CME

Drug Treatment of Personality Disorder Traits

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Personality disorders have a long history of being difficult to treat. Not many years ago it was felt that they could only be treated by skilled experts in intensive long-term psychotherapy. As our understanding of these disorders has improved with empirical research, so has our vision of what treatments can and should be. Although there will always be patients treated by intensive methods by individual experts over long periods, that is not the only approach now conceptualized. In psychotherapy there is now more emphasis on the team approach used by dialectic behavior therapy that relies on modified cognitive/behavioral techniques. This provides an alternative to psychoanalytic techniques.

Our concept of psychopharmacologic treatment has also changed. At one time it was thought counterproductive to use drugs in the treatment of personality disordered patients at all as it would interfere with psychotherapy. Of course, as with any difficult patient group, clinicians will try whatever might work. This led to the realization that at least in some circumstances in some patients, drug treatment could be beneficial. What we have found, in general, is that we do not have specific drug treatments for categorical personality disorders as we might have, for instance, with major depression or with panic disorder. What we have is an array of drugs that help to some extent with certain symptoms and traits commonly found in personality disorders.

This article examines these pharmacological treatments. It first examines some of the drugs that have been used and some of the evidence for their effectiveness. It then takes the mindset of a clinician and looks at how some symptom clusters might be approached.

EVIDENCE FOR TREATMENT OF PERSONALITY TRAITS FOR DIFFERENT DRUGS

Traditional Neuroleptics

Because they are established as effective in the treatment of psychotic symptoms, traditional neuroleptics have been used extensively to treat paranoia, dissociation, ideas of reference, and illusions in personality disordered patients.

In a double-blind placebo-controlled study comparing low dose haloperidol, tricyclic antidepressant (TCA), and placebo Soloff et al.[1] found that patients on haloperidol experienced gains in a number of areas. Improvements were reported in depression, anxiety, anger, hostility, impulsiveness, and paranoia. The superiority of haloperidol was not replicated in a subsequent study that compared it to phenelzine (monoamine oxidase inhibitor [MAOI]) and placebo.[2] In this latter study phenelzine produced superior results in the areas of depression,

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anxiety, anger, hostility, and other measures. Soloff hypothesized that haloperidol might be more effective in more impaired individuals. This was consistent with the conclusions of Goldberg et al.[3] who used thiothixene in a double-blind placebo-controlled study and found some usefulness in psychotic symptoms only for severe borderline and schizotypal patients.

Cornelius et al.[4] performed a double-blind placebo controlled continuation study comparing haloperidol (neuroleptic), phenelzine (MAOI), and placebo in patients with borderline personality disorder. The purpose of the study was to determine whether patients could receive benefit from drug treatment past the initial crisis stage. Haloperidol lacked strong efficacy, but did reduce irritability beyond the acute treatment phase. When dropout rates are examined, haloperidol was again unimpressive. Mean survival time was 8.4 weeks compared to 13.4 weeks for phenelzine and 17.8 weeks for placebo.

Cowdry and Gardner[5] did a double-blind study on 16 women with borderline personality disorder comparing alprazolam (benzodiazepine), carbemazepine (mood stabilizer), tranylcypromine (monoamine oxidase inhibitors), trifluperazine (neuroleptic), and placebo. This was a crossover design where all patients received all five conditions. Although there were some reported gains with trifluperazine in anxiety reduction, suicidality, depression, and sensitivity rejection, 50% discontinued this trial arm due to side effects or exacerbation of symptoms.

Although some gains have been reported using traditional neuroleptics, the results are not impressive after the initial crisis and the dropout rate is high. The literature indicates neuroleptics should be used in low doses and even then there is a high dropout rate. The risk of tardive dyskinesia should always be kept in mind. Neuroleptics seem to be of most use in the most severely ill patients.

Atypical Antipsychotics

The literature on the atypical neuroleptics is not as extensive as that on traditional neuroleptics. There are several trials with clozapine. An open label report by Frankenburg et al.[6] on 15 patients with severe borderline personality disorder showed some improvement of psychotic symptoms. The doses were relatively high and there were many side effects. Another study of 12 patients with borderline personality disorder using lower doses of clozapine also found reduced psychotic symptoms and increase in global functioning. There were fewer side effects in this study, most likely due to the lower dose.[7] A report on seven severe patients with borderline personality disorder treated with clozapine indicated a significant reduction in self-mutilation.[8]

Risperdone was shown to reduce psychotic symptoms in seven borderline paitents[9] and there are two case reports of decreased self-mutilation.[10,11] There are two reports on olanzapine. The first studied 11 patients with borderline personality disorder on olanzapine monotherapy and reports significant reductions in five global ratings.[12] A case report indicates decreased self-mutilation behavior.[13]

The atypical antipsychotics appear to be promising agents, especially for psychotic personality disorder symptoms, although much work remains to be done.

