

Identifying Difficult-to-Treat Depression: Differential Diagnosis, Subtypes, and Comorbidities

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Treatment-resistant depression (TRD) is a common clinical presentation responsible for much of the burden of major depressive disorder worldwide. For this reason, TRD requires aggressive identification and management. Although several models have been proposed to describe TRD, consensus is still needed on the criteria (ie, dose, duration, compliance, number of trials required) used to define treatment response and resistance. When diagnosing patients with depression, clinicians should identify risk factors associated with treatment resistance, including clinical subtypes of depression and medical or psychiatric comorbidities that could affect the course of treatment. When evaluating a patient who has not responded to a first course of antidepressant treatment, the clinician should verify the primary diagnosis and ensure that the patient has adhered to a treatment regimen that was of adequate dose and duration.

(J Clin Psychiatry 2009;70[suppl 6]:10–15)

Depression is recognized as a major public health problem and a leading cause of disease burden worldwide.¹ Because more than half of all patients with depression do not achieve remission after first-line antidepressant treatment,² treatment-resistant depression (TRD) accounts for much of the disability and cost associated with the disorder.³ The greater severity and duration of illness, the higher likelihood of comorbid disorders, and the higher risk of recurrence—all associated with TRD—add to the burden.⁴ Better understanding of TRD is needed to more effectively treat this common and—in terms of both human suffering and health care dollars—extremely costly illness.

DEFINITION OF TREATMENT-RESISTANT DEPRESSION

At this time, no agreed-upon definition of TRD exists. A review⁵ of randomized controlled trials for therapeutic strategies for TRD chronicled the various criteria that have been used to define treatment nonresponse, and the criteria

included failure of treatment to reduce depressive severity by at least 50%, failure to reduce absolute depressive scores below a specific cut-off point or remission threshold, and failure to produce an asymptomatic state. In the studies reviewed, the minimum number and type of failed antidepressant trials required to assess the presence of treatment resistance differed greatly (Table 1). Additionally, various measures were used regarding the necessary dose and duration of the prescribed treatment required to qualify a patient as having treatment resistance. The studies did not consistently assess the patient's degree of adherence to previous antidepressant trials as a factor in treatment resistance, differed on the number of baseline depressive symptoms necessary for enrollment in the trials or did not use baseline at all to determine eligibility, and often employed different assessment scales to determine those symptoms. However, the basic definition of TRD that is emerging from the literature is an inadequate response to at least 2 antidepressant trials of adequate dose, duration, and treatment adherence. Some have suggested that the patient's drug trials should involve 2 different pharmacologic classes before assigning the label of treatment resistance. However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial⁶ data did not support such a distinction; treatment resistance rates did not differ on the basis of switching within or outside the class of the initial agent.

Several methods for staging TRD in a more systematic and consistent way have also been proposed.⁷ Most recently, Fekadu et al⁸ proposed a staging model that incorporates treatment, severity of illness, and duration of the presenting episode (Table 2). Whether any of these methods have been used consistently is unclear; again, consensus is needed in order to translate a model for staging treatment resistance into widespread clinical practice.

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This article is derived from the planning teleconference series "Tackling Partial Remission to Depression Treatment," which was held in March and April 2009 and supported by an educational grant from Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.

Dr Gaynes is a consultant for Bristol-Myers Squibb and has received grant/research support from the National Institute of Mental Health, the Agency for Healthcare Research and Quality, M3 Corporation, Bristol-Myers Squibb, and Novartis.

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doi:10.4088/JCP.8133su1c.02

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FOR CLINICAL USE

- ◆ Treatment-resistant depression is a common clinical presentation and a leading cause of disease burden worldwide.
- ◆ Clinicians should identify risk factors for treatment resistance in their patients with depression to guide treatment choices and management.
- ◆ Clinicians should evaluate treatment-resistant patients by verifying the initial diagnosis, identifying untreated medical or psychiatric comorbidities, and ensuring patient adherence to a treatment regimen of adequate dose and duration.

RESIDUAL SYMPTOMS AND RELAPSE

Partial response is a serious problem that requires aggressive management, as the presence of residual symptoms puts patients at risk for relapse and recurrence of major depressive disorder (MDD). In one long-term naturalistic study,⁹ patients with asymptomatic recovery were approximately 2.5 times more likely to remain well over 10 years of follow-up than patients with residual symptoms, and patients with residual symptoms relapsed to a new major depressive episode 3 times faster than asymptomatic patients.

