Unipolar major depression in adults: Choosing initial treatment

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INTRODUCTION

Unipolar depression is highly prevalent and disabling. Community surveys in 14 countries have estimated that the lifetime prevalence of unipolar depressive disorders is 12 percent [1], and the World Health Organization ranks unipolar major depression as the 11th greatest cause of disability and mortality in the world [2]. In the United States, major depression ranks second among all diseases and injuries as a cause of disability, and persistent depressive disorder (dysthymia) ranks 20th [3].

In addition, major depression is highly recurrent. Following recovery from one episode, the estimated rate of recurrence over two years is greater than 40 percent; after two episodes, the risk of recurrence within five years is approximately 75 percent [4].

This topic reviews the choice of therapy for the initial treatment of depression. Other aspects of the initial treatment of depression are discussed separately, as are continuation and maintenance treatment of major depression, the treatment of resistant depression, and the clinical manifestations and diagnosis of depression.

- (See "Unipolar depression in adults and initial treatment: General principles and prognosis".)
- (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)

- (See "Unipolar depression in adults: Investigational and nonstandard treatment".)
- (See "Unipolar depression in adults: Continuation and maintenance treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)

DEFINITION OF UNIPOLAR MAJOR DEPRESSION

Unipolar major depression (major depressive disorder) is diagnosed in patients with a history of at least one major depressive episode and no history of mania or hypomania; in addition, the depressive episode is not caused by medications or concurrent general medical conditions (table 1) [5]. 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; at least one of the symptoms must be depressed mood or anhedonia. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

OVERVIEW OF TREATMENT

Many studies describe treatment outcome using the terms "response" and "remission," based upon the amount of improvement from baseline on a clinician administered depression rating scale [6,7]:

- Response – Improvement ≥50 percent but less than the threshold for remission.
- Remission – Resolution of the depressive syndrome, which can be operationalized by a depression rating scale score less than or equal to a specific cutoff that defines the normal range. As an example, studies using the 17 item Hamilton Rating Scale for Depression (table 2) or the Montgomery-Asberg Depression Rating Scale (figure 1A-C) often define remission as a score ≤7, while studies using the Patient Health Questionnaire – Nine Item (PHQ-9) (table 3) often define remission as a score <5.

The goal of initial treatment for depression is symptom remission and restoring baseline functioning [8-10]. In the prospective Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 3671 outpatients with unipolar major depression who improved following treatment with pharmacotherapy and/or psychotherapy were subsequently followed for up to

12 months [11]. Relapse appeared to occur less frequently in patients who remitted, compared with patients who responded but did not remit.

We suggest that clinicians monitor treatment outcomes with patient self-report scales such as the PHQ-9 (table 3). (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

Choosing a treatment regimen — For the initial treatment of unipolar major depression, we suggest the combination of pharmacotherapy and psychotherapy, based upon randomized trials that found combination treatment was more effective than either of these treatments alone [12,13]. However, clinical trials have not established the superiority of any specific medication/psychotherapy combination [8]. Rather, clinicians select each modality using the same principles when choosing a monotherapy. (See 'Selecting a specific antidepressant' below and 'Selecting a specific psychotherapy' below.)

A reasonable alternative to combination therapy for the initial treatment of major depression is pharmacotherapy alone or psychotherapy alone. Antidepressants and psychotherapy each have demonstrated efficacy as monotherapy and produce comparable outcomes in randomized trials [14,15].

Antidepressants alone have been studied and used more often than combination treatment or psychotherapy alone because antidepressants are generally more available and convenient than psychotherapy [8,16], and some patients prefer pharmacotherapy [17]. Other factors to consider in choosing a treatment regimen are comorbidity, psychosocial stressors, and cost.

We also suggest exercise and other evidence-based supportive care interventions for patients with major depression. For those with mild symptoms (eg, PHQ-9 score 5 to 9), exercise or other supportive care interventions alone are reasonable alternatives to pharmacotherapy or psychotherapy, provided patients are closely monitored for any worsening of depression. (See 'Supportive care' below.)

The use of pharmacotherapy plus psychotherapy, pharmacotherapy alone, or psychotherapy alone for unipolar major depression is consistent with practice guidelines from the American Psychiatric Association and the United Kingdom National Institute for Health and Care Excellence (NICE) [8,18]. However, the NICE guidelines recommend psychotherapy for the initial treatment of patients with mild depression, based upon the judgment that the risk benefit ratio for pharmacotherapy does not justify its use for relatively mild symptoms [18].

Evidence for the efficacy of combination therapy, pharmacotherapy alone, and psychotherapy alone are discussed elsewhere in this topic. (See 'Efficacy of antidepressants plus

psychotherapy' below and 'Efficacy of antidepressants' below and 'Efficacy of psychotherapy' below and 'Efficacy of antidepressants compared with psychotherapy' below.)

Efficacy of antidepressants plus psychotherapy — For the initial treatment of unipolar major depression, randomized trials indicate that the combination of pharmacotherapy and psychotherapy (eg, cognitive-behavioral therapy or interpersonal psychotherapy) is more efficacious than either pharmacotherapy alone or psychotherapy alone [12,13].

Evidence supporting the superiority of combination therapy over pharmacotherapy alone for the initial treatment of unipolar major depression includes many randomized trials [15,19]. As an example, a meta-analysis of 25 randomized trials compared combination therapy with antidepressants alone in patients with depressive disorders (n>2000) [12]. The analysis found a significant, clinically small to moderate effect favoring combination therapy. In addition, discontinuation of treatment for any reason was lower with combination treatment (odds ratio 0.7, 95% CI 0.5-0.8). Separate analyses of the three subgroups that received cognitive-behavioral therapy (seven trials), interpersonal psychotherapy (eight trials), or other psychotherapies (10 trials) found that in each case, combined therapy was superior to antidepressants alone.

Evidence supporting the superiority of antidepressants plus psychotherapy over psychotherapy alone for the initial treatment of unipolar major depression includes many randomized trials [15,20,21]. As an example, a meta-analysis of 16 randomized trials compared combination treatment with psychotherapy alone in patients with depressive disorders (n>1700) [13]. Recovery was more likely with combination therapy (relative risk 1.3, 95% CI 1.2-1.4). However, one concern that we have in evaluating trials that include psychotherapy is the lack of blinding.

