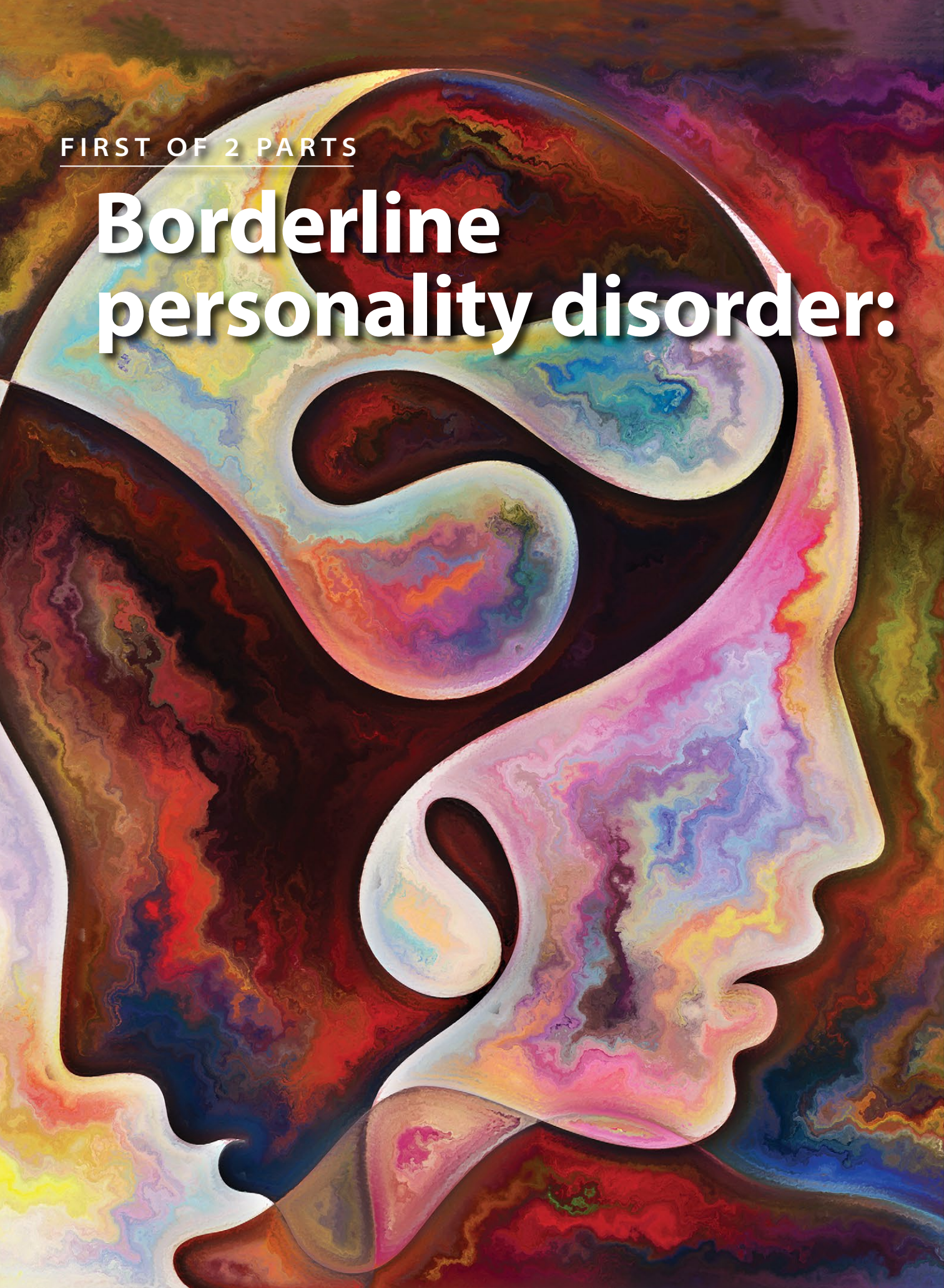


FIRST OF 2 PARTS

Borderline personality disorder:



6 studies of biological interventions

Research suggests possible benefits from tDCS, oxytocin, asenapine, olanzapine, and memantine

Sy Ateزاز Saeed, MD, MS

Professor and Chair
Department of Psychiatry and Behavioral Medicine
East Carolina University Brody School of Medicine
Greenville, North Carolina

Angela C. Kallis, MD

Clinical Assistant Professor
Department of Psychiatry and Behavioral Medicine
East Carolina University Brody School of Medicine
Greenville, North Carolina.

