

# Clinical Outcome of Psychopharmacologic Treatment of Borderline and Schizotypal Personality Disordered Subjects

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This paper reviews the biological and psychopharmacologic nature of personality disordered subjects, specifically those with borderline (BPD) and schizotypal (ScPD) personality disorder. Generally speaking, there is no agent of choice for the treatment of either BPD or ScPD. Many agents of different classes appear to offer some benefit to selected subjects depending upon their symptom presentation. For example, ScPD or BPD subjects with prominent cognitive/perceptual distortion may respond to neuroleptic agents, while some BPD subjects with depressed mood may respond best to antidepressants. The hypothesis that biological and behavioral dimensions underlie the psychopharmacologic response to treatment in personality disordered subjects, proposed over the past decade, is now being tested. The most salient example of this is the testing of serotonin-specific agents (e.g., fluoxetine) for potential antiaggressive efficacy in personality disordered subjects with prominent histories of impulsive aggressive behavior and putative reduced serotonin system function.

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Of the various personality disorders, borderline (BPD) and schizotypal (ScPD) personality disorder have historically been among the more critical of Axis II disorders for clinicians to identify and treat. Since the 1950s psychiatrists have recognized the existence of patients that were "borderline" in some way; that is, not quite "psychotic" but with more psychopathology than seen in the typically "neurotic" individual. For years, some of these individuals were referred to as "psuedoneurotic schizophrenics." In some studies, these individuals were reported to be characterized by "massive anxiety, obsessive-compulsive symptoms and adaptations, somatic preoccupations, anhedonia and frequent agitation,"<sup>1</sup> a picture consistent with a mixed personality disorder with features from both the dramatic and anxious Axis II Cluster traits of currently recognized DSM-IV personality disorders. Another group of subjects who would have been considered "borderline" were characterized as being "emo-

tionally instable" with marked and frequent shifts of mood within the course of a day.<sup>2</sup>

Finally, in a landmark paper, Spitzer et al.<sup>3</sup> proposed that individuals clinicians considered to have "borderline personality," "borderline personality organization," or "borderline schizophrenia" broke out phenomenologically into three groups of subjects: (1) a group with features like those of the DSM-III criteria for BPD, (2) a group with features like those of the DSM-III criteria for ScPD, and (3) a group with both BPD and ScPD features. Accordingly, this work led to the operationalization of the two types of "borderline" personality disorders now referred to as BPD and ScPD.

With the separation of "borderline" individuals into BPD and ScPD Axis II categories, work began on understanding the nature of these two personality disorders and how they related to other, better known Axis I disorders. Specifically, BPD individuals were noted to be highly emotional and in many respects resembled individuals with mood disorders. Similarly, ScPD individuals were odd in both cognitive and perceptual spheres and appeared to resemble schizophrenics with residual symptoms. This led to the hypothesis that BPD may be related to mood disorder while ScPD may be related to schizophrenia. This hypothesis served more than a heuristic purpose. It also guided initial efforts in determining the optimal psychopharmacologic treatment strategy for individuals with these personality disorders.

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### **BORDERLINE PERSONALITY DISORDER: A MOOD DISORDER SPECTRUM CONDITION?**

In addition to a more than passing phenomenologic similarity of BPD with mood disorders, BPD subjects are reported to have a high incidence of current and/or past mood disorder. This observation naturally led to the testing of a familial link with mood disorders by the family history method. Initially, early studies reported that first-degree relatives of BPD subjects in fact had higher morbid risk of mood disorder than non-BPD and/or normal control subjects.<sup>4-6</sup> Later studies revealed, however, that when comorbidity of mood disorder in the BPD proband is controlled for, first-degree relatives of BPD probands do not have a higher morbid risk of mood disorder than do relatives of non-BPD probands.<sup>7</sup> Instead, what appears to be transmitted in families is a higher morbid risk for the presence of personality traits of affective dysregulation and impulsive aggression.

Studies of various biological markers of affective disorder have also been conducted in an attempt to test the "Mood Disorder Hypothesis of BPD." Like family history studies, initial work in this area also appeared to support the hypothesis.<sup>8</sup> BPD subjects were reported, like depressed individuals, to have elevated rates of dexamethasone nonsuppression and thyroid-stimulating hormone blunting on thyrotropin-releasing hormone stimulation. Later work revealed that both findings were closely related to the presence of current or recent affective disorder in these subjects.<sup>8</sup> Accordingly, these data do not offer support for the idea that BPD, itself, is biologically related to mood disorder.

