Assessing the Risk Factors for Difficult-to-Treat Depression and Treatment-Resistant Depression

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Depression is the leading cause of disability among people across the globe, according to the World Health Organization. Among those who have been diagnosed, many fail to achieve remission after following recommended antidepressant medication and psychosocial therapies. In particular, difficult-to-treat and treatment-resistant depression may cause severe impairments for patients, including diminished cognitive functioning, increased medical bills, and decreased workplace performance, as well as an increased risk of developing comorbid illnesses. However, many tools are available to clinicians for identifying treatment-resistant depression, including rating scales such as the 9-question Patient Health Questionnaire (PHQ-9) and the Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$), as well as clinical evidence related to risk factors for difficult-to-treat or treatment-resistant depression. Accurately identifying treatment-resistant depression is the first step toward changing treatment regimens to help patients achieve remission.

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Depression is a serious medical illness that affects approximately 350 million people worldwide.[1] In 2012, approximately 16 million US adults (about 7% of the population) reported at least one major depressive episode in the previous year.[2] The primary treatment objective for clinicians who diagnose patients with major depressive disorder (MDD) is to help them to achieve remission.[3]

In treatment guidelines,[3] *remission* is defined as a patient who has demonstrated at least 3 weeks without the 2 core symptoms (ie, sad mood and diminished interest) and no more than 2 of the other symptoms in the MDD criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*).[4] In addition, patients in remission should be functioning at their premorbid psychosocial levels.[3]

Unfortunately, many patients have only partial or no response at all to treatments. About one-third of patients achieve remission following initial antidepressant therapy, and approximately two-thirds of all patients reach remission after up to 4 acute treatment trials.[5] If patients do not achieve remission, their MDD may be considered *treatment-resistant*, but exactly when to apply this term is vague. This article addresses the definition of treatment-resistant depression (TRD), the consequences of not achieving remission from MDD, and the risk factors for TRD. Also discussed are residual symptoms that can remain after remission. It is critical for clinicians to identify features of depression that can be difficult-to-treat as early as possible so that they can closely monitor patients and then decide whether a more aggressive treatment plan is needed.

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WHAT IS TREATMENT-RESISTANT DEPRESSION?

No universally accepted definition of difficult-to-treat or TRD exists.[6] However, an overview of the phases of MDD treatment can put the concept of resistance into context and lead to a clearer understanding.

Treatment Phases

The American Psychiatric Association (APA) recognizes 3 main phases of treatment for patients who have been diagnosed with MDD—the acute phase, the continuation phase, and the maintenance phase.[3] Once remission of the depressive episode occurs, the acute phase of treatment is considered to be over and the continuation phase begins (Figure 1).[7]

Acute phase. Following a thorough examination of the patient and a careful review of all symptoms, clinicians should focus primarily on helping their patients achieve remission from a major depressive episode, and then on returning them to a normal level of functioning at work/school and in interpersonal relationships.[3] Treatment in this phase can include a number of approaches including pharmacotherapy, depression-focused psychotherapy, and somatic therapy.[3] Clinicians should recommend that their patients take antidepressants for 4 to 6 weeks to ensure that they have had a sufficient duration of time to respond.[3] Psychotherapy may require more time, up to a few months, for meaningful improvement.

Several scales are available for clinicians to use to measure depressive severity in their patients, and treatment guidelines[3] recommend using them not only in the diagnostic process but also in the ongoing assessment of

therapeutic benefits. On the self-administered 9-item Patient Health Questionnaire[8] (PHQ-9), a score of less than 10 indicates partial response while a score under 5 signals remission. A score of 5 or less on the 16-item self-report Quick Inventory of Depressive Symptomatology[9] (QIDS-SR_{16}) would also be considered remission. These 2 questionnaires are easy to use in clinical practice because they address all of the *DSM* criteria for MDD, are short and simple enough for patients to complete on their own, and do not require specialized training to calculate scoring like the Montgomery-Asberg Depression Rating Scale and the Hamilton Depression Rating Scale.[8,9]