The STAR*D trial¹⁰ results supported these findings; patients who had more residual symptom domains had a higher risk of relapse. In the trial, approximately one-third (36.8%) of the patients remitted after an initial antidepressant treatment, and another 30.6% remitted after treatment with a second antidepressant.² Rates dropped off substantially in the third and fourth steps (13.7% and 13.0%, respectively). However, remission was associated with a better prognosis at follow-up, even if that remission required several treatments.

DIAGNOSTIC STRATEGIES TO IMPROVE TREATMENT RESPONSE

Several risk factors for inadequate response to antidepressant treatment have been identified, including misdiagnosis, specific depressive subtypes, and psychiatric and medical comorbidities. Physician-related factors and individual patient compliance or pharmacokinetics can also play a role. A key initial strategy for clinicians then is to identify those patients who are at risk of nonresponse or partial response and aggressively treat and monitor them.

Differential Diagnosis

When a patient appears to have TRD, the first question a clinician should ask is whether the primary diagnosis is correct. The initial differential diagnosis may not have uncovered factors that are affecting treatment. For example, is there a primary disorder, such as a substance use disorder, that is not being treated? Does the patient have an untreated primary medical condition? Rather than treatment resistance, the patient's problem may actually be related to receiving treatment for an incorrect diagnosis.

Subtypes

The patient's apparent treatment resistance may also be related to the presence of a different primary disorder (eg, a bipolar disorder presenting with a current depressive episode, or a dysthymia) or an undiagnosed depressive subtype that might require different treatment than pure MDD (Table 3).^{11,12} Clinically relevant subtypes include psychotic depression, atypical depression, chronic depression, and severe depression.

In patients with bipolar disorder, depressive symptoms are more prevalent than manic symptoms, making it more likely that a patient will present in a depressive episode.^{13,14} Bipolar depressive episodes can be difficult to distinguish from MDD, so obtaining key facts from the patient's history as well as corroborating information from friends and family of the patient may be necessary to identify a bipolar history.

Atypical depression is characterized by reversed vegetative signs such as oversleeping, overeating, rejection sensitivity, leaden paralysis, and reactive mood. Patients with atypical depression appear to respond preferentially to treatment with monoamine oxidase inhibitors.^{15,16}

Depression with psychotic features is relatively common and is associated with longer time to syndromal recovery and a higher likelihood of severe depression.¹⁷ However, psychotic features can be present in patients with mild or moderate depressive episodes.¹⁸ Determining the presence of psychotic symptomatology can be difficult but is important because antidepressant monotherapy may exacerbate psychotic symptoms,¹⁹ and antipsychotic agents may be needed.

Dysthymic disorder, a chronic low-grade but impairing depressive subtype, puts patients at risk of difficult-to-treat depression. More than 75% of patients with dysthymic disorder will meet the criteria for a major depressive episode at some point,²⁰ and this double depression (MDD superimposed on dysthymic disorder) is associated with a high rate of relapse and a protracted course of illness.^{21,22}

Depressive severity is an important additional specifier that indicates risk of a difficult-to-treat depression.²³ Greater severity is associated with more comorbidities, longer time to achieve response, greater functional impairment, a greater risk of recurrent episodes, and a greater likelihood

Table 1. Categorical Definitions of Treatment-Resistant Depression According to Current Randomized Controlled Trials^a

Required Number/Type of Previous Antidepressant (AD) Trials	Number of Studies (%)
= 1 trial	5 (10.6)
≥ 1 trial	8 (17)
= 2 trials	6 (12.8)
= 2 trials with DIFF ADs	3 (6.4)
≥ 2 trials	9 (19.1)
≥ 2 trials with DIFF ADs	8 (17)
NA	8 (17)

^aReprinted with permission from Berlim and Turecki.⁵

Abbreviations: DIFF = different classes and/or mechanisms of action, NA = information not available.

of suicidal ideation.⁴ The STAR*D²⁴ study found that patients with greater symptom severity were approximately 3 times less likely to remit than those with mild or moderate depression.

Chronic depression, in which patients are symptomatic more days than not over a 2-year period, is associated with a high rate of treatment resistance.²³ A study²⁵ that contrasted patients with chronic depression with patients with episodic depression (in which patients reach full remission between the 2 most recent depressive episodes) showed that patients with chronic depression had more comorbid anxiety-related and somatic syndromes, had an earlier age at onset of symptoms, and needed treatment more often than patients with episodic depression.