Efficacy of antidepressants — Antidepressants can help patients with unipolar major depression [22-24]. Meta-analyses of randomized trials have found that many specific antidepressants, as well as antidepressant classes, are efficacious in unipolar major depression, including agomelatine (not available in the United States) [25], amitriptyline [26], citalopram, [27], duloxetine [28], escitalopram [29], imipramine [30], mirtazapine [31], paroxetine [32], sertraline [33], monoamine oxidase inhibitors [34], selective serotonin reuptake inhibitors [35], and tricyclics [26,30,34-37]. As an example, a meta-analysis of patient-level data from 37 randomized trials (n>8400 patients with major depression) compared either fluoxetine (modal dose 20 mg per day) or venlafaxine (modal dose range 75 to 150 mg per day) with placebo for six weeks; remission occurred in more patients who received active drug than placebo (43 versus 29 percent) [38]. In addition, antidepressants were efficacious regardless of baseline severity. The rate of remission in milder depressive episodes (scores on the Hamilton Rating Scale for Depression ≤19; (table 2)) was greater with active drug than placebo (50 versus 37

percent of patients); the rate of remission in more severe episodes (scores >20) was also greater with active drug than placebo (38 versus 25 percent).

The advantage of antidepressants over placebo is typically 2 to 4 points on a standard rating scale, such as the 17-item Hamilton Rating Scale for Depression (table 2), which ranges from 0 to 52 points [39]. As an example, a meta-analysis of patient-level data (37 randomized trials, n>8400 patients with unipolar major depression who were assessed with the Hamilton scale) found that improvement with antidepressants and placebo differed by 3 points [38].

The small advantage of antidepressants over placebo in depressed patients is due in part to the nonspecific clinical effects of placebo treatment; receiving placebos in clinical trials is not equivalent to receiving no treatment. Depressed study patients who are treated with placebos receive nonspecific support by meeting regularly with clinicians and research assistants to discuss symptoms and functioning [39]. Placebos may act by instilling hope, raising expectations of improvement, and motivating patients to please investigators [40]. In addition, placebo responses may be related to genetic polymorphisms [41]. The effects of placebos often lead to remission. As an example, a meta-analysis of individual patient data from 37 randomized trials found that among patients with unipolar major depression who were treated with placebo (n>3300), remission occurred in 29 percent [38].

Meta-analyses based upon published randomized trials may overestimate the effect of antidepressants because of selective publication of trials (publication bias) [42]. A study of 12 second-generation antidepressants compared drug trials that were published with trials that were registered with the US Food and Drug Administration (FDA); drug companies are required to submit all trials when registering a drug for approval by a regulatory agency [43]. The primary findings included the following:

- Of the 74 trials that were registered, 31 percent (23 trials) were not published.
- Among the 51 published trials, the results were presented as positive (ie, improvement was greater with the drug than placebo) in 94 percent (48 trials); by contrast, the FDA found that among the 74 registered trials, only 51 percent were positive.
- Of the 48 trials that were published as positive, the FDA determined that 23 percent (11 trials) were negative.
- The clinical effect of antidepressants was larger in the journal reports than the registered trials.

The evidence for the efficacy of antidepressants in primary care patients and in the context of general medical illnesses is discussed separately. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)

Efficacy of psychotherapy — Psychotherapy is efficacious for the initial treatment of unipolar major depression, based upon numerous randomized trials [44-46]. As an example, a meta-analysis of 92 trials (n>6900 patients) compared psychotherapy (primarily CBT) with a control condition (eg, waiting list or usual care) [47]. The primary findings were as follows:

- Remission occurred in more patients treated with psychotherapy, compared with controls (41 versus 21 percent).
- Heterogeneity across studies was large; subgroup analyses found that the benefits of psychotherapy were smaller in older patients, and for group therapies (compared with individual therapies).
- Number of therapy sessions was not associated with the effect of psychotherapy.

It is worth noting that meta-analyses appear to overestimate the clinical benefit of nearly all types of psychotherapy in treating depression [48-50]. These inflated effects may be due to low-quality studies, as well as publication bias.

Psychotherapy studies are methodologically variable, like pharmacotherapy studies. Some psychotherapy trials are rigorous and specify a priori hypotheses and analytic tests, develop manuals for the psychotherapies and measure adherence on the part of therapists, use active psychotherapy comparators that control for the nonspecific aspects of psychotherapy, use standardized diagnostic criteria and outcome measures, stratify patients on predetermined risk variables, and blind assessment of outcome ratings. Less meticulous studies use open-label designs, less rigorous comparators (eg, treatment as usual or waiting lists), or fail to adequately blind outcome ratings. Although it is commonly believed that blinding of patients in psychotherapy is less successful compared with pharmacotherapy trials, this has never been studied.

The evidence for the efficacy of psychotherapy in primary care patients and in the context of general medical illnesses is discussed separately. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)

Efficacy of antidepressants compared with psychotherapy — For patients with unipolar major depression, the evidence indicates that the efficacy of antidepressants compared with psychotherapy at the end of treatment is generally comparable [51-53]. A meta-analysis of 30

randomized trials compared psychotherapy (primarily CBT or interpersonal psychotherapy) with antidepressants in patients with depressive disorders (n>3100) and found that improvement was comparable for both groups [54].

However, one advantage provided by psychotherapy (particularly CBT or interpersonal psychotherapy) is that following an acute course of treatment, the benefits often persist and patients remain well [8,55]. By contrast, the benefits of an acute course of antidepressants are often lost if the drug is discontinued. As an example, a meta-analysis of 28 randomized trials compared psychotherapy with pharmacotherapy for the acute treatment of 3381 patients with unipolar depressive disorders, and found that improvement was comparable; heterogeneity across studies was moderate [56]. In the 11 studies (602 patients) that followed patients after treatment ended and assessed their depressive symptoms (mean length of follow-up 15 months), there was a significant, clinically small to moderate effect favoring psychotherapy over antidepressants. Relapse is common in patients who remit after acute treatment with antidepressants and then discontinue their medications. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Relapse/recurrence in the absence of treatment'.)

There are no well-established biologic, genetic, or clinical predictors of sufficient utility to help choose between antidepressants and psychotherapy, or to make a selection among specific antidepressants or psychotherapies [57-66]. However, the results of two randomized trials in patients with depression suggested that comorbid personality disorder (eg, avoidant or obsessive-compulsive) or neuroticism (marked by fearfulness, worrying, and irritability) may be associated with better outcomes in patients receiving antidepressants rather than cognitive-behavioral therapy [67,68].

