

The Journal of Clinical Psychiatry

AUDIOGRAPH SERIES



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Recognizing Treatment-Resistant Depression

*A. John Rush, M.D.; John F. Greden, M.D.; Susan G. Kornstein, M.D.;
Andrew A. Nierenberg, M.D.; and Harold A. Sackeim, Ph.D.*

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CME Objectives

After completing this educational activity, participants should be able to:

- Define the terms *treatment response*, *remission*, *nonresponse*, and *partial response* as they apply to patients with depression
- Use an instrument to assess a depressed patient for treatment resistance
- Discuss the prevalence of treatment resistance and its impact on function, prognosis, and health care utilization
- Identify the clinical features of treatment-resistant depression, including symptoms, course of illness, and comorbidity

Statement of Need and Purpose

Physicians responding to surveys in *The Journal of Clinical Psychiatry* and related CME activities have requested updated information on recognizing and managing treatment-resistant depression, which may occur in about half of patients with depression. This CME activity was designed to improve the recognition of treatment-resistant depression. There are no prerequisites for this activity.

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Faculty Disclosure

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this continuing medical education activity were asked to complete a full disclosure statement. The information received is as follows:

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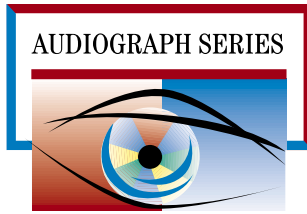
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Disclosure of Off-Label Usage

To the best of his knowledge, Dr. Rush has determined that no investigational information about pharmaceutical agents has been presented that is outside U.S. Food and Drug Administration–approved labeling.

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Recognizing Treatment-Resistant Depression

A. John Rush, M.D.; John F. Greden, M.D.; Susan G. Kornstein, M.D.;
Andrew A. Nierenberg, M.D.; and Harold A. Sackeim, Ph.D.

Recognizing treatment-resistant depression is one of the first steps in planning treatment for depressed patients. Many patients who present for treatment may not have ever been treated for depression, but others have received some form of treatment. The success or failure of prior treatment in prior episode(s) informs the clinician about which treatments to employ or avoid in the current episode. Other patients may have received inadequate treatment for depression in the past, and their depression was then wrongly labeled as resistant to treatment. Clinicians must be able to recognize whether patients are treatment resistant despite some inconsistencies in the literature regarding the definition of treatment resistance.¹

Important issues in the recognition of treatment resistance include the following topics:

1. Definitions of *treatment response*, *remission*, *nonresponse*, and *partial response* as they apply to patients with depression;
2. Clinical features of treatment-resistant depression, including symptoms, course of illness, and comorbidity;
3. Prevalence of treatment resistance and its impact on function, prognosis, and health care utilization; and
4. Use of instruments to assess depressed patients for treatment resistance.

Defining Treatment Response, Remission, Nonresponse, and Partial Response

Dr. Rush: Dr. Nierenberg, please define terms related to treatment resistance, to help clinicians recognize it.

Dr. Nierenberg: Depressive symptoms are regularly measured in research studies, but it is quite rare for clinicians to use rating scales. Most clinicians judge in a global way whether or not a medication has been helpful. So, one challenge of research is to make data translatable into the regular clinical encounter and to encourage clinicians to actually measure what they're treating so that they know, in fact, whether or not patients have responded.²

Frank and colleagues³ defined terms describing change points in the course of major depression. Definitions by necessity are somewhat arbitrary, but some conventions exist. *Nonresponse* can be defined as having no clinically meaningful response. Many investigators say that having less than a 25% improvement by the end of a trial is a nonresponse. Whether the cutoff to define nonresponse is a 25% improvement, a 30% improvement, or even a 50% improvement depends on the purpose of the study. Many investigators define a *partial response* as more than 25% but less than 50% improvement. Patients with a partial response still have residual psychopathology and dysfunction. *Treatment response* has been

widely accepted to be a 50% or greater reduction in the score on almost any scale—whether it’s the gold standard Hamilton Rating Scale for Depression or the Montgomery-Asberg Depression Rating Scale or the Inventory for Depressive Symptomatology.

