Pharmacotherapy of Borderline Personality Disorder

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Borderline personality disorder can be classified into four groups of symptoms: affective, impulsive, ego-interpersonal, and psychotic. Pharmacotherapy of borderline personality disorder should be directed at the severity of the symptoms in each of these groups, rather than by the presence or absence of the overall syndrome. This article reviews the pharmacotherapy of borderline personality disorder, with special emphasis on affective and impulsive symptoms. Overall, the MAOIs, the SSRIs, and the newer antidepressants (such as venlafaxine) provide the widest spectrum of effective treatment for the symptoms of borderline personality disorder. *(J Clin Psychiatry 1997;58[suppl 14]:48–52)*

The term *borderline* has historically been used to describe patients who were on the borderline between neurotic and psychotic disorders. Such patients exhibited "neurotic" lifestyles and self-doubt, but also demanded large amounts of attention and support. This combination often frustrated and exhausted therapists. Such patients often would seek to exceed the usual therapist/patient boundaries. The psychotherapy of such patients has been written about extensively (see review by Gunderson and Phillips[1]). In the late 1960s, Kernberg and James Masterson suggested that borderline patients could be treated with psychotherapy or through hospitalization, sparking a great deal of interest in the disorder.[1] In recent years, borderline has come to describe a loosely defined spectrum of symptoms with mild thought disorder at one end and affective instability at the other.[2]

In DSM-IV, the syndrome is considered to be among the personality disorders. A personality disorder is defined in DSM-IV as "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment."[3(p629)] Borderline personality disorder is defined in DSM-IV as "a pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity."[3(p629)]

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The prevalence of borderline personality disorder in the general population is estimated to be about 2%.[3] In mental health settings, its prevalence is 10% in outpatient clinics and about 20% for inpatient units.[3] Borderline personality disorder is much more common among women, who make up about 75% of the cases.[3]

COMPONENTS OF BORDERLINE PERSONALITY DISORDER

The syndrome of borderline personality disorder may be classified into four groups of symptoms: affective, impulsive, ego/interpersonal, and psychotic (see Table 1).

Affective aspects include the characteristic labile affect with marked shifts in mood and instability of mood. Patients with borderline personality disorder often react with great emotional intensity to relatively modest stress. They often complain of irritability. Minor-to-modest distress can trigger abrupt "crashes" in mood, leading to substantive interpersonal clashes. These clashes may precipitate suicide attempts, self-destructive and injurious behavior, and other serious problems. Emergency calls to therapists and emergency room visits often result.

Differential diagnoses for the affective aspects include bipolar disorders (particularly bipolar II and cyclothymia), dysthymia, and major depressive disorder. Atypical major depressive disorder, which includes rejection sensitivity, has substantial overlap. Substance abuse and multiple personality disorder are also included in the differential diagnosis for the affective aspects.

Impulsive behavior is very characteristic of borderline personality disorder. Often it is the impulsivity (that may be stimulated by the affective aspects) that brings patients to the attention of family members and mental health providers. Included in this group are overdose, self-mutilation, and suicidal behavior. Food and alcohol binges, promiscuity, and assaultive and antisocial acts tend to occur

Table 1. Aspects of Borderline Personality Disorder

Affective	
	Labile affect—marked shifts of mood
	Irritability—inappropriate and intense outbursts of anger and temper
	Instability of mood
	Stress-related, often transient crashes
	Low mood/dysphoria
Impulsive	
	Overdose
	Self-mutilation
	Suicidal behavior
	Food or alcohol binges
	Promiscuity
	Assaultive or antisocial acts
Ego and Interpersonal	
	Frantic efforts to avoid real or imagined abandonment
	Pattern of unstable and intense interpersonal relationships
	Chronic feelings of emptiness
	Identity disturbance
Psychotic	
	Transient, stress-related psychotic "episodes"
	Referential thinking
	Derealization/depersonalization
	Distortions of reality
	Illusions
	Magical thinking

as well. These acts often are related to labile mood and distressful situations.

The differential diagnoses for impulsive aspects are similar to those for affectivity, but also include eating disorders and other cluster B personality disorders (antisocial, histrionic, and narcissistic personality disorder). Schizotypal personality disorder and organic seizure disorder are also included in the differential diagnosis for the impulsive aspects. Occasionally, adjustment disorder may also be involved in the differential diagnosis.

