KAISER PERMANENTE®

Adult and Adolescent Depression Screening, Diagnosis, and Treatment Guideline

Last guideline approval: January 2017

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 January 2017

New	Previous
We now recommend more frequent screening for depression in **pregnant women:** once per trimester (at initial visit and at 16 and 32 weeks) and at the 6-week postpartum visit.	Previously, we recommended that pregnant women be screened at the same frequency as all adults: at well visits and when depression is suspected.
Sertraline is now recommended as the only first-line antidepressant for **pregnant and lactating women.**	Previously, fluoxetine was also recommended as a first-line antidepressant for pregnant and lactating women.
Fluoxetine is now recommended as the only first-line antidepressant for **adolescents.**	Previously, citalopram, escitalopram, fluoxetine, and sertraline were recommended as first-line antidepressants for adolescents.
Citalopram is now recommended as a second-line antidepressant for **adults.**	Previously, citalopram was recommended as a first-line antidepressant for adults.

Target Population

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

Background

Selected populations are at increased risk for depression:

- Individuals with a personal or family history of depression
- Pregnant and postpartum women
- 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 Behavioral Health Services

Consider consultation with a psychiatrist if you have questions about any aspect of diagnosis for your patient. Use the Behavioral Health Services (BHS) Mind Phone consult line.

- If any of the psychiatric comorbidities listed in Table 2 (p. 5) is present, consider referring the patient to BHS for more definitive diagnosis and management.
- If any of the mental health conditions or life stressors listed in Table 3a or 3b (pp. 6–7) is present, consider consultation or referral to BHS for more definitive diagnosis and management.

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

A note about Behavioral Health Integration (BHI): Kaiser Permanente is working to improve access, reliability, and quality of care for patients with mental health and substance use concerns by integrating behavioral health into primary care clinics. The goal of BHI is to create a welcoming environment for patients to address common problems—unhealthy alcohol use, as well as depression—with their primary care teams. A major element of BHI is transitioning primary care social workers to a new role—that of integrated behavioral 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, or short-term (4–6 visits) counseling for individuals with mild to moderate depression and alcohol or substance use disorders. BHI will be implemented in all Kaiser Foundation Health Plan of Washington clinics by mid-2018.

Role of Adolescent Center

The Adolescent Center is a resource for all adolescents (ages 11–18) with depressive symptoms, particularly those with an unclear diagnosis or with mental health, academic, medical, or psychosocial risks and comorbidities. The Center is staffed by a board-certified adolescent medicine physician, a child and adolescent psychologist, a consulting child and adolescent psychiatrist, pediatric and psychiatric nurse practitioners, and masters level therapists. Families are included as integral members of the treatment program. In Epic, use REF ADOLESCENT CENTER to refer.

Note: Adolescents who are acutely suicidal should be referred to BHS rather than the Adolescent Center.

Screening and Diagnosis Using the PHQ-9 or PHQ-9A

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 (see Appendix 3) for guidance. If you are unsure of the diagnosis, consider consultation with a psychiatrist through the BHS Mind Phone.

Table 1. Screening and diagnosis of major depressive disorder using the PHQ-9 or PHQ-9A

Population	Screening frequency	Screening: Questions 1 & 2	Diagnosis: Completed questionnaire
Adults (18 years and older)	At well visits and when depression is suspected. Annually at clinics with Behavioral Health Integration.	For adults and pregnant women: Ask first two questions on PHQ-9: 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 to determine diagnosis. ► If patient answers **0 or 1 to *both* questions,** no further action.	For adults and pregnant women: 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. For ICD-10 coding, see this **job aid** on the staff intranet.
Pregnant women	At initial prenatal visit, 16-week visit, and 32-week visit (once per trimester) and at 6 weeks postpartum.		
Adolescents (12 through 17 years)	At well visits and when depression is suspected.	Ask first two questions on PHQ-9A: Little interest or pleasure in doing things Feeling down, depressed, irritable, or hopeless If patient answers 2 or 3 to *either* question, ask remaining PHQ-9A questions to determine diagnosis. ► 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. For ICD-10 coding, see this **job aid** on the staff intranet.

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.)

Comorbidity Identification

Psychiatric comorbidities to exclude

Table 2. Psychiatric comorbidities to exclude before developing depression treatment recommendations in adults and adolescents

Mental health condition	Screening	Next steps
Bipolar disorder	Additional Depression Question: 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?	Consider referral to BHS.
Psychosis, including postpartum psychosis	Additional Depression Question: 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?	Consider referral to BHS.
Suicidal ideation or suicide plan	PHQ-9/PHQ-9A question: 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 (SRA). Also available as an Epic Flowsheet. Score interpretation: 6 Acute suicide risk 3–5 Moderate risk 0–2 Low risk For more information, see "Strategies for Managing Suicidal Patients" in the BHS section of the staff intranet.	**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 behavioral health professional through: • Warm patient hand-off to clinic social worker/integrated behavioral health specialist, or • Mind Phone **SRA score of 0–2** Arrange a follow-up appointment with Behavioral Health: • Epic order Urgent referral to BHS, or • Warm patient handoff to integrated behavioral health specialist if available • Consider a safety plan

Other mental health conditions and life stressors to consider

Patients who meet major depression diagnostic criteria should be asked the Additional Depression Questions (ADQs) at the initial visit to assess prior history, treatment, family history, and psychiatric comorbidities. There are separate ADQs for adults and adolescents, which appear on the flip side of the PHQ-9 and PHQ-9A, respectively. Some items on the ADQ duplicate questions from the standard wellness questionnaires; during well visits, it may be useful to acknowledge this to patients.

All of the screening questions for mental health conditions or life stressors listed in the following tables are included in the ADQ. See Table 3a for adults, and Table 3b for adolescents. **Consider consultation or referral to BHS** for more definitive diagnosis and management if any of these factors are present.