Remission is the state the patient reaches when no residual psychopathology or dysfunction remains. Remission is the ultimate goal of treatment. Patients who sustain 8 weeks of remission are considered to be recovered. If they can’t sustain that recovery through continuation and maintenance treatment, then what they have is called *depressive breakthrough*, and that’s a form of resistance.

Dr. Rush: So, *response* and *remission* are defined according to how much symptomatology is left after treatment and how long it persists—or how constant it is in its absence.

Dr. Nierenberg: Yes, and symptomatology is different from functioning.

Dr. Greden: Patients with residual symptoms—depending upon what the symptoms are—may have substantial functional impairment.

Dr. Sackeim: Even when people achieve remission, there is often a lag before the functional improvement occurs. It can take weeks or months.

Dr. Nierenberg: Many of these people have been depressed for so long that it takes them time to get used to not being depressed. Plus, their family and friends have also adapted to their being ill, and it takes time for those people to change, too.



Depressive symptoms are regularly measured in research studies, but it is quite rare for clinicians to use rating scales.

Dr. Rush: Does evidence indicate that response with residual symptoms really is different from full remission?

Dr. Nierenberg: Yes, there are 2 lines of evidence.

First, people who have residual symptoms just don’t function as well. A fundamental concept is that the absence of psychopathology is not necessarily the presence of wellness.⁴ Ryff and Singer⁵ defined wellness in their model of positive psychological functioning. Patients who respond to treatment but have residual symptoms are not well; those who have full remission are well and are able to live fuller lives.

The other line of evidence comes from epidemiologic data. Judd et al.⁶ found that the presence of residual symptoms puts people at a much higher risk of having a relapse or a recurrence, as compared with those who reach full remission. This is true whether patients take antidepressants or receive cognitive therapy.⁷

Dr. Greden: Judd et al.⁶ found that if residual symptoms were present,

another major depressive episode was likely to occur 3 times faster than if the symptoms were absent—a median of 23 weeks versus 68 weeks.

Dr. Nierenberg: They also reported that having residual symptoms was more often predictive of a relapse or recurrence than was having a diagnosis of recurrent depression.⁶

Dr. Sackeim: A number of studies of response—not just to pharmacologic treatments but also to electroconvulsive therapy (ECT)—indicate that the extent of residual symptomatology is one of the best predictors of the likelihood of relapse.^{8,9}

Dr. Greden: Essentially, residual symptoms are indicative of incomplete treatment of the current episode. It's the cliché "Better but not well is not good enough."

Clinical Features of Treatment-Resistant Depression

Dr. Rush: Are there any baseline clues as to who might fail to achieve full remission, Dr. Kornstein?



Remission is the state the patient reaches when no residual psychopathology or dysfunction remains.

Remission is the ultimate goal of treatment.

Dr. Kornstein: Yes, but the literature on characteristics of patients who have treatment-resistant depression is sparse and problematic. There is tremendous variability from study to study in how treatment-resistant depression is defined. For example, many studies included patients who were labeled treatment-resistant but actually had had inadequate treatment trials or were misdiagnosed. The studies also vary in the patients' characteristics—different subtypes of depression, different comorbid illnesses, different age groups, or inpatients versus outpa-

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tients. There are also problems with the study designs—most were retrospective and uncontrolled and had small sample sizes. So, my opinions here are based as much on clinical experience as on scientific data. We need more research into predictors of treatment-resistant depression using controlled designs and standardized definitions of treatment resistance.

