

# Using Second-Generation Antidepressants to Treat Depressive Disorders: A Clinical Practice Guideline from the American College of Physicians

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**Description:** The American College of Physicians developed this guideline to present the available evidence on the pharmacologic management of the acute, continuation, and maintenance phases of major depressive disorder; dysthymia; subsyndromal depression; and accompanying symptoms, such as anxiety, insomnia, or neurovegetative symptoms, by using second-generation antidepressants.

**Methods:** Published literature on this topic was identified by using MEDLINE, EMBASE, PsychLit, the Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts from 1980 to April 2007. Searches were limited to English-language studies in adults older than 19 years of age. Keywords for search included terms for depressive disorders and 12 specific second-generation antidepressants—bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine—and their specific trade names. This guideline grades the evidence and recommendations by using the American College of Physicians clinical practice guidelines grading system.

**Recommendation 1:** The American College of Physicians recommends that when clinicians choose pharmacologic therapy to treat patients with acute major depression, they select second-generation antidepressants on the basis of adverse effect profiles, cost,

and patient preferences (Grade: strong recommendation; moderate-quality evidence).

**Recommendation 2:** The American College of Physicians recommends that clinicians assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1 to 2 weeks of initiation of therapy (Grade: strong recommendation; moderate-quality evidence).

**Recommendation 3:** The American College of Physicians recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy for major depressive disorder (Grade: strong recommendation; moderate-quality evidence).

**Recommendation 4:** The American College of Physicians recommends that clinicians continue treatment for 4 to 9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had 2 or more episodes of depression, an even longer duration of therapy may be beneficial (Grade: strong recommendation; moderate-quality evidence).

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Depressive disorders are serious disabling illnesses that affect 16% of adults in the United States during their lifetime (1). The economic burden of depressive disorders is estimated to be \$83.1 billion. Depressive disorders include major depressive disorder (MDD); dysthymia; and subsyndromal depression, including minor depression. The course of depression can be characterized by 3 phases (Figure). Relapse is defined as the return of depressive symptoms during the acute or continuation phases and is therefore considered part of the same depressive episode, whereas recurrence is defined as the return of depressive symptoms during the maintenance phase and is considered a new, distinct episode.

Various treatment approaches can be used to manage depression, such as pharmacotherapy, psychotherapy, and cognitive behavioral therapy. However, the scope of this

guideline is limited to pharmacotherapy with second-generation antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], and selective serotonin norepinephrine reuptake inhibitors [SSNRIs]). First-generation antidepres-

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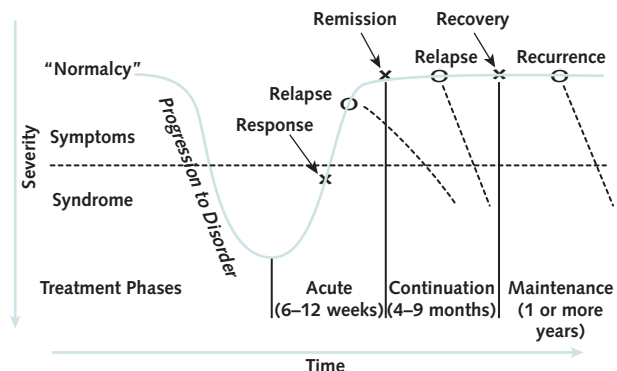
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\* This paper, written by Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Thomas D. Denberg, MD, PhD; Mary Ann Forcica, MD; and Douglas K. Owens, MD, MS, was developed for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (ACP): Douglas K. Owens, MD, MS (Chair); Donald E. Casey Jr., MD, MPH, MBA; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Mary Ann Forcica, MD; Robert H. Hopkins Jr., MD; William Rodriguez-Cintron, MD; and Paul Shekelle, MD, PhD. Approved by the ACP Board of Regents on 13 July 2008.

Figure. Phases of treatment of major depression.



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sants (tricyclic antidepressants and monoamine oxidase inhibitors) are less commonly used than second-generation antidepressants, which have similar efficacy to and lower toxicity in overdose than first-generation antidepressants.

