KAISER PERMANENTE®

Adult & Adolescent Depression Screening, Diagnosis, and Treatment Guideline

Last guideline approval: May 2024

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

Changes as of May 2024

- Electrocardiogram (EKG) monitoring recommendations for patients taking citalopram and escitalopram have been updated and are now based on patient age, risk factors, and medication dose. Previously, EKG monitoring was recommended annually for all patients over age 40, regardless of medication dose.
- New guideline content has been added on:
    - Collaborative Care Model
    - Group therapy options
    - Lack of evidence for vitamin D treatment
    - Tertiary treatments for treatment-resistant depression

Target Population

The recommendations in this guideline apply to adolescents aged 13 through 17 years and to adults aged 18 years and older.

For pregnant and postpartum patients and for patients currently on antidepressants who are considering becoming pregnant, please see the KPWA Perinatal Depression Guideline.

Background

Selected populations are at increased risk for depression:

- Individuals with a personal or family history of depression
- Women with a history of domestic violence
- Individuals with chronic health conditions (e.g., diabetes, heart disease, asthma, COPD, cancer, arthritis, chronic pain, terminal illness, or neurological disorders such as stroke or Parkinson's disease)
- Individuals with a history of drug or alcohol misuse
- Individuals who identify as lesbian, gay, bisexual, or transgender (LGBT)
- Adolescents who have been subjected to bullying

Common presentations of depression include:

- Feeling down, depressed, or hopeless, or expressing little interest or pleasure in usual activities (anhedonia)
- Frequently seeking care for unexplained physical symptoms
- Persistent pain
- Difficulty adhering to medical treatment
- Irritability (in teens)

Role of Mental Health and Wellness

Consider consultation with a psychiatrist if you have questions about any aspect of diagnosis for your patient. Use **E-Consult** (available for both Adult and Child/Adolescent Psychiatry) or the **Mind Phone** consult line.

Inform patients that you are requesting a consultation from Mental Health, explain its purpose, and represent it in a nonthreatening manner (e.g., "a consult with Mental Health helps us determine the best strategy to treat many physical and emotional symptoms"). Use the Mind Phone or E-Consult for psychiatric consultation regarding patients who are not in active mental health treatment.

The **Integrated Mental Health (IMH)** model has been incorporated in all KPWA clinics. Primary care social workers function as provider extenders to address patient needs without disrupting patient flow and team cycle time. Social workers offer consultation to providers, brief interventions, and short-term (4–6 visits) counseling for individuals with mild to moderate depression and alcohol or substance use disorders. The goal is to improve access, reliability, and quality of care for patients with mental health and substance use concerns by integrating mental health into primary care clinics.

The **Collaborative Care Model (CoCM)** is an emerging approach at KPWA that expands on the IMH model. As of April 2024, CoCM has been implemented in several clinics, with plans to be rolled out to all KPWA clinics by 2026. In this model, collaborative care clinicians (CCCs) work with patients aged 13 and older with moderate to moderately severe depression and anxiety, while IMH clinicians focus on patients with mild to moderate symptoms. CCCs include social workers, who provide therapeutic counseling and monitor patient progress, and RNs, who provide medication management. Psychiatric consultants (MDs) work with the CCCs and primary care providers to advise about treatment options and discuss patients who might not be improving as expected. See the Collaborative Care SharePoint site for more information about the program.

Role of the Adolescent Center

The Adolescent Center is a resource **for adolescents who need more comprehensive integrated care** because their depressive symptoms are accompanied by comorbid medical conditions or other increased psychosocial, academic, or family risk factors. The Adolescent Center is staffed by pediatricians who are board certified in adolescent medicine; advanced registered psychiatric, family, and pediatric nurse practitioners; licensed psychotherapists; clinical psychologists; and a consulting child and adolescent psychiatrist. In KP HealthConnect, use REF ADOLESCENT CENTER to refer new patients aged 11–17 years.

Note: Adolescents who are acutely suicidal, or who only need to see a therapist, should be referred to Mental Health rather than the Adolescent Center.

Screening and Diagnosis

Table 1. Screening and diagnosis of major depressive disorder

Population	Screening frequency	Screening tool	Preliminary diagnosis via PHQ-9/PHQ-9A*
Adults (18 years and older)	Annually and when depression is suspected. .	Ask first two questions on **Annual Mental Health Questionnaire:** • Little interest or pleasure in doing things • Feeling down, depressed, or hopeless ►If patient answers **2 or 3 to *either* question,** ask remaining PHQ-9 questions on the back of the Annual Mental Health Questionnaire to further assess for depression. ►If patient answers **0 or 1 to *both* questions,** no further action.	If patient's answers to questions 3–9 bring the total score to 10 or higher on the completed PHQ-9, this is highly suggestive of major depressive disorder. Proceed to additional questions (Table 2a).
Adolescents (13 through 17 years)	Annually and when depression is suspected.	Ask first two questions on **13-17 Integrated Mental Health Screen:** • Little interest or pleasure in doing things • Feeling down, depressed, irritable, or hopeless ►If patient answers **2 or 3 to *either* question,** ask remaining questions on the PHQ-9A to further assess for depression. ► If patient answers **0 or 1 to *both* questions,** no further action.	If patient's answers to questions 3–9 bring the total score to 10 or higher on the completed PHQ-9A, this is highly suggestive of major depressive disorder. Proceed to additional questions (Table 2b).

* ***Note:*** If a patient's score on the PHQ-9 doesn't seem to accurately reflect observed clinical symptoms, refer to the **DSM-5 criteria** for guidance. If you are unsure of the diagnosis, consider consultation with a psychiatrist through the Mind Phone.

Psychiatric comorbidities and other mental health conditions and life stressors to consider

Patients with a PHQ-9 score of 10 or higher should be asked additional questions at the initial visit to assess prior history, treatment, family history, and psychiatric comorbidities.

