Unipolar depression in adults: Continuation and maintenance treatment

AUTHORS: Robin B Jarrett, PhD, Jeffrey Vittengl, PhD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITORS: Sara Swenson, MD, David Solomon, MD

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INTRODUCTION

Continuation and maintenance treatment are generally indicated for patients with unipolar major depression because the illness is highly recurrent [1-3]. Standard treatments include pharmacotherapy, psychotherapy, or pharmacotherapy plus psychotherapy.

This topic reviews continuation and maintenance treatment for nonpsychotic, unipolar major depression in adults. Choosing a regimen for the initial treatment of depression and treatment of resistant depression is discussed separately, as is maintenance treatment of psychotic depression, geriatric depression, and pediatric depression.

- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar major depression with psychotic features: Maintenance treatment and course of illness".)
- (See "Diagnosis and management of late-life unipolar depression", section on 'Duration of treatment'.)
- (See "Overview of prevention and treatment for pediatric depression".)

DEFINITIONS

Unipolar major depression — Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania or hypomania [4]. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. Additional information about the clinical presentation and diagnosis of major depressive disorder is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis".)

Continuation and maintenance treatment — Continuation treatment and maintenance treatment are distinguished from each other, as are remission and recovery, and relapse and recurrence (table 1) [5,6]. Continuation treatment is administered after resolution of a major depressive episode to preserve and enhance remission, and prevent relapse of the presenting episode. Remission represents a period of time with minimal or no symptoms; the duration of this time period varies among different studies (eg, two to eight consecutive months) [4-8]. Continuation treatment is followed by maintenance treatment, which is provided after recovery from the presenting episode to prevent recurrence of new, subsequent episodes. Recovery is said to occur when patients remain well for a period of time exceeding the interval used to define remission.

However, there is no established cutoff that separates the end of remission from the beginning of recovery; thus, the distinction between continuation and maintenance treatment is not standardized [9]. Many studies therefore use the terms "continuation treatment" and "maintenance treatment" interchangeably to describe treatment that is provided after patients respond to acute therapy. Likewise, "relapse" and "recurrence" are often used interchangeably because distinguishing relapse of the presenting episode from recurrence of a new episode is arbitrary and depends upon duration requirements for defining remission and recovery. Continuation treatment has been studied more frequently than maintenance treatment [10], and systematic reviews of "maintenance treatment" typically include both continuation and maintenance trials [11-13].

Additional information about recovery from and recurrence of major depressive episodes is discussed separately. (See "Unipolar depression in adults: Course of illness".)

RELAPSE/RECURRENCE IN THE ABSENCE OF TREATMENT

Relapse and recurrence (table 1) are common in patients with unipolar major depression [14], including acutely ill patients who remit/recover with treatment and then discontinue it [1,2]:

- In a meta-analysis of 11 randomized trials that included 1019 patients who were successfully treated with acute pharmacotherapy and then assigned to placebo, relapse/recurrence occurred within one year in 51 percent and within two years in 62 percent [15].

- In a meta-analysis of 13 randomized and observational studies that included 364 patients with major depression who were successfully treated with acute cognitive-behavioral therapy (CBT) and received no subsequent treatment, relapse and recurrence during follow-up (mean 74 weeks) occurred in 39 percent [11]. By two years, the estimated rate was 54 percent.

Patients acutely ill with unipolar major depression who improve with pharmacotherapy and subsequently discontinue it are generally at greater risk for relapse/recurrence than patients who improve with and discontinue CBT:

- A meta-analysis of eight randomized trials (393 patients followed for up to one year) found that the probability of remaining well was greater in patients treated acutely with CBT than pharmacotherapy (odds ratio 2.6, 95% CI 1.6-4.3) [16].

- In a meta-analysis of seven randomized and observational studies (335 patients with major depression) with a mean follow-up of 68 weeks, relapse/recurrence occurred in more patients who received acute pharmacotherapy than acute CBT (61 versus 39 percent) [11].

One hypothesis for the decreased risk of relapse/recurrence in patients treated with acute phase, depression-specific psychotherapy is that patients learn skills to resolve maladaptive thought patterns, respond more adaptively to stressful life events, and reduce their problematic behaviors [17,18]. After psychotherapy ceases, these changes may persist and forestall reemerging symptoms. By contrast, the neurochemical changes that occur with medications may dissipate if pharmacotherapy is stopped.

However, some data suggest that recurrence may be comparable in patients who respond to acute treatment with either pharmacotherapy or psychotherapy, and then discontinue it. One study enrolled patients who recovered from major depression with acute pharmacotherapy alone or pharmacotherapy plus CBT, and randomly assigned them to maintain pharmacotherapy or discontinue it; CBT was not administered beyond the acute phase [19].

Among patients who recovered with medication alone and stopped it (n = 69), and patients who recovered with medication plus CBT and stopped both treatments, the rate of recurrence over three years of follow-up was similar (75 and 77 percent).

Relapse and recurrence are also common in patients with unipolar major depression who are successfully treated with acute electroconvulsive therapy, but do not subsequently receive continuation/maintenance treatment. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Durability of response'.)

INDICATIONS

Continuation treatment (table 1) (lasting, for example, four months to less than a year) is generally indicated for patients who respond to acute treatment of unipolar major depression [1,2,18,20,21]. Additional maintenance treatment (lasting, for example, one to three years) is often indicated for patients with an increased risk of recurrence due to factors such as [22,23]:

- Childhood maltreatment (physical or sexual abuse, neglect, or family violence or conflict)
- Early age of onset of unipolar major depression (eg, ≤18 to 21 years of age)
- A lifetime history of at least two or three major depressive episodes
- Persistent or emergent residual depressive symptoms, especially sleep disturbances and/or suicidal ideation
- Comorbid anxiety disorders
- Prominent depressive cognitions, such as hopelessness or rumination
- Psychosocial stressors or impairment (eg, marital conflict or inability to work)

For patients with unipolar major depression who respond to acute therapy, continuation/maintenance treatment is consistent with multiple practice guidelines [24], including those from the American Psychiatric Association [1,2], United Kingdom National Institute of Health and Clinical Excellence [3], Canadian Network for Mood and Anxiety Treatments [25,26], British Association for Psychopharmacology [27], and World Federation of Societies of Biological Psychiatry [28].