The goal of this guideline is to present the available evidence on the pharmacologic management of the acute, continuation, and maintenance phases of MDD; dysthymia; and accompanying symptoms, such as anxiety, insomnia, or neurovegetative symptoms. The target audience for this guideline is all clinicians, and the target population is all patients with depressive disorders. These recommendations are based on the systematic evidence review by Gartlehner and colleagues (2) and the Agency for Healthcare Research and Quality–sponsored RTI International–University of North Carolina Evidence-based Practice Center evidence report (1).

**METHODS**

The reviewers searched MEDLINE, EMBASE, PsychLit, the Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts from 1980 to April 2007. In addition, the reviewers manually searched reference lists of pertinent review articles and letters to the editor and used the Center for Drug Evaluation and Research database (up to September 2007) to identify unpublished research submitted to the U.S. Food and Drug Administration. The Medical Subject Heading terms and keywords included for literature search involved combining depressive disorders with 12 specific second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine) and their specific trade names. The criteria for electronic search included adults 19 years of age or older, human, and English-language articles. This guideline is based on evidence derived from 203 studies.

Two persons independently reviewed abstracts and relevant full-text articles; studies were excluded if both reviewers agreed that they did not meet eligibility criteria. Disagreements were resolved by a third reviewer. The reviewers used head-to-head trials when available; however, no head-to-head evidence was available for many drug comparisons. The review included placebo-controlled trials for indirect comparisons in the absence of head-to-head trials. For adverse events, the reviewers included data from observational studies with 100 or more participants and follow-up of 12 or more weeks.

Major depressive disorder is a clinical syndrome lasting at least 2 weeks during which the patient experiences either depressed mood or anhedonia plus at least 5 of the following symptoms: depressed mood most of the day, nearly every day; markedly diminished interest or pleasure in most activities most of the day; significant weight loss or gain or appetite disturbance; insomnia or hypersomnia; psychomotor agitation or retardation; inappropriate guilt; diminished ability to think or concentrate or indecisiveness; or recurring thoughts of death, including suicidal ideation. Dysthymia is defined as a chronic depressive disorder that is characterized by depressed mood on most days for at least 2 years (3). Subsyndromal depression (also called minor depression) is a mood disturbance of at least 2 weeks' duration with fewer symptoms of depression than MDD (3). Melancholia is defined as a depressive subtype that is a severe form of MDD and has the essential feature of the loss of interest or pleasure in all, or almost all, activities or a lack of reactivity to usually pleasurable stimuli. Other characteristic physical symptoms, including early morning awakening, marked psychomotor retardation or agitation, and significant anorexia or weight loss, are also present.

This guideline rates the evidence and recommendations by using a slightly modified version of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system (Table 1).

Table 1. The American College of Physicians Guideline Grading System\*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced with Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I-recommendation	

\* Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) workgroup.

The objective of this guideline is to synthesize the evidence for the following key questions.

Key question 1: For adults with MDD or dysthymia, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?

Key question 2a: For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (preventing relapse or recurrence)?

Key question 2b: For adults receiving antidepressant treatment for a depressive syndrome that has not responded (acute phase), has relapsed (continuation phase), or has recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness?

Key question 3: Do second-generation medications used to treat depression differ in their efficacy or effectiveness for treating accompanying symptoms, such as anxiety, insomnia, and neurovegetative symptoms?

Key question 4: How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations: elderly or very elderly patients; other demographic groups, defined by age, race or ethnicity, or sex; and patients with medical comorbid conditions, such as ischemic heart disease or cancer?

Key question 5: For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea; diarrhea; headache; tremor; daytime sedation; decreased libido; failure to achieve orgasm; nervousness; insomnia; and more severe events, including suicide.

## Treatment of MDD

### *Efficacy for Acute Phase*

The reviewers gathered evidence from 80 head-to-head RCTs of good to fair quality that offered direct evidence for 36 of the possible 66 comparisons among second-generation antidepressants (2). The trials compared SSRIs with other SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) with SSNRIs (duloxetine) and SNRIs (mirtazapine, venlafaxine); and SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, paroxetine), SNRIs (mirtazapine, venlafaxine), SSNRIs (duloxetine), and other second-generation antidepressants (bupropion, nefazodone) with other second-generation antidepressants (bupropion, nefazodone, trazodone).