All the screening questions for mental health conditions or life stressors listed in the following tables are included in the additional depression questions (ADQ). See Table 2a for adults, and Table 2b for adolescents. **Consider consultation or referral to Mental Health** for more definitive diagnosis and management if any of these factors are present.

Table 2a. Psychiatric comorbidities, other mental health conditions, and life stressors to consider in ADULTS		
Mental health condition or life stressor	**Additional depression questions (ADQs)** (on back of Annual Mental Health Questionnaire)	**Next steps**
Bipolar disorder	ADQ #1: At any point in your life, have you gone through periods when you felt the opposite of being depressed—very “high” or “speeded up,” with lots of energy? Didn’t need to sleep? Felt you could do anything?	If yes, consider referral to Mental Health.
Psychosis, including postpartum psychosis	ADQ #2: In the past 2 weeks, have you occasionally heard or seen things that other people couldn’t see or hear, things that might not really be there?	If yes, consider referral to Mental Health.
Abuse/violence	ADQ #3: Have you, within the past 1 to 2 years, been the victim of threats, physical hurting, or forced sexual contact?	If yes, follow up with open-ended, non-leading questions to encourage self-disclosure.
Bereavement and adjustment disorders	ADQ #4: Have you recently experienced some stressful event or life change, like the death of a friend or family member, loss of job, or relationship problems?	If yes, counsel or refer as appropriate.
Post-traumatic stress disorder (PTSD)	ADQ #5: In your life, have you ever had any experience that was so frightening, horrible, or upsetting that in the past month you: • Have had nightmares about it or thought about it when you did not want to? • Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? • Were constantly on guard, watchful, or easily startled?	If yes, refer to Mental Health for diagnosis and management.

Table 2b. Psychiatric comorbidities, other mental health conditions, and life stressors to consider in ADOLESCENTS		
Mental health condition or life stressor	**Additional depression questions (ADQs)** (on back of PHQ-9A)[1]	**Next steps**
ADHD	ADQ #12: Are you having difficulty with school work?	If yes, consider assessing for ADHD.
Anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, and panic disorder	GAD-2 ADQ #20: Over the last 2 weeks, how often have you been bothered by the following problems? • Feeling nervous, anxious, or on edge • Not being able to stop or control worrying	If score of 3 or higher, follow with GAD-7 (available in KP HealthConnect).
Being bullied[2]	ADQ #13: Are you having trouble with fighting or any kind of bullying?	If yes, assess frequency, severity, and threat level and consider referral to Mental Health.
Abuse/violence	ADQ #10: Has anyone ever hit you or touched you in a way that made you uncomfortable or afraid?	If yes, follow up with open-ended, non-leading questions to encourage self-disclosure.
Alcohol and drug use	13–17 Integrated Mental Health Screen #10–14 ("Screening to Brief Intervention," or SB2I)	If yes to 1 or more, see the Adolescent Alcohol Use Guideline for management.
Bereavement and adjustment disorders	ADQ #11: Has a close friend or family member passed away within the past 2 months?	If yes, counsel or refer as appropriate.
Medication side effects	Review medications for those that commonly can produce symptoms of depression.	Reduce or change medications as appropriate.
Post-traumatic stress disorder (PTSD)	In your life, have you ever had any experience that was so frightening, horrible, or upsetting that in the past month you: • Have had nightmares about it or thought about it when you did not want to? • Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? • Were constantly on guard, watchful, or easily startled? • Felt numb or detached from others, activities, or your surroundings?	If yes to 3 or more, refer to Mental Health for diagnosis and management.

[1] There are separate ADQs for adolescents, which appear on the flip side of the PHQ-9A. Some items on the ADQ duplicate questions from the standard wellness questionnaires; during well visits, it may be useful to acknowledge this to patients.

[2] Types of bullying include:
- Verbal: name-calling (the most common form of bullying)
- Physical: punching or pushing
- Relational: purposely leaving someone out of a game or group
- Extortion: stealing someone's money or toys
- Cyber-bullying: using computers, the Internet, or mobile phones to bully others

Severity Assessment

For adults and adolescents, depression severity is correlated with PHQ-9 and PHQ-9A scores as follows:

PHQ-9 or PHQ-9A score of:

- 20–27: Severe major depression
- 15–19: Moderately severe major depression
- 10–14: Moderate major depression
- 5–9: Indeterminate or mild depression (People with this score could have had major depression that is now improved, chronic mild depression [dysthymia], or transient mild depression. The PHQ-9 and PHQ-9A cannot distinguish among these. Use clinical judgment to determine appropriate next steps.)

Screening for Suicidal Ideation

Table 3. Screening for suicidal ideation in adults and adolescents

Suicidal ideation or suicide plan	PHQ-9/PHQ-9A Question #9: Over the past 2 weeks, how often have you been bothered by any of the following problems: thoughts that you would be better off dead, or hurting yourself in some way?	
	If the patient scores 2 or 3 on this question (or otherwise expresses suicidal thoughts or behaviors, or has suicide risk factors), administer the Columbia Suicide Risk Assessment (C-SRA). Also available as a Flowsheet. Score interpretation: 6 Acute suicide risk 3–5 Moderate risk 0–2 Low risk	**C-SRA score of 3 or higher** Requires completion of a crisis response plan and lethal means removal. While the patient is still in the room, obtain immediate consultation with a mental health professional through: • Warm patient hand-off to clinic social worker/integrated mental health specialist, or • Mind Phone. • Use **.LOCK2LIVE** to direct patients to a web-based decision aid to help individuals at risk of suicide make decisions about lethal means safety, particularly firearms and prescription medications. **C-SRA score of 0–2** Arrange a follow-up appointment with Mental Health: • Order Urgent referral to Mental Health, or • Warm patient handoff to integrated mental health specialist. • Consider a safety plan.