However, patients with unipolar major depression who respond to acute treatment with cognitive-behavioral therapy (CBT) and are not at increased risk of relapse/recurrence may reasonably decline continuation treatment, if acute phase remission is stable [29]. Multiple

randomized trials indicate that acute phase CBT can provide enduring effects beyond the end of therapy [11,16,30]. The efficacy of continuation and maintenance CBT is described elsewhere in this topic. (See 'Cognitive-behavioral therapy' below.)

Patients with unipolar major depression who respond to acute treatment with behavioral activation may also reasonably decline continuation treatment, provided that they are not at increased risk of relapse/recurrence. Behavioral activation focuses on increasing rewarding activities, promoting behaviors that decrease rumination, and improving problem solving skills [31,32]. A one-year randomized trial found that relapse of major depression was comparable for patients who remitted with acute phase behavioral activation and received no further treatment (n = 27), and for patients who remitted with and continued paroxetine (maximum dose 50 mg per day; n = 28) [33].

Patients who recover from their first lifetime episode of unipolar major depression with acute and continuation pharmacotherapy may reasonably decline maintenance treatment, provided that the presenting episode was neither chronic nor severe, that remission was stable rather than marked by subsyndromal symptoms, that symptoms did not emerge during discontinuation of treatment, and that patients are not at increased risk of relapse/recurrence [1,2,28]. Support for this approach includes findings from a nationally representative survey in the United States that identified individuals with no lifetime history of major depression (n = 27,609) and individuals with a lifetime history of one uncomplicated major depressive episode (which did not include suicidal ideation, psychotic features, psychomotor retardation, or severe impairment, and remitted within six months; n = 418) [34]. During follow-up that lasted three years, the incidence of depressive episodes and suicide attempts was comparable for both groups.

CHOOSING TREATMENT

Acute unipolar major depression that resolves is generally managed with continuation treatment and maintenance treatment, which are distinguished from each other (table 1) [5,6] (see 'Continuation and maintenance treatment' above). The subsections below discuss choosing continuation and maintenance treatment.

Standard approach — For patients with unipolar major depression who respond to acute phase therapy, standard continuation and maintenance treatments (table 1) include pharmacotherapy, psychotherapy, or pharmacotherapy plus psychotherapy. The same treatment that was successfully used acutely is typically selected for continuation/maintenance treatment [1,2,35]. Pharmacotherapy alone has been most widely studied and used for acute

treatment and thus continuation and maintenance treatment as well because of convenience and availability [1,2,36]. Other factors to consider in choosing maintenance treatment include the patient's past response as well as that of family members, patient preference, and cost. The efficacy of standard continuation/maintenance treatments is discussed elsewhere in this topic. (See 'Efficacy' below.)

Continuation/maintenance pharmacotherapy for unipolar major depression generally includes antidepressant medications, which should be used at the same dose that achieves remission [1,2,35] (see 'Dose' below). Although selective serotonin reuptake inhibitors and tricyclics have been most widely studied, other reasonable options include serotonin-norepinephrine reuptake inhibitors, serotonin modulators (eg, vilazodone and vortioxetine), atypical antidepressants (eg, bupropion and mirtazapine), and monoamine oxidase inhibitors [12,13,37]. Head-to-head randomized trials do not indicate that any one medication or medication class is superior [37]. Patients may want to discontinue the acute phase antidepressant and switch to a different drug or to psychotherapy for continuation/maintenance treatment; indications for switching include adverse effects, specific residual depressive symptoms (eg, insomnia may respond to sedating medications), comorbid general medical conditions, and drug-drug interactions. Switching antidepressants and switching to psychotherapy are discussed separately. (See "Switching antidepressant medications in adults", section on 'Switching antidepressant medications' and 'Sequential treatment' below.)

During acute treatment of unipolar major depression, antidepressants may be augmented with other medications such as second-generation antipsychotics, lithium, triiodothyronine, or a second antidepressant [1,2]. However, there are no high-quality continuation/maintenance studies of medication combinations. Augmentation of antidepressants for acute treatment is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics" and "Unipolar depression in adults: Treatment with lithium" and "Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone" and "Unipolar depression in adults: Treatment with antidepressant combinations".)

For continuation phase treatment of major depression, cognitive-behavioral therapy (CBT) or interpersonal psychotherapy alone can be efficacious [1,2,26] (see 'Psychotherapy' below). However, the efficacy of maintenance phase pharmacotherapy may possibly exceed the efficacy of maintenance interpersonal psychotherapy [38-40]. (See 'Interpersonal psychotherapy' below.)

The most widely studied psychotherapy for continuation and maintenance treatment of unipolar major depression is CBT [26]. Other reasonable choices include interpersonal psychotherapy and mindfulness-based cognitive therapy. No head-to-head randomized trials

have compared different continuation/maintenance phase psychotherapies; thus, the choice frequently depends upon availability and patient preference. (See 'Psychotherapy' below.)

Randomized trials indicate that continuation and maintenance treatment with pharmacotherapy plus interpersonal psychotherapy is superior to either pharmacotherapy alone or interpersonal psychotherapy alone. (See 'Antidepressant medications plus interpersonal psychotherapy' below.)