Comorbidities

Comorbid psychiatric disorders. Anxiety disorders commonly coexist with major depression.²⁶ These comorbidities increase the likelihood of greater severity of depressive symptoms, a history of suicide attempts, decreased responsiveness to treatment, and greater susceptibility to side effects.^{23,24,26} The more clinically relevant of these disorders include social anxiety disorder, posttraumatic stress disorder, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder. Variables associated with treatment resistance in a study of MDD are listed in Table 4, and comorbid anxiety disorder was found to have the highest statistical significance.

Additional comorbid diagnoses important for the clinician to identify are substance use and personality disorders, both of which are indicators of a harder-to-treat depression that may require multiple treatment modalities. Substance use or dependence disorders frequently co-occur with depression and are associated with increased symptom severity and a lower likelihood of remission.^{24,27} Even among patients with depression who do not abuse alcohol, the degree of alcohol use at baseline—including even moderate consumption—correlates with poorer response to antidepressant treatment.²⁸ Personality disorders have been implicated as a factor in treatment resistance to antidepressants, particularly in relation to tricyclic antidepressants.²³

Table 2. Maudsley Staging Parameters and Suggested Scoring Conventions^a

Parameter/Dimension	Parameter Specification	Score
Duration	Acute (≤ 12 months)	1
	Subacute (13–24 months)	2
	Chronic (> 24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures	Antidepressants	
	Level 1: 1–2 medications	1
	Level 2: 3–4 medications	2
	Level 3: 5–6 medications	3
	Level 4: 7–10 medications	4
	Level 5: > 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		(15)

^aReprinted with permission from Fekadu et al.⁸ Resistance may be presented as a single numerical digit between 3 and 15; as 1 of 3 severity categories (mild, scores = 3–6; moderate, scores = 7–10; severe, scores = 11–15); or descriptively, incorporating the main factors in the description (eg, moderate, subacute level 2 resistance).

The STAR*D study provided information on the clinical relevance of comorbid symptom clusters—as opposed to full comorbid diagnoses—that can increase the likelihood of TRD. Patients with major depression with anxious features were approximately one-third as likely to remit compared to those without these features.²⁹ Additionally, patients with melancholic features appear less likely to remit.^{24,30}

Comorbid medical disorders. Comorbid medical conditions are a risk factor for nonresponse to treatment and for recurrent depressive episodes, underscoring the need for a complete patient history and physical and laboratory evaluation.^{31,32} Further, Iosifescu et al³³ showed that the correlation between poor treatment response and medical comorbidity increases with the overall burden of comorbid medical illness, with a patient's likelihood of responding to treatment decreasing by approximately 20% for each additional organ system affected by illness.

Many medical conditions are associated with an increased likelihood of MDD treatment resistance. For example, patients with greater numbers of cardiovascular disease risk factors (including diabetes, hypertension, and hypercholesterolemia) have higher rates of treatment resistance than patients with fewer risk factors.³⁴ Chronic painful conditions are reported among more than 40% of patients with MDD and are associated with a greater severity and longer duration of depressive symptoms.³⁵ Other medical conditions highly comorbid with depression include cancer,³⁶ hypertension,³⁷ stroke,³⁸ Parkinson's disease, dementia, and migraine.³⁹

Specific medical conditions may be associated with particular types of depression, which could affect treatment choice. A STAR*D report⁴⁰ found that patients with MDD

Table 3. Paradigm Errors Identifying Potential Antidepressant Treatment Failure^a

Paradigm Error	Description	Quantifying Data
Paradigm error 1	Failure to diagnose and manage bipolar disorder	> 30% of patients never diagnosed with or treated for bipolar disorder
Paradigm error 2	Failure to diagnose and manage psychotic depression	5 patients (3%) incorrectly diagnosed with psychotic depression by referring physician
Paradigm error 3	Failure to diagnose and manage melancholic depression	> 70% of patients misdiagnosed with non-melancholic depression by referring physician (46% satisfied criteria for DSM-IV melancholia; 28% for clinical melancholia). ≤ 77% of patients treated with an SSRI rather than a TCA, MAOI, or SNRI
Paradigm error 4	Diagnosing and/or managing a nonmelancholic condition as if it were melancholic depression	54 patients misdiagnosed with melancholic depression. 93% experienced ≥ 1 contributing psychosocial factor. Adequate psychotherapy (91%) and/or social support/interventions (59%) were not administered to address these factors
Paradigm error 5	Misdiagnosing secondary depression	Comorbid psychiatric conditions (ie, anxiety, panic, social phobia, obsessive-compulsive behavior, and other personality functioning disorders) found to be inadequately diagnosed in patients
Paradigm error 6	Failing to identify organic determinants	≤ 10% of patients assessed to have other medical conditions, such as dementia or stroke, which had not been considered as contributing to patient's depression