The results of individual studies showed no significant differences between SSRIs or between SSRIs and SNRIs, SSNRIs, or other second-generation antidepressants. Some evidence from meta-analyses showed statistically significant differences between treatments; however, the effect sizes were small and the results were probably not clinically significant. For example, evidence from 5 studies (4–8) com-

paring citalopram with escitalopram showed benefits from escitalopram (relative benefit, 1.14 [95% CI, 1.04 to 1.26]). However, the clinical significance of this finding was doubtful when the results were pooled on the Montgomery-Asberg Depression Rating Scale.

### *Effectiveness for Acute Phase*

The reviewers gathered evidence from 3 studies that evaluated effectiveness of different SSRIs (9–11) and found no significant differences among them for the treatment of MDD.

### *Quality of Life*

Evidence from 18 fair-quality efficacy trials that evaluated quality of life or functional capacity as secondary outcomes showed no differences among second-generation antidepressants (4, 11–27). Two fair-quality effectiveness trials showed that fluoxetine, paroxetine, and sertraline similarly improved health-related quality of life (work, social and physical functioning, concentration and memory, and sexual functioning) (10, 11).

### *Speed of Response for Acute Phase*

Evidence from 7 fair-quality studies showed that mirtazapine had a statistically significantly faster onset of action than that of citalopram, fluoxetine, paroxetine, or sertraline (19, 25, 27–32). However, after 4 weeks, most response rates were similar. Also, the response rates of mirtazapine and venlafaxine did not differ (18).

### *Response to a Second Agent in Treatment-Resistant MDD*

Studies showed that 38% of patients did not achieve a treatment response during 6 to 12 weeks of treatment with second-generation antidepressants and 54% did not achieve remission. One large good-quality study, STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) (33), provided the best evidence for assessing alternative medications (sustained-release bupropion, sertraline, and extended-release venlafaxine) in patients whose initial therapy failed; it showed that 1 in 4 patients became symptom-free after switching medications and found no difference among the 3 drugs. However, 2 small studies (34, 35) showed greater response rates with venlafaxine than with other second-generation antidepressants.

### *Maintenance of Response or Remission*

Four fair-quality trials (36–40) demonstrated no substantial difference between fluoxetine and sertraline, fluvoxamine and sertraline, duloxetine and paroxetine, and trazodone and venlafaxine for maintaining response or remission of MDD. A meta-analysis (41) of 31 randomized trials supports the continuation of antidepressant therapy to reduce the risk for relapse.

In summary, when treating acute-phase MDD, the second-generation antidepressants did not significantly differ in efficacy, effectiveness, or quality of life. Mirtazapine

had a significantly faster onset of action. Almost 38% of patients did not achieve a treatment response during 6 to 12 weeks of treatment with second-generation antidepressants and 54% did not achieve remission. Second-generation antidepressants did not differ in the rate of achieving remission.

### Treatment of Depression in Patients with Accompanying Symptom Clusters

The evidence review evaluated the comparative effectiveness of second-generation antidepressants for treatment of depression associated with symptom clusters, such as anxiety, insomnia, and pain.

#### Anxiety

Evidence from 6 fair-quality head-to-head trials comparing fluoxetine or paroxetine with sertraline, sertraline with bupropion, and sertraline with venlafaxine showed similar antidepressive efficacy for patients with MDD and anxiety symptoms (23, 42–47). One fair-quality trial showed a statistically significantly better response and remission rate for venlafaxine than for fluoxetine (42).

#### Insomnia

Limited evidence (48, 49) showed similar efficacy among fluoxetine, nefazodone, paroxetine, and sertraline for treating depression in patients with accompanying insomnia.

#### Melancholia

Evidence from 2 fair-quality head-to-head trials (44, 50) and 1 poor-quality head-to-head study (51) showed that sertraline had a greater response rate than fluoxetine and that venlafaxine was better than fluoxetine; however, small sample sizes and high attrition decrease confidence in these findings.

