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Management of Depression in Adults
A Review

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IMPORTANCE Approximately 9% of US adults experience major depression each year, with a lifetime prevalence of approximately 17% for men and 30% for women.

OBSERVATIONS Major depression is defined by depressed mood, loss of interest in activities, and associated psychological and somatic symptoms lasting at least 2 weeks. Evaluation should include structured assessment of severity as well as risk of self-harm, suspected bipolar disorder, psychotic symptoms, substance use, and co-occurring anxiety disorder. First-line treatments include specific psychotherapies and antidepressant medications. A network meta-analysis of randomized clinical trials reported cognitive therapy, behavioral activation, problem-solving therapy, interpersonal therapy, brief psychodynamic therapy, and mindfulness-based psychotherapy all had at least medium-sized effects in symptom improvement over usual care without psychotherapy (standardized mean difference [SMD] ranging from 0.50 [95% CI, 0.20-0.81] to 0.73 [95% CI, 0.52-0.95]). A network meta-analysis of randomized clinical trials reported 21 antidepressant medications all had small- to medium-sized effects in symptom improvement over placebo (SMD ranging from 0.23 [95% CI, 0.19-0.28] for fluoxetine to 0.48 [95% CI, 0.41-0.55] for amitriptyline). Psychotherapy combined with antidepressant medication may be preferred, especially for more severe or chronic depression. A network meta-analysis of randomized clinical trials reported greater symptom improvement with combined treatment than with psychotherapy alone (SMD, 0.30 [95% CI, 0.14-0.45]) or medication alone (SMD, 0.33 [95% CI, 0.20-0.47]). When initial antidepressant medication is not effective, second-line medication treatment includes changing antidepressant medication, adding a second antidepressant, or augmenting with a nonantidepressant medication, which have approximately equal likelihood of success based on a network meta-analysis. Collaborative care programs, including systematic follow-up and outcome assessment, improve treatment effectiveness, with 1 meta-analysis reporting significantly greater symptom improvement compared with usual care (SMD, 0.42 [95% CI, 0.23-0.61]).

CONCLUSIONS AND RELEVANCE Effective first-line depression treatments include specific forms of psychotherapy and more than 20 antidepressant medications. Close monitoring significantly improves the likelihood of treatment success.

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In 2022, annual prevalence of major depression among US adults was approximately 7.0% among men and 10.4% among women, with variation across racial and ethnic groups, ranging from 6.3% among Asian people to 9.2% among non-Hispanic White people.[1] Lifetime prevalence of depression in the US is approximately 17% for men and 30% for women.[2] Risk of depression among young adults increased during the COVID-19 pandemic, with a 13.0% increase among those aged 18 to 24 years and a 9.8% increase among those aged 25 to 34 years.[3] A meta-analysis of 83 studies including 41 344 patients found an overall prevalence of 27.0% (95% CI, 24.0%-29.0%) across primary care and medical specialty outpatients.[4]

Compared with people without significant symptoms of depression, major depression is associated with an 8-fold increase in risk of suicide,[5] and moderate or severe depression symptoms are associated with an increase in all-cause mortality among adults, from 5.62 to 9.48 per 1000 person-years.[6] Annual economic burden of depression in the US includes approximately $38 billion due to time missed from work and $43 billion due to decreased productivity at work.[7] Despite 30 years of practice guidelines aiming to improve care, only 18% of people identified with significant symptoms of depression experience a 50% or greater decrease in symptoms after 6 months.[8] This review summarizes current evidence regarding the diagnosis and treatment of unipolar depression in adults.

Methods

We searched PubMed from January 2010 through February 2024 for relevant English-language systematic reviews and meta-analyses regarding 50 specific questions listed in the eAppendix in

Table 1. Screening for Complicating Factors That May Indicate Need for Consultation/Referral or Affect Management Decisions

	Prevalence among patients with depression	Screening questions or tools	Implications for management
Bipolar disorder I and II	5%[24, 25]	Screening questions (positive response requires assessment): "Do you sometimes have 'up' or 'high' periods lasting at least a few days when you have lots of energy or feel speeded up?" "Has a doctor or professional ever told you they thought you had bipolar disorder or manic-depressive illness?" 13-Item Mood Disorder Questionnaire[25] includes more detailed questions.	Specialty consultation or referral generally recommended. Antidepressant without mood stabilizer can precipitate mania.
Psychotic symptoms	NA	Screening questions (positive response requires assessment): "Have you had strange or odd experiences lately that you cannot explain?" "Do you hear things that other people cannot hear or see things that other people cannot see?" "Has it seemed like people were talking about you or taking special notice of you?"	Specialty consultation or referral generally recommended. Antidepressant and antipsychotic medication may be indicated.
Suicidal ideation	5%[20]	Score of 2 or 3 on item 9 of PHQ-9 indicates elevated risk.[20] Score of 3 or higher on Columbia Suicide Severity Rating Scale[22] indicates recent suicidal planning and score of 4 or higher indicates recent suicidal intent.	If elevated risk, additional structured risk assessment indicated. If recent suicidal planning or intent, specialty consultation recommended. If current suicidal intent, safety planning and urgent consultation or referral recommended.
Alcohol use disorder	20%[32]	Score of 4 or higher on AUDIT-C screening questionnaire can indicate need for additional assessment.[30]	Psychotherapy and/or pharmacotherapy specific for alcohol use disorder may be indicated.
Opioid or other drug use disorder	12%[32]	"How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?"[31]	Psychotherapy and/or pharmacotherapy specific for opioid use disorder may be indicated.
Anxiety disorder	40%[28]	Score of 3 or higher on GAD-2[19] screening questionnaire can indicate need for additional assessment with GAD-7.	Combined psychotherapy and medication preferred. Some antidepressants preferred.[a]

Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test; GAD, General Anxiety Disorder; NA, not applicable; PHQ-9, Patient Health Questionnaire-9.