Ego and interpersonal aspects perhaps form the core of borderline personality disorder psychopathology. Much of the interpersonal behavior of the borderline patient often involves frantic efforts to avoid real or imagined abandonment. Romantic disappointments are frequently extremely devastating due to these fears, coupled with the sense of emptiness. As might be expected, the interpersonal relationships of those with borderline personality disorder are characterized by storminess, idealization, devaluation, and difficulties. Those with borderline personality disorder commonly have a weak and changing self-image, and their sense of self will change over time. They lack a strong sense of who they are.

Although less common, psychotic features may occur in those with borderline personality disorder. Under stress, patients may exhibit psychotic or psychotic-like symptoms, including referential thinking, paranoid ideation, derealization or depersonalization, and distortions of reality. Obviously, the differential diagnosis of these psychotic aspects includes schizotypal and schizoid and paranoid personality disorder.[4] Schizophrenia may also be included in the differential diagnosis.

PHARMACOTHERAPY OF BORDERLINE PERSONALITY DISORDER

A large amount of literature exists on the treatment of borderline personality disorder,[4] much of which focuses on the psychotherapy of borderline personality disorder. Much less has been written about the pharmacotherapy of borderline personality disorder, but the research literature on this topic has been growing. What follows is a review of the research on the pharmacotherapy of borderline personality disorder, focusing particularly on its affective and impulsive aspects. It is divided into sections on lithium, other mood stabilizers, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, and serotonin selective reuptake inhibitors (SSRIs) and newer agents (Table 2).

Lithium

In the 1970s, there were two studies involving lithium in the treatment of borderline personality disorder. Both involved placebos and were double-blind. In a study by Sheard and colleagues,[5] 66 nonpsychotic prisoners with histories of chronic impulsive/aggressive behavior were enrolled in a 12-week, double-blind, placebo-controlled trial. Sheard described the subjects as "an extremely manipulative, hostile, and aggressive group of young men who were extroverted, highly impulsive, and action oriented."[5(p1411)] Lithium significantly reduced their aggressive behavior as seen by a decrease in the number of infractions committed by the inmates. Infractions included serious threatening behavior and actual assaults.

In 1972, Rifkin and associates[6] administered lithium in a 6-week, double-blind, crossover trial of inpatients with emotionally unstable character disorder (EUCD). EUCD involves short mood swings (which are often unprecipitated by life events and have a life of their own), emotional over-reactivity, substance abuse, antisocial tendencies, and resistance to authority. EUCD by definition overlaps substantially with borderline personality disorder in terms of affective and impulsive aspects. In this study, lithium was significantly better than placebo.

Other Mood Stabilizers

In 1986, Gardner and Cowdry[7] involved 16 female outpatients in a double-blind, placebo-controlled trial of carbamazepine in patients with borderline personality disorder with an extensive history of behavioral dyscontrol. The study lasted 33 days, and carbamazepine significantly decreased the severity of the dyscontrol.

A 6-week open trial of valproate was reported by Wilcox[8] in 1995 of 30 inpatients meeting DSM-III-R criteria for borderline personality disorder. He achieved a high blood level of valproate (100 mg/mL) using a mean of 1500 mg of valproate per day. No changes in anxiety or depression were reported, but the Brief Psychiatric Rating

