Pharmacology of Personality Disorders

The prevalence and debilitating nature of some of the personality disorders has impeded the study of psychopharmacology in these conditions. However, important advances have been made in the last several years.

If psychopharmacology sometimes feels like walking a fine line between undertreatment and overtreatment or between letting patients suffer and turning to medications as an "easy fix," then the psychopharmacology of personality disorders can feel like walking a tightrope without a net. Unfortunately, the published literature is helpful only up to a point. There are not many peer-reviewed randomized controlled trials, given the prevalence and debilitating nature of some of the personality disorders. Studies have tended to be comparatively small and, especially in light of the chronic nature of much Axis II pathology, short in duration. Few, if any, trials have compared in size and scope to the large government- or industry-funded studies of the major mood and psychotic disorders.

The studies that have been published often have had high dropout rates, with positive results limited to certain domains and other areas of disturbance largely unimproved. There also has been a growing trend, perhaps caused by liability or institutional review board concerns, for treatment studies to include only patients who are comparatively stable and free of active suicidality. Few recent personality disorder drug studies have included, for example, the intermittently unsafe borderline patients often seen in clinical practice. This means that there are virtually no randomized clinical trials of increasingly popular agents like topiramate, lamotrigine, or the atypical antipsychotic in borderline or other personality disordered patients who are or recently have been actively suicidal. Nevertheless, meaningful strides have been made over the past several years, with several novel agents demonstrating statistically significant results. Most promising are major discoveries relating to neurobiologic abnormalities and neurobiologic changes in response to provocation or treatment that have helped elucidate the constitutional factors that underlie personality disturbance. Much of this recent outcome and neurobiologic research has focused on aspects or dimensions of the Axis II disorders in addition to or instead of the categoric syndromes defined by the DSM. Personality disorders are phenotypic expressions of biologic vulnerabilities and arise from a combination of predisposing genotypes and experiential factors. These factors may consist of present-day life stressors and/or early abuse and neglect, the effects of all of which may be modulated by damage to the CNS as it develops during childhood and adulthood. Although the strong correlation between negative life experiences and personality disorders has become a cornerstone of our understanding of some Axis II pathology, it should be remembered that heredity also appears to play a crucial role in the pathogenesis of personality disorders.

A Norwegian twin study suggested that personality disorders are more strongly determined by genetics than are almost all the Axis I disorders. Moreover, the psychological damage caused by abuse and neglect may be modulated by deleterious effects on the "hard-wiring" of the CNS. It should not, therefore, be surprising that many patients with personality disorders exhibit structural and functional brain abnormalities, or that certain medications may be beneficial in these disorders.

Borderline personality disorder

By far the most studied personality disorder, borderline personality disorder (BPD), is also the only one to be the subject of an American Psychiatric Association practice guideline. Pioneering BPD studies that suggested the utility of neuroleptics and mood stabilizers, as well as the risks of benzodiazepines and tricyclic antidepressants, are by now well known. Early neurobiologic
research implicated disturbances of the serotonin system in the suicidality and impulsive aggression characteristics of this population.\textsuperscript{12,13} Currently, the best validated medications for BPD may be the selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), antipsychotics, and anticonvulsants.

In placebo-controlled trials, fluoxetine has been shown to be helpful with anger,\textsuperscript{14} irritability, aggression, and overall clinical status,\textsuperscript{15} although it did not appear to benefit patients receiving concurrent dialectical behavior therapy (DBT)\textsuperscript{16} and was less efficacious than olanzapine or the olanzapine-fluoxetine combination for depression and impulsivity-aggression.\textsuperscript{17} In a rare pharmacologic study using decreases in suicide attempts as the principal outcome measure, paroxetine was superior to placebo in a mixed sample of multiple attempters, the majority of whom had BPD.\textsuperscript{18} Both sertraline and citalopram were found to decrease the frequency of BPD—and of several other personality disorders—in patients entered into a randomized, non-placebo-controlled depression treatment study.\textsuperscript{19} Most recently, fluvoxamine was better than placebo for rapid mood shifts in BPD but not for impulsivity or aggression.\textsuperscript{20}

