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CLINICAL GUIDELINE

Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians

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Description: The purpose of this guideline from the American College of Physicians (ACP) is to present updated clinical recommendations on nonpharmacologic and pharmacologic interventions as initial and second-line treatments during the acute phase of a major depressive disorder (MDD) episode, based on the best available evidence on the comparative benefits and harms, consideration of patient values and preferences, and cost.

Methods: The ACP Clinical Guidelines Committee based these recommendations on an updated systematic review of the evidence.

Audience and Patient Population: The audience for this guideline includes clinicians caring for adult patients in the acute phase of MDD in ambulatory care. The patient population includes adults in the acute phase of MDD.

Recommendation 1a: *ACP recommends monotherapy with either cognitive behavioral therapy or a second-generation antidepressant as initial treatment in patients in the acute phase of moderate to severe major depressive disorder (strong recommendation; moderate-certainty evidence).*

Recommendation 1b: *ACP suggests combination therapy with cognitive behavioral therapy and a second-generation antidepressant as initial treatment in patients in the acute phase of moderate to severe major depressive disorder (conditional recommendation; low-certainty evidence).*

The informed decision on the options of monotherapy with cognitive behavioral therapy versus second-generation antidepressants or combination therapy should be personalized and based on discussion of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences.

Recommendation 2: *ACP suggests monotherapy with cognitive behavioral therapy as initial treatment in patients in the acute phase of mild major depressive disorder (conditional recommendation; low-certainty evidence).*

Recommendation 3: *ACP suggests one of the following options for patients in the acute phase of moderate to severe major depressive disorder who did not respond to initial treatment with an adequate dose of a second-generation antidepressant:*

- *Switching to or augmenting with cognitive behavioral therapy (conditional recommendation; low-certainty evidence)*
- *Switching to a different second-generation antidepressant or augmenting with a second pharmacologic treatment (see Clinical Considerations) (conditional recommendation; low-certainty evidence)*

The informed decision on the options should be personalized and based on discussion of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences.

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Major depressive disorder (MDD) is a leading cause of disability, resulting in great costs to individuals, society, and health care systems (1). In the United States, more than 20% of adults experience MDD in their lifetime, with around 10% experiencing it in a given year (2). In 2020, an estimated 21 million adults in the United States had at least 1 MDD episode, representing 8.4% of all U.S. adults (3, 4). An average of 13 million ambulatory care visits per year have a primary diagnosis of MDD (5).

See also:

Editorial comment 280
Related articles 196, 212, 217
Summary for Patients I-26

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Supplement

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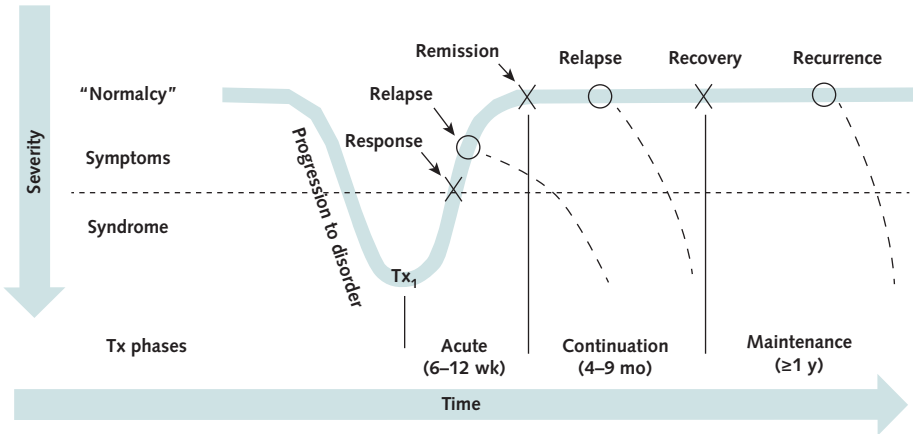
Figure 1. Phases of treatment of major depression.



Dashed lines indicate a hypothetical worsening of depression severity. Remission (the goal of treatment) refers to resolution of symptoms and a return to premorbid functioning. Response refers to a substantial clinical improvement, which may or may not reach remission. Tx = treatment; Tx1 = treatment attempt 1. (Reproduced with permission from Physicians Postgraduate Press [15] and reprinted from references 22 and 25.)

The estimated economic burden attributable to MDD in the United States was $120 billion in 2020, including direct medical and pharmaceutical costs ($36 billion) of treating MDD, suicide-related costs ($13 billion), and effects on workplace productivity ($70 billion) (6).

Major depressive disorder is defined as the presence of a depressed mood or a loss of interest or pleasure in normally enjoyable activities that occurs along with at least 4 additional diagnostic criteria or symptoms for at least 2 weeks (7) and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (see **Table 1a** of **Supplement 1** [available at Annals.org] for diagnostic criteria for MDD). Based on severity of symptoms, functional impairment, and level of patient distress, MDD can be characterized as mild, moderate, or severe (**Table 1b** of **Supplement 1**) (8–13). One third of patients with MDD have severe MDD, which is associated with more difficulty in achieving treatment response and remission (8). In addition, about 75% of people with MDD also have a co-occurring anxiety disorder (2), which can make their symptoms worse and recovery more difficult (14).