Sequential treatment — Patients with unipolar major depression who successfully complete acute phase pharmacotherapy may switch to or add psychotherapy (eg, CBT or mindfulness-based cognitive therapy) for continuation/maintenance treatment; this strategy is called sequential treatment [26]. Switching from pharmacotherapy to depression-specific psychotherapy can be used to:

- Avoid adverse medication side effects
- Avoid potential teratogenic and postnatal risks of antidepressants
- Manage poor adherence with pharmacotherapy
- Resolve residual symptoms (eg, hopelessness)
- Improve interpersonal or occupational functioning

Adding psychotherapy to pharmacotherapy can be used for:

- Poor adherence
- Residual symptoms
- Impaired functioning

Evidence supporting the benefit of sequential treatment includes meta-analyses of randomized trials. As an example, a meta-analysis of 17 trials compared sequential treatment with a control treatment in patients with major depression who responded to acute phase pharmacotherapy (n >2200) [41]. In the sequential treatment group, patients received CBT or therapies based upon CBT (eg, mindfulness-based cognitive therapy), and antidepressants were either continued or were tapered and discontinued. The control groups received usual care, clinical management plus antidepressants, or clinical management alone. The primary findings were as follows:

- Across all 17 trials, relapse/recurrence occurred less often in patients who received sequential treatment than controls (relative risk 0.84, 95% CI 0.74-0.94).

- In 12 trials, sequential treatment consisted of psychotherapy plus continuation of antidepressants, and the control groups received antidepressants or usual care.

Relapse/recurrence occurred less often in patients who received sequential treatment (relative risk 0.82, 95% CI 0.71-0.95).

- In six trials, sequential treatment consisted of psychotherapy and discontinuation of antidepressants, and the control groups received antidepressants or clinical management alone. Relapse/recurrence tended to occur less often in patients who received sequential treatment, but the difference was not statistically significant (relative risk 0.86, 95% CI 0.71-1.04).

Additional evidence supporting sequential treatment includes a meta-analysis of patient-level data from four trials that included 714 depressed patients who remitted with antidepressant medication [42]. Patients were randomly assigned to either continuation/maintenance medication or to acute and continuation/maintenance psychotherapy (cognitive therapy or mindfulness-based cognitive therapy) with medication tapering and discontinuation. During follow-up lasting 65 to 104 weeks, relapse in the two groups was comparable (hazard ratio 0.9, 95% CI 0.6-1.2).

For patients with major depression who respond to acute phase cognitive therapy but remain at high risk for relapse, it is reasonable to stop cognitive therapy and initiate pharmacotherapy for continuation/maintenance treatment. As an example, a randomized trial compared fluoxetine (modal dose 40 mg per day) with placebo as continuation treatment for eight months in 155 patients who initially responded to acute phase cognitive therapy but remained at higher risk for relapse due to partial or unstable remission during acute phase therapy [43]. Relapse occurred in fewer patients who received fluoxetine than placebo (18 versus 33 percent).

DURATION

Acute unipolar major depression that resolves is generally managed with continuation treatment and maintenance treatment, which are distinguished from each other (table 1) [5,6] (see 'Continuation and maintenance treatment' above). The subsections below discuss the duration of continuation and maintenance treatment.

Continuation treatment — Continuation treatment occurs after acute treatment and serves to preserve and enhance remission and prevent relapse of the index episode (table 1) [5,6]. Remission represents a period of time with minimal or no symptoms; the duration of this time period varies among different studies (eg, two to eight consecutive months) [4-8]. (See 'Continuation and maintenance treatment' above.)

For patients with acute unipolar major depression who respond to antidepressant medications, we suggest continuation treatment (table 1) for four months to less than a year (eg, six months) to:

- Prevent relapse
- Eliminate residual symptoms (which are associated with relapse)
- Restore baseline psychosocial functioning

Evidence that supports continuation treatment for six months following response to acute treatment includes randomized trials:

- A pooled analysis of nine trials included patients (n >800) who initially were treated for one to two months with open-label antidepressants and responded; patients were then randomly assigned to continue antidepressants or switch to placebo for six months [12]. Relapse occurred in fewer patients who received antidepressants than placebo (15 versus 34 percent).

- A review identified 14 randomized trials that included patients (nearly 4000) who initially responded to open-label antidepressants during treatment generally lasting 6 to 12 weeks; patients were then randomly assigned to continue antidepressants or switch to placebo [44]. Each trial demonstrated that time to relapse was greater with antidepressants than placebo. However, after six months of continuation treatment, the difference in the rate of relapse between active treatment and placebo became less obvious, such that the proportion of patients in each group who were relapsing appeared to be comparable.

- A pooled analysis identified 45 randomized trials that included patients who initially were treated for 2 to 52 weeks with open-label antidepressants and responded; patients were then randomly assigned to continue antidepressants or switch to placebo [45]. Among the patients who received placebo (n >5000), the risk of relapse was minimal in patients who initially were treated and stabilized for six months with antidepressants before switching to placebo. By contrast, the risk of relapse was substantially greater for patients who received active treatment for a relatively short period (eg, six weeks) before switching to placebo.

The use of continuation treatment for six months is consistent with recommendations from treatment guidelines and reviews [1-3,25,28].

Maintenance treatment — Maintenance treatment follows continuation treatment and represents ongoing treatment after patients recover from acute unipolar major depression

(table 1) [5,6]. Recovery occurs when patients remain well for a period of time, which varies across different studies (eg, two to eight consecutive months) [4-8]. Maintenance treatment serves to prevent recurrence of new depressive episodes. (See 'Continuation and maintenance treatment' above.)

Patients with risk factors for recurrence should receive at least one to three years of maintenance treatment (table 1) following continuation treatment, as should patients who recover from a chronic (duration ≥2 years) or severe episode (eg, the episode includes a suicide attempt) (algorithm 1) [3,25,35]. Risk factors for recurrence are discussed elsewhere in this topic. (See 'Indications' above.)

Evidence supporting the use of maintenance treatment includes randomized trials lasting up to three years:

- A meta-analysis of 10 randomized maintenance trials lasting 18 to 36 months (703 recovered patients) found that recurrence occurred in fewer patients who received antidepressants than placebo (24 versus 63 percent) [12].
- In a subsequent study, 95 patients who remitted on randomly assigned monotherapy (antidepressants or cognitive therapy) subsequently received 21 months of maintenance treatment (continued medication or three cognitive therapy booster sessions/year) [23]. Recurrence did not differ with regard to type of treatment, and the mean rate of recurrence across all patients was 16 percent.

