Mood Stabilizers and Novel Antipsychotics in the Treatment of Borderline Personality Disorder

July 01, 2006 | Bipolar Disorder [1], Personality Disorders [2], Schizoaffective [3], Schizophrenia [4], Borderline Personality [5], Antisocial Personality Disorder [6], Mood Disorders [7], Bipolar II Disorder [8], Mania [9], Forensic Psychiatry [10], Neuropsychiatry [11], Addiction [12], Alcohol Abuse [13], Dysthymia [14]

By Silvio Bellino, MD [15], Erika Paradiso, MD [16], and Filippo Bogetto, MD [17]

This article focuses on data concerning the efficacy of mood stabilizers in the treatment of BPD.

Borderline personality disorder (BPD) is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, and affect, in addition to marked impulsivity. 2 Although psychotherapy plays a significant role in the treatment of borderline patients by focusing on maladaptive personality traits and patterns of interpersonal relationships, 2,3 pharmacotherapy is indicated by the American Psychiatric Association guidelines to manage vulnerability traits, symptoms, and crises. 4

Treatment strategies for BPD target different domains of psychopathology, such as cognitive-perceptual, affective, and impulsive-behavioral symptoms. Guidelines specify the use of antidepressant agents—in particular, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors—and mood stabilizers for affective dysregulation; SSRIs and mood stabilizers for impulsive-behavioral dyscontrol; and antipsychotics for cognitive-perceptual symptoms. This article focuses on data concerning the efficacy of mood stabilizers in the treatment of BPD.

The role of mood stabilizer

A consensus definition of mood stabilizer remains to be established, and international regulatory authorities do not officially recognize the term as a mode of drug activity. 5 Clinicians and researchers apply the concept of mood stabilization to a range of compounds used in the treatment of bipolar disorder, although considerable variability can be found in the literature concerning the meaning and use of the term. 6-11 In its broadest form, a mood stabilizer has been operationally described as an agent that is useful in at least 1 of the 3 phases of bipolar disorder (mania, bipolar depression, or long-term maintenance) while not increasing the frequency or severity of any of the other phases of the illness. 6

Although no drugs used as mood stabilizers have been approved by the FDA for the treatment of BPD, these drugs are often prescribed off-label in clinical practice and are suggested for treating BPD-related symptoms by the guidelines of the American Psychiatric Association. 4 Some investigators have proposed that the same mechanism may drive both the affective instability of BPD and the rapid mood cycling of bipolar disorder and that this could be a rationale for the use of mood stabilizers in BPD. 12

To date, several open-label and controlled trials have been undertaken to test the efficacy of these agents in BPD and to define their effects on different dimensions of borderline psychopathology (Table 1).

Lithium carbonate

The first mood stabilizer considered for the treatment of patients with BPD is lithium carbonate; its effectiveness has been reported in 3 reviews since the late 1980s. 13-15 Concerning the mechanism of action, 3 interacting systems appear critical for lithium activity: modulation of neurotransmitters, which may contribute to neuroprotection by readjusting excitatory and inhibitory activity balance; modulation of signals impacting on the cytoskeleton, including glycogen synthase kinase-3β, cyclic AMP-dependent kinase, and protein kinase C, which may be critical for the neural plasticity involved in mood stabilization; and regulation of second messengers, transcription factors, and gene expression. 16
The results of a 6-week, doubleblind, placebo-controlled crossover study that compared lithium with desipramine in 10 patients with BPD showed the efficacy of lithium on core features of borderline psychopathology, such as irritability, anger, and selfmutilation. A review by Stein concerning lithium and the anticonvulsant agent carbamazepine in the treatment of patients with BPD or antisocial personality disorder pointed out the effectiveness of both agents on behavioral dysregulation and aggressiveness.

**Carbamazepine**

At about the same time, further data concerning treatment of BPD with carbamazepine were published. This agent blocks voltage-gated sodium channels and is indicated by the FDA as an anticonvulsant. Although its use in the treatment of BPD is common in clinical practice, this has not been officially approved. In a crossover trial with a sample of 11 female outpatients with BPD, Gardner and Cowdry demonstrated decreased frequency and severity of behavioral dyscontrol. Their results were confirmed by other studies: a 6-week controlled investigation comparing carbamazepine (mean dose, 820 mg/d), alprazolam (4.7 mg/d), trifluoperazine (7.8 mg/d), and tranylcypromine (40 mg/d) in the treatment of 16 patients with BPD and comorbid hysteroid dysphoria, and a review of double-blind clinical trials. Both showed that carbamazepine induced a marked improvement in impulsive aggression.