[a] See Table 3.

the Supplement (eg, *depression + screening + systematic review or meta-analysis*). References of identified papers were reviewed and a search of published articles citing identified papers was performed. Of 176 articles retrieved, 110 that reported the largest and most recent samples are cited in this review, including 51 meta-analyses, 12 systematic reviews, 15 narrative reviews, 12 randomized clinical trials, 16 cohort studies, and 4 clinical practice guidelines. For meta-analyses comparing treatments, we reported standardized mean differences (SMDs) for changes in symptom scores when available and alternative measures, such as odds ratios for treatment response (traditionally defined as a 50% or greater decrease in symptom scores[9]), when SMD was not reported. When comparing depression treatments, SMDs of 0.2, 0.5, and 0.8 are usually considered small, medium, and large, respectively.[10]

Discussion

Clinical Presentation

The syndrome of depression is defined by symptoms of sad or depressed mood and/or loss of interest in usual activities, accompanied by other psychological symptoms (difficulty concentrating, feelings of worthlessness or excessive guilt, thoughts of death or suicide) and somatic symptoms (fatigue, changes in sleep, changes in appetite, psychomotor slowing or agitation).[11,12] The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*[11] and the World Health Organization's *International Classification of Diseases and Related Health Problems*[12] define a major depressive episode by depressed mood or loss of interest, accompanied by other psychological or somatic symptoms, persisting for most of the day, most days, over 2 weeks or more.

The presenting symptoms of depression can vary across care settings and cultures and within individuals over time. In a study of primary care clinics in 15 countries, the percentage of patients with major depression who initially presented with somatic symptoms, such as pain or fatigue, ranged from 45% to 95%.[13] However, systematic assessment identified similar core symptoms of depression, both somatic and psychological, across clinical settings, languages, and cultures.[13,14]

The US Preventive Services Task Force recommends screening for depression in primary care settings among adults and adolescents, including during pregnancy and postpartum,[15] citing evidence regarding the accuracy of screening tools and benefits of organized treatment for those identified by screening.[15] However, screening for depression that is not linked to effective treatment has no clear benefit.[16]

The Patient Health Questionnaire (PHQ-9)[17,18] accurately identifies depression across a range of populations and clinical settings. Compared with a structured research interview, a PHQ-9 score of 10 or more identifies major depression with sensitivity of approximately

Table 2. First-Line Psychotherapies for Depression

Psychotherapy	Typical formats	Key elements	Other considerations	Improvement vs usual care,[a] SMD (95% CI)
Cognitive or cognitive behavioral therapy	Individual or group, 6 to 16 sessions	Identifying and challenging or interrupting negative thoughts	Often effective for anxiety symptoms and combined with behavioral therapy (cognitive behavioral therapy)	0.67 (0.56-0.79)
Behavioral activation	Individual or group, 6 to 12 sessions	Increasing the engagement in activities that are pleasurable or bring a sense of accomplishment	Effective for anxiety symptoms	0.73 (0.52-0.95)
Problem-solving therapy	Individual or group, 6 to 12 sessions	Identifying problems and stressors and developing strategies to manage them	Effective for anxiety symptoms; specific versions tailored for older adults	0.64 (0.40-0.88)
Interpersonal therapy	12-16 individual sessions	Focuses on improving quality of interpersonal relations and interactions	Useful for unresolved grief, social isolation, and difficult life transitions (eg, divorce, retirement)	0.54 (0.32-0.76)
Psychodynamic therapy	20-50 individual sessions	Explores how unconscious motivations, often originating in childhood experiences, affect emotions, cognitions, and behaviors	Effective for anxiety disorders	0.50 (0.20-0.81)
Mindfulness-based therapy	8 group sessions	Uses meditation to bring awareness to feelings, thoughts, and situations to reduce automatic responses	Includes sessions longer than the usual 45-50 min; may be effective for patients who have not responded to other psychotherapies	0.69 (0.45-0.93)

Abbreviation: SMD, standardized mean difference.

[a] From network meta-analysis[30] including 331 randomized trials and 34 285 participants. Usual care comparison group typically included primary care treatment, with or without antidepressant medication, but no psychotherapy. When comparing depression treatments, SMDs of 0.2, 0.5, and 0.8 are usually considered small, medium, and large, respectively.[8]

85% and specificity of approximately 85%.[17,18] Screening with the first 2 items of the PHQ-9 (termed the PHQ-2), reserving the remaining items for those with scores of 2 or greater, does not reduce sensitivity.[17] PHQ-9 scores of 5 to 9 typically represent mild symptoms of depression; 10 to 14, moderate symptoms; 15 to 19, moderately severe symptoms; and 20 or more, severe symptoms.[19]

