Confounding Factors in TRD (Part 1): The Role of Subtyping and Bipolarity

July 18, 2012 | Bipolar Disorder [1], Addiction [2], Bipolar II Disorder [3], Catatonic Schizophrenia [4], Comorbidity In Psychiatry [5], Major Depressive Disorder [6], Mania [7], Mood Disorders [8]
By Michael I. Casher, MD [9], Daniel Gih, MD [10], Joshua D. Bess, MD [11], and Prachi Agarwala, MD [12]

The current system of payment for mental health care in the US can lead, or even incentivize, clinicians to focus on and code for Axis I disorders and their more readily reimbursed psychopharmacological treatment approaches.

In psychiatric practice, treatment-resistant depression (TRD) is not unusual. In his 2008 review of the various definitions for TRD, including that of adequate clinical trials of at least 1 antidepressant, and perhaps 2, Barbee concluded with the view that the simplest definition of TRD is “failure to achieve a response to a medication to any degree short of remission.” We can gain much by stepping back from a patient with TRD and doing a careful assessment for complicating factors that can prevent remission of depressive symptoms.

In this 2-part article (see "Confounding Factors in TRD Part 2: Comorbidities and Treatment Resistance"), we discuss a number of the most common confounding factors of TRD. Here we look at subtyping and bipolarity and their role in TRD. Personality factors also affect treatment response in patients with depression. Unrecognized (or ignored) comorbid Axis II pathology, such as borderline personality disorder (BPD), can closely mimic various Axis I depression diagnoses, to the point where the clinician questions whether persistent or lingering dysphoric states are truly “depression.” In Part 2, we will discuss comorbidities in depression and their role in treatment resistance. Outcomes are worse for patients with a history of childhood adversity or for patients who are in stressful or untenable psychosocial situations (eg, an abusive relationship, an ongoing custody battle). Depressive illnesses are both common and difficult to eradicate in such patients without attention to the “whole picture.” Poor treatment responsiveness is also associated with lack of social supports. Likewise, when the incentives, conscious or unconscious, for the “sick role” and psychiatric disability are greater than the rewards of euthymia, clinicians can easily find themselves thwarted in their treatment attempts.

SUBTYPING AND BIPOLARITY

Melancholic features in TRD

Treatment resistance can occur when subtyping of depression is inaccurate or disregarded. This can be seen with melancholic features, which are presented as a specifier for major depression in DSM-IV-TR. The criteria for the melancholic features specifier are, in some measure, exaggerations of the neurovegetative symptoms of depression (Table).
Melancholic features specifier for major depressive episode

“Melancholia” has been suggested as a separate diagnostic category for DSM-5; the criteria would include:

- Disturbed mood of apprehension, worry, or despondency
- Psychomotor disturbance of agitation, retardation (including stupor or catatonia or both)
- At least 2 vegetative signs: poor sleep, poor appetite, disturbed libido, problems with cognition
- At least 1 of the following: abnormal dexamethasone suppression test or high nighttime cortisol levels; or decreased REM latency or other sleep abnormalities

Independent of the classification issues with respect to melancholic features, findings suggest differential responses to treatment when major depression is accompanied by melancholic signs and symptoms. These differences include a more favorable response profile with medications, especially with TCAs and other dual-action antidepressant classes, than with psychotherapies, as well as an increased response to ECT.

Catatonic features in TRD

Catatonic subtyping involves considerations similar to those for melancholic features. Signs of catatonia are easily missed and are often mistaken for the less ominous “psychomotor slowing” seen so commonly with many depressions. The basic catatonic features are motoric immobility or overactivation (catatonic excitement), negativism, mutism, posturing, and echophenomena. Many psychiatric residents and even some experienced practitioners are not well versed in examining patients for catatonia, even though the condition is relatively common on psychiatric inpatient units, where many patients with refractory depressions are admitted.

Patients with psychotic features and/or melancholic features are more likely to have accompanying catatonic features as well, which is consistent with the notion that all of those specifiers point to a more severe biological process than that seen in uncomplicated major depression. When catatonic features are recognized by elicited history or on examination, special treatment considerations come into play. These include the need for high-dose benzodiazepines; consideration of ECT; and special care with use of antipsychotic medications (especially high-potency conventional antipsychotics) because of their tendency to worsen catatonic symptoms.