Controlled trials suggest the efficacy of carbamazepine not only in reducing impulsive-aggressive behaviors but also on affective dysregulation, which is often the main goal of mood stabilizer use in the treatment of BPD. A clinical practice survey by Denicoff and colleagues compared carbamazepine with many other agents (lithium, valproate, neuroleptics, clonazepam, phenytoin, calcium antagonists) and electroconvulsive therapy in 1257 patients with different neurologic and psychiatric disorders, and found a significant global improvement in the subgroup of patients with BPD treated with carbamazepine.

<table>
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<th>Table 1</th>
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<td><strong>Agent</strong></td>
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<td>Double-blind vs placebo</td>
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<td>Double-blind vs placebo</td>
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TFP, TCM

Retrospective vs other drugs and ECT
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<table>
<thead>
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<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Outcome</th>
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<tr>
<td>Frankenburg</td>
<td>Double-blind vs placebo</td>
<td>6 months</td>
<td>Decreased interpersonal sensitivity, anger/hostility, aggressiveness</td>
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<td>Lamotrigine</td>
<td>Open-label</td>
<td>1 year</td>
<td>Decreased behavioral dyscontrol; improved global functioning</td>
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<td>Green</td>
<td>Review</td>
<td>NA</td>
<td>Decreased mood instability</td>
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<td>Preston</td>
<td>Retrospective</td>
<td>14</td>
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<tr>
<td>Tritt</td>
<td>Double-blind vs placebo</td>
<td>8 weeks</td>
<td>Decreased anger</td>
</tr>
</tbody>
</table>

NA, not available; ALP, alprazolam; TFP, trifluoperazine; TCM, tranylcypromine; ECT, electroconvulsive therapy.

**Oxcarbazepine**

Oxcarbazepine is another anticonvulsant structurally related to carbamazepine, with the same mechanism of action of blocking voltage-gated sodium channels, but it is less likely to induce cytochrome P-450 and drug interactions. A series of studies indicated the efficacy of oxcarbazepine in the treatment of several psychiatric disorders, such as bipolar disorder, substance abuse, resistant psychosis, and schizoaffective disorder. However, as in the case of carbamazepine, oxcarbazepine has been approved by the FDA for treating only seizure disorder. Our research group recently performed a 12-week pilot study of oxcarbazepine in 13 outpatients with BPD. A statistically significant improvement was observed in global psychopathology; anxiety; interpersonal relationships; and BPD core features, including impulsivity, affective instability, and outbursts of anger.

**Divalproex sodium and valproate**

Among mood stabilizers, divalproex sodium has been extensively studied in patients with BPD. Its mechanism of action consists of facilitating transmission of y-aminobutyric acid. Wilcox was the first to suggest the role of divalproex in reducing agitation in patients with BPD. In 1994, Wilcox
tested the efficacy of valproate in a group of patients with psychomotor agitation caused by various underlying psychiatric conditions. The decrease in agitation after treatment was particularly evident in patients with bipolar disorder or BPD. These data were replicated in a subsequent study by Wilcox, concerning the treatment of BPD with divalproex sodium. An 8-week open-label trial of valproate (daily dose titrated to reach blood levels of 50 to 100 μg/mL) in 11 patients with BPD by Stein and colleagues provided further data on this agent. Of the 8 who completed the study, half were responders on clinician-rated measures of overall psychopathology, mood, anxiety, anger, impulsivity, and rejection sensitivity. Kavoussi and Coccaro administered valproate (up to 2000 mg/d) to 10 patients with several Axis II diagnoses who had failed to respond to an SSRI (2 patients met criteria for BPD). After 8 weeks of treatment, irritability and impulsive aggressiveness were significantly reduced. Subsequently, 3 placebo-controlled trials were published. Hollander and colleagues performed a 10-week double-blind study of valproate (plasma level of 80 μg/mL) in 16 patients with BPD and found a marked improvement in global symptomatology; social functioning; and BPD features, such as depressive symptoms, aggressiveness, irritability, and suicidal ideation or behavior. However, a high dropout rate precluded finding significant differences between treatment groups. More recently, the same study group confirmed the efficacy of valproate (mean daily dose, 1325 mg) on impulsive aggression of 52 outpatients with BPD in a 12-week double-blind trial. Frankenburg and Zanarini included 30 women with BPD and comorbid bipolar II disorder in a 6-month controlled study and showed that valproate (plasma level of 50-100 μg/mL) had significant effects on interpersonal sensitivity, anger, hostility, and aggressiveness.

