

# Adult & Adolescent Depression Screening, Diagnosis, and Treatment Guideline

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**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.

## Major Changes as of April 2021

New	Previous
The use of pharmacogenetic tests in adult patients with MDD is <b>not</b> recommended, based on insufficient evidence of clinical utility.	—
The use of CBD or THC for depression is <b>not</b> recommended in either adults or adolescents.	—
Watchful waiting may be considered for adults and adolescents with mild depression.	—
Omega-3 fatty acids and SAMe are possible adjunctive options for patients with depression.	Previously, omega-3s and SAMe were not recommended for treatment of depression due to insufficient evidence.

## Target Population

The recommendations in this guideline apply to adolescents aged 12 through 17 years and to adults aged 18 years and older.

For pregnant and postpartum women and for women 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 Pediatric 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.

**A note about Integrated Mental Health:** Kaiser Permanente is working 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 goal is to create a welcoming environment for patients to address common problems— alcohol and substance use disorders as well as depression—with their primary care teams. A major element is transitioning primary care social workers to a new role—that of integrated mental health specialist—in which they will work 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. IMH is currently implemented in all KP Washington clinics.

## 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; PhD 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.	<p>Ask first two questions on <b>Annual Mental Health Questionnaire</b>:</p> <ul style="list-style-type: none"> <li>• Little interest or pleasure in doing things</li> <li>• Feeling down, depressed, or hopeless</li> </ul> <p>▶ If patient answers <b>2 or 3 to either question</b>, ask remaining PHQ-9 questions on the back of the Annual MH Questionnaire to further assess for depression.</p> <p>▶ If patient answers <b>0 or 1 to both questions</b>, no further action.</p>	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 (12 through 17 years)	Annually and when depression is suspected.	<p>Ask first two questions on <b>PHQ-9A</b>:</p> <ul style="list-style-type: none"> <li>• Little interest or pleasure in doing things</li> <li>• Feeling down, depressed, irritable, or hopeless</li> </ul> <p>▶ If patient answers <b>2 or 3 to either question</b>, ask remaining PHQ-9A questions to further assess for depression.</p> <p>▶ If patient answers <b>0 or 1 to both questions</b>, no further action.</p>	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).
* <b>Note:</b> If a patient's score on the PHQ-9 doesn't seem to accurately reflect observed clinical symptoms, refer to the <b>DSM-5 criteria</b> 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**

<b>Mental health condition or life stressor</b>	<b>Additional depression questions (ADQs)</b> (on back of Annual MH Questionnaire)	<b>Next steps</b>
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: <ul style="list-style-type: none"> <li>• Have had nightmares about it or thought about it when you did not want to?</li> <li>• Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?</li> <li>• Were constantly on guard, watchful, or easily startled?</li> </ul>	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) <sup>1</sup>	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? <ul style="list-style-type: none"> <li>• Feeling nervous, anxious, or on edge</li> <li>• Not being able to stop or control worrying</li> </ul>	If score of 3 or higher, follow with GAD-7 (available in KP HealthConnect).
Being bullied <sup>2</sup>	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	CRAFFT ADQ #14–19 or use SmartPhrase .CRAFFTSCREEN.	If yes to 2 or more, provide a brief intervention and refer to Adolescent Center or Mental Health. (See the Adolescent Alcohol Use Guideline.)
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: <ul style="list-style-type: none"> <li>• Have had nightmares about it or thought about it when you did not want to?</li> <li>• Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?</li> <li>• Were constantly on guard, watchful, or easily startled?</li> <li>• Felt numb or detached from others, activities, or your surroundings?</li> </ul>	If yes to 3 or more, refer to Mental Health for diagnosis and management.
<sup>1</sup> 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.		
<sup>2</sup> Types of bullying include: <ul style="list-style-type: none"> <li>• Verbal: name-calling (the most common form of bullying)</li> <li>• Physical: punching or pushing</li> <li>• Relational: purposely leaving someone out of a game or group</li> <li>• Extortion: stealing someone's money or toys</li> <li>• Cyber-bullying: using computers, the Internet, or mobile phones to bully others</li> </ul>		