Assessment and Diagnosis

For individuals presenting with depression or those identified by screening, assessment should consider factors that usually require specialty consultation or referral, including suicidal ideation with planning or intent, likely bipolar disorder, or psychotic symptoms (**Table 1**). Approximately 5% of patients treated for depression in primary care report suicidal ideation "more than half the days" or "nearly every day" in response to item 9 of the PHQ-9, and those patients have an approximately 1% risk of self-harm or suicide attempt over the following 90 days.[20] Data from mental health specialty or inpatient samples[21] suggest that structured assessments, such as the Columbia-Suicide Severity Rating Scale,[22] can identify individuals with current or recent suicidal ideation for whom specialty consultation is recommended and those with suicidal planning and intent for whom urgent consultation or referral is recommended. When same- or next-day specialty consultation is not available, primary care clinicians can collaborate with patients and caregivers to create a safety plan or crisis response plan[23] that includes steps to reduce access to lethal means, such as firearms. At least 7% of people treated for depression in primary care may have unrecognized bipolar disorder (type I or II).[24,25] For patients with bipolar disorder, mood stabilizer medications may be indicated and treatment with antidepressants alone can precipitate mania or mood instability. Questionnaires to screen for bipolar disorder may be useful,[26] but sensitivity may be as low as 50% in primary care settings.[25,27]

Assessment should also consider co-occurring conditions that may influence treatment decisions (Table 1). Approximately 40% of people with major depression have clinically significant anxiety,[28] which may be detected through screening questionnaires such as the PHQ anxiety scale or General Anxiety Disorder-7 scale.[19] As discussed below, co-occurring anxiety may necessitate a recommendation for psychotherapy and/or selection of specific antidepressant medications that are also effective for anxiety[29] (**Table 2** and **Table 3**). Assessment should also include screening for substance use,[31,32] including alcohol use disorder (likely to be present in up to 20% of people with major depression), cannabis use disorder (likely to be present in up to 12%), or other drug use disorder (likely to be present in up to 12%).[33] Neither alcohol use disorder nor drug use disorder should preclude diagnosis of depression or delay initiation of depression treatment[34]; co-occurring substance use disorders may warrant additional pharmacologic or behavioral treatment. Medical conditions, such as chronic pain, may contribute to depression[35] and depression often amplifies pain or fatigue due to medical conditions. Some medications, such as corticosteroids and interferon alfa, may cause or exacerbate depression, although the causal relationship between β-blocker medications and depression is not clear.[36]

Unless indicated by history or examination, laboratory testing (including thyroid testing[37]), imaging, or other diagnostic procedures are not recommended to confirm the diagnosis of depression or guide treatment.

Treatment

Treatment planning should consider severity of depression, patient preferences, and treatment availability and should address patients' concerns, such as fatigue, insomnia, persistent pain, and current life stressors.

Table 3. First-Line Pharmacotherapy for Depression

AHFS classification/ generic name	Usual starting dose	Usual dose range	Additional approved indications[a]	Common adverse effects[b]	Specific precautions[c]	Improvement compared with placebo, SMD (95% CI)[d]	Discontinuation compared with placebo, OR (95% CrI)[d,e]
Selective serotonin reuptake inhibitors							
Citalopram	10 mg daily	20-40 mg daily		Dry mouth, nausea, somnolence, insomnia, sexual dysfunction	May prolong QT interval on electrocardiogram	0.24 (0.17-0.31)	0.94 (0.80-1.09)
Escitalopram	5 mg daily	10-20 mg daily	Generalized anxiety disorder	Headache, nausea, insomnia, sexual dysfunction		0.29 (0.24-0.35)	0.90 (0.80-1.02)
Fluoxetine	10 mg daily	20-60 mg daily	Panic disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, bulimia	Insomnia, nausea, headache, diarrhea, nervousness, tremor, sexual dysfunction		0.23 (0.19-0.28)	0.88 (0.80-0.96)
Paroxetine	10 mg daily	20-50 mg daily	Panic disorder, social anxiety disorder, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, menopausal vasomotor symptoms	Nausea, insomnia, dry mouth, headache, constipation, diarrhea, sexual dysfunction, tremor	More anticholinergic, avoid in elderly	0.32 (0.28-0.37)	0.95 (0.87-1.03)
Sertraline	50 mg daily	100-200 mg daily	Panic disorder, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, premenstrual dysphoric disorder	Nausea, diarrhea, insomnia, dry mouth, fatigue, dizziness, sexual dysfunction		0.27 (0.21-0.34)	0.96 (0.85-1.08)
Other antidepressants							
Bupropion[f]	150 mg daily	300-450 mg daily	Seasonal affective disorder, smoking cessation	Dry mouth, nausea, loss of appetite, insomnia, tremors	May increase risk of seizures	0.25 (0.16-0.33)	0.96 (0.81-1.14)
Mirtazapine	15 mg at bedtime	30-45 mg at bedtime		Somnolence, weight gain, dry mouth, increased appetite, constipation		0.37 (0.28-0.45)	0.99 (0.85-1.15)
Selective serotonin and norepinephrine reuptake inhibitors							
Duloxetine	30 mg daily	60-120 mg daily	Generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain	Nausea, dry mouth, headache, somnolence, fatigue		0.37 (0.31-0.44)	1.08 (0.96-1.23)
Venlafaxine[f]	75 mg daily	150-300 mg daily	Generalized anxiety disorder, social anxiety disorder, panic disorder	Headache, nausea, insomnia, fatigue, somnolence, sexual dysfunction, increased sweating, nervousness, dry mouth	May increase blood pressure	0.33 (0.28-0.39)	1.04 (0.93-1.05)