Treatment of MDD can be characterized by 3 phases (**Figure 1**): acute, continuation, and maintenance (16). During the acute phase–the focus of this guideline–symptoms are treated to remission, which is defined as the resolution of symptoms. Response to treatment refers to substantial clinical improvement. Both response to treatment and remission should ideally be quantified using various tools, such as the Patient Health Questionnaire-9 (PHQ-9) (12) or the Hamilton Depression Rating Scale (HAM-D; also known as the HDRS), which defines response as a 50% or greater decrease in depression severity and defines remission as a score of 7 or lower (13). The continuation phase aims to preserve remission and prevent relapse, which is defined as the return of symptoms during the acute or continuation phase and is considered part of the same episode. The goal of the maintenance phase is to prevent recurrence, which is defined as the return of symptoms and is considered a new, distinct episode. Recovery is defined as sustained remission during the maintenance phase, meaning that the episode has ended.

Treatment approaches for the management of MDD include pharmacologic treatments and nonpharmacologic therapies, such as psychotherapy, complementary and alternative medicine (CAM), and exercise. Primary care clinicians most frequently prescribe second-generation antidepressants (SGAs) for initial (first-line) treatment (16–19). However, approximately up to 70% of patients with MDD do not achieve remission and remain in the acute phase after the initial pharmacologic treatment attempt (20, 21).

Scope and Purpose

The purpose of this guideline from the American College of Physicians (ACP) is to present updated clinical recommendations on nonpharmacologic and pharmacologic interventions as initial and second-line treatments during the acute phase of an MDD episode, based on the best available evidence on the comparative benefits and harms, consideration of patient values and preferences, and costs (**Figure 2**). New evidence on second-line treatments has appeared since publication of the 2016 ACP guideline (22). This update also adds new key questions on patient values and preferences and costs of interventions and incorporates network meta-analysis on initial treatment strategies. This update evaluates the comparative effectiveness between treatment options but does not evaluate the effectiveness of the included treatments compared with no treatment.

For initial treatment, the systematic review limited pharmacologic treatment to SGAs, including selective serotonin reuptake inhibitors; serotonin–norepinephrine reuptake inhibitors; and others such as bupropion, mirtazapine, nefazodone, trazodone, vilazodone, and vortioxetine, as SGAs are the most commonly prescribed

Figure 2. Initial and second-line treatments of adults in the acute phase of MDD: recommendations summary.

Continued on following page

ACP = American College of Physicians; CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; MDD = major depressive disorder; SGA = second-generation antidepressant.
* See **Appendixes 1** to **3** of **Supplement 2** (available at Annals.org) or the accompanying systematic review (26) for evidence on interventions that were not recommended.
† Evidence is either very uncertain (insufficient) or unavailable for reduction of suicidal ideas, functional capacity, and quality of life.

