The Efficacy of Pharmacotherapy for Borderline Personality Disorder: A Review of the Available Randomized Controlled Trials

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ABSTRACT
Although there are no medications approved by the US Food and Drug Administration for the treatment of borderline personality disorder (BPD), polypharmacy is commonly encountered in individuals with BPD. This review summarizes the results of randomized controlled trials on the efficacy of pharmacologic agents in BPD. Pharmacotherapy in BPD is an adjunctive treatment aimed at stabilizing symptoms and behavior in a crisis situation, and it should be avoided whenever possible. Further studies are needed, including large, randomized controlled trials with long-term follow up, to examine the efficacy of psychiatric medications in patients with BPD. [Psychiatr Ann. 2015;45(8):431-437.]

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Borderline personality disorder (BPD) is present in about 6% of primary care patients and in 15% to 20% of patients in psychiatric hospitals and outpatient clinics. BPD affects men and women equally, and is associated with increased medical and psychiatric use and health care expenses. Although there are no medications approved by the US Food and Drug Administration (FDA) for the treatment of BPD, polypharmacy is a common occurrence in patients with BPD. Approximately 80% of patients with the disorder take medications regularly, and more than 40% take three or more medications daily. This review summarizes results of randomized controlled trials (RCTs) on the efficacy of pharmacologic agents that have been studied in BPD. Results from open trials, case reports, case series, and RCTs rejected from the 2010 Cochrane review were not used. Studies were identified from searches up to December 2014 in PubMed and Medline.

ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors

Salzman et al. described the results of a 13-week, double-blind, placebo-controlled study of the effects of fluoxetine on anger in patients with BPD or BPD traits. Thirteen patients received fluoxetine and nine received placebo. All patients began with a single 20-mg capsule or identical placebo, and doses were titrated up to a maximum of 60 mg/day. The authors found a reduction in anger among the fluoxetine recipients but no reduction in depression.

In 2004, the therapeutic effect of fluoxetine added to dialectical behavior therapy (DBT) for the treatment of BPD was examined by Simpson et al. in a 12-week, randomized, double-blind, placebo-controlled study. Of the 20 patients that completed treatment, 9 were randomly assigned to receive up to 40 mg/day of fluoxetine and 11 were randomly assigned to placebo. The result showed no significant group differences in scores from pretreatment to posttreatment on any measure.

Sertraline was more effective in decreasing symptoms of depression, hypersensitivity in interpersonal relationships, and obsession.

Rinne et al. conducted a double-blind, placebo-controlled, randomized trial of fluvoxamine (mean dose 150 mg/day) for 6 weeks followed by a blind half-crossover for 6 weeks and an open follow-up for another 12 weeks in 38 women with BPD. Fluvoxamine improved rapid mood shifts (standardized mean changes [SMD], -0.646) but not impulsivity and aggression.

Jariani et al. compared sertraline (50-100 mg/day) to olanzapine (5-10 mg/day) for the treatment of BPD in 120 patients on methadone maintenance therapy for heroin dependence who were also diagnosed as having BPD. The results (evaluation of Symptom Checklist-90 [SCL-90] questionnaire before treatment and in the 4th, 8th, and 12th weeks of treatment) indicated that both drugs could generally ameliorate depression, anxiety, hypersensitivity in interpersonal relationships, aggression, obsession, and somatization symptoms in a 12-week treatment. Sertraline was more effective in decreasing symptoms of depression, hypersensitivity in interpersonal relationships, and obsession. Olanzapine was more useful for anxiety, aggression, and paranoia symptoms. There was no difference in decreasing somatization symptoms between both drugs. In regard to self-mutilation, there was a significant difference in the olanzapine group.

Tricyclic Antidepressants

Soloff et al. described a 5-week, double-blind, placebo-controlled study of amitriptyline and haloperidol in 90 BPD inpatients. They found a significant effect for depression (SMD, -0.596) with amitriptyline, at a mean dose of 149 mg/day.

Monoamine Oxidase Inhibitors

Soloff et al. examined the data collected in a 5-week, double-blind, placebo-controlled trial of phenelzine (average dose, 60 mg/day), haloperidol, or placebo for atypical depression in 108 inpatients with BPD. Three-way comparisons between groups indicated superior efficacy for phenelzine on measures of depression, borderline psychopathologic symptoms, and anxiety. Pair-wise comparisons between medication and placebo revealed significant efficacy for phenelzine against anger and hostility but no efficacy against atypical depression.

Mianserin

In 1983, Montgomery et al. compared 30 mg/day of mianserin to placebo in a 6-month, RCT of 38 individuals with a personality disorder and a history of a suicidal act causing hospitalization. They found no significant difference in outcome between the groups. (Please note that mianserin is not approved by the FDA for use in the United States; its analogue is mirtazapine.)