(continued)

Table 3. First-Line Pharmacotherapy for Depression (continued)

AHFS classification/ generic name	Usual starting dose	Usual dose range	Additional approved indications[a]	Common adverse effects[b]	Specific precautions[c]	Improvement compared with placebo, SMD (95% CI)[d]	Discontinuation compared with placebo, OR (95% CrI)[d,e]
Desvenlafaxine	50 mg daily	50-100 mg daily		Nausea, dry mouth, dizziness, insomnia, increased sweating, constipation, fatigue	May increase blood pressure	0.25 (0.15-0.35)	1.08 (0.88-1.33)
Levomilnacipran	20 mg daily	40-120 mg daily		Nausea, sexual dysfunction		0.27 (0.13-0.40)	1.19 (0.93-1.53)
Serotonin modulators							
Vortioxetine	5 mg daily	10-20 mg daily		Nausea		0.28 (0.20-0.36)	1.01 (0.86-1.09)
Vilazodone	10 mg daily	20-40 mg daily		Nausea, diarrhea		0.27 (0.15-0.38)	1.14 (0.88-1.47)
Tricyclic antidepressants							
Nortriptyline	25 mg at bedtime	50-100 mg at bedtime		Dry mouth, somnolence, fatigue, constipation	More anticholinergic, avoid in elderly	NA[g]	NA[g]
Desipramine	50 mg daily or at bedtime	100-200 mg daily or at bedtime		Dry mouth, somnolence, fatigue, constipation	More anticholinergic, avoid in elderly	NA[g]	NA[g]

Abbreviations: AHFS, American Hospital Formulary Service; CrI, credible interval; NA, not applicable; OR, odds ratio; SMD, standardized mean difference.

[a] Includes only indications approved by the US Food and Drug Administration. Additional off-label indications may be supported by evidence.

[b] Reported by more than 10% of participants in clinical trials.

[c] See text for general precautions regarding precipitation of suicidal ideation or behavior.

[d] From network meta-analysis[40] including 522 randomized trials and 116 477 participants. When comparing depression treatments, SMDs of 0.2, 0.5, and 0.8 are usually considered small, medium, and large, respectively.[8]

[e] Includes discontinuation for any reason.

[f] Bupropion and venlafaxine are most often prescribed in once-daily sustained-release forms.

[g] Not included in network meta-analysis.[40]

Efficacy of Psychotherapy and Antidepressant Medication

Randomized clinical trials have demonstrated the efficacy of specific types of psychotherapy (Table 2), including cognitive or cognitive behavioral therapy, behavioral activation, interpersonal therapy, problem-solving therapy, short-term psychodynamic psychotherapy, and "third-wave" or mindfulness-based therapies.[30,38] A network meta-analysis[30] including 331 randomized clinical trials and 34 285 participants found all 6 of those specific psychotherapies similarly more efficacious than usual care without psychotherapy, all with at least medium effect (SMDs ranging from 0.50 [95% CI, 0.20-0.81] for short-term dynamic psychotherapy to 0.73 [95% CI, 0.52-0.95] for behavioral activation). Those differences correspond to typical response rates of 50% with psychotherapy compared with 25% without psychotherapy. Nondirective supportive counseling, excluding the specific elements in Table 2, has smaller benefit than the specific therapies listed above.[30] A meta-analysis of 18 randomized clinical trials including 1913 participants with mild depression found specific psychotherapies more efficacious than usual care without psychotherapy with small to medium effect (SMD, 0.35 [95% CI, 0.23-0.47]).[39]

Similarly, randomized clinical trials demonstrate the efficacy of commonly used antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and other newer antidepressants.[40,41] One systematic review and network meta-analysis including 522 randomized clinical trials and 116 477 participants[40] found 21 different antidepressant medications were all more efficacious than placebo, with generally similar small to medium effects (SMDs ranging from 0.23 [95% CI, 0.19-0.28] for fluoxetine to 0.48 [95% CI, 0.41-0.55] for amitriptyline). Those differences correspond to typical response rates of 50% with antidepressant medication compared with 30% for placebo. The advantage of antidepressants over placebo varies with depression severity, with a meta-analysis of 232 placebo-controlled trials including 73 388 patients finding only small effect (SMD of approximately 0.15) for patients with mild symptoms of depression and small to medium effect (SMD of approximately 0.38) for those with severe symptoms of depression.[41]

Selection of First-Line Treatment

First-line treatment strategies for depression include psychotherapy, antidepressant medication, or a combination of the 2 (**Box**). Randomized clinical trials comparing the efficacy of first-line treatments have generally found no difference between specific psychotherapies and antidepressant medications but modestly greater efficacy for combined medication and psychotherapy over either alone, especially for more severe or chronic depression.[42,43] A network meta-analysis including 101 randomized clinical trials and 11 901 patients[42] reported no difference between psychotherapy alone and medication alone (SMD, 0.04 [95% CI, −0.09 to 0.16]), but reported combined treatment had a small to medium effect size compared with psychotherapy alone (SMD, 0.30

Box. Commonly Asked Questions About Depression

Is psychotherapy or medication more effective for treatment of major depression?
Research comparing antidepressant medication and specific psychotherapy for depression has found them equally effective. Combining medication and psychotherapy is probably more effective than either alone.

