Unipolar depression in adults: Choosing treatment for 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 choosing a specific treatment for resistant depression. Other topics discuss the general principles of treating resistant depression; the epidemiology, risk factors, assessment, and prognosis of treatment-resistant depression; the initial treatment of depression; and the clinical features and diagnosis of depression.

- (See "Unipolar depression in adults: General principles of treating 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) is diagnosed in patients who have suffered at least one major depressive episode (table 1) and have no history of mania (table 2) or hypomania (table 3) [3]. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms, at least one of which is depressed mood or anhedonia: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration or memory, 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: Clinical features" and "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 at sufficient doses for sufficient duration; however, the definition has not been standardized [4]. 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

The general principles and issues that are involved in treating resistant depression in adults include the following:

- Confirming the diagnosis
- Comorbidity
- Adherence with treatment
- Treatment strategies
- Nonspecific care management
- Duration of an adequate drug trial
- Referral

These general principles are discussed in detail separately. (See "Unipolar depression in adults: General principles of treating resistant depression".)

MILD TO MODERATE DEPRESSION

Determining the severity of a depressive syndrome has not been standardized. The three paragraphs immediately below describe different means of establishing severity, in descending order of preference.

Mild to moderate unipolar major depression is indicated by a score <20 points on the Patient Health Questionnaire – Nine Item (PHQ-9) (table 4). The PHQ-9 is a self-report assessment that is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

Alternatively, one study classified episodes of major depression as mild to moderate in those individuals who had only five to seven of the nine symptoms that define major depression (table 1) [5]. This is consistent with the approach used in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [3].

Many studies have assessed severity of depression using clinician-administered instruments, such as the Hamilton Rating Scale for Depression (table 5) [6] or Montgomery-Asberg Depression Rating Scale (figure 1A-C) [7]. However, these rating scales are generally not used as part of standard care.

Mild to moderate major depression is characterized by the following clinical features:

- No suicidal or homicidal ideation or behavior is present. If suicidal ideation is present, it does not pose an imminent risk; examples include the wish or hope that death will overtake oneself (eg, “Life is not worth living” or “I would be better off dead”); or fleeting thoughts of killing oneself, with nonexistent or vague plans to commit suicide and no intent.
- No psychotic features (eg, delusions or hallucinations).
- Little to no aggressiveness.
- Intact judgment such that the patient or others are not at imminent risk of being harmed.
- Impaired functioning is not obvious.

Mild to moderate depression can generally be treated in an outpatient or partial (day) hospital program setting.

Treatment algorithm — For patients with treatment-resistant, unipolar major depression, treatment strategies include augmentation (adding a treatment) and switching treatment (eg, switching antidepressants) [8-11]. Regardless of which strategy is used, we make one change at a time, which allows us to better understand whether a particular therapeutic is helpful.

For mild to moderate unipolar major depression that is treatment resistant, our general approach is as follows (algorithm 1):

- We suggest initially using augmentation interventions; some evidence suggests that the benefit of augmentation is modestly superior to switching antidepressants (see 'Efficacy of primary treatment strategies' below). Augmenting an antidepressant with a second drug may provide faster, complimentary, or synergistic effects, compared with switching antidepressants [12]. In addition, augmentation avoids withdrawal symptoms that may arise when the initial antidepressant is discontinued. If patients do not respond to augmentation with a second drug, we then switch antidepressants (ie, administer monotherapy with a new antidepressant), or augment with or switch to psychotherapy or repetitive transcranial magnetic stimulation (TMS). This approach, augmentation followed by switching, is consistent with multiple treatment guidelines and systematic reviews [9,13,14].

- However, it is reasonable to reverse the order of these treatment strategies and initially switch antidepressants. Some studies of treatment-resistant depression suggest that the benefits of switching and augmentation are comparable, and some patients may prefer antidepressant monotherapy [10]. In addition, switching antidepressants may be preferable to augmentation because adherence is generally better with monotherapy than combination treatment [15,16]. Monotherapy may also cost less and may be less likely to cause adverse events and drug-drug interactions, compared with adding a second drug [12].

- Treatment-resistant patients who cannot tolerate an adequate dose of the initial antidepressant, or who encounter drug-drug interactions, should initially switch antidepressants [17].

Given that the efficacy of augmentation is not clearly superior to switching antidepressants, shared decision making with patients is important. Patients who partially benefit from the initial antidepressant and experience few adverse effects generally prefer adjunctive pharmacotherapy rather than switching [18]. Conversely, patients who experience less symptomatic improvement and more side effects with the antidepressant prescribed at first

presentation typically prefer switching antidepressants. For treatment-resistant depression, multiple practice guidelines suggest either augmentation or switching [9,11,13,19-23].

Among patients with treatment-resistant depression who augment antidepressants with a second drug and do not respond, it is not clear how many trials of add-on therapy that clinicians should administer before switching the antidepressant. We generally provide one to three courses of augmentation before switching the antidepressant. When switching the antidepressant, we typically continue the current adjunctive drug, based upon the principle of making only one change at a time.

Although monotherapy often causes fewer adverse effects than multidrug regimens [24], this is not always the case. The prospective Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study compared side effects in 269 treatment-resistant patients who selected switching (from citalopram to bupropion, sertraline, or venlafaxine) as next-step treatment, and 269 patients who selected augmentation of citalopram (with bupropion or buspirone); propensity scoring was used to match the two groups for potential confounders observed at baseline [25]. The overall incidence of distressing side effects for each group was similar.

For patients with treatment-resistant depression who initially switch antidepressants and do not respond, it is not clear how many trials of antidepressant monotherapy that clinicians should administer before augmenting the antidepressant with a second treatment. We generally provide one to three courses of next-step antidepressant monotherapy before using augmentation.

An alternative to switching antidepressants or augmenting the antidepressant with a second medication is to switch from pharmacotherapy to psychotherapy (eg, cognitive-behavioral therapy [CBT]) or to TMS, or retain the initial antidepressant and add psychotherapy or TMS [13,26,27]. In addition, it is reasonable to augment the initial antidepressant with both pharmacotherapy and psychotherapy. However, psychotherapy is often not available, and many patients decline it [18]. The efficacy of switching to and augmenting with psychotherapy are each discussed elsewhere in this topic. (See 'Psychotherapy' below and 'Psychotherapy' below.)

Implementation of augmentation and switching are discussed elsewhere in this topic. (See 'Initial approach' below and 'Next step treatment' below.)

Efficacy of primary treatment strategies — For treatment-resistant depression, relatively few head-to-head randomized trials have compared augmentation with switching treatments. Although results across the trials are mixed, the most compelling evidence suggests that add-on therapy may be at least modestly superior to switching antidepressants:

- A 12-week, open-label, randomized trial enrolled patients (n = 1522; 85 percent male) with unipolar major depression who remained depressed despite treatment with at least one course of antidepressant therapy [28]. Nearly half of the patients had comorbid posttraumatic stress disorder, and most patients were currently receiving psychotherapy. Patients were assigned to one of three treatment strategies: augment the current antidepressant with aripiprazole (target dose 5 to 15 mg/day), augment with bupropion sustained release (target dose 300 to 400 mg/day) or switch to bupropion monotherapy. The primary findings included the following:

  - Remission was statistically greater in the augment-aripiprazole group than the switch group, but the clinical difference was modest (29 versus 22 percent of patients). In the augment-bupropion group, remission occurred in 27 percent, which did not differ statistically from the other two groups. In patients 65 years and older, the benefit of augmentation with aripiprazole vis a vis switching to bupropion was more prominent (n = 226, 38 versus 21 percent) [29].

  - Patients who remitted during acute treatment (n = 396) received continuation treatment for another 24 weeks; relapse at week 36 was comparable for the three treatment groups (approximately 25 percent of patients in each group).

  - Adverse effects that occurred more often in the augment-aripiprazole group, compared with the other two groups, included akathisia, somnolence, and weight gain, as well as multiple abnormal laboratory tests. As an example, at week 36, weight gain from baseline ≥7 percent occurred in 25 percent of the augment-aripiprazole group, compared with 5 percent in each of the other two groups.

    Anxiety occurred more often in the augment-bupropion group and the switch group, compared with the augment-aripiprazole group.