Psychotic features in TRD

Failure to detect “hidden” psychosis accompanying depression or inattention to special considerations with known psychotic depression can lead to ineffective treatment with antidepressants alone. Even with optimal treatment, the presence of psychosis in patients with major depression is often associated with a more severe course and includes more repeated hospitalizations, decreased responsiveness to treatment, and higher relapse rates.

Accurate subtyping of depression thus dictates that clinicians become adept at ferreting out psychotic symptoms in patients who do not have obvious delusions or hallucinations. This often requires a high index of suspicion and intensive interview techniques. Patients may not spontaneously mention, for instance, that they are seeing malevolent “shadowy figures” out of the corners of their eyes. Likewise, without probing questions in the interview, subtle evidence of a delusional thought process (e.g., is the patient really financially broke or is he or she suffering from a delusion of poverty?) can easily be overlooked.

In a recent chart review, symptoms of psychosis in depression were missed 27% of the time in an aggregate of patients on the inpatient psychiatric units of 4 academic medical centers. Estimates of the incidence of psychosis in depression range from 14% to 20%, which represents a considerable number of patients who would be categorized as having TRD if the psychosis is not recognized and they subsequently fail to respond to antidepressant treatment. Current evidence supports the
Atypical features in TRD
The atypical features of increase in appetite or weight and hypersomnia are sometimes referred to as “reverse vegetative signs,” but the full atypical syndrome also includes mood reactivity, a “leaden” feeling in the extremities, and exquisite sensitivity to social rejection. Earlier studies showed superiority of MAOIs to TCAs for atypical depression, but with the ascendance of SSRIs and SNRIs, MAOIs have generally fallen out of favor. MAOIs are further disadvantaged by their associated diet and medication restrictions and less favorable adverse-effect profile. Nonetheless, recognition of atypical features of depression in a given patient should lead to consideration of use of an MAOI. Lack of recognition of atypical features may lead to an impression of TRD.

Missed bipolarity in TRD
Patients who have bipolar disorder may show poor, erratic, or even “paradoxical” responses to therapy with antidepressants alone. When subtle evidence of bipolarity is overlooked and patients subsequently have numerous unsuccessful trials of non–mood-stabilizing antidepressant agents, these patients are thought to have treatment-resistant unipolar depression. When a patient who presents with a depressive state reports a history of classic manic symptoms, such as spending sprees, elation, flight of ideas, and grandiosity, very few experienced clinicians would overlook a bipolar diagnosis. Beginning with the work of Akiskal and Pinto, there has been heightened recognition that genotypic bipolarity may not fully manifest itself phenotypically. There are patients with bipolar spectrum illness who do not present obvious historical accounts of mania or hypomania. It is often only after a period of years of illness that a patient is recognized as having bipolar II disorder rather than unipolar depression. The Mood Disorder Questionnaire (MDQ), designed for use in primary care clinics, is useful in screening for bipolarity in patients with depression. The MDQ can be combined with a comprehensive clinical interview for detection of hidden bipolar variants. Once a bipolar component is strongly suspected, the pharmacological strategy should shift from use of pure antidepressant agents (eg, monotherapy with SSRIs, SNRIs, or TCAs) toward a predominance of mood-stabilizing agents or ECT.

Personality factors in TRD
Most psychiatrists with extensive experience in treating depressed patients develop an intuitive sense that there are patients with “personality issues” who do not respond to treatment as readily as psychologically healthy peers with similar degrees of depression. One way that this is conceptualized is resistance directed toward or involving medication. Numerous studies have examined the comorbidity of Axis II disorders and depression, but fewer studies have looked at the impact of personality disorders on overall treatment responsiveness. Other studies have bypassed DSM categories altogether and have focused instead on more basic personality traits, attitudes, and/or temperament variables that create the “culture” in which depression can both germinate and sustain itself despite seemingly adequate treatments. The relationship between personality factors and depression is complex and difficult to study for a number of reasons. Depression itself confounds the accurate assessment of personality. Patients in the throes of a depressive episode may appear to have—indeed, often meet criteria for—a personality disorder. Many patients who do meet criteria for an Axis II diagnosis during a mood episode no longer meet those criteria once their depression has been adequately treated. In short, depression can induce a psychological state that resembles a personality disorder. Personality disorders are currently conceptualized not as static configurations of traits but rather as fluid constellations that can fluctuate with internal and external stressors. In this dynamic system, the development of a major depression would represent a “negative” internal factor that could disrupt personality homeostasis to the point where a personality disorder emerges. Further complicating the relationship between depression and personality is the observation that evidence of personality pathology in late adolescence or early adulthood may actually represent the early signs of a mood disorder. Finally, for many patients, the relationship between mood symptoms and personality variables may be mediated through complex, cascade-like mechanisms. For instance, patients with BPD may lead a chaotic and self-defeating lifestyle that results in alienation from social support, which, in turn, leads to loneliness and isolation—and ultimately to depression. The intricate relationship between personality and depression defies easy understanding. Nevertheless, in the following section, we break down the issue into a number of general categories and highlight the implications for the evaluation and treatment of TRD.