Screening for Substance Use Disorders in Adults

Table 4. Substance use disorders to consider in ADULTS		
Alcohol misuse (From AUDIT-C)	• Annual MH Questionnaire #3: How often did you have a drink containing alcohol in the past year? • Annual MH Questionnaire #4: How many drinks containing alcohol did you have on a typical day when you were drinking in the past year? • Annual MH Questionnaire #5: How often did you have 6 or more drinks on one occasion in the past year?	See the Adult Unhealthy Drinking Guideline.
Marijuana misuse	• Annual MH Questionnaire #6: In the past year, have you used marijuana?	If daily or almost daily, use the Substance Use Symptom Checklist in KP HealthConnect.
Drug misuse	• Annual MH Questionnaire #7: In the past year, have you used an illegal drug (not marijuana) or used a prescription medication for non-medical reasons?	If yes, use the Substance Use Symptom Checklist in KP HealthConnect.

Treatment: Goals

- Achieve complete remission.
- Prevent relapse or recurrence of depression.

Treatment: Overview of Options

Treatment recommendations are based on the patient's PHQ-9 or PHQ-9A score (see Table 1) and may include psychotherapy, antidepressants, or both. On average, antidepressant medication and psychotherapy have similar effectiveness.

Several SmartPhrases are available for use in the patient's after visit summary: .AVSDEPRESSIONWITHMEDS and .AVSDEPRESSIONWITHOUTMEDS (for adults) and .AVSDEPRESSIONADOLESCENT (for adolescents).

Supportive care is recommended for **all** patients receiving care for depression.

Supportive care

Support and education in the primary care setting are critical and contribute to the likelihood of good follow-through on treatment.

Patient education should include:

- The cause, symptoms and natural history of major depression
- Shared decision-making about treatment options
- Information on what to expect during treatment
- Follow-up (office visits, e-mail, and/or telephone)

In addition to patient education, supportive care includes emotional support and guidance. Providers can engage in behavioral activation by encouraging patients to consider and adopt some self-management responsibilities, such as writing in a journal or reading self-help books, scheduling pleasant activities, spending time with people who support them, and engaging in physical activity. Patients who are receiving supportive care but are not prescribed medications should be encouraged to follow up with a member of their clinical team within 2–4 weeks of diagnosis, **as early behavioral activation may**

improve patients' self-efficacy and continued investment in treatment. If possible, schedule follow-up at the time of diagnosis.

Psychotherapy

Psychotherapy often involves a series of structured sessions in which a provider helps the patient identify and change behaviors (isolation, inactivity, avoidance of problem-solving) and cognitions (negative rumination, magnification of bad news, minimization of good news). Individual therapy can be accessed internally via REF MENTAL HEALTH and IMH social workers, and through external partners. Both in-person and virtual care options are available. Online cognitive behavioral therapy (CBT) may be an attractive option as access to psychotherapy may be a significant barrier to care. We continue to recommend use of apps and telehealth services as adjunct or first-line treatment, based on patient preference.

Group therapy (e.g., depression and anxiety, emotional regulation, mindfulness) is an alternative or adjunct to individual therapy. Primary care providers do not refer to groups directly but instead refer the patient for MHW and then Mental Health Access Center (MHAC) contacts the patient to help determine the specific groups that patient would be eligible for.

Combination therapy

For some patients, particularly those with moderately severe to severe depression (PHQ-9 score of 15 or higher), combining psychotherapy and antidepressants may be more effective than using either treatment alone.

Antidepressants

Patients considering antidepressants need to be informed of the risks and benefits of pharmacologic treatment through a **shared decision-making process**. (See shared decision-making handout and Table 5.)

Consider consultation with a psychiatrist through the Mind Phone if you have questions about any aspect of treatment for your patient.

Treatment Recommendations by PHQ-9/PHQ-9A Score

20–27: Severe major depression

For patients with severe major depression, **combined antidepressant medication and psychotherapy** is the preferred treatment recommendation. Antidepressant medication alone is an alternative recommendation. Psychotherapy alone is **not** recommended for these patients.

Moderately severe (15–19) and moderate (10–14) major depression

For patients with moderately severe or moderate major depression, **shared decision-making** around treatment options—antidepressants, psychotherapy, and combination therapy—is recommended.

5–9: Indeterminate or mild depression

For patients with indeterminate or mild depression, treatment with antidepressants or psychotherapy is usually not recommended. **Supportive care,** including patient education and emotional support and guidance, is recommended.

Table 5. Shared decision-making regarding treatment options and recommendations		
Modality	**Advantages**	**Disadvantages**
Psychotherapy	Effective and safe—no physical side effects. Supportive visits with a specialist in addition to a primary care provider. Benefit continues after active therapy is completed.	Possible increased number of visits and copayments.
Antidepressant	Achieves greater improvement than psychotherapy in the first 2 months, after which results are equivalent. Generally well tolerated and convenient to take. More effective than psychotherapy in severe depression.	Medication side effects. See p. 12. Possible increased suicidal ideation. See “Pharmacologic Options: FDA black box warning,” below. No long-term effect after medication is discontinued.
Combination therapy	As above.	As above.

Treatment: Pharmacologic Options

FDA black box warning for all patients aged 24 years or younger

The Food and Drug Administration (FDA) requires a "black box" warning that **antidepressant medications may sometimes increase suicidal ideation** in children, adolescents, and young adults (aged 18–24) during initial treatment (generally the first 1–2 months) and at times of dose changes.

The warning reads, in part:

> Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and emergence of suicidal thoughts and behaviors.

Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, and unusual changes in behavior.

Providers should follow up with these patients a minimum of three times during the first 2 months (see Follow-up, p. 16). In high-risk patients, more frequent contact may be needed.

The overall rate of suicidal ideation is lower in patients treated with antidepressants compared to those given placebo, and this should be considered when discussing the risks and benefits of antidepressant therapy.