#### Pain

Two studies showed that duloxetine (52) and paroxetine (53) had the same response rate compared with placebo in patients with MDD and pain.

#### Psychomotor Changes

Evidence from 1 fair-quality head-to-head trial showed that fluoxetine and sertraline had similar antidepressive efficacy in patients with psychomotor retardation but sertraline had better efficacy in patients with psychomotor agitation (44). However, these results should be interpreted with caution because of the small number and size of the studies.

In summary, when treating depression in patients with accompanying symptom clusters, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, insomnia, and pain. However, limited evidence suggests that sertraline had better efficacy for managing melancholia and psychomotor agitation. Also, venlafaxine may be superior to fluoxetine for treating anxiety.

### Treatment of Symptom Clusters in Patients with Accompanying Depression

The reviewers evaluated the comparative effectiveness of second-generation antidepressants for treatment of symptom clusters associated with depression.

#### Anxiety

Evidence from 10 fair-quality head-to-head trials (19, 23, 42, 43, 46, 47, 54–57) showed no difference in the efficacy of antidepressant medications (fluoxetine, paroxetine, and sertraline; sertraline and bupropion; sertraline and venlafaxine; citalopram and mirtazapine; and paroxetine and nefazodone) for treatment of anxiety associated with MDD.

#### Insomnia

Research showed an improvement in sleep scores for escitalopram over citalopram (58), nefazodone over fluoxetine (49), and trazodone over fluoxetine (13) and venlafaxine (36). However, 5 fair-quality head-to-head trials (13, 25, 36, 48, 49) and a pooled analysis of 3 RCTs (58) provide limited evidence about comparative effectiveness of antidepressants on insomnia in patients with depression.

#### Pain

In 3 fair-quality head-to-head trials (39, 59, 60) and 1 poor-quality trial (61), pain relief did not significantly differ between duloxetine and paroxetine in patients with MDD.

#### Somatization

One fair-quality study showed no differences among fluoxetine, paroxetine, and sertraline in improving somatization (10).

In summary, when treating symptom clusters in patients with accompanying depression, second-generation antidepressants did not differ in efficacy in treating accompanying anxiety, pain, and somatization. Limited evidence suggests that some agents may be more effective in treating insomnia.

### Treatment of Depression in Selected Patient Populations

No studies compared efficacy, effectiveness, and harms of second-generation antidepressants among subgroups and the general population for treatment of depressive syndromes. However, numerous studies conducted subgroup analyses or used subgroups as study populations.

#### Age

Evidence from head-to-head trials (10, 17, 26, 31, 62–70), meta-analyses (71, 72), and placebo-controlled trials (73–79) showed no differences in efficacy of second-generation antidepressants in elderly (65 to 80 years of age), very elderly (>80 years of age), or younger patients.

#### Sex

Second-generation antidepressants were equally effective in men and women (71, 80, 81).

**Race or Ethnicity**

One poor-quality trial showed no differences in efficacy among racial subgroups (82).

**Comorbid Conditions**

No studies directly compared the effect of second-generation antidepressants on depressed patients with comorbid conditions versus the general population. In 1 poor-quality head-to-head trial (83), fluoxetine, paroxetine, and sertraline differed in efficacy or tolerability.

In summary, second-generation antidepressants did not differ in efficacy among subgroups and special populations categorized according to age, sex, race or ethnicity, or comorbid conditions.

**Risk for Harms and Adverse Events**

The reviewers gathered evidence from 80 head-to-head efficacy studies and 42 additional studies (see Gartlehner and colleagues' (2) Appendix Table 9, available at [www.annals.org](http://www.annals.org)) (2). The methods used to assess adverse events varied greatly, and few studies used objective scales.

**Adverse Events Profile**

The most commonly reported adverse events included constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. Most of the second-generation antidepressants had similar adverse events, with some differences in the incidence of specific adverse events: Venlafaxine had a higher incidence of nausea and vomiting than other SSRIs; sertraline had a higher rate of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, or venlafaxine; mirtazapine and paroxetine resulted in higher weight gain than sertraline, trazodone, or venlafaxine; and trazodone was associated with a higher incidence of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, or venlafaxine.