Sex

Female sex was proposed in older literature as a risk factor for treatment resistance. Of course, in any sample of depressed patients, there will be more women because of the sex difference in prevalence of depression. But newer studies have generally not found sex to be a predictor of resistance. However, gender may help predict response to one treatment versus another. Women may be less responsive than men to tricyclic antidepressants (TCAs) and respond preferentially to selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors. In an analysis of patients with chronic major or double depression, my group¹⁰ showed that premenopausal women responded significantly better to the SSRI sertraline than to the TCA imipramine, while men responded significantly better to imipramine, according



A positive response in a family member may predict a similarly positive response in the patient.

to scores on various rating scales. There was no difference in response to the 2 drugs in postmenopausal women. I think the reason that older literature mentions female gender as a risk factor for treatment resistance is because the mainstay of antidepressant treatment at that time was the TCAs, and women don't respond well to those agents.

Family History

A positive family history of depression is another factor mentioned in the literature as a predictor for treatment resistance, but there is little evidence to support this. Nelsen and Dunner¹¹ matched 26 patients who had been labeled treatment-resistant with a group of nonresistant patients by age, gender, and depressive subtype. The treatment-resistant patients were more likely to have a family history of affective disorder. But some of the patients labeled as treatment-resistant were found to have had inadequate treatment trials and may not have been truly resistant. It can be useful to know if a family member with depression has sought treatment because a positive response in the family member may predict a similarly positive response in the patient.



The extent of residual symptomatology is one of the best predictors of the likelihood of relapse.

Age at Onset

Both early and late onset of depression have been described as risk fac-



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tors for treatment resistance. Early onset of depression is associated with higher rates of comorbid disorders, substance abuse, a family history of mood disorders, a chronic course of illness, and an incomplete remission of symptoms.¹² In a study by Klein and colleagues,¹³ early onset failed to predict nonresponse in patients with chronic depression. However, their results may not be generalizable to other subtypes of depression.

Late onset of depression (in patients over 60 years) may also affect treatment outcome.¹⁴ In older patients, the likelihood of psychotic depression—which would be less responsive to antidepressant medication alone—is greater. Also, comorbid medical conditions in older patients may affect both evaluation and treatment of depression. There is also a high risk of pseudo-resistance in geriatric patients—for example, the diagnosis of an organic mood disorder could have been missed, or the patient may be unable to reach an adequate dosage of medication because of greater sensitivity to side effects. In addition, geriatric patients may respond more slowly to antidepressant treatment, so there is a

risk that they could be prematurely declared treatment-resistant, which is another form of pseudo-resistance.

Severity

Severe depression is another risk factor for treatment-resistance. Severe depression tends to be associated with greater functional impairment, longer duration of illness, lower likelihood of spontaneous remission, and greater risk of recurrence. Patients with severe depression are also more likely to have psychotic features and comorbid psychiatric or general medical disorders. There has been controversy about whether the SSRIs are as effective as the TCAs in severe depression, but in a review Dr. Nierenberg concluded that no differential efficacy exists.¹⁵ In addition, a recent meta-analysis¹⁶ found that patients with severe and recurrent illness responded significantly better to combined treatment with medication and psychotherapy than to psychotherapy alone.

Comorbidity

The presence of a comorbid general medical or psychiatric disorder increases the likelihood of treatment-resistance or pseudo-resistance. Comorbid disorders are common in depressed patients. Keitner and colleagues¹⁷ found that 53% of patients admitted with major depression had a coexisting Axis I, II, or III condition. So, it's important to systematically evaluate patients with treatment-resistant depression for the presence of comorbid disorders. Often, disorders comorbid with depression are unrecognized or suboptimally treated, and they affect the severity and course of the depres-



Chronicity also may increase the likelihood of treatment resistance.

sion as well as response to treatment. In some cases, they may actually be causing the mood disturbance—as in the case of a substance-induced mood disorder or an endocrine disorder such as hypothyroidism—and when the primary disorder is treated, the depression improves too. In an early study by Keller and colleagues,¹⁴ the diagnosis of secondary depression emerged as a major predictor of chronicity and non-response, but this was most likely because the primary, nonaffective disorder was inadequately treated.

Psychiatric disorders that are most often comorbid with depression include anxiety disorders, substance abuse, and personality disorders.