Figure 2–Continued

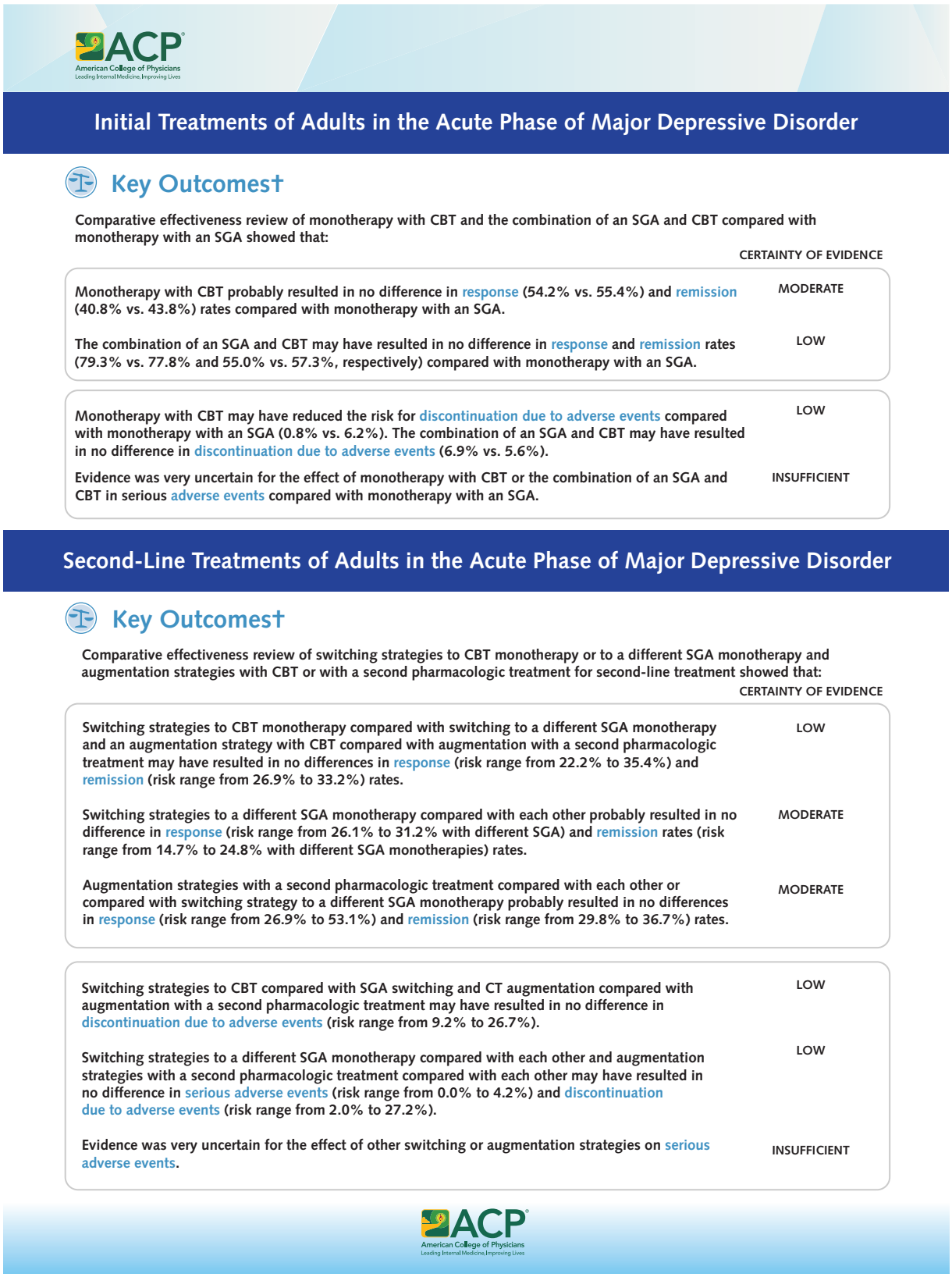
Continued on following page

agents in the primary care setting (16, 17, 23). Given that a previous systematic review (24) informing a previous ACP clinical guideline (25) found no substantial differences in effectiveness among SGAs, the systematic review accompanying this guideline (26) evaluated SGAs as a class and compared them with monotherapy or combination therapy with nonpharmacologic treatments. Nonpharmacologic treatments included psychotherapy (such as cognitive behavioral therapy [CBT], which includes cognitive therapy, rational emotive behavior therapy, and problem-solving therapy; integrative therapies; psychodynamic therapies; third-wave CBT [an extension of traditional CBT]; behavior therapy; behavior modification; and humanistic therapy; see **Table 2** of **Supplement 1** for definitions [27, 28]), CAM (such as acupuncture, omega-3 fatty acids, S-adenosyl-L-methionine [SAMe], and St. John's wort [*Hypericum perforatum*]), and exercise.

For second-line treatment, the systematic review evaluated the comparative effectiveness of strategies that included switching from an SGA to a different SGA, switching from an SGA to a nonpharmacologic treatment, or augmenting an SGA with nonpharmacologic treatment or additional pharmacologic treatment (such as a different SGA, atypical antipsychotics, psychostimulants, or the anxiolytic buspirone). Second-line treatments were limited to those that followed an initial treatment strategy with SGA monotherapy; second-line treatments after initial treatment with nonpharmacologic interventions are not covered in this guideline. Studies of second-line treatments that did not include an SGA as new monotherapy or as part of combination therapy were excluded.

This guideline does not apply to treatment beyond the acute phase (such as the continuation or maintenance phase in patients responding to treatment or achieving remission) or adults with dysthymia, subsyndromal depression, bipolar depression, perinatal depression, chronic depression, seasonal affective disorder,

Figure 2–Continued



psychotic depression, treatment-resistant depression (for example, ≥2 treatment failures), or depression as a sequela of an underlying disease (such as depression in patients with cancer or with posttraumatic stress disorder).

POPULATION

The population is adults in the acute phase of MDD.

INTENDED AUDIENCE

The intended audience is clinicians caring for adult patients in the acute phase of MDD in ambulatory care.

GUIDELINE DEVELOPMENT PROCESS

The Clinical Guidelines Committee (CGC) developed this guideline according to ACP's guideline development process (29) and its policy on disclosure of interests and management of conflicts of interest (30). The CGC used Evidence-to-Decision tables when reporting the evidence (**Appendixes 1** and **2** of **Supplement 2**, available at Annals.org) and graded the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method (31) (**Appendix Figure**, available at Annals.org). **Appendix 3** of **Supplement 2** lists the key questions for the supporting systematic review and details the methods for the guideline and systematic review. **Supplement 1** provides definitions for MDD diagnosis and common psychological interventions, serious adverse events for SGAs, and resource and cost information. ACP completes a Guidelines International Network (GIN) standards reporting form for each guideline it publishes, which can be found in GIN's International Guidelines Library or on ACP's website (www.acponline.org/clinical-information/guidelines/guideline-process).

The CGC is planning to maintain this topic as a living guideline with quarterly literature surveillance and periodic updating of the systematic review and the clinical recommendations, given that the topic is a priority for clinical care and there is active and ongoing research on new and innovative drugs for MDD indications (32, 33). The CGC will consider quantitative and qualitative factors, such as the certainty of the evidence, the balance between benefits and harms, and contextual considerations, to assess whether the new evidence may lead to changes to the recommendations and the need for an update. The CGC may decide to retire the topic from living status if it is no longer considered a priority for decision making, when there is confidence that conclusions are not likely to change with new evidence, or if it becomes unlikely that new evidence will emerge (34).

SYSTEMATIC REVIEW AND SUMMARY OF THE EVIDENCE

This guideline is based on an accompanying comparative effectiveness systematic review and network meta-analysis (26) and on 2 additional rapid reviews completed by the ACP Center for Evidence Reviews at Cochrane Austria/University for Continuing Education Krems (Danube University Krems) (35, 36). The accompanying systematic review (26) and the Appendixes in **Supplement 2** provide a detailed appraisal of benefits and harms of evaluated nonpharmacologic and pharmacologic treatments, and the rapid reviews provide summaries of findings on patient values and preferences (35) and cost-effectiveness (36).

