



Identification and Management of Clinical Depression in Adults 18 years or Older

Clinical Practice Guideline

MedStar Health

“These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient’s primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations”.

General Principles:

This guideline is intended to support primary care practitioners in the detection, diagnosis, and management of clinical depression in adults aged 18 years and older.

Depression is one of the most common conditions encountered in primary care—more prevalent than hypertension, with rates estimated at 6–17% compared to 5.8% for hypertension. According to the CDC/National Center for Health Statistics, 8.1% of U.S. adults aged 20 and over experience depression in a given two-week period, and approximately 1 in 6 Americans will experience depression at some point in their lifetime. Prevalence is higher among women and individuals with lower socioeconomic status.

The World Health Organization (WHO) ranks unipolar major depression as the 11th leading cause of global disability and mortality. In the United States, major depression ranks second among all diseases and injuries as a cause of disability, while persistent depressive disorder (dysthymia) ranks 20th.

Approximately 75% of patients with depression will present to a primary care provider, often with somatic symptoms. Despite this, only about 50% of cases are correctly identified. Therefore, it is essential for primary care providers to be skilled in recognizing and diagnosing this common and serious condition.

Clinical depression is highly treatable, with 66–80% of patients responding to therapy. However, only about 10% of diagnosed individuals receive adequate treatment. Depression is also a recurrent illness, with a greater than 40% relapse rate within two years after a single episode, and up to 75% after two episodes within five years.

The consequences of untreated depression are profound, extending beyond functional impairment and lost productivity to include patient suffering, family burden, and increased risk of suicide.

Disease Definition: Clinical depression can occur in many situations.

In DSM-5, the depressive disorders that can be diagnosed include:

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- A. Unipolar major depression (major depressive disorder)
- B. Bipolar Major Depression
- C. Persistent depressive disorder (dysthymia)
- D. Disruptive mood dysregulation disorder
- E. Premenstrual dysphoric disorder
- F. Substance/medication induced depressive disorder
- G. Depressive disorder due to another medical condition
- H. Other specified depressive disorder (e.g., minor depression)
- I. Unspecified depressive disorder

A. Unipolar Major Depression:

Unipolar Major Depression is characterized by one or more major depressive episodes without any history of mania or hypomania. A major depressive episode is defined as a period of at least two weeks during which five or more of the following symptoms are present, representing a change from prior functioning. At least one of the symptoms must be depressed mood or loss of interest or pleasure (anhedonia):

- Depressed mood most of the day, nearly every day, as self-reported or observed by others
- Diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Decrease or increase in appetite nearly every day +/-weight loss when not dieting, or weight gain
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan

To meet diagnostic criteria, symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The episode must not be attributable to the physiological effects of a substance or another medical condition. Bereavement does not preclude the diagnosis of a major depressive episode if the full criteria are met and symptoms persist beyond what is considered culturally appropriate grieving.

Depression can be characterized as mild (few symptoms, minor functional impairment), moderate, or severe (many more symptoms than required for diagnosis with significant functional impairment).

A seasonal pattern (commonly known as Seasonal Affective Disorder) is a recognized subtype of major depression. It is characterized by the onset and remission of depressive episodes at characteristic times of the year, most often in fall or winter, with full remission in spring or summer.

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Depressive episode subtypes (specifiers) — The DSM-5 includes several specifiers to further characterize depressive episodes. While these subtypes may not consistently guide treatment decisions, they can provide valuable insight into diagnosis, prognosis, and treatment monitoring.

The diagnostic criteria for depressive episode subtypes are as follows:

● **Anxious distress** – Anxious distress is characterized by the presence of two or more of the following symptoms during most days of the depressive episode:

- Tension
- Restlessness
- Impaired concentration due to worry
- Fear that something awful may happen
- Fear of losing self-control

● **Atypical features** – Mood reactivity (mood brightens in response to positive events)

Plus at least **two** of the following:

- Increased appetite or weight gain.
- Hypersomnia (e.g., sleeping at least 10 hours per day, or at least two hours more than usual when not depressed).
- Heavy or leaden feelings in limbs.
- Longstanding pattern of interpersonal rejection sensitivity (i.e., feeling deep anxiety, humiliation, or anger at the slightest rebuff from others), which is not limited to mood episodes, and which causes social or occupational conflicts.

● **Catatonia**

- Marked psychomotor disturbance (e.g., stupor, mutism, rigidity, posturing, negativism)

● **Melancholic features** – Melancholic features are characterized by at least four of the following symptoms during a depressive episode; at least one of the symptoms is either loss of pleasure or lack of reactivity to pleasurable stimuli ^[8]:

- Loss of pleasure in all or almost all activities (anhedonia)
- Unreactive to usually pleasurable stimuli (i.e., does not feel better in response to positive events)
- Depressed mood marked by profound despondency, despair, or gloominess
- Early morning awakening (e.g., two hours before usual hour of awakening)
- Psychomotor retardation or agitation
- Anorexia or weight loss
- Excessive guilt

B. Bipolar Disorder is a mood disorder marked by episodes of pathologic mood elevation, including mania or hypomania.

- **Bipolar I disorder** involves one or more manic episodes and typically includes both hypomanic and major depressive episodes.
- **Bipolar II disorder** is characterized by at least one hypomanic episode and one or more major depressive episodes.

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Psychotic features such as delusions and hallucinations commonly occur during depressive episodes, especially in patients with bipolar I disorder.

C. Persistent Depressive Disorder [Dysthymia]: Depressed mood for most of the day, for more days than not, for at least two consecutive years without a period of greater than two months of absence of symptoms. In addition, at least two of the following must be present:

- Poor appetite or overeating
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

D. Premenstrual Dysphoric Disorder (PMDD)— PMDD is a mood disorder characterized by significant distress and impairment in functioning occurring during most menstrual cycles over the past year. Symptoms arise during the week before menstruation and typically resolve within a few days after the onset of the menstrual period.

One or more of the following must be present:

- Mood swings, sudden sadness, increased sensitivity to rejection
- Anger or irritability
- Hopelessness, depressed mood, self-critical thought
- Tension, anxiety, feeling on edge

One or more of the following symptoms must also be present (to total five when combined with symptoms above)

- Difficulty concentrating
- Change in appetite, overeating, food craving
- Diminished interest in usual activities
- Low energy, fatigue
- Feeling overwhelmed or out of control
- Insomnia or hypersomnia
- Breast tenderness, weight gain, bloating, joint or muscle aches

Other Depressive Disorders:

E. Substance/medication induced depressive disorder — This disorder is characterized by a mood disturbance marked by persistent depressed or irritable mood, or a diminished interest or pleasure in most activities. The mood changes develop during or shortly after the use of substances—either recreational drugs or prescribed medications—that are capable of causing such disturbances. The resulting symptoms cause significant distress or impair psychosocial functioning.

Substance/medication-induced depressive disorder is not diagnosed in the following situations:

- The mood disturbance precedes onset of substance intoxication or withdrawal, or exposure to medications

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- The disturbance persists for a long period of time (e.g., one month) after cessation of acute intoxication or withdrawal
- There is a prior history of recurrent depressive episodes
- The disturbance occurs solely during an episode of delirium

Depressive syndromes may be caused by intoxication or withdrawal from a wide range of substances that are encountered in substance-related and addictive disorders, including alcohol, amphetamines, cannabis, cocaine, and stimulants.

Substance/medication-induced depressive disorder is often referred to as “secondary depression.”

F. Depressive disorder due to another medical condition — This disorder involves a mood disturbance characterized by persistent depressed or irritable mood, or diminished interest or pleasure in most activities. The diagnosis is supported by clinical findings—through history, physical examination, or laboratory tests—that indicate the mood disturbance is directly caused by a medical condition. Examples of such conditions include adrenal insufficiency, Huntington disease, hypercortisolism, hypothyroidism, mononucleosis, multiple sclerosis, obstructive sleep apnea, Parkinson disease, stroke, systemic lupus erythematosus, traumatic brain injury, and vitamin B12 deficiency.

The mood disturbance typically causes significant distress or impairs psychosocial functioning and usually begins within the first month following the onset of the medical condition. In some cases, depressive symptoms may be an early sign or prodrome of the underlying illness.

It is important to differentiate this from depression caused by treatments for chronic illness (e.g., corticosteroids or interferon), which should be classified as substance/medication-induced depressive disorder.

Clinicians should maintain a high index of suspicion for an underlying medical cause in the following situations:

- Severe new-onset depression, including melancholia or psychotic features
- New-onset depression in older adults or younger adults with significant chronic or acute medical conditions
- Depression that is unexplained by psychosocial stressors
- Depression refractory to standard treatments

Depressive disorder due to another medical condition is not diagnosed if:

- The mood disturbance clearly precedes the onset of the medical condition
- Symptoms occur exclusively during an episode of delirium

Coexisting significant anxiety or neurocognitive impairment often complicates the clinical picture and should be carefully evaluated.

Disease Detection and Screening:

A. Screening: The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to

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ensure accurate diagnosis, effective treatment, and appropriate follow-up. (Grade B recommendation).

Depression detection in primary care can be improved by using validated screening tools. The **Patient Health Questionnaire-2 (PHQ-2)** and **Patient Health Questionnaire-9 (PHQ-9)** are widely used instruments that assist in identifying at-risk individuals, supporting diagnosis, and guiding treatment decisions and follow-up.

- PHQ-2 is a brief initial screen (2 items) (Appendix C)
- PHQ-9 provides a more comprehensive assessment (9 items) (Appendix D)
- Sensitivity: 88% | Specificity: 85% ^[28]

Specialized screening tools are also available for particular populations:

- **Edinburgh Postnatal Depression Scale** – for pregnant and postpartum individuals
- **Geriatric Depression Scale (GDS)** – for older adults

However, these tools are not clearly superior to the PHQ-9 and may be used based on provider preference or clinical context.

B. High Risk Groups:

1. The primary risk factors for depression are the following:

Prior episodes of depression	Prior suicide attempts
Family history of depression	Female gender
Age of onset under 40	Postpartum period*
Medical co-morbidity*	Lack of social support
Stressful life events	Current alcohol or substance abuse

2. **Medical Co-morbidities***: Certain medical conditions are associated with a significantly increased risk of chronic depression. In these populations, undiagnosed or undertreated depression can adversely affect the course and prognosis of the underlying medical illness. Clinicians should maintain a high index of suspicion and consider routine depression screening in the following groups:

- Stroke** - Subgroups of post-CVA patients have depression that appears to be causally related to the injury, especially if the insult is the left basal ganglia or left dorsal lateral frontal cortex.⁽²⁹⁻³¹⁾
- Dementia** - Depression is often seen in patients with or antecedent to primary dementia. Thirty to forty percent of Alzheimer's disease patients demonstrate depressive mood symptoms sometime during their illness.
- Diabetes** - Major depressive syndrome is three times more common in this population.
- Cardiac disease** - ischemic heart disease, heart failure and cardiomyopathy. The prevalence of various forms of depression is estimated at 40 - 65%.⁽³²⁻³⁴⁾
- Cancer** - Major depression occurs in approximately 25% of this population
- Fibromyalgia**⁽³⁵⁾
- HIV/AIDS**

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Special Case: Postpartum Depression*:

Major depressive episodes, as distinct from the transient “baby blues,” affect approximately 9% of American women within the first 12 months postpartum. While commonly referred to as postpartum depression, symptoms may begin prior to delivery in up to 50% of affected women. Among those with symptom onset after delivery, over 90% develop symptoms within the first four months.

All healthcare providers caring for women during and after pregnancy should be vigilant for postpartum depression, ensure appropriate screening, and provide or facilitate timely treatment

Other possible risk factors associated with postpartum depression in addition to those listed above:

- Depression before or during the pregnancy
- Young age
- Poor perinatal physical health (gestational diabetes, hypertension, complications post-delivery)
- Single
- Multiparity
- Family history of postpartum depression or psychiatric illness
- Unintended pregnancy/negative attitude about pregnancy
- Adverse pregnancy outcome or difficult infant or trouble breast feeding
- Intimate partner violence

The clinical features are consistent with those of major depressive disorder, including persistent sadness, anhedonia, fatigue, changes in sleep or appetite, and feelings of worthlessness. In postpartum depression, lack of interest in the child and self is particularly concerning.

All evaluation should include assessment for suicidal ideation, homicidal thoughts and psychotic symptoms (e.g., hallucinations, delusions). Emergency referral to a mental health provider or an emergency department is indicated if any of the above are present.

Suicidal ideation is reported to occur in 3% of postpartum women but the rate of actual suicide is about half the rate of the general population. Potential adverse outcomes of untreated postpartum depression include, impaired mother-infant bonding, developmental and behavioral issues in the child, and missed preventive care (e.g., vaccinations).

Screening is recommended by USPTF and ACOG for all postpartum women. Recommended tools include: The Edinburgh Postnatal Depression Scale (Appendix E) or the PHQ-9 (Appendix D).

The PHQ-9 is particularly useful for diagnosis, severity assessment, and monitoring treatment response. (Integrated into MedConnect).

C. Differential Diagnosis:

1. **Psychiatric:** Differentiation from other psychiatric and substance use disorders can be difficult.

Consider:

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- **Bipolar disorder** – if there have been features of mania/hypomania. Diagnosis can be challenging since depression can be the initial manifestation of bipolar disease, and hypomania may not be perceived by the patient as “disease”. **Caution:** Antidepressants, including SSRIs and tricyclics, may precipitate manic episodes in individuals with bipolar disorder. A family history of bipolar disorder increases the likelihood that a depressive episode may be part of a bipolar spectrum.
 - **Alcohol dependence/drug dependence** – Substance-induced depression is a well-established etiology of various substances and is likely to resolve after 4-8 week of abstinence. Consider this diagnosis when symptoms emerge in the context of ongoing substance use or recent withdrawal.
 - **Personality disorders**- Long-standing patterns of emotional instability, interpersonal difficulties, or maladaptive behavior may complicate the clinical picture. While personality disorders can coexist with depression, they often contribute to chronicity and treatment resistance.
2. **Bereavement:** Distinguishing normal grief from major depressive disorder can be challenging, as both may present with profound sadness, sleep and appetite disturbances, and difficulty functioning. Cultural context and individual variation significantly influence the grieving process. However, certain features favor bereavement over clinical depression:

- **Sadness occurs in waves or pangs**, often triggered by reminders of the deceased, rather than a pervasive low mood
- **Self-esteem is generally preserved**, unlike in depression, where feelings of worthlessness are common
- The grieving individual retains **hope for the future**, whereas depression is often marked by a sense of hopelessness or despair
- **Gradual improvement** in mood and functioning over time—typically week to week—is a key indicator of a normal grief response

While symptoms may overlap, persistent functional impairment, suicidal ideation, psychosis, or lack of improvement should prompt evaluation for major depressive disorder.

D. Assessing the Patient for Suicide Potential

All patients presenting with depression should undergo an **initial evaluation for suicide risk** as part of their clinical assessment. Suicide is a serious and potentially preventable outcome of untreated or undertreated depression.

Risk Factors for Suicide Include:

- male sex
- family history of suicide
- psychotic symptoms or comorbid schizophrenia
- hopelessness
- chronic or severe general medical illnesses
- Social isolation or living alone with limited support
- Prior suicide attempts (the strongest predictor of future suicide)
- Borderline personality disorder
- Bipolar Depression (associated with higher suicide risk)

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Clinical Considerations:

- Directly inquire about suicidal thoughts, plans, and access to lethal means (especially firearms).
- Over 50% of men who complete suicide use a firearm—reducing access can significantly lower risk.
- Always ask about past suicide attempts, current ideation, intent, and specific plans.

Next Steps When Risk Is Identified:

- Any indication of suicidal risk should prompt immediate referral for a psychiatric evaluation.
- Emergency services should be contacted in cases of high risk, imminent threat, or inability to ensure patient safety.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS Short Version is a structured tool recommended for assessing suicide risk in clinical settings.

- **Embedded in MedConnect** for ease of use during office visits.
- **Trigger for use:**
 - PHQ-9 score of 5 or higher, or
 - Answering “Yes” to item 9: “*Thoughts that you would be better off dead or of hurting yourself in some way.*”

Accessing the C-SSRS in MedConnect:

Navigate to “**Scales and Assessments**” in the provider workflow

Or select “**Ad Hoc Charting**” → “**Additional Assessments**” → “**Suicide - CSSRS Short Version**”

- The tool automatically categorizes risk as Negative, Low, Moderate, or High, based on responses.
- Providers should be notified of all positive screenings.
 - Actions following the screen should adhere to entity-specific policies

For Providers Without MedConnect Access:

The C-SSRS Short Version is available online: [C-SSRS Community Card \(PDF\)](#)

Clinical Management:**A. Goals**

- 1) **Remission** – Resolution of depressive symptoms, typically defined by a rating scale cutoff indicating normal range (e.g., PHQ-9 score < 5)
- 2) **Restore functioning** – Improvement in occupational, social, and daily functioning.
- 3) **Prevent relapse and recurrence** – Reduce the risk of future depressive episodes through ongoing management.

B. Types of Treatment:

1. **Pharmacotherapy** - Patients with moderate to severe clinical depression are appropriate candidates to be treated with medication, whether or not formal psychotherapy is also used^(39, 40, 41, 45-48). For patients in acute phase of mild MDD for whom CBT is not available/feasible monotherapy with Second

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Generation Antidepressants is a reasonable alternate approach. First-line treatment typically consists of starting a second-generation antidepressant.

Second-generation antidepressants that are available to treat unipolar major depression include:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants: such as Bupropion or Mirtazapine
- Serotonin modulators

Older, first-generation antidepressants are less commonly used and include:

- Tricyclic antidepressants TCA
- Monoamine oxidase inhibitors (MAOIs): while MAOIs might show greater effectiveness due to less receptor specificity, this also results in higher rates of side effects).
(39-41)

2. **Psychotherapy** – Psychotherapy is considered a first-line treatment for mild to moderate depression and is generally as effective as pharmacotherapy. A meta-analysis of 53 trials found no significant difference in response rates across various psychotherapeutic approaches⁽³⁶⁻³⁸⁾. Common types include:

- Cognitive behavioral therapy (CBT) and behavioral activation: Patients identify negative thoughts and patterns and reframe and modify these in a constructive way
- Interpersonal therapy (IPT): Patients identify and address the role those interpersonal relationships have on perpetuating depressive symptoms
- Problem solving therapy- Patients identify strategies to solve problems in a practical manner and increase self-efficacy
- Psychodynamic therapy-Patients identify and explore the unconscious elements that contribute to current issues. Mild to moderate clinical depression (usually dysthymia or depressive disorder NOS) may be managed with psychotherapy alone if the patient prefers. If symptoms do not improve within 2-3 months, then medication should be strongly considered.
- Behavioral Activation (during which patients identify negative thoughts and patterns and reframe and modify these in a constructive way)
- Supportive psychotherapy
- Family and couple's therapy

CBT and IPT have the strongest evidence supporting their effectiveness. (39, 41, 42, 43, 44).

The primary limitations to psychotherapy are cost, insurance coverage, and access to treatment.

Telehealth-based delivery of psychotherapy has been shown to be an effective way to improve outcomes in resource-limited and time-limited settings with similar patient satisfaction as in-person interventions.⁽²⁰⁾

3. **Medication and Psychotherapy**- Combining medication and psychotherapy may benefit patients with complicated or chronic depression, partial response to monotherapy, severe depression (e.g., PHQ-9 > 20, hospitalization), recurrent episodes, or psychosocial barriers to treatment adherence (Appendix A).

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4. **Electroconvulsive therapy (ECT)** - ECT is reserved for select patients after psychiatric consultation. It is primarily indicated for severe, life-threatening depression or cases with significant functional impairment. ECT is the most effective and fastest-acting acute treatment for major depression.
5. **Transcranial Magnetic Stimulation** - TMS is used for treatment-resistant depression. It is generally well-tolerated but contraindicated in patients with seizure risk, implanted metallic or electrical devices (e.g., cochlear implants), or unstable medical conditions.
6. **Esketamine**-an analogue of ketamine, is a newer FDA-approved therapy for treatment-resistant depression, used alongside an oral antidepressant. Administered intranasally, esketamine offers a rapid onset of action. Medstar Health Esketamine clinic at Medstar Good Samaritan Hospital accepting referrals for patients who have been on three trials of antidepressant medications.
https://www.spravatohcp.com/files/patient_referral_form.pdf fax to 855-778-6866.
7. **Bright light therapy in nonseasonal major depression (February 2025)**
Although bright light therapy is a well-established treatment for seasonal affective disorder, its effectiveness for nonseasonal major depression remains less certain. A recent meta-analysis of eight randomized trials with 547 participants showed that bright light therapy (e.g., 10,000 lux for 30 minutes daily over four weeks) led to a higher remission rate compared to control interventions (41% vs. 24%)^[3]. However, the inclusion of both unipolar and bipolar depression patients limits the certainty of these findings. For individuals with nonseasonal major depression, bright light therapy may be considered as an adjunct to pharmacotherapy and/or psychotherapy.

C. Medication Selection and Management

A landmark meta-analysis by Cipriani et al., reviewing 522 trials comparing 21 antidepressants, found that all agents were significantly more effective than placebo⁽¹⁹⁾.

Most effective: amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine

Least effective: fluoxetine, fluvoxamine (SSRI), and trazodone

Better tolerated: citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine

Highest dropout rate (mostly due to side effects or lack of efficacy): amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine.

1. Selective Serotonin Re-uptake Inhibitors (SSRI)

SSRIs are generally the first-line antidepressants unless contraindicated by a history of intolerable side effects, potential drug interactions, or a personal/family history favoring another class. Advantages include easy dosing, minimal histaminic, muscarinic, or adrenergic antagonism, and efficacy in treating comorbid psychiatric conditions (e.g., panic disorder, bulimia, OCD, PMS) and some medical conditions (e.g., headaches, chronic pain, Raynaud's phenomenon). However, SSRIs often cause sexual dysfunction; the exception is their off-label use in treating premature ejaculation due to delayed orgasm effects.

Common side effects include agitation, akathisia, gastrointestinal symptoms, weight changes, insomnia or sedation, serotonin syndrome, Parkinsonian tremor, and sexual dysfunction. Elderly patients have a higher risk of hyponatremia.

Examples:

- Fluoxetine: good tolerability, minimal weight gain
- Escitalopram: most potent and selective SSRI, but no greater clinical efficiency
- Citalopram: better tolerated, but increased risk of QTc prolongation

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- Paroxetine: highest weight gain risk, notable sexual side effects, and significant discontinuation syndrome (development of withdrawal-like symptoms including headache, agitation, irritability, diaphoresis, “electric shock-like” sensations and even hallucinations following abrupt cessation or taper of antidepressant)
- Sertraline: fewer drug interactions (no specific CYP inhibition), increased bioavailability with food, higher rate of GI side effects

Special considerations:

Older Adults: Preferred first-line agents: sertraline, citalopram, and escitalopram.

Caution: FDA recommends lower doses of citalopram and escitalopram due to QTc prolongation risk, especially in women and those with cardiac vulnerability. Avoid paroxetine and fluoxetine because of higher anticholinergic side effects and overstimulation risk.

End-Stage Renal Disease (ESRD): Sertraline is preferred since it requires no renal dose adjustment

Breast Cancer Patients: Avoid fluoxetine and paroxetine due to their inhibition of CYP2D6, which can interfere with tamoxifen metabolism.

2. **Serotonin Norepinephrine Reuptake Inhibitors:**

- Side effect profile similar to SSRIs, including gastrointestinal symptoms, sexual dysfunction, and headaches.
- Increased risk of hyponatremia compared to SSRIs.

Specific examples include:

- Venlafaxine: Extended-release (ER) preferred over immediate-release (IR) due to better tolerability and simpler dosing; most studied SNRI.
- Duloxetine: Requires cautious dosing in renal impairment; frequently used for comorbid chronic neuropathic pain.

3. **Atypical Antidepressants:** Often used to augment effects of SSRIs but may also be used as first line treatments.

- Mirtazapine: increased appetite (also causes weight gain), improves symptoms of insomnia (but can also cause increased fatigue)
- Bupropion: A dopamine and norepinephrine reuptake inhibitor, sustained release bupropion exhibits lower rates of sexual side effects and weight gain than other second-generation anti-depressants (SGAs) but may lower seizure threshold in susceptible hosts.

4. **Serotonin Modulators:** Advances in understanding brain neurophysiology have led to the development of serotonin modulators. These are distinct from other classes of antidepressants that include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, tricyclics, and monoamine oxidase inhibitors.

Serotonin modulators act as antagonists and agonists at postsynaptic serotonin receptors and inhibit reuptake of postsynaptic serotonin to varying degrees; effects upon norepinephrine reuptake are minimal.

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Examples:

- Trazodone, Vilazodone, Vortioxetine

The recently FDA-approved agents vortioxetine (serotonin modulator, similar to SSRI) and levomilnacipran (SNRI) have been classified as first-line therapy, and vilazodone (serotonin modulator) as second line by the Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines. U.S. guidelines do not yet formally recommend these due to high cost and lack of generics ⁽²¹⁾

Drug interactions and metabolism — Coadministration of serotonin modulators with another drug can decrease or increase the metabolism of the serotonin modulator, which may necessitate either adjusting the dose of the serotonin modulator or using a different antidepressant. Thus, prior to initiating or altering therapy with serotonin modulators, clinicians should check interactions with other medications. The drug interaction tool provides specific dose recommendations for prescribing serotonin modulators concomitantly with drugs that affect the serotonin modulator's metabolism. Serotonin modulators are metabolized by hepatic cytochrome P450 3A4 (CYP3A4) or 2D6 (CYP2D6) enzymes. Administering a serotonin modulator in conjunction with another drug that inhibits these enzymes can increase serum concentrations of the serotonin modulator, resulting in drug accumulation and toxicity. Prescribing a serotonin modulator concurrently with medications that induce the enzymes can decrease serum concentrations of the serotonin modulator and lead to therapeutic failure.

The hepatic metabolism of the serotonin modulators includes the following:

- Trazodone and vilazodone – Trazodone and vilazodone undergo extensive hepatic metabolism by CYP3A4 [2,3]. Strong CYP3A4 inhibitors and inducers are listed in the table (table 1).
- Vortioxetine – Vortioxetine undergoes extensive metabolism by CYP2D6 and is also metabolized by other CYP enzymes [4]. Drug-drug interactions can occur when vortioxetine is co-administered with medications that inhibit CYP2D6 metabolism, or medications that induce other CYP metabolic pathways. CYP2D6 inhibitors are listed in the table (table 2).

Serotonin modulators can also interact with other medications that elevate serotonin in the central nervous system, potentially resulting in the serotonin syndrome with the potential serious effects of altered mental status, agitation, myoclonus, and hyperreflexia. These drug-drug interactions (e.g., with monoamine oxidase inhibitors) can be severe. Other medications with MAOI activity include the antibiotic linezolid. Very rarely serotonergic antidepressants may produce a serotonin syndrome with the concomitant use of buspirone, dextromethorphan, tramadol, or St. John's Wort. All SGA are contraindicated in patients who receive MAIOs in the previous two weeks because of drug-drug interactions that can cause serotonin syndrome and, in some cases, hypertensive crisis.

Combination and Augmentation Therapy: Combining antidepressants or adding augmentation medications should be managed by a psychiatrist for complex or resistant cases.

The use of pharmacogenomics, particularly CYP2C19 and CYP2D6 phenotypes, while not yet mainstream, represent an emerging technology to guide antidepressant dose and choice. If results are available, refer to evidence-based clinical practice guidelines from the Clinical Pharmacogenetics

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Implementation Consortium (CPIC; cpicpgx.org) or consult the MedStar pharmacogenomics team. To obtain a consult with the MedStar pharmacogenomics team, place an order in MedConnect for *Consult to Pharmacogenomics and Pharmacogenetics*. These consults can also advise on whether testing could be beneficial and how to order testing if desired.

- D. Expectations of Treatment:** When initiating treatment for depression, clinicians expect an active response to therapy, defined as at least a 50% improvement in symptoms. This response may be observed as early as one week after starting treatment, but in some cases, it can take up to eight weeks before the full effect is evident. If no meaningful response occurs within this period, it is advisable to reconsider the treatment plan and explore alternative options.

It is important to distinguish response from remission; remission refers to the complete resolution of depressive symptoms and may require a longer duration to achieve. Regardless of the treatment modality that led to improvement, ongoing therapy should be maintained to sustain remission and prevent relapse.

Typically, medication should be continued for four to six months following remission before considering a gradual taper to avoid withdrawal symptoms. Patients and their families should be educated about early warning signs of recurrence to ensure prompt recognition and intervention. Relapse rates are notably high, with approximately 50% of patients experiencing a recurrence after their first depressive episode. This risk increases to 70% after a second episode, more than 80% after a third, and over 90% following a fourth episode. For patients with recurrent depression, prolonged or even lifelong maintenance therapy may be necessary, though long-term treatment does not guarantee complete prevention of relapse.

If the decision is made to try to discontinue the selected medication, it should be tapered to prevent withdrawal symptoms. Patients, and their families, should be warned about early signs of recurrence of the depression.

Antidepressant use is associated with modest weight gain, but limited data compare weight gain with different antidepressants. In over 183,000 adults who started one of eight commonly used antidepressants (sertraline, fluoxetine, escitalopram, paroxetine, duloxetine, citalopram, venlafaxine and bupropion), mean absolute weight changes at six months ranged from -0.01 to 0.63 kg ^[5]. Compared with sertraline as the reference standard, escitalopram, paroxetine, and duloxetine were associated with the greatest weight gain, fluoxetine was weight neutral, and bupropion was associated with slight weight loss. Awareness of these differences can help clinicians and patients make informed choices when selecting an antidepressant.

Patients should be seen 2-4 weeks after starting therapy to assess medication adherence, and to monitor emergence of mania, tolerability, suicide risk and early response. Addressing specific adverse effects is important to maintaining adherence until patients respond. There should be 3 contacts within the first 12 weeks. Patients on stable, long-term medication should be seen in the office every 3-6 months for re-evaluation of the treatment plan and efficacy. Some side effects are more noticeable with certain medications than others.

- **Diarrhea** occurs more often with sertraline than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, and venlafaxine (16 versus 8 percent of patients).

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- **Nausea and vomiting** occurs more often with venlafaxine than SSRIs as a class (33 versus 22 percent).
 - **Sexual dysfunction** occurs less often with bupropion than escitalopram, fluoxetine, paroxetine, and sertraline (6 versus 16 percent; paroxetine is especially problematic).
 - **Somnolence** occurs more often with trazodone than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine (42 versus 25 percent)
 - **Weight gain** is greater with mirtazapine (0.8 to 3.0 kg after six to eight weeks of treatment) than fluoxetine, paroxetine, trazodone, and venlafaxine. And is less likely with Bupropion
- E. **Evaluating Response to Treatment:** Serial scores on the PHQ-9 can be used to evaluate a response to treatment. A drop of 5 or more points is considered an adequate response with no change in treatment regimen. A drop of 2-4 points is a partial response. A score below 5 is considered a remission. Additional details may be found at www.phqscreeners.com.
- F. **Continuation of Treatment:** If this is a first episode of clinical depression in a patient with a good premorbid mood history and without a significant family history of depression, then effective medication should be continued at least for 6-12 months before considering discontinuation. Some patients are candidates for indefinite medication maintenance. These patients should be re-evaluated every 3-6 months. If medicines are tapered or discontinued, patients should be warned about early signs of recurrence.
- G. **Collaborative Care Approach:** For patients with mild to moderate major depressive disorder, consider referral to a collaborative care model, when it is locally available. This model has a care manager who meets with patients, discusses care recommendations with a psychiatrist, and coordinates medications and referrals with the primary care physician. The collaborative care team tracks this population over time, paying attention to measurement-based outcomes (such as PHQ-9) and progressively intensifying treatment until the specified outcomes are achieved
- H. **Psychiatric Referral:** Referral for mental health consultation, treatment and/or psychotherapy can occur at any time at the PCP's discretion and/or the patient's choice.
 Immediate referral is recommended for:
 - *significant evidence of danger to self and/or others*
 - *presence of psychotic symptoms*
 Referral is strongly recommended for:
 - *depression with co-morbid psychiatric or substance abuse disorders*
 - *suspicion of bipolar disorder*
 - *depression during pregnancy and the postpartum*
 - *treatment-resistant depression*
 - *childhood depression*
 - *depression with dementia*
- I. **Treatment of postpartum depression by non-specialists (January 2025)**
 Although cognitive-behavioral therapy (CBT) is an established treatment for postpartum depression, access may be limited due to the restricted availability of specialists to administer it. A recent trial of over 700 individuals with postpartum depression found that recovery was two times more likely with CBT provided by non-specialist health workers than with usual care. These results support our recommendation of standard

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psychotherapies such as CBT, administered by specialists or non-specialists, for all patients with mild to moderate postpartum depression to improve outcomes for patients and their offspring.

Patient Education:

A. Clinician counseling:

Natural history of the disease: Depression isn't just a brief blue mood or a passing sadness that lifts in a few hours or even a few days. Clinical Depression occurs when a person experiences physiologic symptom such as changes in sleep, appetite, sexual function, feeling of sadness and difficulty in the ability to function normally. These symptoms last for several weeks or more.

1. Treatment Plan:

- *Medication* - Patients with moderate to severe clinical depression are appropriate candidates for medication. Compliance with antidepressants can be a problem. Discuss with patients that usually 4-6 weeks of medication is required for a full response. Explain and discuss common side effects of medications such as sexual dysfunction, restlessness, anticholinergic effects, orthostatic hypotension, and GI symptoms. Medication guides regarding the risk of suicidal thoughts and actions with antidepressants will be provided by the pharmacy when medications are dispensed.
- *Psychotherapy* - Can be successful for patients with mild to moderate clinical depression. If symptoms do not significantly improve within 2-3 months, then medication should be considered.
- *Medication and Psychotherapy* - This combination can be beneficial for complicated, chronic depression or with individuals who have experienced only partial response to either treatment alone.
- *Recovery* - The term recovery is used to indicate the resolution of a depressive episode. Although different definitions of recovery exist, many long-term observational studies require at least two consecutive months with no more than one or two mild symptoms of depression and no impairment of psychosocial functioning. Prospective studies have found that the probability of recovery from major depression progressively decreases as the duration of the episode increases

2. Self-help Strategies:

- Identify activities that make you feel better and try to focus on them. Do things for yourself. Take up hobbies. Listen to music. Participate in activities even when you may not want to.
- Do not withdraw from others. Join a support group and talk to your friends. Call on your support group or therapist for help when you need it. Ask for assistance at home and work if the load is too great to handle.
- *Exercise:* While exercise, in low quality studies, was described to be comparable to CBT⁽²³⁾, a comparison to the use of second-generation antidepressants remained inconclusive⁽²⁰⁾. Furthermore, it is unclear what the "dose" of exercise should be to achieve a clinical benefit.⁽¹⁵⁾ However, patients, if able to exercise, should not be discouraged given that the risk of harm is low, and it provides other health benefits
- Eat nutritious, well-balanced meals. Avoid drinking alcohol and coffee. Get adequate rest and keep your sleep cycle as regular as possible.
- Concentrate on good grooming and cleanliness.
- Perform progressive relaxation exercises daily and diaphragmatic breathing exercises during times of high stress.

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- Perform frequent mental imaging of good life experiences. Develop and maintain an attitude that things will work out.
- Learn new, positive problem-solving techniques.
- Call the Suicide & Crisis Lifeline at 988 or your provider or therapist if you feel suicidal.
- Complementary and alternative medicine approaches: The most notable complementary and alternative medicine therapies generally have a low level of evidence and include St. John's wort (more effective than placebo, comparable efficacy to first- and second-generation antidepressants, lower side effect profile) and acupuncture (possibly more effective than no treatment, unclear if effect comparable to medication or psychotherapy, unclear adverse risk profile due to inadequate reporting in studies). Furthermore, data remain inconclusive on the efficacy of meditation, yoga, SAdenosylmethionine, and omega-3 fatty acids. Moderate quality evidence exists for the addition of music therapy to treatment as usual to decrease anxiety and improve functioning in depression.⁽¹⁷⁾ Of note, St. John's wort has significant drug-drug interactions and should not be used in conjunction with SSRIs or MAO-inhibitors.

B . Resources for patients:

- National Institute Mental Health: 866-615-6464 or <http://www.nimh.nih.gov/health/publications/index.shtml>
- Center for Disease Control: <https://www.cdc.gov/reproductivehealth/depression/resources.htm>
- National Alliance on Mental Health (NAMI) <https://www.nami.org/#>; Call 1-800-95-6264
- National Suicide Prevention Lifeline: 1-800-273-TALK or 1-800-273-8255; Suicide & Crisis Lifeline: Call or text 988; The Lifeline provides 24/7, free and confidential support for people in distress, prevention, and crisis resources.
- American Psychiatric Association: <http://www.psychiatry.org/mental-health>
- Mental Health America: <http://www.nmha.org/mental-health-information>
- <https://www.nimh.nih.gov/health/topics/depression/index.shtml>
- <https://www.cdc.gov/learnmorefeelbetter/programs/depression.htm>
- <https://www.cdc.gov/tobacco/campaign/tips/diseases/depression-anxiety.html>

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Selected Formulary for Medical Management of Depression

I. Selective Serotonin Reuptake Inhibitors (SSRI's)

Drug name	Initial Dose	Dosing Range	Positives	Limitations
citalopram <i>Celexa</i> [®] (\$84)	20mg daily Dosing has been adjusted down to 20 mg/d max for women due to concerns about QTc prolongation	20-40mg daily max dose 20 mg for age >60 or hepatic impairment	<ul style="list-style-type: none"> Minimal drug interactions compared with other SSRIs Generic available Lower incidence of sexual dysfunction 	<ul style="list-style-type: none"> Do not use doses >40 mg due to risk of QT prolongation. Discontinue in patients with QTc interval >500ms.
escitalopram <i>Lexapro</i> [®] (\$148)	10mg daily (adjusted down to 10 mg max for women due to concerns about QTc prolongation)	10-20mg daily	<ul style="list-style-type: none"> Minimal drug interactions compared with other SSRIs Possible quicker onset in resolving panic-related symptoms 	<ul style="list-style-type: none"> Risk of QT prolongation
fluoxetine <i>Prozac</i> [®] (\$320)	10-20mg daily (Elderly dose 10mg/day)	20-80mg daily	<ul style="list-style-type: none"> Energizing feeling Lower cost of care 	<ul style="list-style-type: none"> Longer half life More agitation
Fluvoxamine (\$158)	50mg daily	100-200mg daily Divide doses >100mg	<ul style="list-style-type: none"> Less cognitive disturbance 	<ul style="list-style-type: none"> Similar side effect profile to other SSRIs IR and CR formulations are interchangeable on a mg to mg basis
fluvoxamine CR (\$611)	100mg daily	100-200mg daily		
paroxetine <i>Paxil</i> [®] (\$95)	10-20mg daily (CrCl <30mL/min dose 10mg/day)	20-50mg daily Maximum dose 40 mg if CrCl <30mL/min	<ul style="list-style-type: none"> Better for agitation Usually has better pricing 	<ul style="list-style-type: none"> More problems with withdrawal More anticholinergic side effects
paroxetine <i>Paxil</i> [®] CR (\$180)	25 mg daily (CrCl <30mL/min dose 12.5mg/day)	25-62.5 mg daily Maximum dose 50mg if CrCl <30mL/min		

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sertraline <i>Zoloft</i> [®] (\$172)	25-50mg daily	25-200mg daily	<ul style="list-style-type: none"> • More helpful in Parkinson's patients 	<ul style="list-style-type: none"> • Usually needs higher doses to be effective • More titration
vilazodone <i>Viibryd</i> [®] (\$360)	10 mg daily	20-40 mg daily	<ul style="list-style-type: none"> • May have lower incidence of sexual dysfunction • May lead to less weight gain 	
vortioxetine <i>Trintellix</i> [®] (\$617 – brand only)	5-10 mg daily	20 mg daily	<ul style="list-style-type: none"> • May be alternative to partial or non-responders to SSRIs due to multi-modal mechanism; minimal effect on weight and sexual function 	

Potential side effects of all SSRI's include agitation, nausea, diarrhea, sexual side effects, akathisia, and serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability, and potentially delirium and coma, hypo-natremia in elderly persons; potential for drug-drug interactions; contraindicated with MAOI; Increased risk of bleeding with SSRIs and SNRIs (especially in combo with NSAIDs).

II. Norepinephrine Dopamine Reuptake Inhibitors (NDRI's)

Drug name	Initial Dose	Dosing Range	Positives	Limitations
bupropion <i>Wellbutrin</i> [®] (\$120)	100mg 2x/day	200-450mg daily in 3- 4 divided doses Max single dose=150mg	<ul style="list-style-type: none"> • Low sexual side effects • May help with nicotine addiction • Increases total REM time • Effective in many SSRI non-responders 	<ul style="list-style-type: none"> • Seizures 0.4% (dose dependent, more common with immediate release) • GI upset • Tinnitus • Agitation • Tremor <p>Contraindicated if history of seizures or eating disorders</p>
<i>Wellbutrin SR</i> [®] (\$230)	150mg q am	Max 400mg in divided doses Max single dose=200mg		
<i>Wellbutrin XL</i> [®] (\$502)	150 mg q am	150-450mg daily		

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III. Serotonin Norepinephrine Reuptake Inhibitors (SNRI's)

Drug name	Initial Dose	Dosing Range	Positives	Limitations
duloxetine <i>Cymbalta</i> [®] (\$235)	40-60 mg/day as single dose or as two divided doses	20-30mg 2x/day or 60mg once daily Max 60mg/day	<ul style="list-style-type: none"> Benefit in neuropathic pain 	<ul style="list-style-type: none"> Possible urinary retention and hepatotoxicity Possible elevation in BP Use not recommended in patients with renal insufficiency (creatinine clearance < 30) or end stage renal disease Use not recommended in patients with hepatic disease given potential for contributing to hepatic failure. Cigarette smoking reduces plasma levels of duloxetine
venlafaxine <i>Effexor</i> [®] (\$209)	37.5-75mg daily in divided doses	75-375mg daily (w/food)	<ul style="list-style-type: none"> Possible greater efficacy Low side effects Possible greater efficacy w/chronic pain 	<ul style="list-style-type: none"> BP elevation Weight gain Frequent dosing Sexual side effects
<i>Effexor XR</i> [®] (\$652)	37.5-75mg daily	75-375mg daily (w/food)		
desvenlafaxine <i>Pristiq</i> [®] (\$174)	50 mg daily	50 mg daily 25mg daily or 50mg every other day if CrCl < 30mL/min	<ul style="list-style-type: none"> Once daily administration 	<ul style="list-style-type: none"> Doses of 50-400 mg daily have been studied; no additional benefit has been observed at doses > 50 mg Possible BP elevation Nausea/dizziness Similar side effect profile to venlafaxine

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levomilnacipran <i>Fetzima</i> ® (\$632) (Brand only)	20 mg daily x 2 days then 40 mg daily	40-120 mg daily Max 80mg daily if CrCl <60mL/min Max 40mg daily if CrCl <30mL/min	<ul style="list-style-type: none"> • May be more beneficial for treatment of symptoms related to norepinephrine deficiency (decreased concentration, mental and physical slowing, decreased self-care) 	
milnacipran <i>Savella</i> ® (\$614) (Brand only)	25-50mg twice daily	100-200mg daily Divide doses >100mg	<ul style="list-style-type: none"> • Less agitation than other SNRIs 	

Potential side effects of all SNRI's include agitation, nausea, diarrhea, sexual side effects, akathisia, and serotonin syndrome (hyperthermia, rigidity, myoclonus, autonomic instability, and potentially delirium and coma).

IV. Serotonin Antagonist and Reuptake Inhibitors

Drug name	Initial Dose	Dosing Range	Positives	Limitations
trazodone (\$163)	50mg 2x/day (Depression)	200-400mg daily in divided doses (w/food)	<ul style="list-style-type: none"> • Sedative properties 	<ul style="list-style-type: none"> • Over-sedation and/or possible orthostasis • Priapism

V. Tetracyclic Antidepressants

Drug name	Initial Dose	Dosing Range	Positives	Limitations
mirtazapine <i>Remeron</i> ® (\$86)	15mg daily hs	15-45mg hs	<ul style="list-style-type: none"> • Appetite stimulation • Sedative properties • Minimal GI side effects 	<ul style="list-style-type: none"> • Over sedation • Weight gain • Metabolic disorders. Caution in patients with renal impairment

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VI. Tricyclic Antidepressants (TCA's)

Drug name	Initial Dose	Dosing Range	Positives	Limitations
amitriptyline (\$229)	25-50mg hs (Elderly dose 10mg/ day)	100-300mg daily	<ul style="list-style-type: none"> • Sedative properties • Efficacy in neuropathic pain • Well known therapeutic and toxic levels 	<ul style="list-style-type: none"> • Weight gain • Cardiac arrhythmia • Orthostatic hypotension • Anticholinergic • Not recommended for elderly
nortriptyline <i>Pamelor</i> [®] (\$253)	25-50mg hs	50-150 mg/day as single or divided doses	<ul style="list-style-type: none"> • Well known therapeutic and toxic levels • Less anticholinergic 	<ul style="list-style-type: none"> • Cardiac arrhythmias
amoxapine (\$204)	25-50mg daily 1-3 times daily	100-400mg daily Doses >300mg/day should be divided Max dose 300mg in older adults	<ul style="list-style-type: none"> • Potential benefit in depression with psychosis 	<ul style="list-style-type: none"> • EPS or tardive dyskinesia (avoid in Parkinson's) • Sedation • Orthostasis
desipramine <i>Norpramin</i> [®] (\$390)	25-50mg daily	100-200mg daily Max 300mg/day	<ul style="list-style-type: none"> • Sedative properties 	<ul style="list-style-type: none"> • Weight gain • Cardiac complications
doxepin <i>Silenor</i> [®] (\$200)	25-50mg hs	100-300mg daily one dose hs or in divided doses Max single dose 150mg	<ul style="list-style-type: none"> • Sedative properties • Patients with neurodermatitis 	<ul style="list-style-type: none"> • Over sedation • Weight gain • Cardiac complications
imipramine (\$238)	25-50mg hs	100-300mg Once daily or in divided doses	<ul style="list-style-type: none"> • Minimal drug Interactions • Patients with insomnia • Patients with enuresis 	<ul style="list-style-type: none"> • Contraindicated in post MI patients • Dose 30-100mg/day recommended in elderly and peds
protriptyline (\$1080)	10-20mg in 3- 4 doses	20-60mg/day in 3-4 doses	<ul style="list-style-type: none"> • Good for withdrawn or anergic patients 	<ul style="list-style-type: none"> • Multiple daily dosing • Cardiac complications • Weight gain
trimipramine (\$2825)	25-50 mg hs or in divided doses	75-300mg hs	<ul style="list-style-type: none"> • Patients with insomnia or anxiety 	<ul style="list-style-type: none"> • Weight gain • Sedation

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VII. Monoamine Oxidase Inhibitors (MAOIs)

Drug Name	Initial Dose	Dosing Range	Positives	Limitations
isocarboxazid <i>Marplan</i> [®] (\$1022 – brand only)	10mg 2x/day	40-60mg/day divided 2-4x/day	<ul style="list-style-type: none"> • Patients with resistant or atypical depression or anxiety 	<ul style="list-style-type: none"> • Dietary restrictions • Drug interactions • Hypertensive crisis • Avoid in patients with HTN or cardiac conditions
phenelzine <i>Nardil</i> [®] (\$151)	15mg ti1-3x/day	60-90mg/day divided 3x/day	<ul style="list-style-type: none"> • As above 	<ul style="list-style-type: none"> • As above
selegiline transdermal patch <i>Emsam</i> [®] (\$2702) (brand only)	6mg/24 hours	6-12mg/24 hours	<ul style="list-style-type: none"> • As above • Less weight gain • Less sexual dysfunction 	<ul style="list-style-type: none"> • Caution in Parkinson's • As above
tranylcypromine <i>Parnate</i> [®] (\$650)	10-30mg daily in divided doses	30-60 mg/day in divided doses	<ul style="list-style-type: none"> • As above 	<ul style="list-style-type: none"> • As above

VIII. N-Methyl-D-Aspartate Receptor Antagonist

Drug name	Initial Dose	Dosing Range	Positives	Limitations
esketamine <i>Spravato</i> [®] (\$501/28mg – brand only)	56-84mg twice weekly, evaluating need for continued use after 4 weeks	56-84mg once-twice weekly (goal is least frequent dosing interval needed to maintain response)	<ul style="list-style-type: none"> • Useful for treatment-resistant depression • Not a daily PO dose - may be useful for patients with poor adherence 	<ul style="list-style-type: none"> • Abuse potential • Must be administered in a certified medical office

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APPENDIX A: Geriatric Depression Scale

Name _____ PCP _____
 DOB _____ Date Completed _____

Circle your answer of YES or NO for each of the following items, do not skip any items.

- | | | |
|---|-----|----|
| 1. Are you basically satisfied with your life? | YES | NO |
| 2. Have you dropped many of your activities and interests? | YES | NO |
| 3. Do you feel that your life is empty? | YES | NO |
| 4. Do you often get bored? | YES | NO |
| 5. Are you in good spirits most of the time? | YES | NO |
| 6. Are you afraid that something bad is going to happen to you? | YES | NO |
| 7. Do you feel happy most of the time? | YES | NO |
| 8. Do you often get restless and fidgety? | YES | NO |
| 9. Do you prefer to stay at home, rather than going out and doing new things? | YES | NO |
| 10. Do you feel you have more problems with memory than most? | YES | NO |
| 11. Do you think it is wonderful to be alive now? | YES | NO |
| 12. Do you feel pretty worthless the way you are now? | YES | NO |
| 13. Do you feel full of energy? | YES | NO |
| 14. Do you feel that your situation is hopeless? | YES | NO |
| 15. Do you think that most people are better off than you are? | YES | NO |

<p>Cut point for positive response: ≥ 6 Time to administer: 2-5 minutes Can be used to monitor treatment response</p>
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APPENDIX B: Patient Health Questionnaire 2 (PHQ-2)

Name _____ DOB _____

Date Completed _____

Over the past two weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things.	0	1	2	3
Feeling down, depressed, or hopeless.	0	1	2	3

Total point score: _____

These questions, which can be used by practitioners as part of a general medical review of systems, can help identify which patients are exhibiting signs and symptoms of depression, and which of them may benefit from completing the PHQ-9. It can be administered by asking for responses as yes/no or rated on a scale of zero to three. Any “yes” or a score of three or more indicates possible depression and requires further evaluation.

Score interpretation: Cut point for positive response ≥ 3

<i>PHQ-2 score</i>	<i>Probability of major depressive disorder (%)</i>	<i>Probability of any depressive disorder (%)</i>
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

Information from Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003;41: 1284-92.

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APPENDIX C: Patient Health Questionnaire 9 (PHQ-9)

Patient's name: _____ Date: _____

Over the past two weeks, how often have you been bothered by any of the following problems?

(For each question, circle the number that represents the best answer.)

	Not at all	Several days	More than one half of 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 asleep 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 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
Add Columns				

SUM OF ALL COLUMNS=

10. If you have had any of these problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people? (Circle the best answer)

Not difficult at all Somewhat difficult Very difficult Extremely difficult

Patient Health Questionnaire-9 (PHQ-9). The PHQ was developed by Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues. For research information, contact Dr. Spitzer at ris8@columbia.edu. PRIME-MD (Primary Care Evaluation of Medical Disorders) is a trademark of Pfizer, Inc. Copyright© 1999. Pfizer, Inc. All rights reserved.

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Scoring PHQ-9: Confirmation of Depression and Patient Monitoring

- A. Scoring instructions: The total PHQ-9 score is the sum of the scores for the responses to questions 1 through 9.
- B. If there are at least 4 checks in the gray highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Interpretation of Total Score

Total Score Depression Severity

- 1-4 Minimal depression
- 5-9 Mild depression
- 10-14 Moderate depression
- 15-19 Moderately severe depression
- 20-27 Severe depression

C. Consider Major Depressive Disorder

If there are at least 5 checks in the gray highlighted section (one of which corresponds to Question #1 or #2)

D. Consider Other Depressive Disorder

If there are 2 to 4 checks in the gray highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (bipolar disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

E. To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

Initial response after Four weeks of an Adequate Dose of an Antidepressant		
PHQ 9	Treatment Response	Treatment Plan
Drop of 5 points from baseline	Adequate	No change, follow up 4 weeks
Drop of 2-4 points from baseline	Possibly Inadequate	May warrant an increase in antidepressant dose
Drop of 1 point or no change or increase	Inadequate	Increase dose; augmentation; switch medicine; psych consultation; add counseling

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Initial response after Six weeks of Psychological Counseling		
PHQ 9	Treatment Response	Treatment Plan
Drop of 5 points from baseline	Adequate	No change, follow up 4 weeks
Drop of 2-4 points from baseline	Possibly Inadequate	Probably no treatment change needed. Share results with psychotherapist
Drop of 1 point or no change or increase	Inadequate	<p>If depression-specific psychological counseling (Cognitive – Behavioral Therapy, etc.) discuss with therapist and consider adding antidepressant</p> <p>For patient satisfied with other type of counseling, consider starting antidepressant</p> <p>For patients dissatisfied in other psychological counseling, review treatment options and preferences</p>

Adapted from MacArthur Depression Toolkit www.depression-primarycare.org

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APPENDIX D: Edinburgh Postnatal Depression Scale (EPDS)

In the past 7 days:	
4. I have been anxious or worried for no good reason	
— No, not at all	0
— Hardly ever	1
— Yes, sometimes	2
— Yes, very often	3
5. I have felt scared or panicky for no very good reason	
— Yes, quite a lot	3
— Yes, sometimes	2
— No, not much	1
— No, not at all	0
6. Things have been getting on top of me	
— Yes, most of the time I haven't been able to cope	3
— Yes, sometimes I haven't been coping as well as usual	2
— No, most of the time I have coped quite well	1
— No, I have been coping as well as ever	0
7. I have been so unhappy that I have had difficulty sleeping	
— Yes, most of the time	3
— Yes, sometimes	2
— Not very often	1
— No, not at all	0
8. I have felt sad or miserable	
— Yes, most of the time	3
— Yes, quite often	2
— Not very often	1
— No, not at all	0
9. I have been so unhappy that I have been crying	
— Yes, most of the time	3
— Yes, quite often	2
— Only occasionally	1
— No, never	0
10. The thought of harming myself has occurred to me	
— Yes, quite often	3
— Sometimes	2
— Hardly ever	1
— Never	0

A score of 12 or more identifies most women with postpartum depression. Women who report depressive symptoms without suicidal ideation or major functional impairment (or score between 5 and 9 on the EPDS) should be re-evaluated within one month.

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APPENDIX E: Columbia Suicide Severity Rating Scale-Screen

Columbia Suicide Severity Rating Scale - Screen	
<p>(i) This icon indicates that the associated charting box has reference text. Right click on the charting box to view the reference text.</p>	
<p>1. In the past month have you wished you were dead or wished you could go to sleep and not wake up? (i)</p>	<input type="radio"/> Past month, yes <input type="radio"/> Past month, no
<p>2. In the past month have you actually had any thoughts of killing yourself? (i)</p> <p>If YES to 2, ask questions 3,4,5, and 6. If NO to 2, go directly to question 6.</p>	<input type="radio"/> Past month, yes <input type="radio"/> Past month, no
<p>3. In the past month have you been thinking about how you might kill yourself? (i)</p> <p>E.g. "I thought about taking an overdose but I never made a specific plan as to when or how I would actually do it...and I would never go through with it"</p>	<input type="radio"/> Past month, yes <input type="radio"/> Past month, no
<p>4. In the past month have you had these thoughts and had some intention of acting on them? (i)</p> <p>As opposed to "I have the thoughts but I definitely will not do anything about them"</p>	<input type="radio"/> Past month, yes <input type="radio"/> Past month, no
<p>5. In the past month have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? (i)</p>	<input type="radio"/> Past month, yes <input type="radio"/> Past month, no
<p>6. Have you ever done anything, started to do anything, or prepared to do anything to end your life? (i)</p> <p>If NO to question 6 the screening is complete. If YES to 6 ask the following question.</p>	<input type="radio"/> Yes <input type="radio"/> No
<p>Was this within the past THREE months?</p>	<input type="radio"/> Yes <input type="radio"/> No
<p>CSSRS - Screen Risk Level</p>	<input type="radio"/> Negative Screen <input type="radio"/> Low Risk Screen <input type="radio"/> Moderate Risk Screen <input type="radio"/> High Risk Screen
<p>CSSRS Screen Risk of Low, Moderate or High: Notify Provider/APP</p>	

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