Examination of specific neurotransmitter function also does not support a biological link between BPD and mood disorders. Abnormalities in central serotonin (5-HT) function have been found to be present in both mood disordered and BPD subjects. However, reduced 5-HT function does not correlate with a history of depression or the severity of state depression in either group.<sup>9</sup> Instead, reduced 5-HT function appears to correlate inversely with the presence of a history of suicide attempt in both groups and with impulsive aggression in personality disordered subjects only. With regard to central norepinephrine function, a reduction in  $\alpha_2$ -norepinephrine receptor function is reported in mood disordered,<sup>10</sup> but not in personality disordered,<sup>11</sup> subjects. Recently, work with the indirect acetylcholine agonist physostigmine has suggested that BPD subjects have a heightened sensitivity to cholinergic stimulation.<sup>12</sup> While this is also true for mood disordered subjects,<sup>13</sup> BPD subjects were more sensitive to physostigmine in terms of affective lability rather than depression specifically.

Overall, family history and biological data appear not to support the hypothesis that BPD is a mood-disorder spectrum condition. Instead, there appear to be dimen-

sions of personality, affective dysregulation/lability, and impulsive aggression that better characterize BPD and are both transmitted in families and correlated with biological features. Review of the psychopharmacologic data below will provide further evidence of this idea.

### **SCHIZOTYPAL PERSONALITY DISORDER: A SCHIZOPHRENIA-RELATED DISORDER SPECTRUM CONDITION?**

Unlike BPD, there is more evidence supporting the hypothesis that ScPD falls on a spectrum with schizophrenia-related disorders (e.g., schizophrenia, schizoaffective disorder). First, several family history studies report a higher morbid risk of schizophrenia-related, but not mood, disorders in first-degree relatives of probands with ScPD.<sup>4,14</sup> Second, smooth-pursuit eye movement (SPEM), which is impaired in schizophrenic subjects, is also impaired in ScPD, but not other personality disordered subjects.<sup>15</sup> SPEM is thought to be a marker of neurointegrative function. Accordingly, an impairment in SPEM in ScPD subjects suggests the presence of subtle defects in the processing of sensory stimuli and in motoric responses to these stimuli. Since some studies report a direct relationship with the negative symptoms of schizotypy,<sup>16</sup> it is possible that SPEM represents a neurobiological marker of these traits.

Examination of specific neurotransmitter function, while not as extensive as that for BPD, also supports a biological link between ScPD and schizophrenia-related disorders. Both plasma and cerebrospinal fluid concentrations of homovanillic acid (plasma/CSF HVA) have been reported to be elevated in ScPD subjects compared with non-ScPD subjects.<sup>17,18</sup> In addition, plasma HVA concentrations have been reported to correlate positively with the number of "positive" (e.g., magical thinking, ideas of reference, recurrent illusions, suspiciousness), but not "negative" (e.g., social isolation, odd speech, constricted affect, undue social anxiety) symptoms of schizotypy.<sup>17</sup> The finding that plasma HVA correlates directly with positive schizotypal symptoms is consistent with previously reported findings reporting a direct correlation with severity of schizophrenia.<sup>19,20</sup>

Accordingly, both family history and biological data appear to support the hypothesis that ScPD lies on a spectrum with other Schizophrenia-related disorders. As will be seen below, this idea provides the rationale for treating ScPD with drugs similar to those used to treat schizophrenia.

### **USE OF PSYCHOPHARMACOLOGIC AGENTS IN BORDERLINE AND SCHIZOTYPAL PERSONALITY DISORDER**

#### **Neuroleptics**

While neuroleptics have, when effective, generally been useful in treating positive schizotypal symptoms in personality disordered subjects, early studies (in subjects who