Depressed patients with comorbid anxiety tend to be more severely depressed, have a greater risk for suicide, and have greater functional impairment.¹⁸ They also have increased rates of chronicity, relapse, and recurrence. Depressed patients with anxiety tend to have a slower response to medication and an incomplete remission of symptoms and are often more susceptible to side effects.

Comorbid substance abuse can worsen depression and affect compliance with treatment and treatment response. Even moderate use of alcohol can contribute to treatment resistance, and, in turn, the depression may affect the substance abuse and make the pa-

tient more prone to relapse.¹⁹ So, these patients often need aggressive multimodal treatment.

The relationship between personality disorders and depression is complex.²⁰ Generally, depressed patients with personality disorders are less responsive to treatment compared with patients without Axis II pathology. In our study¹⁰ of patients with chronic major or double depression, about 50% of the patients had at least one Axis II disorder; about 25% had avoidant personality disorder and almost 20% had obsessive-compulsive personality disorder. The presence of comorbid personality disorders did not affect treatment outcome, but patients with severe borderline, schizotypal, or antisocial personality disorders were excluded from the study, which may explain that result.

Depression can cloud the presentation of personality. A patient who appears to have significant Axis II pathology when depressed may seem quite different once the depression clears. Fava and colleagues²¹ reported that 44% of depressed patients with borderline personality disorder no longer met criteria for the personality disorder after 8 weeks of fluoxetine treatment. So, one must be careful about prematurely diagnosing personality disorders in depressed patients.

Psychiatric disorders that may be comorbid with depression and may easily be missed because the patient is often secretive about them include eating disorders, obsessive-compulsive disorder, and body dysmorphic disorder. Unrecognized, these may contribute to treatment resistance.

In terms of comorbid general medical conditions, the presence of diabe-

tes, chronic pain, fibromyalgia, or chronic fatigue syndrome complicates evaluation and treatment of depression. In diabetic patients, the presence of depression is associated with poor glycemic control, which may result from both direct neuroendocrine effects and indirect effects by influencing patient compliance.²² Medications used to treat general medical conditions can sometimes cause mood symptoms themselves—as in the case of antihypertensives or steroids—and can confound treatment. So, comorbidity is an important issue in evaluating and treating refractory depression.

Chronicity

Chronicity also may increase the likelihood of treatment resistance. The chronic subtypes include chronic major depression, which is a major depressive episode of at least 2 years' duration; double depression, which is major depressive disorder superimposed on dysthymia; and recurrent major depressive disorder with incomplete interepisode recovery.

About 20% of patients with major depressive disorder develop a chronic course of illness, and this same 20% risk of chronicity persists with each new episode of depression.²³ Patients with double depression tend to return to their dysthymic state when major depressive episodes end, and they are at higher risk for recurrence than patients with major depressive disorder alone.²⁴

Chronic depressions are also associated with substantial comorbidity—particularly anxiety disorders, alcoholism, and personality disorders—all of which tend to worsen



Clinicians may give up too soon and declare patients treatment resistant who might have responded if the treatment were continued longer.

treatment outcome. In the Keller et al. study²⁵ of chronic major or double depression, 24% of the patients had at least 1 lifetime comorbid anxiety disorder. Over a third reported a lifetime history of alcohol or substance abuse, and more than 50% had at least 1 Axis II disorder. Chronic depression is also associated with severe and pervasive functional impairment, to a greater degree than is seen with acute major depressive disorder and more severe than is seen with many chronic medical disorders, including hypertension, diabetes, and arthritis. Patients with chronic depression also show a greater frequency of suicide attempts and hospitalizations and an earlier onset of their illness, which increases the risk for treatment resistance.

Underrecognition and undertreatment are problems with depression in general, but even more so with chronic depression because these patients are ill for so many years that they don't have a normal baseline for comparison. Patients, their families, and even physicians may accept the chronically ill

state as normal for that patient. Keller et al.²⁶ found that only 26% of patients with chronic depression had received an adequate antidepressant trial.

