Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis

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INTRODUCTION

Many patients presenting with unipolar major depression (major depressive disorder) do not recover after their initial treatment. As an example, one prospective observational study found that among 3671 outpatients who were treated with citalopram, remission occurred in 37 percent [1]. In addition, patients who fail their initial treatment often do not respond to subsequent trials, and health care utilization and costs are higher among patients with treatment-resistant depression than for patients with either no depression or nonresistant depression [2,3]. The course of illness in treatment-resistant depression is thus frequently marked by chronic depression, impaired psychosocial functioning, poor overall general health, and increased all-cause mortality [4,5].

This topic reviews the epidemiology, risk factors, assessment, identification, and prognosis of treatment-resistant depression. The treatment of resistant depression, the initial treatment of depression, and the clinical features and diagnosis of depression are each discussed separately.

- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)

DEFINITIONS

Unipolar major depression — Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania [6]. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (table 1). Additional information about the clinical presentation and diagnosis of major depressive disorder is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis".)

Treatment-resistant depression — The term “treatment-resistant depression” typically refers to major depressive episodes that do not respond satisfactorily after two trials of antidepressant monotherapy; however, the definition has not been standardized [7-9]. Evidence that supports a categorical definition based upon two treatment failures includes results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which prospectively administered up to four sequential trials of pharmacotherapy to 3671 patients who presented with unipolar major depression [1,10,11]. The rate of remission appeared to be comparable for the initial and second-course of treatment (37 and 31 percent), and then to decline more substantially for the third and fourth steps of treatment (14 and 13 percent).

However, it is not established that there is a natural cut-off or distinction between patients who fail one or two courses of treatment and patients who do not [12]. Some studies thus conceptualize treatment resistance as a continuum and have devised staging systems based upon the number and types of treatments that failed to resolve the depressive episode. (See 'Staging' below.)

The term “difficult to treat” depression has also been used to describe patients who do not respond sufficiently to antidepressants [13]. In addition, “pseudoresistance” has been used to describe treatment failures due to an inadequate dose or duration of pharmacotherapy, or nonadherence to treatment [14,15].

Defining treatment-resistant depression is also complicated by the lack of consensus in describing acute antidepressant responses [16]. In many studies, response is classified according to the amount of improvement from baseline on the depression rating scale [17-22]:

- No response – Improvement <25 percent.

- Partial response – Improvement 25 to 49 percent.
- Response – Improvement ≥50 percent but less than the threshold for remission.
- Remission – Depression rating scale score less than or equal to a specific cutoff that defines the normal range. As an example, studies using the 17-item Hamilton Rating Scale for Depression (table 2) or the Montgomery-Asberg Depression Rating Scale (figure 1A-C) often define remission as a score ≤7.

EPIDEMIOLOGY

The prevalence of unipolar treatment-resistant major depression is not clear due to the lack of a standard definition. Across different studies of patients with unipolar major depression who receive initial treatment, the prevalence of treatment resistance ranges from approximately 30 to 70 percent:

- The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which initially treated 3671 outpatients (most had recurrent or chronic depression, as well as multiple comorbid medical and psychiatric illnesses) for up to 14 weeks with full doses of citalopram, found that remission did not occur in 63 percent [23]. Among the 1439 patients who received next-step treatment, remission did not occur in 69 percent [1].
- A pooled analysis of 31 randomized antidepressant trials (1712 patients; length of trial was 6 weeks in 22 trials) found that response (reduction of baseline symptoms ≥50 percent) did not occur in 46 percent [24].
- A pooled analysis of four similarly designed health care claims studies estimated that the 12-month prevalence of unipolar major depression was 31 percent treatment-resistant depression [25].

