings are those concerning haloperidol.

Soloff et al. [60] compared haloperidol (4 mg/day), the MAOI phenelzine (60 mg/day), and placebo in a 5 week RCT on a large sample of BPD inpatients (n=108). Although haloperidol demonstrated efficacy in reducing hostility and impulsive-aggressive behaviours among BPD symptoms, it failed to improve global severity, depression, anger, and psychoticism, thereby providing results that are inconsistent with previous reports of the same authors [59]. The difference in results might be due both to the controlled design and to the lower severity of psychopathology reported in the 1993 study.

Cornelius et al. [61] followed the 54 subjects of the Soloff's trial sample in a continuation study over 16 weeks, in which haloperidol (highest dose: 6 mg/day) failed to demonstrate significant effects. During prolonged haloperidol treatment depressive symptoms significantly increased and only irritability showed a modest improvement. Moreover, during the follow-up phase the dropout rate in the haloperidol group amounted to a very high rate of 64% of patients.

In conclusion, administration of classical neuroleptics to BPD patients might be limited to acute states with anger and psychotic-like symptoms, and treatment should be prescribed in low doses and for short periods of time due to commonly reported and severe side effects (extrapyramidal symptoms) and the consequent elevated dropout rate.

3.2) Second generation antipsychotics

Several open-label studies with different new generation antipsychotics, such as clozapine [62-65], paliperidone [66,67], and asenapine [68] have shown benefits in the treatment of cognitive perceptual symptoms, anger, and impulsivity in BPD patients. Among the new antipsychotics that have been tested in placebo-controlled trials are risperidone, olanzapine, aripiprazole, ziprasidone, and quetiapine. Risperidone was initially tested in BPD patients in a few open trials [69-72] that showed an improvement across a spectrum of symptoms, such as aggressiveness, affective instability, anxiety, and impulsivity. The only controlled trial of risperidone in BDP was performed by Schulz and colleagues [73], who recruited 27 patients treated for 8 weeks with a mean dose of 2.5 mg/day versus placebo. No differences between the two treatment groups emerged with regard to global functioning. However, risperidone was found more effective in decreasing psychoticism, paranoid ideas, phobic anxiety, and interpersonal sensitivity.

Olanzapine has been the most widely studied second generation antipsychotic in the treatment of BPD patients. Four studies investigated the effects of olanzapine versus placebo, and three trials compared olanzapine with other active drugs, psychotherapy, or the combination of both.

Zanarini and Frankenburg [74] compared olanzapine (mean dose 5.33 mg/day) and placebo in 28 women with BPD for 6 months. The active treatment arm reported a significant improvement in a wide range of symptoms, including interpersonal sensitivity, anxiety, anger, hostility, paranoia, psychoticism, and global functioning. Bogenschutz and Nurnberg [75] published a study in which 40 BPD patients were treated over 12 weeks with olanzapine (5-10 mg/day) or placebo and they observed a significant improvement in anger and global symptoms. In another RCT [76] with a similar design and a larger sample, 314 patients were randomly assigned to olanzapine (2.5-20 mg/day) or placebo for 12 weeks. No differences in efficacy between the two groups was significant with regard to BPD symptomatology. Nevertheless the time to response was significantly shorter for olanzapine.

More recently, Zanarini et al. [77] compared different doses of olanzapine (low: 2.5 mg/day and moderate: 5-10 mg/day) against placebo in a large population of 451 BPD outpatients. Olanzapine in moderate doses showed a significantly greater efficacy in improving the overall severity of BPD over placebo, in particular in the early phase of treatment (first 6 weeks). Furthermore, the drug was associated to a higher response rate and a shorter time to response compared to the other treatments. The risk of adverse events (particularly weight gain) was consistent in the treatment groups, with a dose-related trend.

The efficacy of olanzapine was also evaluated in combination with psychological treatments, in particular DBT [78]. Sixty BPD outpatients were randomly assigned for 12 weeks to olanzapine (mean dose 8.83 mg/day) or placebo. All participants received DBT sessions. Olanzapine evidenced a superior efficacy versus placebo in reducing anxiety, depressive symptoms, and impulsive-aggressive behaviours. A similar study [79] involving 24 women with BPD treated with olanzapine (mean dosage 5 mg/day) or placebo, in addition to DBT psychotherapy obtained analogous findings. In addition, a significant improvement of self-injuries was registered in the olanzapine group.

The efficacy of olanzapine was also tested in comparison with other active drugs, such as SSRIs (see the paragraph concerning antidepressants) and other antipsychotics. In particular, olanzapine (mean dose 7 mg/day) or haloperidol (mean dose 7 mg/day) were randomly administered to 28 female inpatients with BPD over 8 weeks [80]. No significant differences were found between treatment drugs in reducing the severity of general behavioural symptoms (anxiety, depressive mood, and hostility). The absence of a placebo-controlled group constitutes a major shortcoming of this study.

Some initial data on aripiprazole come from open trials and case reports [81, 82], in which an improvement in global psychopathology, impulsivity, affective instability, and cognitive-perceptual symptoms was reported. The only RCT on aripiprazole (15 mg/day) was performed by Nickel et al. [83]. Fifty-seven BPD patients were enrolled and randomly assigned to the active treatment or the placebo arm. Aripiprazole was found to be significantly effective in reducing psychotic symptoms, depression, anxiety, and hostility after 8 weeks of treatment. The clinical benefits were confirmed after 18 months of follow-up [84]. Less encouraging findings have been obtained with ziprasidone.

Pascual et al. [85] conducted a 12-week RCT to test the efficacy of oral ziprasidone (mean daily dose 84 mg) versus placebo in treating psychoticism, depression, anxiety, impulsivity, and hostility in 16 BPD patients [86]. The results of this trial were not in favour of the efficacy of oral ziprasidone in

BPD. In fact, no significant effects of treatment with ziprasidone were reported. To date, no other studies on this drug have been published in BPD patients.

Quetiapine has been extensively studied over the years in several open-label trials of BPD patients [87-92], and the accumulated evidence suggested remarkable efficacy of this drug in reducing impulsive-aggressive behaviours, affective instability, and anxious-depressive symptoms.

Effects of quetiapine in treatment of BPD were more recently investigated in two RCTs. One of them compared the effects of different doses of this medication versus placebo over 8 weeks in 95 BPD patients [93]. Participants were randomly assigned to three subgroups: quetiapine 150 mg/day (n=33), quetiapine 300 mg/day (n=33), or placebo (n=29). Low dosage quetiapine treatment group obtained a significant improvement of BPD symptoms over placebo, with the most prominent therapeutic effects on affective instability, cognitive-perceptual symptoms, and aggressiveness. Comparison in efficacy between the moderate dose of quetiapine and placebo did not reach the significance threshold. Furthermore, the time to response was shorter in both the active treatment groups compared with placebo. Adverse events, such as sedation, dry mouth, dizziness, and change in appetite, were more likely in the moderate dosage group and were related to a higher dropout rate. The same sample was further examined by Lee et al. [94] that used another evaluation tool. In this second analysis both doses of quetiapine demonstrated a significant efficacy in reducing levels of overall psychological distress, interpersonal sensitivity, depression, and hostility compared to placebo.

In summary, among second generation antipsychotics there is some evidence to support the therapeutic effect of olanzapine on cognitive symptoms, aggressiveness, anxiety and depression of BPD patients. Further controlled investigations are needed to confirm the preliminary and inconclusive data on other drugs, such as aripiprazole, risperidone, ziprasidone, and quetiapine.

Findings of RTCs are summarized in Table 2.3.

4) Other drugs

Other psychotropic agents, such as opiate antagonists, oxytocin, clonidine, and omega-3 fatty acids have received attention with regard to their efficacy in treating BPD symptoms.

Opioid antagonists

One small double-blind study [95] including 9 BPD patients failed to show the efficacy of i.v. administration of naloxone (0.4 mg) in the treatment of acute dissociative states. Similarly, Schmahl et al. [96] evaluated oral naltrexone administration in treating dissociative symptoms in BPD in 29 patients who received naltrexone (50 or 200 mg/day) over 3 weeks versus placebo. Naltrexone evidenced a numerically (but not statistically) superior efficacy in reducing both the intensity and the duration of dissociative symptoms.