Which antidepressant medication is the best first choice?
Commonly prescribed antidepressants have similar efficacy but differ in tolerability and acceptability. Of commonly prescribed medications, escitalopram and sertraline rank well for both efficacy and acceptability.

What if first-line depression treatment doesn't work?
Up to half of people starting antidepressant medication and/or psychotherapy do not improve significantly even with adequate treatment. If initial treatment with psychotherapy alone is not effective, adding antidepressant medication should be considered. If initial treatment with medication is not effective, options include adding psychotherapy, changing medications, or adding a second medication.

[95% CI, 0.14-0.45]) or medication alone (SMD, 0.33 [95% CI, 0.20-0.47]). Those differences correspond to typical response rates of 50% with psychotherapy or medication alone compared with 65% for combined treatment. Psychotherapy or combined treatment may yield more durable benefit than antidepressant medication alone. A network meta-analysis including 81 randomized clinical trials and 13 722 patients[44] reported an odds ratio of 1.53 (95% CI, 1.00-2.35) for response sustained through 12 months for psychotherapy alone compared with antidepressant medication alone and an odds ratio of 2.52 (95% CI, 1.66-3.85) for combined treatment compared with antidepressant medication alone (absolute differences were not reported). No specific symptom patterns have reliably predicted more favorable response to antidepressant medications or specific psychotherapies.[45,46]

Based on the efficacy evidence reviewed above, as well as recent evidence-based guidelines[47-50] summarized in the **Figure**, first-line treatment depends on depression severity, patient preference, and access to specific treatments. For mild depression (PHQ-9 scores lower than 10), psychotherapies such as cognitive or cognitive behavioral therapy, behavioral activation, problem-solving therapy, interpersonal therapy, or mindfulness-based psychotherapy have moderate benefit, and antidepressant medications are usually not indicated. Exercise, St John's wort nutritional supplements, or digital interventions (discussed below) may be helpful. For moderate depression (PHQ-9 scores 10 to 14), either antidepressant medications or specific psychotherapies listed above are recommended first-line treatments. Combined medication and psychotherapy may be superior to either treatment alone. For moderately severe or severe depression (PHQ-9 scores 15 or higher), combined treatment with psychotherapy and antidepressant medication is recommended.

Treatment decisions should also consider duration of depressive symptoms and level of impairment. For example, treatment with antidepressants[51] or psychotherapy[52] may be beneficial for patients with milder symptoms of long duration (sometimes referred to as *dysthymia*).

Recommendation for or referral to psychotherapy should respect patients' preferences.[53,54] Effective referral often requires education regarding the components of psychotherapy, assessment of motivation, and addressing reservations or practical barriers. When financial barriers, lack of health insurance, and clinician shortages preclude access to effective psychotherapy, primary care clinicians can provide brief information regarding elements of effective psychotherapies (**Table 4**). However, brief advice or self-care resources do not substitute for effective psychotherapy and are not recommended treatments for moderate or more severe depression.

Meta-analyses have reported that conventional depression treatments, both medications and psychotherapy, had medium effect sizes in people with chronic medical illness[55,56] (SMD for antidepressants vs placebo, 0.42 [95% CI, 0.30-0.54]; SMD for psychotherapy vs no psychotherapy, 0.62 [95% CI, 0.52-0.79]), people who have experienced childhood trauma[57] (SMD for antidepressants or psychotherapy vs placebo or no psychotherapy, 0.61 [95% CI, 0.29-0.92]), and those recently bereaved (SMD for psychotherapy vs no psychotherapy, 0.35 [95% CI, 0.08-0.62]).[58]

Antidepressant Selection and Prescribing

While antidepressant medications have generally equal efficacy, they vary in frequency of adverse effects[40] and in US Food and Drug Administration approval for treatment of conditions that may be associated with depression (Table 3). A systematic review and network meta-analysis including 522 randomized clinical trials and 116 477 participants reported discontinuation of medication due to adverse effects was modestly lower for citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine compared with other antidepressants, with odds ratios for discontinuation for any reason of 0.43 to 0.77 compared with placebo (no absolute rates presented).[40] In that comparison of 21 antidepressants, escitalopram and sertraline were the 2 medications licensed in the US that ranked in the top half for both efficacy and acceptability. Antidepressants with stronger anticholinergic effects, such as paroxetine, desipramine, and nortriptyline, are not recommended for older patients because of increased risk of falls, delirium, and dementia.[59] Specific genetic variations affect the metabolism of antidepressant drugs, and selection of medication based on pharmacogenomic testing may reduce frequency or intensity of self-reported adverse effects.[60,61] However, antidepressant selection based on pharmacogenomic testing did not increase the likelihood of a sustained favorable treatment response.[61,62] Medications may be selected based on associated conditions, such as anxiety disorders[29] or pain conditions, for which antidepressants may be helpful (Table 3); acceptability of anticipated adverse effects; and cost.