Exploration of serotonergic abnormalities has continued to dominate neurobiologic research into BPD and its component dimensions. Trait impulsivity in persons with personality disorders has been associated with blunted hormonal responses to the serotonergic probe ipsapirone.\textsuperscript{21} Positron emission tomography (PET) scans of patients who have personality disorders with impulsive aggression have shown blunted metabolic responses to fenfluramine in the orbitofrontal, adjacent ventromedial, and cingulate cortices.\textsuperscript{22} Fluoxetine treatment of BPD in a sample of patients with impulsive aggression was associated not only with clinical improvement but with PET findings of increased metabolic rate in the orbitofrontal cortex.\textsuperscript{23} During the first wave of pharmacologic research in BPD, neuroleptics were among the most consistently efficacious agents, although follow-up studies to one famous set of trials failed to support haloperidol's overall usefulness.\textsuperscript{24,25} Two important studies demonstrated a decrease in suicide attempts or self-harm behaviors with depot neuroleptics.\textsuperscript{26,27} Unsurprisingly, atypical antipsychotics have supplanted neuroleptics in more recent research. Olanzapine has proved better than placebo on scales of anxiety, paranoia, anger/hostility, and interpersonal sensitivity, although not depression\textsuperscript{28}; overall clinical status\textsuperscript{29}; and when added to DBT depression, anxiety, and impulsive aggression.\textsuperscript{30} More recently, aripiprazole was found to be superior to placebo for depression, anxiety, anger, and most of the domains measured by the SCL-90-R.\textsuperscript{31} The (partial) efficacy of antipsychotics in BPD may reflect underlying causative abnormalities of the dopaminergic system.\textsuperscript{32}

Anticonvulsants have proved attractive to clinicians and researchers working with BPD because of the disorder's resemblance, in certain respects, to bipolar disorder, and because BPD patients' "anger attacks" sometimes seem seizure-like in their suddenness and irresistibility. Early encouraging results with carbamazepine\textsuperscript{10} were followed by a published trial in which the active drug showed no greater efficacy than placebo.\textsuperscript{33} In a controlled study of the effect of divalproex on aggression, the intent-to-treat analysis failed to reveal any significant benefit, but subgroups with cluster B personality disorders\textsuperscript{34} and BPD\textsuperscript{35} showed improvements on various measures of anger, aggression, and overall clinical status. Divalproex has also been associated with amelioration of interpersonal sensitivity, anger/hostility, and aggression in BPD patients with comorbid bipolar II disorder.\textsuperscript{36}

Newly popular anticonvulsants for BPD include lamotrigine and topiramate, both of which have been associated with decreases in self-report measures of anger in BPD patients.\textsuperscript{37-39} A recent topiramate study is noteworthy among BPD drug trials for using an usually broad range of outcome measures. Significant treatment-associated improvements were noted in somatization, interpersonal sensitivity, anxiety, hostility, phobic anxiety, and global severity on the SCL-90-R; 4 of 8 scales of the Inventory of Interpersonal Problems; and all 8 scales of the SF-36 Health Survey, an instrument measuring health-related quality of life.\textsuperscript{40} Innovative, recently studied agents to treat BPD include ethyl-eicosapentaenoic acid, which sometimes is used for bipolar and other mood disorders, and was found to be superior to placebo at reducing aggression and the severity of depressive symptoms in BPD.\textsuperscript{41} Two different doses of the -adrenergic agonist, clonidine, were given to BPD patients experiencing strong urges to engage in self-injurious behavior; both were associated with significant decreases in dissociative symptoms, suicidal ideation, and wishes to commit self-harm.\textsuperscript{42} Intravenous naloxone, in the only published placebo-controlled trial of an opiate antagonist known to us, appeared to reduce dissociative symptoms but failed to show greater efficacy than placebo.\textsuperscript{13} Nevertheless, BPD treatments that mimic or block narcotic activity show some promise. Many BPD
patients mutilate themselves or engage in other behaviors like bulimia and substance abuse that also may reflect abnormalities of the endogenous opiate system. BPD patients who self-mutilate have shown diminished pain sensitivity, which, in turn, has been correlated with dissociation. It may be that physical self-destructiveness, impulsivity, and dissociation in BPD represent the final pathways of various possible disturbances in the painprocessing system, and that medications that help offset these disturbances will provide substantial benefit.

**Schizotypal personality disorder**

As with schizophrenia, functional impairment in schizotypal personality disorder (SPD) may be due more to patients' social withdrawal and cognitive abnormalities than to their odd beliefs and perceptual experiences. Several early BPD pharmacologic studies included persons with SPD and found little difference in medication responsiveness between the 2 groups. Unfortunately, little randomized research has been undertaken in the intervening years. One exception is a placebo-controlled study using low-dose risperidone that found significant treatment-associated improvements in both positive and negative symptoms. Promising agents for schizophrenia-spectrum disorders include drugs that enhance executive function, for example, through potentiating effects on noradrenergic neurons with termini in the prefrontal cortex or through prefrontal D1 agonism.

**Antisocial personality disorder**

Randomized studies in antisocial personality disorder have generally focused on forensic populations, often male prison inmates. Published research of this type has all but disappeared during the last 10 years, perhaps because of regulatory obstacles to enrolling prisoners in drug trials. In older studies, both lithium and phenytoin were found to be useful in decreasing aggression and/or rule infractions in incarcerated violent offenders.