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Borderline personality disorder (BPD) is marked by an ongoing pattern of mood instability, cognitive distortions, problems with self-image, and impulsive behavior, often resulting in problems in relationships. BPD is associated with serious impairment in psychosocial functioning.¹ Patients with BPD tend to use more mental health services than patients with other personality disorders or those with major depressive disorder (MDD).² However, there has been little consensus on the best treatment(s) for this serious and debilitating disorder, and some clinicians view BPD as difficult to treat.

Current treatments for BPD include psychological and pharmacological interventions. Neuromodulation techniques, such as repetitive transcranial magnetic stimulation, may also positively affect BPD symptomatology. In recent years, there have been some promising findings in the treatment of BPD. In this 2-part article, we focus on current (within the last 5 years) findings from randomized controlled trials (RCTs) of BPD treatments. Here in Part 1, we focus on 6 studies that evaluated biological interventions (*Table*,³⁻⁸ *page 28*). In Part 2, we will focus on RCTs that investigated psychological interventions.

1. Lisoni J, Miotto P, Barlati S, et al. Change in core symptoms of borderline personality disorder by tDCS: a pilot study. *Psychiatry Res.* 2020;291:113261. doi: 10.1016/j.psychres.2020.113261

Impulsivity has been described as the core feature of BPD that best explains its behavioral, cognitive, and clinical manifestations. Studies have repeatedly demonstrated the role of the prefrontal cortex in modulating



Borderline personality disorder

Clinical Point

Patients with BPD who received tDCS experienced significant reductions in impulsivity, aggression, and craving



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Table

Biological treatments for borderline personality disorder

Study	Design	Outcomes
Lisoni et al ³	Double-blind, sham-controlled RCT of 30 adults with BPD randomized to 3 weeks (15 sessions) of right anodal/left cathodal DLPFC tDCS or sham tDCS	Participants who received active tDCS experienced significant reductions in impulsivity, aggression, and craving
Molavi et al ⁴	Single-blind, sham-controlled, parallel-group study of 32 adults with BPD randomized to receive 10 consecutive daily sessions of left anodal/right cathodal DLPFC tDCS or sham tDCS	Participants who received active tDCS experienced significant improvements in executive function, emotion regulation, and emotional processing
Crawford et al ⁵	A 2-arm, parallel-group, double-blind, placebo-controlled trial of 276 adults with BPD randomized to receive lamotrigine (up to 400 mg/d) or placebo for 52 weeks	At 52 weeks, there was no difference in ZAN-BPD scores between the lamotrigine and placebo groups. No difference was found in any secondary outcome measures
Domes et al ⁶	A double-blind, between-subject trial in which 61 women with BPD and 68 matched healthy controls were randomized to receive intranasal oxytocin, 24 IU, or placebo 45 minutes before completing an empathy task	Compared to placebo, oxytocin significantly increased affective empathy and approach motivation in patients with BPD
Bozzatello et al ⁷	Open-label RCT of 51 adults with BPD assigned to receive asenapine or olanzapine for 12 weeks	Asenapine and olanzapine had similar effects on BPD-related psychopathology, anxiety, and social and occupational functioning. Neither medication significantly decreased depressive or aggressive symptoms
Kulkarni et al ⁸	An 8-week, double-blind, placebo-controlled trial of 33 adults with BPD randomized to receive memantine or placebo in addition to treatment as usual	Beginning with Week 2, compared with the placebo group, the memantine group experienced a significant reduction in total symptoms as measured by ZAN-BPD

BPD: borderline personality disorder; DLPFC: dorsolateral prefrontal cortex; RCT: randomized controlled trial; tDCS: transcranial direct current stimulation; ZAN-BPD: Zanarini Rating Scale for Borderline Personality Disorder

impulsivity. Dysfunction of the dorsolateral prefrontal cortex (DLPFC) has been implicated in BPD. DLPFC transcranial direct current stimulation (tDCS) is a well-tolerated, noninvasive neurostimulation technique that can be used to alter cortical brain activity. Lisoni et al³ examined whether a bilateral right anodal/left cathodal tDCS montage could modulate the psychopathology of BPD.

Study design

• In a double-blind, sham-controlled trial, adults who met DSM-IV-TR criteria for BPD were randomized to 3 weeks (15 sessions) of right anodal/left cathodal DLPFC tDCS (n = 15) or sham tDCS (n = 15). This study included patients with comorbid psychiatric disorders, including substance use disorders. Discontinuation

or alteration of existing medications was not allowed.