Clonidine

The α_2 adrenergic agonist clonidine is commonly used for treatment of high blood pressure, and it has been applied in treatment of many neuropsychiatric conditions such as attention-deficit and hyperactivity disorder (ADHD), anxiety disorders, post-traumatic stress disorder (PTSD), withdrawal from either alcohol, benzodiazepine or nicotine. Recently, two RCTs examined potential efficacy of clonidine in the treatment of BPD.

Philipsen et al. [97] recruited 14 BPD female patients to evaluate the acute effect of two different doses (75 μg versus 150 μg) of orally administered clonidine on strong aversive inner tension and dissociative symptoms as major reasons for self-injurious behaviours and suicidal ideation. No placebo control group was considered in the design. The outcomes were assessed before and 30, 60 and 120 minutes after clonidine administration, using self-rating instruments. Aversive inner tension, dissociative symptoms, the urge to commit self-injurious behaviours and suicidal ideation significantly decreased after administration of both dosages of clonidine, with the strongest effect between 30 and 60 minutes. Blood pressure positively correlated with aversive inner tension and dissociative symptoms before and after clonidine administration.

In another RCT with a crossover design, Ziegenhorn and colleagues [98] tested clonidine (maximum dosage 0.3 mg/day orally administered) with regard to hyperarousal symptoms (sleep problems, irritability, concentration problems, hypervigilance and exaggerated startle), BPD-specific symptoms, general psychopathology, and some adjunctive items such as sleep and eating problems, feelings of guilt and suicidality. The study sample included 18 patients with BPD, with or without comorbid PTSD. Hyperarousal was shown to improve significantly in the active treatment group compared with placebo, and this was independent of PTSD comorbidity. Improvements in general and BPD-typical psychopathology (particularly self-destruction and self-perception) were mainly observed in the PTSD-positive subgroup, while amelioration of sleep latency and quality was observed in the whole sample.

Omega-3 fatty acids

The first placebo-controlled study performed to investigate the effects of omega-3 fatty acids in the treatment of 30 female BPD patients over 8 weeks reported a significant improvement of depressive symptoms and aggressive behaviours in response to ethyl-eicosapentaenoic acid (1g/day) [99].

Hallahan et al. [100] evaluated the efficacy of eicosapentaenoic acid (EPA, dose 1.2 g) plus docosahexaenoic acid (DHA, dose 0.9 g) in addition to psychiatric care in 49 subjects with self-harm behaviours (35 with diagnosis of BPD) over 12 weeks. The group treated with omega-3 fatty acids had significantly greater improvements on depression, suicidality, and reaction to daily stress.

Amminger et al. [101] performed a 12 week double-blind RCT comparing long-chain omega-3 polyunsaturated fatty acids and placebo in BPD patients with high risk of psychosis. The treatment group showed a significantly greater improvement in global functioning compared over placebo group. Moreover, a significant positive effect on psychotic-like symptoms was observed in the treatment group. No clinically significant adverse effects were reported during omega-3 fatty acids administration.

In another 12 week RCT Bellino et al. [102] compared the efficacy of the association of EPA and DHA with valproic acid versus valproic acid monotherapy in 43 BPD outpatients. Both treatment modalities were found efficacious on the general symptoms and BPD related psychopathology, with no significant differences between groups. Nevertheless, supplementation with omega-3 fatty acid showed to be significantly superior to a single therapy in reducing severity of some specific BPD symptoms, in particular impulsivity, anger, and self-mutilating conducts. No significant antidepressant effect was found in the combined therapy group in comparison with controls.

In conclusion, the initial results of studies of omega-3 fatty acids are promising for the treatment of BPD patients, in particular considering the good tolerability of these agents. Nevertheless, there is no agreement among authors about the type of BPD symptoms that can benefit from omega-3 fatty acids, with some of them indicating a predominant effect on affective symptoms and others suggesting a better response of impulsive behavioural symptoms.

Oxytocin

Simeon et al. [103] recruited 14 BPD and 13 healthy controls who received 40 UI of intranasal oxytocin or placebo in double-blind randomized order. Single-dose oxytocin administration in patients group resulted in greater attenuation of the dysphoric emotional response to stress, with childhood

trauma as the strongest predictor of this response. Oxytocin administration was also related to a more dampened hypothalamic-pituitary-adrenal axis response to stress (measured by plasma cortisol levels). Insecure attachment was the strongest predictor of this response.

In another RCT performed by Bertsch et al. [104], 40 non medicated female BPD patients and 41 healthy women took part in an emotion classification task after intranasal administration of 26 UI of oxytocin or placebo. Initial reflexive eye movements, manual response latency and fNMR (functional Nuclear Magnetic Resonance) level of activation of the amygdala were measured. BPD patients exhibited more frequent and rapid initial fixation changes combined with increased amygdala activation in response to angry faces compared with the control group. These abnormal behavioral and neural patterns in response to a social threat were normalized after oxytocin administration.

A similar design study was conducted by Brüne et al. [105] comparing reactions to happy and angry faces in a patients group (n=13) and a control group (n=13) after intranasal application of oxytocin or placebo. Patients with BPD evidenced an avoidant reaction to angry faces in the placebo condition. The strength of the avoidant reaction correlated with the severity of childhood trauma (measured with the childhood trauma questionnaire). In the oxytocin condition this behavioral response was abolished.

In 2015 the same research group examined the effect of intranasal oxytocin versus placebo on nonverbal behaviour during a clinical interview in patients with BPD and in healthy controls [106]. Patients group showed less affiliative behaviours compared with controls. Oxytocin administration determined a prosocial effect in the control group (but not in the BPD patients) mainly in situations in which interlocutors were unfamiliar to the subject. Oxytocin administration was also associated with less flight behaviours compared with placebo in both patients and controls group. No correlation emerged between childhood trauma and the patients' nonverbal expressivity.

Another RCT on oxytocin was performed by Ebert et al. [107] with regard to the modulation of interpersonal trust. Oxytocin showed a "paradoxical" trust-lowering effect in BPD, which was correlated with patients' history of childhood trauma. The "anti-social" effect of oxytocin was confirmed in an open-trial by Bartz and colleagues [108]. Authors observed that oxytocin decreased trust and likelihood of cooperative responses in BPD patients compared to healthy subjects. Chronic interpersonal insecurities and possible neurochemical differences in oxytocin system are supposed to be a likely explanation of this different response.

In conclusion, intranasally administered oxytocin seems to provide partially encouraging, but not homogeneous results with regard to its efficacy in improving social cognition, social behaviour and stress response in healthy subjects and in BPD patients.

Results of RTCs are displayed in Table 2.4.

5) Treatment guidelines and meta-analyses

The first set of guidelines for the treatment of borderline personality disorder was published in 2001 by the American Psychiatric Association [6]. These first recommendations were based on a three symptom dimensions model of BPD and proposed a pharmacotherapy approach targeted at them: affective dysregulation (including depressed mood, anxiety, anger, and mood lability), impulsive-behavioural dyscontrol, and cognitive-perceptual symptoms. APA guidelines and following updates [109] recommended pharmacotherapy to treat both state symptoms during acute phase of decompensation and more stable trait vulnerabilities. In particular antidepressants (SSRIs and MAOIs) and mood stabilizers were recommended as first and second-line interventions for the two dimensions of affective dysregulation and impulsive-behavioural dyscontrol. The recommended therapeutic strategy for cognitive-perceptual symptoms, according to APA guidelines, was represented by antipsychotic drugs.

In 2007, the WFSBP [110] published a set of practical and biological-based guidelines for the pharmacological treatment of borderline, schizotypal, and anxious/avoidant personality disorders. Four evidence levels for each class of medications were considered (from the strongest to the weakest): level A: at least 3 RCTs; level B: at least 2 RCTs or 1 RCT and ≥1 prospective, large, open-label study; level C: 1 RCT and 1 prospective, open-label study/case series or at least 2 prospective, open-label study/case series; level D: expert opinion-based. The recommendations that came from the WFSBP International Task Force were: atypical antipsychotics for STPD (evidence level C) and antidepressants for anxious/avoidant PD (evidence level A). With regard to BPD treatment, antidepressants, mood stabilizers, and second generation antipsychotics were indicated respectively on a fair (level B) and minimal (level C) research-based evidence level. The main symptomatic targets of pharmacotherapy in personality disorders, according to WFSBP guidelines, are affective dysregulation, cognitive-perceptual symptoms, impulsivity and anger. The effects of pharmacotherapy in these patients can also be useful to increase response to combined psychosocial interventions.