In addition, maintenance treatment for longer than three years may be efficacious. In a two-part study, 20 patients who were initially randomized to imipramine and remained well for three years were then randomized again to imipramine or placebo for two more years [46]. The mean time to recurrence was significantly longer with imipramine than placebo (99 versus 54 weeks).

Patients with a history of multiple (eg, three), chronic, or severe major depressive episodes, or with comorbid psychiatric and general medical disorders, are encouraged to maintain treatment indefinitely [1,2]. Such patients may be discouraged by the prospect of treatment that lasts “forever.” For these patients, it is important to emphasize the long-term nature of the relationship between the clinician and patient, and that the need for maintenance treatment will be reevaluated periodically (eg, annually) in light of the patient's progress in maintaining symptomatic and functional stability, as well as changes in risk factors for recurrence (eg, residual depressive symptoms or psychosocial stressors may resolve). It may be useful to help the patient conceptualize recurrent major depression as a chronic disease and to point out that other chronic illnesses such as hypertension, diabetes mellitus, and asthma often require life-time medications.

MONITORING PATIENTS

Patients receiving continuation and maintenance treatment (table 1) for unipolar major depression should be regularly monitored for reemerging symptoms, with particular emphasis upon suicidal ideation. Patients treated with pharmacotherapy are also evaluated for adverse side effects. For patients who remit and remain stable, monitoring can be tapered, with progressively longer intervals between assessments. As an example, a patient who is seen every two weeks at the beginning of remission can be seen every two weeks for one to three more visits, and then every month for one to three visits. Continuously stable patients receiving pharmacotherapy can eventually be seen every three to six months [1,2,35]. Stable patients receiving psychotherapy are typically seen once per month [1,2], following careful tapering from weekly to twice a month visits. More frequent visits should be scheduled for patients who develop symptoms or side effects; monitoring acutely ill patients is discussed separately.

For patients with unipolar depression who receive maintenance treatment, we suggest measurement based care using a self-report instrument such as the Patient Health Questionnaire – Nine Item (PHQ-9) (table 2) [1,2]. Measurement based care is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

ADHERENCE

Many patients have difficulty adhering to (complying with) continuation and maintenance treatment [47-52]. Strategies that can improve adherence are discussed separately. (See "Unipolar depression in adults and initial treatment: General principles and prognosis", section on 'Adherence to treatment'.)

REEMERGING SYMPTOMS DURING TREATMENT

Relapse/recurrence of unipolar major depression (table 1) may occur despite ongoing continuation/maintenance treatment with antidepressants; this phenomenon is called tachyphylaxis. In randomized continuation/maintenance trials lasting up to three years, relapse/recurrence of major depression occurred in approximately 10 to 60 percent of patients, and a prospective observational study found that during continuation/maintenance treatment, relapses/recurrences occurred 25 percent of the time [53].

If symptoms of unipolar major depression reemerge during continuation/maintenance pharmacotherapy, doses of medications should be optimized. If this does not control symptoms within four to eight weeks, or doses are already at the maximum of the therapeutic range, we suggest adding a depression specific psychotherapy (ie, a psychotherapy shown to reduce depressive symptoms); this strategy is called sequential treatment (see 'Sequential treatment' above). If a full-blown episode occurs despite optimizing medication doses and adding psychotherapy, the treatment regimen should be switched. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

If symptoms reemerge during continuation/maintenance psychotherapy, the frequency of sessions should be increased to that used during acute phase treatment. If a full-blown episode occurs despite increasing the frequency of psychotherapy sessions, the treatment regimen should be switched. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

DISCONTINUATION

Prior to discontinuing continuation and maintenance treatment for unipolar major depression, clinicians should discuss the potential for relapse and recurrence with patients, and the signs and symptoms that may arise [1,2]. These discussions often include family members and generate contingency plans for seeking treatment should the need arise. In addition, the date for termination of psychotherapy should be discussed at the outset of continuation/maintenance treatment.

We suggest tapering continuation/maintenance medications prior to discontinuation to minimize the discontinuation syndrome. (See "Discontinuing antidepressant medications in adults".)

In addition, tapering allows clinicians to detect recrudescent symptoms of major depression and reinstitute the full dose used initially to achieve remission. If a full-blown episode develops despite increasing the dose and does not improve within four to eight weeks, we suggest augmenting or switching treatment. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

Following discontinuation of continuation/maintenance pharmacotherapy or psychotherapy for unipolar major depression, it is prudent to monitor patients for several (eg, three to eight) months, because the risk of relapse or recurrence is greatest in the first several months after

stopping treatment [1,2]. For patients who suffer a relapse or recurrence, we suggest restarting the same treatment that was discontinued.

EFFICACY

Acute unipolar major depression that resolves is generally managed with continuation treatment and maintenance treatment, which are distinguished from each other (table 1) [5,6] (see 'Continuation and maintenance treatment' above). The subsections below discuss the efficacy of different regimens for continuation and maintenance treatment.

Antidepressants medications plus psychotherapy — For continuation and maintenance treatment of patients with unipolar major depression (table 1), randomized trials indicate that combining antidepressants and psychotherapy is more efficacious than antidepressants alone. As an example, a meta-analysis of eight randomized trials compared combination treatment with antidepressants alone in 867 patients who were followed for at least six months [54]. Psychotherapy consisted of cognitive-behavioral therapy (CBT), interpersonal psychotherapy, or social skills training, and antidepressants consisted of selective serotonin reuptake inhibitors (SSRIs) or tricyclics. Relapse/recurrence was less likely with combination treatment than antidepressants alone (odds ratio 0.6, 95% CI 0.4-0.9).