**Severe Adverse Events**

**Sexual Dysfunction.** Bupropion had a significantly lower rate of sexual adverse events than fluoxetine or sertraline (84–88). Paroxetine had higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, or sertraline (30, 48, 56, 89). Absolute rates of sexual dysfunction are probably underreported.

**Suicidality.** Studies evaluating the risk for suicidality (suicidal thinking or behavior) in patients showed no differences among second-generation antidepressants (90–94). However, 1 meta-analysis showed that although no evidence indicated an increase in the risk for suicide with SSRIs (odds ratio, 0.85 [CI, 0.20 to 3.40]), the risk for nonfatal suicide attempts did increase (odds ratio, 1.57 [CI, 0.99 to 2.55]) (91). Another meta-analysis of published data (95) showed similar results, with SSRIs associated with an increased risk for suicide attempts compared with placebo (odds ratio, 2.25 [CI, 3.3 to 4.6]).

**Other Severe Adverse Events.** Evidence evaluating adverse events, such as seizures, cardiovascular risks (increases in systolic or diastolic blood pressure and pulse or heart rate), hyponatremia, hepatotoxicity, or the serotonin syndrome, is scarce but should be kept in mind when patients are being treated with a second-generation antidepressant. Weak evidence indicates that bupropion may be associated with an increased risk for seizures, venlafaxine may be associated with an increased risk for cardiovascular events, and nefazodone may be associated with an increased risk for hepatotoxicity.

In summary, most of the second-generation antidepressants had similar adverse effects. The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. Paroxetine was associated with an increased risk for sexual dysfunction. Selective serotonin reuptake inhibitors resulted in an increased risk for nonfatal suicide attempts.

**Treatment of Dysthymia**

One good-quality (16) and 4 fair-quality placebo-controlled trials (22, 24, 96–99) showed mixed evidence on the efficacy and effectiveness of fluoxetine, paroxetine, and sertraline for the treatment of dysthymia.

**SUMMARY**

The available evidence does not support clinically significant differences in efficacy, effectiveness, or quality of life among SSRIs, SNRIs, SSNRIs, or other second-generation antidepressants for the treatment of acute-phase MDD. However, mirtazapine had a faster onset of action than fluoxetine, paroxetine, or sertraline. Also, 38% of the patients did not achieve a treatment response during 6 to 12 weeks of treatment with second-generation antidepressants, and 54% did not achieve remission.

Although the evidence base was limited, second-generation antidepressants did not differ in efficacy in patients with accompanying symptoms or subgroups based on age, sex, race or ethnicity, or other comorbid conditions.

The most commonly reported adverse events were constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual side effects, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies. Although studies evaluating the risk for suicidality (suicidal thinking or behavior) in patients showed no differences between second-generation antidepressants, patients receiving SSRIs had an increased risk for nonfatal suicide attempts.

**FUTURE RESEARCH**

Research using multiple-group or head-to-head trials is needed to evaluate the efficacy and effectiveness of second-generation antidepressants for the treatment of dysthymia

and subsyndromal depression. Effectiveness trials with less stringent eligibility criteria that include health outcomes, long duration of follow-up, and primary care populations would be valuable for determining whether existing differences among second-generation antidepressants are clinically meaningful in real-world settings. A focus on variations in efficacy and effectiveness in subgroups, such as very elderly persons, patients with comorbid conditions, or different sexes, is also needed. More research is urgently needed to evaluate the most appropriate duration of antidepressant treatment for maintaining remission. It is important to evaluate the effectiveness of combination therapy and whether any second-generation antidepressant is better than another in patients who either did not respond to or could not tolerate a first-line treatment.