Tricyclic Antidepressants

The use of TCAs has been fairly well investigated in borderline personality disorder. Early open label trials showed some benefit.[14,15] Later double-blind trials found a modest improvement in some patients treated with amitriptyline; however, there was a paradoxical effect in some patients with an increase in hostility and affective instability.[16,17] The paradoxical effects, low efficacy, and side effects (lethality in overdose, weight gain, sedation, and dry mouth) are strong relative contraindications to its use, at least in patients with borderline personality disorder.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors have been of interest for personality features before the borderline personality diagnosis was widespread. It was hypothesized that MAOI treatment would be useful for an atypical type of depression with extreme rejection sensitivity called hysteroid dyshporia. Leibowitz et al. examined the effects of phenelzine (MAOI), imipramine (TCA), and placebo in this population.[18] Phenelzine was

superior to imipramine and placebo. Parsons et al. examined a subsample from the study who had maintained mood reactivity while depressed.[19] Among these patients there was a response rate of 92% on phenelzine, 35% for imipramine, and 25% for placebo.

In a double-blind placebo study of borderline personality[2] Soloff et al. found phenelzine produced superior results compared to a TCA and placebo. This superiority included the areas of depression, anxiety, and hostility. Cowdry and Gardner in their crossover study[5] found significant improvement for tranylcypromine in the areas of depression, anger, loneliness, and rejection sensitivity. (These were patients who had comorbid borderline personality and hysteroid dsyphoria and who therefore had extreme rejection sensitivity.)

Monoamine oxidase inhibitors represent a possible treatment of borderline personality traits of affective lability, hostility, and rejection sensitivity. Their use is limited by their lethality in overdose and drug interactions ("beer, wine, cheese reaction") in patients who tend to react suddenly and impulsively.

Selective Serotonin Reuptake Inhibitors

There are now nine double-blind studies on the effect of selective serotonin reuptake inhibitors (SSRIs) on personality traits.[20-28] Cocarro et al. examined a population of personality disordered patients without concurrent affective disorder, schizophrenia, or substance abuse.[20] Treatment with fluoxetine resulted in sustained reduction of irritability and aggression scores. A study of a normal population treated with paroxetine demonstrated a reduction in hostility and negative affect.[21]

There are a number of studies of the treatment of personality traits in patients with depressive illness. Fava et al.[22] found a general reduction in personality disorder traits treated with paroxetine. Salzman et al.[23] studied an outpatient borderline population with anxiety and depressive symptoms, but not major depression. Treatment with fluoxetene resulted in a significant decrease in anger. A treatment study of major depression with sertraline or paroxetine over 24 weeks demonstrated reductions in all three *DSM* personality clusters.[24]

Ekselius et al.[25] examined the effect of treatment of sertraline and citalopram on the personality status of depressed patients in primary care. Both active treatments reduced the frequency of measured paranoid, avoidant, and dependent personality disorder diagnoses. Reductions of dimensional personality traits were found in most categories. Importantly, the effect of state changes on the outcome was examined. Although the change in state depression did effect the reduction in personality traits, the R^2 never exceeded 0.24 (this was in the cluster C personality disorders).

Another report examining the use of paroxetine, fluvoxetine, and fluoxetine indicated a general reduction in personality pathology.[26] A large double-blind study of sertraline on dysthymic patients showed a significant reduction in harm avoidance.[27] One report examined the effect of paroxetine on chronically suicidal patients who did not have major depression.[28] A significant reduction in both personality traits and suicidal behavior was found.

The overall findings indicate that SSRIs can be of significant help in the reduction of personality pathology. This is most notable in the area of irritability and aggression, but may affect much broader areas of personality functioning. The onset can be relatively rapid at 1 to 2 weeks. Dosage ranges are from those used to treat depression up to the dosages used to treat obsessive compulsive disorder.

Mood Stabilizers

Lithium. There have been a number of studies of lithium for mood lability in the personality disorders. Early work using the diagnosis emotionally unstable character disorder demonstrated some evidence against mood lability in adolescent girls.[29] Lithium was also reported to have efficacy against impulsive aggression in adult criminal subjects[30,31] and in delinquent adolescents.[32] There is a report of treatment of patients with borderline personality disorder with some positive effects.[33]

There has been only one double-blind placebo-controlled study. Links et al.[34] compared lithium to desipramine in a double-blind crossover study. Therapists rated their patients as more improved

on lithium on measures of irritability, anger, and suicidal symptoms.