were probably not ScPD by today's DSM-IV criteria) found little efficacy for neuroleptic agents. The earliest study of neuroleptic treatment in what today would be considered a personality disorder study group was in "borderline" subjects treated double-blind with trifluoperazine, diazepam, or meprobamate/benactyzine.<sup>21</sup> This study reported that diazepam was more effective than trifluoperazine in relieving overall symptoms and that the latter was marginally better than meprobamate/benactyzine. Three years later, Klein<sup>1</sup> reported results from his double-blind, placebo-controlled study comparing chlorpromazine with imipramine in "pseudoneurotic schizophrenics." This study found that imipramine, but not chlorpromazine, was more effective than placebo on global outcome ratings. Curiously, the reverse was true for emotionally unstable character disordered subjects. Four years later, a similar study comparing a neuroleptic with a thymoleptic reported that treatment with the monoamine oxidase inhibitor tranylcypromine led to higher general improvement than did trifluoperazine.<sup>22</sup> The very next year, however, a report of an open-label study of pimozide in DSM-II personality disorder subjects suggested that pimozide was associated with good to excellent global improvement in 69% of subjects with the best results in subjects with paranoid or schizoid personality disorders.<sup>23</sup> This was followed by case reports,<sup>24</sup> and other open trials,<sup>25,26</sup> in DSM-III ScPD and BPD subjects that suggested that low-dose haloperidol or thioridazine was moderately effective in reducing symptomatology including that related to ideas of reference, odd communication, and social isolation. Controlled treatment trials in ScPD/BPD subjects, comparing low-dose chlorpromazine and loxapine<sup>27</sup> and low-dose thiothixene and haloperidol,<sup>28</sup> also reported improvements in suspiciousness, hostility, depressed mood, and anxiety. In the latter study, in which 84% of subjects were moderately to markedly improved, it is of note that all study subjects had experienced mild, transient psychotic episodes prior to admission to the trial.

The first placebo-controlled trials involving neuroleptics in the treatment of DSM-III ScPD/BPD or BPD subjects were published in 1986. One study,<sup>29</sup> examining treatment response to thiothixene in a predominantly ScPD outpatient population with pretreatment history of brief psychotic disturbances, reported a clear therapeutic effect associated with the neuroleptic. The second study,<sup>30</sup> examining treatment response to haloperidol or amitriptyline in a mixed ScPD/BPD inpatient population, reported moderate efficacy of haloperidol as reflected by measures of psychoticism, paranoid ideation, hostility, depression, and anxiety. Follow-up studies by Soloff et al.<sup>31</sup> in an extended ScPD/BPD sample reported that severity of schizotypal symptoms, suspiciousness, and hostility best predicted favorable outcome with haloperidol. The most recent study from this group,<sup>32</sup> in which a different inpatient ScPD/BPD group was treated with either haloperidol,

tranylcypromine, or placebo, however, found little efficacy for haloperidol in these subjects. The authors suggested that a reason for this was that their sample contained less subjects with "pure" ScPD than in their previous studies.

More recent treatment studies with atypical agents involving ScPD and/or BPD subjects have tested the efficacy of open-label amoxapine,<sup>33</sup> an atypical thymoleptic with a neuroleptic-like metabolite, and open-label clozapine<sup>34</sup> and risperidone,<sup>35,36</sup> atypical neuroleptics. In the amoxapine study, five ScPD subjects and five subjects with BPD were treated for at least 3 weeks with amoxapine and oxazepam as needed for sedation. Only the ScPD subjects demonstrated any benefit in global psychopathology as reflected by the Brief Psychiatric Rating Scale (BPRS) total score, BPRS "schizophrenia-like" symptom score, or the Hamilton Rating Scale for Depression score. The clozapine study involved eight BPD or seven ScPD/BPD patients with atypical psychosis who had been started on clozapine after failure on three neuroleptic trials or intolerable side effects during these failed trials. After clozapine treatment ranging from 2 to 9 months, the authors reported significant improvement in global function and on seven of eight BPRS "positive symptom" items and significant improvement on three of five BPRS "negative symptom" items. Two case reports<sup>35,36</sup> have examined risperidone in BPD. One patient experienced improved mood and increased energy during 3 months of combined therapy with 1 mg/day of risperidone and 300 mg/day of fluvoxamine. Impulses leading to self-mutilating behavior decreased in another patient who was treated with 4 mg/day of risperidone.

In addition to their potentially positive therapeutic effects on "positive" schizotypal symptoms and depressed mood, neuroleptics (e.g., flupenthixol) have been reported to reduce recurrent suicidal behavior in double-blind placebo-controlled studies of severely personality disordered individuals.<sup>37</sup> This may be due, in part, to an effect of neuroleptics on hostile depression as reported by Soloff et al.<sup>31</sup>