ANTIDEPRESSANT PHARMACOTHERAPY

Treatment options — Second-generation antidepressants (table 4 and table 5) that are available to treat unipolar major depression include:

- Selective serotonin reuptake inhibitors (SSRIs) (see "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects")
- Serotonin-norepinephrine reuptake inhibitors (see "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects")
- Atypical antidepressants (see "Atypical antidepressants: Pharmacology, administration, and side effects")

- Serotonin modulators (see "Serotonin modulators: Pharmacology, administration, and side effects")

Older, first-generation antidepressants (table 4 and table 5) include:

- Tricyclic antidepressants (see "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects")
- Monoamine oxidase inhibitors (MAOIs) (see "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects")

Selecting a specific antidepressant — For patients with unipolar major depression whose initial treatment includes antidepressants, we suggest SSRIs based upon their efficacy and tolerability in randomized trials. SSRIs are the most widely prescribed class of antidepressants [16,69,70].

Reasonable alternatives to SSRIs for the initial treatment of major depression include other second-generation antidepressants, such as serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, and serotonin modulators (table 4). Multiple reviews have concluded that the efficacy of different antidepressants is generally comparable across and within classes [8,57,71-73], and that there are no robust or replicated results that have established clinically meaningful differences [8,71,74]. Tricyclic antidepressants and monoamine oxidase inhibitors are typically not used as initial treatment because of concerns about safety (particularly in overdose) and adverse effects.

Although sertraline is one of the most widely prescribed SSRIs [69], and there is evidence that suggests escitalopram and sertraline provide the best combination of efficacy and acceptability [75], each SSRI (table 4 and table 5) is suitable for the initial treatment of depression.

Studies that suggest antidepressants (including SSRIs) differ in their efficacy include a network meta-analysis of 117 randomized trials (mean duration eight weeks), which compared 12 second-generation antidepressants in nearly 26,000 patients with unipolar major depression [75]. The investigators concluded that escitalopram and sertraline showed the best combined profile of efficacy and acceptability, based upon the findings that:

- Response (reduction of baseline symptoms ≥50 percent) was more probable with escitalopram, mirtazapine, sertraline, and venlafaxine, compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine.
- Discontinuation of treatment for any reason was less probable with citalopram, escitalopram, and sertraline, compared with other antidepressants.

However, a second network meta-analysis (93 randomized trials, >20,000 patients with unipolar major depression) evaluated 13 second-generation antidepressants and concluded that there were no substantial differences in efficacy and discontinuation rates [71,74]. In contrast to the first network meta-analysis, the second one excluded trials with a high risk of bias and open label designs. The primary findings from the second study included the following:

- Most of the differences between antidepressants that were found in the first study were not replicated in the second study.
- Although the second study did find a few statistically significant differences, these were judged to be small and not clinically relevant. As an example, improvement was greater with escitalopram than citalopram, but the average difference on the Montgomery-Asberg Depression Rating Scale (figure 1A-C), which ranges in score from 0 to 60 points, was 1.5 points.

Information about interpreting results from conventional and network meta-analyses is discussed separately. (See "Systematic review and meta-analysis", section on 'Meta-analysis'.)

Onset of action may be faster with mirtazapine than other antidepressants [76]. A systematic review identified seven randomized trials that found response occurred sooner with mirtazapine than citalopram, fluoxetine, paroxetine, or sertraline [71,74]. However, all of the studies were funded by the manufacturer of mirtazapine, and after four weeks, response rates were generally comparable.

Most depressed patients who are treated with antidepressants require continuation treatment, and beyond that, maintenance treatment may be indicated as well. However, randomized trials have found no evidence that one antidepressant is superior in preventing relapse or recurrence. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Antidepressant medications'.)

Given the lack of clear superiority in efficacy among antidepressants, selecting a drug is based upon other factors, such as [8,77]:

- Safety
- Side effect profile (table 5)
- Specific depressive symptoms
- Comorbid illnesses
- Concurrent medications and potential drug-drug interactions
- Ease of use (eg, frequency of administration)
- Patient preference or expectations

- Cost
- Patient response to antidepressants during prior depressive episodes
- Family (eg, first degree relative) history of response to antidepressants

As an example, bupropion is useful for patients who prefer to avoid sexual dysfunction or want treatment for comorbid tobacco dependence, citalopram and escitalopram may be less likely to cause drug-drug interactions, and mirtazapine is often not used for patients who want to avoid weight gain [71,74,78]. In addition, bupropion may be less effective for patients with co-occurring anxiety [79]. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management" and "Pharmacotherapy for smoking cessation in adults", section on 'Bupropion' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions' and 'Side effects' below.)

Specific interactions between antidepressants and concomitant medications can be determined using the Lexicomp drug interactions tool included in UpToDate. This tool can be accessed from the UpToDate online search page or through the individual drug information topics in the section on Drug interactions.

Patient response to antidepressants during prior episodes and family history of response to antidepressants are often used in choosing an antidepressant. However, there is little evidence that patient outcomes are improved by selecting an antidepressant on the basis of these factors.

Clinicians should also bear in mind that nonspecific factors (eg, conveying empathy, establishing rapport, developing a therapeutic alliance and sense of collaboration, and instilling hope) may affect patient outcomes as much as the choice of antidepressant [39].

One preliminary study found that low baseline levels of C reactive protein (<1 mg/L) were associated with a better response to escitalopram than nortriptyline, whereas higher baseline levels were associated with a better response to nortriptyline [80]. Nevertheless, the use of biomarkers to select initial treatment for depression is not standard practice.

Side effects — For initial treatment of depression, it is important to select medications that patients can tolerate at doses sufficient to achieve remission. Self-report scales are available for eliciting antidepressants side effects during treatment. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Adverse side effects scale'.)

Although some adverse effects (eg, gastrointestinal toxicity) (table 5) are common across second-generation antidepressants, the incidence of specific side effects during short-term treatment (eg, 6 to 12 weeks) differs among drugs [71,74]:

- **Diarrhea** occurs more often with sertraline than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine (16 versus 8 percent of patients).

- **Nausea and vomiting** occurs more often with venlafaxine than SSRIs as a class (33 versus 22 percent).

- **Sexual dysfunction** occurs less often with bupropion than escitalopram, fluoxetine, paroxetine, and sertraline (6 versus 16 percent; paroxetine is especially problematic). (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

- **Somnolence** occurs more often with trazodone than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine (42 versus 25 percent).

- **Weight gain** is greater with mirtazapine (0.8 to 3.0 kg after six to eight weeks of treatment) than fluoxetine, paroxetine, trazodone, and venlafaxine.