Pharmacogenetic tests

KPWA recommends ***against*** the routine use of pharmacogenetic testing to guide depression treatment due to limited, low-quality evidence of efficacy (primarily from industry-sponsored studies with a high risk of bias), limited clinical utility, and large out-of-pocket costs for most patients.

Overview of preferred antidepressant medications by population

Table 6. Medication preferences by population		
Line	**Adult** Full recommendations: Table 7a	**Adolescent** [4] Full recommendations: Table 7b
1st	Escitalopram[1] Fluoxetine Sertraline	Fluoxetine
2nd	Bupropion[2] Citalopram[1] Mirtazapine Paroxetine[3] Venlafaxine	Escitalopram [1] Sertraline

[1] At high doses, may cause problems with QT prolongation. See "QT prolongation and SSRIs," below.

[2] Bupropion should generally be avoided in patients with anxiety disorders.

[3] Paroxetine has a short half-life compared to other SSRIs, which may lead to serotonin withdrawal effects after missing one dose.

[4] The following are FDA approved for use in children and adolescents: fluoxetine for depression in patients aged 8 years and older; escitalopram for depression in patients aged 12 years and older; and sertraline for obsessive compulsive disorder in patients aged 6 years and older.

SSRIs

For both adults and adolescents, an SSRI is recommended as first-line pharmacological treatment. The SSRIs escitalopram, fluoxetine, and sertraline are generally better tolerated than the second-line options and are all reasonable options with similar effectiveness for treatment of major depression. A fourth SSRI, citalopram, is listed as a second-line option for new starts, but patients currently doing well on citalopram may continue to take it. The literature indicates that the efficacy of these four SSRIs does not differ significantly by sex, or among elderly or very elderly patients compared to younger patients.

Individuals vary widely in their response and tolerance to specific therapies and drugs, and it is difficult to predict which medication will be both effective and tolerable for an individual patient. Overall, SSRIs and SNRIs (such as venlafaxine) all have similar efficacy.

The decision of which SSRI to start with may be based on patient or provider preference or on previous trials with a medication.

If the first SSRI isn't successful at maximally tolerated dose of an adequate duration, switch to another first-line SSRI before moving to a second-line option. Poor response to one drug does not necessarily indicate poor response to another. Providers should assess compliance and patient response 4–8 weeks after beginning an SSRI before considering switching to another one.

QT prolongation and SSRIs

Citalopram and, to a lesser extent, **escitalopram** have been associated with QT interval prolongation. Drug-induced QT prolongation is a marker for risk of progression to torsades de pointes (TdP). While all SSRIs likely cause a slight QT prolongation, it is not thought to be clinically significant in most cases, except in patients who have certain risk factors for TdP (see Box 1).

To mitigate the potential risk of QT prolongation in patients taking SSRIs, **electrocardiogram (EKG) monitoring is recommended beginning 1–2 months after starting the medication in select clinical situations.**

For patients with **low** baseline risk for TdP (risk score of 0 or 1, see Box 1):

- **If under age 60,** EKG monitoring is recommended for citalopram/escitalopram dose **> 40 mg daily.** Obtain EKG 1–2 months after starting or increasing dose.
- **If age 60 or older,** EKG monitoring is recommended for citalopram/escitalopram dose **> 20 mg daily.** Obtain EKG 1–2 months after starting or increasing dose.

For patients with **higher** baseline risk for TdP (risk score of 2 or greater, see Box 1):

- Consider baseline EKG before initiating citalopram/escitalopram. Recheck EKG 1 month after starting citalopram/escitalopram or increasing dose. Consider ongoing monitoring based on provider discretion/risk factors.
- Use shared decision-making to review risks and benefits of citalopram/escitalopram with patients.

Note: Escitalopram is typically not recommended at doses above 20 mg/day. Also, although clinical efficacy stems from s-citalopram only (i.e., 100% of escitalopram or 50% of citalopram), s-citalopram and r-citalopram (r is the inactive enantiomer) each contribute equally to QTc prolongation risk.

Box 1: Risk factors for torsades de pointes (individual risk score in brackets)

Higher baseline risk = risk score of 2 or greater

Female [1]
Age ≥ 65 years [1]
Starvation, alcohol use disorder, methamphetamine use disorder* [1]
Potassium (K) < 3.2 mmol/L [2]
Magnesium (Mg) < 1.4 mg/dL [2]
Heart rate < 60 [2]
Heart disease (coronary artery disease, congestive heart failure, structural heart disease) [2]
Congenital or acquired long QT syndrome [3]
History of sudden cardiac death in first-degree family member [3]
Two or more QTc-prolonging agents [2]
Methadone disease ≥120 mg daily [2]

* These conditions are often associated with electrolyte deficits such as hypokalemia and hypomagnesemia.

Source: Xiong GL, Pinkhasov A, Mangal JP, et al. QTc monitoring in adults with medical and psychiatric comorbidities: Expert consensus from the Association of Medicine and Psychiatry. *J Psychosom Res.* 2020;135:110138. doi:10.1016/j.jpsychores.2020.110138

Non-SSRI medications

Patients may be prescribed non-SSRIs without a trial of SSRIs, based on patient preference or previous failure with other medications.

Medication side effects

Although antidepressant medications often have side effects, many of these can be addressed or treated:

- Headache: Try over-the-counter analgesics initially.
- Nausea: Take medication with food or divide the dose (half with breakfast, half with lunch).
- Diarrhea: Take medication before meals or divide the dose (morning and noon).
- Jitteriness or tremor: Avoid caffeinated beverages.
- Insomnia: Change timing of dose.
- Sexual dysfunction: May present as decreased libido, erectile dysfunction, anorgasmia, or ejaculatory difficulties. First, switch to an alternative antidepressant. If sexual dysfunction persists, there is evidence from a Cochrane Library meta-analysis that sildenafil improves erectile dysfunction in men with antidepressant-induced erectile problems (Rudkin 2004).
- Sedation: Uncommon but may occur. Try decreasing dose or switching to an alternative SSRI (consider a more “activating” medication like fluoxetine).