17

In 2009 Guidelines from the National Institute for Health and Clinical Excellence (NICE) on management of borderline and antisocial personality disorders were published [111,112]. Despite considering approximately the same evidences, NICE authors reached different conclusions from the preceding guidelines. They did not recommend drug therapy other than for treatment of mental disorders in comorbidity or to control, during a crisis and with a short-term prescription, specific acute symptoms. A reason for this discordance is that the NICE group considered several parameters to draw up clinical recommendations, such as evidence of cost-effectiveness, not only for medications, but also for clinical management and psychological therapies. Moreover, the NICE guidelines have been developed looking at the unique care pathway followed in England and Wales.

The Australian National Health and Medical Research Council guidelines [113], published in 2012, confirmed psychotherapy as the first line treatment in BPD and suggested to use pharmacotherapy, as a second line intervention combined with psychotherapy, for a limited period of time in order to treat specific BPD symptoms or comorbid conditions.

In the last years, following the recent results of pharmacological trials in patients with BPD, a growing number of meta-analyses on BPD treatment have been published. One of them was performed by the Cochrane Collaboration [114] and focused on RCTs published between 1980 and 2001. Ten studies were selected predominantly focused on classical antipsychotics and antidepressants and poor evidence for medication efficacy in BPD emerged.

In the same year, Nosè et al. [115] conducted a meta-analysis on 22 RCTs. The authors obtained different conclusions regarding antidepressants, mood stabilizers, and antipsychotics. The first two drug classes demonstrated to be effective against affective instability and anger, whereas the most positive effects on impulsive-aggressive behaviours and global functioning were evidenced with antipsychotics.

A recent and remarkable trend in the literature consists in a shift from the recommendation of antidepressants to the preference for mood stabilizers and second generation antipsychotics in the treatment of BPD [116]. However, considerable differences remain among the conclusions of different authors.

In a meta-analysis focusing on anger and depression in BPD, Mercer et al. [117] found mood stabilizers to be superior to SSRIs in treating affective symptoms, including depressed mood and anger. Antipsychotics showed a moderate effect on anger, but failed to demonstrate efficacy on depression.

18

Ingenhoven et al. [118] evaluated the available literature about pharmacotherapy for borderline and schizotypal personality disorders, following a symptom dimensions approach. Global functioning, impulsive-behavioural dyscontrol, anger, and anxiety resulted to be better improved by mood stabilizers, while antipsychotics had a moderate efficacy on cognitive-perceptual symptoms and anger. On the contrary, antidepressants failed to demonstrate efficacy in the treatment of impulsive-behavioural dyscontrol and mood symptoms.

Another study by the same research group [119] focused on the potential benefits of antipsychotic drugs (including both classic neuroleptics and atypical antipsychotics) in treating BPD. Antipsychotics resulted to be weakly effective in cognitive perceptual symptoms, mood lability and global functioning, with a more pronounced positive effect on anger. Impulsive behavioral dyscontrol, depressed mood and anxiety did not benefit from antipsychotic drugs at all.

In another meta-analysis, including both RCT and open trials, Vita et al. [120] found mood stabilizers and antipsychotics to be effective for treating affective dysregulation and impulsive behavioral dyscontrol. The only effect in reducing cognitive perceptual symptoms was observed with antipsychotics, whereas antidepressants failed to show efficacy in treating BPD symptoms dimensions other than affective dysregulation.

Saunders and Silk [121] provided further evidence for the efficacy of antipsychotics by collecting and analyzing data from placebo-controlled trials classifying BPD target symptoms into the following trait dimensions: affective instability, anxiety inhibition, cognitive perceptual disturbance, and impulsivity aggression. All these dimensions were shown to benefit from the treatment with antipsychotics.

An oxytocin focused meta-analysis [122] explored potential benefits and limitations of its pharmacotherapeutic application. Intranasally administered oxytocin leads to better emotion recognition and more trust in others in healthy subjects. In clinical population, including BPD patients, this effect seems to be lower or absent because of negative childhood experiences.

A small meta-analysis [123] was recently conducted on acute movement disorders associated with the use of second generation antipsychotics in BPD. Data from three olanzapine and one ziprasidone studies were collected and revealed that the risk of acute parkinsonism and akathisia in patients treated with low dose (5-10 mg/day) of olanzapine was not significantly increased compared with placebo. Other adverse effects, such as weight gain and metabolic syndrome, had a significant association with

olanzapine administration. Of course, these results cannot be generalized to other second generation antipsychotics.

The Cochrane Systematic Review [124, 125] of pharmacological interventions for BPD indicated mood stabilizers, second-generation antipsychotics, and omega-3 fatty acids as effective agents in the treatment of BPD symptoms. Nevertheless, the authors emphasized the need for stronger evidences as the majority of the current recommendations are still based on single study effect estimates. The previous dominating role of antidepressant is no more supported by evidences, except in the case of comorbid conditions (i.e. depression or anxiety disorders). Also first generation antipsychotics failed to demonstrate evidence of treatment efficacy for BPD patients. Polypharmacy is not supported and should be avoided, if possible. Finally, is noticeable that some specific BPD symptoms, such as avoidance of abandonment, chronic feelings of emptiness, identity disturbance, and dissociation are hardly controlled by pharmacotherapy and remain the target of non-pharmaceutical treatments, such as specific interventions of psychotherapy. The recent update of Cochrane Review [24] confirmed these findings and underlined the researchers' growing interest in dietary omega-3 supplementation and oxytocin.

Findings from the most recent studies and reviews raised considerable questions on the initial recommendations to administer SSRIs or related antidepressants to treat affective dysregulation and impulsive-behavioural dyscontrol. On the contrary, the role of mood stabilizers and new antipsychotics in the treatment of main symptom dimensions of BPD is gradually increased in last years. A limit to their use is the lack of systematic studies of adverse effects in BPD samples. Another significant limitation of literature on pharmacotherapy of BPD concerns the lack of data that allow to evaluate separately treatment results in case of acute phase of decompensation or in case of stable trait vulnerabilities. Investigations focusing on this relevant distinction are needed to complete and specify recommendation of treatment guidelines.

Pharmacotherapy for antisocial personality disorder

With regard to antisocial personality disorder (ASPD), eight placebo-controlled studies have been published. However, the existing evidence is too limited to suggest that any drug is effective in the treatment of this personality disorder.

The drugs tested belong to four classes.

1) Antidepressants

Two placebo-controlled studies tested the efficacy of desipramine. One of them involved methadone-maintained in-patients with opioid and cocaine dependency [126], whereas the other considered methadone-maintained outpatients with cocaine dependence [127]. Both studies reported no treatment effects. More encouraging results were reported for nortriptyline (25–75 mg/day), with some evidence of efficacy in reducing mean of drinking days, alcohol dependence, anxiety levels, but not severity of alcohol misuse in 20 males with alcohol addiction [128].

2) Antiepileptics

Phenytoin (300 mg/day) was compared to placebo in one trial [129]. Results indicated reduced frequency and intensity of aggressive behaviours in 126 male prisoners with impulsive aggression. Valproate was tested against placebo in two trials of outpatients with aggression [130, 131]. However, neither of them reported significant findings with regard to ASPD symptoms. The efficacy of carbamazepine (450 mg/day) in treating aggression was tested in incarcerated men with aggression [130], but no significant effects were described in this ASPD group.

3) Dopamine agonists

Two placebo-controlled trials tested the efficacy of amantadine and bromocriptine. While the former was found not better than placebo in men with opioid and cocaine dependency [126, 128], the later evidenced some efficacy in reducing anxiety symptoms in males with alcohol addiction.

4) Opioid antagonists

The only controlled study of this drug category involved administration of naltrexone to subjects with alcohol dependency with and without ASPD or BPD [132]. No difference in response to medication as a function of diagnosis was evidenced.