• The presence, severity, and change over time of BPD core symptoms was assessed at baseline and after 3 weeks using several clinical scales, self-questionnaires, and neuropsychological tests, including the Barratt Impulsiveness Scale-11 (BIS-11), Buss-Perry Aggression Questionnaire (BP-AQ), Difficulties in Emotion Regulation Scale (DERS), Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), Irritability-Depression Anxiety Scale (IDA), Visual Analog Scales (VAS), and Iowa Gambling Task.

Outcomes

• Participants in the active tDCS group experienced significant reductions in impul-

sivity, aggression, and craving as measured by the BIS-11, BP-AQ, and VAS.

- Compared to the sham group, the active tDCS group had greater reductions in HAM-D and BDI scores.

- HAM-A and IDA scores were improved in both groups, although the active tDCS group showed greater reductions in IDA scores compared with the sham group.

- As measured by DERS, active tDCS did not improve affective dysregulation more than sham tDCS.

Conclusions/limitations

- Bilateral tDCS targeting the right DLPFC with anodal stimulation is a safe, well-tolerated technique that may modulate core dimensions of BPD, including impulsivity, aggression, and craving.

- Excitatory anodal stimulation of the right DLPFC coupled with inhibitory cathodal stimulation on the left DLPFC may be an effective montage for targeting impulsivity in patients with BPD.

- Study limitations include a small sample size, use of targeted questionnaires only, inclusion of patients with BPD who also had certain comorbid psychiatric disorders, lack of analysis of the contributions of medications, lack of functional neuroimaging, and lack of a follow-up phase.

2. Molavi P, Azizaram S, Basharpour S, et al. Repeated transcranial direct current stimulation of dorsolateral-prefrontal cortex improves executive functions, cognitive reappraisal emotion regulation, and control over emotional processing in borderline personality disorder: a randomized, sham-controlled, parallel-group study. *J Affect Disord.* 2020;274:93-102. doi: 10.1016/j.jad.2020.05.007

Emotional dysregulation is considered a core feature of BPD psychopathology and is closely associated with executive dysfunction and cognitive control. Manifestations of executive dysfunction include aggressiveness, impulsive decision-making, disinhibition, and self-destructive behaviors. Neuroimaging of patients with BPD has shown enhanced activity in the insula, posterior cingulate cortex, and amygdala, with

reduced activity in the medial PFC, subgenual anterior cingulate cortex, and DLPFC. Molavi et al⁴ postulated that increasing DLPFC activation with left anodal tDCS would result in improved executive functioning and emotion dysregulation in patients with BPD.

Study design

- In this single-blind, sham-controlled, parallel-group study, adults who met DSM-5 criteria for BPD were randomized to receive 10 consecutive daily sessions of left anodal/right cathodal DLPFC tDCS (n = 16) or sham tDCS (n = 16).

- The effect of tDCS on executive dysfunction, emotion dysregulation, and emotional processing was measured using the Executive Skills Questionnaire for Adults (ESQ), Emotion Regulation Questionnaire (ERQ), and Emotional Processing Scale (EPS). Measurements occurred at baseline and after 10 sessions of active or sham tDCS.

Outcomes

- Participants who received active tDCS experienced significant improvements in ESQ overall score and most of the executive function domains measured by the ESQ.

- Those in the active tDCS group also experienced significant improvement in emotion regulation as measured by the cognitive reappraisal subscale (but not the expressive suppression subscale) of the ERQ after the intervention.

- Overall emotional processing as measured by the EPS was significantly improved in the active tDCS group following the intervention.

Conclusions/limitations

- Repeated bilateral left anodal/right cathodal tDCS stimulation of the DLPFC significantly improved executive functioning and aspects of emotion regulation and emotional processing in patients with BPD. This improvement was presumed to be the result of increased activity of left DLPFC.

Clinical Point

tDCS was associated with significant improvements in executive function, emotion regulation, and emotional processing



Borderline personality disorder

Clinical Point

There was no difference in ZAN-BPD scores between the lamotrigine and placebo groups at 52 weeks

- Study limitations include a single-blind design, lack of follow-up to assess durability and stability of response over time, reliance on self-report measures, lack of functional neuroimaging, and limited focality of tDCS.

3. Crawford MJ, Sanatinia R, Barrett B, et al; LABILE study team. The clinical effectiveness and cost-effectiveness of lamotrigine in borderline personality disorder: a randomized placebo-controlled trial. *Am J Psychiatry*. 2018;175(8):756-764. doi: 10.1176/appi.ajp.2018.17091006

One of the hallmark symptoms of BPD is mood dysregulation. Current treatment guidelines recommend the use of mood stabilizers for BPD despite limited quality evidence of effectiveness and a lack of FDA-approved medications with this indication. In this RCT, Crawford et al⁵ examined whether lamotrigine is a clinically effective and cost-effective treatment for people with BPD.