Table 3a. Other mental health conditions and life stressors to consider in ADULTS

Mental health condition or life stressor	Screening questions	Next steps
Anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, and panic disorder	GAD-2 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 the GAD-7. (Available in Epic.)
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?	Refer to BHS for diagnosis and management.
Drug misuse	In the past 12 months, have you used drugs other than those required for medical reasons?	If yes, use the Substance Disorder Checklist in Epic.
Marijuana misuse	In the past 12 months, how often have you used marijuana?	If daily or almost daily, use the Substance Disorder Checklist in Epic.
Alcohol misuse	AUDIT-C See the ADQ for Adults, questions 14–16.	See the Adult Unhealthy Drinking Guideline.
Bereavement [1] and adjustment disorders	Has a close friend or family member passed away within the past 2 months?	Counsel or refer as appropriate.
Abuse/violence	Have you, within the past 1 to 2 years, been the victim of threats, physical hurting, bullying, or forced sexual contact?	If yes, follow up with open-ended, non-leading questions to encourage self-disclosure.
Medication side effects	Review medications for those that commonly can produce symptoms of depression, including sedative-hypnotics, beta-blockers, steroids, and isotretinoin (Accutane).	Reduce or change medications.

[1] In DSM-IV, individuals experiencing bereavement (lasting less than 2 months following the death of a loved one) were excluded from being diagnosed with major depression. In DSM-5, the bereavement exclusion was omitted. See Appendix 3 for more information.

Table 3b. Other mental health conditions and life stressors to consider in ADOLESCENTS		
Mental health condition or life stressor	**Screening questions**	**Next steps**
ADHD	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 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 Epic).
Being bullied [1]	Are you having trouble with fighting or any kind of bullying?	If yes, assess frequency, severity, and threat level and consider referral to Adolescent Center or BHS.
Abuse/violence	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 See the ADQ for Adolescents, questions 14–19 or use SmartPhrase .CRAFFTSCREEN.	If yes to 2 or more, provide a brief intervention and refer to Adolescent Center or BHS. (See the Adolescent Alcohol Use Guideline.)
Bereavement [2] and adjustment disorders	Has a close friend or family member passed away within the past 2 months?	Counsel or refer as appropriate.
Medication side effects	Review medications for those that commonly can produce symptoms of depression, such as isotretinoin (Accutane).	Reduce or change medications.
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 BHS for diagnosis and management.

[1] 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

[2] In DSM-IV, individuals experiencing bereavement (lasting less than 2 months following the death of a loved one) were excluded from being diagnosed with major depression. In DSM-5, the bereavement exclusion was omitted. See Appendix 3 for more information.

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, p. 4) 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). For pregnant or lactating women starting or continuing antidepressant medications, see Table 7a, p. 14.

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 the course of 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, and 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

Behavioral Health Services offers therapy for major depression. 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). Patients may be referred to group therapy to learn skills and to lessen isolation.

Social workers in clinics where Behavioral Health Integration has been implemented offer brief interventions and short-term counseling (4–6 weeks), which is better suited to patients with mild to moderate depression.

Combination therapy

For some patients, particularly those with severe depression, 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 Table 4, p. 9.)

Consider consultation with a psychiatrist through the BHS 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. (See previous page.)

Table 4. 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 physician. 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. 11. Possible increased suicidal ideation. See “Pharmacologic Options: FDA black box warning,” p. 10. 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:

> 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. 18). 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. For further information about the FDA review and advisory, visit the FDA website at www.fda.gov/cder/drug/antidepressants/default.htm.

Overview of preferred antidepressant medications by population

Table 5. Medication preferences by population

Line	Adult Full recommendations: Table 6	Pregnant or breastfeeding Full recommendations: Table 7a	Adolescent [4] Full recommendations: Table 8
1st	Escitalopram [1] Fluoxetine Sertraline	Sertraline	Fluoxetine
2nd	Bupropion [2] Citalopram [1] Mirtazapine Paroxetine [3] Venlafaxine	Citalopram [1] Fluoxetine	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. It is also contraindicated during pregnancy.
[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 all populations in this guideline—adults, pregnant or breastfeeding women, 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 the 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 to 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 those 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.
- Weight loss: Although it is considered a side effect of SSRIs, in actual practice there is little evidence for significant weight loss in most patients—approximately 1% per year versus placebo (Goldstein 1994).

Recommended pharmacologic options for ADULTS

Table 6. 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	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 [2]	150 mg daily in the morning.	Increase to 300 mg daily.	300–450 mg
	Citalopram [3]	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

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

Prescribing notes – Table 6

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%. If prescribing bupropion or venlafaxine, start with the immediate-release formulation and titrate before switching to the extended-release formulation.

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

Recommended pharmacologic options for PREGNANT OR BREASTFEEDING WOMEN

Table 7a. Pharmacologic options for PREGNANT OR BREASTFEEDING WOMEN with major depression

For women starting or continuing antidepressants during or after pregnancy, use SmartPhrases .AVSPREGDEPRESSIONMEDSTART, .AVSPREGDEPRESSIONMEDCONT, or .AVSPREGDEPRESSIONBREASTFEEDING.

Line	Medication	Initial dose	Titration schedule If unsatisfactory clinical response after 2–4 weeks, then:	Usual therapeutic dose range
1st	Sertraline	50 mg daily x 7 days, then increase to 100 mg daily.	Increase by 50 mg increments at 4-week intervals.	50–200 mg
2nd	Citalopram	10 mg daily x 7 days, then increase to 20 mg daily.	Increase to 40 mg after 2 weeks.	20–40 mg
	Fluoxetine	10 mg daily x 7 days, then 20 mg daily x 4 weeks.	Increase by 10 mg increments at 4-week intervals.	20–40 mg

Prescribing notes – Table 7a

Based on animal studies and human experience, sertraline, citalopram, escitalopram, fluoxetine, venlafaxine, and bupropion are not expected to increase the risk of major congenital anomalies in pregnant women.

Sertraline
Sertraline is the preferred SSRI in late pregnancy and during lactation due to lower drug levels in breast milk. For women stable on fluoxetine or citalopram during pregnancy, the possible benefits of switching to sertraline for breastfeeding must be balanced against the possible disruption of switching medication.

Fluoxetine
The average amount of drug in breast milk is higher with fluoxetine than with most other SSRIs and the long-acting, active metabolite norfluoxetine is detectable in the serum of most breastfed infants during the first 2 months postpartum and in a few thereafter. Adverse effects such as colic, fussiness, and drowsiness have been reported in some breastfed infants. However, if the mother was taking fluoxetine during pregnancy or if other antidepressants have been ineffective, most experts recommend against changing medications during breastfeeding.

Citalopram
Citalopram is excreted into human breast milk. Compared with other SSRI antidepressants, the relative dose to the infant from citalopram was comparable to fluoxetine but higher than that for sertraline and paroxetine. If citalopram is required by the mother, it is not a reason to discontinue breastfeeding. See “QT prolongation and SSRIs,” p. 11.

Escitalopram
Based on limited data, escitalopram appears to be preferable to racemic citalopram during breastfeeding because of the lower dosage and milk levels and general lack of adverse reactions in breastfed infants. See “QT prolongation and SSRIs,” p. 11.

Venlafaxine and bupropion
While evidence for use of these medications during pregnancy and lactation is less clear than with other antidepressants, it is reasonable to consider continuing their use in women who are responding to them. The American Academy of Pediatrics classifies bupropion and venlafaxine as drugs whose effect on the nursing infant is unknown but may be of concern.

Paroxetine
Paroxetine is associated with an increased risk of congenital malformations when taken in the first trimester and is therefore **contraindicated** during pregnancy.
See “Antidepressant Use During Pregnancy and Lactation” on the staff intranet. For pregnant or breastfeeding women who are stable on other antidepressants, consult with BHS via Mind Phone.

Resources for providers on antidepressant use during pregnancy/lactation

- Briggs’ *Drugs in Pregnancy and Lactation*
- LactMed (NIH-sponsored drug and lactation database)
  https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- Massachusetts General Hospital Center for Women’s Mental Health
  https://womensmentalhealth.org/

Table 7b. Shared decision making for PREGNANT OR BREASTFEEDING WOMEN
Use SmartPhrase .SSRISANDPREGNANCY to support shared decision making.

SSRIs during PREGNANCY

Advantages/Benefits

There are no good studies about the long-term effects of SSRI exposure in pregnancy. Only small, less rigorous studies are available and seem to indicate **no effect** on the child's behavioral, language or IQ development.

During pregnancy, women with depression have a high risk of relapse whether they are on or off medications. Relapse occurs in approximately 68% of those who go off medication compared with 25% of those who continue antidepressants.

In addition to reducing the risk of relapse, use of antidepressants during pregnancy can potentially reduce other risks that are associated with untreated maternal depression. In babies, untreated maternal depression is associated with:

- Low birth weight
- Decreased fetal growth
- Increased crying and difficulty being consoled
- Increased postnatal complications

Later in life, children of mothers whose depression was untreated during pregnancy have increased suicidal behavior, conduct problems, and emotional instability.

In women, untreated depression is associated with increased life stress, decreased social support, poor maternal weight gain, smoking, and alcohol and drug use.

Disadvantages/Risks

The rate of birth defects is similar to that for women who don't take SSRIs during pregnancy (about 3–5%).

About 8% of babies born to mothers who take SSRIs during pregnancy will be born early (before 36 weeks), versus about 4% in mothers who do not.

Up to 30% of babies may have withdrawal symptoms at birth, such as jitteriness or irritability, tremors, or trouble feeding. These symptoms tend to be mild and are usually treated conservatively with monitoring of the baby, symptomatic support, increased skin-to-skin contact, and swaddling.

Less than 1% of babies may develop persistent pulmonary hypertension, which may require care in the specialty care nursery for a few days after birth.

There isn't clear evidence that babies born to mothers who take SSRIs during pregnancy will have long-term developmental problems.

SSRIs during BREASTFEEDING

Advantages/Benefits

The benefits of breastfeeding generally seem to outweigh the potential side effects of SSRIs.

Infant drug exposure is generally higher through placental passage than through breast milk. Thus, if a woman has taken an antidepressant during pregnancy, it generally makes sense to continue with the same antidepressant during breastfeeding to minimize the number of medications the infant is exposed to.

In severely depressed postpartum women, the risk of SSRIs is generally considered less than the risk of disturbing the development of the maternal-infant bond.

Disadvantages/Risks

There is weak evidence (e.g., from case studies) linking antidepressant use in breastfeeding mothers with mild adverse events in infants, but because the reported adverse effects were non-specific (e.g., irritability, sedation, and "colic"), it is unclear whether they were directly related to the medication exposure.

Recommended pharmacologic options for ADOLESCENTS

Table 8. 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	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
2nd	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. 11.

Fluoxetine

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

Non-prescription pharmacologic treatment options

St. John's wort

Although there is some evidence that suggests that St. John's wort may be beneficial for mild to moderate depression, caution should be used when recommending this option as it 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). Consult a pharmacist to determine any possible drug interactions before recommending this treatment option. Additionally, do **not** use St. John's wort as a treatment for severe depression.

Other

There is insufficient evidence to recommend the use of the following for treatment of depression: 5HTP, folate, Ginkgo biloba, ginseng, glutamine, inositol, polyunsaturated fatty acids (including omega-3 fatty acids, DHEA, and EPA), or S-adenosyl-L-methionine (SAMe).

Follow-up

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 PHQ-9 or -9A 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 PHQ-9 or -9A and clinical judgment. Significant improvement is typically defined as a 50% decrease in PHQ-9 score. The PHQ-9 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.

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 or in the midst of their first depression, or who have lapsed in the middle of a previous course of treatment.

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. [1]
History of **two or more prior episodes** of major depression and taking antidepressants	Continue treatment for 3 years or longer after remission.

[1] For adolescents, antidepressants should not be stopped near the end of a school semester or at exam time.

Treatment discontinuation

- In order to prevent adverse effects, antidepressants should be slowly tapered rather than discontinued abruptly. A single safest and most effective medication taper has not been established.
- **Slow tapering** in two to 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 history of hospitalization or suicide attempts, **consider tapering more slowly**, over a period of 4–6 months**.**
- **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.

Screening

The current U.S. Preventive Services Task Force (USPSTF) guideline recommends screening for depression in the general adult population, including older adults and pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up (USPSTF 2016).

The USPSTF recommends screening for major depressive disorder (MDD) in adolescents aged 12 to 18 years. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for MDD in children aged 11 years or younger.

Screening tools

There is evidence to support the use of the PHQ-9 for screening and/or diagnosis. Two validation studies were conducted by similar groups of investigators (Kroenke 2001, Löwe 2004). Kroenke found an association between severity of depression according to the PHQ-9 score and self-report measures of disability days and symptom-related difficulty. Löwe and colleagues found that the PHQ-9 performed significantly better at identifying patients with major depressive disorder than two other commonly used screening instruments. The investigators confirmed a PHQ-9 cut-off score of 10 or higher for diagnosing major depressive disorder, which had a sensitivity of 95% (95% CI, 87–99) and a specificity of 87% (95% CI, 84–90). Both studies have limitations: neither used randomly selected participants and thus may not have included a representative sample of depressed patients, and only a minority of participants in either study received confirmatory structured clinical interviews.

Screening in pregnant women

- The published literature indicates that screening pregnant and postpartum women for depression, followed by intervention for those who screen positive, may reduce their symptoms of depression.
- There is insufficient evidence to determine the impact of screening on pregnancy.
- There is insufficient evidence to determine the optimal time and frequency for screening pregnant and postpartum women for depression. There was variation between studies in the timing of screening. Pregnant women were screened between 24 and 28 weeks gestation, and postpartum women between the fourth and eighth weeks after delivery.

Antidepressant treatment

Overall effectiveness in adults

A pooled analysis of all available published data on placebo-controlled antidepressant trials (Turner 2008) found an overall mean weighted effect size of 0.37* (95% CI, 0.33–0.41). For unpublished studies, the effect size was 0.15 (95% CI, 0.08–0.22), suggesting a publication bias is present.

Sugarman and colleagues' 2014 meta-analysis of published and unpublished studies comparing paroxetine (SSRI) to placebo also showed a standardized mean pre-post effect difference (SMD) of 0.32* (95% CI, 0.26–0.38). This and other analyses suggest that the drug-placebo differences increase with the severity of initial depression.

* Cohen's *d* effect size with Hedges correction for small size (0.2 indicates small, 0.50 moderate, and 0.80 large differences between interventions).

Overall effectiveness in adolescents

A Cochrane review (Hetrick 2012) examined the efficacy and adverse outcomes, including definitive suicidal behavior and ideation, of newer-generation antidepressants compared to placebo in the treatment of depressive disorders in adolescents. The analysis included 19 trials involving 3,335 participants aged 6–18 years diagnosed with a depressive disorder. Children and adolescents at high risk of suicide and many comorbid conditions were generally excluded from the trials.

SSRIs studied were paroxetine (4 trials), fluoxetine (5 trials), citalopram (2 trials), escitalopram oxalate (92 trials), and sertraline (2 trials). In the SNRI class there were 2 trials on venlafaxine, and in the TCA class there were 2 trials on mirtazapine. The pooled results suggest that adolescent patients with depression treated with drug therapy had lower depression severity and higher remission versus those who received a placebo. However, the effect size is too small (reduction of depression symptoms of 3.5 points on a scale from 17–113). There was evidence of increased risk of suicide with antidepressants compared to placebo. This risk was highest with venlafaxine (only one study, with 367 patients and a wide confidence interval [RR=12.93; 95% CI, 1.71–97.82]).

Comparative effectiveness of second-generation antidepressants

A number of Cochrane reviews and other meta-analyses directly or indirectly compared the efficacy and tolerability of one antidepressant versus others or made comparisons of all second-generation antidepressants in network meta-analyses. Cochrane reviews included the comparison of citalopram versus other antidepressive agents (Cipriani 2012), duloxetine versus other antidepressive agents (Cipriani 2012), agomelatine versus other antidepressive agents (Guaiana 2013), fluoxetine versus other types of pharmacotherapy (Magni 2013), and paroxetine versus other antidepressive agents (Purgato 2014).

The results of the more recently published systematic reviews and meta-analyses suggest that there are no or only minor differences in clinical response between the various antidepressants evaluated. Overall, the results support the previous findings that second-generation antidepressants do not differ significantly in their efficacy and/or effectiveness in treating major depressive disorder symptoms. However, these drugs are not identical, and they do have some variations in respect to onset of action, acceptability, tolerability, and side effects that may affect treatment choices.

Gartlehner and colleagues (2011) updated the earlier systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) to compare the benefits and harms of second-generation antidepressants for treating major depressive disorder in adults. The review included 13 drugs: bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The analysis included 234 fair- to good-quality studies; 118 were head-to-head randomized controlled trials (RCTs). Overall, 37% of patients did not achieve response within 6 to 12 weeks, and 53% did not achieve remission. Direct and indirect comparisons between these second-generation drugs showed some small statistically significant differences between drugs, which according to the authors were unlikely to be clinically relevant. There were no differences in efficacy in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. However, there were differences between the drugs in their onset of action, adverse events, and some measures of health-related quality of life.

Koo and colleagues (2015) conducted a network meta-analysis to compare the relative efficacy of 10 second-generation antidepressants (duloxetine, escitalopram, agomelatine, fluvoxamine, fluoxetine, mirtazapine, paroxetine, sertraline, trazadone, and venlafaxine). The analysis included 76 trials (published between 1989 and 2014) with head-to-head comparisons and at least 6 weeks' duration of treatment of acute MDD in adults (excluding pregnant women). The primary outcomes for efficacy were response and remission rates and mean change in Hamilton Depression Rating Scale (HDRS) scores. The pooled results show a small difference in effectiveness between the 10 agents. The analysis also showed that:

- Mirtazapine and agomelatine were most efficacious in achieving response and remission, respectively.
- Among the SSRIs, escitalopram was the most efficacious agent.
- Using the composite outcome of response, remission, and tolerability, agomelatine, escitalopram, and mirtazapine had a favorable balance between efficacy and tolerability.

- Mirtazapine and duloxetine resulted in the greatest change in HDRS score.
- Agomelatine, escitalopram, and sertraline were the best tolerated.
- Duloxetine and venlafaxine were the least well tolerated.

Antidepressants versus psychotherapy

A 2016 meta-analysis by Gartlehner and colleagues showed no statistically significant differences in response or remission rates between second-generation antidepressants (SGAs) and cognitive behavioral therapy (CBT) received either as monotherapy or in combination. There was, however, significant heterogeneity between studies, mainly due to the differences in the types of CBT used and the types of providers delivering the psychotherapy. Subgroup analyses by subtype and duration of CBT as well as sensitivity analyses yielded similar results.

Sub-analyses by subtypes of psychological therapies showed a statistically significant increased improvement in response and remission only with third-wave cognitive therapy versus SGA. The authors, however, concluded that the evidence was insufficient to determine this effect.

The meta-analysis also showed that rates of therapy discontinuation due to adverse events were higher with SGA than CBT, but that the difference was not statistically significant. There were also statistically insignificant differences between the two therapies in the rates of treatment discontinuation due to lack of efficacy.

Steinert and colleagues' 2014 meta-analysis investigated the overall rates of relapse more than 2 years after psychotherapy, and whether psychotherapy has more enduring effects beyond 2 years versus non-psychotherapeutic comparisons, including pharmacotherapy and treatment as usual. The analysis included 11 studies involving 966 patients, with a mean follow-up duration of 4.4 years. Six of the trials included a non-psychotherapeutic comparison. Their pooled results indicate that psychotherapy resulted in significantly fewer relapses than the comparison treatment (53.1% vs. 71.1%, OR 0.51; 95% CI, 0.32–0.82, p=0.005, and number needed to treat [NNT]=6). These results have to be interpreted with caution due to the small number of studies and patients included, heterogeneity between studies, and other limitations.

A 2013 meta-analysis by Cuijpers, Sijbrandij and colleagues compared psychotherapy and antidepressant medications for the treatment of depressive and anxiety disorders. The analysis included 67 RCTs involving 5,993 patients; 40 studies focused on depressive disorders and 27 on anxiety disorders. The primary outcome was the effect size indicating difference between psychotherapy and pharmacotherapy in reducing the symptoms of the disorders studied. The overall results of the analysis showed no significant difference in effect between psychotherapy and pharmacotherapy for the treatment of major depressive disorder. (The results also applied for panic disorders and seasonal affective disorder.)

A 2013 meta-analysis by Cuijpers, Hollon and colleagues compared the effects of acute-phase CBT without any subsequent treatment versus the effects of pharmacotherapy that was either continued or discontinued during 6–18 months of follow-up in patients with depressive disorders. The meta-analysis included 9 RCTs involving 506 patients with a diagnosed depressive disorder. The pooled results showed no significant difference in response between CBT and pharmacotherapy at the end of acute treatment, but patients who received CBT had significantly better long-term outcomes (were less likely to relapse) than those who were withdrawn from pharmacotherapy (NNT=5). There was a trend toward better outcome but no significant difference when patients treated with acute-phase CBT were compared with those on continued pharmacotherapy in 5 studies. The meta-analysis had valid methodology and the studies it included were judged to be of relatively high quality. However, the number of studies and participants was relatively small, and there were variations in the studies in the drugs used and in the outcome measures. In addition, some studies only included the responders to acute therapy in their follow-up analysis, which would bias the results, as more severe cases may respond better to pharmacotherapy than to CBT. Considering these limitations, the results of the analysis have to be interpreted cautiously.

Combined treatment

Several meta-analyses of RCTs, the most recent from 2014 (Cuijpers 2014), found that combined treatment with antidepressants and psychotherapy in adults is more effective than either pharmacotherapy or psychotherapy given alone (effect sizes 0.37 [95% CI, 0.12–0.63] and 0.38 [95% CI, 0.16–0.59], respectively), with an NNT of 5 for each.

One RCT (Hollon 2014) compared the effects of combined cognitive behavioral therapy (CBT) and antidepressants versus antidepressants alone on remission and recovery among 452 adults with major depressive disorder. Treatment was continued for up to 42 months until recovery (defined as 6 months without relapse after remission) was achieved. The results of the trial showed that patients treated with both CBT and antidepressants had a higher recovery rate than those treated with antidepressants alone. The authors calculated an NNT=10 (NNT=5 for patients with more severe depression).

Treatment options and recommendations for major depressive disorder: numbers needed to treat

Sources: Cuijpers, Hollon, et al 2013; Cuijpers 2014.

Modality		Number needed to treat (NNT) to achieve one positive outcome [1]
Psychotherapy	vs. placebo	**7**
	Sustained effect (2 years post-therapy)	**5–6**
	CBT vs. other psychotherapies	**NS** [2]
Antidepressant	vs. placebo	**5–7**
	vs. psychotherapy	**NS** [2]
	Any second-generation antidepressant [3] vs. another	**NS** [2]
Combination therapy	vs. antidepressants alone	**4–10**
	vs. antidepressants alone – high severity	**5**
	vs. antidepressants alone – low severity	**NS** [2]
	vs. psychotherapy alone	**4**

[1] Calculated by the authors of the meta-analyses. Outcomes and follow-up periods varied by study. Follow-up periods for acute outcomes ranged from 8 to 16 weeks; for long-term outcomes, 6 months to 2 years. All subjects in the included studies had severe depression.

[2] NS = No significant difference. NNT not calculated.

[3] Second-generation antidepressant = SSRI or SSNI.

Complementary alternative medicine, herbal remedies, and nutritional supplements

- There is low- to moderate-quality evidence suggesting that exercise may have a statistically significant higher but clinically moderate effect on reducing depression symptoms when compared to no intervention or usual care (such as wait list). The observed effect, however, was reduced to a statistically insignificant level during the follow-up, which may suggest that the effect of exercise diminishes after its cessation.
- Low-quality evidence shows no significant difference in effectiveness of exercise used alone when compared to psychological therapy, drug treatment, or a combination of antidepressant and exercise. Unblinded studies and those without intention-to-treat analysis seemed to exaggerate the effect of exercise on the treatment of depression.
- There is insufficient evidence to determine the effectives of yoga in treating depression when used alone or in combination with standard depression treatment.
- There is insufficient evidence to determine the effect of acupuncture used alone for the treatment of major depressive disorder. Low-quality evidence suggests that acupuncture combined with

antidepressant medication may be more effective than antidepressants used alone in reducing depression symptoms during the first 6 weeks of treatment.

- There is low- to moderate-strength evidence suggesting that St. John's wort given as a monotherapy for mild to moderate depression may be superior to placebo in improving symptoms, and that treatment with St. John's wort has lower risk of adverse events or treatment discontinuation due to adverse events compared to antidepressant treatment. There is insufficient evidence, however, to determine the differences between the treatments in serious adverse events. St. John's wort interacts with several other commonly used medications, its preparations differ widely, and there is no U.S. standard for its purity and potency.
- There is insufficient evidence to draw firm conclusions on the comparative efficacy and safety of vitamin D, SAMe monotherapy, or omega-3 fatty acids—either as monotherapy or in combination with second-generation antidepressants—versus standard therapies used for managing major depressive disorder.

Pregnant and postpartum women

There is a lack of published RCTs that directly compare fetal, infant, or long-term outcomes of children born to mothers with untreated depression versus those exposed to antidepressants during pregnancy. There is also a lack of direct evidence on the maternal benefits and harms of treating versus not treating depression during pregnancy or postpartum.

Risks of untreated depression

A systematic review of 43 articles published through August 2015 (Gentile 2015) indicates that untreated gestational depression or even depressive symptoms during pregnancy may have negative effects on the developing fetus and the newborn that may last through childhood or adolescence. These include increased cortisol and norepinephrine levels, decreased dopamine levels, stress/depressive-like behaviors, increased rates of premature death of the newborn, and internalizing and externalizing problems, as well as other problems in childhood. The authors did not find a conclusive association between gestational depression and increased risks of prematurity and low birth weight.

The published literature suggests that uncontrolled and untreated depression in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia, excessive bleeding and painful labor, and increased need for cesarean section or instrumental delivery. Untreated depression late in pregnancy was also found to be associated with postpartum depression, suboptimal infant care, suboptimal mother-child attachment, lack of care of other children, and adverse relationship with partner (Gadot 2015).

Harms of antidepressant drugs used during pregnancy

The literature search identified a number of recent meta-analyses and cohort studies that examined the association between prenatal exposure to antidepressants and risks to the newborn; fewer studies investigated the maternal risk associated with the use of antidepressants.

The overall results of these studies can be summarized as:

- There is fair evidence suggesting an association between maternal use of antidepressants and increased risk of the following:
  - Preterm birth, especially when antidepressants are used later in pregnancy (Huybrechts 2014 [any antidepressant], Huang 2014 [any antidepressant], Eke 2016 [SSRIs]).
  - Persistent pulmonary hypertension (Grigoriadis 2014, Huybrechts 2015).
  - Postpartum hemorrhage (Jiang 2016).
- The absolute risk for most infant outcomes was very small.
- The evidence on the effect of antidepressants on congenital cardiac defects is mixed.
- The findings of the literature on the teratogenic effects of SSRIs are conflicting.
- There is growing but insufficient evidence linking the use of SSRIs during the second or third trimester of pregnancy to autism spectrum disorder (Boukhris 2016).
- There is insufficient evidence to determine the association of individual agents with fetal adverse events.
- The majority of the studies focused on the risk to the fetus and only a few examined the impact on the mother. Gadot and Koren's 2015 review of 7 studies that focused on maternal risks associated with the use of antidepressants (SSRIs and SNRIs) indicates that women who received antidepressants during pregnancy had an increased risk of gestational hypertension,

preeclampsia, and delivery complications including placenta abruption, premature rupture of membranes, need for labor induction or cesarean section, and postpartum hemorrhage. The observed risks tended to be higher when the medication was used throughout pregnancy or late in the pregnancy, and occurred at a slightly higher rate with SNRIs and TCAs than with SSRIs.

Other risks associated with second-generation antidepressants include preeclampsia, miscarriage, neonatal or post-neonatal deaths, infant seizures, and neonatal respiratory distress (O'Connor 2016).

Non-pharmacological therapy

Cognitive behavioral therapy

There is fair evidence suggesting that CBT is more effective than no treatment or usual care in reducing the symptoms of mild to moderate perinatal depression that is not associated with other comorbidities, and that it increases the likelihood of remission in the short term. However, the observed treatment effect sizes were small to moderate.

A systematic review (O'Connor 2016) indicates that there is evidence that CBT increases the likelihood of remission in the short term, and reduces symptom severity of postpartum depression compared with usual care. The results may not be generalized to severe cases of depression or to depression associated with other comorbidities, as such patients were excluded from the trials. The review also concluded that there was a lack of published evidence on the adverse effects or harms of CBT.

A meta-analysis (Sockol 2015) of 40 randomized and quasi-randomized controlled trials showed:

- CBT was significantly more effective in reducing perinatal depressive symptoms compared to the control interventions (treatment as usual, wait list, or active control) in both treatment and prevention studies. The treatment effect sizes were small to moderate in both the treatment and prevention trials.
- The interventions initiated during the postpartum period were more effective than the antenatal interventions.
- In the prevention trials, individually administered treatments were more effective than group interventions.
- Greater reductions in depressive symptoms were found in studies that included higher proportions of non-white, single, and multiparous participants.

Alternative treatment/CAM interventions for the treatment of antenatal depression

There is a lack of published high-quality evidence to determine the effectiveness of alternative treatments in preventing or reducing the symptoms of depression in pregnant and postpartum women. The published studies were small in size and had methodological limitations, with variability in the diagnostic criteria, potency, intensity, and duration of the alternative therapies, a lack of standardized doses, and variations in outcome measures. Because of these limitations determinations cannot be made on the effectiveness and safety of the alternative interventions in preventing or treating perinatal depression.

Comparative effectiveness and safety of pharmacological and psychological therapies during pregnancy and the postpartum period

There is a lack of direct evidence comparing pharmacological and psychological treatment of antenatal or postnatal depression. There is also a lack of direct evidence on the comparative effectiveness and harms of different antidepressant drug families and individual agents used in the treatment of depression during pregnancy.

A systematic review (McDonough 2014) compared the benefits and harms of pharmacological treatments versus one another, and versus non-pharmacological treatments, usual care, or no treatment. The review focused on women with a diagnosis of major depressive disorder (according to DSM-IV criteria) during pregnancy and the 12 months after delivery. The review included 124 observational studies and 6 RCTs. The outcomes included both maternal and infant or child benefits and harms. The authors concluded that there was insufficient evidence to make any conclusion on the comparative benefits and harms of antidepressants used during pregnancy or the postpartum period on maternal or infant outcomes. They found low-strength evidence suggesting that neonates of women with depression taking SSRIs during pregnancy had higher risk of respiratory distress than neonates of untreated women, but risk of preterm

birth or neonatal convulsions did not differ between these groups. They also concluded that low-strength evidence did not show a benefit from adding brief psychotherapy or CBT to SSRIs.

An earlier meta-analysis (Sockol 2011) of 27 studies (16 RCTs, 2 quasi-randomized trials, and 9 nonrandomized trials) showed the following:

- A significant improvement in depressive symptoms from pre-treatment to post-treatment, with the intervention groups having significantly greater reductions in depressive symptoms compared to control groups.
- Individual psychotherapy was superior to group psychotherapy with regard to changes in symptoms from pre-treatment to post-treatment.
- Interventions including an interpersonal therapy component were found to have greater effect sizes than interventions including a cognitive-behavioral component.
- The authors could not compare the effect sizes of pharmacological and psychological interventions as there was only one study included in that analysis.
- The number of studies with long-term follow-up was insufficient to determine the long-term outcomes of the therapies.

Safety of continuing the use of antidepressants during pregnancy and lactation in women treated for major depressive disorder prior to the pregnancy

There is a lack of published RCTs to determine the safety of continued antidepressant use during pregnancy and lactation in women treated for major depressive disorder prior to the pregnancy.

Recommendations in this guideline are based upon a joint report by the American Psychiatric Association and the American College of Obstetricians and Gynecologists (Yonkers 2009).

Adolescents

Comparative effectiveness, safety, and tolerability of antidepressants for major depressive disorder

Qin and colleagues' 2015 meta-analysis compared the efficacy and acceptability of selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) in children, adolescents, and young adults (aged 7–25 years) diagnosed with unipolar depressive disorder. The meta-analysis included 5 trials with a total of 422 patients. (One study only included patients 18–24 years of age, one included children 7–16 years of age, and the other 3 included mainly adolescents [12–18 years in one study, 12–20 in another, and 15–20 in a very small trial]). The treatment was received for a duration ranging from 6 to 12 months, and the main outcomes were efficacy and acceptability of the drugs. The pooled results indicate that studies directly comparing the two drug classes found that SSRI therapy had superior efficacy and was better tolerated than TCA therapy in the young patients studied. Subgroup analyses suggest that fluoxetine had a higher effect size than paroxetine; however, this was not based on a head-to-head comparison. The authors did not perform a subgroup analysis based on age or sex, or on other variables that may have had an impact on the treatment response.

Cipriani and colleagues' 2016 network meta-analysis compared and ranked antidepressants and placebo for major depressive disorder in children and adolescents. The analysis included 34 RCTs involving 5,260 participants and 14 antidepressant treatments. The primary outcomes were the mean overall change in depressive symptoms from baseline to endpoint and the proportion of patients who discontinued treatment due to any adverse event. The pooled results show that:
For efficacy,

- Fluoxetine was the only antidepressant superior to placebo (SMD -0.51; 95% CI, -0.99 to -0.03).
- Nortriptyline was significantly less effective than 7 other antidepressants and placebo, with an SMD ranging between -1.65 and -1.14.
- Most effective was fluoxetine (76.6%) and least effective was nortriptyline (3.7%).

For tolerability,

- Fluoxetine was better tolerated than duloxetine and imipramine.
- Citalopram and paroxetine were better tolerated than imipramine.
- Imipramine, venlafaxine, and duloxetine were less tolerated than placebo.
- Best tolerated was fluoxetine (75.7%) and worst tolerated was imipramine (13.1%).

For suicidal risk,

- Venlafaxine was associated with a significantly higher risk of suicidal behavior or ideation compared to placebo and 5 other antidepressants (escitalopram, imipramine, duloxetine, fluoxetine, and paroxetine).

Overall, the results of the network meta-analysis suggest that fluoxetine may be the more effective and better tolerated antidepressant drug for adolescents. No comparison was made versus psychotherapy. The results have to be cautiously interpreted due to a number of limitations, including but not limited to: the design was a network meta-analysis that indirectly compared different agents; the majority of trials included in the analysis were rated as poor-quality, with relatively small sample size and short follow-up duration insufficient to determine the long-term effectiveness and safety of the different drugs evaluated. In addition, the meta-analysis included a number of unpublished studies as well as studies published 3 decades ago, and excluded treatment-resistant patients, which may have led to an overestimation of the effectiveness of the antidepressants examined.

Comparative benefits and harms of antidepressants and psychological therapy for major depressive disorder

A Cochrane review and meta-analysis (Cox 2014) of 11 RCTs involving 1,307 participants aged 6–18 years evaluated and compared the effectiveness of psychological therapies and antidepressant medications used alone or in combination for the treatment of depressive disorders in children and adolescents. The primary outcomes were remission from depressive disorders, acceptability of treatment measured by number of dropouts, and suicide-related adverse events.

The meta-analysis had valid methodology and analysis; however, it included a small number of trials which had risk of bias; differences in design, inclusion criteria, medications, and doses used; and variability of the type, quality, and intensity of CBT provided. In addition, the studies included children with comorbidities such as anxiety (in 50% of the studies) and alcohol use, substance abuse, or gaming in 3 trials. The overall results do not provide sufficient evidence to make any conclusion on the comparative effectiveness and safety of psychological therapy and antidepressants given alone or in combination for the treatment of children and adolescents with depression.

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Guideline Development Process and Team

Development process

The guideline team developed the Adult and Adolescent Depression Guideline using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in January 2017.

Team

The Depression Guideline development team included representatives from the following specialties: adolescent medicine, behavioral health, family medicine, nursing operations, obstetrics/gynecology, pediatrics, and pharmacy.

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Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care–related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Depression Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.

PHQ-9 for ADULTS
Patient Health Questionnaire

Name: _____Date:_____

Over the **last 2 weeks**, how often have you been bothered by any of the following problems? (Please **CIRCLE** to indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

Note: Clinic Staff - Please file electronically in the EpicCare PHQ9 Document Flow sheet.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc.

GroupHealth.

Additional Depression Questions for Adults

Name: _____Date:_____

Instructions: This questionnaire will help us understand how you have been feeling. The results will help you and your doctor follow your progress.

Patient Questionnaire (Please **CIRCLE** to indicate your answer.) Y, N or N/A			
1. Have your symptoms of depression lasted longer than two years?	Y	N	N/A
2. Have you had similar symptoms lasting at least two weeks in the past? If yes, how many times?	Y	N	N/A
3. Have you had counseling in the past for depression?	Y	N	N/A
4. If you have taken medications for depression in the past, did they help?	Y	N	N/A
5. If you have taken medications for depression in the past, did you have a problem with any medication?	Y	N	N/A
6. Have you ever made plans to harm or kill yourself?	Y	N	N/A
7. Has any family member attempted or committed suicide?	Y	N	N/A
8. 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 sleep? Felt you could do anything? Circle "yes" if you had these symptoms and they lasted at least a few days and caused trouble for you in your life.	Y	N	N/A
9. In the past two weeks, have you heard or seen things that other people couldn't see or hear that might really not be there?	Y	N	N/A
10. Have you recently been the victim of threats, physical hurting, or forced sexual contact?	Y	N	N/A
11. Have you recently experienced the death of a close friend or family member?	Y	N	N/A
12. Have you recently experienced some stressful event or life change?	Y	N	N/A
13. 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 from others, activities, or your surroundings?	Y	N	N/A
14. In the past 12 months, have you used drugs other than those required for medical reasons?	Y	N	N/A
15. How often did you have 1 drink containing alcohol in the last year? ☐ Never [0] ☐ Monthly or less [1] ☐ 2 to 4 times per month [2] ☐ 2 to 3 times per week [3] ☐ 4 or more times per week [4]			
16. How many drinks containing alcohol did you have on a typical day when you were drinking in the last year? ☐ I don't drink alcohol [0] ☐ 1 to 2 [0] ☐ 3 to 4 [1] ☐ 5 to 6 [2] ☐ 7 to 9 [3] ☐ 10 or more [4]			
17. How often did you have 6 or more drinks on one occasion in the last year? ☐ Never [0] ☐ Less than monthly [1] ☐ Monthly [2] ☐ Weekly [3] ☐ Daily or almost daily [4]			

18. Over the last two weeks, how often have you been bothered by the following problems:	Not at all [0]	Several days [1]	Over half the days [2]	Nearly every day [3]
• Feeling nervous, anxious, or on edge?	Not at all [0]	Several days [1]	Over half the days [2]	Nearly every day [3]
• Not being able to stop or control worrying?				

Clinic Staff - Please file electronically in the EpicCare PHQ9 Document Flow sheet.

PHER Rev. Date 2013094

PHQ-9 for ADOLESCENTS
Modified Patient Health Questionnaire

Name: _____Date:_____

Over the **last 2 weeks**, how often have you been bothered by any of the following problems? (Please **CIRCLE** to indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, irritable, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite, weight loss, or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as school work, reading or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

Note: Clinic Staff - Please file electronically in the EpicCare PHQ9A Document Flow sheet.

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc.

GroupHealth.

Additional Depression Questions for Adolescents

Name: _____Date:_____

Instructions: This questionnaire will help us understand how you have been feeling. The results will help you and your doctor follow your progress.

Patient Questionnaire	(Please **CIRCLE** to indicate your answer.)	Y,	N or N/A
1. Have your symptoms of depression lasted longer than two years?	Y	N	N/A
2. Have you had similar symptoms lasting at least two weeks in the past? If yes, how many times?	Y	N	N/A
3. Have you had counseling in the past for depression?	Y	N	N/A
4. If you have you taken medications for depression in the past, did they help?	Y	N	N/A
5. If you have taken medications for depression in the past, did you have a problem with any medication?	Y	N	N/A
6. Have you ever made plans to harm or kill yourself?	Y	N	N/A
7. Has any family member attempted or committed suicide?	Y	N	N/A
8. 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 sleep? Felt you could do anything? Circle "yes" if you had these symptoms and they lasted at least a few days and caused trouble for you in your life.	Y	N	N/A
9. In the past two weeks, have you heard or seen things that other people couldn't see or hear that might really not be there?	Y	N	N/A
10. Has anyone ever hit you or touched you in a way that made you uncomfortable or afraid?	Y	N	N/A
11. Have you recently experienced the death of a close friend or family member?	Y	N	N/A
12. Are you having difficulty with school work?	Y	N	N/A
13. Are you having trouble with fighting or any kind of bullying?	Y	N	N/A
14. Have you ever ridden in a car driven by someone (including yourself) who was "high" or had been using alcohol or drugs?	Y	N	N/A
15. Do you ever use alcohol or drugs to relax, feel better about yourself, or fit in?	Y	N	N/A
16. Do you ever use alcohol or drugs while you are by yourself, alone?	Y	N	N/A
17. Do your family or friends ever tell you that you should cut down on your drinking or drug use?	Y	N	N/A
18. Do you ever forget things you did while using alcohol or drugs?	Y	N	N/A
19. Have you gotten into trouble while you were using alcohol or drugs?	Y	N	N/A

20. Over the last two weeks, how often have you been bothered by the following problems:	Not at all [0]	Several days [1]	Over half the days [2]	Nearly every day [3]
• Feeling nervous, anxious, or on edge?	Not at all [0]	Several days [1]	Over half the days [2]	Nearly every day [3]
• Not being able to stop or control worrying?				

Clinic Staff - Please file electronically in the EpicCare PHQ9-A Document Flow sheet

PHER Rev. Date 2014155

Appendix 3: DSM-5 Criteria for Major Depressive Episode

For adults and adolescents,

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   ***Note**:* Do not include symptoms that are clearly attributable to another medical condition.

   (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note: In children and adolescents, can be irritable mood.**
   (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
   (3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note: In children, consider failure to make expected weight gains.**
   (4) Insomnia or hypersomnia nearly every day
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   (6) Fatigue or loss of energy nearly every day
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

   Note: Criteria A–C represent a major depressive episode.

   Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

   In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in MDE. In grief, self-esteem is generally preserved, whereas in MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in MDE

such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or hypomanic episode.
Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Differences between DSM-IV and DSM-5

In DSM-IV, there was an exclusion criterion for a major depressive episode that was applied to depressive symptoms lasting less than 2 months following the death of a loved one (i.e., the bereavement exclusion). This exclusion is omitted in DSM-5 for several reasons, including the recognition that bereavement is a severe psychosocial stressor that can precipitate a major depressive episode in a vulnerable individual, generally beginning soon after the loss, and can add an additional risk for suffering, feelings of worthlessness, suicidal ideation, poorer medical health, and worse interpersonal and work functioning. It was critical to remove the implication that bereavement typically lasts only 2 months, when both physicians and grief counselors recognize that the duration is more commonly 1–2 years. A detailed footnote has replaced the more simplistic DSM-IV exclusion to aid clinicians in making the critical distinction between the symptoms characteristic of bereavement and those of a major depressive disorder.