A small case series is available to suggest the efficacy of quetiapine treatment (600-800 mg/day) in reducing hostility, impulsivity, aggression, and rage reactions in four antisocial personality disorder inpatients in a maximum security services [133]. In another case series of 7 patients with ASPD and

high psychopathic traits a low dose of clozapine led to improvement in all symptom domains, in particular aggression, violence, impulsive-behavioural dyscontrol, and anger [134]. However, these preliminary findings have not been confirmed by controlled data.

Two meta-analyses of trials of pharmacological interventions for ASPD concluded that there was no clear indication for the use of pharmacotherapy in patients with ASPD [112, 135]. Thus, the NICE guidelines [112] recommended that drugs should be used only to treat comorbid mental disorders such as anxiety and depression, and not be used for the primary treatment of anger, aggression, impulsivity or other ASPD associated behaviours.

Findings of RCTs are summarized in Table 3.

Treatment of Cluster C personality disorders

With regard to cluster C personality disorders, we found no systematic investigations of drug treatment of patients satisfying criteria for any of these diagnostic categories. Nevertheless, antidepressants (SSRIs, SNRIs, and MAOIs) are indicated to treat the anxious, depressed, and phobic symptoms that are common in cluster C personality disorders [110].

Given that avoidant personality disorder (AvPD) often coexists with social phobia and the two disorders are considered only quantitatively different [136], it is therefore assumed that drugs applied to social phobia can also have a positive effect on traits of AvPD. Phenelzine led to decreased avoidant personality traits, anxiety, and social avoidance in subjects with social phobia [137]. In another study [138], the core features of AvPD such as shyness, distorted cognitions related to self-criticism, and rejection sensitivity improved after treatment with MAOis, SSRIs, and venlafaxine in a sample of patients with generalised social phobia half of whom met criteria for AvPD. In the same way, treatment guidelines for obsessive compulsive personality disorders are extrapolated from empirical research on OCD, based on some similarities of their clinical features [139, 140]. Preliminary data suggested that, like other OCD spectrum disorders, OCPD might respond to SSRIs [141]. However, these results have not been confirmed by controlled studies.

Discussion

We reviewed placebo-controlled studies published between 1990 and 2016, and concluded that systematic randomized controlled trials of medication effects existed only for borderline and schizotypal personality disorders, with controversial data for antisocial personality disorder and only indirect evidence with regard to pharmacotherapy for cluster C personality disorders.

The amount of efficacy studies on BPD made it possible to conduct 7 meta-analysis [115, 117-119, 120-122] which generated somewhat discordant results. The evidences indicated therapeutic benefits of mood stabilizers, such as topiramate, valproate, and lamotrigine in treating affective dysregulation, impulse dyscontrol, and anger. Quetiapine, aripiprazole, olanzapine and the neuroleptic haloperidol provided therapeutic effects on affective and impulsive dysregulation and the cognitive-perceptual distortion. In particular, paranoid ideation and suspiciousness were shown to benefit from treatment with these agents. Importantly, while some core features of BPD such as emotional dysregulation may benefit from pharmacotherapy, no individual drug led to such improvement of global symptoms that the patient no longer met criteria for the disorder [142]. Moreover, certain symptom domains, albeit being core symptoms, for instance interpersonal relationships, identity disturbances, self-injury and suicidal behaviours, and fear of abandonment, received little attention in psychopharmacological research. While the early guidelines proposed antidepressant, in particular SSRIs, as the primary treatment for some core symptoms of BPD due to their more favourable side-effect profile [6], the current evidence suggests that they are indicated only for the treatment of comorbid anxiety and depression.

Finally, new data emerge on therapeutic effects of some novel drugs, such as oxytocin, omega-3 fatty acids, and clonidine. However, their efficacy is yet to be confirmed and weighed against possible side-effects.

While pharmacotherapy for personality disorders should rely on robust evidence of lasting effects on the core symptoms of these disorders and the associated interpersonal functioning, the only convincing evidence supports the efficacy of pharmacotherapy in treatment of BPD. With regard to other personality disorders, limited findings of low-quality research are difficult to interpret and transfer into evidence-based practice.

With regard to cluster A personality disorders, no well-organised randomized controlled trials are available to conclude that pharmacotherapy is effective in treating these disorders. Although some studies demonstrated the efficacy of antipsychotics in treating psychotic-like symptoms, and dopamine and adrenaline agonists in improving cognitive performances, they are however difficult to interpret because STPD patients were included in these studies together with BPD subjects due to concurrence of psychotic symptoms [16,17,20]. An alternative explanation therefore can be that the improvement of BPD-related symptoms accounted for the clinical benefits reported in these heterogeneous groups of STPD patients. Furthermore, the high dropout rates due to pronounced sensitivity to side effects in this population, and the lack of sufficient statistical power to assess treatment efficacy hamper interpretations of the results. It has been suggested that differences in patients willingness to receive treatment may account for the variation between the amount of evidences of treatment efficacy for different personality disorders [143]. Thus, while BPD patients often present with demands to be treated, only 1 out of 10 patients with paranoid and schizoid personality disorder is prone to treatment, hence the large difference in research proportion for these disorders. It may be therefore useful to differentiate between treatment-seeking and treatment-resisting patients with personality disorders [143].

Although ASPD received some research attention to suggest that mood stabilizers, atypical antipsychotics, and antidepressants may have some effect on anxiety, impulsivity, and anger, respectively, none of the existing studies focused on core symptoms of ASPD without confounding comorbidity of substance and alcohol misuse, thereby demonstrating the impact of medication on substance use, rather than the risk of antisocial behaviors in the future [128, 144]. Moreover, findings are difficult to generalise to non-incarcerated individuals, as majority of these studies used prisoners with ASPD giving rise to issues of informed consent, incentives, and expectations linked to privileges. Although a few data suggest that specific symptoms of ASPD can benefit from drugs, the use of pharmacotherapy beyond controlled settings rises concerns with regard to low compliance and high risk for substance abuse typical of this group.

Evidence based practice for cluster C personality disorders currently relies on indirect evidence from research on Axis I disorders, such as social phobia and obsessive compulsive disorder (OCD), as no study included patients satisfying the full diagnostic criteria for any of the cluster C personality disorders. However, available data indicate that, although medications are able to improve OCD

symptoms, they have little effect on obsessive compulsive personality disorder (OCPD) cognitions and behaviours, and seem to be effective only if OCD is also present [139].

Despite controversies and uncertainties surrounding pharmacotherapy of personality disorders, a collaborative longitudinal personality disorder study [145] reported that medications are prescribed frequently, with 81% of patients with BPD, STPD, AvPD, or OCPD receiving psychotropic drugs. Moreover, Zanarini et al [55] reported that out of 78% of patients with BPD being on medications for 75% of the time over a 6-year period, 37% were on 3 or more medications. The NICE guidelines recommend that caution needs to be exercised in prescribing practices and evidence-based practice requires weighing potential benefits against risk of side-effects. For instance, antipsychotics are associated with neurological and metabolic side effects [146], whereas valproate may potentially be dangerous for women of childbearing age, which constitute a large proportion of BPD patients in clinical practice. A better knowledge of adverse effects of medications in populations with personality disorders, not obviously the same found in schizophrenia or bipolar disorder, is a fundamental goal of forthcoming investigations.

Conclusions

Results of our review concerning pharmacotherapy of personality disorders indicated that the overwhelming majority of available studies focused on patients with BPD. The accumulation of evidences in the last years resulted in 7 meta-analyses which have been interpreted into better strategies for evidence-based practice. Several sets of treatment guidelines for BPD have also been published since the first proposal presented by APA in 2001 [6]. Although different guidelines sometimes express discordant points of view about treatment strategies in BPD and recommendations are still uncomplete and partially questionable, these guidelines represent a fundamental tool to guide everyday practice of clinicians.

Concerning other personality disorders, some data are currently available but they are much more limited in number of studies and quality of research. RCTs on patients with STPD and ASPD are also significantly affected by continuum with psychotic disorders in the first case and comorbidity with

substance use disorders in the second case. Only indirect efficacy evidence has been obtained for OCPD and AvPD. Actually, the majority of data concerns effects on symptoms of OCD and social phobia, more than modifications of personality traits.