Outcomes of Interest

Comparative Benefits and Harms

The CGC and the CGC Public Panel independently rated the importance of clinical outcomes and prioritized the following outcomes as critical: reduction of suicidal ideas or behaviors, remission, response to treatment, functional capacity, quality of life, reduction of mental suffering, and serious adverse events. When developing the recommendations, the CGC prioritized interventions with no increase in serious adverse events that showed improvement or no difference in remission and response compared with SGAs (see **Appendix Tables 3b** and **3c** of **Supplement 2** for the complete list of outcomes rated as critical and important). The CGC judged the overall comparative effectiveness of each intervention by considering the effect sizes and certainty of evidence across all available critical clinical outcomes, even if there was no evidence for certain critical outcomes.

Public and Patient Values and Preferences

The CGC assessed findings from the accompanying rapid review on patient values and preferences (35) and incorporated them when determining the value of the interventions.

Costs

The CGC assessed findings from the accompanying rapid review on cost-effectiveness (36), data from the validated U.S. Centers for Medicare & Medicaid Services databases (37–39), and data from mental health billing services (40) and incorporated costs and burden of care when determining the value of the interventions.

RECOMMENDATIONS

Figure 2 presents visual summaries of the recommendations, evidence and rationales, and clinical considerations.

Initial Treatments of Adults in the Acute Phase of MDD

Recommendation 1a: ACP recommends monotherapy with either cognitive behavioral therapy or a second-generation antidepressant as initial treatment in patients in the acute phase of moderate to severe major depressive disorder (strong recommendation; moderate-certainty evidence).

Recommendation 1b: ACP suggests combination therapy with cognitive behavioral therapy and a second-generation antidepressant as initial treatment in patients in the acute phase of moderate to severe major depressive

disorder (conditional recommendation; low-certainty evidence).

The informed decision on the options of monotherapy with cognitive behavioral therapy versus second-generation antidepressants or combination therapy should be personalized and based on discussion of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences.

Recommendation 2: ACP suggests monotherapy with cognitive behavioral therapy as initial treatment in patients in the acute phase of mild major depressive disorder (conditional recommendation; low-certainty evidence).

Rationale

Moderate to Severe MDD. Monotherapy with either CBT (including cognitive therapy, rational emotive behavior therapy, and problem-solving therapy in the CBT umbrella) or an SGA or combination therapy with CBT and an SGA are reasonable approaches to initial treatment of patients in the acute phase of moderate to severe MDD. Use of SGAs is common because of their availability, ease of use, and effectiveness. Although there is evidence of no substantial differences in benefits among SGAs (16), there are differences in common adverse effect profiles (**Figure 3**), serious adverse events (**Table 3a** of **Supplement 1**), contraindications and precautions (**Figure 4**), and especially costs (**Figure 3**; **Tables 4a** to **4d** of **Supplement 1**) (37, 39, 41). However, approximately up to 70% of patients with MDD do not achieve remission after initial pharmacologic treatment with an SGA (26). It is important to take an individualized approach using shared decision making when treating MDD because there may be important variability in patients' preferences for different treatment options. Overall, moderate-certainty evidence showed that there were probably no differences between monotherapy with CBT or SGAs, and low-certainty evidence showed that there may have been no additional benefit of combination therapy with an SGA and CBT relative to monotherapy with an SGA. In the United States, CBT may be more expensive for patients than SGAs, but it is also covered by some insurers and is generally more common and established than other psychotherapies. Patients may have more difficulty accessing CBT than using SGAs due to barriers such as limited availability of mental health professionals, transportation to and from appointments, time needed to attend appointments, and costs associated with care. Hence, it is important to individualize approaches and increase options for treatments that have shown similar effects on response and remission, as aligning with a patient's preferences may help to improve treatment adherence and response rates.

Comparative Benefits and Harms of Initial Treatments for Moderate to Severe MDD. Moderate-certainty evidence showed that there were probably no differences in treatment response, remission rates, and improvement in functional capacity between monotherapy with CBT or SGAs after 8 to 16 weeks (**Appendix Table 1a** of **Supplement 2**). Low-certainty evidence showed that there may have been no differences in treatment response, remission rates, and functional capacity in patients treated with combination therapy with CBT and SGAs compared with SGA monotherapy after 12 weeks (**Appendix Table 1a** of **Supplement 2**). Evidence was insufficient about differences in overall serious adverse events between SGA monotherapy and CBT alone or in combination with an SGA (**Appendix Table 1a** of **Supplement 2**). However, specific types of adverse events differed between the different types of treatments and among individual SGAs (**Figure 3** and **Appendix Table 3a** of **Supplement 1**). Compared with SGA monotherapy, low-certainty evidence showed that discontinuation due to adverse events may have been lower with CBT monotherapy (absolute risk difference, 54 fewer events per 1000 patients) and that there may have been no differences for combination therapy with CBT and an SGA (**Appendix Table 1a** of **Supplement 2**) (26).

Mild MDD. The CGC extrapolated from the evidence on using CBT as initial treatment because studies mainly enrolled patients with moderate to severe MDD and downgraded the overall certainty of evidence to low and the strength of the recommendation to conditional due to the lack of direct evidence in patients with mild MDD. Furthermore, the CGC had concerns about adverse effects of SGAs, including those serious enough to result in discontinuation. There is also a lack of direct evidence on the comparative efficacy for this population. Hence, CBT can be considered as initial treatment in patients in the acute phase of mild MDD. The CGC suggests that use of SGAs as initial treatment in these patients should be based on additional considerations, such as limited access to or cost of CBT, history of moderate or severe MDD, or patient preferences.