Antidepressant medication should usually be initiated at one-third to one-half of the usual dose and increased to the lower end of the usual dosing range in 1 or 2 steps over 1 to 2 weeks (Table 3). Evidence is mixed regarding the value of higher doses. One systematic review and meta-analysis found modest evidence for greater improvement with SSRI antidepressant doses at the upper end of recommended ranges,[63] although 2 subsequent larger meta-analyses reported that higher doses did not increase the likelihood of response and may increase adverse effects.[64,65] Less severe adverse effects, such as nausea and headache, often subside over 1 to 2 weeks and improvement in depression may not appear for 2 weeks or more

Figure. Evidence-Based Guideline Recommendations for Initial First-Line Treatment of Depression According to Severity

	Mild (PHQ-9 score <10)	Moderate (PHQ-9 score 10-14)	Moderately severe (PHQ-9 score 15-19)	Severe (PHQ-9 score ≥20)
American College of Physicians (2023)[50]	Cognitive behavioral therapy (conditional recommendation, low-certainty evidence)	Cognitive behavioral therapy OR second-generation antidepressant[a] (strong evidence, moderate-certainty evidence) Cognitive behavioral therapy AND second-generation antidepressant (conditional recommendation, low-certainty evidence)		
American Psychological Association (2019)[48]	Psychotherapy[b] (conditional recommendation for use)	Psychotherapy[c] OR second-generation antidepressant (recommendation for use)		
National Institute for Health and Care Excellence (2022)[49]	Guided self-help or group or individual psychotherapy[d]		Cognitive behavioral therapy and antidepressant medication Cognitive behavioral therapy alone Behavioral activation alone Antidepressant medication alone Problem-solving therapy alone Short-term psychodynamic psychotherapy alone Interpersonal psychotherapy alone	
Veterans Affairs and Department of Defense (2022)[47]	Clinician-guided internet-based cognitive behavioral therapy either alone or with antidepressant medication (weak recommendation)	Psychotherapy[e] OR antidepressant medication (strong recommendation)		Evidence-based psychotherapy[d] AND antidepressant medication (weak recommendation)

[a]Includes citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, venlafaxine, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine, and bupropion.

[b]Cognitive behavioral therapy, interpersonal counseling, problem-solving therapy, and life review therapy.

[c]Behavioral therapy, cognitive therapy, mindfulness-based cognitive therapy, interpersonal therapy, psychodynamic psychotherapies, and supportive therapy.

[d]Group cognitive or individual cognitive behavioral therapy, behavioral activation, or mindfulness and meditation.

[e]Acceptance and commitment therapy, behavioral activation, cognitive behavioral therapy, interpersonal therapy, mindfulness-based cognitive therapy, problem-solving therapy, and short-term psychodynamic psychotherapy (weak recommendation regarding choice of psychotherapy).

after starting an antidepressant medication. Consequently, communication and encouragement early in treatment are important for early adherence. A typical schedule for follow-up visits to measure symptom improvement, adjust dose, and manage adverse effects includes initial contact at 2 weeks with subsequent visits every 4 to 6 weeks until depression remission or satisfactory treatment response. For many patients, follow-up by telephone or online messaging may substitute for in-person visits.[66,67] Absence of any benefit after 4 weeks of treatment with a dose in the recommended range should prompt consideration of second-line treatment (discussed below).

Although antidepressants can decrease preexisting suicidal ideation along with other symptoms of depression,[68] all antidepressants carry a black box warning regarding new onset of suicidal ideation and behavior after starting antidepressant treatment. A meta-analysis of 372 placebo-controlled trials including 99 231 patients reported the rate of new-onset suicidal ideation or behavior to be 5.34% higher (95% CI, 0.61%-10.1%) with antidepressants than with placebo among patients aged 18 to 25 years with no significant difference in patients aged 25 to 64 years and a 6.34% lower risk with antidepressants than placebo in patients aged 65 years and older.[69] A target trial emulation observational study of SSRI treatment and suicidal risk[70] found a similar increase in risk among patients aged 25 years or younger. Regardless of age, patients should be advised that antidepressants can rarely prompt new onset of thoughts of self-harm or suicide within a few weeks of starting treatment or increasing the dose and patients should urgently report any of these symptoms to their treating clinicians. Clinicians should also monitor patients for emergence of suicidal ideation.[71]

Alternative, Complementary, and Emerging Treatments

As summarized in a 2022 systematic review and practice guideline,[72] specific nutritional supplements may be useful adjuncts to antidepressant treatment or appropriate treatments for milder depression. A meta-analysis of 13 randomized clinical trials including 1233 participants[73] reported that omega-3 fatty acid augmentation of antidepressant medication was modestly more effective than placebo augmentation for reducing depression symptoms (SMD, 0.40 [95% CI, 0.11-0.68]). A meta-analysis of 13 randomized clinical trials including 786 participants[74] found that probiotic augmentation of antidepressant medication was modestly more effective than placebo augmentation for reducing depression symptoms (SMD, 0.36 [95% CI, 0.24-0.49]). A systematic review and meta-analysis of 18 randomized clinical trials including 2922 participants[75] found that St John's wort was more effective than placebo among patients with mild to moderate depression (SMD, 0.49 [95% CI, 0.23-0.74]). None of these nutritional supplements have strong evidence as primary treatments for moderate or severe depression.

Both acupuncture and structured exercise may augment the benefits of medication or psychotherapy. A meta-analysis of 16 randomized clinical trials including 1958 participants[76] reported that acupuncture added to antidepressant treatment was modestly more effective at reducing depression symptoms than medication alone (SMD, 0.44 [95% CI, 0.33-0.53]). A meta-analysis of 22 randomized clinical trials including 1025 participants[77] reported that structured exercise (primarily aerobic training) added to antidepressant medication or psychotherapy was moderately more effective than medication or psychotherapy alone for reducing depression symptoms (SMD, 0.62 [95% CI, 0.37-0.86]).