Recommended pharmacologic options for ADULTS

Table 7a. Pharmacologic options for ADULTS with major depression

Line	Medication[1]	Initial dose	Titration schedule If unsatisfactory clinical response after 2–4 weeks, then:	Usual therapeutic dose range
1st	Escitalopram	5 mg daily x 7 days, then increase to 10 mg daily.	Increase to 20 mg daily.	10–20 mg
	Fluoxetine (caps preferred)	10 mg daily before noon x 7 days, then increase to 20 mg daily before noon.	Increase by 20 mg increments at 4-week intervals.	20–60 mg
	Sertraline	50 mg daily x 7 days, then increase to 100 mg daily.	Increase in 50 mg increments at 4-week intervals.	50–200 mg
2nd	Bupropion SR	150 mg daily in the morning x 7 days, then increase to 150 mg b.i.d.	Increase to 200 mg b.i.d.	300–400 mg
	Bupropion XL	150 mg daily in the morning.	Increase to 300 mg daily.	300–450 mg
	Citalopram[2]	10 mg daily x 7 days, then increase to 20 mg daily.	Increase to 40 mg unless patient is over 60 years of age.	20–40 mg
	Mirtazapine	15 mg daily at bedtime x 7 days, then increase to 30 mg daily at bedtime.	Increase to 45 mg daily at bedtime.	15–45 mg
	Paroxetine	10 mg daily x 7 days, then increase to 20 mg daily.	Increase by 10 mg increments at 4-week intervals.	10–50 mg
	Venlafaxine XR (caps preferred)	37.5–75 mg daily with food x 7 days, then increase as tolerated to 150 mg daily.	Increase to 225 mg daily.	75–225 mg

1 Medications listed as first-line are all equally effective. They are listed in alphabetical order.
2 Citalopram is not recommended for new medication starts, but patients currently doing well on citalopram may continue to take it.

Prescribing notes – Table 7a

Frail, elderly patients and those with comorbid anxiety
Frail, elderly patients and patients with anxiety may require lower initial doses and slower titration schedules. Frail, elderly patients may require lower therapeutic doses as well. The initial antidepressant dose and titration rate may be reduced by 50%.

Citalopram and escitalopram
See “QT prolongation and SSRIs,” p. 11.

Recommended pharmacologic options for ADOLESCENTS

Table 7b. Pharmacologic options for ADOLESCENTS with major depression				
Line	**Medication**	**Initial dose**	**Titration schedule** If unsatisfactory clinical response after 2–4 weeks, then:	**Usual therapeutic dose range**
1st	Fluoxetine (caps preferred)	10 mg daily x 7 days, then 20 mg daily.	Increase by 10 mg increments at 4-week intervals (e.g., 30 mg daily x 4 weeks, then 40 mg daily).	20–40 mg
2nd	Escitalopram	5 mg daily x 7 days, then 10 mg daily.	Increase to 20 mg daily after 4 weeks.	10–20 mg
	Sertraline	25 mg daily x 7 days, then increase to 50 mg daily.	Increase by 50 mg increments at 4-week intervals.	50–200 mg (mean dose in clinical trials 130 mg)

Prescribing notes – Table 7b

The antidepressants in the table above are all reasonable treatment options for adolescents. However, some families or caregivers may prefer medications that are FDA-approved for adolescent populations.

- Both fluoxetine and escitalopram are FDA-approved for depression in adolescents.
- Sertraline is FDA-approved for obsessive-compulsive disorder in adolescents.

Escitalopram
See “QT prolongation and SSRIs,” p. 11.

Fluoxetine
Fluoxetine is FDA-approved for the treatment of depression in children as young as 8 years.

Other treatment options for depression

Supplements

See “Helping Patients Choose A Supplement” Clinical Pearl.

Omega-3s
There is some evidence that omega-3 fatty acids are more effective than placebo in reducing depression symptoms, but not enough to recommend them over standard antidepressants. Use of omega-3s as an adjunct medication may be a reasonable option.

Omega-3s are available as an over the counter supplement in fish oil. Most fish oil supplements contain a combination of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Data suggests that EPA-predominant formulations demonstrate efficacy in the treatment of depression. The recommended dose of EPA is 1–2 g daily, divided into morning and evening doses.

SAMe
With evidence findings similar to those on omega-3s, S-adenosyl-L-methionine (SAMe) may be effective as an adjunct to traditional antidepressants and may help treatment-resistant patients achieve remission of depression. The recommended dose of SAMe is 400–800 mg daily, divided into morning and evening doses.

St. John’s wort
Recent evidence suggests that St. John's wort monotherapy may be beneficial for mild to moderate depression in adults who have not responded to psychotherapy or have not tolerated other forms of pharmacotherapy. However, St. John’s wort should not be used to treat severe depression, due to a lack of evidence.

Use caution and consult a pharmacist to determine any possible drug interactions before recommending this treatment option. St. John’s wort interacts with a number of medications, including cyclosporine, digoxin, iron supplements, oral contraceptives, theophylline, warfarin, certain antidepressant medications (e.g., paroxetine, amitriptyline), and medications to treat HIV infection (e.g., indinavir).

There is a lack of studies evaluating the effects of St. John’s wort in adolescents.

Supplements that are *not* recommended
There is insufficient evidence to recommend the following supplements for treatment of depression: 5HTP, folate, Ginkgo biloba, ginseng, glutamine, or inositol.

Vitamin D
There is insufficient published evidence to recommend for or against the use of vitamin D supplementation for patients with MDD (major depressive disorder) and vitamin D deficiency. While serum vitamin D levels are inversely correlated with clinical depression, it is not clear whether this is causal, and the evidence is not strong enough to recommend universal vitamin D screening in depression.

