Pharma cologic treatment
Evidence suggests symptom-targeted pharmacotherapy can be beneficial

As psychiatry’s understanding of borderline personality disorder (BPD) grows, the literature clearly describes the seriousness of BPD, as well as these patients’ high utilization of treatment. Pharmacotherapy for BPD remains controversial. The most recent American Psychiatric Association practice guidelines focus on using symptom domains of this heterogeneous illness to guide medication selection, yet when these guidelines were published, there was a lack of data to support this recommendation.\(^1\)

This article evaluates medications for BPD and emerging data supporting matching medications to BPD symptom domains, with an emphasis on making choices that advance clinical practice. We conclude by reviewing studies of combined pharmacotherapy and dialectical behavior therapy (DBT) and describing how a multidisciplinary team approach can enhance BPD treatment.

**Early research**

Early studies of pharmacotherapy for BPD began after the development of the Diagnostic Interview for Borderlines\(^2,3\) and DSM-III criteria for BPD.\(^4\) Researchers recruited patients who fulfilled the diagnostic criteria; however, these participants’ symptom profiles were highly heterogeneous. Although such studies can be useful when starting to test new treatments—especially if they are able to show efficacy over placebo or explore safety—they are less helpful in guiding clinical practice.

During the 1980s, low doses of first-generation antipsychotics were evaluated based on hypotheses that BPD was related to schizophrenia. Case series\(^5\) and placebo-controlled trials\(^6,7\) pointed to symptom reduc-
tion over time and greater than placebo for BPD patients. Interestingly, in a small study of BPD inpatients, Soloff et al. compared the first-generation antipsychotic haloperidol to amitriptyline and found amitriptyline led to symptom worsening in some patients. Cowdry and Gardner compared alprazolam, carbamazepine, trifluoperazine, and tranylcypromine in a double-blind, placebo-controlled crossover trial of 16 female BPD outpatients. They found antipsychotics were not useful. Further, the study found behavioral disinhibition when a benzodiazepine (alprazolam) was used alone in impulsive patients.

These studies provided a basis for the idea that medications could help reduce BPD symptoms. However, some early investigators noted that antipsychotics’ side effects led some patients to discontinue treatment. Next-generation studies

Antidepressants. Interest in exploring pharmacologic treatments for BPD diminished after the early efficacy trials. Several events led to a reemergence of this interest, including the FDA’s approval of the selective serotonin reuptake inhibitor fluoxetine for depression in 1987. Some investigators hypothesized fluoxetine’s antidepressant properties could help treat BPD symptoms and perhaps the serotonin reuptake action could diminish impulsivity. Case series and a double-blind, placebo-controlled trial demonstrated fluoxetine’s efficacy in BPD. In 1 study, Salzman et al. found fluoxetine’s greatest impact was on “anger,” a major affective dimension of BPD.

Mood stabilizers. When valproic acid emerged as a successful treatment for bipolar disorder, researchers turned their attention to mood-stabilizing anticonvulsants for BPD. Numerous case series and controlled trials provided evidence of its efficacy. This was the first time subtypes of BPD patients were tested prospectively—with the hypothesis that the mood-stabilizing anticonvulsants would diminish impulsivity and aggression. The positive results of Hollander et al. and Frankenburg and Zanarini in assessing divalproex in BPD patients with bipolar II disorder has implications for targeted treatment (discussed below).

Newer antipsychotics. The introduction of second-generation antipsychotics (SGA) led some researchers to explore whether these agents could decrease BPD symptoms. Case series and some (but not all) placebo-controlled trials have demonstrated benefit from SGAs such as olanzapine, aripiprazole, and quetiapine. Initial research on risperidone and ziprasidone also suggested efficacy for BPD. Two placebo-controlled studies of olanzapine examined which symptom groups were most helped; each reported a broad effect. However, not all studies of SGAs for BPD patients have been positive. Further, metabolic side effects have been noted for several SGAs, including olanzapine.