Future perspectives

Future investigations on drug treatment of personality disorders should provide more extensive and complete data on severe personality disorders and should focus on some relevant open questions:
- adverse effects of medication, in particular antipsychotics, should be registered and evaluated specifically in sample of patients with personality disorders;
- doses of each drug that allow to obtain a good level of efficacy with a low incidence of side effects should be systematically investigated and defined;
- effects of pharmacotherapy on acute phase of decompensation should be evaluated separately from effects on stable trait vulnerabilities;
- physiopathological mechanisms underlying trait vulnerabilities and symptom clusters of personality disorders should be studied with techniques of brain imaging. Changes of brain activity after drug treatment should be examined

Executive Summary

Introduction

Although a growing number of studies on treatment of personality disorders (PDs) have been performed in the last decades, pharmacotherapy of PDs is still relatively new and evolving. Randomized controlled trials (RCTs) are limited and the majority of them have focused on patients with borderline personality disorder (BPD). This review considered RCTs conducted in PDs between 1990 and 2016.

Treatment of Cluster A personality disorders

Four placebo-controlled studies have been published in schizotypal personality disorder (STPD). No RCTs are available for other cluster A personality disorders. Although some studies demonstrated the efficacy of antipsychotics in treating psychotic-like symptoms, and dopamine and adrenaline agonists in improving cognitive performances, they are difficult to interpret because of the high rate of drop-outs and the inadequate inclusion criteria.

Treatment of Cluster B personality disorders

Among Cluster B PDs, the available RCTs concern BPD and antisocial personality disorder (ASPD).

Pharmacotherapy for BPD

Antidepressants

The available evidence demonstrated some efficacy of SSRIs, in particular fluoxetine, in decreasing impulsivity and affective symptoms, such as depressed mood, anxiety, and anger. However, these results have been obtained in rather old studies and have not been replicated after 2010.

Mood stabilizers

Several RCTs including lithium, carbamazepine, valproate, topiramate, and lamotrigine have been performed in BPD patients. In particular valproate, topiramate, and lamotrigine provided initial evidence of efficacy for the treatment of affective symptoms related to anger and impulsive aggression.

Antipsychotics

a) Classical neuroleptics

Classical neuroleptics might be administered to BPD patients during acute states with anger and psychotic-like symptoms in low doses and for short periods because of common and debilitating adverse effects.

b) Second generation antipsychotics

Olanzapine has been the most thoroughly studied atypical antipsychotic in the treatment of BPD. This drug was found efficacious on affective symptoms, aggressiveness, and cognitive-perceptual symptoms. Further controlled investigations are needed to confirm the initial data on other drugs, such as aripiprazole, risperidone, ziprasidone, and quetiapine.

Other drugs

Data were collected on effects of some novel drugs, such as opioid antagonist, clonidine, omega-3 fatty acids, and oxytocine in reducing affective instability, impulsivity, self-injuries, and dissociative symptoms.

Treatment guidelines and meta-analyses

Findings from the most recent trials and reviews raised considerable questions on the initial guidelines recommendations to administer antidepressants for affective dysregulation and impulsive-behavioural dyscontrol. In fact, many authors retain that prescription of this class of drugs should be limited to cases with concomitant depression. On the contrary, the role of mood stabilizers, second generation antipsychotics, and new agents (e.g.omega-3 fatty acids) in the treatment of main symptom clusters of BPD is gradually increased in research and practice.

Pharmacotherapy for ASPD

The existing evidence is too limited to draw any conclusion on the treatment of this personality disorder. Results suggested that mood stabilizers, atypical antipsychotics, and antidepressants may have some effect on anxiety, impulsivity, and anger, respectively. None of the existing studies focused on core symptoms of ASPD without confounding comorbidity of substance and alcohol misuse.

Treatment of Cluster C personality disorders

Only indirect evidence has been obtained for obsessive compulsive personality disorder and avoidant personality disorder. To date, the majority of findings concerned the effects on symptoms of obsessive-compulsive disorder and social phobia, more than modifications of personality traits.

References

1. Cloninger C. A systematic method for clinical description and classification of personality variants. *Arch. Gen. Psych.* 44(6), 573-588 (1987).

2. Cloninger C. The temperament and character inventory-revised. A practical way to diagnosis personality disorder: a proposal. *J. Person. Disord.* 14(2), 99-108 (1999).

3. Cloninger CC, Svrakic DM, Przybeck T. A psychobiological model of temperament and character. *Arch. Gen. Psych.* 50(12), 975-990 (1993).

4. Siever LJ, Davis KL. A psychobiological perspective on the personality disorders. *Am. J. Psychiatry.* 148(12), 1647–1658 (1991).

5. Soloff PH. Algorithms for pharmacological treatment of personality dimensions: symptom specific treatments for cognitive perceptual, affective, and impulsive behavioral dysregulation. *Bull. Menninger. Clin.* 62(2), 195–214 (1998).

6. *American Psychiatric Association. Practice guideline for the treatment of patients with borderline personality disorder. *Am. J. Psychiatry* 158, 1–52 (2001).
    The first set of guidelines for treatment for borderline personality disorder with detailed recommendations for drug choice.

7. Linehan MM, Heard ML, Armstrong H. Naturalistic follow-up of a behavioral treatment for chronically parasuicidal borderline patients. *Arch. Gen. Psych.* 50(12), 971– 974 (1993).

8. Kendler KS. Kraepelin and the differential diagnosis of dementia praecox and manic-depressive insanity. *Compr. Psychiatry.* 27(6), 549-58 (1986).

9. Tyrer P, Bateman W. Drug treatment for personality disorders. *Adv. Psych. Treat.* 10(5), 389-398 (2004).

10. *Bellino S *et al.* Recent approaches to pharmacotherapy of personality disorders. *Neuropsych.* 1(3), 259–273 (2011).

    A recent and comprehensive review of trials of medications in personality disorders.

11. Ripoll LH, Triebwasser J, Siever LJ. Evidence-based pharmacotherapy for personality disorders. *Int. J. Neuropsychopharmacol.* 14(9), 1257–1288 (2011).

12. Battaglia M, Torgersen S. Schizotypal disorder: at the crossroads of genetics and nosology. *Acta. Psychiatr. Scand.* 94(5), 303–310 (1996).

13. Cadenhead KS, Light GA, Geyer MA, McDowell JE, Braff DL. Neurobiological measures of schizotypal personality disorder: defining an inhibitory endophenotype? *Am. J. Psychiatry.* 159(5), 869-871 (2002).

14. McClure MM, Romero MJ, Bowie CR, Reichenberg A, Harvey PD, Siever LJ. Visual-spatial learning and memory in schizotypal personality disorder: continued evidence for the importance of working memory in the schizophrenia spectrum. *Arch. Clin. Neuropsychol.* 22(1), 109–116 (2007).

15. Rosell DR, Zaluda LC, McClure MM. Effects of the D1 dopamine receptor agonist dihydrexidine (DAR-0100A) on working memory in schizotypal personality disorder. *Neuropsychopharmacol.* 40(2), 446-53 (2015).

16. Soloff PH, George A, Nathan S, Schulz PM, Ulrich RF, Perel JM. Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. *Psychopharmacol. Bull.* 22(1), 177–182 (1986).

17. Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorder treated with low-dose thiothixene vs placebo. *Arch. Gen. Psychiatry* 43(7), 680–686 (1986).

18. Keshavan M, Shad M, Soloff P, Schooler N. Efficacy and tolerability of olanzapine in the treatment of schizotypal personality disorder. *Schizophr. Res*. 71(1), 97-101 (2004).

19. Serban G, Siegel S. Response of borderline and schizotypal patients to small doses of thiothixene and haloperidol. *Am. J. Psychiatry* 141(11), 1455-1458 (1984).

20. Koenigsberg HW, Reynolds D, Goodman M, *et al.* Risperidone in the treatment of schizotypal personality disorder. *J. Clin. Psychiatry* 64(6), 628-634 (2003).