Study design

- In this 2-arm, parallel-group, double-blind, placebo-controlled trial, 276 adults who met DSM-IV criteria for BPD were randomized to receive lamotrigine (up to 400 mg/d) or placebo for 52 weeks.

- The primary outcome was the score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) at 52 weeks. Secondary outcomes included depressive symptoms, deliberate self-harm, social functioning, health-related quality of life, resource use and costs, treatment adverse effects, and adverse events. These were assessed using the BDI; Acts of Deliberate Self-Harm Inventory; Social Functioning Questionnaire; Alcohol, Smoking, and Substance Involvement Screening Test; and the EQ-5D-3L.

Outcomes

- Mean ZAN-BPD score decreased at 12 weeks in both groups, after which time the score remained stable.

- There was no difference in ZAN-BPD scores at 52 weeks between treatment arms. No difference was found in any secondary outcome measures.

- Difference in costs between groups was not significant.

Conclusions/limitations

- There was no evidence that lamotrigine led to clinical improvements in BPD symptomatology, social functioning, health-related quality of life, or substance use.

- Lamotrigine is neither clinically effective nor a cost-effective use of resources in the treatment of BPD.

- Limitations include a low level of adherence.

4. Domes G, Ower N, von Dawans B, et al. Effects of intranasal oxytocin administration on empathy and approach motivation in women with borderline personality disorder: a randomized controlled trial. *Transl Psychiatry*. 2019;9(1):328. doi: 10.1038/s41398-019-0658-4

A core feature of BPD is impairment in empathy; adequate empathy is required for intact social functioning. Oxytocin is a neuropeptide that helps regulate complex social cognition and behavior. Prior research has found that oxytocin administration enhances emotion regulation and empathy. Women with BPD have been observed to have lower levels of oxytocin. Domes et al⁶ conducted an RCT to see if oxytocin could have a beneficial effect on social approach and social cognition in women with BPD.

Study design

- In a double-blind, placebo-controlled, between-subject trial, 61 women who met DSM-IV criteria for BPD and 68 matched healthy controls were randomized to receive intranasal oxytocin, 24 IU, or placebo 45 minutes before completing an empathy task.

- An extended version of the Multifaceted Empathy Test was used to assess empathy and approach motivation.



Borderline personality disorder

Clinical Point

Oxytocin significantly increased affective empathy and approach motivation in patients with BPD

continued from page 30

Outcomes

- For cognitive empathy, patients with BPD exhibited significantly lower overall performance compared to controls. There was no effect of oxytocin on this performance in either group.

- Patients with BPD had significantly lower affective empathy compared with controls. After oxytocin administration, patients with BPD had significantly higher affective empathy than those with BPD who received placebo, reaching the level of healthy controls who received placebo.

- For positive stimuli, patients with BPD showed lower affective empathy than controls. Oxytocin treatment increased affective empathy in both groups.

- For negative stimuli, oxytocin increased affective empathy more in patients with BPD than in controls.

- Patients with BPD demonstrated less approach motivation than controls. Oxytocin increased approach motivation more in patients with BPD than in controls. For approach motivation toward positive stimuli, oxytocin had a significant effect on patients with BPD.

Conclusions/limitations

- Patients with BPD showed reduced cognitive and affective empathy and less approach behavior motivation than healthy controls.

- Patients with BPD who received oxytocin attained a level of affective empathy and approach motivation similar to that of healthy controls who received placebo. For positive stimuli, both groups exhibited comparable improvements from oxytocin. For negative stimuli, patients with BPD patients showed significant improvement with oxytocin, whereas healthy controls received no such benefit.

- Limitations include the use of self-report scales, lack of a control group, and inclusion of patients using psychotherapeutic medications. The study lacks generalizability because only women were included; the effect of exogenous oxytocin on men may differ.

5. Bozzatello P, Rocca P, Uscinska M, et al. Efficacy and tolerability of asenapine compared with olanzapine in borderline personality disorder: an open-label randomized controlled trial. *CNS Drugs*. 2017;31(9):809-819. doi: 10.1007/s40263-017-0458-4

The last decade has seen a noticeable shift in clinical practice from the use of antidepressants to mood stabilizers and second-generation antipsychotics (SGAs) in the treatment of BPD. Studies have demonstrated therapeutic effects of antipsychotic drugs across a wide range of BPD symptoms. Among SGAs, olanzapine is the most extensively studied across case reports, open-label studies, and RCTs of patients with BPD. In an RCT, Bozzatello et al⁷ compared the efficacy and tolerability of asenapine to olanzapine.