Risk factors — Unipolar treatment-resistant major depression has been associated with many factors, including:

- Comorbid general medical disorders [7,26,27] (eg, coronary heart disease [28] and hypothyroidism [29])
- Chronic pain [30,31]
- Medications (eg, glucocorticoids and interferons) [32,33]

- Comorbid psychiatric disorders (eg, anxiety, personality, and substance use disorders) [9,31,32,34,35]
- Severe intensity of depressive symptoms [31,34-36]
- Suicidal thoughts and behavior [9,34-37]
- Adverse life events (eg, childhood trauma or marital discord) [38-46]
- Personality traits (eg, low reward-dependence, low extraversion, and high neuroticism) [47,48]
- Early age of onset of major depression (eg, age <18 years) [30,34,49]
- Recurrent depressive episodes [30,34,35,49]
- Loss of employment and low socioeconomic status [50-52]

Studies have found that the association of other factors with treatment resistance is inconsistent and thus less clinically useful. As an example, subsyndromal manic/hypomanic symptoms that do not meet criteria for hypomania are associated with treatment-resistant depression in some studies [53], but not others [54].

PATHOGENESIS

The pathogenesis of treatment-resistant depression is not known.

Genetics — Genetic factors may affect response to antidepressants by influencing drug distribution and metabolism, serum and brain drug concentrations, and target molecules [9,55]. Examples of pharmacogenetic effects include the following:

- Cytochrome P450 enzymes are responsible for the metabolism of many antidepressants, and allelic variations in the 2D6 and 2C19 isoenzymes have been associated with variations in serum concentrations of antidepressants (eg, selective serotonin reuptake inhibitors and tricyclics) [55,56]. These variations may possibly influence clinical responses, and laboratory kits are available to characterize P450 isoenzyme profiles. However, the clinical utility of such testing remains unclear because the limited evidence suggests that the predictive value of testing is modest at best [57,58].
- In preclinical studies, expression of P-glycoprotein (a major constituent of the blood-brain barrier) was associated with differences in brain concentrations of several antidepressants

[59,60].

- Polymorphisms in the genes that code for drug targets such as the serotonin transporter [61], 5HT2A receptor [62], 5HT1A receptor [63], N-methyl-D-aspartate receptor (GRIN2B) [64], and brain-derived neurotrophic factor [65] have been have been linked to antidepressant nonresponse. As an example, a meta-analysis of seven studies (745 depressed patients treated with selective serotonin reuptake inhibitors) found that remission was less likely in patients with the short allelic variant of the serotonin transporter gene (odds ratio 0.5, 95% CI 0.3-0.7) [66]. However, subsequent studies indicate that serotonin transporter polymorphisms have at most a limited role in determining response to treatment [67,68].

Genetic factors involved in pathophysiologic processes may also be related to treatment resistance. A study of 74 patients with unipolar major depression who were treated with antidepressants found that nonresponse was associated with higher baseline expression of inflammatory system genes [69].

An overview of how inherited and acquired genetic factors influence drug response is discussed separately. (See "Overview of pharmacogenomics".)

Neurobiology — Functional magnetic resonance imaging and positron emission tomography have found that treatment resistance in patients with unipolar major depression is associated with functional abnormalities in specific brain regions and neural networks, including the:

- Prefrontal cortex [70]
- Subcallosal cingulate gyrus [71]
- Cortical-thalamic circuits [72]
- Cortical-limbic-cerebellar white matter networks [73]

Magnetic resonance imaging studies have also identified structural abnormalities in treatment-resistant depression, including:

- Decreased volume of frontal, temporal, and limbic gray matter structures [74]
- Decreased gray matter volume of the putamen [75]
- Microstructural white matter abnormalities [76]

Inflammatory or autoimmune processes are also associated with treatment resistance. In a six-year, prospective study of 581 patients with unipolar major depression, blood methylation markers assayed at baseline predicted a treatment-resistant course of illness [77]. Other studies have found that treatment-resistant depression was associated with elevations in specific

markers of inflammation, including C-reactive protein, tumor necrosis factor, interleukin 1, and interleukin 6 [78].

In addition, a small, prospective observational study (n = 33 patients with treatment-resistant depression) identified cerebral spinal fluid metabolic abnormalities in most patients; the most common was cerebral folate deficiency (n = 12 patients) despite normal serum folate levels [79].

Information about the neurobiology of unipolar depression in the general populations of depressed patients is discussed separately. (See "Unipolar depression: Neurobiology".)