Personality style characteristics, traits, and temperament
Researchers and psychologists tend to favor dimensional classifications of personality over the categorical approach put forth in DSM texts through DSM-IV-TR. (The upcoming DSM-5 personality section is heavily influenced by the dimensional approach to diagnosis.) An advantage of dimensional approaches is that they include psychological variables that are reliably rated. Some of these factors are inheritable and therefore can be linked with biological markers, specific neurotransmitters, or neuroimaging variations. One popular way to conceptualize personality dimensionally is the 5-factor model that includes the polar dimensions of neuroticism-stability, introversion-extraversion, openness-closedness to experience (in other systems, this is called thrill seeking vs harm avoidance), agreeableness-antagonism, and conscientiousness-negligence. A similar dimensional system is Cloninger’s temperament/character model, which includes 4 temperament dimensions (harm avoidance, novelty seeking, reward dependence, and persistence) and 3 character dimensions (self-directedness, cooperativeness, and self-transcendence). All are thought to represent significant genetically based contributions to overall personality.

In one study, the Tridimensional Personality Questionnaire was given to patients with major depression to see whether 3 of Cloninger’s dimensions (novelty seeking, harm avoidance, and reward dependence) remained stable with changes in mood. Reward dependence and novelty seeking were stable in the face of affective changes, while harm avoidance tended to be heightened with depressive illness and reduced with treatment.

Findings from a study using still another dimensional personality model suggest that the distinct personality style traits of perfectionism and anxious worrying contributed to depression in a group of 54 patients. The researchers speculated that these traits also had a role in treatment resistance. Drawing from among the various dimensional systems, poor outcome in treatment of depression has also been associated with high levels of neuroticism, high scores on harm avoidance, and a tendency toward introversion. In patients with TRD, those with high degrees of neuroticism respond better to TCAs than to MAOIs. Introversion includes social inhibition, which reflects a tendency to avoid mixing with others. Social inhibition is overrepresented in patients who have hard-to-treat depressions.

There is also consistent evidence that the trait of harm avoidance is associated with serotonergic functioning, which suggests that medications that target the serotonin system are useful for patients with TRD who have high harm-avoidance scores. Although further associations of different traits with various neurotransmitter systems have been postulated, studies to reliably demonstrate these relationships have been inconsistent.

**Axis II comorbidity with TRD**

Despite its limitations, the categorical approach to personality disorder diagnosis is firmly ensconced in the practice of American psychiatry and is likely to remain so, even with the anticipated changes in DSM-5. So, does a comorbid personality disorder—as defined by current DSM (pre-DSM-5) criteria—predict a poor treatment outcome in patients with depression?