Summary of Antidepressants

Few antidepressants have been studied in BPD. There seems to be a benefit for tricyclic antidepressants (TCAs) in the reduction of depressive
pathology. No statistically significant effects were observed for the selective serotonin reuptake inhibitors (SSRIs), phenelzine, and mianserin.

MOOD STABILIZERS

Carbamazepine

In a double-blind, parallel, placebo-controlled trial involving 20 hospitalized BPD patients, De la Fuente and Lotstra reported no significant positive effects from carbamazepine.

Divalproex Sodium

Divalproex sodium has been tested in three small RCTs. In the first, Hollander et al. conducted a 10-week, parallel, double-blind study comparing divalproex sodium to placebo in 16 outpatients with BPD. Only six patients completed the study. Five of the six completers were considered to be responders, as defined by a Clinical Global Impressions (CGI)-I score of 1 or 2 at endpoint.

In the second investigation, Frankenburg and Zanarini studied 30 women with BPD in a 6-month, placebo-controlled, double-blind trial comparing divalproex sodium to placebo. Divalproex sodium proved to be superior to placebo in diminishing interpersonal sensitivity (SMD, -1.046) and anger/hostility as measured by the SCL-90, as well as overall aggression as measured by the modified Overt Aggression Scale.

In a study by Moen et al., 17 of 31 patients with BPD received 4 weeks of “condensed DBT,” and then those patients with SCL-90 scores higher than 150 after this treatment were randomly and blindly assigned to placebo or divalproex extended-release for 12 weeks. There were no significant differences between the participants assigned to divalproex extended-release compared with placebo.

Lamotrigine

Reich et al. studied 28 patients with BPD in a 12-week, double-blind, placebo-controlled study of lamotrigine. Patients in the lamotrigine group had significantly greater reductions of affective instability and impulsivity.

A study by Tritt et al. compared the efficacy of lamotrigine versus placebo in the treatment of aggression in women with BPD. In comparison with the placebo group, significant changes on anger (SMD, -1.696) were observed after 8 weeks in those patients treated with lamotrigine.

Topiramate

Topiramate was evaluated in three RCTs by the same group of researchers. First, Nickel et al. examined the effect of topiramate on aggression in 29 women with BPD. Significant improvements on four subscales of the STAXI (state-anger, trait-anger, anger-out, anger-control) were observed in the topiramate-treated individuals after 8 weeks in comparison with the placebo group.

A similar RCT by Nickel et al. this one with 42 male outpatients, also found significant changes on anger.

An RCT by Loew et al. aimed to determine whether topiramate could influence borderline psychopathology, health-related quality of life, and interpersonal problems in 58 women with BPD. Topiramate was found to reduce psychiatric symptoms (SMD, -1.196), anxiety (SMD, -1.406), anger (SMD, -3.006), and interpersonal difficulties (SMD, -0.916), and to improve health-related quality of life at 8 and 10 weeks.

Summary of Mood Stabilizers

RCTs involving the mood stabilizers were limited by low statistical power. Divalproex sodium shows an effect for anger and interpersonal sensitivity. Topiramate and lamotrigine were found to have an effect on anger. No statistically significant effects were found for carbamazepine.

ANTIPSYCHOTICS

Loxapine versus Chlorpromazine

Leone studied 80 outpatients with BPD in a 6-week, double-blind study of loxapine (mean average dose 14.5 mg/day) and chlorpromazine (mean average dose 110 mg/day). The outcomes measured were BPD severity, affective instability using the Profile of Mood State scale, psychotic symptoms using the Brief Psychiatric Rating Scale, and mental health status using the CGI and the Systematic Nurses’ Observation of Psychopathology. The author reported both groups improved significantly from baseline, and the individuals prescribed loxapine improved significantly more than the individuals prescribed chlorpromazine in several symptom areas, particularly depression and anger/hostility.

Flupenthixol

Flupenthixol (which is not approved by the FDA for use in the United States) given as depot injections was found to significantly reduce the number of suicide attempts compared to placebo after 4 months and for the remainder of a 6-month RCT of patients with personality disorders (23 of the 30 completers had BPD).

Thiothixene

In a study by Goldberg et al., 50 outpatients with borderline and/or schizotypal personality disorder were randomly allocated to thiothixene or placebo treatment that was continued for 12 weeks (after 1 week of placebo washout). The mean daily dose of thiothixene in the final week of the study was 8.7 mg. Significant drug-placebo
differences were found for psychotic symptoms but not for depression.