Until the past decade or so, chronic depression was viewed as a problem of character pathology and unresponsive to medication. In recent years, the chronic depressions have been reconceptualized as mood disorders and shown to be responsive to antidepressant treatment if an adequate dose and duration are used. But the response rates are somewhat lower than with episodic depression, and patients are less likely to show a complete remission of symptoms, increasing the risk for relapse and recurrence. A longer time to response is also common. In our chronic depression study¹⁰ with sertraline and imipramine, a significant number of patients responded between weeks 8 and 12 of the acute phase, but 46% of patients who were classified as partial responders at week 12 became full responders by the end of the continuation phase (week 28). So, clinicians may give up too soon and declare patients treatment resistant who might have responded if the treatment were continued longer.

Keller et al.²⁷ compared nefazodone, psychotherapy, and their combination in patients who had chronic major depression, double depression, or recurrent depression with incomplete interepisode recovery. The Cognitive-Behavioral Analysis System of Psychotherapy (CBASP), developed specifically to treat chronic depression,²⁸ was used. The response rate to the combination treatment was dramatically better than to either treatment alone. Thus, if you choose

the right treatment and provide an adequate trial, patients are less likely to be classified as treatment resistant.

Duration of Episode

Dr. Rush: Does evidence show that a longer duration of the current episode is related to a reduced likelihood of responding to an adequate trial in patients who have not had prior treatment?

Dr. Kornstein: The longer a patient does not receive treatment, the more likely a poor outcome is.

Dr. Sackeim: Is it possible that the depression itself has an iatrogenic effect such that the longer it lasts the harder it is to treat? Or, are some patients simply prone to long episodes and resistance to treatment? Does having a longer episode increase the likelihood of having already received treatment, and having had prior treatment resistance predicts later resistance? Or, does ineffective treatment during an episode engender resistance?

Dr. Greden: It's probably a combination of all of those factors.



Some severely ill patients . . . show evidence of hippocampal and amygdala neuronal degeneration. This atrophy can be seen with magnetic resonance imaging (MRI).



Undertreatment should not be confused with treatment resistance. Patients can't be considered to have failed a trial unless the trial was adequate.

Dr. Kornstein: It's important to treat aggressively toward a full remission. That will have the best long-term outcome for the patient.

Prevalence and Impact of Treatment Resistance

Dr. Greden: Depression affects approximately 340 to 360 million people worldwide, and perhaps 18 million in the United States.²⁹ The onset of depressive symptoms frequently occurs earlier than is generally believed. Between 15 and 19 years of age, many patients develop what are called adjustment reactions and conduct disorders, and sometimes the emphasis is placed somewhat appropriately but also misleadingly on accompanying substance abuse. But the underlying disorder—depression—isn't diagnosed. Stress makes it worse, but stressors aren't avoidable. Adolescent or childhood major depressive disorder increases the risk of subsequent episodes.

It is important to treat depression early and vigorously in order to avoid resistance. When depression isn't diagnosed and treated early, or if patients aren't treated all the way to remission,

there may be morphologic consequences in the brain. Some severely ill patients who have spent many days of their lives depressed show evidence of hippocampal and amygdala neuronal degeneration.³⁰ This atrophy can be seen with magnetic resonance imaging (MRI). Etiologic investigations suggest that chronic stress wasn't treated and, subsequently, levels of glucocorticoids, steroids, or stress hormones increased. When coupled with use of alcohol, toxins, or other drugs of abuse, a sequence of abnormalities begins, including a decrease in neurotrophins. The end result is brain degeneration.

Dr. Rush: But, some types of depression have an easily detectable set of changes in the brain. The question is whether the degeneration or the depression came first.