Study design

- In this open-label RCT, adults who met DSM-5 criteria for BPD were assigned to receive asenapine (n = 25) or olanzapine (n = 26) for 12 weeks.

- Study measurements included the Clinical Global Impression Scale, Severity item, HAM-D, HAM-A, Social and Occupational Functioning Assessment Scale, Borderline Personality Disorder Severity Index (BPDSI), BIS-11, Modified Overt Aggression Scale, and Dosage Record Treatment Emergent Symptom Scale.

Outcomes

- Asenapine and olanzapine had similar effects on BPD-related psychopathology, anxiety, and social and occupational functioning.

- Neither medication significantly decreased depressive or aggressive symptoms.

- Asenapine was superior to olanzapine in reducing the affective instability score of the BPDSI.

- Akathisia and restlessness/anxiety were more common with asenapine, and somnolence and fatigue were more common with olanzapine.

Conclusions/limitations

- The overall efficacy of asenapine was not different from olanzapine, and both medications were well-tolerated.

- Neither medication led to an improvement in depression or aggression, but asenapine was superior to olanzapine in reducing the severity of affective instability.

- Limitations include an open-label design, lack of placebo group, small sample size, high drop-out rate, exclusion of participants with co-occurring MDD and substance abuse/dependence, lack of data on prior pharmacotherapies and psychotherapies, and lack of power to detect a difference on the dissociation/paranoid ideation item of BPDSI.

6. Kulkarni J, Thomas N, Hudaib AR, et al. Effect of the glutamate NMDA receptor antagonist memantine as adjunctive treatment in borderline personality disorder: an exploratory, randomised, double-blind, placebo-controlled trial. *CNS Drugs*. 2018;32(2):179-187. doi: 10.1007/s40263-018-0506-8

It has been hypothesized that glutamate dysregulation and excitotoxicity are crucial to the development of the cognitive disturbances that underlie BPD. As such, glutamate modulators such as memantine hold promise for the treatment of BPD. In this RCT, Kulkarni et al⁸ examined the efficacy and tolerability of memantine compared with treatment as usual in patients with BPD.

Study design

- In an 8-week, double-blind, placebo-controlled trial, adults diagnosed with BPD according to the Diagnostic Interview for Borderline Patients were randomized to receive memantine (n = 17) or placebo

Related Resource

- Black DW. A clinical approach to pharmacotherapy for personality disorders. *Current Psychiatry*. 2021;20(4):26-32. doi:10.12788/cp.0112

Drug Brand Names

Asenapine • Saphris	Memantine • Namenda
Lamotrigine • Lamictal	Olanzapine • Zyprexa

(n = 16) in addition to treatment as usual. Treatment as usual included the use of antidepressants, mood stabilizers, and antipsychotics as well as psychotherapy and other psychosocial interventions.

- Patients were initiated on placebo or memantine, 10 mg/d. Memantine was increased to 20 mg/d after 7 days.

- ZAN-BPD score was the primary outcome and was measured at baseline and 2, 4, 6, and 8 weeks. An adverse effects questionnaire was administered every 2 weeks to assess tolerability.

Outcomes

- During the first 2 weeks of treatment, there were no significant improvements in ZAN-BPD score in the memantine group compared with the placebo group.

- Beginning with Week 2, compared with the placebo group, the memantine group experienced a significant reduction in total symptoms as measured by ZAN-BPD.

- There were no statistically significant differences in adverse events between groups.

Conclusions/limitations

- Memantine appears to be a well-tolerated treatment option for patients with BPD and merits further study.

continued

Clinical Point

Asenapine and olanzapine had similar effects on BPD-related psychopathology, anxiety, and functioning

Bottom Line

Findings from small randomized controlled trials suggest that transcranial direct current stimulation, oxytocin, asenapine, olanzapine, and memantine may have beneficial effects on some core symptoms of borderline personality disorder. These findings need to be replicated in larger studies.



Borderline personality disorder

Clinical Point

Patients with BPD who received memantine experienced a significant reduction in total symptoms

• Limitations include a small sample size, and an inability to reach plateau of ZAN-BPD total score in either group. Also, there is considerable individual variability in memantine steady-state plasma concentrations, but plasma levels were not measured in this study.

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