Although antidepressants may be associated with an increased risk of diabetes, the evidence is not compelling, and the possible association should not deter clinicians from using antidepressants when indicated. A nested case-control study found that in approximately 166,000 patients with depression and no sign of diabetes, long-term (>24 months) use of an antidepressant in moderate to high doses was associated with an increased risk of diabetes (incidence rate ratio 1.8, 95% CI 1.4-2.5) [81]. However, depression itself may be a risk factor for developing diabetes. In a prospective observational study of people 65 years and older (n = 1000), who were followed for up to 10 years, depressed individuals were more than twice as likely to develop diabetes compared with those without depression, regardless of antidepressant treatment (hazard ratio 2.3, 95% CI 1.3-4.1) [82].

A retrospective study found that antidepressants were associated with stroke [83]. Problems with the study, including confounds and the possibility of reverse causality, lead us to suggest that clinicians should not change their practice with regard to this issue until better designed studies have been conducted. Information about SSRIs and stroke is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Bleeding'.)

Antidepressants can rarely injure the liver. A review of 158 studies estimated that among patients taking antidepressants, asymptomatic mild elevation of serum aminotransferases occurs in 0.5 to 1 percent of patients taking SSRIs or serotonin-norepinephrine reuptake inhibitors, and up to 3 percent of patients taking MAOIs or tricyclics [84]. Liver failure leading to

liver transplantation or death has also been reported. Hepatotoxicity generally appears within the first six months of treatment, and can manifest with anorexia, fatigue, nausea, and weakness. Although antidepressant-induced liver injury is generally idiosyncratic, unpredictable, and not related to dose, patients who are older adults or taking multiple medications may be at higher risk. Initial management of drug-induced liver injury is withdrawal of the offending drug. Additional information about drug-induced liver injury, including hepatotoxicity due to agomelatine and nefazodone, are discussed separately. (See "Drug-induced liver injury" and "Atypical antidepressants: Pharmacology, administration, and side effects" and "Serotonin modulators: Pharmacology, administration, and side effects".)

Additional information about side effects of antidepressants is discussed separately in the drug information topic for each drug, as well topics that review antidepressant classes.

Dose — We suggest starting antidepressants at low doses in order to reduce side effects and improve adherence [85]; typical starting doses are shown in a table (table 4). However, doses lower than the typical starting doses may further reduce adverse effects, particularly in older patients and those sensitive to side effects. As an example, depressed patients with comorbid anxiety disorders who are started on SSRIs may better tolerate half of the usual starting dose. The dose can then be titrated up to the minimum usual total daily dose (therapeutic dose).

For depressed patients who do not respond to the minimum therapeutic dose of SSRIs, most clinicians increase the dose within the therapeutic dose range [70,86,87], which is consistent with suggestions in multiple practice guidelines [8,18,72,88]. Evidence that supports this approach includes a meta-analysis of 40 randomized trials that compared different doses of SSRIs with placebo in patients with unipolar major depression (n>10,000) [89]. The analyses found that improvement with SSRIs was statistically greater at higher doses than lower doses, and that the increased efficacy with higher doses outweighed the higher rate of treatment discontinuation due to side effects. Nevertheless, the clinical benefit of higher doses was small and appeared to plateau (eg, at approximately 50 mg/day with fluoxetine or paroxetine). In addition, there is a risk of QTc interval prolongation with higher doses of citalopram. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Citalopram'.)

Some patients benefit from doses that exceed the maximum therapeutic dose, provided the drug is safely tolerated. Patients receiving high doses should be regularly monitored for side effects and nonadherence [72]. (See "Unipolar depression in adults and initial treatment: General principles and prognosis", section on 'Adherence to treatment'.)

Additional information about starting doses, titration schedules, and target doses of antidepressants (table 4) is discussed in topics that review antidepressant classes.

Pharmacogenetics — Genetic factors may influence antidepressant pharmacokinetics, including metabolism, which in turn can affect the dose required to achieve a therapeutic serum concentration [90].

Patients may rapidly metabolize drugs due to genetic polymorphisms of hepatic enzymes and thus require larger doses [91]. Reviews have noted that the prevalence of increased CYP2D6 metabolism in different racial and ethnic groups was as follows [86,90]:

- African Americans – 5 percent
- Asian Americans – rarely seen
- Ethiopians (Black population) – 16 to 29 percent
- Saudi Arabians – 20 percent
- White population:
    - Spain – 7 to 10 percent
    - Sweden – 1 to 2 percent
    - United States – 4 percent

Conversely, other hepatic isoenzymes may slowly metabolize antidepressants; patients with these genetic variants need lower doses. As an example, the US Food and Drug Administration has warned that patients with CYP2C19 variants that poorly metabolize citalopram should receive no more than 20 mg per day, due to the risk of QT interval prolongation. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Citalopram'.)

Additional information about the role of genetic factors in drug metabolism and response is discussed separately. (See "Overview of pharmacogenomics".)

Early improvement and response — Among patients with unipolar major depression who start antidepressants, improvement is often apparent within one to two weeks [92-94]:

- A meta-analysis of 28 randomized trials (n>5000 patients with unipolar major depression) that compared SSRIs with placebo found that superior improvement with SSRIs occurred within one week [95].

- A pooled analysis of four randomized trials found that the mean time to improvement (reduction of baseline symptoms ≥20 percent) in patients treated with antidepressants (n>2000) was approximately 13 days [96].

Early improvement during initial treatment of depression with antidepressants may predict eventual remission [97-99]. A pooled analysis of 41 randomized trials (n>6000 patients with unipolar major depression who were generally treated for six weeks) found that early improvement (reduction of baseline symptoms within the first two weeks of treatment ≥20 percent) was a sensitive predictor of eventual remission (range 87 to 100 percent, depending upon the specific treatment) [100]. Among all the patients who remitted, more than 90 percent were early improvers.

Duration of an adequate trial — We generally treat unipolar major depression for 6 to 12 weeks before deciding whether antidepressants have sufficiently relieved symptoms [101-103]. However, for patients who show little improvement (eg, reduction of baseline symptoms ≤25 percent) after four to six weeks, it is reasonable to administer next-step treatment [104]. Our approach, which is consistent with multiple practice guidelines [8-10,88], is based upon the following:

- The large majority of randomized antidepressant trials for the initial treatment of unipolar major depression last 6 to 12 weeks [74,105]. In addition, the prospective Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which treated a sample that was more generalizable than is typically enrolled in randomized trials, found that among 943 patients who were treated with open-label citalopram, nearly 25 percent required 10 or 12 weeks of treatment to achieve remission [106]. Other prospective observational studies (n = 804 and 627) found that many patients required 8 to 12 weeks to substantially improve or remit [107,108].