Comparative Benefits and Harms of Initial Treatments for Mild MDD. In the included studies, patients with MDD typically scored in the moderate to severe range (defined by scale scores). Several eligible studies specifically mentioned including patients with mild MDD, but none reported separately on outcomes for these patients. Evidence from randomized controlled trials was very uncertain (insufficient) (26) to assess whether response and remission rates varied in patient subgroups defined by symptom severity when comparing SGAs with various psychotherapies and aerobic exercise (26).

Applicability

Included studies assessing initial treatment enrolled adults (the majority of whom were female) with an initial or subsequent episode of moderate to severe MDD who were between the ages of 18 and 85 years and were undergoing 6 to 26 weeks of treatment (26). Limited evidence is inconclusive to determine how selection of treatment strategies might differ on the basis of a patient's severity of depression, common accompanying psychiatric symptoms, or demographic characteristics.

Figure 3. Second-generation antidepressants and anxiolytics: usual total daily dose ranges for adults, costs, and common adverse events.

Class	Drug	Usual Daily Dose Range	Average Annual Medicare Spending per Beneficiary, 2019	Common Adverse Events																		
				Agitation	Anxiety	Asthenia	Chest Pain	Constipation	Diarrhea	Dizziness	Dyspepsia	Headache	Hypotension (Orthostatic)	Insomnia	Restlessness	Somnolence	Anorexia/Weight Loss	Appetite Increase/ Weight Gain	Nausea	Vomiting	Palpitations	Sexual Dysfunction
SSRIs	Citalopram	20–40 mg	Generic: $39 Brand-name: $2685	✓	✓				✓	✓	✓			✓		✓	✓		✓	✓		✓
	Escitalopram	10–20 mg	Generic: $78 Brand-name: $3289					✓	✓	✓	✓	✓		✓		✓	✓		✓	✓		✓
	Fluoxetine	20–80 mg (90 mg/wk)	Generic: $78 Brand-name: $8130		✓	✓		✓	✓	✓	✓	✓		✓		✓	✓		✓	✓		✓
	Fluvoxamine	50–300 mg	Range: $310–$2450	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓	✓		✓	✓	✓	✓
	Paroxetine	20–50 mg	Generic: $70–$871 Brand-name: $3668	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓	✓		✓		✓	✓
	Sertraline	50–200 mg	Generic: $53 Brand-name: $3727	✓	✓			✓	✓	✓	✓	✓		✓		✓	✓		✓	✓	✓	✓
SNRIs	Desvenlafaxine	50 mg	Generic: $567 Brand-name: $2985		✓			✓		✓			✓	✓		✓	✓		✓	✓		✓
	Duloxetine	20–60 mg	Generic: $227 Brand-name: $3056	✓	✓			✓	✓	✓	✓	✓		✓		✓	✓		✓	✓	✓	✓
	Levomilnacipran	40–120 mg	$3451.73					✓					✓				✓		✓	✓	✓	✓
	Venlafaxine	75–225 mg	Generic: $170 Brand-name: $6432.02	✓	✓	✓		✓	✓	✓		✓		✓		✓	✓		✓	✓	✓	✓
Others	Bupropion	150–450 mg	Generic: $141 Brand-name: $16 616	✓	✓		✓	✓	✓	✓		✓		✓			✓		✓		✓	
	Mirtazapine	15–45 mg	Generic: $111 Brand-name: $1280			✓		✓		✓						✓		✓				
	Nefazodone	100–600 mg	$1015			✓		✓	✓	✓	✓	✓	✓	✓		✓		✓	✓			
	Trazodone	50–400 mg	Generic: $59					✓	✓	✓		✓	✓			✓			✓	✓		✓
	Vilazodone	20–40 mg	$2087						✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓
	Vortioxetine	5–20 mg	$2687					✓	✓	✓									✓	✓		✓
Anxiolytic	Buspirone	15–30 mg	$107.80						✓	✓		✓		✓					✓			

Common adverse events are defined as adverse reactions that occurred in >5% of patients and at ≥2 times the rate seen with placebo in pooled placebo-controlled clinical trials of patients with major depressive disorder. SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor. (From reference 41.)

Values and Preferences

The rapid review (35) found insufficient evidence on how patients value beneficial outcomes. In addition, low-certainty evidence suggests that insomnia, anxiety, fatigue, weight gain, agitation, and sexual dysfunction may have been the most important nonserious adverse events for patients treated with antidepressants. For most outcomes related to patient preferences, evidence was insufficient and no conclusions could be drawn. Moderate-certainty evidence showed that patients with an initial expectation of improvement in their depression probably did not differ according to planned treatment with either supportive-expressive psychotherapy or depression medications. Low-certainty evidence showed that after treatment, men may have preferred depression medications over talk therapy, whereas women may have had no specific preference overall. In addition, when participants were stratified by racial or ethnic group, non-Hispanic White participants also may have preferred treatment with depression medications over talk therapy, whereas Hispanic and non-Hispanic Black participants may have had no posttreatment preferences between the treatments (35).