### Tricyclic/Monoamine Oxidase Inhibitor Agents

Although the earliest studies involving tricyclic<sup>1</sup> and monoamine oxidase inhibitor<sup>22</sup> agents found some efficacy in subjects with "pseudoneurotic schizophrenia," more recent studies in carefully diagnosed personality disordered subjects offer less compelling results in this regard. Soloff et al.<sup>30,31</sup> reported modestly beneficial effects on depressed mood from treatment with amitriptyline in a hospitalized BPD and/or BPD/ScPD sample. However, in a significant subgroup of subjects (e.g., those characterized by hostility), amitriptyline treatment was associated with a worse outcome than placebo treatment as manifested by greater suicidal threats and physical assaultiveness toward others.<sup>38</sup> This is similar to the result that

Klein<sup>1</sup> reported with imipramine treatment in a subgroup of emotionally unstable character disordered subjects. More recently, Links et al.<sup>39</sup> reported that desipramine had little efficacy, and significantly less efficacy than lithium carbonate, in the treatment of patients with DSM-III BPD. Hence, it is possible that tricyclic agents may be either of little benefit, or perhaps contraindicated, in some personality disordered (e.g., BPD) patients.

The first study involving MAOI agents in the DSM-III era was reported by Cowdry and Gardner.<sup>40</sup> In this study, tranylcypromine was found to be quite efficacious, over placebo, alprazolam, carbamazepine, and trifluoperazine, in elevating the depressed mood of 16 female BPD subjects. A retrospective review of placebo-controlled data by Parsons et al.<sup>41</sup> suggested a role for MAOI agents in depressed BPD patients. In this study, phenelzine, but not imipramine, was found to be efficacious in treating atypically depressed BPD subjects; in atypically depressed non-BPD subjects, phenelzine and imipramine appeared equally efficacious. Soloff et al.<sup>32</sup> followed up these reports with a larger, prospectively designed trial comparing phenelzine, haloperidol, and placebo in hospitalized BPD and/or BPD/ScPD subjects. In contrast to the earlier studies, phenelzine was found to have very limited and modest efficacy, with positive findings over placebo or haloperidol for hostility only.

### Anxiolytics

Anxiolytics have not been widely studied in subjects with BPD or ScPD. Early reports suggested that these agents may offer some global benefit to personality disordered subjects.<sup>21,42</sup> The best controlled study to date, however, suggests that anxiolytics (i.e., alprazolam) can disinhibit BPD subjects and lead to serious episodes of dyscontrol characterized by suicide attempts and other behavioral outbursts.<sup>40</sup>

### Lithium

The phenomenologic similarity between the rapid mood swings of emotionally unstable character disordered (EUCD) subjects and the longer lasting mood swings of bipolar subjects suggested the possibility that lithium treatment might be beneficial in individuals with EUCD. This was confirmed in a placebo-controlled, double-blind study of lithium in EUCD subjects by Rifkin et al.<sup>2</sup> In this study, lithium was associated with a significant reduction in the magnitude, though not the frequency, of mood swings in EUCD subjects. While it is unclear what specific personality disorder(s) EUCD subjects would meet in the current DSM-IV, it is very likely that EUCD subjects would at least meet criteria for a "dramatic cluster," if not borderline, personality disorder. The most recent controlled study of lithium in BPD subjects tends to generally support lithium's global efficacy. In a small double-blind study comparing lithium, desipramine, and placebo, lithi-

um treatment appeared more efficacious than placebo, although the statistically significant finding was of lithium's superiority over desipramine.<sup>39</sup>

Lithium's putative capability to enhance central serotonergic activity,<sup>43</sup> and the widely observed inverse relationship between serotonin activity and impulsive aggressive behavior,<sup>8</sup> may explain lithium's antiaggressive efficacy in impulsively aggressive prison inmates who were most likely DSM-II antisocial personality disordered. In a double-blind, placebo-controlled study, Sheard et al.<sup>44</sup> reported that impulsive aggressive, but not other antisocial, behavior of prison inmates diminished markedly over a 3-month course of lithium treatment. Crossover treatment to placebo was associated with a full return of impulsive aggressive behavior in these subjects, suggesting that lithium's antiaggressive effect is suppressive, rather than curative, in nature.