^aReprinted with permission from Souery et al.⁷ Based on data from Parker et al.¹¹

Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 4. Factors Associated With Treatment Resistance (2-step logistic regression model using nonresistance/resistance as the dependent variable), N = 702^{a,b}

Variable	Initial Univariate Logistic Regression		
	P Value	Odds Ratio	95% CI of Odds Ratio
Comorbid anxiety disorder	< .001	2.6	1.8 to 3.6
Comorbid panic disorder	< .001	3.2	2.1 to 5.0
Current suicidal risk	< .001	2.2	1.6 to 3.0
Severe intensity vs moderate intensity	.001	1.7	1.2 to 2.3
No. of hospitalizations > 1	.003	1.6	1.2 to 2.1
Social phobia	.008	2.1	1.2 to 3.6
Recurrent episodes vs single episode	.009	1.5	1.1 to 2.0
Age at onset before 18 y	.009	2.0	1.2 to 3.3
Melancholic features	.018	1.5	1.1 to 2.3
Nonresponse to first antidepressant treatment lifetime	.019	1.6	1.1 to 2.5
Personality disorder (DSM-IV criteria)	.049	1.7	1.0 to 2.9

^aReprinted with permission from Souery et al.¹²

^bTable includes only variables where $P < .05$. Variables are ranked from highest to lowest level of statistical significance on the basis of the univariate analysis.

and diabetes were more likely to experience certain physical symptoms of depression (eg, increased appetite, psychomotor slowing, and leaden paralysis) than patients with MDD without diabetes. Hypothyroidism is recognized as a cause of depression, but subclinical hypothyroidism has also been associated with an increased prevalence of depressive and anxiety symptoms and with refractory depression.⁴¹⁻⁴³

Some medications used for somatic conditions, including opiate analgesics and calcium channel blockers, are associated with either causing or exacerbating depression, at least in certain subsets of the population.⁴⁴ Especially strong evidence is available for the corticosteroids⁴⁴ and the interleukins and interferons.^{45,46}

Clinician and Patient Risk Factors

Several factors should be considered when evaluating a patient who has not responded to an initial course of treatment. Once the clinician has established that another primary psychiatric disorder or depressive subtype has not

gone undiagnosed, he or she should then verify that the dose and duration of the antidepressant treatment trial was adequate. Prescribing inadequate doses of medication for an inadequate period of time can contribute to patients being incorrectly labeled as treatment resistant.^{47,48} The STAR*D trial³¹ results have provided support for the need for longer periods of treatment and for adequate dosing strategies tailored to individual patients for optimal outcomes.

Patient factors such as noncompliance with treatment⁴⁷ or unusual pharmacokinetics⁴⁹ can contribute to difficult-to-treat depression. A patient who is a poor metabolizer may be especially sensitive to adverse side effects despite receiving the standard dose of an antidepressant, whereas a patient with an ultrarapid metabolism may need higher doses of the same medication to achieve response.⁴⁹ Lack of response and intolerable side effects contribute to poor treatment adherence, which may account for as many as 20% of patients labeled as treatment resistant.⁵⁰ Other factors that may affect treatment adherence are the ease of use and cost of a particular agent, the treatment history of the patient, and the patient's family members.

CONCLUSION

Treatment-resistant depression is a common clinical presentation that requires aggressive identification and management. However, consensus is needed on the criteria used to define treatment response and resistance. When evaluating patients with apparent treatment resistance, clinicians should clarify that the primary diagnosis is correct, identify particular clinical subtypes that increase

the risk of TRD, ascertain whether psychiatric or medical comorbidities or medications that might affect the course of treatment are present, and ensure that the patient is adhering to a treatment regimen of adequate dose and duration. Properly evaluating treatment resistance risk factors can guide the clinician in choosing treatment strategies for optimum outcomes for individual patients.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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