  One limitation of the study was attrition; during the 12-week acute phase, 25 percent of the patients withdrew from the study. Other limitations included the lack of blinding for patients and treating clinicians, as well as the predominantly male sample; major depression occurs twice as often in females than in males. Nevertheless, other randomized trials indicate that aripiprazole augmentation may be more efficacious in females than in males [30]; if true, the present study may have underestimated the benefit of aripiprazole augmentation [31].

- Another trial enrolled 96 patients (77 percent female) with unipolar major depression who did not respond to their initial antidepressant within six weeks and randomly assigned them to add-on treatment with aripiprazole (mean dose 4 mg/day) or to switch

antidepressants [32]. Study treatments were administered for six weeks, and patients and treating clinicians were not blind to treatment. Remission occurred more often with aripiprazole augmentation than switching antidepressants (54 versus 20 percent of patients) and functioning also improved more with aripiprazole.

In addition, tolerability appeared to be comparable, such that discontinuation of treatment due to adverse effects for augmentation and switching occurred in 6 and 10 percent of patients. Weight gain during the six weeks with augmentation and switching was 0.6 and 1.0 kg, and akathisia and sexual functioning in the two groups were also comparable.

- A third trial in treatment-resistant geriatric depression (n = 413 patients) also found that improvement was greater with aripiprazole augmentation than switching to bupropion [33].

More limited evidence suggests that for treatment-resistant depression, the benefits of augmenting with pharmacotherapy and switching antidepressants are comparable:

- An eight-week randomized trial enrolled 375 patients and randomly assigned them to various therapies that included five augmentation options, two switch options, and continuing paroxetine monotherapy [34,35]. Pooled remission rates for the augmentation and the switch strategies appeared to be comparable (37 and 41 percent; difference was not statistically tested).

- Multiple reviews that examined randomized, placebo-controlled trials of augmentation and separate randomized, placebo-controlled trials of switching concluded that the two strategies achieved comparable results [36,37]. As an example, a pooled analysis in one review found that the mean rate of response (reduction of baseline symptoms ≥50 percent) for augmentation and switching was 38 and 40 percent [38].

- A prospective observational study compared outcomes in 269 patients who selected augmentation of citalopram (with bupropion or buspirone) and 269 patients who selected switching (from citalopram to bupropion, sertraline, or venlafaxine) as next-step treatment; propensity scoring was used to match the two groups for potential confounders observed at baseline [39]. The probability of remission for the two groups was comparable.

In some cases, switching antidepressants may be more efficacious than augmentation. One open-label, 10-week trial randomly assigned patients who did not remit with venlafaxine (n = 112) to switch to imipramine or to add-on treatment with mirtazapine [40]. Remission occurred

in more patients who switched to imipramine than those who added mirtazapine (71 versus 39 percent).

Initial approach — For mild to moderate unipolar major depression that does not respond to an antidepressant, our initial approach generally relies upon augmentation interventions [41].

Standard augmentation strategies for managing treatment-resistant depression include pharmacotherapy and psychotherapy [8]. The choice between the two is generally based upon availability and patient preference because there is no compelling evidence that one is superior to the other for acute outcomes [42]. Pharmacotherapy is typically used for augmentation because it is more available and often preferred. However, patients acutely ill with unipolar major depression who improve with pharmacotherapy and subsequently discontinue it appear to be at greater risk for relapse, compared with patients who improve with and discontinue psychotherapy (eg, CBT). (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Relapse/recurrence in the absence of treatment'.)

If augmentation with either pharmacotherapy or psychotherapy is not effective, add-on treatment with the other modality may be beneficial. In a trial of patients with unipolar major depression who were initially randomized to monotherapy for 12 weeks with an antidepressant or CBT, 112 did not remit and subsequently received augmentation with the other modality for another 12 weeks [43]. Remission with combination treatment occurred in 62 percent.

Another standard augmentation intervention for acute resistant depression is TMS. However, it is not known if maintenance treatment with TMS for unipolar major depression is beneficial.

Treatment-resistant depression that is managed with add-on pharmacotherapy or psychotherapy may also benefit from supplementary interventions such as exercise [44]. A 10-week randomized trial enrolled 42 patients with major depression who did not respond to at least six weeks of antidepressant treatment and compared adjunctive aerobic exercise (two sessions per week, each lasting one hour, in a physical therapy setting) with a single consultation focused upon advice for physical activity [45]. Improvement of both depression and cardiovascular fitness was greater with exercise.

Pharmacotherapy — For patients with treatment-resistant depression who receive augmentation, drug-drug interactions between antidepressants and add-on medications (eg, second-generation antipsychotics, lithium, or triiodothyronine) are generally not a problem. However, combining a monoamine oxidase inhibitor (MAOI) with another antidepressant, such as a selective serotonin reuptake inhibitor (SSRI), can cause the serotonin syndrome or a hypertensive crisis [12,46]. Specific interactions between an antidepressant and another

medication may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Treatment-resistant patients who are treated with an add-on drug and do not respond within 6 to 12 weeks of reaching the target dose, or do not tolerate the combination, should be treated with a second medication combination. We suggest tapering and discontinuing the failed adjunctive medication over one to two weeks at the same time another adjunctive medication is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease. As an example, aripiprazole 15 mg per day is decreased by 5 mg per day every one to three days. At the same time, the antidepressant is continued at the same dose. However, it is reasonable to switch the antidepressant after the adjunctive drug has been switched. Switching antidepressants is discussed elsewhere in this topic. (See 'Next step treatment' below.)

Lack of response to numerous standard treatments may impel clinicians to prescribe a relatively large number of concomitant medications (≥4 psychotropic drugs). However, we generally avoid complex medication regimens because there are no data supporting their utility, and patients may feel worse due to the cumulative side effects.

Choosing a drug — For patients with mild to moderate depression who are treatment resistant and receiving add-on pharmacotherapy, several options are available. The most widely studied drugs include [8,28,36,47-52]:

- Second-generation antipsychotics
- Lithium
- Second antidepressant from a different class
- Thyroid hormone

Our specific choice of add-on therapy depends primarily upon the patient's values and preferences. Some patients may prioritize treatment efficacy, and others may prioritize tolerability and avoiding adverse effects. These approaches are described in the subsections below. (See 'Patients who prioritize efficacy' below and 'Patients who prioritize tolerability' below.)

However, it is reasonable for clinicians to augment with any of these four pharmacotherapy options, because in the few head-to-head trials that compared different drugs, efficacy was generally comparable [1,53]. As an example:

- An eight-week randomized trial compared paroxetine plus risperidone, paroxetine plus trazodone, and paroxetine plus thyroid hormone in 140 treatment-resistant patients and

found that remission was statistically comparable (27, 43, and 38 percent of patients) [34].

- A network meta-analysis of 48 randomized trials (n >6000 depressed patients) evaluated the efficacy of augmentation agents by using results from direct comparisons between the drugs (in head-to-head trials), as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo) [54]. Response (reduction of baseline symptoms ≥50 percent) or remission occurred more often with add-on aripiprazole, lithium, olanzapine, quetiapine, risperidone, or thyroid hormone (T3 or T4), compared with placebo. However, among the active treatments, the relative benefits were comparable.

Other factors to consider in choosing add-on pharmacotherapy include past response, safety, comorbid general medical conditions, adverse effects, ease of use, patient preference, and cost. As an example, patients with a history of extrapyramidal symptoms should avoid aripiprazole; overweight patients should avoid quetiapine, risperidone, and olanzapine; patients with renal or thyroid disease should avoid lithium; and patients with compromised cardiovascular function should avoid thyroid hormone. In addition, adding a second antidepressant may involve fewer baseline laboratory tests and monitoring than adding an antipsychotic, lithium, or triiodothyronine.

Patients who prioritize efficacy — For patients with resistant depression who prioritize efficacy and can tolerate the initial antidepressant, we suggest augmenting antidepressants with a second-generation antipsychotic as first-step treatment and augmentation with lithium for patients who do not respond to second-generation antipsychotics [9,13,23]. Second-generation antipsychotics appear to better balance efficacy and tolerability than lithium. However, it is reasonable to first augment with lithium. Augmentation with a second-generation antipsychotic or lithium is consistent with practice guidelines [9-11,13,23].

The rationale for using second-generation antipsychotics or lithium is that their efficacy is better established, compared with other drugs that are commonly used for augmentation, such as a second antidepressant or thyroid hormone. However, adverse effects also appear to be greater with second-generation antipsychotics and lithium, and it is thus reasonable to augment with a second antidepressant or thyroid hormone instead. (See 'Patients who prioritize tolerability' below.)