### Anticonvulsants

Early studies in "neurotic outpatients," who may have had an unspecified personality disorder, suggest that anticonvulsants may have efficacy in treating anger and irritability. Two studies specifically reported beneficial effects in these spheres with diphenylhydantoin.<sup>45,46</sup> Reports of EEG abnormalities in some BPD subjects<sup>47,48</sup> may or may not explain the efficacy of anticonvulsants in this regard because of the possibly nonspecific nature of this EEG feature for BPD subjects.<sup>49</sup> Regardless of mechanism, recent studies do suggest efficacy for anticonvulsants in BPD subjects. Specifically, a recent double-blind, placebo-controlled study of carbamazepine, in carefully diagnosed BPD subjects, suggests a significant, and specific, effect of anticonvulsants on severe episodic dyscontrol.<sup>40</sup> In addition, an open-label study of valproic acid in BPD subjects demonstrated an overall improvement in 50% of BPD subjects and a significant reduction in SCL-90 scores and in global subjective irritability.<sup>50</sup>

### Serotonin Uptake Inhibitors

Serotonin uptake inhibitors were openly studied in BPD subjects soon after the release of fluoxetine. Initial open-label studies<sup>51-53</sup> reported positive therapeutic effects in BPD subjects along a number of dimensions including depression, obsessive-compulsive symptoms, and self-injurious and suicidal behavior. Later open-label studies suggested an antiaggressive effect of fluoxetine<sup>54</sup> and sertraline<sup>55</sup> in personality disordered subjects with prominent histories of impulsive aggressive behavior. This was followed by a report which indicated that fluoxetine could reduce the frequency of "anger attacks" in depressed subjects, many of whom were personality disordered.<sup>56</sup> These findings led to further double-blind, placebo-controlled studies of fluoxetine in BPD and other impulsive aggressive personality disordered subjects. The first of these studies in BPD subjects<sup>57</sup> demonstrated clear efficacy for

**Table 1. Summary of Potential Efficacy of Neuroleptics and Thymoleptics in Personality Disordered Subjects**

Neuroleptics	Potentially effective for psychotic-like symptoms and nonspecifically effective for depressed mood.
Thymoleptics	
Tricyclics	Potentially effective for depressed mood but a subgroup of personality disorders (e.g., impulsive-aggressive) may do poorly.
Monoamine oxidase inhibitors	
Serotonin uptake inhibitors	Potentially effective for depressed mood and for impulsive-aggressive behavior.
Lithium	Potentially effective for impulsive-aggressive behavior and rapid intra-daily mood lability (?)
Anticonvulsants	
Anxiolytics	Potentially enhances episodic dyscontrol in borderline personality disorder and other impulsive aggressive subjects (?)

fluoxetine over placebo along a number of dimensions, including depression, anxiety, and global function in a small group of BPD outpatients. The second controlled fluoxetine study was performed in community-referred subjects with BPD or BPD traits.<sup>58</sup> This study reported improvement in a number of areas but statistically significant improvement in aggression against objects only. The most recent study, performed prospectively to examine fluoxetine's antiaggressive efficacy, over a 3-month period, was conducted in nondepressed outpatient personality disordered subjects with histories of impulsive aggressive behavior.<sup>59</sup> This study reported clear antiaggressive efficacy for fluoxetine over placebo during the third month of treatment and for all subjects at their last assessment. Dosages ranged from 20 to 60 mg, but averaged approximately 30 mg per day. The primary difference between fluoxetine responders and nonresponders was length of time in trial, with responders completing approximately 3 more weeks of treatment than nonresponders.

## CONCLUSIONS

While psychopharmacologic research into the treatment of personality disordered subjects has been conducted for more than 30 years, there are few clear results in terms of clinical outcome for treatment with the various psychotropic agents available. In general, most agents are nonspecific in mechanism and nonspecific in effect. This is due both to the nonselective nature of the agents and to the heterogeneity of BPD, ScPD, and personality disordered subjects in general. Review of the literature suggests that symptom, or personality, dimensions are best correlated with central biological systems and treatment effects. The best example of this may be the recent findings that serotonin uptake inhibitors are effective for treating impulsive aggressive behavior despite the heterogeneous nature of the personality disordered sample.<sup>54-56,58,59</sup> In addition to this, some general conclusions (summarized in Table 1)

may be made about the efficacy of certain classes of agents in the treatment of personality disordered subjects. Future work should probably focus on targeting specific therapeutic agents to treat specific symptom and/or personality dimensions associated with clinical dysfunction in personality disordered subjects.

*Drug names:* alprazolam (Xanax), amitriptyline (Elavil and others), amoxapine (Asendin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), haloperidol (Haldol and others), imipramine (Tofranil and others), loxapine (Loxitane), oxazepam (Serax and others), pimozide (Orap), sertraline (Zoloft), thioridazine (Mellaril and others), thiothixene (Navane), tranylcypromine (Parnate), trifluoperazine (Stelazine), valproic acid (Depakene and others).

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