If a patient is not responding, treatment strategies may need to be reassessed.[3] However, before changing treatment strategies, clinicians should recognize that patients who are thought to have TRD could have been misdiagnosed or are being inadequately treated.[3] A reexamination of potential primary and comorbid causes of depression is recommended. Clinicians need to consider whether the patient has psychotic depression, bipolar disorder, or comorbid psychiatric disorders that may be preventing adequate response. Once the diagnosis of MDD is confirmed, clinicians should assess the patient's level of adherence to the prescribed treatment regimen. If adherence is problematic, reasons why should be examined. If adherence is not an issue, the solution may be to optimize the dose of medication or increase the frequency of psychotherapy. If the patient has reached remission, clinicians should then proceed to the continuation phase.

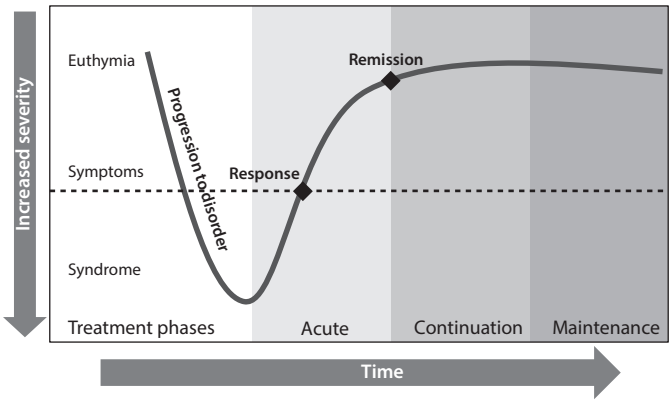
Continuation phase. During the continuation phase, clinicians should monitor patients for 4 to 9 months to ensure that no recurring depressive symptoms are present.[3] If symptoms return during this time, patients would then be classified as having a relapse of the same depressive episode. However, if during this period patients show no relapse of depressive symptoms, they are in recovery. If patients develop depressive symptoms at a later time, their diagnosis is a recurrent episode or the presentation of a new, separate depressive episode. The American Psychiatric Association (APA) suggests depression-focused psychotherapy (specifically cognitive-behavioral therapy) as the preferred choice of treatment since data suggest that it provides the most consistently efficacious results for preventing relapse in patients diagnosed with difficult-to-treat depression or TRD.[3]

Maintenance phase. The maintenance phase primarily serves those patients who have had 3 or more depressive episodes in their lifetime or have been diagnosed with chronic MDD. However, those with risk factors for recurrence (eg, residual symptoms, early age at onset, ongoing stressors) or with comorbid illnesses should also be considered as candidates for maintenance treatment.[3] During this phase, clinicians should strive to maintain recovery and prevent relapse by continuing any medication or adjunctive therapies that have proven effective. Patients should also continue any successful psychotherapy, but at a reduced frequency from the acute phase.

Clinical Points

- Clinicians should closely evaluate patients for signs of potential treatment resistance before beginning any treatment.
- Residual symptoms can remain in patients who have achieved remission and can signify difficult-to-treat depression.
- Clinicians should ensure that patients receive adequate dosages and durations of antidepressant therapies or psychotherapies before considering augmentation or switching strategies.
- Some patients who appear to have TRD may actually have treatment adherence problems, which should be addressed.