Antidepressant medications plus interpersonal psychotherapy

Compared with antidepressants alone — For patients with acute unipolar major depression who respond to the combination of pharmacotherapy and interpersonal psychotherapy, randomized trials indicate that continuation and maintenance treatment with combination treatment is superior to pharmacotherapy alone [55]. As an example, a meta-analysis of six randomized trials (number of patients not reported) found that relapse/recurrence was less likely in patients who received continuation/maintenance pharmacotherapy plus interpersonal psychotherapy than pharmacotherapy alone (odds ratio 0.3, 95% CI 0.1-0.8) [56]. However, heterogeneity across studies was moderate to large. Additional information about the advantage of maintenance treatment with pharmacotherapy plus interpersonal psychotherapy over pharmacotherapy alone is discussed separately. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy", section on 'Recurrent unipolar major depression'.)

Compared with interpersonal psychotherapy alone — Based upon randomized maintenance trials in patients with unipolar major depression, pharmacotherapy plus interpersonal psychotherapy is superior to interpersonal psychotherapy alone. A meta-analysis

of four randomized trials (number of patients not reported) found that relapse/recurrence was less likely in patients who received continuation/maintenance pharmacotherapy plus interpersonal psychotherapy rather than interpersonal psychotherapy alone (odds ratio 0.3, 95% CI 0.1-0.7) [56]. However, heterogeneity across studies was moderate.

Antidepressant medications plus cognitive-behavioral therapy — For patients with acute unipolar major depression who remit or recover with antidepressant medications alone, adding CBT can be useful for continuation and maintenance treatment. (See 'Sequential treatment' above.)

Antidepressant medications — For patients with unipolar major depression who respond to antidepressant medications, continuation and maintenance treatment can delay or prevent reemerging episodes [1,2,35,37]. It appears that the efficacy of different antidepressants is comparable. In head-to-head randomized trials, relapse or recurrence was comparable between [37,57]:

- Desvenlafaxine and escitalopram
- Duloxetine and paroxetine
- Escitalopram and paroxetine
- Fluoxetine and sertraline
- Fluoxetine and venlafaxine
- Fluvoxamine and sertraline
- Trazodone and venlafaxine

Compared with placebo — Randomized trials that compare antidepressants with placebo for continuation and maintenance treatment of unipolar major depression are typically designed such that initially, acutely ill patients receive open-label antidepressants for a specified time. Those patients who remit or recover are then randomly assigned to either continue/maintain their antidepressant or to switch to placebo.

Meta-analyses of randomized trials demonstrate that continuation and maintenance treatment with antidepressants is beneficial [58], and pooled results consistently indicate that relapse and recurrence occurs in fewer patients treated with antidepressants than placebo (approximately 20 to 30 versus 40 to 45 percent) [12,44,59]. However, it is not clear whether discontinuation of treatment for any reason (eg, adverse effects or lack of efficacy) is greater with antidepressants or placebo, due to conflicting results across studies.

Pooled analyses that indicate continuation/maintenance treatment with antidepressants is superior to placebo include the following [44]:

- One meta-analysis of 31 randomized trials compared antidepressants with placebo in 4410 depressed patients who initially responded to acute treatment with antidepressants; the trials lasted for up to three years (most lasted 12 or fewer months). The primary findings were as follows [12]:
  - Relapse and recurrence occurred in fewer patients who received antidepressants than placebo (18 versus 41 percent).
  - Benefits appeared to be comparable for SSRIs and tricyclics, based upon separate analyses for each medication class.
  - Discontinuation of treatment for any reason occurred in more patients who received antidepressants than placebo (18 versus 15 percent).
- A meta-analysis of patient-level data from four randomized trials compared antidepressants (duloxetine or fluoxetine) with placebo in 1462 depressed patients who initially responded to acute treatment with antidepressants [59]. Acute phase treatment lasted 10 to 13 weeks and randomly assigned treatment lasted 14 to 52 weeks. Relapse/recurrence occurred in fewer patients who received antidepressants than placebo (31 versus 43 percent).
- A subsequent trial lasting one year enrolled primary care patients (n = 478) who had recovered from their most recent depressive syndrome with an antidepressant, continued taking the drug for at least nine months, and felt well enough to discontinue treatment [60]. Patients were randomly assigned to maintain their antidepressant or to taper and discontinue it over two months (with placebo substitution). Recurrence of depression was observed in fewer patients in the maintenance group than the discontinuation group (39 versus 56 percent; hazard ratio 2.1, 95% CI 1.6-2.7). In addition, anxiety symptoms and withdrawal symptoms occurred in fewer patients who maintained their antidepressant, and side effects in the two groups were comparable.

Continuation/maintenance antidepressants may provide fewer benefits in patients with multiple lifetime episodes of major depression than patients with one lifetime episode. In a meta-analysis of 30 randomized continuation/maintenance trials (4890 patients) that compared antidepressants with placebo, antidepressants reduced the probability of relapse in patients with a history of at least one depressive episode prior to the presenting episode (odds ratio 0.37, 95% CI 0.31-0.44), as well as patients with no episodes prior to the presenting episode (odds ratio 0.12, 95% CI 0.06-0.26); however, the benefit was less in patients with multiple prior episodes [13]. This suggests that patients with recurrent episodes are at greater risk of additional recurrences.

Compared with psychotherapy — Psychotherapy alone may be more effective than antidepressants alone for preventing relapse or recurrence of unipolar major depression. A meta-analysis of 13 randomized trials (sample size not reported) compared psychotherapy (CBT, mindfulness-based cognitive therapy, or interpersonal psychotherapy) with antidepressants and found that relapse or recurrence was less likely with psychotherapy (relative risk 0.83, 95% CI 0.70-0.97) [61]. Some of the trials employed the strategy of sequential treatment. (See 'Sequential treatment' above.)

However, the relative efficacy of antidepressants and psychotherapy for continuation/maintenance treatment may vary depending upon the specific psychotherapy. Randomized trials that compared antidepressants with cognitive therapy have found that relapse/recurrence was comparable, whereas the efficacy of maintenance treatment with antidepressants may possibly exceed that of interpersonal psychotherapy.