The CGC Public Panel reported preferences for the use of psychological treatments in combination with or instead of SGA monotherapy as initial treatment for MDD. Consistent with the research evidence, preferences for psychological treatments were driven by the similar benefits of psychological treatments and SGAs as well as the potential for added lifestyle benefits with psychological treatments. Despite preferences for psychological treatments, the Public Panel was supportive of the recommendations. The Public Panel expressed that the recommendations take into account the benefits and the minimal, bearable harms while allowing for a flexible and personalized approach to treatment, especially given variability in the availability and affordability of CBT.

Costs

Both CBT and SGAs vary in cost. However, annual Medicare spending for selected SGAs was less than the total estimated annual CBT cost (**Appendix Figure 1** of **Supplement 2**) (37). Cost-effectiveness analyses in the United States provided low-certainty evidence that the economic value of CBT increased over time to being a cost-saving option at 5 years compared with SGAs (36, 42). However, for a time horizon of less than 5 years, data from U.S. and non-U.S. settings (Canada and Germany) were insufficient to draw conclusions about the comparative cost-effectiveness of CBT and SGAs (36). Cost consideration should support selection of the less expensive and similarly

Figure 4. Second-generation antidepressants: cautions and contraindications.

! = Caution ⦸ = Contraindication

Class	Drug	Alcohol Use Disorder or Alcohol Use	Bipolar Disorder	Bleeding Disorder	Bradycardia	Bulimia or Anorexia Nervosa	Cardiac Disease or Recent Myocardial Infarction	Child–Pugh Class A to C Hepatic Impairment or Chronic or Acute Hepatic Disease	Congestive Heart Failure	Diabetes (Type 1 or 2)	Electrolyte Abnormalities (Uncorrected)	Monoamine Oxidase Inhibitor Use Within 14 Days	Renal Impairment (Moderate to Severe)	Seizure Disorder or Seizure History	QT Prolongation
SSRIs	Citalopram	!	NR	!	⦸	NR	⦸	!	⦸	NR	⦸	⦸	NR	!	⦸
	Escitalopram	!	NR	!	!	NR	!	!	!	NR	!	⦸	NR	!	!
	Fluoxetine	!	NR	!	!	NR	!	!	!	!	!	⦸	NR	!	!
	Fluvoxamine	!	NR	!	NR	NR	NR	!	NR	NR	NR	⦸	NR	!	NR
	Paroxetine	!	NR	!	NR	NR	NR	!	NR	NR	NR	⦸	!	!	NR
	Sertraline	!	NR	!	!	NR	!	⦸	!	NR	!	⦸	NR	!	!
SNRIs	Desvenlafaxine	!	NR	!	NR	NR	!	!	NR	NR	NR	⦸	!	!	NR
	Duloxetine	⦸	NR	!	NR	NR	!	⦸	NR	!	NR	⦸	⦸	!	NR
	Levomilnacipran	!	NR	!	NR	NR	!	NR	NR	NR	NR	⦸	!	!	NR
	Venlafaxine	!	NR	!	!	NR	!	!	!	NR	!	⦸	!	!	!
Others	Bupropion	!	!	NR	NR	⦸	NR	!	NR	!	NR	⦸	!	⦸	NR
	Mirtazapine	NR	!	NR	!	NR	!	!	!	NR	!	⦸	!	!	!
	Nefazodone	NR	!	NR	NR	NR	!	⦸	NR	NR	NR	⦸	NR	!	NR
	Trazodone	!	!	!	!	NR	⦸	NR	!	NR	!	⦸	NR	!	!
	Vilazodone	NR	!	!	NR	NR	NR	NR	NR	NR	NR	⦸	NR	!	NR
	Vortioxetine	NR	!	!	NR	NR	NR	NR	NR	NR	NR	⦸	NR	!	NR
Anxiolytic	Buspirone	NR	NR	NR	NR	NR	NR	!	NR	NR	NR	⦸	⦸	NR	NR

NR = not reported; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor. (From reference 41.)

efficacious generic SGAs compared with brand-name formulations (**Figure 3**). An analysis of use of equally effective interventions of health services showed that only 50.4% of U.S. adults with MDD received psychotherapy, 81% received pharmacotherapy, and 39% received both in 2015 (43). There are ongoing initiatives to reduce economic burden for medication cost, including discounted online pharmacies for generic medications (44) and value-based pricing (45). Variation in coverage between psychotherapy and SGAs may contribute to disparate rates of use. We were unable to identify all coverage rates for psychotherapy for public and private insurers (**Tables 4e** and **4f** of **Supplement 1**). The Mental Health Parity and Addiction Equity Act (MHPAEA) had some positive effects on utilization of outpatient behavioral health services (46). However, public and private insurers' compliance with the MHPAEA is not systematically appraised.

Second-Line Treatments of Adults in the Acute Phase of MDD

Recommendation 3: ACP suggests one of the following options for patients in the acute phase of moderate to severe major depressive disorder who did not respond to initial treatment with an adequate dose of a second-generation antidepressant:

- *Switching to or augmenting with cognitive behavioral therapy (conditional recommendation; low-certainty evidence)*
- *Switching to a different second-generation antidepressant or augmenting with a second pharmacologic treatment (see Clinical Considerations) (conditional recommendation; low-certainty evidence)*

The informed decision on the options should be personalized and based on discussion of potential treatment benefits, harms, adverse effect profiles, cost, feasibility, patients' specific symptoms (such as insomnia, hypersomnia, or fluctuation in appetite), comorbidities, concomitant medication use, and patient preferences.