Figure 1. Treatment Phases of Major Depression[a]



[a]Adapted with permission from Kupfer.[7]

Treatment Resistance

A useful definition of TRD would require consensus on the criteria for an adequate treatment trial (ie, minimum dose and duration of therapy, with a particular adherence level) as well as on the specific number of unsuccessful treatment trials that are required before the episode is deemed resistant. In studies of therapies for patients with "treatment-resistant" MDD over the years, researchers have used a variety of definitions. For example, some investigators have defined treatment-resistance as a failure to decrease depressive severity by at least 50%, or below a specific cutoff point on a rating scale, and have differed on whether resistance begins after only 1 adequate treatment trial or whether more unsuccessful trials are required.[10] Although the APA treatment guidelines not only define remission but also describe therapeutic options for TRD, they acknowledge that the definition of treatment resistance needs to be clarified.[3]

In general, resistance is often considered to be the failure of 2 adequate treatment trials to bring about remission.[11] Studies suggest that after 2 failed treatment trials, the odds of achieving remission significantly decrease.[5] Researchers have proposed

multiple staging models of treatment resistance based on the number and complexity of failed treatment trials.[6] By focusing on the different levels of treatment-resistance that patients may experience, these models may aid clinicians in better understanding the full complexity of TRD.

The Thase and Rush staging model[6] presents clinicians with 5 separate stages of treatment resistance with each level increasing in severity. This model may be a helpful tool for some clinicians; however, it relies primarily upon monitoring patients for failed antidepressant trials and makes no concession for psychotherapy. Also, by separating classes of antidepressants into different stages, this model suggests that a hierarchy of effectiveness exists regarding antidepressants, which the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study has shown to be inaccurate and may cause clinicians to prescribe a medication that may not be the best fit for their patient.

The Massachusetts General Hospital staging method (MGH-S)[6] also monitors treatment-resistance based on the number of previously failed antidepressant trials. Unlike the Thase and Rush method, the MGH-S assigns a point value for each unsuccessful trial, inquires specifically about the adequacy of dosage and duration of each trial, and accounts for augmented and combined treatment strategies.

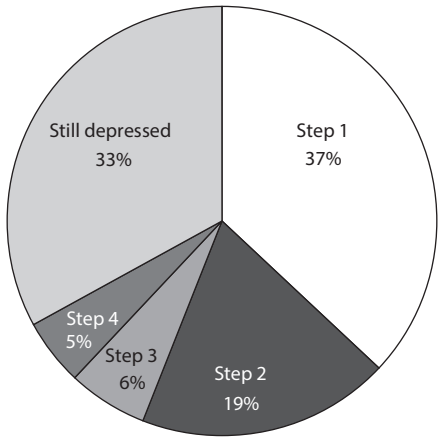
The Maudsley Staging Method (MSM)[6] is the most recent staging model to be adapted and focuses on using a multidimensional staging method, unlike its predecessors. While it focuses only on monitoring the number of unsuccessful antidepressant trials, the MSM does not differentiate between classes of medications.

WHY IS UNDERSTANDING TREATMENT RESISTANCE IMPORTANT?

Prevalence

Treatment-resistance is common among patients who have been diagnosed with depression. Studies have found that approximately 10%–30% of patients diagnosed with MDD develop chronic major depression—meaning that symptoms exist for 2 years or longer—despite having been adequately treated.[12] The STAR*D trial (which included a broad range of adults diagnosed with MDD) found that, among individuals who received antidepressant medication as initial acute treatment, only 37% achieved remission, according to QIDS-SR_{16} scores (Figure 2).[5] Among those who received the second level of acute treatment, 31% reached remission, or 19% of the original sample, meaning that 56% of those who began acute treatment remitted after 1 or 2 treatment trials.[5] If treatment resistance is defined as the failure of 2 or more treatment trials to achieve remission, then the study suggests that 44% of those treated for nonpsychotic MDD have TRD.[5] The STAR*D study findings also suggested that switching between different classes of antidepressants does not appear to make any significant difference in achieving remission compared with switching to another agent in the same class.[11]

Figure 2. Remission Rates of Antidepressant Treatment Among Patients With MDD During a 12-Month Period[a]



[a]Data from Rush et al.[5]
Abbreviation: MDD = major depressive disorder.