Dr. Greden: That is not easily answered. Sheline et al.³¹ compared MRIs of 24 severely depressed women with age- and sex-matched control subjects with no history of depression. The only significant predictor of the severity of MRI-observed atrophy was the number of days that patients had spent depressed in their lifetimes. The longer the depression, the more severe the damage. They didn't address the question of causality. DeBellis et al.³² noted hippocampal degenerative changes with adolescent alcohol abuse. Starkman and colleagues³³ found the same pattern in patients with Cushing's disease. In that population, the damage was reversible by removing pituitary tumors; then, the glucocorticoid levels decreased and regenerative responses were seen. But, while this evidence suggests that we can reverse damage done over time,

a far better strategy would be to prevent the damage from occurring in the first place.

Dr. Sackeim: There is evidence³⁴ of cell loss in the prefrontal cortex just below the genu of the corpus callosum in first-episode mood disorders before treatment. But those populations do not yet seem to have the hippocampal changes associated with having a longer history of the illness.

Using Instruments to Assess Depressed Patients for Treatment Resistance

Dr. Rush: Dr. Sackeim, given the research that you and others have done, how can the clinician recognize resistance?

Dr. Sackeim: The field of therapeutics has spent a lot more time developing approaches to diagnosis than we have to assessing the adequacy of treatments. Figuring out what has and has not worked for the patient in the past is key in determining how you're going to treat the patient.

Knowing what constitutes an adequate trial and what constitutes treatment resistance are also central to approaching treatment. The major variables are the dose of the medication that has been administered, the duration at which that dose was given, blood level if it's relevant, compliance with the regimen, tolerability, and the outcome of that particular trial.

Treatment practices in the community have high rates of lack of response and lack of remission that are associated with inadequate dosing and/or duration of treatment. The acceptable thresholds—such as a minimum of 200 mg/day of imipramine or 20 mg/day of



Once one establishes that a medication was regularly taken at a sufficient dose for a sufficient duration, then one can consider that to have been an adequate trial.

fluoxetine, given for a minimum duration of 4 to 6 weeks—are often not the trials that patients receive. The majority of depressed patients are undertreated.³⁵

Undertreatment should not be confused with treatment resistance. Patients can't be considered to have failed a trial unless the trial was adequate. Patients also shouldn't be considered treatment resistant if they never reached an adequate dose or did not take a medication long enough because of side effects. There is no indication that intolerance to one treatment predicts lack of response to the next medication trial, whereas treatment resistance does imply a lower probability of response to a subsequent trial. Compliance is an important factor as well; if patients did not take the drug, then the trial should not be considered adequate. Once one establishes that a medication was regularly taken at a sufficient dose for a sufficient duration, then one can consider that to have been an adequate trial.

Unfortunately, patients may have been treated by a number of past providers. Patients themselves are often



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poor historians with regard to prior treatments.³⁶ Getting information about past trials can be key to deciding how to guide subsequent treatment, but obtaining that information can be difficult.

Dr. Rush: We should emphasize to patients that no drug is a panacea and sometimes multiple treatment attempts are needed, so keeping a careful record of their medication type, dose, and duration could help the next practitioner, should there be a change in practitioners.

Dr. Sackeim: Since depression will be a recurrent and often lifelong illness in many people, psychoeducational approaches to teach patients from the outset to track what they receive and for how long, and what treatment helped or did not help, would be worthwhile.

Dr. Rush: If you have a patient in the second untreated episode of moderately severe depression, which has lasted for 6 to 9 months, would the patient have a 50% chance of responding to treatment?

Dr. Greden: That scenario is probably what usually happens in naturalistic settings, because early episodes are seldom diagnosed and/or treated. About half of patients with major

depression do not respond to the first treatment or respond but do not achieve remission.³⁷ Clinicians still view treatment-resistant patients as being a minority, but this problem is far more prevalent than we thought. Treatment-resistant depressed patients place high demands on the time of their families and their clinicians, leading to high human, family, and social costs.¹

Dr. Nierenberg: With or without treatment, will the depressive episode lift at some point simply because it's time for it to go away?

Dr. Sackeim: We used to teach that the average duration of a depressive episode was 6 to 9 months. However, many patients are chronically ill for much longer durations. Could treatment be prolonging these episodes?