- A meta-analysis of 28 randomized trials (n>5000 patients with unipolar major depression) that compared SSRIs with placebo found that the advantage of SSRIs over placebo continued to increase for at least six weeks of treatment, but at a progressively smaller rate [95].

- A 16-week study enrolled 566 patients with unipolar major depression who were initially treated with open label escitalopram (10 mg per day) for four weeks and showed minimal improvement (<30 percent reduction of baseline symptoms) [109]. Patients were randomly assigned to switch immediately to duloxetine (60 to 120 mg per day) for 12 weeks, or to continue escitalopram (10 to 20 mg per day) for another four weeks. Patients who received escitalopram for eight weeks were then evaluated for response (reduction of baseline symptoms ≥50 percent); responders remained on escitalopram for the duration of the trial, whereas nonresponders switched to duloxetine. Remission at week 16 occurred in more patients who switched immediately after four weeks of open-label treatment,

compared with patients who were assigned to the other treatment strategy (43 versus 36 percent).

- An eight-week, prospective, observational study examined response (reduction of baseline symptoms ≥50 percent) to fluoxetine 20 mg per day in 143 patients with unipolar major depression [110]. Among patients who showed minimal improvement (reduction of baseline symptoms ≤20 percent) by week 4, response by week 8 occurred in 19 percent. Among patients who showed minimal improvement by week 6, response by week 8 occurred in 7 percent.

Next-step treatments for patients unresponsive to initial treatment of depression are discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

Primary care patients — Primary care patients with unipolar major depression can benefit when antidepressant treatment occurs within the context of collaborative care. Collaborative care involves treating patients with a team that usually includes a primary care clinician (who prescribes antidepressants), a case manager who provides support and outreach to patients, and a mental health specialist (eg, psychiatrist) who provides consultation and supervision. Meta-analyses of randomized trials have shown that depression outcomes are superior with collaborative care, compared with usual care (antidepressants alone). In addition, treating depressed primary care patients in the context of collaborative care is consistent with recommendations by the American College of Physicians [111]. Nevertheless, antidepressants alone or psychotherapy alone are reasonable alternatives to collaborative care for patients who are treated in primary care settings.

The evidence for the efficacy of collaborative care for treating depression in primary care patients and in the context of general medical illnesses is discussed separately. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)

PSYCHOTHERAPY

Treatment options — Psychotherapies that are available to treat unipolar major depression include [8,18,55,112-115]:

- Cognitive-behavioral therapy (CBT) (see "Overview of psychotherapies", section on 'Cognitive and behavioral therapies')

- Interpersonal psychotherapy (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")
- Behavioral activation
- Family and couples therapy (see "Unipolar depression in adults: Family and couples therapy")
- Problem solving therapy (see "Overview of psychotherapies", section on 'Integrated primary and specialty care')
- Psychodynamic psychotherapy (see "Unipolar depression in adults: Psychodynamic psychotherapy")
- Supportive psychotherapy (see "Unipolar depression in adults: Supportive psychotherapy")

Selecting a specific psychotherapy — Among the major psychotherapies, there is no compelling evidence that one is superior to the rest [47,116,117]; thus, the choice is usually made upon the basis of availability and patient preference. CBT and interpersonal psychotherapy are frequently selected for the initial treatment of unipolar depression because they have been more widely studied than other types of psychotherapies [8,55,118-120].

Randomized trials studying various psychotherapies for unipolar depression indicate that differences in efficacy are at most minor [116,121]. As an example, a network meta-analysis of 198 trials (n>15,000 depressed patients) compared the efficacy of seven psychotherapies (behavioral activation, cognitive-behavioral therapy, interpersonal psychotherapy, problem solving therapy, psychodynamic therapy, social skills training, and supportive therapy) [122]. The primary findings were as follows:

- Each therapy was superior to the waiting list control condition, and the clinical benefits were moderate to large.
- Each therapy (except social skills training) was superior to usual care, with clinical benefits that were small to moderate.
- The benefits of each therapy were generally comparable.

Family and couples therapy can also be effective for patients with major depression. (See "Unipolar depression in adults: Family and couples therapy", section on 'Evidence of efficacy'.)

In addition, different psychotherapies often overlap with each other. As an example, techniques from supportive psychotherapy have been adopted by other psychotherapies, such as psychodynamic psychotherapy [123,124]. Another example is behavioral activation, which is derived from and represents the behavioral component of cognitive-behavioral therapy [125].

Adherence — Among patients with depression who commence psychotherapy, early dropout is common (just as it is with pharmacotherapy). Clinicians referring a patient for psychotherapy should thus follow up regarding adherence and effectiveness, just as they would when starting a medication.

SUPPORTIVE CARE

Clinician-guided self-help — For initial treatment of milder episodes of unipolar major depression, clinician-guided self-help therapy is a reasonable alternative to psychotherapy that is administered face-to-face by a therapist each session. Clinician-guided self-help therapy relies upon structured workbooks (hardcopy, compact disc, or internet-based), audiotapes, or videotapes, and involves minimal, intermittent contact with a clinician or paraprofessional who provides encouragement and monitors progress [126].

Evidence supporting the use of clinician-guided self-help for depression includes randomized trials [126,127]. A meta-analysis of individual patient data from 13 trials (n>2400 patients) compared clinician-guided self-help therapy with usual care and found that active treatment provided a significant, small to moderate clinical benefit [128]. In addition, patients with moderate depression at baseline appeared to benefit at least as much as mildly ill patients.

The use of clinician-guided self-help therapy for initial treatment of milder episodes of depression is consistent with multiple practice guidelines [18,55].

Relaxation and positive activities — For patients with unipolar major depression, we suggest adding relaxation techniques (eg, progressive muscle relaxation or relaxation imagery [imagining beautiful or peaceful places], or autogenic training [visualizing and inducing a state of warmth and heaviness throughout the body]) to the primary treatment regimen. A meta-analysis of five randomized trials (136 patients) compared relaxation with no treatment and found a clinically moderate benefit favoring relaxation [129]. However, a second analysis of nine trials (286 patients) found that relaxation was less effective than psychotherapy (primarily cognitive-behavioral therapy) [129].

Clinicians should also encourage patients to pursue positive activities ("behavioral activation") that may have ceased due to depression. Patients may take the position that they will engage in

those activities after they are less depressed; clinicians need to explain that engaging in these activities is a means of relieving depression.

Exercise

- **Our approach** – We suggest exercise as adjunctive treatment for patients with unipolar major depression, based upon randomized trials suggesting a moderate impact of exercise on depression symptoms and limited harms.