21. McClure MM, Koenigsberg HW, Reynolds D *et al.* The effects of risperidone on the cognitive performance of individuals with schizotypal personality disorder. *J. Clin. Psychopharmacol.* 29(4), 396–398 (2009).

22. McClure MM, Barch DM, Romero MJ *et al.* The effects of guanfacine on context processing abnormalities in schizotypal personality disorder. *Biol. Psychiatry*, 61(10), 1157–1160 (2007).

23. McClure MM, Harvey PD, Goodman M *et al.* Pergolide treatment of cognitive deficits associated with schizotypal personality disorder: continued evidence of the importance of the dopamine system in the schizophrenia spectrum. *Neuropsychopharmacol.* 35(6), 1356–1362 (2010).

24. *Stoffers JM, Lieb K. Pharmacotherapy for borderline personality disorder--current evidence and recent trends. *Curr. Psychiatry Rep.* 17(1), 534 (2015).
The recent update of the Cochrane review reporting evidences of efficacy of available drugs in borderline personality disorder

25. Markovitz P. Pharmacotherapy of impulsivity, aggression, and related disorders. In: *Impulsivity and Aggression.* Hollander E, Stein DJ (Eds). John Wiley & Sons, New York, NY, USA, 263–287 (1995).

26. Salzmann C, Wolfson AN, Schatzberg A *et al.* Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J. Clin. Psychopharmacol.* 15(1), 23–29 (1995).

27. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behaviour in personality disordered subjects. *Arch. Gen. Psychiatry* 54(12), 1081–1088 (1997).

28. Simpson EB, Yen S, Costello E *et al.* Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J. Clin. Psychiatry* 65(3), 379–385 (2004).

29. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary randomized trial of fluoxetine, olanzapine, and the olanzapine fluoxetine combination in women with borderline personality disorder. *J. Clin. Psychiatry* 65(7), 903–907 (2004).

30. Bellino S, Rinaldi C, Bogetto F. Adaptation of interpersonal psychotherapy to borderline personality disorder: a comparison of combined therapy and single pharmacotherapy. *Can. J. Psychiatry.* 55(2), 74-81 (2010).

31. Bozzatello P, Bellino S. Combined therapy with interpersonal psychotherapy adapted for borderline personality disorder: A two-years follow-up. *Psychiatry Res.* 240, 151-156 (2016).

32. 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* 159(12), 2048–2054 (2002).

33. Jariani M, Saaki M, Nazari H, Birjandi M. The effect of Olanzapine and Sertraline on personality disorder in patients with methadone maintenance therapy. *Psychiatr. Danub.* 22(4), 544-7 (2010).

34. Markovitz PJ, Wagner SC. Venlafaxine in the treatment of borderline personality disorder. *Psychopharmacol Bull.* 31(4), 773-7 (1995).

35. Bellino S, Paradiso E, Bozzatello P, Bogetto F. Efficacy and tolerability of duloxetine in the treatment of patients with borderline personality disorder: a pilot study. *J. Psychopharmacol.* 24(3), 333-9 (2010).

36. Links P, Steiner M, Boiago I, Irwin D. Lithium therapy for borderline patients: preliminary findings. *J. Personal. Disord.* 4(1), 173–181 (1990).

37. De la Fuente J, Lotstra F. A trial of carbamazepine in borderline personality disorder. Eur. *Neuropsychopharmacol.* 4(4), 479–486 (1994).

38. Hollander E, Allen A, Lopez RP *et al.* A preliminary double blind, placebo controlled trial of divalproex sodium in borderline personality disorder. *J. Clin. Psychiatry* 62(3), 199–203 (2001).

39. Hollander E, Tracy KA, Swann AC *et al.* Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacol.* 28(6), 1186–1197 (2003).

40. Hollander E, Swann AC, Coccaro EF *et al.* Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am. J. Psychiatry* 162(3), 621–624 (2005).

41. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double blind placebo controlled pilot study. *J. Clin. Psychiatry* 63(5), 442–446 (2002).

42. Moen R, Freitag M, Miller M *et al.* Efficacy of extended-release divalproex combined with "condensed" dialectical behavior therapy for individuals with borderline personality disorder. *Ann. Clin. Psychiatry* 24(4), 255-60 (2012).

43. Nickel MK, Nickel C, Mitterlehner FO *et al.* Topiramate treatment of aggression in female borderline personality disorder patients: a double blind, placebo controlled study. *J. Clin. Psychiatry* 65(11), 1515–1519 (2004).

44. Nickel MK, Nickel C, Kaplan P *et al.* Treatment of aggression with topiramate in male borderline patients: a double blind, placebo controlled study. *Biol. Psychiatry.* 57(5), 495–499 (2005).

45. Nickel MK. Topiramate treatment of aggression in male borderline patients. *Aust. NZ J. Psychiatry* 41(5), 461–462 (2007).

46. Nickel M. Topiramate reduced aggression in female patients with borderline personality disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* 257(7), 432–433 (2007).

47. Nickel MK, Loew TH. Treatment of aggression with topiramate in male borderline patients, part II: 18 month follow up. *Eur. Psychiatry* 23(2), 115–117 (2008).

48. Loew TH, Nickel MK, Muehlbacher M *et al.* Topiramate treatment for women with borderline personality disorder: a double blind, placebo controlled study. *J. Clin. Psychopharmacol.* 26(1), 61–66 (2006).

49. Tritt K, Nickel C, Lahmann C *et al.* Lamotrigine treatment of aggression in female borderline patients: a randomized, double blind, placebo controlled study. *J. Psychopharmacol.* 19(3), 287–291 (2005).

50. Reich DB, Zanarini MC, Bieri KA. A preliminary study of lamotrigine in the treatment of affective instability in borderline personality disorder. *Int. Clin. Psychopharmacol.* 24(5), 270–275 (2009).

51. Leiberich P, Nickel MK, Tritt K, Pedrosa Gil F. Lamotrigine treatment of aggression in female borderline patients, part II: an 18 month follow up. *J. Psychopharmacol.* 22(7), 805–808 (2008).

52. Crawford MJ, Sanatinia R, Barrett B *et al.* Lamotrigine versus inert placebo in the treatment of borderline personality disorder: study protocol for a randomized controlled trial and economic evaluation. *Trials.* 18,16-308 (2015).

53. Montgomery SA, Montgomery D. Pharmacological prevention of suicidal behaviour. *J. Affect.Disord.* 4(4), 291–298 (1982).

54. Leone NF. Response of borderline patients to loxapine and chlorpromazine. *J. Clin. Psychiatry* 43(4), 148–150 (1982).

55. Soloff PH, George A, Nathan S *et al.* Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J. Clin. Psychopharmacol.* 9(4), 238–246 (1989).

56. Soloff PH. Psychopharmacology of borderline personality disorder. Psychiatr. *Clin. North Am.* 23(1), 169–192 (2000).

57. Goldberg SC, Schulz SC, Schulz PM, Resnick RJ, Hamer RM, Friedel RO. Borderline and schizotypal personality disorder treated with low dose thiothixene vs placebo. *Arch. Gen. Psychiatry* 43(7), 680–686 (1986).

58. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch. Gen. Psychiatry* 45(2), 111–119 (1988).

59. Soloff PH, George A, Nathan S *et al.* Progress in pharmacotherapy of borderline disorders. A double blind study of amitriptyline, haloperidol, and placebo. *Arch.Gen.Psychiatry* 43(7), 691–697 (1986).

60. Soloff PH, Cornelius J, George A, Nathan S, Perel JM, Ulrich RF. Efficacy of phenelzine and haloperidol in borderline personality disorder. *Arch.Gen. Psychiatry* 50(5), 377–385 (1993).

61. Cornelius JR, Soloff PH, Perel JM, Ulrich RF. Continuation pharmacotherapy of borderline personality disorder with haloperidol and phenelzine. *Am. J. Psychiatry* 150(12), 1843–1848 (1993).

62. Chengappa KN, Ebeling T, Kang JS, Levine J, Parepally H. Clozapine reduces severe self-mutilation and aggression in psychotic patients with borderline personality disorder. *J. Clin. Psychiatry* 60(7), 477–484 (1999).

63. Frankenburg FR, Zanarini MC. Clozapine treatment of borderline patients: a preliminary study. *Compr. Psychiatry.* 34(6), 402–405 (1993).

64. Benedetti F, Sforzini L, Colombo C, Maffei C, Smeraldi E. Low-dose clozapine in acute and continuation treatment of severe borderline personality disorder. *J. Clin. Psychiatry*. 59(3), 103–107 (1998).

65. Parker GF. Clozapine and borderline personality disorder. *Psychiatr Serv.* 53(3), 348-9 (2002).

66. Bellino S, Bozzatello P, Rinaldi C, Bogetto F. Paliperidone ER in the treatment of borderline personality disorder: a pilot study of efficacy and tolerability. *Depress. Res. Treat.* (2011) DOI: 10.1155/2011/680194.

67. Palomares N, Montes A, Díaz-Marsá M, Carrasco JL. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. *Int. Clin. Psychopharmacol.* 30(6), 338-41 (2015).

68. Martín-Blanco A, Patrizi B, Villalta L, Gasol X, Soler J, Gasol M, Pascual JC. Asenapine in the treatment of borderline personality disorder: an atypical antipsychotic alternative. *Int. Clin. Psychopharmacol.* 29(2),120-3 (2014).

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

70. Friedel RO, Jackson WT, Huston CS, May RS, Kirby NL, Stoves A. Risperidone treatment of borderline personality disorder assessed by a borderline personality disorder-specific outcome measure: a pilot study. *J. Clin. Psychopharmacol.* 28(3), 345-7 (2008).

71. Díaz-Marsá M, Galian M, Montes A, *et al.* [Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report]. *Actas. Esp. Psiquiat*r. 36(2), 70-4 (2008).

72. Carrasco JL, Palomares N, Marsá MD. Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. *Psychopharmacol*. 224(2), 347-8 (2012).

73. Schulz SC, Camlin KL, Barry S, Friedman L. Risperidone for borderline personality disorder: A doble-blind study. Presented at: *American College of Neuropsychopharmacology, 37th Annual Meeting,* December 14-18 (1998).

74. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double blind, placebo controlled pilot study. *J. Clin. Psychiatry* 62(11), 849–854 (2001).

75. Bogenschutz MP, Nurnberg GH.l Olanzapine versus placebo in the treatment of borderline personality disorder. *J. Clin. Psychiatry* 65(1), 104–109 (2004).

76. Schulz SC, Zanarini MC, Bateman A *et al.* Olanzapine for the treatment of borderline personality disorder: variable dose, 12 week, randomised double blind placebo controlled study. *Br. J. Psychiatry* 193(6), 485–492 (2008).

77. Zanarini MC, Schulz SC, Detke HC, *et al.* A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry.* 72(10), 1353-62 (2011).

78. Soler J, Pascual JC, Barrachina J *et al.* Double blind, placebo controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am. J. Psychiatry* 162(6), 1221–1224 (2005).

79. Linehan MM, McDavid JD, Brown MZ, Sayrs JHR, Gallop RJ. 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* 69(9), 999–1005 (2008).

80. Shafti SS, Shahveisi B. Olanzapine versus haloperidol in the management of borderline personality disorder: a randomized double blind trial. *J. Clin. Psychopharmacol.* 30(1), 44–47 (2010).

81. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of aripiprazole augmentation in sertraline-resistant patients with borderline personality disorder. *Psychiatry Res.* 161(2), 206-12 (2008).

82. Geoffroy PA, Rolland B, Guardia D, Warembourg F, Cottencin O. Use of aripiprazole in treatment of cannabis dependence in a patient presenting with Borderline Personality Disorder. *J. Neuropsychiatry Clin. Neurosci.* 24(2), E37 (2012).

83. Nickel MK, Muehlbacher M, Nickel C *et al.* Aripiprazole in the treatment of patients with borderline personality disorder: a double blind, placebo controlled study. *Am. J. Psychiatry* 163 (5), 833–838 (2006).

84. Nickel MK, Loew TH, Pedrosa Gil F. Aripiprazole in treatment of borderline patients, part II: an 18 month follow up. *Psychopharmacol.* 191(4), 1023–1026 (2007).

85. Pascual JC, Soler J, Puigdemont D *et al.* Ziprasidone in the treatment of borderline personality disorder: a double blind, placebo controlled, randomized study. *J. Clin.Psychiatry* 69(4), 603–608 (2008).

86. Pascual JC, Madre M, Soler J, *et al.* Injectable atypical antipsychotics for agitation in borderline personality disorder. *Pharmacopsych.* 39(3), 117-8 (2006).

87. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of quetiapine in the treatment of borderline personality disorder: A pilot study. *J. Clin. Psychiatry.* 67(7), 1042-6 (2006).

88. Adityanjee, Romine A, Brown E, Thuras P, Lee S, Schulz SC. Quetiapine in patients with borderline personality disorder: an open-label trial. *Ann. Clin. Psychiatry.* 20(4), 219-26 (2008).

89. Roepke S, Merkl A, Dams A, *et al*. Preliminary evidence of improvement of depressive symptoms but not impulsivity in cluster B personality disorder patients treated with quetiapine: an open label trial. *Pharmacopsychiatry.* 41(5), 176-81 (2008).

90. Van den Eynde F, Senturk V, Naudts K, *et al.* Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. *J. Clin. Psychopharmacol.* 28(2), 147-55 (2008).

91. Van den Eynde F, De Saedeleer S, Naudts K, *et al.* Quetiapine treatment and improved cognitive functioning in borderline personality disorder. *Hum. Psychopharmacol.* 24(8), 646-9 (2009).

92. Podobnik J, Foller Podobnik I, Grgic N, Marcinko D, Pivac N. The effect of add-on treatment with quetiapine on measures of depression, aggression, irritability and suicidal tendencies in children and adolescents. *Psychopharmacology.* 220(3), 639-41 (2012).

93. Black DW, Zanarini MC, Romine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *Am. J. Psychiatry.* 171(11), 1174-82 (2014).

94. Lee SS, Allen J, Black DW, Zanarini MC, Schulz SC. Quetiapine's effect on the SCL-90-R domains in patients with borderline personality disorder. *Ann. Clin. Psychiatry.* 28(1), 4-10 (2016).

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

96. Schmahl C, Kleindienst N, Limberger M, *et al.* Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *Int. Clin. Psychopharmacol.* 27(1), 61-8 (2012).

97. Philipsen A, Richter H, Schmahl C, *et al.* Clonidine in acute aversive inner tension and self-injurious behavior in female patients with borderline personality disorder. *J. Clin. Psychiatry.* 65(10), 1414-9 (2004).

98. Ziegenhorn AA, Roepke S, Schommer NC, *et al.* Clonidine improves hyperarousal in borderline personality disorder with or without comorbid posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychopharmacol.* 29(2), 170-3 (2009).

99. Zanarini MC, Frankenburg FR. Omega 3 fatty acid treatment of women with borderline personality disorder: a double blind, placebo controlled pilot study. *Am. J. Psychiatry* 160(1), 167–169 (2003).

100. Hallahan B, Hibblen JR, Davis JM, Garland MR. Omega 3 fatty acid supplementation in patients with recurrent self harm: single center double blind randomized controlled trial. *Br. J. Psychiatry* 190, 118–122 (2007).

101. Amminger GP, Chanen AM, Ohmann S, *et al.* Omega-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: a post hoc subgroup analysis of a double-blind, randomized controlled trial. *Can. J. Psychiatry.* 58(7), 402-8 (2013).

102. Bellino S, Bozzatello P, Rocca G, Bogetto F. Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of the association with valproic acid. *J. Psychopharmacol.* 28(2), 125-32 (2014).

103. Simeon D, Bartz J, Hamilton H, *et al.* Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study. *Psychoneuroendocrinol.* 36(9), 1418-21 (2011).

104. Bertsch K, Gamer M, Schmidt B, *et al.* Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *Am. J. Psychiatry.* 170(10), 1169-77 (2013).

105. Brüne M, Ebert A, Kolb M, Tas C, Edel MA, Roser P. Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder. *Hum. Psychopharmacol.* 28(6), 552-61 (2013).