Cannabis

Neither **CBD nor THC** is recommended for treating depression in adults and adolescents, as low-quality evidence suggests that cannabis increases depressive symptoms of anhedonia, insomnia/hypersomnia, psychomotor problems, and body weight change; there is also a lack of evidence of efficacy.

Bright light therapy

Low to moderate evidence suggests that light therapy may be safe, tolerable, and effective in improving depressive symptoms among patients with non-seasonal major depression. The recommended “dose” is 10,000 lux for 20–30 minutes per day. However, there is insufficient evidence to recommend light therapy in patients with seasonal major depression. Evidence is also insufficient to recommend light therapy as preventive treatment for patients with a history of seasonal affective disorder (SAD). Patients interested in bright light therapy should be aware that it is not a covered benefit, but light boxes are available online and in many retail locations.

Watchful waiting

Based on weak evidence, watchful waiting may be considered for adolescents and adults with mild depression who do not want an intervention. This would not be a recommendation in moderate or severe depression, given insufficient evidence.

Exercise

Exercise is recommended as an adjunct to traditional depression treatment for both adults and adolescents based on low-quality evidence that exercise may have an antidepressant effect in adult patients with MDD. Despite a lack of studies in adolescents, regular physical activity is recommended due to a low risk of harm.

Tertiary treatment options for treatment-resistant depression

Treatment-resistant depression is a type of major depressive disorder that fails to respond to treatment despite multiple trials of at least two different antidepressants. E-Consult Mental Health, staff message P MIND PHONE, or call 1-888-844-4662 for medication treatments options (e.g. lithium) for these patients.

Tertiary treatment options for treatment resistant depression (all of which require an external referral) are listed in Table 8. Information about these tertiary treatment options are included in the guideline to serve as talking points when answering questions from patients who may have heard about them in the lay literature.

Table 8. Tertiary treatment options for treatment-resistant depression

	Coverage?	FDA approved?	Comments
Pharmacologic options			
Esketamine (intranasal spray)	Coverage criteria	Yes	Weak recommendation due to limited evidence of benefits and high risk of harms (e.g., sedation and dissociation). Administration is logistically challenging, requires monitoring patient for a minimum of 2 hours post administration for adverse side effects.
Ketamine	Not covered	No	Not recommended based on insufficient evidence of efficacy and high risk of harms.
Psilocybin	Not covered	No	Not recommended. Psilocybin is classified as a Schedule I controlled substance, has a high potential for abuse, and is not currently accepted for medical use in the US.
Nonpharmacologic options			
Electroconvulsive therapy	Coverage criteria	Yes	Recommended as a safe and effective treatment for patients meeting coverage criteria.
Transcranial magnetic stimulation	Coverage criteria	Yes	Not recommended due to insufficient evidence of efficacy compared to ECT or other alternative therapies.
Vagus nerve stimulation	Coverage criteria	Yes	Not recommended based on insufficient evidence of safety and efficacy for the treatment of depression.
Deep brain stimulation	Coverage criteria	No	Not recommended based on insufficient evidence of safety and efficacy for the treatment of depression.

Follow-up

Collaborative care interventions improve treatment adherence in depression care, especially for underserved racial-ethnic populations such as African American and Latino populations. Moderate evidence has demonstrated that monthly telephone monitoring reduced depressive symptoms and increased remission rates of depression.

Patient contacts

For patients who have been prescribed medication, a minimum of three patient contacts (all can be by secure message, phone, or in person, based on clinical judgment) should be made after diagnosis. Additional contacts may be necessary depending on clinical circumstances (e.g., suicidal thoughts, side effects that may not be fully resolving).

The SmartPhrase .SMDEPFOLLOWUP can be used as part of all follow-up contacts with patients taking antidepressant medications.

- **Contact 1** (at 1 to 2 weeks): Outreach to check adherence, encourage. Can be done by appropriately trained team member.
- **Contact 2** (between 2 and 4 weeks): Assessment for side effects, treatment response, and dosage adjustment if needed. By MD/APP (advanced practice provider). Reassess depression symptoms using the Mental Health Monitoring Tool (for adults) or the PHQ-9A (for teens) and clinical judgment. Significant improvement is typically defined as a 50% decrease in PHQ-9 score. For adult patients, the PHQ-9 may be attached to an outgoing secure message.
- **Contact 3** (between 4 and 8 weeks): Ongoing assessment for side effects, treatment response, and dosage adjustment if needed. By MD/APP. Reassess depression symptoms using the Mental Health Monitoring Tool or the PHQ-9A and clinical judgment. Significant improvement is typically defined as a 50% decrease in PHQ-9 score. The Mental Health Monitoring Tool may be attached to an outgoing secure message.

For patients who are undergoing psychotherapy but have not been prescribed medications, consider follow-up in 1–2 weeks after diagnosis. Additional contacts may be needed, based on clinical judgment.

Note: Follow-up on depression symptoms is a HEDIS® measure. Use of the Mental Health Monitoring Tool at every visit meets this metric.

> **Utilization of PHQ-9 to Monitor Depression Symptoms**
> Members 12 years of age or older who had an outpatient encounter for depression/dysthymia and had a documented PHQ-9 score at that visit or during the same assessment period. The measurement year is divided into three 4-month assessment periods.

Adherence and response

For antidepressant medications, adherence to a therapeutic dose and meeting clinical goals are more important than the specific drug selected. Successful treatment often involves dosage adjustments and/or trial of a different medication to maximize response and minimize side effects. Patients who may be at higher risk for non-adherence include those who:

- Are newly diagnosed and experiencing their first episode of depression,
- Have concerns about side effects and skepticism about effectiveness,
- Have other psychological conditions or alcohol/substance abuse, or
- Have lapsed in the middle of a previous course of treatment.

Factors that may increase adherence include shared decision-making, use of a higher initial antidepressant dose, and consultation with a psychiatrist.