In choosing a second-generation antipsychotic as augmentation for treatment-resistant depression, our general order of preference is as follows, based upon the evidence of benefits and harms: aripiprazole, risperidone, quetiapine, brexpiprazole, and less often, cariprazine, ziprasidone, or olanzapine [42,49,54-58]. This recommended order is consistent with practice

guidelines [13]. However, few head-to-head trials have compared the second-generation antipsychotics for augmentation, and it is reasonable to use these drugs in a different sequence.

Aripiprazole is often used first because it appears to cause fewer side effects than other second-generation antipsychotics (table 6). If aripiprazole fails because of intolerance due to akathisia, we discontinue aripiprazole and initiate brexpiprazole, based upon studies that indicate akathisia occurs in approximately half as many patients taking brexpiprazole than aripiprazole [59].

Among second-generation antipsychotics that are used for depression, we typically avoid olanzapine, especially for longer-term treatment (eg, ≥12 weeks), because it carries the highest risk of weight gain and diabetes [60-62]. If olanzapine is to be used for augmentation, we suggest combining it samidorphan, which can mitigate weight gain [63].

For patients with treatment-resistant depression who do not respond to one second-generation antipsychotic within 6 to 12 weeks of reaching the target dose, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one to two weeks while starting and titrating up a different second-generation antipsychotic at the same time. We generally attempt treatment with no more than two second-generation antipsychotics before augmenting with lithium.

- **Efficacy of second-generation antipsychotics** – Multiple trials have demonstrated that adjunctive treatment with different second-generation antipsychotics can be efficacious for unipolar, nonpsychotic major depression that has not responded to antidepressant monotherapy [14,49,54,64-66]. However, adverse effects and discontinuation of treatment are more likely with these drugs, compared with antidepressant monotherapy. In addition, most of the trials that studied the antipsychotics were funded by the manufacturer.

  Evidence supporting augmentation with a second-generation antipsychotic includes an open-label, six-week randomized trial in patients with resistant major depression (n = 103), which compared augmentation of an SSRI with add-on aripiprazole (mean dose 3 mg/day) or bupropion (mean dose 199 mg/day) [67]. Remission occurred in more patients who received adjunctive aripiprazole than bupropion (55 versus 34 percent). None of the patients discontinued treatment because of adverse events, and the incidence of extrapyramidal symptoms and of akathisia was comparable in the two groups. Other trials have demonstrated that response is greater in patients who receive add-on aripiprazole than bupropion [28].

In addition, several placebo-controlled trials (mean duration seven weeks) have demonstrated that add-on second-generation antipsychotics can be efficacious for nonpsychotic, resistant, unipolar major depression:

- A meta-analysis of 28 randomized trials in patients with who failed at least one course of antidepressant monotherapy (n >7300) found that response was 40 percent greater with add-on second-generation antipsychotics than placebo (relative risk 1.4, 95% CI 1.3-1.5) [68]. However, discontinuation of treatment due to adverse effects was more than twice as large with active treatment than placebo (relative risk 2.4, 95% CI 1.7-3.4).

- A network meta-analysis of 33 trials (n >10,000 patients) evaluated the efficacy and tolerability of add-on antipsychotics by using results from direct comparisons between the drugs (in head-to-head trials), as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo) [58]. The primary findings included the following:

  - The probability of response was greater with each antipsychotic (except ziprasidone) than placebo, and the probability was greatest with aripiprazole (odds ratio 1.8, 95% CI 1.5-2.2) and risperidone (odds ratio 2.2, 95% CI 1.4-3.4).

  - The probability of response with aripiprazole exceeded that for brexpiprazole, cariprazine, and olanzapine.

  - Discontinuation of treatment due to adverse effects was generally more likely with each antipsychotic than placebo. However, the likelihood of discontinuation among patients treated with risperidone and placebo was comparable.

Additional information about the efficacy of second-generation antipsychotics for treatment-resistant depression, including patients with a minimal response to the initial antidepressant, as well as information about safety issues (eg, metabolic syndrome and tardive dyskinesia) and the administration and side effects of these drugs (table 6), is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- **Efficacy of lithium** – Lithium augmentation has been used for treatment-resistant depression since the 1960s [69], and multiple studies have subsequently demonstrated its efficacy [42]. As an example, a meta-analysis of nine randomized trials (237 patients) compared adjunctive lithium with placebo and found that response was superior with lithium [70]. In addition, subgroup analyses found that lithium was efficacious for

augmenting either first-generation antidepressants (eg, tricyclics) or second-generation antidepressants (eg, SSRIs). Augmentation with lithium is consistent with multiple practice guidelines [9,10,13,23].

Another possible benefit of lithium is reduced risk of suicide. (See "Suicidal ideation and behavior in adults".)

Nevertheless, augmentation with drugs other than lithium may be preferred due to the risk of toxicity, the need to monitor serum concentrations, and adverse effects. Additional information about using lithium in treatment-resistant depression, including its dose, safety issues, and side effects, is discussed separately. (See "Unipolar depression in adults: Treatment with lithium".)

Patients who prioritize tolerability — For patients who prioritize tolerability and avoiding adverse effects, we suggest augmentation with a second antidepressant from a different class as first-step treatment. If patients do not respond to a second antidepressant, we suggest augmentation with thyroid hormone (typically triiodothyronine). However, it is reasonable to first augment with triiodothyronine. Augmentation with another antidepressant or triiodothyronine is consistent with practice guidelines [10,13,23].

For resistant depression in patients who prioritize tolerability, the rationale for using a second antidepressant or thyroid hormone is that their adverse effects appear to be less, compared with other drugs that are commonly used for augmentation, such as second-generation antipsychotics and lithium. However, the efficacy of a second antidepressant or thyroid hormone is less well established, and it is thus reasonable to augment with a second-generation antipsychotic or lithium instead.

- **A second antidepressant** – Depressive syndromes that respond incompletely to antidepressant monotherapy are often treated by adding a second antidepressant from a different class. However, certain antidepressant combinations should be avoided; as an example, an MAOI plus an SSRI, a serotonin-norepinephrine reuptake inhibitor (SNRI), a serotonin modulator, an atypical antidepressant, or a tricyclic can cause the serotonin syndrome or a hypertensive crisis [46]. (See "Serotonin syndrome (serotonin toxicity)" and "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

  Specific interactions between antidepressants may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

  The evidence suggests that combining two antidepressants is generally limited:

- A meta-analysis of 20 randomized trials compared antidepressant combinations with antidepressant monotherapy in patients with depressive disorders that did not respond to initial treatment (n >4500) [71]. Improvement was greater with combination therapy, and withdrawal from treatment due to adverse effects appeared to be comparable for the two groups. However, the clinical advantage of combination therapy was small.

  The results suggested that it is preferable to combine a monoamine reuptake inhibitor (SSRI, SNRI, or tricyclic antidepressant) with mianserin, mirtazapine, or trazodone. In addition, antidepressant combinations that included bupropion were superior to monotherapy.

- A 10-week, open-label randomized trial compared add-on citalopram with add-on lithium in patients (n = 104) who did not respond to initial treatment with imipramine [72]. Citalopram was titrated up to 30 mg/day and target lithium serum concentrations were 0.6 to 0.8 mEq/L (0.6 to 0.8 mmol/L). Remission occurred in more patients who received adjunctive citalopram than lithium (40 versus 21 percent). Tolerability was not systematically assessed.

Additional information about the use and efficacy of antidepressant combinations is discussed separately. (See "Unipolar depression in adults: Treatment with antidepressant combinations", section on 'Treatment resistant depression'.)

- **Thyroid hormone** – Thyroid hormone (eg, triiodothyronine) has been used as augmentation for treatment-resistant depression since the 1960s [73], and subsequent studies have provided low-quality evidence supporting its efficacy. As an example, a meta-analysis of four randomized trials (95 depressed patients unresponsive to a tricyclic) compared adjunctive triiodothyronine (T3) to a control condition (either adjunctive placebo or thyroxine [T4]) [51]. Although the clinical benefit of T3 was moderately large, and response (reduction of baseline depressive symptoms ≥50 percent) occurred in 53 percent more patients who received T3, the difference in the frequency of response between T3 and the control condition was not statistically significant (relative risk 1.53, 95% CI 0.70-3.35). In addition, it is not clear whether T3 augmentation is efficacious with antidepressants other than tricyclics [74,75]. The efficacy, dose, safety issues, and side effects of thyroid hormone in treatment-resistant depression are discussed separately. (See "Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone" and "Unipolar depression in adults: Treatment with lithium", section on 'Triiodothyronine (T3)'.)