Table 4. Brief Counseling Strategies for General Medical Clinicians

	Examples of brief advice
Behavioral activation: scheduling positive activities	Setting small, achievable goals for positive activities can help build motivation and improve mood. Can we identify one or two positive things you could plan over the next week? When would you do those things? Can we write that down? Is there anything that might get in the way of doing these things? How could you manage those? What would help you to get started when the time comes?
Cognitive therapy: identifying and interrupting negative thoughts	What are some of the negative or self-critical thoughts you can get stuck in? How can you recognize when you're getting stuck in those exaggerated or extreme negative thoughts? What could help you to interrupt those thoughts or take away their power? What would help you to take a step back and look at the evidence about those negative thoughts?
Mindfulness-based therapy: brief mindfulness exercises	Instead of fighting against negative thoughts, it can be helpful to try just disconnecting from them. You can try to disconnect from negative thoughts by focusing on sensations in the present moment – like your breathing or things you listen to. Some ways you can do this: There are lots of mindfulness and meditation exercises on the internet or on apps. You may find you like some more than others, so try a few. Mindfulness practice is often helpful in groups. You might try searching for a group near you. These groups can vary in their approach, so it might be worth trying a few.
Problem-solving therapy: planning small, specific steps	Often when we are depressed, our lives get more disorganized, which makes us feel even worse. Try taking a few minutes to plan your day the evening before so you know what to expect and what you may need to postpone. Set 1 to 3 small, achievable goals for the next day. If you aren't able to achieve those goals, don't beat yourself up. Use it as a learning opportunity and see what got in the way. Congratulate yourself for achieving any goals, no matter how small they may seem.
Interpersonal therapy: increasing social support	There are lots of ways people can support us. Sometimes it's having someone to talk to about problems and other times it may be just doing something with someone who can help give you a sense of belonging. Is there someone in your life you feel comfortable talking with? Is there someone you'd like to spend a little time with, even if it is something like going for coffee or to a movie?

A 2023 randomized clinical trial[78] including 104 participants with moderate to severe depression observed a 42% sustained depressive symptom remission rate among those who received a single 25-mg dose of psilocybin compared with 11% among those who received an active placebo dose of niacin (adjusted absolute difference, 30.3% [95% CI, 13.5%-47.1%]) at day 43 after study drug administration. Current evidence, however, does not clearly support the effectiveness or adequately evaluate the safety of psychedelics for depression treatment.[79-81]

Digital mental health apps and programs, when designed using evidence-based psychological strategies and guided by human therapists or coaches, may be as effective as face-to-face psychotherapy.[82,83] However, many stand-alone or unguided digital interventions do not include evidence-based content, have high rates of discontinuation, and have much smaller effects on symptoms of depression.[84,85] Although unguided digital interventions are not recommended as primary treatments for moderate or severe depression, guided and validated digital interventions may be useful as a primary treatment for mild depression.

Prognosis and Second-Line Treatments

Among patients starting depression treatment in community practice, only 40% to 45% respond within 2 to 3 months of starting first-line treatment,[86-88] reflecting both early treatment discontinuation and unfavorable response to adequate treatment.

While combined psychotherapy and medication may be recommended for first-line treatment, many patients receive only 1 of these treatments. Among patients not responding to initial treatment with psychotherapy or medication alone, one-third to one-half responded favorably to adding psychotherapy to medication, adding medication to psychotherapy, changing antidepressant medication, or adding a second medication.[86] Available evidence does not indicate that changing to an antidepressant of a different type or class has greater likelihood of success than changing to a similar medication.[89,90]

Network meta-analyses[43,91] have found alternative second-line treatments have approximately equal likelihood of success, but selection depends on experience with initial treatment. For individuals who discontinue initial antidepressant treatment due to adverse effects, either depression-specific psychotherapy or an alternative medication less likely to yield similar adverse effects can be recommended. For patients not responding to initial treatment with psychotherapy alone, adding a first-line antidepressant should be considered. For those not responding to adequate dose and duration of initial antidepressant treatment, options include adding depression-specific psychotherapy, changing to an alternative antidepressant, or augmenting with a second antidepressant (typically either bupropion or mirtazapine) or with a nonantidepressant medication (**Table 5**).

When second-line treatment is ineffective, psychiatry consultation or referral to mental health specialty care should be considered. Third-line treatment options can include an alternative second-line medication (Table 4) as well as transcranial magnetic stimulation,[92,93] intranasal esketamine,[94] electroconvulsive therapy,[95] or intravenous racemic ketamine used off-label.[94,96]

Meta-analyses[97-99] do not support a specific treatment duration of either antidepressant medication or psychotherapy, but guidelines based on expert consensus[47,49] recommend varying duration of treatment depending on severity and duration of depression. For patients who experience at least 6 months of favorable response to initial medication treatment during a first episode of depression, gradually tapering and discontinuing medication over 2 to 3 months may be considered. For those experiencing a favorable outcome to first-line psychotherapy, a gradual reduction in visit frequency leading to discontinuation after 4 to 6 months is also reasonable. Tapering and discontinuing medication or psychotherapy should include discussion of warning signs of relapse and a plan for follow-up assessment a few months after end of treatment. For patients with recurrent or chronic depression, severe symptoms prior to treatment, or need for second-line treatment, treatment lasting several years or more and individualized decisions regarding tapering are recommended.[49] Abrupt discontinuation or rapid tapering of some antidepressants can precipitate discontinuation symptoms, including tinnitus, dizziness, headache, and insomnia. Systematic reviews[100,101] have reported varying prevalence of symptoms after