Overall it appears that lithium may be of use in some patients for impulsive aggressive symptoms. This should be balanced against its toxicity in overdose.

Carbamezepine. There are two double-blind studies of carbamezepine. There is a 1986 study of 16 borderline personality disorder patients (all female) with a history of behavioral dyscontrol.[35] The study lasted 33 days and carbamezepine significantly reduced the severity of the dyscontrol. The same authors did a later four drug placebo controlled crossover study described earlier.[5] This study showed significantly less behavioral dyscontrol taking carbamezepine at an average dose of 820 mg. Unexpectedly, three subjects developed melancholic depression that improved when the medication was discontinued.

Carbamezepine appears to have potential use in some patients with episodic dyscontrol. It is a bit more complicated to use in patients on multiple medication due to its tendency to autoinduce its own metabolism and change blood levels of various medications.

Divalproex sodium. Divalproex sodium is another mood stabilizer that has received attention as a possible treatment. There is only one double-blind placebo controlled study that I am aware of. Hollander et al. performed a 10-week trial in patients with borderline personality disorder.[36] There was a significant improvement in global measures in the actively treated group, but a high dropout rate precluded finding significant differences between active treatment and placebo.

There are some open label studies. Stein et al.[37] performed an 8-week treatment trial in patients with borderline personality disorder without comorbid depression or history of bipolar disorder. Only four of eight patients completing the trial reported significant improvement in mood and impulse symptoms. Wilcox studied a severe borderline population without comorbid disorders.[38] When divalproex was added to ongoing medications patients improved globally, especially in anxiety and tension. Global improvement was also shown in a small study of borderline outpatients.[39]

Kavoussi and Coccaro reported a study showing divalproex to be useful across multiple personality diagnoses against irritability and impulsive aggressive behavior in patients who had failed treatment with an SSRI antidepressant.[40]

Overall it appears that there is some promise that divalproex will be proven useful for the treatment of impulsive and aggressive symptoms in personality disorders. The best estimate for effective blood levels is between 50 and 100 μm/mL.

Lamotrigine. There is one chart review report on lamotrigine in borderline personality disorder.[41] Eight patients were identified who had failed numerous prior trials of antidepressants and mood stabilizers. One developed a rash, one was non-compliant, and three failed the trial. The other three showed significant response on doses of 75 to 300 mg/d.

Benzodiazepines. Benzodiazepines have a long history of effectiveness for anxiety. The tendency to reduce anxiety and promote disinhibition makes them potentially useful in personality disorders characterized by anxiety and inhibition (ie, avoidant personality disorder). However, disinhibition and anxiety reduction can be a problem in personality disorders characterized by impulsive behavior, hostile behavior, or behavior that is already disinhibited or self-destructive.

There is only one double-blind study of a benzodiazepine in a borderline population, the Cowdry and Gardner crossover study.[5] Here alprazolam (a short half-life benzodiazepine) increased suicide and episodes of behavioral dyscontrol. Four of the 16 patients had to be removed from the alprazolan arm prior to completion. Of the remaining 12, seven experienced heightened aggression. There was a paradoxical effect in some patients where they had improved mood while they had increased behavioral dyscontrol. (They "felt good about themselves" while they did bad things.) On the basis of this study, short-acting benzodiazepines appear to be somewhat strongly contraindicated in maintenance treatment of patients with borderline personality disorder.

Benzodiazepines are often used during acute episodes of dyscontrol instead of traditional neuroleptics. Clonazepam, which has been associated with an increase in serotonin levels and has a long half-life, is sometimes used to treat anxiety symptoms in personality disorders that are impulsive or irritable.

Benzodiazepines are useful for acute crisis situations and personality disorders involving inhibition. A history of either substance abuse or impulsive behavior is a strong relative contraindication

to their use. Although the data are sparse, it would appear that if used in patients with a history of impulsive behavior over a longer term, clonazepam or a longer acting benzodiazepine should be used, not short-acting benzodiazepines.

Naltrexone. There are only two open label and one case report on the use of naltrexone for personality disorder traits. Although preliminary, the results are intriguing. One report on 13 patients attempted to reduce dissociative episodes with naltrexone and reported a significant reduction in the duration and intensity of dissociative phenomena.[42] Another trial of seven patients examined self-injurious behavior (cutting).[43] In six of seven patients there was significant improvement on naltrexone. A case report of one patient also indicated an improvement of self-injurious behavior on naltrexone.[44]

Although not a strong data base, these preliminary findings are of interest. They indicate that, in some patients, naltrexone at doses from 50 to 400 mg/d may be useful in the treatment of dissociative behavior and/or self-injury.