Rationale

If a clinically satisfactory response or remission of symptoms (measured by validated scales, such as the PHQ-9) is not achieved with initial monotherapy with an SGA (including dose optimization), switching to monotherapy with CBT or to a different SGA or augmenting SGA monotherapy with CBT or with a second pharmacologic treatment (such as mirtazapine, bupropion, or buspirone) are reasonable approaches, as these second-line treatment strategies show similar efficacy when compared with each other.

Comparative Benefits and Harms of Second-Line Treatments

Moderate-certainty evidence showed that switching from one SGA to another probably resulted in similar response and remission rates, and an initial lack of response with one SGA does not preclude response to a different one. Low-certainty evidence showed that switching SGAs may have similarly affected functional capacity and quality-of-life measures. Evidence was very uncertain (insufficient) about the effect on suicidal ideation of switching to another SGA (**Appendix Table 2a** of **Supplement 2**). Low-certainty evidence showed that switching to a different SGA may also have resulted in similar response and remission rates compared with switching from an SGA to cognitive therapy (a type of CBT) or treatment augmentation with mirtazapine (47, 48). Similar findings were observed when augmentation of an SGA with cognitive therapy was compared with pharmacologic augmentation (with bupropion or buspirone) (low certainty) (49) and when different pharmacologic augmentation strategies (with bupropion or buspirone) were compared with each other (moderate certainty) (26, 49, 50).

Evidence showed that switching from one SGA to another may have resulted in no differences in serious adverse events (low certainty) and discontinuation due to adverse events (low certainty), regardless of the type of SGA. Evidence on serious adverse events was very uncertain (insufficient) for switching to a different SGA compared with second-line switching to CBT or augmenting with CBT and when second-line pharmacologic augmentation (with bupropion or buspirone) was compared with augmenting with CBT. Low-certainty evidence showed that discontinuation due to adverse events may have been similar when second-line switching to a different SGA was compared with second-line switching to CBT or when second-line augmentation with CBT was compared with pharmacologic augmentation.

Applicability

Studies assessing second-line treatment enrolled adults (the majority of whom were female) between the ages of 18 and 65 years who had moderate to severe MDD and were diagnosed with validated scales (such as the HAM-D or the PHQ-9). Patients in these studies were initially treated with an SGA for 2 to 12 weeks before starting a second-line treatment. Most of the studies excluded patients with bipolar disorder, schizophrenia, psychotic disorders, significant risk for suicide, substance use, or severe medical conditions.

Values and Preferences

The rapid review (35) identified 1 study assessing patient expectations for treatment improvement, which also included second-line treatment involving a switch from one SGA to another in patients who did not respond after 8 weeks of treatment with the initial SGA (51). However, no specific data were reported on specific patients undergoing second-line treatment.

The feedback from the CGC Public Panel indicated a willingness to use second-line treatment options if symptoms continued after initial treatment, and the panel was supportive of the recommendation. Some panel members preferred augmentation with a second pharmacologic treatment, citing evidence of small benefit, whereas others preferred to avoid adding a pharmacologic treatment. The Public Panel expressed that the recommendation appropriately allowed for a flexible and personalized approach to treatment. Because of variation in individual patient values and preferences, offering patients alternative treatment options that are as effective as SGAs is important and may help to improve adherence and response rates.

Costs

Cost data are very sparse for the different strategies that can be used as second-line therapy (36). The only non–industry-sponsored cost-effectiveness study that was identified compared strategies involving switching from one SGA to another and reported that at a 9-week time horizon, there were no differences among bupropion, sertraline, or venlafaxine after unsuccessful treatment with citalopram (52), but evidence is very uncertain (insufficient) to allow conclusions to be drawn (36). No cost-effectiveness analysis was identified that compared nonpharmacologic versus pharmacologic treatments for adults with MDD who did not achieve remission after adequate initial treatment (36).

CLINICAL CONSIDERATIONS

- **Tables 1a** and **1b** of **Supplement 1** describe the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for MDD and categories of symptom severity. An accurate diagnosis of MDD and symptom severity is important for decisions regarding treatment and monitoring.
- When an SGA is used as initial treatment for the acute phase of moderate to severe MDD in ambulatory care (see **Figure 3** for usual total daily dose ranges for adults, costs, and common adverse events), clinicians should:
  - o Prescribe a generic SGA, if possible, rather than a far more expensive brand-name medication (53).
  - o Be aware and inform patients that up to 70% of patients may not achieve remission during the initial treatment attempt (26) and more than 60% of patients may have at least 1 adverse effect. Adverse effects including constipation, diarrhea, nausea, dizziness, insomnia, somnolence, and sexual dysfunction are common across different SGAs (seen in >5% of treated patients and at ≥2 times that with placebo) (16). All SGAs are contraindicated in patients who have used a monoamine oxidase inhibitor within the prior 2 weeks.
  - o Start treatment with a low or minimum dose to reduce the likelihood of adverse effects and improve adherence.
  - o Monitor for worsening symptoms after 1 to 2 weeks of treatment with an SGA.
  - o Verify that the optimal tolerated dose of the SGA is used if symptoms do not improve despite adherence, and consider gradually increasing the dose up to the approved maximum before switching to a second-line treatment strategy.

o Monitor for new or increased suicidal or self-harming thoughts and behaviors during the first 1 to 2 months of treatment (25, 54, 55).