Table 5. Second-Line Medication Options for Depression

	Prescription method	Common adverse effects[3]
Antidepressant switch	Start second medication over 2-3 weeks, then taper first medication over 4-6 weeks	NA[a]
Augmenting with bupropion or mirtazapine	Start second medication over 2-3 weeks and continue both	NA[a]
Augmenting with nonantidepressant		
Aripiprazole	5 mg daily, increasing after 1 week to 10 mg daily	Headache, agitation, insomnia, anxiety, weight gain, nausea, hyperglycemia, dyslipidemia
Brexpiprazole	0.5 or 1 mg daily, increasing after 1 week to 1 or 2 mg daily	Headache, agitation, insomnia, anxiety, weight gain, nausea, hyperglycemia, dyslipidemia
Quetiapine	100 mg at bedtime, increasing weekly as tolerated up to 400 mg at bedtime	Somnolence, weight gain, dry mouth, constipation, headache
Olanzapine	5 mg at bedtime, increasing weekly as tolerated up to 15 mg daily	Somnolence, weight gain, dry mouth, constipation, tremor, hyperglycemia, dyslipidemia
Buspirone[b]	15 mg daily, increasing weekly as tolerated up to 15 mg 3 times daily	Somnolence, dizziness
Liothyronine[c]	25 µg daily with possible increase to 50 µg after 2 weeks	Tremors, anxiety
Lithium[c]	300 mg at bedtime, increasing weekly as tolerated to 900 mg at bedtime	Tremors, nausea, diarrhea

Abbreviation: NA, not applicable.

[a] See Table 3.

[b] Approved for treatment of generalized anxiety disorder.

[c] Used off-label.

antidepressant discontinuation, with rates of 50% or higher when medications with shorter half-life, especially venlafaxine and paroxetine, were tapered over 14 or fewer days.

Practical Considerations

Depression treatment in community practice often falls short of guideline recommendations. For example, data from 6 large health systems indicated that only 35.7% of 24 251 primary care patients with new diagnoses of depression started antidepressant medication or psychotherapy within 90 days,[102] only 71% of 184 967 patients starting antidepressant medication for depression in primary care or mental health specialty care refilled the initial prescription,[103] and only 47.6% of 242 765 patients starting psychotherapy for depression attended a second visit within 45 days.[104] A primary care clinician's role should extend beyond initial diagnosis, prescription, or referral to ensure the initiation and continuation of effective treatment and improvement in symptoms.

Organized follow-up programs, often called collaborative care in primary care or measurement-based care in specialty mental health care, address gaps in depression care by systematically monitoring treatment adherence and outcomes and then applying evidence-based algorithms to adjust or intensify treatment when symptoms do not improve.[87,88] Collaborative care programs also facilitate collaboration between primary care clinicians and consulting psychiatrists and introduce care managers to facilitate systematic follow-up. A meta-analysis of 29 randomized clinical trials including 15 255 patients[88] found collaborative or measurement-based care superior to usual care without systematic follow-up (SMD, 0.42 [95% CI, 0.23-0.61]).Those differences correspond to typical response rates of 40% to 45% in usual care and 60% to 65% in collaborative care programs.

Randomized clinical trials support efficacy of telehealth psychotherapy for depression,[105,106] with 1 meta-analysis of 155 randomized clinical trials of different delivery formats including 15 191 patients[82] reporting equivalent efficacy of telehealth and in-person cognitive behavioral therapy. The technical capacity for and familiarity with telehealth that developed during the COVID-19 pandemic may facilitate access to effective psychotherapy for patients in rural areas and for others unable to access in-person care.

Antidepressant medications and specific psychotherapies for depression are equally efficacious for Black, Hispanic, and non-Hispanic White individuals,[107,108] but Black and Hispanic patients are less likely to receive effective treatment. For example, data from 6 large health systems indicated that Black and Hispanic patients were less likely than non-Hispanic White patients to start medication or psychotherapy following a new depression diagnosis (29.9% and 30.7% vs 39.9%),[102] less likely to refill an initial antidepressant prescription (61.8% and 60.1% vs 77.0%),[103] and less likely to return following an initial psychotherapy visit (41.3% and 39.6% vs 50.1%).[104] Collaborative care programs can reduce racial and ethnic disparities in quality and effectiveness of treatment, with 2 systematic reviews[109,110] reporting that collaborative care programs improve engagement in and effectiveness of depression treatment in Black and Hispanic patients.

Limitations

This review has limitations. The quality of included studies was not formally evaluated and some relevant publications may have been missed. Regarding some questions, meta-analyses not cited reported different quantitative results. Findings regarding treatment efficacy may not translate to real-world effectiveness. Recommendations based on meta-analytic evidence may not apply to individual patients.

Conclusions

Depression is among the most common conditions treated in primary care. Effective first-line treatments include more than 20 antidepressant medications and several specific forms of psychotherapy. Close monitoring and follow-up improve the likelihood of treatment success.

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