Table 2. Pharmacotherapy of Borderline Personality Disorder*

Study	Number of Subjects	Duration (weeks)	Results
Lithium			
Sheard et al, 1976[5]	66	12	Lithium significantly reduced aggressive behavior
Rifkin et al, 1972[6]	21	6	Lithium significantly better than placebo in patients with EUCD
Anticonvulsants			
Gardner and Cowdry, 1986[7]	16	6	Carbamazepine significantly decreased the severity of behavioral dyscontrol
Wilcox, 1995[8]	30	6	Valproate significantly reduced BPRS total score and aggressive outbursts
Cowdry and Gardner, 1988[9]	16	6	Tranylcypromine and carbamazepine were effective, and carbamazepine was associated with a marked decrease in behavioral dyscontrol
MAOIs and TCAs			
See Cowdry and Gardner above			
Liebowitz et al, 1988[10]	119	6	Phenelzine superior to imipramine and placebo on CGI severity scale, SADS-C, GAS, SADS supplement for borderline, labile personality, and atypical depression subscales. Phenelzine also superior to placebo on scales of depression, hysteroid dysphoria, hostility, and obsessions and compulsions
Parsons et al, 1989[11]	75	12	92% response rate with phenelzine, 35% response with imipramine, 24% response with placebo
Soloff et al, 1993[12]	108	5	Haloperidol superior to phenelzine on control of impulsivity and psychoticism. Phenelzine more effective than haloperidol on depression
Soloff et al, 1986[13]	61	5	Amitriptyline and haloperidol effective in alleviation of depression. Haloperidol effective in reducing impulsivity
SSRIs and newer agents			
Salzman et al, 1995[14]	22	13	Fluoxetine significantly more effective in decreasing anger independent of its effectiveness in alleviating depression
Kavoussi et al, 1994[18]	11	8	Sertraline significantly reduced irritability and aggression
Markovitz and Wagner, 1995[19]	44	12	Venlafaxine significantly reduced all scales of the SCL-90R. Somatic symptoms such as migraines and PMS were also substantially reduced

*Studies involving only neuroleptics are not included in this review. Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, EUCD = emotionally unstable character disorder, GAS = Global Assessment Scale, PMS = premenstrual syndrome, SADS-C = Schedule for Affective Disorders and Schizophrenia-Change version, SCL-90R = Symptom Checklist-90-Revised.

Scale total score and the aggressive outbursts were significantly reduced.

In 1988, Cowdry and Gardner[9] reported on a complicated and intensive study of borderline personality disorder at the National Institutes of Health involving 16 female outpatients. Alprazolam, carbamazepine, trifluoperazine, tranylcypromine, and placebo were administered in a double-blind, placebo-controlled fashion over a number of months. Each medication was administered for 6 weeks followed by a week of tapering the medication and at least a 1-week placebo washout in between. The authors found that tranylcypromine and carbamazepine were effective, and further that carbamazepine was associated with a marked decrease in behavior dyscontrol. Interestingly, alprazolam was associated with an increase in behavioral dyscontrol.

MAOIs and Tricyclics

A 6-week, double-blind study of 119 outpatients was conducted by Liebowitz and colleagues[10] at New York State Psychiatric Institute and reported in 1988. The study was of atypical depression, which is defined as a major depression with a substantial mood reactivity and at least one of the following: increased appetite or weight gain, oversleeping, leaden paralysis, and pathologic sensitivity to rejection. In this study, overall response rates were determined using the Clinical Global Impressions scale (CGI): 71% responded to phenelzine, 50% to imipramine, and 28% to placebo. Phenelzine was found to be superior to imipramine and placebo on the CGI severity scale, the Schedule for Affective Disorders and Schizophrenia Change version (SADS-C), the Global Assessment Scale (GAS), and the SADS supplement for borderline, labile personality, and atypical depression subscales. Phenelzine was also superior to placebo on scales of depression, hysteroid dysphoria, hostility, and obsessions and compulsions.

Parsons et al.[11] evaluated a subsample of patients from the above study. The subsample included patients who met Research Diagnostic Criteria for major, minor, or intermittent depression; maintained mood reactivity while depressed; exhibited one of the following: increased appetite or weight gain, oversleeping, leaden paralysis, or pathologic sensitivity to rejection; and had no other Axis I diagnosis. There was a 92% response rate among the 27 patients taking phenelzine, 35% response rate for the 23

patients taking imipramine, and a 24% response rate for the 25 patients taking placebo. In those patients who had less than four of these borderline symptoms, the response rates between imipramine and phenelzine did not differ.

In a 5-week, double-blind, placebo-controlled study reported by Soloff and colleagues[12] in 1993 of 108 inpatients meeting DSM-III-R and Gunderson criteria for borderline personality disorder, haloperidol was found to be superior to phenelzine on the control of impulsivity and psychoticism. As expected, phenelzine was found to be more effective than haloperidol on depression.