Dr. Greden: Even if long-term treatment might increase the likelihood that upon discontinuation the individual will promptly relapse, the risk-benefit ratio seems to favor sustaining wellness via long-term treatment rather than risking the consequences of the deteriorating course of untreated depression.

Dr. Nierenberg: Causality is difficult to tease out.

Dr. Rush: Clinical experience shows that overtreatment of depressive episodes is not the problem leading to treatment resistance. The problem is undertreatment—underrecognition and underdosing.

Dr. Greden: If we intervened earlier and treated more aggressively, we could lower the prevalence of treatment resistance.

Dr. Rush: When we go into clinics or consult with colleagues, I think we're all surprised sometimes to learn that a patient is more symptomatic than we

think; we have declared treatment a full success, but although substantial improvement has occurred, the patient has not achieved remission. How can clinicians better appraise outcome in depressed patients?

Dr. Greden: We need to emphasize the use of self-rating instruments and also start using new technological rating tools.

Dr. Kornstein: Many times patients will tell you that they've markedly improved, but they'll still have significant residual symptoms that are only captured by a symptom rating scale.

Dr. Sackeim: Ironically, the assessment of depressive symptoms is one of the areas in psychiatry that can be done with remarkable reliability, even in the clinical context. It's surprising that clinicians are not using rating scales to measure symptomatology. In the treatment of depression—whether with pharmacotherapy, psychotherapy, or somatic treatments—the degree of improvement that clinicians report generally exceeds the degree of improvement that patients report. Clinicians

may be overestimating the amount of improvement in their patients.

Dr. Kornstein: Some patients are reluctant to believe they have improved. It takes a while to be convinced. They're also, I think, overweighting the mood symptoms, whereas we're rating the mood and all the other neurovegetative symptoms that go along with mood.

Dr. Rush: Some of the clinicians' rating scales focus more on the vegetative symptomatology, while some of the self reports like the Beck Depression Inventory refer more to cognitive symptoms.

Conclusion

Dr. Rush: Defining, recognizing, and predicting treatment resistance are important parts of a clinician's repertoire. In summary, the aim of treatment is remission, not just response. Treatment resistance, or less than a perfect remission to an initial treatment, is to be expected in more patients than not, and when it does appear, it is not a basis for discouragement but a basis for re-engineering the treatment approach.

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Drug Names: fluoxetine (Prozac), nefazodone (Serzone), sertraline (Zoloft).

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- 1. Patients who have improved 60% over their baseline scores on a depression rating scale can be said to have achieved:**
 - a. Remission
 - b. Nonresponse
 - c. Response
 - d. Relapse
- 2. If patients sustain a state of remission for 8 weeks, they are considered to have:**
 - a. Recovered
 - b. Relapsed
 - c. Experienced a recurrence
 - d. Experienced residual symptoms
- 3. Although it is rare for researchers to use rating scales, many clinicians use measurements of depressive symptoms regularly.**
 - a. True
 - b. False
- 4. Patients who have treatment-resistant depression:**
 - a. Function as well as those who have achieved remission
 - b. Rarely visit health care professionals
 - c. Have a better prognosis the more residual symptoms they have
 - d. May have been wrongly given this label due to receiving inadequate prior treatment
- 5. The clinical features of treatment-resistant depression do NOT include:**
 - a. A high rate of comorbid disorders
 - b. Incomplete remission of symptoms
 - c. Female sex
 - d. Early or late onset of depressive symptoms
- 6. Chronic depression is:**
 - a. Associated with a low rate of comorbid illnesses
 - b. A synonymous term for treatment-resistant depression
 - c. Often undertreated because the patients have been depressed for so long that there is no normal baseline for comparison
 - d. Actually a problem of character pathology and is not responsive to medication
- 7. If untreated, a prolonged depressive episode seems to:**
 - a. Be related to hippocampal degeneration
 - b. Respond only to electroconvulsive therapy (ECT)
 - c. Be associated with lower costs of time and money for patients, families, and health care services than if treated
 - d. Cause psychosis

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