A reasonable alternative to a second antidepressant or thyroid hormone, particularly in patients with either cognitive impairment secondary to depression or comorbid attention-deficit hyperactivity disorder, is augmentation with stimulants. (See "Unipolar major depression in adults: Augmentation of antidepressants with stimulants and stimulant-like drugs".)

Psychotherapy — For patients with unipolar major depression who receive an antidepressant as initial treatment and do not improve sufficiently, augmentation with psychotherapy is often beneficial and is consistent with practice guidelines [4,8,10,11,23,76-79]. As an example:

- A meta-analysis of six randomized trials compared antidepressants plus add-on psychotherapy with antidepressants alone in 635 patients with treatment-resistant depression [80]. Remission was nearly twice as likely with adjunctive psychotherapy (relative risk 1.9, 95% CI 1.5-2.5), and discontinuation of treatment was comparable for the two groups. Heterogeneity across studies was small to moderate.

- A subsequent meta-analysis of 20 randomized trials compared antidepressants plus add-on psychotherapy with antidepressants alone in nearly 3000 patients [81]. The primary findings included the following:

  - Improvement was greater with adjunctive psychotherapy and the clinical benefit was small to moderate. However, heterogeneity across studies was moderate.

  - The efficacy of specific psychotherapies, including CBT, interpersonal psychotherapy, and mindfulness-based cognitive therapy (MBCT), appeared to be comparable.

  - Greater baseline severity (intensity) of depressive symptoms was associated with greater improvement.

However, treatment-resistant patients may decline psychotherapy despite its demonstrated benefits [18]. In addition, psychotherapy may not be available.

The specific choice of an adjunctive psychotherapy is usually based upon availability and patient preference because few head-to-head randomized trials have compared different psychotherapies in treatment-resistant depression. In addition, randomized trials in patients who present for initial treatment of depression indicate that there is no compelling evidence that one psychotherapy is superior to the rest. (See "Unipolar major depression in adults: Choosing initial treatment".)

Specific psychotherapies that have demonstrated efficacy for treatment-resistant depression include the following:

- **Cognitive-behavioral therapy** – The most widely studied and utilized add-on psychotherapy for treatment-resistant depression is CBT. Meta-analyses of randomized trials indicate that adding CBT to pharmacotherapy provides a small to moderate clinical benefit [81]. As an example, a meta-analysis of three randomized trials compared antidepressants plus add-on CBT with antidepressants alone in 522 patients who did not respond to antidepressants [80]. Improvement was greater with adjunctive CBT, and the clinical effect was small to moderate. Results from the specific trials indicated that adjunctive CBT led to remission in 30 to 40 percent of patients [82,83].

  The principles of CBT are discussed separately. (See "Overview of psychotherapies", section on 'Cognitive and behavioral therapies'.)

- **Interpersonal psychotherapy** – Evidence supporting add-on interpersonal psychotherapy with pharmacotherapy for treatment-resistant depression includes a meta-analysis of three randomized trials in patients who did not respond to pharmacotherapy (n = 233) [81]. Improvement was greater in those treated with add-on interpersonal psychotherapy, and the clinical effect was small to moderate.

  As an example, a four month trial enrolled patients (n = 64) who had not responded to an average of three antidepressants and were acutely depressed on average for approximately 26 months, and randomized them to an intervention consisting of interpersonal psychotherapy, occupational therapy, and pharmacotherapy or to treatment as usual (pharmacotherapy and/or psychotherapy) [84]. Remission occurred in more patients who received interpersonal psychotherapy (35 versus 13 percent).

  General information about interpersonal psychotherapy is discussed separately. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy" and "Interpersonal Psychotherapy (IPT) for depressed adults: Specific interventions and techniques".)

- **Mindfulness-based cognitive therapy** – Multiple randomized trials indicate that adjunctive MBCT can help patients with treatment-resistant depression. A meta-analysis of four trials in 325 patients who had not responded to pharmacotherapy compared ongoing pharmacotherapy plus add-on MBCT with pharmacotherapy alone [81]. Improvement was greater with adjunctive MBCT, and the clinical benefit was moderate.

  General information about MBCT is discussed separately. (See "Unipolar major depression: Treatment with mindfulness-based cognitive therapy".)

- **Psychodynamic psychotherapy** – Psychodynamic psychotherapy has also demonstrated efficacy for treatment-resistant unipolar major depression [85]. A 20-week randomized trial (n = 60 patients) compared ongoing pharmacotherapy plus weekly add-on psychodynamic psychotherapy with usual care consisting of pharmacotherapy and/or psychotherapy (eg, CBT) [86]. Remission occurred in more patients who received add-on psychodynamic psychotherapy than usual care (36 versus 4 percent).

  The principles and administration of psychodynamic psychotherapy are discussed separately. (See "Unipolar depression in adults: Psychodynamic psychotherapy".)

Other psychotherapies that are suitable for add-on treatment in patients with resistant depression include behavioral activation, family and couples therapy, problem solving therapy, and supportive psychotherapy. Each of these are discussed separately in UpToDate.

Transcranial magnetic stimulation — For patients with major depression that does not respond to initial treatment with an antidepressant, multiple randomized trials indicate that augmentation with TMS can be effective. As an example, a pooled analysis of six randomized trials compared active TMS with sham TMS as augmentation in patients (n = 230) with treatment-resistant depression who continued their antidepressant drugs [87]. Patients received 10 to 30 sessions of high frequency, left surface cortical TMS. Response (eg, reduction of baseline symptoms ≥50 percent) occurred in more patients who received active than sham TMS (47 versus 22 percent). Augmentation with TMS is consistent with practice guidelines [9,11,88].

However, patients who respond to acute TMS generally require continuation and maintenance treatment with antidepressants, psychotherapy, or both. It is not known if maintenance treatment with TMS for unipolar major depression is beneficial. The efficacy of maintenance treatment with antidepressants, psychotherapy, or TMS are discussed separately, as is the technique for performing TMS. (See "Unipolar depression in adults: Continuation and maintenance treatment" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Maintenance TMS' and "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)".)

Next step treatment — For resistant, mild to moderate depression that does not respond to augmentation interventions, we suggest switching to a different treatment. Standard options include:

- A different antidepressant
- Psychotherapy
- TMS

The choice between these three options is generally based upon availability and patient preference because there is no compelling evidence that one is superior to the others for acute outcomes. Most patients switch antidepressants because this option is readily accessible and often preferred. In addition, patients with unipolar depression who do not respond to initial treatment with either pharmacotherapy or psychotherapy may respond to switching to the other modality. (See 'Psychotherapy' below.)

Other factors may determine the choice when switching treatments. As an example, patients acutely ill with unipolar major depression who improve with pharmacotherapy and subsequently discontinue it appear to be at greater risk for relapse than patients who improve with and discontinue psychotherapy (eg, CBT). In addition, maintenance treatment with antidepressants or psychotherapy can forestall relapse. Although maintenance treatment with TMS for unipolar major depression is common, its efficacy has not been demonstrated in randomized trials. (See "Unipolar depression in adults: Continuation and maintenance treatment" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Maintenance TMS'.)

Patients with treatment-resistant depression who switch to a different treatment may also benefit from supplementary interventions such as exercise. (See "Unipolar major depression in adults: Choosing initial treatment".)

Antidepressants — For patients with major depression who are resistant to treatment with an SSRI at first presentation and are switching antidepressants, many options are available (table 7). The most commonly studied antidepressants are as follows, and are presented in our general order of preference based upon the number and quality of randomized trials that studied each option, as well as safety issues, side effect profiles (table 8), potential for drug-drug interactions, and ease of use (algorithm 2) [1,47,89]. Other factors to consider in changing antidepressants include treatment history, patient preference, cost, and comorbid general medical conditions. Patients with seizure disorders should avoid bupropion, patients with obesity should avoid mirtazapine, and patients with cardiovascular disease should avoid tricyclics and MAOIs.