Omega-3 fatty acids. Some studies examining omega-3 fatty acids have sparked an ongoing interest in this compound. In an 8-week, double-blind, pilot study of 30 women with BPD, Zanarini found omega-3 fatty acids demonstrated efficacy over placebo.

Targeted treatment

Most studies of BPD pharmacotherapy have used a classic clinical trial design, which does not easily translate into recommendations regarding medication selection for individual patients, especially those with BPD and comorbid illnesses. Also, existing trials have not fully explored starting doses, and no maintenance studies have been published. Therefore, many clinical application questions remain unresolved. However, some early treatment recommendations are supported by recent meta-analyses that demonstrate effects of medication classes for specific symptom domains.

Careful identification of comorbid psychiatric disorders is a rational first step in treating patients with borderline personality disorder.
Frankenburg and Zanarini\textsuperscript{14} found divalproex had a statistically significant effect compared with placebo and could be considered for this specific population.

When treating a BPD patient who has a comorbid illness, it is important not to ignore BPD symptoms. The chronic emotional dysregulation and ongoing safety issues require psychiatrists to educate patients about these symptoms and to address them in a multidisciplinary manner.

Clarifying prominent symptom domains can help steer pharmacologic management. Many trials have attempted to focus on specific symptom domains, including cognitive-perceptual disturbances, impulsivity, and affective dysregulation. Table 1\textsuperscript{24} lists BPD symptom domains and associated characteristics.

**Dosing strategy**

Developing a medication management strategy for BPD patients requires a thoughtful approach. When faced with a patient who has overwhelming distress, it is tempting to start with high medication doses; however, clinical experience suggests starting cautiously with lower doses will yield better tolerability and adherence. Based on our clinical experience, patients with BPD tend to be highly perceptive to physiologic stimuli and medication side effects.

Further research is needed to answer clinical questions regarding optimal dosing strategy and treatment, but some studies suggest when using SGAs, doses equivalent to one-third or one-half the dose used for treating schizophrenia may be appropriate.\textsuperscript{1,2,17,18} However, for fluoxetine, investigators have espoused using a dosage higher than generally used for depression.\textsuperscript{10} For mood-stabilizing anticonvulsants, almost all studies employed the same doses used for bipolar disorder.\textsuperscript{25} Some studies of valproic acid have verified appropriate blood levels—generally 50 to 100 µg/mL.

Controlled trials have not determined whether medications for patients with BPD should be used briefly during times of stress or for longer periods. Many studies of medication for BPD have been relatively brief trials that explored whether the drug has any potential efficacy. In our opinion, this issue currently is being addressed in clinical practice in a trial-and-error manner.

**Clues to targeted treatment**

Although pharmacotherapy for BPD subtypes remains controversial, recent meta-analyses by Ingenhoven\textsuperscript{24} and Nose\textsuperscript{26} and a Cochrane Review\textsuperscript{27} (with subsequent online update\textsuperscript{28}) have identified evidence that supports the use of specific medications for treating BPD symptoms. These studies’ authors acknowledge replication studies are required because of the limited nature of the available data. In contrast, a meta-analysis conducted by the National Collaborating Centre for Mental Health\textsuperscript{29} did not identify sufficient evidence for medication use in BPD on which to base official guidelines to advise health care providers in the United Kingdom. The only medication recommendation in this