Cognitive therapy — Based upon randomized trials, the efficacy of antidepressants for continuation/maintenance treatment is comparable to that of cognitive therapy [62]. As an example:

- A randomized trial compared eight months of continuation phase fluoxetine (10 to 40 mg per day) with cognitive therapy (10 sessions, each lasting 60 minutes) in 172 patients who initially responded to acute phase cognitive therapy [43]. Response was defined as no longer meeting criteria for major depression and scores on the Hamilton Rating Scale for Depression (table 3) <13. Relapse rates in the two groups were nearly identical (18 percent). Following termination of the continuation phase, patients were followed for up to 24 months; relapse/recurrence rates during posttreatment follow-up for fluoxetine and cognitive therapy remained comparable (41 and 45 percent of patients).

- In a randomized trial, 95 patients who remitted on randomly assigned monotherapy (duloxetine, escitalopram, or cognitive therapy) subsequently received 21 months of maintenance treatment (continued medication or three cognitive therapy booster sessions/year) [23]. The rate of recurrence was comparable for duloxetine, escitalopram, and cognitive therapy (16, 11, and 22 percent of patients).

Interpersonal psychotherapy — Based upon small randomized trials that compared pharmacotherapy with interpersonal psychotherapy for maintenance treatment of major depression, the efficacy of pharmacotherapy may be superior:

- A two-year randomized continuation/maintenance trial compared pharmacotherapy (paroxetine monotherapy or paroxetine plus a second antidepressant) with monthly interpersonal psychotherapy plus pill placebo in 70 patients who recovered or partially

recovered from an episode of major depression; relapse/recurrence occurred in fewer patients who received pharmacotherapy than interpersonal psychotherapy (37 versus 68 percent) [40].

- A three-year trial (n = 54 patients) found that the mean time to recurrence for patients who received imipramine (mean dose 208 mg per day) and patients who received interpersonal psychotherapy (one session per month) was 124 and 82 weeks [39]. Although the difference between treatments was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

- In a three-year trial that compared nortriptyline (target serum concentration 80 to 100 ng per mL, n = 28) with monthly interpersonal psychotherapy (n = 25), recurrent episodes occurred in 12 (43 percent) patients treated with nortriptyline and 16 (64 percent) patients who received interpersonal psychotherapy plus placebo [38]. Although the difference between treatments was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

Dose — The same antidepressant dose that is used to acutely treat unipolar major depression is typically used for continuation/maintenance treatment [1,2,12,28,35]. A meta-analysis of five randomized trials compared maintaining the full dose with reducing the dose in 1009 patients who had remitted/recovered with acute pharmacotherapy. Relapse/recurrence occurred in fewer patients who received the full dose (15 versus 25 percent) [63]. However, for patients who cannot tolerate the full dose, it is reasonable to attempt to decrease the dose. Persistent side effects or loss of efficacy at lower doses is managed by switching treatment. (See "Switching antidepressant medications in adults", section on 'Switching antidepressant medications'.)

Psychotherapy — For patients with unipolar major depression who respond to depression specific psychotherapy, continuation and maintenance psychotherapy can delay or prevent reemerging episodes [1,2,26,64]. As an example, a meta-analysis of 17 randomized trials (sample size not reported) compared psychotherapy (CBT, mindfulness-based cognitive therapy, or interpersonal psychotherapy) with usual care and found that relapse or recurrence was less likely with psychotherapy (relative risk 0.6, 95% CI 0.5-0.8); however, heterogeneity across studies was moderate and publication bias was likely [61]. Psychotherapy may be especially beneficial for patients with early age of depression onset, a lifetime history of multiple unipolar major depressive episodes, or residual depressive symptoms [18,65].

Although few head-to-head trials have compared different psychotherapies for continuation and maintenance treatment, some evidence suggests that the efficacy of CBT, mindfulness-based cognitive therapy, and interpersonal psychotherapy may perhaps be comparable:

- One trial randomly assigned patients (n = 177) to CBT or interpersonal psychotherapy for 16 weeks of acute treatment plus 24 weeks of continuation treatment [66]. The rate of remission at some point in treatment was similar with CBT and interpersonal psychotherapy (77 and 75 percent of patients), and the reduction of symptoms in both groups persisted through the 10 months of treatment.

- A study included three separate meta-analyses of randomized trials that compared usual care with CBT (16 trials), mindfulness-based cognitive therapy (6 trials), or interpersonal psychotherapy (3 trials) for preventing relapse/recurrence of major depression [61]. Each psychotherapy was superior to usual care and the magnitude of the clinical effect for each psychotherapy was comparable.

Cognitive-behavioral therapy — CBT is a time-limited, structured therapy that combines cognitive therapy and behavior therapy to help depressed patients change dysfunctional cognitions (distorted thoughts and beliefs about oneself, the world, and future) and problematic behaviors (eg, inactivity) [67,68]. Additional information about CBT is discussed separately. (See "Overview of psychotherapies", section on 'Cognitive and behavioral therapies'.)

Continuation and maintenance CBT reduces relapse/recurrence of unipolar major depression:

- A meta-analysis of four randomized trials compared continuation CBT with no continuation treatment in 234 patients who initially remitted with acute CBT; over a mean follow-up of 41 weeks, relapse occurred in fewer patients who received CBT (12 versus 38 percent) [11].

- In a meta-analysis of nine randomized trials (n = 626) that compared continuation/maintenance CBT with treatment as usual (eg, routine clinical management, waiting list control, or no treatment), CBT reduced the risk of relapse/recurrence by approximately 30 percent (relative risk 0.7, 95% CI 0.5-0.9) [61]. However, heterogeneity across studies was moderate.