- **Serotonin-norepinephrine reuptake inhibitors** – For patients with resistant depression who are switching antidepressants, we generally choose the SNRI venlafaxine extended release because it has been widely studied. However, other SNRIs are reasonable alternatives.

  Multiple trials support switching to venlafaxine in resistant depression [89]. As an example, a pooled analysis of three randomized trials, in patients with major depression

who did not respond sufficiently to initial treatment with an SSRI (n = 3375), compared switching to venlafaxine with switching to a different SSRI [90]. Remission occurred in more patients who received venlafaxine (54 versus 45 percent), and the number of dropouts because of side effects was comparable for the two groups.

The pharmacology, administration, and side effects of venlafaxine and other SNRIs are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

- **Atypical antidepressants** – For depressed patients who are resistant to initial treatment with an SSRI, randomized trials indicate that remission is statistically comparable for patients who switch to either an atypical antidepressant (eg, bupropion or mirtazapine) or a different SSRI. Clinicians may expect that an atypical antidepressant will lead to remission in roughly 20 to 35 percent of patients:

  - The STAR*D study included a 14-week trial that compared bupropion sustained release (mean dose 283 mg per day) with sertraline (mean dose 136 mg per day) in 477 treatment-resistant patients; medications were administered on an open-label basis and assessment of outcome was blinded [91]. Remission was comparable for bupropion and sertraline (21 and 18 percent), as was tolerability.

  - An eight-week trial in 100 treatment-resistant patients found that remission with either mirtazapine (45 mg per day) or paroxetine (20 mg per day) was comparable (36 and 47 percent), as was tolerability [35].

  Another atypical antidepressant option is dextromethorphan-bupropion. Although this medication is approved for treatment of unipolar major depression, and may have greater benefit than bupropion alone, no trials have compared the drug with other antidepressants.

  The pharmacology, administration, and side effects of atypical antidepressants are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects".)

- **Tricyclic antidepressants** – Tricyclic antidepressants are fourth- or fifth-line drugs for treatment of depression due to their greater safety hazards (eg, cardiotoxicity and potential lethality with overdose) and less favorable side effect profiles [92]. However, for patients with treatment-resistant depression, the efficacy and tolerability of tricyclics may be comparable to other antidepressants and SSRIs, and clinicians may expect that a tricyclic will lead to remission in 20 to 70 percent of patients [93,94]:

- In the STAR*D study, an open-label, 14-week randomized trial (n = 235) compared switching to nortriptyline (mean dose 97 mg per day) with switching to mirtazapine (mean dose 42 mg per day) and found that remission was statistically comparable (20 and 12 percent), as was tolerability [95].

- In another trial, patients were initially treated with venlafaxine; those who did not remit (n = 112) were randomly assigned to switch to imipramine or to add-on treatment with mirtazapine 30 mg/day [40]. Imipramine was dosed to achieve a combined serum imipramine plus desipramine concentration of 175 to 300 ng/mL. After 10 weeks, remission occurred in more patients who switched to imipramine than those who added mirtazapine (71 versus 39 percent). However, all-cause discontinuation was two-fold greater with imipramine (9 and 4 percent).

The pharmacology, administration, and side effects of tricyclics are discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

- **Monoamine oxidase inhibitors** – MAOIs are seldom prescribed because of potentially lethal drug-drug and drug-food interactions, as well as adverse effects and the danger that MAOIs pose in overdoses [92,96]. Nevertheless, switching to an MAOI may be beneficial for patients with major depression that is resistant to other drug classes (table 7) [90,97].

  Evidence that supports switching to MAOIs includes a network meta-analysis of 52 randomized trials that compared an MAOI to another antidepressant and/or placebo in patients with depressive disorders (n >6400) [98]. The meta-analysis used results from direct comparisons between drugs, as well as indirect comparisons of the drugs through their relative effect with a common comparator (typically placebo). The efficacy (response rate) and acceptability (all-cause discontinuation) of the MAOIs moclobemide, phenelzine, selegiline, and tranylcypromine were comparable to the three SSRIs and six tricyclics that were included. Among the 13 antidepressants that were studied, the drug with the greatest efficacy was phenelzine.

  The pharmacology, administration, dietary restrictions (table 9), and side effects of MAOIs are discussed separately. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

In addition, it is reasonable to switch patients from an ineffective SSRI to a serotonin modulator such as vortioxetine and vilazodone [52]. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

In switching from initial treatment with an SSRI to another antidepressant, is reasonable to use the drugs listed above in a different sequence, or to switch to a different SSRI at any point in the sequence [90]. In the few head-to-head studies that have compared different antidepressants for treatment-resistant depression, efficacy is often comparable [1]. As an example, an eight-week randomized trial (n = 105 patients) compared switching to either venlafaxine extended release 225 mg per day or mirtazapine 45 mg per day and found that remission was comparable (42 and 36 percent) [35].

We typically use a drug from a different class when switching antidepressants for treatment-resistant depression, rather than switching to an antidepressant within the same class, especially if there are problematic, class-wide adverse effects (eg, sexual dysfunction, which can occur with different SSRIs) [17]. Evidence supporting a switch to an antidepressant in a different class includes a pooled analysis of four randomized trials involving patients with unipolar major depression who were resistant to initial treatment with an SSRI (n = 1496), and were switched either to a non-SSRI antidepressant (bupropion, mirtazapine, or venlafaxine) or to a different SSRI [89]. Remission was statistically greater in patients who switched to a different drug class (28 versus 24 percent); in addition, discontinuation due to side effects was comparable for the two groups. However, given the modest difference in remission (4 percent), switching from one SSRI to another is reasonable [99,100].

For treatment-resistant patients who are switching antidepressants, we generally cross-taper, that is, taper and discontinue the failed medication over one to two weeks while another antidepressant is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease. As an example, venlafaxine extended release 225 mg per day is decreased by 37.5 to 75 mg per day every one to three days. Implementing switches is discussed separately. (See "Switching antidepressant medications in adults", section on 'Switching antidepressant medications'.)

If cross-tapering is used for antidepressant switches, clinicians should be aware of overlapping side effect profiles (table 8), as well as potential drug-drug interactions such as the serotonin syndrome (see "Serotonin syndrome (serotonin toxicity)") [101]. Specific interactions between antidepressants may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Preliminary studies have examined the clinical utility of selecting an antidepressant based upon tests that assess genes involved in a drug's pharmacokinetics and pharmacodynamics [102,103]. However, using these pharmacogenetic tests is not standard practice because they do not consistently lead to clinically meaningful outcomes for treating depression [104]. As an example, a 24-week, open-label randomized trial in patients with treatment-resistant unipolar

major depression (n = 1944) compared pharmacogenetic testing with usual care for choosing a new antidepressant [105]. Although remission at week 12 was greater with testing-guided care than usual care, the clinical effect was small and at week 24, remission in the genomic testing and control groups was nearly identical (17 and 16 percent).

Although some studies suggest that switching antidepressants may not be effective for treatment-resistant depression, the methods used are problematic. As an example, a meta-analysis of eight randomized trials, which enrolled patients (n = 1627) who did not respond to an antidepressant, found that switching antidepressants was no better than continuing the initial antidepressant [106]. However, the duration of treatment with the initial antidepressant was typically inadequate, such that the initial treatment trial lasted only two weeks in 29 percent of the patients and only four weeks in another 38 percent. The duration of an adequate treatment trial with an antidepressant is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Duration of an adequate trial'.)

Psychotherapy — For treatment-resistant major depression, switching to psychotherapy is a reasonable option for patients who prefer it, and is consistent with practice guidelines [10,11,23,52,76,79]. Evidence supporting a switch to psychotherapy includes a 12-week trial that enrolled 122 patients who did not respond to or tolerate citalopram and randomly assigned them to cognitive therapy or to a different antidepressant (bupropion, sertraline, or venlafaxine) [107]. Remission was comparable for cognitive therapy and pharmacotherapy (25 and 28 percent of patients), as was discontinuation of treatment due to side effects (17 and 27 percent). Acceptability of cognitive therapy was greater among patients with more education (eg, college graduates) and a family history of mood disorders [18].

In addition, another trial found that all-cause discontinuation of treatment occurred in fewer patients who received psychotherapy than pharmacotherapy [108].

Although switching from an antidepressant to psychotherapy can be effective for treatment-resistant depression, many patients decline this option [18]. In addition, psychotherapy is often not available.