# 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	
<p>Suicidal ideation or suicide plan</p>	<p>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?</p> <hr/> <p>If the patient scores 2 or 3 on this question (or otherwise expresses suicidal thoughts or behaviors, or has suicide risk factors), administer the Suicide Risk Assessment (SRA). Also available as a Flowsheet.</p> <p>Score interpretation: 6 Acute suicide risk 3–5 Moderate risk 0–2 Low risk</p> <p>For more information, see “Strategies for Managing Suicidal Patients” on the staff intranet.</p>
	<p><b>SRA score of 3 or higher</b> 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:</p> <ul style="list-style-type: none"> <li>• Warm patient hand-off to clinic social worker/integrated mental health specialist, or</li> <li>• Mind Phone.</li> <li>• Use <b>.LOCK2LIVE</b> 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.</li> </ul> <p><b>SRA score of 0–2</b> Arrange a follow-up appointment with Mental Health:</p> <ul style="list-style-type: none"> <li>• Order Urgent referral to Mental Health, or</li> <li>• Warm patient handoff to integrated mental health specialist.</li> <li>• Consider a safety plan.</li> </ul>

# Screening for Substance Use Disorders in Adults

Table 4. Substance use disorders to consider in ADULTS		
Alcohol misuse (From AUDIT-C)	<ul style="list-style-type: none"> <li>Annual MH Questionnaire #3: How often did you have a drink containing alcohol in the past year?</li> <li>Annual MH Questionnaire #4: How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?</li> <li>Annual MH Questionnaire #5: How often did you have 6 or more drinks on one occasion in the past year?</li> </ul>	See the Adult Unhealthy Drinking Guideline.
Marijuana misuse	<ul style="list-style-type: none"> <li>Annual MH Questionnaire #6: In the past year, have you used marijuana?</li> </ul>	If daily or almost daily, use the Substance Use Symptom Checklist in KP HealthConnect.
Drug misuse	<ul style="list-style-type: none"> <li>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?</li> </ul>	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 (Cuijpers 2014). 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). Mental Health offers therapy for major depression and other severe persistent mental illness (SPMI). Social workers are available in every primary care clinic to offer brief interventions and short-term counseling (4–6 weeks), which is better suited to patients with mild to moderate depression (PHQ-9 score from 5 through 14).

Group therapy is an alternative or adjunct to individual therapy. Patients may be referred to group therapy to learn skills and to lessen isolation. Depression and anxiety groups (DAGs) are currently offered in 11 primary care clinics and will be expanding to additional clinics in the coming months. Emotional regulation groups are also being offered in several clinics.

Online cognitive behavioral therapy (CBT) may be an attractive option as access to psychotherapy may be a significant barrier to care.

## Combination therapy

For some patients, particularly those with 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
<b>Psychotherapy</b>	<p>Effective and safe—no physical side effects.</p> <p>Supportive visits with a specialist in addition to a primary care physician.</p> <p>Benefit continues after active therapy is completed.</p>	Possible increased number of visits and copayments.
<b>Antidepressant</b>	<p>Achieves greater improvement than psychotherapy in the first 2 months, after which results are equivalent.</p> <p>Generally well tolerated and convenient to take.</p> <p>More effective than psychotherapy in severe depression.</p>	<p>Medication side effects. See p.12.</p> <p>Possible increased suicidal ideation. See “Pharmacologic Options: FDA black box warning,” below.</p> <p>No long-term effect after medication is discontinued.</p>
<b>Combination therapy</b>	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:

Patients treated with antidepressants should be observed for clinical worsening and new suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy.

A pooled analysis of placebo-controlled trials suggests:

- For patients < 18 years of age: 14 additional cases of new suicidal ideation per 1,000 patients (number needed to harm [NNH]=71)
- For patients 18–24 years of age: 5 additional cases of new suicidal ideation per 1,000 patients (NNH=200)

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 use of pharmacogenetic tests to guide depression treatment. While several pharmacogenetic tests have recently been developed, there is currently insufficient data to support their widespread use in clinical practice.

## Overview of preferred antidepressant medications by population

Table 6. Medication preferences by population		
Line	Adult Full recommendations: Table 7	Adolescent <sup>4</sup> Full recommendations: Table 8
1st	Escitalopram <sup>1</sup> Fluoxetine Sertraline	Fluoxetine
2nd	Bupropion <sup>2</sup> Citalopram <sup>1</sup> Mirtazapine Paroxetine <sup>3</sup> Venlafaxine	Escitalopram <sup>1</sup> Sertraline
<sup>1</sup> At high doses, may cause problems with QT prolongation. See “QT prolongation and SSRIs,” below. <sup>2</sup> Bupropion should generally be avoided in patients with anxiety disorders. <sup>3</sup> Paroxetine has a short half-life compared to other SSRIs, which may lead to serotonin withdrawal effects after missing one dose. <sup>4</sup> 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 maximum dose, 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. While all SSRIs likely cause a slight QT prolongation, it is not thought to be clinically significant in most cases, with these two exceptions:

- **Citalopram** may cause dose-dependent QT prolongation at doses exceeding 40 mg per day. Shared decision-making is recommended to review the risks and benefits of higher-dose citalopram therapy with the patient. Additional clinical monitoring, including obtaining an EKG, is recommended for patients taking doses higher than 40 mg.
  - Use caution in prescribing citalopram at doses higher than 20 mg in patients who may have increased levels of citalopram in the blood (those over 60 years of age, with hepatic impairment, with poor metabolism of CYP 2C19, or taking concomitant CYP 2C19 inhibitors).
  - Use caution in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure.
- Evidence suggests that **escitalopram** may cause similar QT interval prolongation as citalopram at the recommended initial dose and with dose escalation, although the level of evidence is somewhat weaker than it is for citalopram (Castro 2013). Shared decision-making is recommended to review the risks and benefits of this medication with the patient.

### 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 switching to half-strength dosing.

## Recommended pharmacologic options for ADULTS

<b>Table 7. Pharmacologic options for ADULTS with major depression</b>				
<b>Line</b>	<b>Medication <sup>1</sup></b>	<b>Initial dose</b>	<b>Titration schedule</b> If unsatisfactory clinical response after 2–4 weeks, then:	<b>Usual therapeutic dose range</b>
<b>1<sup>st</sup></b>	Escitalopram	5 mg daily x 7 days, then increase to 10 mg daily.	Increase to 20 mg daily.	10–20 mg
	Fluoxetine	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
<b>2<sup>nd</sup></b>	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 <sup>2</sup>	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)	75 mg daily with food x 7 days, then increase to 150 mg daily.	Increase to 225 mg daily.	75–225 mg
<b>1</b>	Medications listed as first-line are all equally effective. They are listed in alphabetical order.			
<b>2</b>	Citalopram is not recommended for new medication starts, but patients currently doing well on citalopram may continue to take it.			

### Prescribing notes – Table 7

#### **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. 12.

## Recommended pharmacologic options for ADOLESCENTS

<b>Table 8. Pharmacologic options for ADOLESCENTS with major depression</b>				
<b>Line</b>	<b>Medication</b>	<b>Initial dose</b>	<b>Titration schedule</b> If unsatisfactory clinical response after 2–4 weeks, then:	<b>Usual therapeutic dose range</b>
<b>1st</b>	Fluoxetine	10 mg daily x 7 days, then 20 mg daily x 3 weeks.	Increase by 10 mg increments at 4-week intervals (e.g., 30 mg daily x 4 weeks, then 40 mg daily).	20–40 mg
<b>2nd</b>	Escitalopram	5 mg once daily x 7 days, then 10 mg once 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 x 3 weeks.	Increase by 50 mg increments at 4-week intervals.	50–200 mg (mean dose in clinical trials 130 mg)

### Prescribing notes – Table 8

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. 12.

#### **Fluoxetine**

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

## Other treatment options

### Supplements

#### **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.

### **Not recommended**

There is insufficient evidence to recommend the following supplements for treatment of depression: 5HTP, folate, Ginkgo biloba, ginseng, glutamine, or inositol.

### **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.

# 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 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

<b>Table 9. Treatment duration for major depression</b>	
<b>Eligible population</b>	<b>Recommended duration of treatment</b>
History of <b>at most one prior episode</b> of major depression and taking antidepressants	Continue antidepressants for 6–12 months after symptoms have improved.
History of <b>two or more prior episodes</b> 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

2019 American Psychological Association (APA) Guideline for the Treatment of Depression

2019 National Institute for Health and Care Excellence (NICE) Depression in children and young people: identification and management <https://www.nice.org.uk/guidance/ng134>

2019 NICE Depression in adults: recognition and management <https://www.nice.org.uk/guidance/cg90>

2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments <https://pubmed.ncbi.nlm.nih.gov/27486148/>

2018 American Academy of Pediatrics (AAP) Guidelines for Adolescent Depression in Primary Care (GLADPC): Part II. Treatment and Ongoing Management <https://pubmed.ncbi.nlm.nih.gov/29483201/>

## Questions to the literature

- 1. In Black, Indigenous, Native American, Hispanic, and Asian patients with major depressive disorder (MDD), which interventions are effective in terms of adherence to treatment? Which factors impact adherence to treatment?**

There is insufficient evidence to determine interventions or factors known to improve antidepressant adherence in patients belonging to racial or ethnic minority groups.