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**Table 1**

<table>
<thead>
<tr>
<th>Symptom domains of BPD</th>
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<tbody>
<tr>
<td><strong>Cognitive-perceptual symptoms</strong></td>
</tr>
<tr>
<td>Suspiciousness</td>
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<tr>
<td>Referential thinking</td>
</tr>
<tr>
<td>Paranoid ideation</td>
</tr>
<tr>
<td>Illusions</td>
</tr>
<tr>
<td>Derealization</td>
</tr>
<tr>
<td>Depersonalization</td>
</tr>
<tr>
<td>Hallucination-like symptoms</td>
</tr>
<tr>
<td><strong>Impulsive-behavioral dyscontrol</strong></td>
</tr>
<tr>
<td>Impulsive aggression</td>
</tr>
<tr>
<td>Deliberate self-harm</td>
</tr>
<tr>
<td>Impulsive sexual behavior</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Impulsive spending</td>
</tr>
<tr>
<td><strong>Affective dysregulation</strong></td>
</tr>
<tr>
<td>Mood lability</td>
</tr>
<tr>
<td>Rejection sensitivity</td>
</tr>
<tr>
<td>Intense anger out of proportion to the stimuli</td>
</tr>
<tr>
<td>Sudden depressive mood episodes</td>
</tr>
<tr>
<td>BPD: borderline personality disorder</td>
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</tbody>
</table>

Source: Reference 24
meta-analysis is to consider prescribing short-term sedative antihistamines during crises; this recommendation is not supported by any clinical trial.

In a meta-analysis of 21 placebo-controlled trials of patients with BPD and/or schizotypal personality disorder, Inghoven et al used multiple domains and subdomains, including cognitive-perceptual symptoms, impulsive-behavioral dyscontrol, affective dysregulation, anger, and mood lability, to assess the efficacy of medication use. They found:

- Antipsychotics seemed to have a moderate effect on cognitive-perceptual symptoms and a moderate-to-large effect on anger.
- Antidepressants had a small effect on anxiety, but no other domains.
- Mood stabilizers had a very large effect on impulsive-behavioral dyscontrol and anger, a large effect on anxiety, and a moderate effect on depressed mood.
- Regarding global functioning, mood stabilizers had a greater effect than antipsychotics. Both led to greater change than antidepressants.

A 2010 Cochrane Review meta-analysis initially conducted by Leib with subsequent online update by Stoffers included 28 studies with a total of 1,742 patients and also identified symptom-targeted BPD domains. This study analyzed pooled data and found support for the use of specific medications, including certain antipsychotics, mood stabilizers, and antidepressants, for specific BPD symptoms. The authors recommended data be interpreted cautiously, however, because many of the clinical trials included in their meta-analysis have not been replicated and generalizability from research populations to clinical populations is not well understood.

### DBT and pharmacotherapy

As is the case with many studies of psychiatric medications, early efficacy studies of pharmacotherapy for BPD did not include structured psychosocial treatment. In 2 double-blind, placebo-controlled trials with a total of 84 patients receiving DBT, those assigned to olanzapine had better outcomes on objective rating scales than those on placebo. Similar trials testing fluoxetine showed no advantage for the drug over placebo. In a pilot study by Moen et al, 17 patients were assigned to “condensed DBT” before being randomized to divalproex extended release or placebo. Two patients remitted in the first 4 weeks and continued to improve without medication. If replicated, this finding may point to a targeted approach to the timing of medication initiation.

### Clinical recommendations

Randomized, placebo-controlled BPD trials have demonstrated striking improvements in patients in placebo groups, which may be attributed to the powerful therapeutic

<table>
<thead>
<tr>
<th>Medication</th>
<th>Symptom domain</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Antipsychotics</td>
<td>Cognitive-perceptual</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Anger</td>
<td>Moderate/large</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Anxiety</td>
<td>Small</td>
</tr>
<tr>
<td></td>
<td>Anger</td>
<td>Small</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Impulsive-behavioral dyscontrol</td>
<td>Very large</td>
</tr>
<tr>
<td></td>
<td>Anger</td>
<td>Very large</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Large</td>
</tr>
<tr>
<td></td>
<td>Depressed mood</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

BPD: borderline personality disorder

Source: Reference 24
Patients with BPD respond well to validation of their symptoms and their experience. Tell patients you take their BPD symptoms seriously and acknowledge their distress. The goal is to partner with patients to improve function, decrease reactivity, and reduce emotional pain. When working with BPD patients, it is appropriate to communicate a sense of optimism and hopefulness about their prognosis and treatment. Performing this approach in a caring way will better preserve the therapeutic alliance.