When antidepressant therapy is prescribed, the following key messages should be highlighted to support medication adherence and completion:

- Side effects from medication often precede therapeutic benefit and typically recede over time. It is important to expect some discomfort prior to the benefit.
- Most people need to be on medication for at least 6–12 months after adequate response of symptoms.
- Patients may show improvement at 2 weeks but need a longer length of time to really see response and remission.
- Take the medication as prescribed, **even after you feel better**. Premature discontinuation of antidepressant treatment has been associated with increased risk of relapse/recurrence of symptoms.
- Do not stop taking the medication without calling your clinician. Side effects often can be managed by changes in the dosage or dosage schedule.
- To shape a recovery that is both robust and durable, do not rely solely on medication. Improved self-care skills may help “boost” the effect of your medication and help long after medication is stopped.

Treatment duration

Table 9. Treatment duration for major depression	
Eligible population	**Recommended duration of treatment**
History of **at most one prior episode** of major depression and taking antidepressants	Continue antidepressants for 6–12 months after symptoms have improved.
History of **two or more prior episodes** of major depression and taking antidepressants	Continue treatment for 3 years or longer after remission.

Treatment discontinuation

- To minimize discontinuation/withdrawal symptoms, antidepressants should be slowly tapered over 6–12 weeks rather than discontinued abruptly. The medical literature does not adequately address which medication algorithms are safest or most successful.
- **Slow tapering** in two or three steps over a period of 2–3 months may reduce the risk of relapse and allows for improved awareness before any symptoms of relapse become severe.
- For patients who have been on treatment for prolonged periods, have recurrent depression, or have a history of hospitalization or suicide attempts, **consider tapering more slowly,** over a period of 4–6 months**.**
- Use of fluoxetine for the management of antidepressant discontinuation symptoms (because of its longer half-life) is discussed in non-systematic reviews and some published case studies, but has not been addressed in randomized controlled trial–level data.
- **Follow-up visits:** Schedule at least one phone contact or office visit during tapering of medications, and another one 2–3 weeks after discontinuing treatment.

Evidence Summary

This guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

External guidelines eligible for adapting/adopting

2023 AACAP Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Major and Persistent Depressive Disorders. Walter 2023

2023 American College of Physicians. A Clinical Guideline Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: Qaseem 2023

2022 American Psychological Association Summary of the clinical practice guideline for the treatment of depression across three age cohorts. Guideline Development Panel 2022

2023 US Preventive Services Task Force. Screening for Depression and Suicide Risk in Adults: US Preventive Services Task Force Recommendation Statement. Barry MJ 2023

2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Department of Veterans Affairs, Department of Defenses. Version 4.0-2022

Questions to the literature

1. **In adult patients with major depressive disorder (MDD) who have not responded to several adequate pharmacologic trials and psychotherapy for their disorder, what is the safety and effectiveness of augmenting the pharmacotherapy with ketamine/esketamine in improving their depression symptoms and reducing remission or relapse rates?**

   Adopted the recommendation of the 2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. For patients with MDD who have not responded to several adequate pharmacologic trials, we suggest ketamine or esketamine as an option for augmentation. (Weak for recommendation, reviewed, new, replaced).

   The literature search for the current guideline update did not identify published evidence that would add or change the VA/DoD 2022 guideline recommendation.

2. **In adult patients with treatment-resistant depression (TRD), what is the safety and effectiveness of using psilocybin in improving depression symptoms?**

   Adopted the strong recommendation of the 2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder: “Given the limited information on the safety and efficacy of psilocybin, MDMA, cannabis, and other unapproved pharmacologic treatments, we recommend against using these agents for MDD outside of a research setting.”

   The studies published after the VA guideline evidence review were phase-2 studies with methodological limitations, and do not provide more evidence to support the use of psylocibin in improving the depression symptoms in adult patients with TRD.

3. **For adults with MDD receiving treatment with citalopram or escitalopram, what is the clinical utility of using EKG monitoring to improve treatment outcomes, and what is the appropriate threshold and interval for monitoring?**

   The literature search did not identify any study examining the clinical utility of EKG monitoring in reducing the potential risk of torsades de pointes (TdP) associated with QTc interval prolongation in patients receiving citalopram. The best published literature consisted of earlier review articles.

   All recommendations on monitoring patients receiving citalopram were based on expert opinion and varied slightly between the reviewers. Overall, the following suggestions were made:
   - Screen patients for risk factors before initiation of citalopram or other QTc interval–prolonging agents and monitor those at risk accordingly.

- Do a baseline EKG for all patients before the initiation of citalopram.

The most stringent and detailed monitoring was recommended by Trinkley 2013, who recommended the following:

- When initiating a QTc interval–prolonging drug, patients must be screened for baseline risk factors.
- Those with a risk factor should undergo baseline and periodic EKGs and electrolyte monitoring throughout the entire course of treatment with QTc interval–prolonging drug.
- For high-risk patients, monitoring of EKG and electrolytes ideally occurs when plasma concentrations of the QTc-prolonging drug reach steady state, which is approximately five half-lives of the drug. This should be followed by repeat EKG measurements every month until month 6, and then every 6–12 months thereafter.
- If any follow-up EKG reveals a QTc interval between 470–500 ms in males or 480–500 ms in females, or an absolute increase in QTc interval of 60 ms, intervention may be needed, including discontinuation of the offending agent, when possible and appropriate, and/or correcting electrolyte imbalances.
- If any follow-up EKG reveals a QTc interval ≥ 500 ms, the offending agent should be discontinued, electrolytes corrected as necessary, and an additional follow-up EKG ordered.

4. For adults with MDD, what is the clinical utility of pharmacogenomic testing (PGx) in guiding medication selection and dosing compared with treatment as usual?

Adopted the recommendation of the 2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder: “There is insufficient evidence to recommend for or against the use of pharmacogenetic testing in the selection or dosing of antidepressants or selecting specific pharmacologic strategies for the treatment of MDD.”