ASSESSMENT AND IDENTIFICATION

The psychiatric evaluation of patients with unipolar major depression who are treatment resistant should assess [32,80,81]:

- Diagnosis – The diagnosis of unipolar major depression should be confirmed, and other diagnoses such as bipolar depression or dysthymic disorder ruled out because of differences in treatment. In addition, clinicians should ask about psychotic features (ie, delusions and hallucinations) as well as suicidal ideation and behavior. (See "Unipolar depression in adults: Assessment and diagnosis" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis' and "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Suicidal ideation and behavior in adults", section on 'Patient evaluation'.)

- Medication history – Glucocorticoids and interferons are associated with depressive symptoms. (See "Unipolar depression: Pathogenesis", section on 'Medications'.)

- Comorbid psychiatric disorders – Comorbid anxiety, substance use, or personality disorders may warrant additional treatment.

- Prior treatment history – Type, dose, duration, benefit, and harm of each prior treatment. Family members may recall specific therapies that patients have forgotten. In addition, adherence to antidepressants should be evaluated with nonjudgmental questions such as: "Many patients forget to take their medication on a regular basis. How often does that happen to you?" Patients with side effects may be especially prone to nonadherence.

The treatment history for patients with major depression who may be treatment resistant is typically assessed through a clinical interview (table 3) [82], as well as a review of the medical record, which may provide more accurate information. The accuracy of patient recall is not clear, in light of conflicting results from retrospective observational studies:

- In one study, 73 patients with major depression were interviewed about their treatment history for the past five years by a psychiatrist, who was blind to the actual history that was collected by an independent chart review [83]. Among the 104 monotherapy trials that had occurred, patients recalled 82 percent. In addition, 94 percent of adequate (dose and duration) trials were correctly reported as such, and 90 percent of inadequate trials were correctly reported as inadequate. The presence of depressive symptoms did not adversely affect patient recall of past regimens. However, among the 46 augmentation trials that had occurred, patients recalled only 26 percent.

- In a second study, 269 patients completed surveys about their treatment during the past five years; results were checked against medical records that included baseline and follow-up Patient Health Questionnaire (PHQ-9) (table 4) scores [84]. Agreement between patient recall and the medical records was poor. As an example, among 77 patients who reported that a specific treatment either was not beneficial or was harmful, response (reduction of baseline symptoms ≥50 percent) occurred in 58 percent. Accuracy of recall was not improved by limiting the sample to patients reporting high confidence in accuracy of recall.

Instruments — Although treatment resistance in unipolar major depression can be assessed with various instruments rather than a clinical interview [14,34,85,86], this is not standard practice and it is not known whether these instruments improve treatment outcomes.

For clinicians who want to systematically assess treatment resistance beyond a review of the medical record, we suggest the Antidepressant Treatment History Form: Short Form [87]. This clinician-administered instrument characterizes features of past treatment trials, including adequacy, duration, adherence, and clinical outcome, and distinguishes various treatment domains, such as pharmacotherapy, psychotherapy, and neuromodulation procedures (eg, electroconvulsive therapy and transcranial magnetic stimulation).

Staging — The prior treatment history in patients with treatment-resistant depression can be staged along a continuum, according to the number and types of treatments that failed to resolve the depressive episode. However, there is no evidence that staging treatment resistance improves outcomes. In addition, staging is often regarded as cumbersome for standard practice and is thus reserved for specialized treatment or research settings. Multiple staging models have been proposed [11,88-92], and although studies are beginning to validate different models (eg, Maudsley Staging Method) [93], it is not clear that one model is superior [94].

PROGNOSIS

Although remission of unipolar major depression frequently does not occur after initial treatment, approximately 67 percent of patients eventually remit after one or more next step treatment trials [95]:

- In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 3671 outpatients were prospectively treated with full doses of citalopram; nonresponders received up to three successive courses of treatment within a randomized trial, with each course lasting up to 14 weeks [1]. The treatments that were offered included monotherapy with different antidepressants or cognitive-behavioral therapy (CBT), an antidepressant combination, and augmentation of the antidepressant with other drugs (eg, lithium or triiodothyronine) or CBT. The estimated cumulative remission rate over the four courses of treatment was 67 percent.