### RECOMMENDATIONS

*Recommendation 1: The American College of Physicians recommends that when clinicians choose pharmacologic therapy to treat patients with acute major depression, they select second-generation antidepressants on the basis of adverse effect profiles, cost, and patient preferences (Grade: strong recommendation; moderate-quality evidence).*

Various approaches, including pharmacotherapy, psychotherapy, and cognitive behavioral therapy, are effective for treatment of depression. Existing evidence does not justify the choice of any second-generation antidepressant over another on the basis of greater efficacy and effectiveness. Efficacy and effectiveness of these agents do not differ among subgroups based on age, sex, or race or ethnicity. However, differences have been reported among some medications in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) adverse effects. Bupropion is associated with a lower rate of sexual adverse events than fluoxetine or sertraline, whereas paroxetine has higher

rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, or sertraline. In addition, SSRIs are associated with an increased risk for suicide attempts compared with placebo. Physicians and patients should discuss adverse event profiles before selecting a medication.

*Recommendation 2: The American College of Physicians recommends that clinicians assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1 to 2 weeks of initiation of therapy (Grade: strong recommendation; moderate-quality evidence).*

The U.S. Food and Drug Administration advises that all patients receiving antidepressants be closely monitored on a regular basis for increases in suicidal thoughts and behaviors (100). Such monitoring should begin 1 to 2 weeks after initiation of therapy. Patients should be monitored for the emergence of agitation, irritability, or unusual changes in behavior, because these symptoms can indicate that the depression is getting worse. The risk for suicide attempts is greater during the first 1 to 2 months of treatment.

*Recommendation 3: The American College of Physicians recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy for major depressive disorder (Grade: strong recommendation; moderate-quality evidence).*

One of the most important aspects of care is assessing the response to treatment and making necessary changes in therapy if the response is not sufficient after adequate treatment. Clinicians should consider whether addition of other therapeutic modalities may be indicated. The response rate to drug therapy may be as low as 50%. In addition, the evidence is insufficient to determine which patient factors can reliably predict response or nonresponse to an individual drug. Multiple pharmacologic therapies might be required for patients who do not respond to first- or second-line treatments. Insufficient evidence exists to prefer one agent over another as second-line therapy. Table 2 summarizes the durations and dosages of treatments used in the trials reviewing the treatment of MDD.

*Recommendation 4: The American College of Physicians recommends that clinicians continue treatment for 4 to 9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had 2 or more episodes of depression, an even longer duration of therapy may be beneficial (Grade: strong recommendation; moderate-quality evidence).*

Duration of therapy depends on the risk for relapse or recurrence. Patients who achieve remission with acute-phase treatment should continue receiving antidepressant therapy for 4 to 9 months to prevent relapse. No evidence indicates differences among second-generation antidepressants in preventing relapse (loss of response during continuation-phase treatment) or recurrence (loss of response during maintenance-phase treatment). Patients who have had 2 or more episodes may benefit from a longer duration of therapy (years to lifelong). Table 3 summarizes the du-

**Table 2. Durations and Dosages of Treatments Used in the Trials Reviewing the Comparative Efficacy and Effectiveness of Treating Major Depressive Disorder**

Drug	Duration of Therapy, wk	Dosage, mg/d
Bupropion*	6–16	100–450
Citalopram	8	20–40
Duloxetine*	8	40–120
Escitalopram	8–24	10–20
Fluoxetine	6–12	20–60
Fluvoxamine*	6–7	50–200
Mirtazapine*	6–8	5–72
Nefazodone*	6–8	100–600
Paroxetine	6–24	20–40
Sertraline	8	50–100
Trazodone*	6	40–450
Venlafaxine	6–12	75–225

\* Trials reviewing comparative efficacy and effectiveness did not report *P* values or did not reach statistical significance.

**Table 3. Durations and Dosages of Treatments Used in the Trials Reviewing the Comparative Efficacy and Effectiveness for Treating Recurrent and Treatment-Resistant Depression**

Drug	Duration of Therapy, wk	Dosage, mg/d
Citalopram	24	20–40
Fluoxetine	24	20–40
Mirtazapine	24	30–45
Paroxetine	24	20–40
Sertraline	24	50–150

rations and dosages of treatments used in the trials that reviewed the comparative efficacy and effectiveness of second-generation antidepressants for treating recurrent and treatment-resistant depression.

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**Note:** Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians’ judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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