In another study conducted by Soloff et al.[13] of 61 inpatients with borderline personality disorder and/or schizotypal personality disorder, the trial involved a 5-week, double-blind study of amitriptyline, haloperidol, and placebo. The mean dose of amitriptyline was 147 mg and haloperidol was 7.2 mg. In this study, amitriptyline and haloperidol were both found to be effective in the alleviation of depression, and haloperidol (but not amitriptyline) was found to be effective in reducing impulsivity.

These studies demonstrate that several different types of medications are effective in treating borderline patients. The samples varied widely and contained patients with very different kinds of symptoms. Overall, the lithium and mood stabilizers tended to be more effective in control of aggression and behavioral dyscontrol. The antidepressants were more effective in treating depressive symptomatology and mood reactivity. Neuroleptics were more effective in reducing psychotic symptoms.

The SSRIs and Newer Agents

There are four studies of fluoxetine in the treatment of borderline personality disorder. In the one placebo-controlled, double-blind study, Salzman et al.[14] found that fluoxetine was significantly more effective in decreasing anger independent of fluoxetine's effectiveness in alleviating depression. The study lasted 13 weeks and involved 22 symptomatic volunteers, most of which had a prior history of psychiatric treatment. The daily dose of fluoxetine was 40 mg. The three open studies reported similar effects.[15–17]

There has been one trial of sertraline, an 8-week open trial involving 11 patients with at least one personality disorder.[18] Eight of the patients had borderline personality disorder. The mean dose of sertraline was 131 mg, and significant reductions in irritability and aggression were reported. Interestingly, there was a substantial change in irritability by Week 2.

There is one study of venlafaxine in the treatment of borderline personality disorder.[19] It was a 12-week open trial involving 44 patients. Mean dose of venlafaxine was 315 mg/day. Markovitz and Wagner reported that all scales of the Symptom Checklist-90-Revised (SCL-90R) were significantly reduced. Self-injury was reduced by 80% for the group as a whole and was completely eliminated in 69%. Somatic syndromes such as migraines and premenstrual syndrome were also substantially reduced.

Overall, the newer agents appear to be effective in the treatment of borderline personality disorder, especially in view of their benign side effect profiles. We will have to wait for further controlled clinical trials for definitive answers.

DISCUSSION

This review of the treatment of pharmacotherapy of borderline personality disorder has revealed that various agents have effects on different aspects of the condition. Overall, the mood stabilizers are most effective in treating impulsivity and aggression. They also have some effect on affective instability. They seem to have relatively little effect on psychoticism or depression. The MAOIs are extremely effective in both impulsivity/aggression and affective instability. They are also extremely effective in the treatment of depression. They are not effective for reducing psychoticism. The tricyclic antidepressants are significantly less effective in the treatment of borderline personality disorder than are the MAOIs. Although efficacy of the depressive aspects is comparable, the tricyclic antidepressants do not appear to be useful in either impulsivity/aggression or affective instability. The benzodiazepines have been relatively unstudied, but the one study that involved alprazolam found behavioral dyscontrol in some of the patients.

Neuroleptics are effective in reducing psychoticism and impulsivity/aggression, but seem relatively unhelpful with regard to affective aspects of borderline personality disorder.

The newer agents, such as venlafaxine, appear to be very useful agents for all of the dimensions of borderline personality disorder, with the exception of psychoticism. They are useful, at least as demonstrated in open-label studies, in reducing impulsivity/aggression and depression.

Summarizing this information in a clinically useful format for treatment of patients with borderline personality disorder, I would recommend that clinicians evaluate patients with this disorder in terms of the dimensions of impulsivity/aggression, affective instability psychoticism, and ego/interpersonal (see Table 3). Then treatment should address each of these dimensions. I would recommend moving cautiously on evaluating and treating the ego and interpersonal aspects because improvement in the other dimensions may substantially change the amount of dysfunction in these two areas.

With this in mind, the impulsivity/aggression is best treated by mood stabilizers, the newer agents, and the MAOIs. Affective instability is best addressed by the MAOIs and the newer agents. Depression is best treated

Table 3. Pharmacotherapy of Dimensions of Borderline Personality Disorder*

Medication	Impulsivity/ Aggression	Affective Instability	Psychoticism	Depression
Mood stabilizers	++	+		
MAOIs	++	++		++
TCAs	+			++
Benzodiazepines	–			
Neuroleptics	++		++	
SSRIs and newer antidepressants	++	++		++

*Symbols: ++ = strong effect, + = modest effect, – = no effect.

by the newer agents, the MAOIs, and the tricyclic antidepressants. Psychotic symptoms are best treated by neuroleptics.