Other. There are two reports on the use of venlafaxine. Both are open label. One, studying 12 social phobic patients[45] indicates that treatment reduced avoidant personality traits. This is not a surprising finding, as it is becoming more recognized that avoidant personality disorder is only quantitatively different from social phobia.[46] It is likely that drugs that treat social phobia will also have a helpful effect on avoidant personality traits.

The second report treated a group of 39 patients with borderline personality disorder with up to 200 mg/d of venlafaxine.[47] The findings are more interesting in that many of these patients had had a previous trial with an SSRI. The report indicates a reduction in overall symptom severity, somatic complaints, and the number of patients who were engaging in self-injurious behavior.

GENERAL RULES FOR TREATMENT

As, with the possible exception of avoidant personality disorder, we have no specific drugs for specific disorders, we are then treating comorbid disorders and personality disorder traits. In this effort we are trying to find the fewest medications that can appropriately treat the individual array of symptoms with which a patient presents. I call this search for the proper combination the search for elegance in psychopharmacologic treatment.

Although comorbidity of both Axis I and Axis II disorders is common in personality disorders, it is less of a problem when traits are being treated rather than specific categorical Axis II diagnoses. Again the goal is to find the smallest combination of drugs that treats both the categorical Axis I disorders and the Axis II traits.

Models of Treatment

The challenge involved in treating personality traits is keeping a model of treatment firmly in mind. Without a model it is more likely that treatment goals become confused because there is not a single treatment model that has preeminence over the others.

Common models of treatment include: (1) the belief that what we are calling Axis II disorders are actually Axis I disorders. This position is best exemplified by Akiskal who argues that borderline personality is an Axis I affective disorder[48]; (2) the concept that Axis II symptoms are merely formes frustes (attenuated versions) of Axis I disorders; (3) the concept that we are treating an underlying temperament, meaning that we are treating dispositions to behaviors such as impulsiveness; (4) the focus of treatment is clusters of Axis II treatments that tend to occur together (although not all authors use exactly the same symptoms in their clusters); (5) the stress-induced personality disorder model[49] (some disorders that appear to be personality disorders are distortions of a vulnerable but relatively normal personality that became distorted under stress).

One treatment model may seem more useful for one patient and another model more useful for another. Often the clinical choices are the same under different models. The important thing may not be which model is used, but deciding a model to follow for any given patient.

Treatment by Cluster

As mentioned above, different authors define different clusters differently and the search for drug treatment elegance can take many paths. I will, however, give a starting place for the treatment of several clusters of personality traits.

Treatment of the paranoid, mild thought disorder, and

dissociation cluster. Except for acute crisis episodes I would tend to avoid the traditional neuroleptics. Their efficacy after initial crisis is not impressive, the dropout rate is high and there is a risk of tardive dyskinesia. My preference is to start with an atypical antipsychotic at one quarter to one half the ordinary top range maintenance dose for psychosis. If there is no response, I would go by steps up to the top maintenance dose. If there is no response, a trial of a different atypical is a reasonable option. Clozapine should be considered in refractory patients. If there is a partial response, a trial of divalproex as an adjunctive agent might be considered. If dissociative symptoms are prominent a trial of naltrexone might be considered.

The depressed, angry, labile mood cluster. I would start with an SSRI antidepressant at antidepressant doses. This should be titrated to dosages used for obsessive compulsive disorder as indicated. If one SSRI fails, a trial of another is a reasonable step. If there is a partial response, an adjunctive atypical neuroleptic or a mood stabilizer could be added. For patients who have good compliance and rejection sensitivity who have failed the above, a trial of an MAOI might be considered. An adjunctive trial of naltrexone for self-harming behavior could be considered if necessary.

The anxious, inhibited behavior cluster. For patients without impulsive behavior, I would start with a trial of an SSRI. If this trial fails, a trial of a second SSRI should be undertaken. A long-acting benzodiazepine may also be added for partial response or tried as a sole agent if there are multiple SSRI failures. If these approaches fail, a trial of beta blockers or atypical antipsychotics might be indicated.

For patients with impulsive, dangerous behavior or a history of substance abuse, I would again start with trials of SSRIs. If SSRIs fail, atypical antipsychotics and beta blockers would be the mainstay of anti-anxiety treatment.