- The more recently published studies and meta-analyses provide low-quality evidence suggesting that the use of PGx to guide antidepressant treatment may increase the rates of response and remission in adults with moderate to severe depression.
- The studies were industry-sponsored and the majority had high risk of bias.
- Different proprietary PGx tests examining different variants were used in the trials, and pooling their results in meta-analyses assumes that they have a class effect.

5. In adolescent and adult patients with MDD and vitamin D deficiency, what is the safety and effectiveness of vitamin D supplementation in reducing depression symptoms?

- There is insufficient published evidence to recommend for or against the use on vitamin D supplementation for adolescents with MDD and vitamin D deficiency.
- The published literature shows an association between vitamin D and clinical depression but does not provide sufficient evidence to determine whether it is a causal effect, nor to recommend universal vitamin D supplementation in patients with depression.
- Ther evidence on the effectiveness of vitamin D supplementation in reducing depression symptoms in patients with MDD and vitamin D deficiency is mixed. Subgroup analysis in one meta-analysis (Wang 2024) suggests that vitamin D supplementation has no significant effect on improving depressive symptoms in patients with primary depression and 25(OH)D levels < 50 nmol/L, but has a beneficial effect on improving depressive symptoms in patients with primary depression and 25 (OH)D levels > 50 nmol/L. On the other hand, a subgroup analysis performed in a different meta-analysis (Xie 2022) indicates that people with low vitamin D levels (< 50 nmol/L) and females may benefit from vitamin D in both prevention and treatment of depression. The effects of vitamin D with a daily supplementary dose of > 2,800 IU and intervention duration of ≥ 8 weeks were considered significant in both prevention and treatment analyses.

6. In adult patients with MDD, including treatment-resistant depression, what is the effectiveness and safety of switching to or adding other somatic interventions—e.g., electroconvulsive therapy (ECT), deep brain stimulation (DBS) transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS)—to their current treatment with behavioral and pharmacological therapies to improve depression symptoms?

These interventions were reviewed earlier by the KPWA Medical Technology Assessment Committee (MTAC). MPC coverage decisions and criteria at https://wa-provider.kaiserpermanente.org/clinical-review/criteria.)

2022 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder recommendations:

Electroconvulsive therapy
The guideline work group strongly recommends offering electroconvulsive therapy (ECT) with or without psychotherapy for patients with severe MDD and any of the following conditions:

- Catatonia
- Psychotic depression
- Severe suicidality
- History of a good response to ECT
- Need for rapid, definitive treatment response on either medical or psychiatric grounds
- The risks associated with other treatments are greater than the risks of ECT for the specific patient (i.e., co-occurring medical conditions make ECT the safest MDD treatment alternative)
- History of poor response or intolerable side effects with multiple antidepressants

Vagus nerve stimulation
For patients with MDD, the guideline work group makes a weak recommendation against using vagus nerve stimulation outside of a research setting.

Repetitive transcranial magnetic stimulation
For patients who have demonstrated partial or no response to two or more adequate pharmacologic treatment trials, the guideline work group makes a weak recommendation for offering repetitive transcranial magnetic stimulation for treatment.

Deep brain stimulation
For patients with MDD, the guideline work group recommends strongly against using deep brain stimulation outside of a research setting. It was determined that the potential harms/risks of deep brain stimulation outweighed its benefits.

7. In adolescents and adult patients with MDD, how did telehealth-based cognitive behavioral therapy (CBT) (computer/internet-, app-, or chat-based)—either as an adjunct to pharmacotherapy or as a first-line treatment—compare to face-to-face psychotherapy or treatment as usual in improving depression symptoms?

- Moderate-quality evidence from several meta-analyses of studies mainly conducted during the COVID epidemic (Scott 2022, Giovanetti 2022, Mamukashvili Delau 2022 and 2023, Bae 2023, Serrano-Ripoli 2022, Park 2020, Wickersham 2022, Christ 2020, Grist 2019) suggests that the overall use of telehealth-based CBT (computer/internet-based or mobile-based) may be feasible, acceptable to patients, and effective in reducing anxiety and depression symptoms in adolescent and adults.
- The meta-analyses combined trials investigating different technologies for delivering virtual/remote CBT compared to various active or non-active controls.
- There were variations between the studies in patient characteristics, diagnosis, and severity of depression as well as variations in methodological quality, risk of bias, and follow-up duration, which was insufficient to determine the long-term effects of the benefits observed.
- The different modalities used for delivering virtual/telehealth-based CBT as well as the variations among studies in the population characteristics, small sizes of individual studies, short follow-up duration, and variable dropout rates, make it hard to determine the most effective mode of delivering telehealth, and the optimal rate and duration of the intervention.

8. In adults, adolescents, and minority populations with MDD, what interventions are safe and effective in improving adherence to treatment and related health outcomes?

The published literature, including the Gonzalez 2022 and Hu 2020 meta-analyses, suggests that:

- Collaborative care is the most effective intervention in improving adherence to antidepressant therapy among adolescents and adults.
- Collaborative care was also found to be effective in improving adherence to antidepressant therapy among patients from racial or ethnic minority populations.
- Multicomponent interventions targeting the different factors that affect medication adherence problems—i.e., the patient, the health care provider, and the health care delivery system—are more effective than single-component interventions in improving medication adherence.
- A multi-professional approach to patient care is more effective than a single primary or mental health care team.
- There is insufficient published evidence to determine the effect of the interventions examined on long-term adherence to antidepressant therapy.

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Guideline Development Process and Team

Development process

The guideline team developed the Adult & Adolescent Depression Guideline using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

This edition of the guideline was approved for publication by the Guideline Oversight Group in May 2024.

Team

The Adult & Adolescent Depression Guideline development team included representatives from the following specialties: adolescent medicine, family medicine, family medicine with OB, mental health and wellness, pediatrics, pharmacy, population health, and residency.

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