Additional suggestions based on our clinical experience include:

- Provide regular medication management visits.
- Consider using a structured symptom rating scale to evaluate symptoms over time, such as the Zanarini Rating Scale for Borderline Personality Disorder or Borderline Evaluation of Severity Over Time.
  - Educate patients with BPD about the disorder by making the appropriate diagnosis and providing reputable educational materials (see Related Resources).
  - Do not diagnose a patient with BPD as having bipolar disorder unless they clearly meet criteria for bipolar disorder.
  - Communicate your limitations in advance.
  - Orient the patient to the possibility of needing to try different medications to determine the most helpful agent or combination.
  - Do not de-emphasize risks of medications or side effects. Serious symptoms require medications that bear a risk of side effects; communicate these risks to patients and carefully weigh the risk-benefit profile.
  - Inform patients you will be responsive to making appropriate changes if problems arise that are associated with phar-

### Table 3
Pharmacotherapy for BPD: Results of a Cochrane review

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive-perceptual symptoms</td>
<td>Olanzapine, aripiprazole</td>
</tr>
<tr>
<td>Impulsive-behavioral dyscontrol</td>
<td>Topiramate, lamotrigine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Affective dysregulation</td>
<td>Amitriptyline (depressed mood)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Topiramate, lamotrigine (anger), valproate (depressed mood)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Haloperidol (anger), olanzapine, aripiprazole</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Fish oil (depression)</td>
</tr>
<tr>
<td>Suicidal behavior/suicidality</td>
<td>Flupenthixol decanoate</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Fish oil</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Interpersonal problems</td>
<td>Valproate, topiramate</td>
</tr>
<tr>
<td>No improvement on any outcome:</td>
<td>ziprasidone, thiothixene, phenelzine, fluoxetine, fluvoxamine, carbamazepine</td>
</tr>
</tbody>
</table>
  - Do not prescribe to suicidal patients

BPD: borderline personality disorder

Source: Reference 28
pharmacotherapy and outweigh the benefit of medication.

**Multidisciplinary teamwork**

Best outcomes for patients with BPD are facilitated by a collaborative team effort. Such an approach addresses both the psychological and biologic underpinnings of the disorder and can significantly decrease the possibility of “splitting” among team members. To determine ways in which a therapist and physician may work together, clinicians should discuss the:

- meaning of medication to the therapist, psychiatrist, and patient
- potential benefits and limitations of medication
- the role of medication in the patient’s overall treatment.

Patients with BPD experience emotional crisis. At times, prescribing patterns unfortunately reflect the practice of adding medications to address emotional crisis. This practice may partially account for the high rates of polypharmacy in BPD patients. Patients with BPD will benefit from interacting with a clinician whose approach is responsive, validating, and nonreactive to the patient’s symptoms and experiences. A comprehensive treatment approach includes screening and treating comorbid conditions, providing education about the diagnosis, and multidisciplinary involvement combined with rational, targeted pharmacotherapy.

**References**


**Drug Brand Names**

- Alprazolam - Xanax
- Amitriptyline - Elavil
- Aripiprazole - Abilify
- Carbamazepine - Tegetol
- Fluoxetine - Prozac
- Fluvoxamine - Luvox
- Haloperidol - Haldol
- Lamotrigine - Lamictal
- Olanzapine - Zyprexa
- Phenytoin - Nardil
- Prozac
- Seroquel
- Risperidone - Risperdal
- Thioridazine
- Topiramate - Topamax
- Trionix
- Trifluoperazine - Stelazine
- Valproic acid - Depakote
- Ziprasidone - Geodon

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**Clinical Point**

Explain to patients that they may need to try different medications to find the most helpful agent or combination.
Emerging evidence supports using pharmacologic therapy to improve specific symptoms of borderline personality disorder. Taking a responsive, validating, nonreactive management approach that includes evidence-based psychotherapy will allow a multidisciplinary team of clinicians to provide better treatment and achieve a stronger therapeutic alliance.