  For patients with mild depression (ie, Patient Health Questionnaire – Nine Item score 5 to 9), exercise is a reasonable alternative to treatment with psychotherapy or antidepressants; although, clinicians should regularly monitor patients (eg, every four weeks) for worsening symptoms.

  To help improve symptoms of depression, we suggest that clinicians prescribe exercise in the following manner [130]:

  - Modality:

    - Moderate or vigorous aerobic exercise (eg, brisk walking, running, or cycling) to achieve 50 to 85 percent maximum heart rate and/or
    - Resistance training (upper and lower body weightlifting involving all major muscle groups)

  - Session frequency and duration – 30- to 60-minute sessions three to five times per week.

  - Intervention duration – At least 10 weeks. We encourage patients to continue exercising indefinitely, provided there are no contraindications.

  - Supervision – Because the evidence base for depression treatment is most robust for supervised exercise interventions, we suggest supervised or group exercise if possible. Supervision may help to motivate patients and minimize injury.

  Exercise also provides additional health benefits, particularly in patients with other chronic medical conditions. Alterative exercise regimens may provide optimal benefit for preventing or treating specific health conditions (eg, more intense aerobic exercise for optimal cardiovascular health). (See "The benefits and risks of aerobic exercise", section on 'Benefits of exercise' and "Exercise and fitness in the prevention of atherosclerotic cardiovascular disease", section on 'Our approach'.)

Additional information about exercise regimens is discussed separately. (See "Exercise prescription and guidance for adults".)

- **Evidence** – Meta-analyses of randomized trials suggest that exercise has a small to moderate effect on depression symptoms; although, conclusions are limited by variability in study design and risk of bias in many studies. Although earlier studies found no benefit from exercise [130-133], subsequent meta-analyses suggest that exercise is beneficial in reducing depression symptoms [134-136].

  As an example, in a meta-analysis of 41 randomized trials (2264 participants), exercise interventions improved depression symptoms compared with nonactive controls, and the clinical effect was large (standardized mean difference = -0.946, 95% CI -1.18 to -0.71) [135]. The effect size was comparable with that found in meta-analyses of psychotherapy and antidepressants, and the estimated number needed to treat to produce a clinically meaningful improvement in symptoms was two. Similar results were seen for both aerobic and resistance exercise. Supervised exercise programs were more effective than nonsupervised interventions. The study found smaller effects when restricting analyses to trials with low risk of bias. Included trials demonstrated substantial clinical and statistical heterogeneity. Two earlier meta-analyses reported similar results [134,136].

Adherence to exercise or selective serotonin reuptake inhibitors appears comparable [130]. Strategies for improving adherence with exercise include altering the type and frequency of activity according to patient preferences, motivational interviewing (motivating the patient to exercise by eliciting both the patient's reasons to do so and the patient's ambivalence about change), goal setting, and providing feedback to patients. Motivational interviewing is discussed separately. (See "Overview of psychotherapies", section on 'Motivational interviewing'.)

Prescribing exercise as adjunctive treatment or monotherapy is consistent with multiple practice guidelines [8,137,138].

SPECIAL CIRCUMSTANCES

Older adults — Treatment of depression in older adults is discussed separately. (See "Diagnosis and management of late-life unipolar depression".)

Pregnancy — Treatment of depression in pregnant women is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

SEVERE MAJOR DEPRESSION

Severe major depression is characterized by seven to nine depressive symptoms (table 1) that occur nearly every day, as indicated by a score ≥20 points on the Patient Health Questionnaire – Nine Item (PHQ-9) (table 3). The PHQ-9 is a self-report assessment that is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Severely ill patients often report suicidal ideation and behavior, typically demonstrate obvious impairment of functioning, are more likely to develop complications such as psychotic features and catatonic features, and should be referred to a psychiatrist for management. Severe major depression sometimes requires hospitalization [8]. Additional information about treating major depression with psychotic features or catatonia is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Catatonia: Treatment and prognosis".)

Choosing a treatment regimen — For patients with severe unipolar major depression, we suggest initial treatment with the combination of pharmacotherapy and psychotherapy, based upon several randomized trials in the general population of patients with unipolar major depression (see 'Efficacy of antidepressants plus psychotherapy' above). In addition, a randomized trial compared interpersonal psychotherapy plus an antidepressant (sertraline or amitriptyline) with clinical management (psychoeducation and support) plus an antidepressant in patients (n = 124) with major depression who were hospitalized for five weeks [139]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with adjunctive interpersonal psychotherapy than clinical management (70 versus 51 percent), and improvement of functioning was also superior with interpersonal psychotherapy. In addition, the benefits of interpersonal psychotherapy persisted for up to 12 months.

However, a reasonable alternative to combination therapy for severe major depression is pharmacotherapy alone, based upon randomized trials in patients with severe depression (see 'Choosing an antidepressant' below), as well as trials in the general population of patients with unipolar major depression. (See 'Efficacy of antidepressants' above.)

Another reasonable alternative to combination therapy for the initial treatment of severe major depression is electroconvulsive therapy (ECT), especially for patients who require a fast response (eg, patients with suicidal ideation or behavior that is life-threatening) [18]. Meta-analyses of randomized trials indicate that ECT is more efficacious than any other treatment for severe major depression [140-143]. However, ECT is associated with safety risks, adverse effects,

logistical constraints, and patient refusal; in addition, relapse rates following remission are high [144,145]. 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 administering 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".)

The use of pharmacotherapy plus psychotherapy, pharmacotherapy alone, or ECT for the initial treatment of severe unipolar major depression is consistent with multiple practice guidelines, including those from the American Psychiatric Association and the United Kingdom National Institute for Health and Care Excellence (NICE) [8,9,18,146].

Open label randomized trials in patients hospitalized for unipolar major depression suggest that adjunctive exercise [147,148] (see 'Exercise' above) or adjunctive bright light therapy [149] may be helpful.

Choosing an antidepressant — For the initial treatment of severe unipolar major depression, we use serotonin-norepinephrine reuptake inhibitors or selective serotonin reuptake inhibitors (SSRIs). Evidence for the efficacy of this approach includes a review of randomized trials in patients with severe depression, which found that serotonin-norepinephrine reuptake inhibitors and SSRIs were each superior to placebo [150]. In addition, randomized trials have demonstrated that antipsychotics combined with either serotonin-norepinephrine reuptake inhibitors or SSRIs are efficacious for unipolar major depression with psychotic features. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Choosing a combination'.)