- A study of 171 patients who were treated with up to three successive, randomized antidepressant monotherapy trials found that the cumulative remission rate was 66 percent [96].

However, the probability of remission in treatment-resistant depression may decrease with successive treatment failures [97], and patients who fail to remit after several successive treatment trials have a relatively low probability of remitting with additional treatment trials [93]. As an example, the STAR*D study found that the rate of remission after each treatment step was as follows [1]:

- Initial treatment – 37 percent
- Step 2 – 31 percent
- Step 3 – 14 percent
- Step 4 – 13 percent

In addition, an observational study of patients with unipolar major depression (n = 417) who did not respond to initial treatment with an antidepressant found that step 2 treatment with venlafaxine led to remission in 20 percent; among patients who did not respond to venlafaxine (n = 170), step 3 treatment with escitalopram led to remission in 23 percent [98]. Likewise, a pooled analysis of nine studies, which evaluated pharmacotherapy, transcranial magnetic stimulation, or deep brain stimulation in treatment-resistant depression, found that remission occurred in 20 percent of patients [99].

Patients with treatment-resistant depression often withdraw from treatment after each unsuccessful next-step treatment. In the STAR*D study, discontinuation of treatment for any reason during each treatment step was as follows [1]:

- Initial treatment – 16 percent
- Step 2 – 20 percent
- Step 3 – 26 percent
- Step 4 – 30 percent

For treatment-resistant depression, response to next step treatments may be worse in patients with anxious depression, that is, major depression accompanied by high levels of anxiety symptoms (eg, worrying, rumination, health anxieties, and panic attacks) [100,101]. In addition, the rate of remission may be reduced by comorbid anxiety disorders (eg, generalized anxiety disorder), obsessive-compulsive disorder, and posttraumatic stress disorder [102], as well as lack of social support [93]. However, other clinical and sociodemographic factors are generally of little value in predicting outcomes [102,103].

Among patients with treatment-resistant depression, relapse seems to occur less frequently in patients who remit compared to those who respond (reduction of baseline symptoms ≥50 percent) but do not remit. As an example, patients who completed step 3 treatment in STAR*D were followed for up to 12 months [1]. The rate of relapse among patients who remitted (n = 35) and patients who responded (n = 66) was 43 and 76 percent. Factors associated with an increased risk of relapse include poor social support [93].

Information about the long term course of illness in major depression is discussed separately. (See "Unipolar depression in adults: Course of illness".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Depression in adults (The Basics)" and "Patient education: When you have depression and another health problem (The Basics)")

- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Electroconvulsive therapy (ECT) (Beyond the Basics)")

SUMMARY

- Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania. Diagnostic criteria for an episode of major depression are listed in the table (table 1). (See "Unipolar depression in adults: Assessment and diagnosis".)

- Treatment-resistant depression typically refers to major depressive episodes that do not respond satisfactorily after two trials of antidepressant monotherapy. However, the definition has not been standardized, and treatment-resistant depression can be viewed as a continuum. (See 'Treatment-resistant depression' above.)

- Among patients with unipolar major depression who receive initial treatment, the estimated incidence of treatment resistance ranges from approximately 45 to 65 percent. Risk factors include general medical and psychiatric comorbidity, severe intensity of depressive symptoms, and adverse life events. (See 'Epidemiology' above.)

- The pathogenesis of treatment-resistant depression is not known. Genetic factors may possibly affect response to antidepressants by influencing drug distribution and metabolism, serum and brain drug concentrations, and target molecules. In addition, deficits in specific neural networks may possibly underlie treatment-resistant depression. (See 'Pathogenesis' above.)

- The psychiatric evaluation of patients with unipolar major depression who are treatment resistant should assess diagnosis (including the presence of psychotic features), suicidal ideation and behavior, history of drugs that can cause depression (eg, glucocorticoids and interferons), comorbid psychiatric disorders, and prior treatment history. (See 'Assessment and identification' above.)

- Unipolar treatment-resistant major depression eventually remits after one or more next step treatment trials in approximately 67 percent of patients. However, the probability of

remission may decrease with successive treatment failures, and withdrawal from treatment may increase after each next-step treatment. (See 'Prognosis' above.)

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