- 2. What is the effectiveness and safety of omega-3 fatty acids (O3FAs) and S-adenosyl-L-methionine (SAME) in adult and adolescent patients with major depressive disorder?**

Three systematic reviews (Bai 2020, Bozzatello 2019, Cuomo 2020) and six randomized controlled trials (RCTs) (Gabbay 2018, Sarris 2018, Sarris 2019, Sarris 2020, Tayama 2019, Saccarello 2020) were reviewed. Depression symptoms were mild to moderate.

O3FAs were compared with placebo and administered to patients as monotherapy or as adjunct treatment. The findings were mixed. Some studies showed that O3FAs reduced depression symptoms in MDD while other trials indicated that O3FAs were comparable to placebo. O3FAs seemed to have a favorable safety profile, as no serious adverse events were reported. The quality of the studies was low.

Mixed results were reported for SAME in low-quality studies. In addition, SAME was reasonably tolerated.

- 3. What is the effectiveness and safety of THC, CBD, and St. John's wort in adult and adolescent patients with major depressive disorder?**

### *St. John's wort*

A systematic review and meta-analysis (Apaydin 2016) with good methodological quality was reviewed. The review included 35 RCTs (6,993 patients) with poor to good quality and sample size varying from 30 to 370 patients. St. John's wort (SJW) was compared to placebo or antidepressants. Follow-up varied from 4 to 24 weeks.

SJW, as monotherapy, may be more effective than placebo for reduction of depressive symptoms and comparable to antidepressants in adult patients with mild to moderate MDD. Although safety assessment was limited, SJW may result in fewer adverse events compared to antidepressants. Two other systematic reviews and meta-analyses of RCTs (Asher 2017, Ng 2017) support the findings above. Long-term outcomes and SJW as adjunctive to antidepressants are not known. The quality of the studies reviewed was low to moderate.

### THC, CBD

Three systematic reviews (Black 2019, Khoury 2019, Botsford 2020) and two secondary analyses (Bahorik 2018, Feingold 2017) were reviewed. Participants were adult patients with depression (MDD, depression secondary to chronic disease). Interventions included cannabinoids, cannabis, THC, CBD, and/or marijuana. Comparators included placebo. Overall, there is no evidence supporting the effectiveness of THC/CBD in adults or adolescents with MDD. THC/CBD may worsen some symptoms of depression.

#### 4. What is the effectiveness of exercise in adult and adolescent patients with major depressive disorder?

Six systematic reviews and meta-analyses were reviewed (Morres 2019, Chen 2019, Asher 2017, Kvam 2016, Krogh 2017, Schuch 2016). Participants were adult patients with mild to moderate MDD. Few patients had minor depression or dysthymia. Physical activity was compared to no exercise, and to placebo, usual care, antidepressants, psychotherapy, no treatment, or waiting list. Exercise duration varied and the length of trials was 3 to 32 weeks. Overall, exercise was associated with reduction of depressive symptoms. However, the quality of the trials included in the reviews was low.

#### 5. When and how should antidepressants be discontinued in adolescents with major depressive disorder? How much antidepressant maintenance is needed in adolescents with MDD in remission? What is the effectiveness of fluoxetine on antidepressant discontinuation symptoms in adults and adolescents?

The AAP 2018 and NICE 2019 guidelines have been adopted.

There is insufficient evidence for or against the effectiveness of fluoxetine for the management of antidepressants discontinuation symptoms. The studies reviewed were case reports, consensus, and review/opinions.

#### 6. What is the clinical utility of genomic testing in major depressive disorder?

There is insufficient evidence to support the clinical utility of pharmacogenetic tests in adult patients with MDD. More studies are needed.

#### 7. What is the effectiveness of watchful waiting in adult and adolescent patients with mild to moderate MDD?

A systematic review of three RCTs (Iglesias-González 2017) compared watchful waiting with antidepressants in a primary care setting in adult patients with subclinical to mild depression. Watchful waiting consisted of supportive care without antidepressants. Follow-up was provided every week or 2 weeks up to 12 weeks. While one of the studies reported a statistically significant improvement in depressive symptoms at 26 weeks (-1.688 [-3.33; -0.05], P=0.043), the remainder reported no statistically significant difference between groups. Thus, watchful waiting may be comparable to antidepressants in adult patients with subclinical or mild depression. High-quality studies are warranted.

Regarding moderate depression, the evidence is insufficient to determine the effectiveness of watchful waiting in adult patients.

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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 April 2021.

## 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, nursing operations, pharmacy, and residency.

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