We typically start with serotonin-norepinephrine reuptake inhibitors, based upon a review of meta-analyses of randomized trials, which found that severe unipolar major depression responds better to serotonin-norepinephrine reuptake inhibitors than SSRIs [151]. As an example:

- A meta-analysis of 31 trials compared venlafaxine with SSRIs (primarily fluoxetine and paroxetine) in 656 patients with severe depression, as indicated by a score ≥30 on the 17 item Hamilton Rating Scale for Depression (table 2) [152]. Remission occurred more often in patients treated with venlafaxine (odds ratio 1.6, 95% CI 1.1-2.2).

- A pooled analysis of 15 trials (n>1700 patients) compared serotonin-norepinephrine reuptake inhibitors (duloxetine, milnacipran, and venlafaxine) with SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) [153]. In the subgroup of hospitalized

patients (n = 436), remission occurred in more patients who received serotonin-norepinephrine reuptake inhibitors than SSRIs (52 versus 29 percent). This was consistent with the finding that remission was greater in outpatients who received serotonin-norepinephrine reuptake inhibitors.

A reasonable alternative to serotonin-norepinephrine reuptake inhibitors or SSRIs is mirtazapine [31]:

- A six-week randomized trial compared mirtazapine (24 to 72 mg per day) with trazodone (150 to 450 mg per day) in 200 patients hospitalized for major depression [154]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with mirtazapine than trazodone (78 versus 61 percent). Although mirtazapine was generally well tolerated, one patient completed suicide and two suicide attempts occurred in the mirtazapine group.

- An eight-week randomized trial compared mirtazapine (mean dose 50 mg per day) with venlafaxine (mean dose 255 mg per day) in 157 inpatients and found that response was comparable (62 and 52 percent) [155]. In addition, discontinuation of treatment due to adverse effects occurred in fewer patients who received mirtazapine than venlafaxine (5 versus 15 percent).

Tricyclic antidepressants are another reasonable alternative, based upon randomized trials that suggest tricyclics are more efficacious than other antidepressants for severely depressed patients. However, tricyclics are frequently avoided due to their greater safety hazards (eg, cardiotoxicity and potential lethality with overdose) and less favorable side effect profiles. Evidence that indicates tricyclics (particularly amitriptyline, clomipramine, and imipramine) are beneficial for severely depressed patients includes the following studies [9,34]:

- A meta-analysis of 104 randomized trials compared amitriptyline with other antidepressants (including other tricyclics) in depressed patients (n>7400) [156]. In the subgroup of 54 randomized trials that enrolled hospitalized patients (sample size not provided), response was more likely with amitriptyline than other antidepressants (odds ratio 1.22, 95% CI 1.04-1.42) and tolerability was comparable. This was consistent with the finding that response was more likely with amitriptyline in the total sample.

- A meta-analysis of 25 randomized trials compared tricyclics (amitriptyline, clomipramine, desipramine, imipramine, and maprotiline) with SSRIs (citalopram, fluoxetine, fluvoxamine, and paroxetine) for treating depression in 1377 hospitalized patients [157]. Improvement was greater with tricyclics than SSRIs, but the clinical difference was small and heterogeneity across studies was significant. In addition, the pooled analysis found that

discontinuation of treatment due to adverse effects occurred in more patients treated with tricyclics than SSRIs (14 versus 9 percent).

The pharmacology, administration, and side effects of serotonin-norepinephrine reuptake inhibitors, SSRIs, mirtazapine, and tricyclics are discussed separately. (See 'Treatment options' above.)

PERSISTENT DEPRESSIVE DISORDER

Persistent depressive disorder (dysthymia) is characterized by dysphoria and at least two other depressive symptoms occurring on more days than not, lasting for two or more years [5]. The diagnosis of persistent depressive disorder subsumes the previously used diagnoses of dysthymic disorder and chronic major depression (major depression lasting for at least two years). The diagnosis of dysthymic disorder is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Persistent depressive disorder (dysthymia)'.)

Choosing a treatment regimen — For initial treatment of persistent depressive disorder, we suggest the following treatment regimens in order of preference, based upon randomized trials:

- Pharmacotherapy plus psychotherapy
- Pharmacotherapy alone
- Psychotherapy alone

The choice of a specific antidepressant drug and/or specific psychotherapy for initial treatment of persistent depressive disorder is similar to selecting a specific drug and psychotherapy for unipolar major depression (see 'Selecting a specific antidepressant' above and 'Selecting a specific psychotherapy' above). Selective serotonin reuptake inhibitors (SSRIs) have been widely studied for persistent depressive disorder, and cognitive behavioral therapy and interpersonal psychotherapy have been more widely studied for persistent depressive disorder than other types of psychotherapies.

Efficacy of treatment — Evidence for the efficacy of antidepressants plus psychotherapy for persistent depressive disorder includes a meta-analysis of nine trials (nearly 1600 patients with chronic major depression or dysthymic disorder) that compared combination treatment with pharmacotherapy alone and psychotherapy alone; the primary findings were as follows [158]:

- There was a trend for greater improvement with combined treatment than pharmacotherapy alone.

- Improvement was superior with combined treatment than psychotherapy alone, and the difference was moderately large such that combination treatment provided one additional positive outcome for every four patients treated with each regimen (number needed to treat of four). Heterogeneity across studies was moderate.

- Discontinuation of treatment for any reason was comparable for combined treatment, pharmacotherapy alone, and psychotherapy alone.

In addition, many randomized trials have demonstrated that in the general population of patients with major depression, combining antidepressants and psychotherapy is superior to either pharmacotherapy alone or psychotherapy alone. (See 'Efficacy of antidepressants plus psychotherapy' above.)

Pharmacotherapy alone is superior to placebo in patients with persistent depressive disorder:

- A meta-analysis of 20 randomized trials (n>2900 patients with depression lasting at least two years) found that remission was greater with SSRIs or tricyclics than with placebo, and was comparable for SSRIs and tricyclics [159]. However, discontinuation of treatment as well as adverse effects occurred less often with SSRIs than tricyclics.

- A pooled analysis of nine randomized trials (n>1400 patients with dysthymic disorder) compared antidepressants with placebo and found that response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with antidepressants than placebo (52 versus 30 percent) [22].

- A network meta-analysis, which used indirect as well as direct comparisons between treatments, found that many antidepressants (amisulpride, fluoxetine, imipramine, moclobemide, paroxetine, ritanserin, and sertraline) were superior to placebo for treatment of persistent depressive disorder [160].