Transcranial magnetic stimulation — For patients with resistant major depression who decide to switch treatment, another reasonable option is repetitive TMS. Switching to TMS is consistent with practice guidelines [9,11,88].

Multiple randomized trials that compared TMS with sham treatment (placebo) as monotherapy indicate that TMS can be efficacious for acute treatment-resistant depression. As an example, a meta-analysis of 43 randomized trials compared high-frequency left TMS with sham TMS in

patients with treatment-resistant depression (n >1900). Response was four times more likely to occur with active TMS (odds ratio 4, 95% CI 2-5) [109].

However, patients who respond to acute TMS generally require continuation and maintenance treatment with antidepressants, psychotherapy, or both. It is not known if maintenance treatment with TMS for unipolar major depression is beneficial. The efficacy of maintenance treatment with antidepressants, psychotherapy, or TMS are discussed separately, as is the technique for performing TMS. (See "Unipolar depression in adults: Continuation and maintenance treatment" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Maintenance TMS' and "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)".)

SEVERE DEPRESSION

Determining the severity of a depressive syndrome has not been standardized. The three paragraphs immediately below describe different means of establishing severity, in descending order of preference.

Severe major depression is indicated by a score ≥20 points on the self-report Patient Health Questionnaire – Nine Item (PHQ-9) (table 4). The PHQ-9 is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

Alternatively, one study classified episodes of major depression as severe in those individuals who had eight or nine of the nine symptoms that define major depression (table 1) [5]. This is consistent with the approach used in the DSM-5-TR [3].

Many studies have assessed severity of depression using clinician administered instruments, such as the Hamilton Rating Scale for Depression (table 5) [6] or Montgomery-Asberg Depression Rating Scale (figure 1A-C) [7]. However, these rating scales are generally not part of standard care.

Patients who are severely ill with major depression often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, and are more likely to develop complications such as psychotic features (eg, delusions and/or hallucinations) and catatonia. These patients should be referred to a psychiatrist for management and frequently require hospitalization [9,10,19,20]. Treatment of major depression with psychotic features or catatonia is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Catatonia: Treatment and prognosis".)

Initial approach — For patients with treatment-resistant, severe, nonpsychotic, noncatatonic unipolar major depression, we suggest initially using ketamine rather than electroconvulsive therapy (ECT), based upon efficacy, safety, adverse effects, and patient preferences [42,52,110-113]. However, a reasonable alternative is esketamine (S-ketamine), which is one of the two enantiomers that constitute racemic ketamine [114-116]. In addition, ECT is well-established as a highly effective intervention for treatment resistance and is thus a reasonable alternative to ketamine/esketamine.

As part of shared decision making, clinicians and patients should review the following aspects of treatment:

- **Efficacy** – Although the relative benefits of ketamine and ECT for severe, nonpsychotic, noncatatonic resistant depression vary across different randomized trials, the best evidence suggests that ketamine is superior.

  Randomized trials that favor each treatment are as follows:

  - Ketamine/esketamine – Studies that indicate ketamine is superior to ECT include an open-label, three-week trial that compared ketamine with ECT in nonpsychotic 365 patients (primarily outpatients) [117]. Intravenous ketamine was administered two times per week at a dose of 0.5 mg/kg over 40 minutes. ECT was administered three times per week, initially using right unilateral ultrabrief pulse at six times the seizure threshold; during the trial, 39 percent of patients were switched to bilateral placement, which many experts regard as the standard of care [118]. Response (reduction of symptoms ≥50 percent) occurred in more patients who received ketamine than ECT (55 versus 41 percent) [117]. During the six-month follow-up of patients who responded, relapse in the ketamine and ECT groups occurred in 35 and 56 percent. However, some patients who did not respond to nine ECT treatments may have responded to a few (eg, three) more treatments.

    Indirect evidence regarding the benefit of ketamine/esketamine includes a 32-week, open-label randomized trial that compared esketamine with quetiapine extended-release (XR) in patients with treatment-resistant major depression (n = 676) [119]. Study treatments were added to ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor. Esketamine was flexibly dosed at 28, 56 or 84 mg, and administered twice weekly during weeks 1 to 4, and weekly or every two weeks during weeks 5 to 32. Quetiapine XR was flexibly dosed at 150 to 300 mg/day. More patients remitted with esketamine than quetiapine XR (49 versus 33 percent). In addition, discontinuation of treatment due to adverse events

occurred in nearly three times as many patients treated with quetiapine XR than esketamine (11 and 4 percent), which contributed to the differences in remission.

- ECT – Prior open-label trials suggest that ECT is superior to ketamine [120]. As an example, a meta-analysis of three trials compared ECT with ketamine in 229 patients, some of whom had psychotic features [121]. ECT was administered a total of 3 to 12 times with either right unilateral or bilateral placement; ketamine was infused 3 to 12 times at a dose of 0.5 mg/kg. Response was modestly greater with ECT (relative risk 1.3, 96% CI 1.1-1.5). Despite the greater benefit with ECT, the relatively small advantage led the investigators to recommend that clinicians use ketamine before ECT, presumably because other aspects of treatment favor ketamine.

- **Suicidal ideation and behavior** – Both ketamine and ECT can be particularly helpful for patients with refractory, active suicidal ideation that includes a plan and intent.

- **Time to onset of response** – A meta-analysis of two trials (total n = 139) found that the number of treatment sessions required to achieve response was comparable with ketamine and ECT [121].

- **Safety** – Although ketamine is approved as a general anesthetic, subanesthetic doses are administered for resistant depression. By contrast, ECT requires brief general anesthesia.

- **Adverse effects**

  - Ketamine

    - Substance use disorder – Ketamine may be misused as an intoxicant/euphoriant and can lead to diversion and physiologic and psychological dependence [122,123]. Thus, depressed patients with comorbid substance use disorders are typically not candidates for ketamine [124].

    - Dissociation and psychotomimetic effects – Potential adverse effects of ketamine include dissociative and psychotomimetic symptoms. As an example, an open-label, randomized trial in 365 patients found that dissociative symptoms were greater in patients who received ketamine than ECT [117]. In addition, a prior meta-analysis of three trials (total n = 230) found that the risk of dissociation was six times greater with ketamine than ECT [121].

  - ECT

- Memory – ECT can cause memory impairment that may persist for at least six months. In a three-week, open-label randomized trial, multiple measures of memory at the end of treatment were worse with ECT than ketamine [117]. At the six-month follow-up of responders, clinician-administered measures showed that ECT related memory impairment resolved within one to six months, but patient self-report measures indicated that memory remained worse among those who received ECT.

- Musculoskeletal effects – A three-week, open-label, randomized trial (n = 365 patients) found that muscle pain or weakness with ECT or ketamine occurred in 5.3 and 0.5 percent [117]. In addition, other trials found that musculoskeletal pain occurred more often with ECT than ketamine [121].

- **Patient preferences** – Patients may typically prefer ketamine over ECT. In a trial that randomly assigned 403 patients to either ketamine or ECT, 4 patients in the ketamine group withdrew from the study before starting their assigned treatment, compared with 31 in the ECT group [117]. Ketamine may be more acceptable to patients because it carries less stigma and causes fewer problems with memory.

  Patient preferences may also affect the choice between ketamine and esketamine. Most studies of ketamine in academic centers have administered it intravenously, but it is also available in intramuscular, intranasal, oral, subcutaneous, and sublingual formulations. In addition, the drug is available in free-standing outpatient clinics. By contrast, intranasal esketamine is available in the United States only through a Risk Evaluation and Mitigation Strategy program, in which the drug is sold to certified medical offices for specific patients who are enrolled in a registry. Patients self-administer the drug in the office and are then monitored for at least two hours by clinicians in the office. Esketamine is kept under lock and key and is not allowed to leave the office.

Information about prescribing intravenous ketamine according to best practices is discussed in the Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders [110].

Additional information about ketamine and ECT, including their efficacy, safety, and adverse effects, are discussed separately. (See "Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)" and "Overview of electroconvulsive therapy (ECT) for adults".)

Next step treatment — Patients with severe, treatment-resistant, nonpsychotic, noncatatonic unipolar major depression who choose ketamine for initial management may not respond. For

these patients, next step treatment is ECT, which is generally regarded as more efficacious than other treatments [125-127]. The efficacy of ECT extends to patients with persistent, serious suicidal ideation, and those with severe weight loss, malnutrition, or dehydration secondary to refusal of food and fluids [88,125,128-130]. Using ECT is consistent with multiple treatment guidelines [9,11,19-21,23,88].