106. Brüne M, Kolb M, Ebert A, Roser P, Edel MA. Nonverbal communication of patients with borderline personality disorder during clinical interviews: a double-blind placebo-controlled study using intranasal oxytocin. *J. Nerv. Ment. Dis.* 203(2), 107-11 (2015).

107. Ebert A, Kolb M, Heller J, Edel MA, Roser P, Brüne M. Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. *Soc. Neurosci.* 8(4), 305-13 (2013).

108. Bartz J, Simeon D, Hamilton H, *et al.* Oxytocin can hinder trust and cooperation in borderline personality disorder. *Soc. Cogn. Affect. Neurosci.* 6(5), 556-63 (2011).

109. Oldham JM. Guideline watch: practice guideline for the treatment of patients with borderline personality disorder. Presented at: *American Psychiatric Association.* Arlington, VA, USA 21–26 May (2005).

110. *Herpertz SC, Zanarini M, Schulz CS, Siever L, Lieb K, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP). Guidelines for biological treatment of personality disorders. *World J. Biol.* Psychiatry Recent guidelines on pharmacotherapy of schizotypal, borderline and anxious personality disorders. 8(4), 212 244 (2007).
Guidelines for treatment of personality disorders provided by the World Federation of Societies of Biological Psychiatry, with particular attention to indications and contributions of pharmacotherapy

111. *NHS National Institute for Health and Clinical Excellence (NICE): Borderline personality disorder: treatment and management. Recent guidelines on general management of borderline personality disorder. www.guidance.nice.org.uk/CG78

112. *NHS National Institute for Health and Clinical Excellence (NICE): Antisocial personality disorder: treatment and management. www.guidance.nice.org.uk/CG77.
The NICE guidelines for treatment for borderline and antisocial personality disorders, representing the British point of view on treatment of personality disorders with a more cautious and limited use of medications.

113. National Health and Medical Research Council (NHMRC) – Australian Government - Clinical Practice Guideline for the Management of Borderline Personality Disorder (2012). https://www.nhmrc.gov.au/guidelines-publications/mh25

114. Binks C, Fenton M, McCarthy L, Lee T, Adams CE, Duggan C. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database Syst. Rev.* 1, CD005653 (2006).

115. Nosè M, Cipriani A, Biancosino B, Grassi L, Barbui C. Efficacy of pharmacotherapy against core traits of borderline personality disorder: meta analysis of randomized controlled trials. *Int. Clin. Psychopharmacol.* 21(6), 345–353 (2006).

116. Abraham PF, Calabrese JR. Evidenced¬based pharmacologic treatment of borderline personality disorder: a shift from SSRIs to anticonvulsants and atypical antipsychotics? *J. Affect. Disord.* 111(1), 21–30 (2008).

117. Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. *J. Pers. Disord.* 23(2), 156–174 (2009).

118. 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* 71(1), 14–25 (2010).

119. *Ingenhoven TJ, Duivenvoorden HJ. Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. *J. Clin. Psychopharmacol.* 31(4), 489-96 (2011).

120. *Vita A, De Peri L, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. *J. Clin. Psychopharmacol*. 31(5), 613-24 (2011).
The two most recent meta-analyses of trial of medications in patients with borderline personality disorder

121. Saunders EFH, Silk KR. Personality trait dimensions and the pharmacological treatment of borderline personality disorder. *J. Clin. Psychopharmacol.* 29(5), 461–467 (2009).

122. Bakermans-Kranenburg MJ, van I Jzendoorn MH. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Transl. Psychiatry.* 3, 258 (2013).

123. Willems AE, Tenback DE, Ingenhoven TJ, van Harten PN. Acute movement disorders associated with the use of second-generation antipsychotics in borderline personality disorder: a meta-analysis. *J. Clin. Psychopharmacol.* 34(4), 520-2 (2014).

124. Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. *Cochrane Database Syst. Rev.* 16(6), CD005653 (2010). Recent review of randomized controlled trials of pharmacological treatment of borderline personality disorder.

125. Klaus Lieb, Birgit Völlm, Gerta Rücker, Antje Timmer, Jutta M. Stoffers Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *British J. Psychiatry.* 196(1), 4-12 (2009).

126. Leal J, Ziedonis D, Kosten T. Antisocial personality disorder as a prognostic factor for pharmacotherapy of cocaine dependence. *Drug Alcohol Depend.* 35(1), 31–35 (1994).

127. Arndt IO, McClellan AT, Dorozynsky L, Woody GE, O'Brien CP. Desipramine treatment for cocaine dependence: role of antisocial personality disorder. *J. Nerv. Ment. Dis.* 182(3), 151–156 (1994).

128. Powell BJ, Campbell JL, Landon JF *et al.* A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcohol. Clin. Exp. Res.* 19(2), 462–468 (1995).

129. Barratt ES, Stanford MS, Felthous AR, Kent TA. The effects of phenytoin on impulsive and premeditated aggression: a controlled study. *J. Clin. Psychopharmacol.* 17(5), 341–349 (1997).

130. Stanford MS, Helfritz LE, Conklin SM *et al.* A comparison of anticonvulsants in the treatment of impulsive aggression. *Exp. Clin. Psychopharmacol.* 13(1), 72–77 (2005).

131. Hollander E, Tracy KA, Swann AC *et al.* Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacol.* 28(6), 1186–1897 (2003).

132. Ralevski E, Ball S, Nich C, Limoncelli D, Petrakis I. The impact of personality disorders on alcohol-use outcomes in a pharmacotherapy trial for alcohol dependence and comorbid Axis I disorders. *Am. J. Addict.* 16(6), 443–449 (2007).

133. Walker,C,Thomas, J. & Allen,T. S. Treating impulsivity, irritability, and aggression of antisocial personality disorder with quetiapine. Internation. *J. Offend. Therapy Comparat. Criminol.* 47(2), 556-567 (2003).

134. Brown, D, *et al.* Clozapine: An Effective Treatment for Seriously Violent and Psychopathic Men With Antisocial Personality Disorder in a UK High-Security Hospital. *CNS Spectr.* 19(5), 391-402 (2014).

135. Khalifa N, Duggan C, Stoffers J, *et al.* Pharmacological interventions for antisocial personality disorder. *Cochrane Database Syst. Rev.* 8 (2010).

136. Reich J. The relationship of social phobia to avoidant personality disorder: A proposal to reclassify avoidant personality disorder based on clinical empirical findings. *European Psychiatry* 15(3):151–159 (2000).

137. Liebowitz MR, Gelenberg AJ, Munjack D. Venlafaxine extended release vs. placebo and paroxetine in social anxiety disorder. *Arch. Gen. Psychiatry* 62(2), 190–198 (2005).

138. Allgulander C. Paroxetine in social anxiety disorder :a randomized placebo-controlled study. *Acta Psych. Scandin.* 100(3), 193–198 (1999).

139. Ansseau M, Troisfontaines B, Papart P, *et al.* Compulsive personality as predictor of response to serotoninergic antidepressants. *BMJ.* 303(6805), 760 -761 (1991).

140. O'Donohue W. Identifying and treating psychological factors in medical settings: The example of borderline personality disorder *J Nurs Manag.* 15(5):547-555 (2007).

141. Stein DJ, Spadaccini E, Hollander H. Meta-analysis of pharmacotherapy trials for obsessive-compulsive disorder. *Intern. Clin. Psychopharmacol.* 10(1), 11–18 (1995).

142. Silk KR, Jibons MD. Personality disorders. In: *The evidence-based guide to antidepressant medication (pp. 139-69).* Rothchild A (Ed.) Washington, DC: American Psychiatric Publishing (2012).

143. Tyrer P, Mitchard S, Methuen C, *et al.* Treatment rejecting and treatment-seeking personality disorders: Type R and Type S. *J. Pers. Disord.* 17(3), 265–270 (2003).

144. Leal J, Ziedonis D, Kosten T. Antisocial personality disorder as a prognostic factor for pharmacotherapy of cocaine dependence. *Drug Alcohol Depend.* 35(1), 31-35 (1994)

145. Bender DS, Dolan RT, Skodol AE, *et al.* Treatment utilization by patients with personality disorders. *Am. J. Psych.* 158(2), 295–302 (2001).

146. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of pharmacotherapies for borderline personality disorder. *CNS Drugs* 22(8), 671–692 (2008).