Consequences of Treatment Resistance and Difficult-to-Treat Depression

Disease course. For patients who have been diagnosed with MDD, not achieving remission can have severe consequences, including an increased risk of suicide.[13] A review[14] of studies found that 17% of patients with TRD had made a suicide attempt. Quality of life is also lower among those with TRD than those who achieve remission.[14]

Individuals with difficult-to-treat depression, who achieve remission but have residual symptoms or who remain functionally impaired despite resolution of symptoms, have faster relapse into major and minor depressive episodes, have more recurrences, have shorter periods of wellness, and have fewer symptom-free weeks than patients in remission without residual symptoms.[15] For physicians seeking to predict who is likely to have a recurrence of a depressive episode, patients with residual symptoms following remission were found to relapse to their next major depressive episode 3 times faster compared with those who fully recovered.[16]

Patients who have residual symptoms of depression after remission are at greater risk of developing a more severe or chronic course of depression in the future than those without residual symptoms.[15] After analyzing the results of the STAR*D study, Rush et al[5] suggested that if patients who develop chronic MDD had been treated earlier with more aggressive treatments, they may have had a higher chance for remission.

Financial repercussions. In addition to affecting the course of the depressive illness itself, not achieving remission has financial consequences. In 2000, approximately $26 billion was spent on medical care, including inpatient and outpatient care and medications, for US patients diagnosed with depression.[17] That amount includes both patients who remitted and those with TRD. By 2010, medical care costs had increased to nearly $99 billion.[18] Individuals with TRD are more likely to be hospitalized and were found to incur

81.5% higher costs annually than patients whose depression is not treatment-resistant.[19]

Problems in social arenas and the workplace. Patients with TRD experience impaired social adjustment and lack of involvement in activities as well as diminished sexual enjoyment.[20] They also are less productive at work. A 2006 study by Kessler et al[21] suggested that patients diagnosed with mood disorders such as bipolar disorder and MDD have a decreased ability to maintain functionality and focus in the workplace. Their study assessed absenteeism (missed days of work) and presenteeism (low performance while at work) using the World Health Organization's Health and Work Performance Questionnaire (HPQ). The same study[21] also discovered that, while patients who have been diagnosed with depression report an average of 8.7 days absent from work annually, they report 18.2 days of decreased performance while at their workplace. These data add up to an average of 225 million workdays and $36.6 billion lost in workplace productivity each year in the United States.[21] A 2015 report[18] found 7.7 days of absenteeism and 31.9 days of presenteeism per worker with MDD annually.

WHAT ARE THE RISK FACTORS FOR TREATMENT RESISTANCE?

The acute phase of treatment should not be considered complete if patients have not reached remission or if, despite meeting remission criteria, they have residual symptoms.[3] By being aware of risk factors associated with TRD, clinicians may be able to identify certain red flags that will help them determine which patients may be potentially nonresponsive and require more aggressive management. In essence, for these individuals, clinicians should have a lower threshold for considering more aggressive treatment regimens, such as maximizing doses sooner or considering augmentation earlier.

Comorbidity

Psychiatric comorbidity. The presence of psychiatric comorbidity is an important factor to consider when treating patients with possible TRD.[3] Patients who have comorbid substance abuse or anxiety disorders have an increased likelihood of developing difficult-to-treat depression or TRD.[22] In addition, the presence of comorbid personality disorders may be associated with an increased rate of TRD.[23] A history of physical, sexual, or emotional abuse can also be associated with a co-occurring posttraumatic stress disorder that can increase the likelihood of suboptimal response to treatment.[24]

Medical comorbidity. In addition to psychiatric comorbidity, medical comorbidity can substantially increase the likelihood of treatment resistance. Patients who are chronically ill have a higher rate of developing depressive disorders than individuals in the general population.[25] In fact, depressive symptoms may also exacerbate medical issues in patients, suggesting that the relationship may be bidirectional.[25] For example, many patients who have been diagnosed with depression also report higher levels of obesity than those patients who are not depressed.[26]