**Haloperidol**

Soloff et al.²⁶,²⁷ published a study of haloperidol in two active drug versus active comparator drug trials. The first one was a 5-week (after 1-week washout) double-blind, placebo-controlled study of amitriptyline and haloperidol in 90 symptomatic BPD inpatients. Haloperidol (average dose 5 mg/day) produced significant improvement over placebo in global functioning, depression, hostility, schizotypal symptoms, and impulsive behavior. (For the Amitriptyline findings from this study, please refer to the discussion of TCAs earlier in the article.) In the second 5-week (after 1-week washout), double-blind, placebo-controlled study, the authors compared the efficacy of haloperidol (average dose 4 mg/day) to phenelzine and placebo against the affective, cognitive, and impulsive-aggressive symptoms of 108 BPD inpatients. The results indicated a tendency for patients receiving haloperidol to suffer less from interpersonal problems as compared to patients receiving phenelzine sulfate. (For the phenelzine findings from this study, please refer to the discussion of monoamine oxidase inhibitors earlier in the article.)

**Aripiprazole**

An RCT by Nickel et al.²⁸ of 52 subjects (43 women and 9 men) with BPD found a large effect of aripiprazole, 15 mg/day for 8 weeks, for depression (SMD, -1.256), interpersonal problems (SMD, -0.77), impulsivity (SMD, -1.846), anger (SMD, 1.146), and paranoid thinking (SMD, -1.056), and a moderate effect for anxiety (SMD, -0.736).

**Ziprazidone**

Pascual et al.²⁹ examined 60 adult patients with BPD in a 12-week, single-center, double-blind, placebo-controlled study of ziprasidone (mean daily dose 84 mg). The CGI scale for use in BPD patients was the primary outcome measure, and other scales and self-reports related to affect, behavior, psychosis, general psychopathology domains, and clinical safety were also included. No statistically significant differences were found between ziprasidone and placebo.

The difference between the moderate-dosage quetiapine group and the placebo group was not statistically significant.

**Quetiapine**

In a recent 8-week RCT comparing low (150 mg/day) and moderate (300 mg/day) dosages of extended-release quetiapine to placebo in 95 adults with BPD, Black et al.³⁰ found that participants treated with 150 mg/day of quetiapine had a significant reduction in the severity of the following BPD symptoms: interpersonal, affectivity, and anger and cognition problems. The effect size was -0.79 for the primary outcome measure (the Zanarini scale total score). No significant effects were found for impulsivity, depression, and general psychopathology. The difference between the moderate-dosage quetiapine group and the placebo group was not statistically significant (d = 20.41, P = .265).

**Olanzapine**

Olanzapine’s effect on BPD has been studied in nine RCTs. Six of these studies compared olanzapine to placebo. These studies are Bogen- schutz and Nurnberg³¹ (n = 40); Linehan et al.³² (olanzapine was added to psychotherapy, n = 24); Schulz et al.³³ (n = 314); Soler et al.³⁴ (all patients were in DBT, n = 60); Zanarini and Frankenberg³⁵ (n = 28); and Eli Lilly³⁶ (n = 301). Of the remaining three studies, one compared olanzapine to haloperidol (Shafti and Shahveisi,³⁷ n = 28); one compared olanzapine to sertraline (Jariani et al.³⁸ n = 120 [all patients were on methadone maintenance therapy]); and one with three different arms of treatment³⁹ compared olanzapine to fluoxetine (n = 30), then olanzapine to olanzapine plus fluoxetine (n = 31), and finally fluoxetine to fluoxetine and olanzapine (n = 29). The intervention times ranged from 12 weeks to 6 months. The trials by Zanarini and colleagues³³,³⁵,³⁸ were supported in part by a grant from Eli Lilly (Indianapolis, IN), the maker of olanzapine.

Regarding the trials of olanzapine versus placebo, significant decreases in affective instability, anger, psychotic paranoid symptoms, and anxiety were found. Of note, two studies³¹,³³ of olanzapine-treated groups had a significantly lower degree of amelioration of recurrent suicidal ideation as compared to the placebo groups. No significant differences were found in the comparison of olanzapine with fluoxetine and olanzapine with haloperidol for any pathology-related outcome. In the study by Jariani et al.,³⁸ olanzapine was more useful for anxiety, aggression, paranoia symptoms, and self-mutilation. There were no significant differences indicating any benefits from combined treatment versus treatment with olanzapine or fluoxetine alone.

**Summary of Antipsychotics**

Olanzapine has the most supporting data of the antipsychotics; studies have shown its use can lead to reductions in anger, paranoia, anxiety, and interpersonal sensitivity. Effects were found for aripiprazole on impulsivity, anger, anxiety, psychosis, and interpersonal differences.
problems. No significant effect was found for ziprazidone. Regarding the typical antipsychotics, statistically significant effects were found for haloperidol on anger and for flupenthixol on suicidal behavior.