Meta-analyses of randomized trials indicate that ECT is superior to pharmacotherapy (other than ketamine) for unipolar major depression [131-133]. As an example, a meta-analysis of 18 trials (1144 patients) compared ECT with pharmacotherapy and found that ECT was more efficacious [134]. In one open-label trial that compared ECT with paroxetine in 39 patients with treatment-resistant depression, response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received ECT than paroxetine (71 versus 28 percent) [135].

In addition, the efficacy of ECT is comparable or superior to other neuromodulation interventions for major depressive episodes, including repetitive transcranial magnetic stimulation (TMS) [136-138]:

- A network meta-analysis of randomized trials evaluated the efficacy of nonsurgical neuromodulation interventions by pooling results from direct comparisons between the therapies in head to head trials, as well as indirectly comparing therapies through their relative effect with a common comparator (sham stimulation) [109]. The probability of response was greatest with bitemporal ECT and high-dose right unilateral ECT, relative to repetitive TMS and transcranial direct current stimulation.

- A pooled analysis of seven randomized trials (either open-label or blinded rater) compared ECT (bilateral or unilateral) with repetitive TMS (applied over the left or right dorsolateral prefrontal cortex) in 275 patients with major depression [139]. Remission occurred in more patients who received ECT than repetitive TMS (53 versus 32 percent). In addition, discontinuation of treatment for any reason was comparable for ECT and repetitive TMS (12 and 14 percent). However, cognitive impairment in specific domains (eg, verbal fluency and visual memory) may be greater with ECT [139-141].

Nevertheless, ECT is associated with safety risks, adverse effects, logistical constraints, and patient refusal, and relapse rates following remission are high, especially in patients with treatment-resistant depression [142,143]. An overview of ECT is discussed separately, as are indications for and efficacy of ECT in unipolar major depression, medical consultation for ECT, and the technique for performing ECT. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Unipolar major depression in adults: Indications for and efficacy of

electroconvulsive therapy (ECT)" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Other options — For treatment-resistant, severely depressed patients who do not respond to or who decline ketamine and ECT, we suggest antidepressants, as well as psychotherapy if it is feasible.

- **Pharmacotherapy** – For these patients, it is not clear that one class of antidepressants (table 7) is superior to others. However, some evidence suggests that tricyclics may be preferred [21]:

  - A meta-analysis of 25 randomized trials compared tricyclics with SSRIs in 1377 hospitalized patients who were not selected for treatment resistance [144]. Although tricyclics were more efficacious than SSRIs, the clinical difference was small, and heterogeneity across studies was significant. In addition, discontinuation of treatment occurred in more patients who received tricyclics than SSRIs (14 versus 9 percent).

  - In a subsequent trial, patients who were initially treated with venlafaxine and did not remit (n = 112) were randomly assigned to switch to open-label imipramine or add-on treatment with mirtazapine 30 mg/day [40]. Imipramine was dosed to achieve a combined serum imipramine plus desipramine concentration of 175 to 300 ng/mL. After 10 weeks, remission occurred in more patients who switched to imipramine than those who added mirtazapine (71 versus 39 percent).

  Additional information about choosing an antidepressant for treatment-resistant, severe depression is discussed elsewhere in this topic in the context of mild to moderate depression. (See 'Antidepressants' above.)

  Other severely ill, treatment-resistant patients may benefit from augmentation with another medication, such as a second antidepressant. In one study, patients with a baseline score on the 17-item Hamilton Rating Scale for Depression (table 5) ≥24 were initially treated with imipramine, which was dosed to achieve a combined serum imipramine plus desipramine concentration of 175 to 300 ng/mL. Patients who did not remit (n = 104) were randomly assigned, on an open-label basis, to add-on either citalopram titrated up to 30 mg/day or lithium dosed to achieve a serum concentration of 0.6 to 0.8 mEq/L (0.6 to 0.8 mmol/L) [72]. After 10 weeks, remission occurred in more patients who received adjunctive citalopram than adjunctive lithium (40 versus 21 percent).

Additional information about augmentation is discussed elsewhere in this topic, in the context of mild to moderate depression. (See 'Initial approach' above.)

For depression resistant to many courses (eg, seven) of pharmacotherapy, a rarely used regimen that may be indicated is the combination of a tricyclic antidepressant and an MAOI. This combination is a treatment of last resort due to potential life-threatening drug-drug interactions, including the serotonin syndrome and hypertensive crisis [21,145,146]. Combining these two drug classes requires a thorough discussion of the risks and benefits, as well as careful monitoring. Generally, the MAOI is added after a failed trial of tricyclic monotherapy, rather than vice versa or simultaneous initiation of both drugs [147]. In addition, the dose for each drug is comparable to the dose used for monotherapy (table 7). Drug-drug interactions (including the serotonin syndrome) between MAOIs and tricyclics may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate. Detailed information about the administration and safety of tricyclics and MAOIs is discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects" and "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

Low-quality evidence supporting the use of a tricyclic plus an MAOI includes a retrospective study of 62 cases [147]. The tricyclics included desipramine, doxepin, and nortriptyline, and the MAOIs included isocarboxazid, phenelzine, and tranylcypromine. The combination appeared to be effective and safe; serotonin syndrome occurred in one case and hypertension was not observed. Other adverse effects were consistent with those that may occur with monotherapy (table 8).

- **Psychotherapy** – We typically include psychotherapy for severe episodes of major depression that are treatment resistant. Most hospitalized patients receive individual and/or group psychotherapy, provided that they are well enough to participate in therapy [148]. Indirect evidence supporting the use of psychotherapy for severe episodes of treatment-resistant depression includes randomized trials in patients with mild to moderate episodes of treatment-resistant depression (see 'Psychotherapy' above). In addition, randomized trials indicate that patients who present for initial treatment of severe major depression can benefit from pharmacotherapy plus psychotherapy. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Choosing a treatment regimen' and "Unipolar major depression in adults: Choosing initial treatment".)

  Only low-quality studies have evaluated psychotherapy in treatment-resistant, severe depression. As an example, two relatively small and old studies yielded conflicting results:

- A 12-week randomized trial compared cognitive-behavioral therapy (CBT) plus pharmacotherapy with pharmacotherapy alone in 20 patients hospitalized for chronic (duration ≥2 years) depression; improvement was comparable for the two groups [149].

- A prospective observational study included 174 patients with treatment-resistant depression who were hospitalized for four to seven months and treated with pharmacotherapy, CBT, milieu therapy, occupational therapy, and couples therapy, as well as ECT if indicated [148]. Response (reduction of baseline symptoms ≥50 percent) occurred in 47 percent.

- **Vagus nerve stimulation** – Another option that we generally do **not** prescribe is vagus nerve stimulation, which involves surgery to attach an electrode around one vagus nerve; the electrode is connected by a wire to a pulse generator implanted subcutaneously in the chest wall. There are no compelling data that indicate vagus nerve stimulation is efficacious for treatment-resistant unipolar major depression. A 10-week trial enrolled 222 patients who did not respond to pharmacotherapy (two to six regimens) and randomly assigned them to vagus nerve stimulation or sham treatment; response in the two groups was comparable (15 and 10 percent of patients) [150]. Avoiding vagus nerve stimulation or limiting its use is consistent with practice guidelines from the American Psychiatric Association, the United Kingdom National Institute for Health and Care Excellence, and other groups [9,19,20,151,152].

  Nevertheless, other clinicians do refer patients for vagus nerve stimulation, based upon prospective observational studies that suggest it may possibly help treatment-resistant depression [153,154]. One proposed explanation for the negative randomized trial described immediately above is that several months may be required for the benefits of vagus nerve stimulation to manifest. The treatment is approved by the US Food and Drug Administration and the European Medicines Agency [155,156]; in addition, prescribing the intervention is consistent with multiple treatment guidelines, including those issued by the Canadian Network for Mood and Anxiety Treatments and British Association for Psychopharmacology [21,22,88,157].

  Additional information about vagus nerve stimulation, including its efficacy, safety, and side effect profile, is discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Vagus nerve stimulation'.)