**Avoidant personality disorder**

Of all the interrelationships between Axis I and Axis II disorders, one of the most widely agreed on is the close resemblance between social anxiety disorder and avoidant personality disorder (APD). In a controlled trial, a monoamine oxidase inhibitor (MAOI) was shown to be useful for social anxiety and, perhaps more strongly, for maladaptive personality traits, with a twofold reduction in the number of brofaromine-treated patients who met criteria for APD.

**Polypharmacy in personality disorders**

Despite the inconclusive evidence at present for the effectiveness of pharmacotherapy for the treatment of many personality disorders, patients with Axis II pathology, especially BPD, are among the most likely populations to be prescribed psychotropic drugs, often several simultaneously. The only combined therapy that has been tested in BPD, to our knowledge, is the olanzapine-fluoxetine combination, which was found not to be superior to olanzapine alone for depressive symptoms and impulsive aggression, although it did result in less weight gain. In our experience, polypharmacy in BPD frequently occurs as the result of a cumulative process: medications with unclear benefits continue to be prescribed for fear of inducing a clinical deterioration in a worrisome patient, while more and more medications are added on because of persistent symptomatology. Clinicians treating patients with BPD and other personality disorders should be on guard against this unwitting polypharmacy, since it is of little empirically supported usefulness and may result in exposing a vulnerable population to dangerous iatrogenic complications.

**Axis I-Axis II comorbidity**

One common approach to patients with personality disorders with comorbid mood or anxiety disorders can be summarized as, "medicate the Axis I symptoms and leave the Axis II problems for psychotherapy." In many clinicians' experience, however, including our own, pharmacologic treatments for mood or anxiety disorders tend to work less well in patients with severe personality disorders. This is a controversial area, with some published research suggesting that Axis II pathology worsens...
the response to medication treatment of Axis I disorders and other studies suggesting that it does not. However, most of the relevant studies have excluded the sickest personality-disturbed patients (eg, ones who were suicidal), or else required that the Axis I disorder be the primary diagnosis, thereby excluding patients who were judged to be personality disturbed with a superimposed mood or anxiety disorder.

**Recommendations and future directions**

Much research remains to be done on personality disorder pharmacotherapy, especially neurobiologic explorations of underlying causes and risk factors. It is imperative that there be larger and longer randomized drug treatment trials, in both healthier and sicker populations, including studies in patients at risk for homicide or suicide. In view of the comparatively limited evidence for the efficacy of medications for Axis II pathology, as well as the marked placebo-responsiveness of some personality disordered patients, it seems both ethical and necessary for there to be further placebo-controlled trials, or at least trials with substantial placebo lead-in periods. For clinicians treating patients with personality disorders, many medication options are available. In BPD, the bestsubstantiated choices include SSRIs/ SNRIs, anticonvulsants, and neuroleptics/ atypical antipsychotics. Most of these drug classes have shown statistically significant benefits for aggression, anger, impulsivity, and/or affective lability, although results have been somewhat inconsistent.

There is evidence that atypical antipsychotics may be helpful for both positive and negative symptoms in SPD and that MAOIs may be a treatment for APD. Aggressiveness in antisocial personality disorder (ASPD) may be reduced by phenytoin or lithium, and it seems reasonable to infer that agents useful in treating aggressiveness in BPD may be useful in ASPD as well, especially given the high rates of comorbidity between the disorders.\(^5^8\)

It is worthwhile to bear in mind that the extreme, dysregulated emotions to which patients with personality disorder are prone are likely to influence their attitudes toward medications. Treaters should expect certain persons with personality disorders, especially those with BPD, to alternate between idealizing the miraculous potential of medications and devaluing them as not worth taking or even considering.

An important pitfall to avoid is fostering in Axis II patients an overly optimistic conviction that a medication "cure" is just around the corner and that it is just a matter of finding "the right drug." Although it is reasonable to encourage patients to participate in rational medication trials, treaters should simultaneously encourage them to participate in evidence-based psychotherapy and to make efforts to sustain their realworld functioning, regardless of whether or not a given medication trial is successful. At the present time, there is little evidence that the difficulties experienced by persons with personality disorders will go into remission as a result of pharmacotherapy. Fully effective medication treatments for these widespread and oftencrippling disorders must await further descriptive and empirical research.

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**Drugs Mentioned in This Article**

Aripiprazole (Abilify)
Brofaromine (Consonar)
Carbamazepine (Carbatrol, Tegretol, others)
Citalopram (Celexa)
Clonidine (Catapres)
Divalproex (Epival, Depakote)
Ethyl-eicosapentaenoic acid
Fenfluramine (Pondimin)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Haloperidol (Haldol)
Ipsapirone
Lamotrigine (Lamictal)
Lithium (Eskalith)
Naloxone (Narcan, Suboxone, Pentazocine)
Olanzapine (Zyprexa)
Paroxetine (Paxil)
Phenytoin (Dilantin)
Risperidone (Risperdal)
Sertraline (Zoloft)
Topiramate (Topamax)

References


Evidence-based References


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