Organic factors such as thyroid disorders,[3] vitamin B12 or folate deficiencies,[3] and anemia[27] can be associated with depressive symptoms, as can side effects from medications for medical illnesses.[3] Patients diagnosed with depression also may have impaired cognitive or neurologic functioning.[3] Chronic depressive symptoms have been associated with cortical atrophy,[28] and even patients who achieve remission may present with cognitive dysfunction.[29] The presence of comorbid medical illnesses and the medications used to treat them are key factors to consider when assessing an individual for TRD and may guide clinicians toward more accurate and efficient methods of treatment for their patients.

Genetic Variations in Drug Responses

Eventually, genetic variations may be able to predict response to an antidepressant medication. Unfortunately, genotyping research has not yet produced applicable clinical data about which individuals will have a greater likelihood of response to a particular antidepressant therapy based on their genetics.[30] Independent of whether clinicians can genetically predict response rate, close monitoring of side effects in patients is key to helping increase the likelihood of adherence and response. More information is being discovered regarding genetic variations in drug responses that may help identify those who are at risk for TRD.

WHAT SHOULD BE DONE NEXT?

If an individual is not responding to an adequate trial of an antidepressant, the first thing the clinician should consider is whether the diagnosis is correct. For example, if psychotic symptoms are present, the patient will most likely not improve with antidepressant monotherapy and might worsen if the symptoms are not fully addressed. Similarly, if the underlying illness is bipolar disorder rather than MDD, adequate treatment would follow a different treatment track. If an individual is experiencing depressive symptoms not from MDD but rather from a substance use disorder, the depression treatment may not be successful. A key point for any clinician to consider when an individual is not responding to initial treatment is whether the diagnosis itself is correct.

Another important decision that psychiatrists must make is whether the treatment trial itself has been adequate. Many individuals may not complete an adequate trial—from either a dosing, duration, or adherence perspective—which consists of at least a moderately dosed antidepressant for a minimum of 4 to 6 weeks. Patient nonadherence also plays a substantial role in TRD. If patients do not follow their clinician's instructions on when to take their medication, they may experience sleep problems which may negatively impact their chances for remission. Patients may also take their medications only when they believe that they need them or may disrupt or stop treatment once they feel better

because they believe that they are in recovery. Clinicians must carefully monitor their patients and ensure that they fully understand what classifies as adherence to medication therapy so that if TRD is a possible diagnosis, it is not made in error.

Physicians should also be aware of any environmental or social stressors that may exacerbate or contribute to their patients' symptoms. These stressors can interfere with the effectiveness of treatment. If by 6 weeks the patient has no quantifiable response to a moderate dose of medication therapy, clinicians should consider a switch or augmentation strategy.[3] Data from the STAR*D study[5] suggests that those who have a partial response may benefit more from augmentation, whereas patients with no response may benefit more from switching to a different treatment option.

CONCLUSION

Difficult-to-treat depression or TRD affects many people worldwide every year. Clinicians should closely monitor their patients for treatment adherence, response, and adverse effects and adjust treatment quickly to increase the chances for remission. Patients who experience TRD have been found to have an overall lower quality of life than those patients who achieve remission. By using rating scales such as the QIDS-SR_{16} and PHQ-9 and monitoring for comorbid illnesses, side effects of treatment, and nonadherence, clinicians are more likely to be able to accurately diagnose their patients with difficult-to-treat depression. Clinicians should also be fully aware of their patients' medical history as some psychiatric and medical conditions can increase the likelihood of developing TRD. For patients who are at risk of developing TRD, clinicians should evaluate whether they have had an adequate trial of antidepressants for both dosage and duration, potentially augment the treatment with psychotherapy, or switch the patient to an antidepressant in a different class.

Disclosure of off-label usage: Dr Gaynes 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 activity.

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