INVESTIGATIONAL TREATMENTS

Psilocybin — Psilocybin is an investigational psychedelic drug that is synthesized or derived from a particular genus of mushrooms, and produces large effects on perception and consciousness (eg, hallucinations) [158]. Four randomized trials in patients with treatment-resistant unipolar major depression, lasting 6 to 12 weeks, have each found that one or two doses of psilocybin (approximately 25 mg) plus supportive psychotherapy can be efficacious [159-162]. The most common adverse effects of psilocybin were headache and nausea. However, suicidal ideation and behavior also occurred in one trial, and blinding to treatment with psychedelics is difficult. The use of psilocybin is usually accompanied by supportive preparatory and post drug "integrative" sessions but conceptualization of this as "drug-assisted psychotherapy" is controversial [158,163-166].

In the trials, most patients had a history of recurrent depression and had not responded to at least two antidepressants during the current depressive episode [159-162]. Exclusion criteria included history of psychosis, serious suicide attempt, substance use disorder, and comorbid psychopathology that could interfere with the therapeutic alliance between the patient and study clinicians (eg, borderline personality disorder). Psilocybin was administered in a controlled setting along with psychological assistance that included preparation for ingesting psilocybin, support during the visits in which psilocybin was dispensed, and subsequent integration sessions to discuss the psilocybin experience. Treatment sessions in which psilocybin was administered lasted 4 to 10 hours.

Other details of the methods and results from two relatively large, randomized trials are as follows:

- A six-week trial compared a single dose of psilocybin (25 mg) with niacin (100 mg) in 104 patients [162]. Improvement was greater with psilocybin than niacin as early as day 8, and persisted until day 43. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients with psilocybin than niacin (42 versus 11 percent). In addition, occupational, social, and family functioning improved more with active treatment, as did anxiety and quality of life.

  Adverse events occurred in more patients with psilocybin than niacin (76 versus 30 percent). Passive suicidal ideation in the psilocybin and niacin groups increased in one and five patients; no suicidal or nonsuicidal self-injurious behavior occurred.

- Another trial assigned 158 patients to one dose of psilocybin at 25 mg or 1 mg [161]. Improvement was greater with 25 mg, and response occurred in twice as many patients with 25 mg than 1 mg at week 3 (37 and 18 percent) and at week 12 (20 and 10 percent).

  However, serious adverse events that occurred included the following:

- By week 3, in the 25 mg group, suicidal ideation occurred in two patients and nonsuicidal self-injury occurred in two other patients; in the 1 mg group, there were no serious adverse events.

- After week 3 and up to week 12, in the 25 mg group, suicidal behavior occurred in three patients; in the 1 mg group, nonsuicidal self-injury occurred in one patient.

These adverse events occurred despite excluding patients with a significant risk of suicide at baseline from the trial.

Other randomized trials have shown that psilocybin can be efficacious for depressive syndromes in patients with life-threatening cancer [165,167,168].

The mechanism of action for psilocybin may involve its direct agonist effects on serotonin 2A receptors [165]. Another hypothesis is that the drug disrupts circuits that underlie maladaptive thoughts of guilt and ruminations about one's inadequacies [163].

We view psilocybin as an investigational intervention for treatment-resistant depression. Although psychiatrists in Australia can register to prescribe the drug, restricting use of psilocybin to registered clinical trials is consistent with practice guidelines [165,169].

Nitrous oxide — Nitrous oxide is a clinically available N-methyl-D-aspartate (NMDA) receptor antagonist akin to ketamine and a standard anesthetic drug that may perhaps help patients with treatment-resistant depression. A randomized trial compared adjunctive inspiratory nitrous oxide (50 percent nitrous oxide plus 50 percent oxygen) with placebo (50 percent nitrogen plus 50 percent oxygen) in patients with treatment-resistant depression who were receiving a stable treatment regimen (n = 20) [170]. Study drugs were administered in a single session lasting one hour. Improvement of depression was greater with add-on nitrous oxide than placebo at 2 hours, 24 hours, and one-week posttreatment. However, nitrous oxide may be abused because of its intoxicating properties, and the longer term benefits and toxicity of nitrous oxide are unknown.

Neuromodulation

- **Noninvasive neuromodulation** – Investigational, noninvasive neuromodulation procedures, which use an electric current or magnetic field to stimulate the central nervous system, may perhaps be helpful for treatment-resistant depression [171]. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Noninvasive neuromodulation therapies'.)

- **Invasive/surgical neuromodulation** – Patients with severe, intractable, and incapacitating unipolar major depression, which does not respond to numerous (eg, 7 to 10) trials of standard therapies and has persisted for years (eg, ≥2 to 5), may be candidates for investigational neurosurgical interventions that lack high-quality efficacy data. The most widely studied surgical intervention is deep brain stimulation; a less common invasive approach is direct cortical stimulation. Invasive treatments should be pursued only at tertiary referral centers that are conducting research and providing rigorous oversight to ensure that the procedure is indicated. The efficacy, safety, and side effects of experimental invasive/surgical neuromodulation procedures are discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches".)

MAINTENANCE TREATMENT

Patients who remit from treatment-resistant depression typically require maintenance treatment. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

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".)

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 AND RECOMMENDATIONS

- **Definition** – Treatment-resistant depression typically refers to unipolar major depressive episodes (table 1) that do not respond satisfactorily after two trials of antidepressant monotherapy at sufficient doses for sufficient duration; however, the definition has not been standardized. (See "Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis", section on 'Treatment-resistant depression'.)

- **General principles** – The general principles and issues that are involved in treating resistant depression in adults include confirming the diagnosis, adherence with treatment, and duration of an adequate drug trial. (See "Unipolar depression in adults: General principles of treating resistant depression".)

- **Patients with mild to moderate depression**

  - **Initial approach: Augmentation** – Our initial approach in patients with resistant, mild to moderate major depression is to augment the current antidepressant with a second medication, psychotherapy, or repetitive transcranial magnetic stimulation (TMS) (algorithm 1). However, switching treatments is a reasonable alternative to augmentation. Patients who cannot tolerate an adequate dose of the initial antidepressant should switch to another antidepressant. (See 'Treatment algorithm' above.)

    Many patients with resistant depression can tolerate the initial antidepressant, and opt for add-on pharmacotherapy:

    - For patients who prioritize efficacy, we suggest add-on treatment with a second-generation antipsychotic (**Grade 2C**). However, lithium is a reasonable alternative to a second-generation antipsychotic.

      Among second-generation antipsychotics, our general order of preference is aripiprazole, risperidone, quetiapine, or brexpiprazole, and less often, cariprazine,

ziprasidone, or olanzapine. (See 'Choosing a drug' above and 'Patients who prioritize efficacy' above.)

- For patients who prioritize tolerability, we suggest augmentation with a second antidepressant from a different class as first-step treatment. (**Grade 2C**). We avoid using monoamine oxidase inhibitors (MAOIs) as the second antidepressant. However, thyroid hormone is a reasonable alternative to a second antidepressant from a different class. (See 'Choosing a drug' above and 'Patients who prioritize tolerability' above.)

  For patients with resistant depression who augment antidepressants with a second drug and do not respond, we generally provide one to two additional courses of augmentation.

- **Next step treatments: Switching** – For patients with resistant depression who do not respond to augmentation with a second drug, we generally switch to a different antidepressant or to psychotherapy or repetitive TMS. When switching to a different antidepressant, we typically maintain the current adjunctive drug. (See 'Treatment algorithm' above.)

  Our approach in patients who switch antidepressants is to select a drug from a different class (table 7) rather than the same class. In choosing a new antidepressant for patients who fail a selective serotonin reuptake inhibitor (SSRI), our general order of preference is serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, tricyclics, and MAOIs (algorithm 2). However, it is reasonable to use these drugs in a different sequence or to switch to a different SSRI or a serotonin modulator at any point in the sequence. (See 'Antidepressants' above.)

- **Patients with severe depression**

  - **Initial approach** – For patients with treatment-resistant, severe, nonpsychotic unipolar major depression, we suggest intravenous ketamine rather than electroconvulsive therapy (ECT) (**Grade 2B**). A reasonable alternative to ketamine is esketamine. In addition, it is reasonable to use ECT rather than ketamine/esketamine. (See 'Initial approach' above.)

  - **Next step** – If severe, treatment-resistant, nonpsychotic does not respond to ketamine, next step treatment is ECT. (See 'Next step treatment' above.)

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