Lamotrigine

The anticonvulsant lamotrigine has been considered in recent years for treating depressive episodes of bipolar disorder and preventing recurrences. This drug inhibits neuronal excitability and modifies synaptic plasticity by inhibiting voltage-activated sodium channels. Indirectly, these effects would be expected to regulate aberrant intracellular and intercellular signalling in critical regions of the limbic forebrain. The use of lamotrigine for treating BPD was initially reported by Pinto and Akiskal in a 1-year open-label trial focused on 8 outpatients. Their results showed that 40% reported a significant improvement in global functioning, sexual impulsiveness, substance abuse, and suicidal behavior. A review by Green of patients with mood disorders suggests the efficacy of this agent in also treating mood instability of BPD. More recently, Preston and colleagues investigated the frequency of comorbid BPD in 35 patients with bipolar disorder who had previously participated in 2 open-label trials with lamotrigine, in order to evaluate the effects of this drug on BPD dimensions. BPD was retrospectively diagnosed in 40% of the patients. Results of the study showed the efficacy of lamotrigine on all BPD traits, with a marked improvement in impulsivity and mood instability. In 2005, Tritt and colleagues compared the efficacy of lamotrigine and placebo in the treatment of aggression in 24 women meeting the criteria for BPD. Highly significant improvements in anger were observed after 8 weeks in patients treated with lamotrigine.

Novel antipsychotics as mood stabilizers in BPD

Second-generation antipsychotics antagonize both dopamine and serotonin-2 (5-HT2) receptors. Because dopamine receptor blockade has been associated with antimanic properties and 5-HT2 antagonism with antidepressant effects, it has been postulated that novel antipsychotics may be effective in the treatment and prevention of bipolar mania and depression. These hypotheses have been substantiated by a number of studies. The mood-stabilizing properties of second-generation antipsychotics have also been considered for treatment of BPD-related symptoms (Table 2). Although this indication has not yet been approved by the FDA, these agents are indicated by BPD treatment guidelines both for their antipsychotic effects on cognitive-perceptual disturbances and for their mood stabilizing action on affective instability, anger, and impulsive aggression. Clozapine was found to be efficacious on overall symptomatology, aggressiveness, and severe psychotic symptoms related to BPD. However, patients with BPD treated with clozapine frequently had Axis I comorbidities and had been refractory to previous treatments. These patients did not have pure BPD and they had already been treated unsuccessfully with other drugs. To date, studies on risperidone in BPD are sparse and derive from some case reports and an
open-label trial. In their 8-week open-label trial of risperidone (3.3 mg/d) in 15 outpatients with BPD, Rocca and colleagues outlined the efficacy of this agent on aggressive behavior, affective instability, and global psychopathology.

More extensive data suggesting mood stabilizing properties have been reported for olanzapine and quetiapine. Olanzapine is a thienobenzodiazepine with a high affinity for dopamine (D2 through D4) and serotonin receptors (5-HT2A), and a lower affinity for histamine (H1), muscarinic (M1 through M5), and α-adrenergic (α1) receptors. Antagonism at D2 through D4 and 5-HT2A receptors is supposed to be the basis for its therapeutic efficacy, while antagonism at H1, M1-M5, and α1 receptors is probably responsible for adverse effects.

Schulz and colleagues performed the first open-label study of olanzapine in a sample of 9 outpatients with BPD who had comorbid dysthymia. After 8 weeks of treatment, patients reported a significant improvement in impulsivity, hostility, global psychopathology, and global functioning. Since then, the findings from several controlled trials have been published. A 6-month double-blind, placebo-controlled trial of olanzapine (mean dose, 5.33 mg/d ± 3.43) in 28 women with BPD was undertaken by Zanarini and Frankenburg, who pointed out the efficacy of this agent on anxiety, paranoid ideation, and interpersonal sensitivity. Bogenschutz and Nurnberg recently reported similar findings in a 12-week double-blind, placebo-controlled trial of olanzapine (5 to 10 mg/d) in 40 outpatients with BPD. A significant improvement in borderline psychopathology and anger was found after the fourth week of treatment.

Zanarini and colleagues compared the efficacy of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination (OFC) in the treatment of 45 women meeting criteria for BPD. In their 8-week randomized double-blind study, the investigators found that all 3 treatment options significantly ameliorated chronic dysphoria and impulsive aggression. However, olanzapine monotherapy and OFC were found to be superior to fluoxetine monotherapy in treating both features of borderline psychopathology.

Soler and colleagues recently compared the efficacy of olanzapine and placebo in a combined treatment with dialectical behavioral therapy. In their 12-week double-blind study of a group of 60 outpatients with BPD, they found that olanzapine (mean dose, 8.83 mg/d) led to a significant reduction of impulsive-aggressive behavior, depression, and anxiety.

Quetiapine is a dibenzothiazepine characterized by low affinity for and rapid dissociation from postsynaptic D2 receptors, which reduces the incidence of adverse events, such as extrapyramidal symptoms, prolactin elevation, and weight gain. Hilger and colleagues described the impact of this agent (400 to 800 mg/d) on 2 women with BPD with severe episodes of self-mutilation and found positive effects on impulsive behavior and overall functioning.