Length of treatment and adjunctive psychotherapy. Treatment trials, barring side effects that require termination, should go for at least 4 to 6 weeks. Symptoms of personality disorders often fluxuate. It can take a longer trial period before it is evident if a given intervention is successful. Although no patient should be on a medication for longer than necessary, it should be remembered that personality problems are often long term. If a drug or combination or drugs improve symptoms or function and has an acceptable low level of side effects, long-term treatment can be justified.

COMMENT ON PSYCHOTHERAPY

Although, as I have described above, drug treatment can help some symptoms of personality disorder dysfunction, no one represents it as a cure and no one would suggest that psychopharmacology should be done in the absence of a psychotherapy treatment program. Discussion of specific psychotherapy treatments is beyond the scope of this article and is discussed in other articles in this issue.

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Models of Treatment

The challenge involved in treating personality traits is keeping a model of treatment firmly in mind. Without a model it is more likely that treatment goals become confused because there is not a single treatment model that has preeminence over the others.

Common models of treatment include: (1) the belief that what we are calling Axis II disorders are actually Axis I disorders. This position is best exemplified by Akiskal who argues that borderline personality is an Axis I affective disorder[48]; (2) the concept that Axis II symptoms are merely formes frustes (attenuated versions) of Axis I disorders; (3) the concept that we are treating an underlying temperament, meaning that we are treating dispositions to behaviors such as impulsiveness; (4) the focus of treatment is clusters of Axis II treatments that tend to occur together (although not all authors use exactly the same symptoms in their clusters); (5) the stress-induced personality disorder model[49] (some disorders that appear to be personality disorders are distortions of a vulnerable but relatively normal personality that became distorted under stress).

One treatment model may seem more useful for one patient and another model more useful for another. Often the clinical choices are the same under different models. The important thing may not be which model is used, but deciding a model to follow for any given patient.

Treatment by Cluster

As mentioned above, different authors define different clusters differently and the search for drug treatment elegance can take many paths. I will, however, give a starting place for the treatment of several clusters of personality traits.

Treatment of the paranoid, mild thought disorder, and

dissociation cluster. Except for acute crisis episodes I would tend to avoid the traditional neuroleptics. Their efficacy after initial crisis is not impressive, the dropout rate is high and there is a risk of tardive dyskinesia. My preference is to start with an atypical antipsychotic at one quarter to one half the ordinary top range maintenance dose for psychosis. If there is no response, I would go by steps up to the top maintenance dose. If there is no response, a trial of a different atypical is a reasonable option. Clozapine should be considered in refractory patients. If there is a partial response, a trial of divalproex as an adjunctive agent might be considered. If dissociative symptoms are prominent a trial of naltrexone might be considered.

The depressed, angry, labile mood cluster. I would start with an SSRI antidepressant at antidepressant doses. This should be titrated to dosages used for obsessive compulsive disorder as indicated. If one SSRI fails, a trial of another is a reasonable step. If there is a partial response, an adjunctive atypical neuroleptic or a mood stabilizer could be added. For patients who have good compliance and rejection sensitivity who have failed the above, a trial of an MAOI might be considered. An adjunctive trial of naltrexone for self-harming behavior could be considered if necessary.

The anxious, inhibited behavior cluster. For patients without impulsive behavior, I would start with a trial of an SSRI. If this trial fails, a trial of a second SSRI should be undertaken. A long-acting benzodiazepine may also be added for partial response or tried as a sole agent if there are multiple SSRI failures. If these approaches fail, a trial of beta blockers or atypical antipsychotics might be indicated.

For patients with impulsive, dangerous behavior or a history of substance abuse, I would again start with trials of SSRIs. If SSRIs fail, atypical antipsychotics and beta blockers would be the mainstay of anti-anxiety treatment.

Length of treatment and adjunctive psychotherapy. Treatment trials, barring side effects that require termination, should go for at least 4 to 6 weeks. Symptoms of personality disorders often fluxuate. It can take a longer trial period before it is evident if a given intervention is successful. Although no patient should be on a medication for longer than necessary, it should be remembered that personality problems are often long term. If a drug or combination or drugs improve symptoms or function and has an acceptable low level of side effects, long-term treatment can be justified.

COMMENT ON PSYCHOTHERAPY

Although, as I have described above, drug treatment can help some symptoms of personality disorder dysfunction, no one represents it as a cure and no one would suggest that psychopharmacology should be done in the absence of a psychotherapy treatment program. Discussion of specific psychotherapy treatments is beyond the scope of this article and is discussed in other articles in this issue.

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