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Dr. Nelson: Strategies for improving pharmacotherapy for patients with BPD

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cologic treatment of borderline personality disorder

Evidence suggests symptom-targeted pharmacotherapy can be beneficial

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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-

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Careful identification of comorbid psychiatric disorders is a rational first step in treating patients with borderline personality disorder

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tion over time and greater than placebo for BPD patients. Interestingly, in a small study of BPD inpatients, Soloff et al[8] compared the first-generation antipsychotic haloperidol to amitriptyline and found amitriptyline led to symptom worsening in some patients. Cowdry and Gardner[9] 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.[6]

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.[10] Case series and a double-blind, placebo-controlled trial[11] demonstrated fluoxetine's efficacy in BPD. In 1 study, Salzman et al[12] 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.[13,14] 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[13] and Frankenburg and Zanarini[14] 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[15] and some (but not all) placebo-controlled trials have demonstrated benefit from SGAs such as olanzapine,[16-18] aripiprazole,[19] and quetiapine.[20,21] Initial research on risperidone[22] 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.[16,17] However, not all studies of SGAs for BPD patients have been positive.[18] Further, metabolic side effects have been noted for several SGAs, including olanzapine.[18]

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[23] 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. Diagnosing comorbid disorders, such as bipolar disorder, will determine medication choice and impact length of treatment. In a double-blind study of 30 women with BPD and comorbid bipolar II disorder,

continued on page 36

continued from page 32

Pharmacotherapy for BPD

Clinical Point

When treating BPD, SGA doses equal to one-half or one-third the dose used for treating schizophrenia may be appropriate

Table 1

Symptom domains of BPD

Cognitive-perceptual symptoms
Suspiciousness
Referential thinking
Paranoid ideation
Illusions
Derealization
Depersonalization
Hallucination-like symptoms
Impulsive-behavioral dyscontrol
Impulsive aggression
Deliberate self-harm
Impulsive sexual behavior
Substance abuse
Impulsive spending
Affective dysregulation
Mood lability
Rejection sensitivity
Intense anger out of proportion to the stimuli
Sudden depressive mood episodes

BPD: borderline personality disorder

Source: Reference 24

Frankenburg and Zanarini[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***[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.[1,2,17,18] However, for fluoxetine, investigators have espoused using a dosage higher than generally used for depression.[10] For mood-stabilizing anticonvulsants, almost all studies employed the same doses used for bipolar disorder.[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[24] and Nose[26] and a Cochrane Review[27] (with subsequent online update[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[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

Table 2

Which medications improve which BPD symptoms?

Medication	Symptom domain	Effect
Antipsychotics	Cognitive-perceptual	Moderate
	Anger	Moderate/large
Antidepressants	Anxiety	Small
	Anger	Small
Mood stabilizers	Impulsive-behavioral dyscontrol	Very large
	Anger	Very large
	Anxiety	Large
	Depressed mood	Moderate

BPD: borderline personality disorder
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[24] 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 (***Table 2***).[24] 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[27] with subsequent online update by Stoffers[28] 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 (***Table 3, page 38***).[28] 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.

Clinical Point

In 1 meta-analysis, mood stabilizers had a greater effect than antipsychotics on BPD patients' global functioning

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.[30,31] Similar trials testing fluoxetine showed no advantage for the drug over placebo.[32] In a pilot study by Moen et al,[25] 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

Pharmacotherapy for BPD

Clinical Point

Patients with BPD respond well to validation of their symptoms and their experience

Table 3

Pharmacotherapy for BPD: Results of a Cochrane review

Class	Medication(s)
Cognitive-perceptual symptoms	
Antipsychotics	Olanzapine, aripiprazole
Impulsive-behavioral dyscontrol	
Mood stabilizers	Topiramate, lamotrigine
Antipsychotics	Aripiprazole
Affective dysregulation	
Antidepressants	Amitriptyline[a] (depressed mood)
Mood stabilizers	Topiramate, lamotrigine (anger), valproate (depressed mood)
Antipsychotics	Haloperidol (anger), olanzapine, aripiprazole
Omega-3 fatty acids	Fish oil (depression)
Suicidal behavior/suicidality	
Antipsychotics	Flupenthixol decanoate
Omega-3 fatty acids	Fish oil
Interpersonal problems	
Antipsychotics	Aripiprazole
Mood stabilizers	Valproate, topiramate
No improvement on any outcome: ziprasidone, thiothixene, phenelzine, fluoxetine, fluvoxamine, carbamazepine	

[a]Do not prescribe to suicidal patients

BPD: borderline personality disorder

Source: Reference 28

impact of regular, structured, nonjudgmental interactions within a research protocol. Prescribers can enhance a medication's therapeutic effect by keeping in mind the same principles that apply to treatment of other common psychiatric disorders.

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[33] or Borderline Evaluation of Severity Over Time.[34]
- 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-

macotherapy 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.[35]

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.[36] 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.

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continued

Related Resources

- Friedel RO. Borderline personality disorder demystified: an essential guide for understanding and living with BPD. New York, NY: Marlowe & Company; 2004.
- Chapman A, Gratz K. Borderline personality disorder survival guide: everything you need to know about living with BPD. Oakland, CA: New Harbinger Publications, Inc; 2007.
- National Education Alliance for Borderline Personality Disorder. www.borderlinepersonalitydisorder.com.

Drug Brand Names

Alprazolam • Xanax
Amitriptyline • Elavil
Aripiprazole • Abilify
Carbamazepine • Tegretol
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Lamotrigine • Lamictal
Olanzapine • Zyprexa
Phenelzine • Nardil
Quetiapine • Seroquel
Risperidone • Risperdal
Thiothixene • Navane
Topiramate • Topamax, Topiragen
Tranylcypromine • Parnate
Trifluoperazine • Stelazine
Valproic acid • Depakote
Ziprasidone • Geodon

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Explain to patients that they may need to try different medications to find the most helpful agent or combination

Pharmacotherapy for BPD

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Patients with BPD will benefit from a clinician whose approach is responsive, validating, and nonreactive to their symptoms

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Bottom Line

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.