Unipolar depression in adults: General principles of treating resistant depression

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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 only 37 percent [1]. In addition, patients who fail their initial treatment often do not respond to subsequent trials and frequently experience chronic depression, impaired psychosocial functioning, and poor overall general health [2].

This topic reviews the general principles of treating resistant depression. Choosing a specific treatment for resistant depression, and the epidemiology, risk factors, assessment, and prognosis of treatment-resistant depression are discussed separately, as are the initial treatment of depression, and clinical features and diagnosis of depression.

- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis".)
- (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) (table 1) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania [3]. 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. 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” often refers to major depressive episodes that do not respond satisfactorily to at least two trials of antidepressant monotherapy; however, the definition has not been standardized [4,5]. The definition of treatment-resistant depression is discussed separately. (See "Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis", section on 'Treatment-resistant depression'.)

GENERAL PRINCIPLES

Reassess the diagnosis — If patients treated for unipolar depression do not respond to initial treatment, they should be re-evaluated to confirm the diagnosis is unipolar depression rather than a different disorder, such as bipolar depression, complicated grief, or substance induced depressive disorder [6,7]. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Differential diagnosis'.)

Comorbidity — Treatment-resistant unipolar major depression is often comorbid with other psychopathology [6]. The therapies recommended for treatment-resistant depression are administered when the depressive syndrome is the primary disorder or when the therapy is compatible with the treatment administered for the comorbid disorder. In addition, a single treatment, such as an antidepressant, may be effective for both treatment-resistant depression and the comorbidity (eg, generalized anxiety disorder). However, treatment of resistant depression may need to be deferred during treatment of a more salient disorder, such as anorexia nervosa.

The comorbid psychopathology that often occurs in patients with unipolar depression is discussed separately. (See "Unipolar depression in adults: Clinical features", section on

'Psychiatric'.)

Assess adherence — Many patients with ongoing symptoms of treatment-resistant depression discontinue pharmacotherapy [8]. Clinicians should attempt to identify and address barriers to adequate adherence [6,9]. Improving adherence with pharmacotherapy may convert nonresponders to responders. (See "Unipolar depression in adults and initial treatment: General principles and prognosis", section on 'Enhancing adherence'.)

Treatment strategies for resistant depression — For patients with unipolar major depression who do not respond to initial treatment with an antidepressant medication, treatment strategies include [10-17]:

- Augmentation (adding a treatment)
  - Medication (eg, second-generation antipsychotic, lithium, a second antidepressant, or triiodothyronine)
  - Psychotherapy
  - Electroconvulsive therapy
  - Repetitive transcranial magnetic stimulation
  - Supplementary and supportive interventions such as exercise
- Switching treatment
  - Different antidepressant
  - Psychotherapy
  - Electroconvulsive therapy
  - Repetitive transcranial magnetic stimulation

Choosing a specific treatment for resistant depression is discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

Nonspecific care management — Patients with treatment-resistant depression who are receiving a specific therapy may benefit from nonspecific care management, in which clinicians [18,19]:

- Educate patients and families about:
  - Depression, including signs, symptoms (table 1), and prognosis (see "Unipolar depression in adults: Assessment and diagnosis" and "Unipolar depression in adults: Course of illness")

- Suicide (see "Suicidal ideation and behavior in adults")
- Treatment options (see "Unipolar depression in adults: Choosing treatment for resistant depression")
- Good sleep practices, including sleep hygiene (table 2), stimulus control (table 3), and sleep restriction (table 4) (see "Overview of the treatment of insomnia in adults")

- Monitor patients:
  - Regularly review and quantify depressive symptoms (see 'Measurement based care' below)
  - Review and manage side effects
  - Review occupational and interpersonal functioning
- Provide a 24-hour on-call service.
- Encourage patients to persist with treatment. We reassure patients that we will not abandon them and will try to help them get better as long as they are willing to work with us.

The relationship between clinicians and patients may affect treatment outcomes independent of the specific treatment that is administered, but the effect is relatively small. In a randomized trial that compared imipramine with placebo in 112 patients with unipolar major depression (not selected for treatment resistance), approximately 8 percent of the variability in outcome was due to the specific treating psychiatrist, separate from the study treatment [20].

Measurement based care — Measurement based care is the systematic, quantitative assessment of symptoms that is typically performed at each visit. Psychosocial functioning, quality of life, treatment adherence, and tolerability of treatment can also be measured.

The nine-item Patient Health Questionnaire is a self-report, standardized depression rating scale (table 5) that measures the frequency of symptoms as a proxy for severity and is widely used to ascertain response to treatment [21,22]. Scores >20 indicate severe depression, whereas scores <5 indicate remission. A decrease ≥50 percent generally indicates a clinically significant response.

Additional information about measurement based care, including the Patient Health Questionnaire, is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Duration of an adequate trial — We generally treat unipolar major depression for 6 to 12 weeks before deciding whether a regimen has sufficiently relieved symptoms [8,23,24]. However, for patients who show little improvement (eg, reduction of baseline symptoms ≤25 percent) after four to six weeks, we administer next-step treatment [25,26]. Additional information about the duration of an adequate treatment trial is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial'.)

Referral — Most depressive episodes are initially treated by internists and primary care clinicians [27,28], and second-step treatment for resistant depression is often provided by these clinicians as well, rather than psychiatrists [29]. In one study, patients (n = 727) who did not respond to initial treatment with citalopram were randomly assigned to next-step treatment; the probability of remission in primary care and psychiatric settings was similar (odds ratio 1.0) [30].

However, referral to a mental health specialist should be considered for depressive episodes that are unresponsive to multiple (eg, two to four) next-step treatment trials [6,8,29]. In addition, referral is generally indicated for severe major depression characterized by suicidal or homicidal ideation or behavior, psychosis, or catatonia. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Severe depression'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- For patients with unipolar major depression who do not respond to initial treatment with an antidepressant medication, treatment strategies include augmentation and switching. (See 'Treatment strategies for resistant depression' above.)
- Patients with treatment-resistant depression who are receiving a specific therapy may also benefit from nonspecific care management, such education and monitoring. (See 'Nonspecific care management' above.)
- We generally treat unipolar major depression for 6 to 12 weeks before deciding whether a regimen has sufficiently relieved symptoms. However, for patients who show little

improvement (eg, reduction of baseline symptoms ≤25 percent) after four to six weeks, we administer next-step treatment. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial'.)

- Referral to a mental health specialist is often made for treatment-resistant depression that does not respond to multiple next-step treatment trials, as well as severe major depression. (See 'Referral' above.)

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