Also, pharmacotherapy alone is generally superior to psychotherapy alone for persistent depressive disorder [15,52,54,56]. As an example, a meta-analysis of eight randomized trials (n>1200 patients with chronic major depression or dysthymic disorder) found a significant, but clinically small effect favoring antidepressants over psychotherapy [158]. However, heterogeneity across studies was moderate [158], and the results of one randomized trial suggest that early childhood trauma (loss of parents at an early age or physical or sexual abuse) may be associated with better outcomes in patients receiving psychotherapy rather than antidepressants [161].

Evidence for the efficacy of psychotherapy alone for patients with persistent depressive disorder includes a meta-analysis of six randomized trials (362 patients with chronic major depression or dysthymic disorder), which found a significant, but clinically small effect favoring psychotherapy (primarily cognitive-behavioral therapy or interpersonal psychotherapy) over control conditions (primarily pill placebo) [158]. Randomized trials that studied interpersonal psychotherapy in patients with persistent depressive disorder (dysthymia) are discussed separately. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy", section on 'Dysthymic disorder'.)

DEPRESSION WITH MIXED FEATURES

Unipolar major depression and persistent depressive disorder (dysthymia) can be accompanied by subthreshold (not meeting full criteria) symptoms of hypomania or mania, and in such cases are referred to as major depression with mixed features and persistent depressive disorder with mixed features. Mixed features may be more common (though often unrecognized) in patients with depression who do not respond to conventional treatment. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Depressive episode subtypes (specifiers)'.)

Major depression with mixed features was not recognized as a distinct diagnostic category until publication of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in 2013 [5], so evidence regarding specific treatment is limited. We presume that mixed features imply a higher risk for antidepressants to precipitate hypomania or mania and may imply that monotherapy with conventional antidepressants is less effective. Consequently, we generally use medications such as second-generation antipsychotics, lithium, divalproex, or lamotrigine, rather than antidepressants.

One high-quality study regarding treatment of depression with mixed features is a six-week randomized trial that compared lurasidone with placebo in 208 patients with unipolar major depression with mixed features (two or three manic/hypomanic symptoms) [162]. Improvement of both depressive and manic symptoms was greater with lurasidone, and remission occurred in more patients with lurasidone than placebo (49 versus 23 percent). Several adverse effects also occurred more frequently with lurasidone, including nausea, somnolence, akathisia, dizziness, dry mouth, and Parkinsonism; however, discontinuation of treatment due to adverse effects was comparable with lurasidone and placebo (3 and 5 percent). This trial supports the use of lurasidone but does not imply that lurasidone is superior to other second-generation antipsychotics, lithium, divalproex, or lamotrigine.

MINOR DEPRESSION

Management and treatment of minor depression are discussed separately, as are the clinical features and diagnosis. (See "Unipolar minor depression in adults: Management" and "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis".)

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: Coping with high drug prices (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)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Choosing a treatment regimen** – For the initial treatment of unipolar major depression, we suggest pharmacotherapy plus psychotherapy, rather than pharmacotherapy alone or psychotherapy alone (**Grade 2B**). However, pharmacotherapy alone and psychotherapy alone are reasonable alternatives. Many specific antidepressant-psychotherapy combinations are available, and the superiority of any particular combination has not been established. (See 'Choosing a treatment regimen' above.)

  Choosing an antidepressant – Several classes of antidepressants (table 4) are available to treat unipolar major depression, and the efficacy of different antidepressants is generally comparable across and within classes. Choosing a drug is thus based upon other factors, including safety, side effect profile (table 5), comorbid illnesses, concurrent medications and potential drug-drug interactions, ease of use, patient preference, and cost.

  For patients with unipolar major depression who are initially treated with antidepressants, we suggest selective serotonin reuptake inhibitors (SSRIs) rather than other antidepressants (**Grade 2B**). However, serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, and serotonin modulators are reasonable alternatives. Tricyclic antidepressants and monoamine oxidase inhibitors are typically not used as initial treatment because of concerns about safety and adverse effects (table 5). (See 'Efficacy of antidepressants' above and 'Selecting a specific antidepressant' above and 'Side effects' above.)

  - **Antidepressant dose** – We typically start antidepressants at low doses (table 4) in order to reduce side effects. (See 'Dose' above.)

  - **Onset of improvement** – Among patients with unipolar major depression who start antidepressants, improvement is often apparent within two weeks. (See 'Early improvement and response' above.)

  - **Duration of an adequate trial** – We generally treat unipolar major depression for 6 to 12 weeks before deciding whether antidepressants have sufficiently relieved symptoms. However, for patients who show little improvement (eg, reduction of baseline symptoms ≤25 percent) after four to six weeks, it is reasonable to administer next-step treatment. (See 'Duration of an adequate trial' above.)

- **Choosing a psychotherapy** – Several psychotherapies are available to treat unipolar major depression. For patients with major depression who are initially treated with psychotherapy, we suggest cognitive-behavioral therapy (CBT) or interpersonal psychotherapy rather than other psychotherapies (**Grade 2C**). However, reasonable alternatives to CBT and interpersonal psychotherapy include behavioral activation, family and couples therapy, problem solving therapy, psychodynamic psychotherapy, and supportive psychotherapy. (See 'Efficacy of psychotherapy' above and 'Psychotherapy' above.)

- **Treating severe major depression** – A severe episode of major depression is characterized by seven to nine depressive symptoms (table 1) that are present nearly every day, as indicated by a score ≥20 points on the Patient Health Questionnaire – Nine Item (table 3). For patients with severe unipolar major depression, we suggest initial treatment with pharmacotherapy plus psychotherapy, rather than other treatment regimens (**Grade 2B**). However, a reasonable alternative is pharmacotherapy alone or electroconvulsive therapy (ECT). For patients with severe suicidality or malnutrition secondary to food refusal, we suggest ECT as initial treatment rather than other treatment regimens (**Grade 2B**). (See 'Choosing a treatment regimen' above and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)".)

  - **Choosing an antidepressant** – For patients with severe unipolar major depression who are treated with antidepressants, we suggest serotonin-norepinephrine reuptake inhibitors or SSRIs, rather than other antidepressants (**Grade 2B**). We typically start with serotonin-norepinephrine reuptake inhibitors. Reasonable alternatives include mirtazapine and tricyclic antidepressants. (See 'Choosing an antidepressant' above.)

- **Treating persistent depressive disorder** – Persistent depressive disorder is characterized by dysphoria and at least two other depressive symptoms lasting for two or more years. For patients with persistent depressive disorder, we suggest antidepressants plus psychotherapy rather than antidepressants alone or psychotherapy alone (**Grade 2C**). However, antidepressants (eg, SSRIs) alone are a reasonable alternative; psychotherapy alone is also reasonable for patients who prefer it. (See 'Persistent depressive disorder' above.)

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