Benzodiazepines may be useful in the treatment of borderline personality disorder in helping to reduce anxiety and sedation. However, they may have a paradoxical opposite effect and lead to behavioral dyscontrol. In such situations, increasing the dose of benzodiazepines may substantially worsen the clinical situation rather than help it.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), carbamazepine (Tegretol and others), fluoxetine (Prozac), haloperidol (Haldol and others), imipramine (Tofranil and others), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trifluoperazine (Stelazine), venlafaxine (Effexor).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for borderline personality disorder: amitriptyline, fluoxetine, imipramine, phenelzine, sertraline, and venlafaxine.

Discussion

Dr. Hirschfeld: I don't know if stimulants would help patients increase their focus or lead to behavior dyscontrol. I have seen no reports about the use of stimulants in borderline personality disorder. Some drugs seem to cause behavioral dyscontrol. For example, amitriptyline nonresponders, when compared with placebo nonresponders, seem to display more behavioral dyscontrol, and similar reports exist for various benzodiazepines.

Dr. Yonkers: For several reasons, one of our biggest challenges is to try to conduct studies about borderline personality disorder. First, we have no idea how we should define response, because borderline personality disorder is a character disorder. Even the target criteria don't help us define response. Then, one would have to expect a certain degree of noncompliance, but people with borderline personality disorder have nightmarish levels of compliance to medication. We don't know if patients take their medication unless, for example, we check plasma levels to find out how much medication is present. Finally, you've alluded to the comorbidity of borderline personality disorder and the heterogeneity of the samples.

It would be immensely helpful to look at these trials methodologically, in order to find out where we are now and to determine what studies are feasible. Also, the pharmacotherapy of personality disorders has been grossly neglected. Many of the basic science data point to modulation of the serotonergic system for ameliorating aggressive tendencies.

Dr. Hirschfeld: I would subscribe to everything you said, with the exception of the definition of response criteria. Measures of impulsivity, affectivity, and psychoticism are available.

Dr. Yonkers: Right, but you have to decide which measure applies to an individual's condition.

Dr. Hirschfeld: The best way to assess the utility of a particular treatment intervention in borderline personality disorder is to look at each measure separately rather than to use the Clinical Global Impressions, which is successfully used to measure outcome in many clinical trials. While many studies of borderline personality disorder have substantial methodological flaws and problems, the researchers did the best they could under difficult circumstances.

Dr. Keller: The gist of my concern is that a personality disorder is at the heart of borderline personality disorder. We need to examine the basic nosology of personality disorders, which would define borderline personality disorder as abiding in the traits of an individual's personality or character over years, beginning in the late teens. If that becomes the nosology for borderline personality disorder, then a change in the disorder defines the outcome. We can't say that we've treated the personality disorder just because we pick one symptom and treat it and certain aspects of the individual's behavior change. We can still find enormous value in treating individuals with personality disorder and seeing if some improvement occurs, but we have to be disciplined and careful in how we articulate and define our goals and objectives. On one hand, we can say that people with borderline personality disorder can achieve some improvement in certain behavioral features. On the other hand, we can try to be more ambitious in our treatment; we can say, "I think I can change the character problems forever." I think clarity is a necessity in the trial, so that our expectations and designs have measurable outcomes.

Dr. Hirschfeld: When Dr. Popper discussed attention deficit disorder (ADD) this morning, he said that some people argue that pure ADD is nonexistent, and ADD is always comorbid. This may be even more true for borderline personality disorder. However, I don't think that we should focus on specific symptoms. In a decade, we will be talking about several different illnesses, so I think we would find the most relevant data from studies focused on the dimensions of borderline personality disorder. There are three important dimensions of this syndrome, each of which we can examine semi-independently: affectivity, impulsivity, and psychoticism. We need to structure our research so the next generation of investigators will have our data on those three aspects. I think we can meet that goal.