- A subsequent randomized trial compared eight weeks of supported self-help cognitive therapy plus usual care with usual care alone in patients (n = 248) with recurrent major depression who were in remission/recovery for at least two months, but no more than five years [69]. On average, patients presented with residual symptoms. Cognitive therapy included a book with eight modules with reading assignments and homework, as well as weekly contact with a counselor who provided brief support lasting no more than 15 minutes. During one year of follow-up, relapse or recurrence occurred in fewer patients who received adjunctive cognitive therapy compared with usual care alone (35 versus 50 percent).

Continuation CBT appears to benefit patients at increased risk for relapse, including patients with an early age of onset (eg, age ≤18 years) of depression [70] and residual symptoms following response to acute phase CBT [26,71].

In addition, acute phase CBT may prevent relapse in the absence of continuation CBT [11,16]. In a randomized trial, depressed patients were treated with pharmacotherapy or CBT; patients who responded to pharmacotherapy (n = 69) were then randomly assigned to continuation medication or placebo for one year, and patients who responded to CBT (n = 35) were withdrawn from treatment except for three booster sessions [30]. Relapse over 12 months occurred in fewer patients withdrawn from CBT compared with patients who discontinued pharmacotherapy (31 versus 76 percent). In addition, relapse occurred in fewer patients who received prior CBT compared with patients who received continuation pharmacotherapy (31 and 47 percent); although the difference between treatments was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful. Additional evidence about the efficacy of acute phase CBT in preventing relapses is discussed elsewhere in this topic. (See 'Relapse/recurrence in the absence of treatment' above.)

Interpersonal psychotherapy — Interpersonal psychotherapy is a time-limited, structured, manual-based therapy that emphasizes current relationships and the connection between recent adverse life events and major depression. Treatment focuses upon resolving interpersonal problems that are due to [72,73]:

- Grief – complicated bereavement
- Role disputes – conflicts with spouses, family members, close friends, or coworkers over different expectations about the relationship
- Role transition – major changes in life circumstances such as divorce or retirement
- Interpersonal deficits – poor social skills that result in loneliness

Evidence for the efficacy of maintenance interpersonal psychotherapy for unipolar major depression includes randomized trials showing recurrence is decreased in patients who receive interpersonal psychotherapy plus placebo compared with patients who receive placebo alone. The efficacy of maintenance interpersonal psychotherapy is discussed separately, as are the specific interventions that therapists use. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy", section on 'Recurrent unipolar major depression' and "Interpersonal Psychotherapy (IPT) for depressed adults: Specific interventions and techniques".)

Mindfulness-based cognitive therapy — Mindfulness-based cognitive therapy is a skills-training group program that combines the clinical application of mindfulness meditation with elements of CBT to delay or prevent recurrence in patients with unipolar major depression who have responded to acute phase treatment (typically with pharmacotherapy) and have a history of at least three lifetime episodes. Mindfulness is purposeful, nonjudgmental attention to the present moment, which is developed through meditation and other practices. CBT is based upon the theory that maladaptive thoughts and behaviors lead to psychopathology such as major depression; the clinician addresses these dysfunctional cognitions, and the patient tries to change the resulting problematic behaviors.

Evidence for the efficacy of mindfulness-based cognitive therapy in patients with unipolar major depression includes randomized trials that compared continuation/maintenance mindfulness-based cognitive therapy with continuation/maintenance pharmacotherapy and found that relapse/recurrence may possibly occur less often with psychotherapy. The efficacy of maintenance mindfulness-based cognitive therapy is discussed separately, as are the specific interventions that therapists use. (See "Unipolar major depression: Treatment with mindfulness-based cognitive therapy".)

Other approaches — Patients with unipolar major depression may benefit from maintenance treatment with:

- Quetiapine – Monotherapy with the second-generation antipsychotic quetiapine may prevent relapse of major depression. A one-year randomized trial compared quetiapine extended release (mean dose 177 mg per day) with placebo in 776 patients with unipolar major depression who were stabilized for at least 12 weeks with open label quetiapine [74]. Relapse occurred in fewer patients treated with quetiapine than placebo (14 versus 34 percent). Adverse effects of quetiapine included sedation, dry mouth, dizziness, increased appetite and weight, and extrapyramidal symptoms.

- Olanzapine **plus** fluoxetine – Among patients with treatment resistant depression who respond to acute treatment with fluoxetine plus adjunctive olanzapine, maintenance treatment with the same regimen can forestall recurrences, but also cause adverse effects. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics", section on 'Maintenance phase'.)

- Lithium – Lithium monotherapy can prevent recurrence of unipolar depression. (See "Unipolar depression in adults: Treatment with lithium", section on 'Lithium monotherapy as maintenance treatment'.)

- **Electroconvulsive therapy** – For patients with unipolar major depression who respond with electroconvulsive therapy (ECT), continuation/maintenance treatment generally consists of pharmacotherapy plus psychotherapy such as CBT [75,76] or pharmacotherapy alone [77]. However, continuation/maintenance ECT is an option for patients who repeatedly (eg, two to three times) respond to acute ECT and then fail standard maintenance treatment. In particular, continuation ECT plus pharmacotherapy (eg, an antidepressant plus lithium) can benefit patients with late-life depression who initially respond to acute treatment with ECT plus pharmacotherapy [78]. The evidence for pharmacotherapy plus psychotherapy as continuation/maintenance following acute ECT is discussed separately, as is the evidence for continuation/maintenance ECT. (See 'Cognitive-behavioral therapy' above and "Overview of electroconvulsive therapy (ECT) for adults", section on 'Continuation and maintenance ECT'.)

- **Repetitive transcranial magnetic stimulation** – For patients with unipolar major depression who respond to repetitive transcranial magnetic stimulation, enduring effects are modest [79,80], and continuation/maintenance treatment generally consists of pharmacotherapy or pharmacotherapy plus psychotherapy [81]. However, continuation/maintenance repetitive transcranial magnetic stimulation may possibly help patients who repeatedly fail standard treatment. (See "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Maintenance TMS'.)