- Periodically assess adherence to treatment (with both SGAs and CBT).
- For patients in the acute phase of mild MDD for whom CBT is not available or feasible, monotherapy with an SGA is a reasonable alternative approach.
- Reevaluate symptoms to monitor treatment efficacy (response and remission) and potential adverse events using validated scales, such as the PHQ-9, and clinical history.
- Once remission is achieved with an SGA, clinicians should continue the treatment strategy for at least an additional 4 to 9 months (25). When SGA treatment is discontinued, the dose should be gradually decreased (tapered) to minimize withdrawal symptoms.
- When using augmentation as a second-line treatment in patients who do not respond to initial treatment, consider augmentation of an SGA with mirtazapine, bupropion, or buspirone.
- Refer patients who have severe symptoms, marked functional impairment, or risk for self-harm to mental health services.
- Encourage exercise as a healthy lifestyle practice for adults with MDD.
- Consider team-based collaborative care involving ambulatory care physicians or practitioners and mental health specialists, such as psychiatrists, in adults with MDD.

Interventions With No Recommendations

We did not make recommendations on third-wave CBT, integrative therapy, psychodynamic therapy, St. John's wort, or the combination of an SGA with acupuncture because of concerns about feasibility, standardization, and availability in the United States. St. John's wort is not currently regulated by the U.S. Food and Drug Administration (FDA); thus, safety and efficacy have not been established and there are no current standards in place regarding the contents and potency of this supplement. Evidence was insufficient or inconclusive to recommend for or against many alternative interventions as initial monotherapy options (such as acupuncture, omega-3 fatty acids, SAMe, and exercise) (**Appendix Tables 1a** and **1b** of **Supplement 2**) or as part of initial combination therapy with an SGA (integrative therapy, third-wave CBT, omega-3 fatty acids, or exercise) (**Appendix Tables 1a** and **1b** of **Supplement 2**). Importantly, many of the CAM trials used fixed-dose SGAs and did not fully implement the FDA-approved dosing ranges (26).

Evidence Gaps and Research Needs

Future randomized controlled trials should assess the effect of different treatment options on outcomes that are important to patients, such as mental suffering, reduction of suicidal ideas and behaviors, and quality of life. Research on comparative effectiveness of newer nonpharmacologic modalities (such as digital CBT) or those that are less standardized in the United States (such as acupuncture) is needed. Research is also needed on the effectiveness of initial treatment options in patients with mild MDD to assess the effect of MDD severity on differences in effectiveness of initial treatment, the effect of comorbid anxiety disorders, second-line treatments in patients not responding to initial treatment, and patient values and preferences related to treatment choice.

Areas With Insufficient Evidence

Very few studies reported on some of the prioritized patient-important outcomes, including reduction of suicidal ideas and behaviors and quality of life (identified evidence was insufficient). The included studies provided too few data to draw conclusions about the comparative effectiveness and risk for harms for augmentation strategies involving the antipsychotic aripiprazole compared with augmentation with bupropion for second-line treatment in patients with MDD. Data on the effect of MDD severity on differences in effectiveness between SGAs and psychological treatments, between aerobic exercise and the combination of exercise and SGAs, or between subgroups of patients with and without comorbid anxiety disorders were also insufficient. Very few studies included elderly patients (such as those aged >70 years).

Areas With No Evidence

Included studies did not report on patient-important mental suffering outcomes or on any specific outcomes for patients with mild MDD receiving initial treatment. No studies were identified that assessed behavior therapy, behavior modification, humanistic therapies, yoga, or meditation for initial treatment of adults with MDD or for any second-line treatment strategies that involved CAM or exercise. No evidence was available on the influence of common psychiatric comorbidities (other than anxiety) on the effectiveness or harms of switching or augmentation strategies. No evidence was available to determine differences in comparative effectiveness and risk for harms of psychological treatments, CAM, or exercise according to different demographic characteristics, such as age, sex, race, or ethnicity. No studies were identified on the cost of adverse events associated with SGAs, other economic outcomes of downstream consequences of the disease (such as U.S. health care utilization or loss of productivity), or cost-effectiveness of nonpharmacologic treatments other than CBT or treatments for patients with mild MDD.

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Note: Clinical guidelines are meant to guide care based on the best available evidence and may not apply to all patients or

individual clinical situations. They should not be used as a replacement for a clinician's judgment. Any reference to a product or process contained in a guideline is not intended as an endorsement of any specific commercial product. All ACP clinical guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued. The CGC is planning to maintain this guideline as living and will update it if evidence emerges that leads to important changes in conclusions.

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Appendix Figure. Grading the certainty of evidence and strength of recommendations in ACP clinical guidelines using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Grading Certainty of Evidence			
High	**Confident that the true effect lies close to that of the estimate of the effect (the intervention "results in" the effect).**		
Moderate	**Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a sizeable possibility that it is substantially different (the intervention "probably results in" the effect).**		
Low	**Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect (the intervention "may result in" the effect).**		
Grading Strength of Recommendations			
Strength	**Balance of Benefits and Harms**	**Applicable Patient Population**	**Policy Implications**
Strong (ACP recommends)	**Confidence that the benefits clearly outweigh risks and burden or vice versa.**	**Applies to most patients in most circumstances.**	**Only strong recommendations could be considered as quality indicators to guide the development of accountability, reporting, and payment programs.**
Conditional (ACP suggests)	**Benefits probably outweigh the risks and burden, or vice versa, but there is appreciable uncertainty.**	**Applies to many patients but may differ depending on circumstances or patients' values and preferences.**	**Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Quality indicators would have to focus on the fact that adequate deliberation about the management options has taken place.**

ACP = American College of Physicians.