MISCELLANOUS
Omega-3 Fatty Acids
Zanarini and Frankenburg conducted an 8-week, placebo-controlled, double-blind study to compare the efficacy of ethyl-eicosapentaenoic acid (EPA) at a dose of 1 g/day versus placebo in 30 women with BPD. The results showed there was a significant effect of ethyl-EPA in reducing aggressive behaviors and depressive symptoms (SMD, -0.346). A 12-week RCT by Hallahan et al. included 35 patients with BPD and found there was a significant improvement of depressive symptoms, suicidality, and reaction to daily stresses in the group using EPA (1.2 g/day) and docosahexaenoic acid (DHA, 0.9 g/day) in addition to standard psychiatric care. A small RCT of EPA, DHA, and vitamin E in 15 adolescents with BPD who also met ultra-high-risk criteria for psychosis found that 1.2 g/day of EPA significantly improved functioning and reduced psychiatric symptoms (SMD, -1.516) compared with placebo. Bellino et al. conducted a 12-week controlled trial aimed to assess the efficacy of the association of EPA and DHA with valproic acid compared to valproic acid alone in 43 consecutive BPD outpatients. The combination therapy of valproate and omega-3 fatty acids produced significant effects in reducing the severity of characteristic BPD symptoms such as impulsive behavioral dyscontrol (SMD, -1.6343), outbursts of anger (SMD, -1.7843), and self-mutilating conduct.

Naltrexone (Opioid Antagonist)
Two small, double-blind, placebo-controlled randomized trials (total N = 25) compared naltrexone (50 or 200 mg/day) to placebo in reducing dissociative symptoms in patients with BPD. In both trials, the intensity and duration of dissociative symptoms were numerically lower with naltrexane than with placebo. However, the effects were too small to reach statistical significance.

Clonidine (Alpha-2 Adrenergic Agonist)
Ziegenhorn et al. used a double-blind, randomized, placebo-controlled crossover study to determine whether clonidine (450 mcg/day orally) was effective in reducing hyperarousal in a sample of 18 patients with BPD, with or without comorbid posttraumatic stress disorder (PTSD), and with a prominent hyperarousal syndrome. Hyperarousal, as measured by the clinician-administered PTSD scale, improved significantly (18% decrease) compared with placebo (P = .003), irrespective of PTSD comorbidity.

Oxytocin
In a small RCT, 14 patients with BPD and 13 healthy control adults received 40 IU of intranasal oxytocin or placebo in a double-blind, randomized order followed by the Trier Social Stress Test. The authors noted a greater attenuation of stress-induced dysphoria in the BPD group after oxytocin administration.

DISCUSSION
Results from the RCTs should be examined with caution, as the data were limited by (1) the small size of the trials; (2) short duration (often lasting between 6 and 12 weeks); (3) high dropout rates; (4) inconsistent outcome measures; (5) enrollment bias (subjects were mostly women, and the heterogeneity of clinical features, treatment settings, and assessment instruments); and (6) lack of replication (most effect estimates were based on single study effects). In addition, individuals with suicidal ideation or recent suicide attempt were excluded from most investigations, which is uncharacteristic of severely ill or hospitalized BPD patients.

The American Psychiatric Association’s practice guidelines endorsement of SSRIs as first-line therapies for BPD is not supported by the current literature. The World Federation of Societies of Biological Psychiatry guidelines for biological treatment of personality disorders conclude that there is no evidence at either level of evidence that any drug improves BPD psychopathology in general. The National Institute for Health and Care Excellence guideline on treatment and management of BPD recommends that “drug treatment should not be used specifically for BPD.”

The authors of this review support a symptom-oriented pharmacologic therapy, as first recommended by Soloff in 1998. A symptom-specific approach to drug trials for BPD will involve outcome measurements defined for the symptom, not the BPD syndrome as a whole. The three main areas that medications should target are (1) affect, (2) impulse, and (3) cognition. For the affective dysregulation symptoms, data indicate beneficial effects for topiramate, lamotrigine, divalproex sodium, haloperidol, aripiprazole, olanzapine, quetiapine extended-release, omega-3 fatty acids, and amitriptyline. The impulsive behavioral dyscontrol symptoms might be decreased by topiramate, lamotrigine, aripiprazole, and omega-3 fatty acids. In regard to the psychotic symptoms, findings show significant beneficial effects for aripiprazole, olanzapine, and quetiapine extended-release. There is some evidence to support the use of aripiprazole, divalproex sodium, and topiramate in managing interpersonal problems. Omega-3 fatty acids produced some beneficial effects, but more research is needed.
acids show promise in terms of reducing elevated suicidality.

CONCLUSION
The mainstay of treatment for BPD is still psychotherapy; pharmacotherapy is an adjunctive treatment aimed at stabilizing symptoms and behavior in a crisis situation. A symptoms-specific approach has response overlap. Polypharmacy should be avoided whenever possible. Further studies are needed, including large RCTs with long-term follow up, to examine the efficacy of psychiatric medications in patients with BPD.

REFERENCES
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