- **Exercise** – Exercise alone or combined with pharmacotherapy, psychotherapy, or pharmacotherapy plus psychotherapy may possibly delay or prevent recurrence of depression. In a prospective observational study, 172 patients with unipolar major depression received pharmacotherapy, psychotherapy, or no treatment; at the one-year assessment, 66 percent were euthymic [82]. Fewer depressive symptoms were found in patients who exercised (moderate to vigorous intensity) for three hours per week compared with patients who did not exercise.

- Esketamine – For patients with acute major depression who initially respond to esketamine an antidepressant, continuation/maintenance treatment with the combination is more efficacious than antidepressant monotherapy. (See "Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects", section on 'Longer term'.)

PREVENTING SUICIDE

Patients with unipolar major depression are at increased risk of suicide, and continuation and maintenance treatment with lithium can prevent suicide. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

SOCIETY GUIDELINE LINKS

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

SUMMARY AND RECOMMENDATIONS

- Unipolar major depression is diagnosed in patients who have suffered at least one major depressive episode and have no history of mania, mixed mania, or hypomania. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: dysphoria, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, anergia, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (table 4). (See "Unipolar depression in adults: Assessment and diagnosis".)

- Continuation treatment is administered to preserve and enhance remission and to prevent relapse of the presenting episode (table 1). Remission represents a period of time (eg, two to eight months) with minimal or no depressive symptoms. Continuation treatment is followed by maintenance treatment, which is used after recovery from the presenting episode to prevent recurrence of new depressive episodes. Recovery occurs when patients remain well for a period of time exceeding the interval used to define remission. However, it is not clear when remission ends and recovery begins, and thus the cutoff between continuation and maintenance treatment is not standardized. (See 'Continuation and maintenance treatment' above.)

- Relapse and recurrence are common in patients with unipolar major depression who improve with treatment and then discontinue it. (See 'Relapse/recurrence in the absence of treatment' above.)

- Continuation treatment is generally indicated for patients with unipolar major depression who respond to acute treatment; additional maintenance treatment is often indicated for patients with an increased risk of recurrence due to [22]:

  - Childhood maltreatment

- Early age of onset of unipolar major depression
- A lifetime history of at least two or three major depressive episodes
- Persistent or emergent residual depressive symptoms
- Comorbid anxiety disorders
- Prominent depressive cognitions
- Psychosocial stressors or impairment

(See 'Indications' above.)

- Patients who respond to acute cognitive-behavioral therapy (CBT) or behavioral activation may reasonably decline continuation treatment, provided they are not at increased risk of relapse and that remission was full and stable. (See 'Indications' above.)

- Standard continuation and maintenance treatments include pharmacotherapy, psychotherapy, and pharmacotherapy plus psychotherapy. Randomized trials indicate that pharmacotherapy plus interpersonal psychotherapy is more efficacious than pharmacotherapy alone or interpersonal psychotherapy alone, and that pharmacotherapy plus CBT is more effective than antidepressants alone. The efficacy of monotherapy with either pharmacotherapy or psychotherapy is superior to no treatment. Psychotherapy alone may be more efficacious than pharmacotherapy alone. (See 'Efficacy' above.)

- For most patients with unipolar major depression who respond to acute therapy, we recommend continuation treatment rather than no treatment (**Grade 1A**). We suggest continuation treatment with the same regimen that was used acutely. (See 'Choosing treatment' above.)

- For patients with unipolar major depression who respond to acute phase and continuation phase therapy and are at risk of recurrence, we suggest maintenance therapy rather than discontinuing treatment (**Grade 2A**). Maintenance treatment typically consists of the same regimen used during the acute and continuation phases. (See 'Choosing treatment' above.)

- For patients with unipolar major depression who respond to acute phase and continuation phase therapy and are at low risk of recurrence, we suggest discontinuing treatment rather than administering maintenance therapy (**Grade 2C**). However, it is reasonable to provide maintenance treatment for patients concerned about recurrence. (See 'Choosing treatment' above.)

- Continuation/maintenance pharmacotherapy for unipolar major depression generally includes antidepressant medications. For patients treated with continuation/maintenance

antidepressants, we suggest maintaining the same dose that achieved remission rather than decreasing the dose (**Grade 2A**). Patients with substantial side effects can reasonably choose to decrease the dose. Head-to-head trials do not indicate that any one medication or medication class is superior. Indications for discontinuing the acute phase antidepressant and switching to a different drug for continuation/maintenance treatment include intolerable adverse effects, specific residual depressive symptoms, comorbid general medical conditions, and drug-drug interactions. (See 'Choosing treatment' above and 'Antidepressant medications' above.)

- The most widely studied psychotherapy for continuation/maintenance treatment of unipolar major depression is CBT; other reasonable choices include interpersonal psychotherapy and possibly mindfulness-based cognitive therapy. (See 'Choosing treatment' above and 'Psychotherapy' above.)

- Patients with unipolar major depression who successfully complete acute pharmacotherapy may switch to or add on psychotherapy for continuation/maintenance treatment (called sequential treatment). Switching can be used to avoid adverse medication side effects, conceive and breastfeed children, manage poor adherence with pharmacotherapy, resolve residual symptoms, or improve psychosocial functioning. Adding psychotherapy can be used for poor adherence, residual symptoms, and impaired functioning. (See 'Sequential treatment' above.)

- The duration of continuation pharmacotherapy is typically six months. Patients with risk factors for recurrence should receive at least one to three years of maintenance treatment following continuation treatment, as should patients who recover from a chronic or severe episode (algorithm 1). Patients with a history of multiple chronic or severe major depressive episodes, or comorbid psychiatric and general medical disorders, are encouraged to maintain treatment indefinitely. (See 'Duration' above.)

- Other options for continuation/maintenance treatment of patients with unipolar major depression include quetiapine, olanzapine plus fluoxetine, lithium, electroconvulsive therapy, repetitive transcranial magnetic stimulation, and exercise. (See 'Other approaches' above.)

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