A few pilot studies on quetiapine in BPD treatment have appeared in recent years. Adityanjee and Schulz evaluated the efficacy of quetiapine (25 to 300 mg/d) in 10 patients who completed an 8-week open-label trial. Results suggested a significant improvement in overall symptomatology, hostility, impulsivity, and functioning. Villeneuve and Lemelin recently replicated these findings. They investigated the effects of quetiapine (175 to 400 mg/d for 12 weeks) in a group of 23 outpatients and found a significant improvement in impulsivity, hostility, depression, anxiety, and social functioning.

Our group performed a 12-week pilot study on the efficacy of quetiapine (mean dose, 309 mg/d) for the treatment of BPD in 14 patients. Our results were mostly concordant with previous findings and confirmed the improvement of global symptomatology, impulsivity, outbursts of anger, anxiety, and social functioning.

Table 2
Clinical trials of some novel antipsychotics in the treatment of borderline personality disorder

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Open-label</td>
<td>15</td>
<td>8 weeks</td>
<td>Decreased global symptom</td>
</tr>
<tr>
<td>Rocca</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Duration</td>
<td>Outcome</td>
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<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Open-label</td>
<td>8 weeks</td>
<td>Decreased global symptoms, impulsive aggression</td>
<td></td>
</tr>
<tr>
<td>Schulz</td>
<td>Double-blind vs placebo</td>
<td>6 months</td>
<td>Decreased anxiety/paranoid ideation, interpersonal sensitivity</td>
<td></td>
</tr>
<tr>
<td>Bogenschutz</td>
<td>Double-blind vs placebo</td>
<td>12 weeks</td>
<td>Decreased global symptomatology, anger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double-blind vs O vs F vs 0 + F</td>
<td>8 weeks</td>
<td>Decreased impulsive aggression, chronic dysphoria (O = O + F &gt; F)</td>
<td></td>
</tr>
<tr>
<td>Soler</td>
<td>Double-blind DBT + O vs DBT + placebo</td>
<td>12 weeks</td>
<td>Decreased impulsive aggression, depression/anxiety</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Case report</td>
<td>NA</td>
<td>Decreased impulsivity, improved global functioning</td>
<td></td>
</tr>
<tr>
<td>Adityanjee</td>
<td>Open-label</td>
<td>8 weeks</td>
<td>Decreased overall symptoms</td>
<td></td>
</tr>
</tbody>
</table>
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Villeneuve et al 2012. Open-labeled 23 weeks Decreased impulsivity/hostility, depression/anxiety; improved global functioning

Bellino et al 2013. Open-labeled 14 weeks Decreased impulsivity/anger/anxiety; improved social functioning

O, olanzapine; F, fluoxetine; DBT, dialectical behavior therapy; NA, not available.

Conclusions
Recent investigations of mood stabilizers in the treatment of BPD are promising and suggest that these drugs can be useful in clinical practice, particularly for controlling affective instability and impulsive aggression. However, further studies are needed to confirm the initial results and to ascertain whether some novel antipsychotics can be used for their mood-stabilizing effects in patients with BPD.

Future investigations should focus on a list of relevant topics: pilot studies of new drugs; controlled trials of drugs already tested in open case series; comparisons of new anticonvulsant agents with better-known mood stabilizers, such as lithium or valproate; head-to-head comparisons of novel and traditional antipsychotics to verify which differences in clinical effects and adverse events specifically occur in patients with BPD; maintenance studies to assess persistence of therapeutic effects in longlasting disorders such as BPD; add-on trials of mood stabilizers and novel antipsychotics in samples of patients with BPD who do not respond to firstline therapy with serotonergic antidepressants; and the relationship of clinical subtypes of patients with BPD (eg, affective labile, self-injurious, psychotofom) with response to drug treatment.

Dr Bellino is assistant professor of psychiatry, Dr Paradiso is a resident in psychiatry, and Dr Bogetto is professor of psychiatry and chairman in the department of neuroscience at the University of Turin in Italy.

Drs Bellino, Paradiso, and Bogetto report that they have no conflicts of interest with the subject matter of this article.

Drugs Mentioned in This Article
Mood Stabilizers and Novel Antipsychotics in the Treatment of Borderline Personality Disorder

Carbamazepine (Carbatrol, Tegretol, others)
Clonazepam (Klonopin, Rivotril)
Clozapine (Clozaril)
Divalproex (Epival, Depakote)
Fluoxetine (Prozac)
Lamotrigine (Lamictal)
Lithium (Eskalith)
Olanzapine (Zyprexa)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Tranylcypromine (Parnate)
Trifluoperazine (Stelazine)
Valproate/valproic acid (Depakote, others)

References


Evidence-based References


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