In a review of the data, Mulder concluded that the evidence for worse outcomes in patients with depression and comorbid personality pathology was inconclusive. However, a meta-analysis of 32 studies of depression treatment outcomes in which the presence of personality disorders was also formally assessed found robust evidence for less response to treatment in patients with a concurrent personality disorder. Furthermore, recent data from the Collaborative Longitudinal Personality Disorders Study of nearly 2000 patients confirm that many DSM personality disorders, and BPD in particular, are associated with persistence of depressive symptoms. Perhaps the strongest evidence for increased treatment resistance in the BPD population is the finding that ECT—arguably the most potent treatment modality for depression—was much less effective in patients with MDD who had comorbid BPD. These patients had a remission rate of only 22% with ECT, compared with 56% for patients with other personality disorders and 70% for patients with no diagnosed personality disorder. Speculations about the reason for disparities in responsiveness to ECT and medications in patients with BPD involve a number of issues in the relationship of mood and affect to BPD. First of all, the diagnosis of BPD includes a number of items with mood content. These items overlap considerably with items on depression rating scales: suicidal ideation and behaviors, affective instability with periods of intense dysphoria, and long-term feelings of emptiness. Clinicians can easily get caught up in unsuccessful efforts to eliminate these character-based vulnerabilities through aggressive somatic treatments. Alternatively, even with a clear diagnosis of both MDD and BPD, the biological features of depression that occur in patients with BPD may be different from those in patients without associated BPD. Whatever the mechanisms of reduced efficacy of depression treatment in BPD, recognizing this
comorbidity is enormously important. Nonpharmacological treatments are first-line and remain the mainstay of continuing treatment even when medications are added. The best evidence-based approach to date is dialectical behavioral therapy (DBT), either added to a partially effective pharmacological regimen or substituted for a regimen that has had no benefit whatsoever. DBT, a form of cognitive therapy with a manualized approach, has shown its greatest effectiveness in decreasing suicidal and parasuicidal behaviors, with consistently positive outcomes in randomized controlled studies. In recent years, evidence has also accumulated for effectiveness of other forms of psychotherapy for BPD, including psychodynamically informed psychotherapies and the group-based program STEPPS (Systems Training for Emotional Predictability and Problem Solving). A solid clinical interview that focuses on the patient’s history of interpersonal and occupational functioning, repertoire of defenses, and interaction with the interviewer is usually sufficient. Some clinicians, especially those in a research or tertiary care setting, also use structured interviews designed to detect personality disorders. Supplemental interviews with family or close friends can be helpful, since the symptoms of a personality disorder are generally ego-syntonic and the patient may not perceive them as problematic.

**Conclusion**

The current system of payment for mental health care in the US can lead, or even incentivize, clinicians to focus on and code for Axis I disorders and their more readily reimbursed psychopharmacological treatment approaches. Busy clinicians might skip the systematic exploration of the patient’s history and current functioning necessary to make a personality disorder diagnosis. Nevertheless, good clinical care mandates that subtyping of depression is taken into account and that the possibility of a confounding personality disorder be considered in all patients with TRD.

**Confounding Factors in Treatment-Resistant Depression: Part 1**

Editor’s Note: Our Category 1 CME articles are on hiatus for the summer. In the meantime, we invite you to test yourself: read the article, take the posttest below, and then check the answer key on the last page of this article for the correct answers.

1. Which of the following criteria for melancholia would be included were it to be a separate diagnostic category in DSM-5?
   A. Prominent hallucinations or delusions
   B. Psychomotor disturbance of agitation, retardation (including stupor, catatonia, or both)
   C. Persistent symptoms of disorganized behavior

2. The recommended treatment when depression is accompanied by melancholic symptoms is psychotherapy.
   A. True
   B. False

3. Which of the following is NOT a treatment option for depression with catatonic features
   A. High-potency conventional antipsychotics
   B. Benzodiazepines
   C. ECT

4. Estimates of the incidence of psychosis in depression range from
   A. Less than 10%
   B. 14% to 20%
   C. 20% to 32%
   D. More than 35%

5. Which of the following symptoms is most suggestive of the diagnosis of depression with atypical features?
   A. Echolalia and echopraxia
   B. Lack of reactivity to usually pleasurable stimuli
   C. Auditory or visual hallucinations
   D. Extreme sensitivity to rejection
6. Which of the following tools can be used in primary care settings to screen for bipolarity in patients with depression?
A. The Mood Disorders Questionnaire
B. The Major Depression Inventory
C. The Clinical Global Impressions Scale
D. The Bipolar Spectrum Diagnostic Scale

7. One way to conceptualize personality dimensionally is the 5-factor model that includes which of the following?
A. Harm avoidance
B. Self-directedness
C. Novelty seeking
D. Neuroticism-stability

8. Poor outcome in treatment of depression has been associated with high levels of neuroticism, high scores on harm avoidance, and a tendency toward introversion.
A. True
B. False

9. The remission rate was only ____ following ECT in patients with MDD and comorbid borderline personality disorder compared with a rate of ____ in patients with no diagnosed personality disorder.
A. 10%; 56%
B. 18%; 56%
C. 22%; 70%
D. 30%; 70%

10. Which of the following is the best evidence-based approach for treating borderline personality disorder?
A. Dialectical behavior therapy
B. Interpersonal therapy
C. Coherence therapy
D. Motivational interviewing

Answer key to the Mine Your Mind posttest:
1, B; 2, B; 3, A; 4, B; 5, D; 6, A; 7, D; 8, A; 9, C; 10, A.

References:


Links: