

Depression

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THE STORY IN ONE SENTENCE

Depression is a medical condition in which the brain's mood and motivation systems stop working properly, causing persistent sadness, loss of interest, and changes in sleep, appetite, energy, and thinking that last at least two weeks.

“Depression is a brain disorder caused by disrupted chemical signals — serotonin (a brain messenger that steadies mood and sleep), norepinephrine (a brain messenger that powers alertness and motivation), and dopamine (a brain messenger that creates pleasure and reward) — often triggered by genes, stress, or both, leading to persistent sadness, loss of interest, and physical symptoms that can become life-threatening if suicidal thoughts arise.”

Normal anatomy — the body's job

The brain uses chemical messengers called neurotransmitters, especially serotonin, norepinephrine, and dopamine, to control mood, motivation, sleep, appetite, energy, and thinking. These chemicals travel between nerve cells, called neurons, in specific brain regions like the prefrontal cortex (the front of the brain that plans and regulates feelings), the limbic system (the emotion center deep inside), and the hypothalamus (the body's control tower for sleep and hunger). When this system is balanced, you feel okay, bounce back from stress, enjoy activities, sleep well, eat normally, and think clearly.

BODY'S JOB

Serotonin, norepinephrine, and dopamine are released by one neuron, cross a tiny gap called a synapse, and attach to receptors on the next neuron to send signals. Serotonin helps stabilize mood and regulate sleep and appetite. Norepinephrine helps you feel alert and motivated. Dopamine helps you feel pleasure and reward. After sending their message, these chemicals are either broken down by enzymes or taken back into the first neuron, a process called reuptake, to be reused. This cycle keeps your mood steady, your energy level normal, and your ability to enjoy life intact. The brain also has circuits that connect emotion centers to thinking centers, so you can recognize how you feel and respond to it in a healthy way.

1. Neurons in the brainstem and deep brain regions, like the raphe nuclei (a cluster of cells in the brainstem) and locus coeruleus (a tiny area in the brainstem), make serotonin and norepinephrine.
2. Neurons in the midbrain, like the ventral tegmental area (a region in the middle of the brain), make dopamine.
3. These chemicals are released into the synapse, the gap between neurons, when the neuron fires a signal.
4. The chemicals attach to receptors on the next neuron, passing the signal forward to brain regions that control mood, motivation, sleep, appetite, and thinking.
5. Extra neurotransmitter in the synapse is either broken down by enzymes or taken back into the first neuron by transporter proteins through reuptake, so the signal stops and the cycle can repeat.
6. The prefrontal cortex (the front of the brain) uses these signals to plan, focus, and put the brakes on big feelings.
7. The limbic system, including the amygdala (the brain's alarm center that flags danger and sadness) and hippocampus (the brain's memory keeper and emotion processor), uses serotonin and norepinephrine to keep emotional responses balanced.
8. The hypothalamus (the control tower for sleep, hunger, and hormones) uses these chemicals to set your sleep-wake cycle, called the circadian rhythm, and control appetite and energy use.

What breaks

In depression, the brain does not make enough serotonin, norepinephrine, and dopamine, or it reabsorbs them too quickly, or the receptors do not respond well, so the mood, motivation, sleep, appetite, and thinking circuits do not get the signals they need. This can be triggered by genes you inherit — family history of depression increases risk — or ongoing stress, which

raises cortisol (the body's main stress hormone) that damages neurons and lowers neurotransmitter production. Trauma, medical illness like thyroid disease or stroke or chronic pain, some medicines like steroids or beta-blockers, or substance use can also set it off. The break often starts in the limbic system (the emotion center) and spreads to the prefrontal cortex (the thinking center), disrupting both emotion and thinking.

CLINICAL TERM

Major depressive disorder (MDD) is characterized by dysregulation of monoaminergic neurotransmission, specifically reduced synaptic availability of serotonin, norepinephrine, and dopamine, due to decreased synthesis, increased reuptake, receptor downregulation, or impaired signal transduction. Contributing mechanisms include hypothalamic-pituitary-adrenal (HPA) axis hyperactivity with chronic cortisol elevation, which reduces hippocampal neurogenesis and prefrontal cortex volume, genetic polymorphisms such as in the serotonin transporter gene SLC6A4, inflammatory cytokine release including interleukin-6 (IL-6) and tumor tissue death (necrosis) factor-alpha (TNF-alpha) that impair neurotransmitter synthesis, and disrupted circadian rhythm regulation. The result is functional hypoactivity in the prefrontal cortex, impairing executive function and emotion regulation, and hyperactivity in the amygdala, amplifying negative emotional processing, leading to the clinical syndrome of persistent depressed mood, anhedonia, neurovegetative symptoms including sleep, appetite, and energy changes, cognitive impairment, and in severe cases, suicidal ideation.

How the body compensates

The body tries to adapt to low neurotransmitter levels by increasing receptor sensitivity or altering sleep and appetite to conserve energy, but these adaptations are not enough to restore normal mood and often make things worse. Vital signs like heart rate and blood pressure usually stay normal, so depression can look stable on the outside even as the person is suffering intensely inside. The critical danger is suicide, especially in the first weeks of treatment, when energy and motivation may improve before mood does, giving the person the ability to act on suicidal thoughts. The goal is to recognize depression early, start treatment, and monitor closely for worsening or suicidal ideation, because untreated depression can become chronic and disabling.

1. The brain tries to increase the number or sensitivity of neurotransmitter receptors to catch more of the limited serotonin, norepinephrine, and dopamine, but this takes weeks and is often not enough to fix the problem.

2. The body slows down activity to conserve energy: you sleep more, or your sleep becomes fragmented and unrefreshing, you eat less or crave high-calorie comfort foods, and you avoid social interaction — this looks like laziness but is actually the body trying to save resources.
3. The prefrontal cortex (the thinking center) tries to regulate the overactive amygdala (the alarm center) by using cognitive control, but with low neurotransmitters, this effort fails, so negative thoughts spiral and you cannot think your way out of depression.
4. The hypothalamus (the body's clock) tries to reset circadian rhythms, but disrupted neurotransmitter signals keep sleep and appetite irregular, so fatigue and poor nutrition worsen mood further.
5. These compensations can mask the severity of depression — the person may still go to work, care for family, or appear fine to others, making it easy for clinicians and loved ones to miss how much the person is struggling inside.
6. The crash point to watch for is suicidal ideation, especially when the person has a plan, access to means like firearms or medicines, or starts giving away belongings, and especially in the first one to two weeks after starting antidepressants, when energy returns before mood improves, a dangerous window when the person now has the energy to act on suicidal thoughts.
7. Monitor every visit for worsening symptoms, including more sadness, more hopelessness, new suicidal thoughts, increased substance use, or withdrawal from support — a stable patient who is slowly getting worse is not really stable and needs treatment escalation.
8. The body cannot compensate its way out of depression — treatment with therapy, medication, or both is needed to raise neurotransmitter levels and retrain thought patterns, and most people start to feel better within four to eight weeks of effective treatment.

Domino effect

1. Genetics, stress, trauma, medical illness, or other triggers lower serotonin, norepinephrine, and dopamine production or increase their reuptake in the brain. — This is the upstream break — when these chemical messengers drop below the level needed to keep mood, motivation, and thinking circuits working, the whole system starts to fail.
2. You feel sad, empty, or hopeless most of the day, nearly every day, for at least two weeks. — Low serotonin and norepinephrine mean the limbic system, the emotion center, cannot stabilize mood, so sadness becomes constant instead of coming and going like it normally does.
3. You lose interest or pleasure in activities you used to enjoy, called anhedonia — hobbies, time with friends, even favorite foods feel flat or meaningless. — Low dopamine means the brain's reward circuit stops working, so nothing feels good or worth doing anymore — the brain cannot generate the feel-good signal that makes life enjoyable.

4. Your sleep changes — you might sleep much more than usual, called hypersomnia, or wake up at three or four in the morning and cannot fall back asleep, called early morning awakening, or have trouble falling asleep at night, called insomnia. — Low serotonin disrupts the hypothalamus, which sets your sleep-wake cycle, called the circadian rhythm, so your brain loses its normal day-night signal and sleep becomes chaotic.
5. Your appetite and weight change — you might eat much less and lose weight without trying, or crave comfort foods and gain weight. — The hypothalamus also controls hunger and satiety signals, and when serotonin is low, these signals break down — some people lose appetite completely, while others overeat to try to feel better, called emotional eating.
6. You feel exhausted and slowed down — even small tasks like getting dressed or making a meal feel impossibly hard, and you might move or speak more slowly than usual, called psychomotor retardation. — Poor sleep and poor nutrition starve the brain and body of energy, and low norepinephrine means the brain's alertness and motivation circuits cannot activate, so you feel physically and mentally drained all the time.
7. You cannot concentrate, remember things, or make decisions — reading, working, or even following a conversation becomes difficult. — The prefrontal cortex, the thinking and planning part of the brain, needs serotonin, norepinephrine, and dopamine to focus and process information, and without them, cognitive function drops — this is sometimes called brain fog in depression.
8. You feel worthless, guilty, or like a burden to others — even blaming yourself for things that are not your fault or for being depressed itself. — The overactive amygdala, the emotion center, amplifies negative thoughts, and the underactive prefrontal cortex cannot regulate them, so your brain gets stuck in loops of self-blame and hopelessness that feel completely real even though they are distorted by the illness.
9. You think about death or suicide — this can range from passive thoughts like I wish I would not wake up to active plans to hurt yourself. — When hopelessness, guilt, and emotional pain become overwhelming, and the brain's circuits for problem-solving and future-thinking are broken, suicide can start to feel like the only way to escape the suffering — this is the most dangerous complication of depression and requires immediate intervention: call 988, go to the ER, or contact a mental health provider right away.
10. Your body might hurt too — headaches, stomach pain, muscle aches, or chest tightness with no clear medical cause. — Serotonin and norepinephrine also control pain pathways in the spinal cord and brain, so low levels lower your pain threshold and amplify physical sensations — chronic stress from depression also raises cortisol and inflammatory molecules, which cause real physical pain and are why depression often shows up as unexplained body symptoms, especially in older adults and some cultures where emotional distress is expressed through physical complaints.

Symptoms · what the patient feels, and why

- Feeling sad, empty, or hopeless most of the day, nearly every day: The brain's messenger chemicals — serotonin (a signal that steadies mood), norepinephrine (a chemical that gives you energy and motivation), and dopamine (the reward messenger) — drop too low. When these messengers run low, the circuits that make you feel hope and pleasure shut down, so everything feels gray and pointless.
- Loss of interest or pleasure in activities you used to enjoy: The nucleus accumbens and ventral striatum (the brain's reward center, deep inside your head) stop responding to fun or meaningful activities because dopamine levels are too low. It's like the 'like' button in your brain is broken — nothing lights up anymore.
- Trouble sleeping (sleeping too much or too little): Depression scrambles the suprachiasmatic nucleus (the brain's master clock in the hypothalamus) and lowers melatonin (the sleep hormone). Some people cannot fall asleep or wake up too early; others sleep all the time trying to escape the low mood.
- Feeling tired or having very low energy almost every day: Low serotonin and norepinephrine slow down your brain and body signals. Your brain is also working overtime trying to manage the chemical imbalance, draining energy like a phone battery stuck at 10 percent all day.
- Changes in appetite or weight (eating much more or much less than usual): The hypothalamus (the control center for hunger and fullness deep in the brain) gets thrown off by low serotonin and dopamine. Some people lose all appetite; others eat more, especially sweets and carbs, trying to boost those feel-good chemicals.
- Trouble concentrating, remembering things, or making decisions: The prefrontal cortex (the front of the brain that handles thinking, planning, and memory) slows down when serotonin and norepinephrine are low. It's like trying to run a computer with not enough power — everything lags and freezes.
- Feeling worthless or excessively guilty about things: The depressed brain misfires in the anterior cingulate cortex (a region that judges yourself and processes emotional pain). It blames you unfairly for things while the circuits that balance those thoughts are underactive, so guilt and shame flood in.
- Moving or speaking more slowly than usual, or being restless and unable to sit still: Depression can slow the basal ganglia (deep brain structures that control movement), making you move and talk in slow motion. Or it can rev up your nervous system with stress hormones like cortisol, making you fidgety and unable to settle.
- Thoughts of death or suicide, or a plan to hurt yourself: Severe, untreated depression crushes the prefrontal cortex's ability to problem-solve and see a future. The pain feels unbearable, and the brain's hope circuits are so impaired that suicide feels like the only way to stop the hurt. This is a medical emergency.

Focused exam

- Patient says 'I feel sad all the time' or 'Nothing makes me happy anymore': This is the core break in depression — the brain's mood system is stuck in a down state. Everything else in depression flows from this one thing. Two weeks or more of feeling this way is the line that separates normal sadness from major depressive disorder.
- Patient avoids eye contact, speaks slowly, or gives one-word answers: These are signs that depression has slowed down the brain's energy and drive. The broken mood system drains power from the circuits that control movement and speech. It shows the break is real and is affecting how the body moves.
- Ask: 'Have you thought about hurting yourself or ending your life?' Patient says yes, hesitates, or says 'Sometimes I wish I wouldn't wake up': Suicide is the deadliest danger in depression. About 5% of people with major depression will attempt suicide. You must ask this question at every visit — it is not rude, it is lifesaving. Asking does NOT plant the idea; it opens the door for the person to get help.
- Patient says 'I can't sleep' or 'I sleep too much' or 'I wake up at 3 AM and can't fall back asleep': Sleep rhythms break in depression because serotonin and norepinephrine (the brain messengers that steady mood) also control the sleep-wake cycle. Broken sleep is proof the break is in the brain's chemistry, not just the person's thoughts or willpower.
- Patient has gained or lost weight without trying; says 'I don't want to eat' or 'I eat when I'm sad': Appetite and eating are controlled by the hypothalamus (the brain's control tower for hunger and mood) and the same neurotransmitters that regulate mood. When depression breaks the mood system, eating breaks too. A change of more than 5% of body weight in a month is significant.
- Patient says 'I can't focus' or 'I can't remember things' or 'I can't make decisions': Depression drains energy from the prefrontal cortex (the front of the brain that handles focus, memory, and decisions). Thinking requires fuel. No fuel means the brain cannot do its job. This is why depression makes simple tasks feel impossible.

Diagnostics · every test answers a question

- PHQ-9 (Patient Health Questionnaire-9) → How severe is the depression, and is suicide risk present?
- TSH (thyroid-stimulating hormone) → Is an underactive thyroid causing the sad mood, tiredness, and brain fog instead of depression?
- Complete blood count (CBC) → Is anemia (too few red blood cells) causing the fatigue and brain fog?
- Comprehensive metabolic panel (CMP) → Are kidney problems, liver problems, or electrolyte imbalances causing the mood change?

- Vitamin B12 and folate levels → Is a vitamin deficiency causing the mood symptoms and brain fog?
- Urine drug screen → Is drug or alcohol use causing or worsening the depression?
- 24-hour urinary free cortisol or late-night salivary cortisol (if Cushing syndrome is suspected based on physical exam findings like central weight gain, purple stretch marks, easy bruising) → Is too much cortisol (the body's main stress hormone) from the adrenal glands causing the depression?
- HIV antibody test (in appropriate clinical context) → Could untreated HIV infection be causing the depression and fatigue?

Treatment logic

- Safety assessment and suicide risk plan → Identifies whether the person is in immediate danger of self-harm and creates concrete steps to stay safe — remove guns and pills from the home, write down a friend's phone number to call, agree to go to the emergency room if thoughts of suicide get stronger. This stops depression from reaching its deadliest outcome.
- Selective serotonin reuptake inhibitor (SSRI, like sertraline, escitalopram, or fluoxetine) or serotonin-norepinephrine reuptake inhibitor (SNRI, like venlafaxine or duloxetine) → Blocks the pump that pulls serotonin (and norepinephrine in SNRIs) back into storage after they are released. This raises the level of these mood messengers in the synapse (the gap between brain cells) and slowly restores the mood system. Takes 4 to 6 weeks to work because the brain needs time to grow new receptors and rewire circuits.
- Cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT) → CBT teaches the person to catch automatic sad, self-blaming thoughts (like 'I'm worthless') and test them against reality. It also changes avoidance behaviors (like skipping social events). This rewires how the brain responds to stress and builds new neural pathways in the prefrontal cortex. IPT focuses on healing relationship problems that trigger or worsen depression.
- Fix sleep schedule (same bedtime and wake time every day, even on weekends) and add regular aerobic exercise (30 minutes, 5 days a week) → A steady sleep-wake schedule resets the circadian rhythm (the body's internal 24-hour clock controlled by the suprachiasmatic nucleus in the brain). Exercise releases endorphins (natural feel-good chemicals) and brain-derived neurotrophic factor (BDNF, a protein that helps brain cells grow and connect). Both support serotonin balance and reduce the fatigue and low mood that fuel depression.
- Stop all drug and alcohol use → Removes substances that disrupt the brain's chemical balance. Alcohol suppresses GABA (the brain's main calming signal) rebound and worsens depression. Stimulants cause dopamine crashes. Cannabis disrupts serotonin and motivation circuits. Stopping these allows the brain's natural mood system to heal.

- Add bupropion, mirtazapine, or switch to a different antidepressant (if first SSRI or SNRI fails after 6 to 8 weeks at full dose) → Uses different brain chemical pathways to fix the mood break. Bupropion boosts dopamine and norepinephrine (the brain's energy and motivation messengers). Mirtazapine increases serotonin and norepinephrine and also improves sleep by blocking histamine receptors. Switching to a different SSRI or SNRI can work if the first one didn't reach the right brain regions.
- Add aripiprazole or quetiapine (atypical antipsychotics), lithium, esketamine nasal spray, or electroconvulsive therapy (ECT) for treatment-resistant depression (failed 2 or more antidepressants) → Aripiprazole and quetiapine boost the effect of antidepressants by modulating dopamine and serotonin receptors. Lithium stabilizes mood circuits and increases BDNF. Esketamine blocks NMDA receptors and rapidly resets neural circuits (works in hours to days instead of weeks). ECT sends controlled electrical pulses through the brain to directly restart mood centers; it is the most effective treatment for severe, resistant depression (response rate 70–90%).

Medications

Sertraline (Zoloft) · SSRI (Selective Serotonin Reuptake Inhibitor)

Depression happens when serotonin — a brain messenger that steadies mood, sleep, and appetite — runs too low or doesn't stick around long enough between nerve cells. Normally, after serotonin carries its message across the gap (synapse) between two cells, the sending cell vacuums it back up through a pump to recycle it. Sertraline blocks that vacuum pump. With the pump blocked, serotonin stays in the gap longer, giving the receiving cell more time to catch the signal. Over four to six weeks, this stronger signaling helps the brain's mood circuits rebalance, lifting sadness, worry, and low energy.

1. Sertraline blocks the serotonin reuptake transporter (SERT), the pump on the sending nerve cell that normally vacuums serotonin back up
2. Serotonin stays in the synapse gap longer instead of being recycled
3. The receiving nerve cell gets a stronger, longer-lasting mood signal
4. Over four to six weeks, the brain adjusts: receptors fine-tune, new connections form, and mood circuits work better

SAFETY WATCH

In the first few weeks, some people — especially teens and young adults under 25 — may feel more restless, agitated, or have stronger thoughts of suicide. Call your doctor right away if this happens. · Common early side effects include upset stomach (nausea), loose stools, headache, trouble falling asleep, or feeling jittery. These usually fade after the first two weeks. · Rarely causes serotonin syndrome (too much serotonin building up). Warning signs: confusion, fast or irregular heartbeat, heavy sweating, shaking, stiff muscles, or fever. This is a medical emergency — call 911 if you notice these. · Do not stop sertraline suddenly. Taper slowly with your doctor's help to avoid withdrawal symptoms like dizziness, tingling, irritability, and 'brain zaps' (brief electric-shock sensations in the head). · Can interact with other drugs that raise serotonin, such as tramadol (a pain medicine), triptans (migraine drugs like sumatriptan), or St. John's wort (a supplement). Always tell your doctor and pharmacist everything you take. · May cause mild sexual side effects (lower desire, delayed orgasm) in some people.

Escitalopram (Lexapro) · SSRI (Selective Serotonin Reuptake Inhibitor)

Escitalopram works the same way as sertraline: it blocks the serotonin vacuum pump (the SERT transporter) so serotonin stays active longer in the gaps between brain cells. This lets the receiving cells catch a stronger mood signal. Over several weeks, the brain's mood circuits rebalance, lifting sadness, worry, and tiredness. Escitalopram is the purified, more active half of an older drug (citalopram), so it often works at lower doses with fewer side effects.

1. Escitalopram blocks the serotonin reuptake transporter (SERT) on the sending nerve cell
2. Serotonin lingers in the synapse instead of being recycled quickly
3. The receiving nerve cell gets a stronger, longer mood signal
4. Over four to six weeks, the brain adjusts: receptors fine-tune, brain-derived neurotrophic factor (BDNF, a growth protein) rises, and mood circuits heal

SAFETY WATCH

Watch for new or worsening thoughts of suicide, especially in the first few weeks and in people under 25. Contact your doctor immediately if this happens. · Common early side effects: nausea, headache, fatigue, trouble sleeping, or mild anxiety. These usually fade within two weeks. · Rarely causes serotonin syndrome (confusion, fast heartbeat, heavy sweating, shaking, stiff muscles, fever). This is a medical emergency — seek help right away. · Taper slowly when stopping to avoid withdrawal symptoms (dizziness, tingling, 'brain zaps', irritability). · Can interact with other serotonin-raising drugs (tramadol, triptans, other antidepressants, St. John's wort). · May cause sexual side effects (lower desire, delayed orgasm) in some people. · At high doses (above 20 mg daily), can slightly prolong the QT interval (a heart rhythm measure), so your doctor may check an EKG if you have heart problems.

Fluoxetine (Prozac) · SSRI (Selective Serotonin Reuptake Inhibitor)

Fluoxetine blocks the serotonin vacuum pump so serotonin stays in the synapse longer, boosting mood signals between nerve cells. What makes fluoxetine different is its very long half-life — it stays in your body for days (even weeks) after each dose. This slow build-up and slow washout means fewer withdrawal symptoms if you miss a dose or stop, but it also means side effects may linger longer if they occur, and it takes longer to fully leave your system when switching to a different medicine.

1. Fluoxetine blocks the serotonin reuptake transporter (SERT) on the sending nerve cell
2. Serotonin stays active in the synapse longer instead of being recycled
3. The receiving cell gets a stronger mood signal
4. Over four to six weeks, the brain adjusts: receptors fine-tune, BDNF rises, and mood circuits heal
5. Because fluoxetine's active metabolite (norfluoxetine) lasts weeks, the drug effect continues even after you stop taking pills

SAFETY WATCH

Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · May cause restlessness, trouble sleeping, nausea, headache, or jitteriness at first. · Long half-life means slower washout — talk to your doctor before switching or stopping; there's usually a 'washout period' if switching to certain other antidepressants (especially MAOIs). · Rarely causes serotonin syndrome (confusion, fast heartbeat, sweating, shaking, stiff muscles, fever) — seek help immediately if this happens. · Can interact with many other medications (tramadol, triptans, other antidepressants, blood thinners, certain heart drugs) — always tell your doctor and pharmacist what you're taking. · May cause sexual side effects (lower desire, delayed orgasm). · Because it stays in the body so long, side effects may take weeks to fully resolve after stopping.

Venlafaxine (Effexor XR) · SNRI (Serotonin-Norepinephrine Reuptake Inhibitor)

Depression can involve two brain messengers: serotonin (which steadies mood, sleep, and appetite) and norepinephrine (which boosts energy, focus, and alertness). Venlafaxine blocks the vacuum pumps for both, so they stay in the synapse longer. This gives a double boost — steadying mood and lifting energy — which can help people who didn't get enough relief from an SSRI that only targets serotonin. At lower doses, it mostly affects serotonin; at higher doses, it adds norepinephrine.

1. Venlafaxine blocks both the serotonin reuptake transporter (SERT) and the norepinephrine reuptake transporter (NET)
2. Both serotonin and norepinephrine linger in the synapse instead of being vacuumed back up
3. Receiving nerve cells get stronger mood and energy signals
4. Over four to six weeks, brain circuits rebalance: mood lifts, energy returns, and focus improves

SAFETY WATCH

Watch for new or worse thoughts of suicide, especially early in treatment and in people under 25. · Can raise blood pressure, especially at higher doses — your doctor should check your blood pressure regularly (before starting, after dose changes, and periodically). · Common side effects: nausea, dry mouth, sweating, dizziness, constipation, trouble sleeping, or mild jitteriness. · Must taper slowly when stopping — stopping venlafaxine suddenly can cause severe withdrawal symptoms (dizziness, 'brain zaps,' irritability, nausea, headache, feeling like you have the flu). · Rarely causes serotonin syndrome (confusion, fast heartbeat, sweating, shaking, stiff muscles, fever) — seek help immediately. · May cause sexual side effects (lower desire, delayed orgasm). · Can interact with other drugs that raise serotonin (tramadol, triptans, other antidepressants) or affect blood pressure.

Duloxetine (Cymbalta) · SNRI (Serotonin-Norepinephrine Reuptake Inhibitor)

Duloxetine blocks the vacuum pumps for both serotonin (the mood and sleep messenger) and norepinephrine (the energy and alertness messenger), so both stay active longer in the gaps between nerve cells. This steadies mood and boosts energy. Duloxetine also works in the spinal cord to dampen pain signals, which is why it helps with physical pain that often comes with depression — like chronic aches, nerve pain (such as diabetic neuropathy), or fibromyalgia pain.

1. Duloxetine blocks both the serotonin reuptake transporter (SERT) and the norepinephrine reuptake transporter (NET)
2. Serotonin and norepinephrine stay in the synapse longer
3. Mood, energy, and pain-control signals improve
4. Over four to six weeks, depressive symptoms lift and physical pain eases

SAFETY WATCH

Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · Common side effects: nausea, dry mouth, fatigue, constipation, sweating, dizziness, or loss of appetite. · May raise blood pressure or liver enzymes (chemicals that show how the liver is working) — your doctor will check these with blood tests and blood pressure readings. · Taper slowly when stopping to avoid withdrawal symptoms (dizziness, 'brain zaps,' irritability, nausea). · Rarely causes serotonin syndrome (confusion, fast heartbeat, sweating, shaking, fever) — seek help right away. · Can interact with other serotonin-raising drugs (tramadol, triptans, other antidepressants). · May cause sexual side effects (lower desire, delayed orgasm). · Avoid in people with severe liver disease or uncontrolled narrow-angle glaucoma (high pressure in the eye).

Bupropion (Wellbutrin) · NDRI (Norepinephrine-Dopamine Reuptake Inhibitor)

Unlike SSRIs, bupropion does not touch serotonin. Instead, it blocks the vacuum pumps for norepinephrine (the energy and alertness messenger) and dopamine (the motivation and reward messenger), so both stay active longer in the synapse. This makes it especially helpful for people whose depression shows up as low energy, no motivation, trouble focusing, or feeling 'flat' inside. Because it doesn't affect serotonin, bupropion usually does not cause weight gain, emotional numbness, or sexual side effects — common problems with SSRIs.

1. Bupropion blocks the norepinephrine reuptake transporter (NET) and the dopamine reuptake transporter (DAT)
2. Norepinephrine and dopamine linger in the synapse instead of being vacuumed back up
3. Receiving nerve cells get stronger energy, motivation, and focus signals
4. Over four to six weeks, depressive symptoms lift — energy returns, motivation improves, concentration sharpens

SAFETY WATCH

Can lower the seizure threshold (the brain's resistance to seizures) — avoid if you have a history of seizures, a current or past eating disorder (anorexia or bulimia, which raise seizure risk), or are withdrawing from alcohol or sedatives. · Common side effects: restlessness, trouble sleeping (insomnia), dry mouth, headache, or mild shakiness. · Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · Can raise blood pressure slightly — your doctor may check it. · Do not combine with MAOIs (an older class of antidepressant) — must wait at least 14 days between stopping an MAOI and starting bupropion. · Lower risk of weight gain and sexual side effects compared to SSRIs, which is why many people prefer it or add it to an SSRI. · Comes in sustained-release (SR) or extended-release (XL) forms; do not crush or chew the tablets.

Mirtazapine (Remeron) · Atypical antidepressant (alpha-2 antagonist and serotonin receptor modulator)

Mirtazapine works differently from SSRIs and SNRIs. It blocks alpha-2 receptors on nerve cells — these receptors normally act like brakes, slowing down the release of serotonin and norepinephrine. With the brakes off, nerve cells release more of both messengers. Mirtazapine also blocks certain serotonin receptors (5-HT₂ and 5-HT₃) that cause nausea, anxiety, and sexual side effects, and it blocks histamine receptors (H₁), which calms the nervous system

and helps with sleep. This makes it especially helpful for people with depression who can't eat, can't sleep, or feel very anxious.

1. Mirtazapine blocks alpha-2 receptors, so nerve cells release more norepinephrine and serotonin (the brakes come off)
2. It blocks 5-HT₂ and 5-HT₃ serotonin receptors, which reduces nausea and anxiety
3. It blocks histamine receptors, which calms the nervous system and helps with sleep
4. Over four to six weeks, mood, appetite, and sleep improve

SAFETY WATCH

Commonly causes increased appetite and weight gain — this can be helpful if you've lost weight from depression, but watch for unwanted weight gain. · Can make you very sleepy (sedation is strongest at lower doses) — usually taken at bedtime. · Common side effects: dry mouth, dizziness, constipation. · Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · Rarely causes a dangerous drop in white blood cells (agranulocytosis, which makes it hard to fight infection) — call your doctor right away if you get a fever, sore throat, or infection that won't go away. · Less likely to cause sexual side effects compared to SSRIs. · Taper slowly when stopping to avoid withdrawal symptoms.

Lithium (Lithobid, Eskalith) · Mood stabilizer

Lithium is a simple natural element (a soft, silvery metal salt, like sodium or potassium) that steadies the wild ups and downs of nerve cell signaling in the brain. It works inside nerve cells to balance second-messenger systems (chemical pathways like inositol and protein kinases that pass signals along inside the cell). This keeps nerve cells from firing too much or too little. Lithium also boosts brain-derived neurotrophic factor (BDNF), a growth protein that helps brain cells grow, connect, and repair. It's used when depression keeps coming back, when other medicines don't work, when depression is part of bipolar disorder, or when suicide risk is high — lithium lowers the risk of suicide more than almost any other treatment.

1. Lithium enters nerve cells and modulates second-messenger systems (like inositol monophosphatase and GSK-3), which balance signaling inside the cell
2. It stabilizes nerve cell membranes so cells don't fire wildly or shut down completely
3. It supports BDNF production, which helps brain cells grow, connect, and heal
4. Over weeks to months, mood becomes more stable, depressive episodes ease, and the brain is more resilient

SAFETY WATCH

Narrow therapeutic window — the difference between a helpful dose and a toxic dose is small. Blood levels must be checked regularly (usually every few months once stable, more often when starting or adjusting dose). Target blood level: 0.6–1.2 mEq/L for most people. · Can harm the kidneys and thyroid over time — your doctor will monitor kidney function (creatinine, eGFR) and thyroid hormones (TSH, free T4) with blood tests every 6–12 months. · Early side effects (usually mild at the right dose): fine hand tremor, increased thirst, frequent urination, mild nausea, or a metallic taste. · Toxic signs (lithium poisoning — blood level too high): severe tremor, confusion, slurred speech, muscle twitching, vomiting, diarrhea, extreme drowsiness. This is a medical emergency — call 911 immediately. · Can interact with many medications, especially diuretics (water pills like hydrochlorothiazide, which raise lithium levels) and NSAIDs (pain relievers like ibuprofen or naproxen, which also raise lithium levels). Always tell every doctor and pharmacist that you take lithium. · Stay well-hydrated and keep salt (sodium) intake steady — dehydration and low salt both raise lithium levels and can push you into toxicity. Drink plenty of water, especially in hot weather, during illness, or if you're sweating a lot. · Avoid starting lithium if you're pregnant (it can harm the developing baby, especially the heart) — talk to your doctor about safer options if you're planning pregnancy or are pregnant. · Lowers suicide risk more than most other treatments — one of lithium's most important benefits.

Aripiprazole (Abilify) · Atypical antipsychotic (used as add-on for treatment-resistant depression)

When an antidepressant alone doesn't lift depression enough (treatment-resistant depression), adding a low dose of aripiprazole can boost the response. Aripiprazole is called a 'dopamine partial agonist' — it fine-tunes dopamine (the motivation and reward messenger) by acting as a stabilizer rather than simply blocking or boosting. Where dopamine is too high, aripiprazole lowers it a bit; where it's too low, it raises it a bit. It also modulates serotonin receptors. This balancing act helps lift mood, motivation, and energy when depression is stubborn.

1. Aripiprazole partially activates dopamine D2 receptors (if dopamine activity is low, this helps; if it's high, aripiprazole's partial activation competes with full dopamine, lowering the overall signal)
2. It activates serotonin 5-HT1A receptors, which can improve mood and reduce anxiety
3. It blocks serotonin 5-HT2A receptors, which can boost mood and improve sleep
4. The overall balance shifts toward better mood, motivation, energy, and emotional stability
5. When combined with an antidepressant (like an SSRI or SNRI), response improves over two to four weeks

SAFETY WATCH

Can cause akathisia (a very uncomfortable inner restlessness and urge to move) — tell your doctor right away if you feel this; lowering the dose or adding a medicine to calm it usually helps. · May cause weight gain, though often less than other antipsychotics like quetiapine or olanzapine. · Can raise blood sugar (glucose) and cholesterol or triglycerides (blood fats) — your doctor will monitor these with blood tests (fasting glucose, HbA1c, lipid panel) before starting and periodically (every few months). · Rarely causes tardive dyskinesia (uncontrolled movements of the face, tongue, or limbs) — risk is higher with long-term use and in older adults. Report any new unusual movements to your doctor. · Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · May cause drowsiness, dizziness, nausea, or headache. · Can rarely cause neuroleptic malignant syndrome (NMS), a life-threatening reaction (very high fever, stiff muscles, confusion, fast heartbeat, sweating) — call 911 if this happens. · Avoid driving or operating machinery until you know how aripiprazole affects you.

Quetiapine (Seroquel) · Atypical antipsychotic (used as add-on or monotherapy for depression)

Quetiapine blocks several different receptors — serotonin (especially 5-HT_{2A}), dopamine (D₂), histamine (H₁), and norepinephrine (alpha-1 and alpha-2) — which helps calm an overactive stress response, steady mood swings, and improve sleep. At low doses (25–100 mg), it's very sedating and mainly used to help with sleep and anxiety in depression. At higher doses (300 mg and up), it can lift depression on its own (monotherapy) or boost another antidepressant (add-on therapy). One of its breakdown products (norquetiapine) blocks the norepinephrine reuptake pump, adding an antidepressant effect.

1. Quetiapine blocks serotonin, dopamine, histamine, and norepinephrine receptors
2. Histamine blockade calms the nervous system and helps sleep (especially at low doses)
3. Serotonin and dopamine blockade steadies mood and reduces anxiety
4. The breakdown product (norquetiapine) blocks the norepinephrine reuptake pump, boosting energy and mood
5. Over two to six weeks, mood stabilizes, sleep improves, and depressive symptoms ease

SAFETY WATCH

Causes significant drowsiness and sedation — usually taken at bedtime. Do not drive or operate machinery until you know how it affects you. · Can cause substantial weight gain and increased appetite — monitor your weight and talk to your doctor about diet and exercise. · May raise blood sugar (glucose), cholesterol, and triglycerides (blood fats) — your doctor will monitor these with blood tests (fasting glucose, HbA1c, lipid panel) before starting and every few months. Can increase the risk of developing diabetes. · Rarely causes tardive dyskinesia (uncontrolled movements of the face, tongue, or limbs) — higher risk with long-term use and in older adults. · Monitor for new or worse thoughts of suicide, especially in the first weeks and in people under 25. · Can cause dizziness or orthostatic low blood pressure (hypotension) (a sudden drop in blood pressure when you stand up, making you feel faint) — stand up slowly from sitting or lying down. · Common side effects: dry mouth, constipation, blurred vision. · Can rarely cause neuroleptic malignant syndrome (NMS), a life-threatening reaction (very high fever, stiff muscles, confusion, fast heartbeat) — call 911 if this happens. · Taper slowly when stopping to avoid withdrawal symptoms (nausea, vomiting, insomnia, restlessness).

Esketamine (Spravato nasal spray) · NMDA receptor antagonist (rapid-acting antidepressant)

Esketamine works faster than traditional antidepressants — often within hours to days instead of weeks. It blocks a receptor called NMDA (N-methyl-D-aspartate), which normally controls the flow of glutamate, the brain's main 'go' signal that excites nerve cells. When NMDA receptors are blocked, there's a brief surge of glutamate release. This surge triggers a burst of brain-derived neurotrophic factor (BDNF), a growth protein that helps brain cells quickly form new connections (synapses) and repair damaged mood circuits. Think of it like jump-starting a stalled car — the quick jolt gets the engine running again. Esketamine is used for severe, treatment-resistant depression (when two or more antidepressants have failed) or for major depression with acute suicidal thoughts when fast action is critical.

1. Esketamine blocks NMDA receptors on certain inhibitory nerve cells (interneurons)
2. This causes a rapid, brief release of glutamate (the brain's main 'go' signal)
3. Glutamate activates AMPA receptors on other nerve cells, triggering a cascade inside those cells
4. The cascade boosts brain-derived neurotrophic factor (BDNF) and other growth signals
5. New synaptic connections form quickly, repairing mood circuits and restoring emotional balance
6. Mood and suicidal thoughts can improve within hours to days (much faster than SSRIs or SNRIs)

SAFETY WATCH

Must be given in a doctor's office or certified clinic under medical supervision — you cannot take it home. You'll be monitored for at least two hours after each dose. · Can cause dissociation (feeling detached from your body, surroundings, or reality — like you're floating or watching yourself from outside), dizziness, nausea, sedation, or a feeling of unreality. These effects usually peak within 30–40 minutes and fade within two hours. · Can raise blood pressure and heart rate temporarily — your blood pressure and pulse will be measured before the dose and monitored during the two-hour observation period. Not safe if you have uncontrolled high blood pressure, recent heart attack, or certain heart rhythm problems. · Risk of misuse or dependence — esketamine is related to ketamine, a controlled substance that some people misuse. Because of this, the drug is tightly regulated under a Risk Evaluation and Mitigation Strategy (REMS) program, and only certified clinics can give it. · Do not drive, operate machinery, or do anything requiring full alertness on the day of treatment. Arrange for someone to drive you home. · Monitor for new or worse thoughts of suicide, though esketamine is specifically used to reduce suicidal thinking in severe depression. · May cause blurred vision, trouble focusing, or sensitivity to light temporarily. · Not recommended if you have a history of psychosis (losing touch with reality) or certain brain conditions (like aneurysm or bleeding in the brain). · Pregnancy category: limited data — discuss risks and benefits with your doctor if you're pregnant or planning pregnancy.

Red flags

- Thoughts of suicide, a plan to hurt yourself, or telling others you want to die
- Hearing voices or seeing things that are not there (psychotic depression)
- Complete inability to care for yourself — not eating, not getting out of bed, not speaking
- Rapid weight loss or severe malnutrition from not eating
- New confusion, severe memory loss, or fast worsening of thinking (may signal severe depression or another medical cause)

Nursing priorities

1. Complete a suicide risk assessment using a screening tool like the Columbia Suicide Severity Rating Scale; remove access to firearms, pills, or other lethal means if any suicidal thoughts are present — Suicide is the most preventable cause of death in depression; the brain's frontal lobe (which controls impulse control) does not work properly in severe depression, so removing easy methods saves lives during the highest-risk period

2. Ask about all current medications, alcohol use, and when the last dose of any psychiatric medication was taken; watch for signs of serotonin syndrome (confusion, fast heart rate, high blood pressure, sweating, muscle twitching) if the patient is on multiple antidepressants — Combining certain antidepressants (especially SSRIs with MAOIs or too many serotonin drugs together) causes serotonin syndrome, a dangerous buildup of serotonin in the brain that can cause seizures, high fever, and death; also, stopping antidepressants suddenly causes withdrawal symptoms
3. Check vital signs, weight, and hydration status; look at skin turgor (pinch test) and mucous membranes to assess for dehydration — Severe depression shuts down appetite and thirst signals from the hypothalamus (the brain's control center); patients may not eat or drink for days, causing dangerous dehydration, electrolyte imbalances, and malnutrition that can damage the heart and kidneys
4. Assess ability to perform basic self-care: bathing, eating, taking medications, getting out of bed; document exactly what the patient can and cannot do independently — Depression depletes dopamine and norepinephrine (brain chemicals needed for motivation and movement); when levels drop too low, the brain cannot send signals to start even simple tasks, which tells us how severe the depression is and whether the patient is safe at home
5. Screen for psychotic symptoms by asking if the patient hears voices, sees things others do not see, or has beliefs that seem unusual; observe for talking to self, responding to internal stimuli, or paranoid statements — Psychotic depression means the brain's dopamine system is severely disrupted; these patients need antipsychotic medication added to their antidepressant and are at very high risk for suicide because the voices may command self-harm
6. Document sleep pattern for the past week: hours of sleep per night, time to fall asleep, nighttime awakenings, and daytime naps — The circadian rhythm (24-hour sleep-wake cycle controlled by the suprachiasmatic nucleus in the brain) is broken in depression; insomnia worsens depression by preventing deep sleep when the brain clears toxins and restores serotonin, and too much sleep means very low norepinephrine
7. Educate the patient that antidepressant medication takes 4 to 6 weeks to work fully; the first changes will be better sleep and energy, then mood improves last — SSRIs and SNRIs increase serotonin or norepinephrine immediately, but the brain's receptors take weeks to adjust and grow new connections (neuroplasticity); patients often stop medication at 2 weeks thinking it failed, before it has time to work
8. Connect the patient with a therapist trained in cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT); give printed resources or app-based CBT tools if in-person therapy is not immediately available — Depression creates negative thought loops in the prefrontal cortex (the brain's thinking center) that reinforce hopelessness; CBT rewires these circuits by practicing new thought patterns, and it works as well as medication for mild to moderate depression

Sources

- APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010, reaffirmed 2015)
- U.S. Preventive Services Task Force (USPSTF) Depression Screening Recommendation (2023)
- DSM-5-TR (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision)
- Cochrane Depression, Anxiety and Neurosis Group

Last reviewed: 2026-07-07