

Major Depressive Disorder (MDD)

MDD is a discrete episode of system-wide shutdown — at least five symptoms, at least two weeks, always including depressed mood or loss of pleasure — that changes how a person eats, sleeps, moves, thinks, and values their own life.

THE STORY IN ONE SENTENCE

MDD is a discrete episode of system-wide shutdown — at least five symptoms, at least two weeks, always including depressed mood or loss of pleasure — that changes how a person eats, sleeps, moves, thinks, and values their own life.

“Not sadness — a whole-body state change: five or more of nine defined symptoms, nearly every day for two weeks or more, at least one of them being low mood or loss of interest, severe enough to bend eating, sleeping, moving, and thinking.”

Normal anatomy — the body's job

Mood, pleasure, sleep, appetite, and thinking are run by interlocking systems: serotonin, norepinephrine, and dopamine (brain messengers that steady mood, attention, and drive) talk between the limbic system (the brain's feeling center) and the prefrontal cortex (the front of the brain that plans and pumps the brakes). The HPA axis (a stress control loop linking the hypothalamus, pituitary, and adrenal glands) releases cortisol (the body's main stress hormone) when challenges come and then turns it back off. The reward pathway (a circuit running through the ventral tegmental area and nucleus accumbens, using dopamine) makes effort feel worth it. Healthy sadness after loss uses these systems and then releases them.

BODY'S JOB

Let mood respond to life while keeping reward, sleep, appetite, energy, and thinking online — sadness may visit, but the machinery keeps running.

1. Loss or stress lowers mood temporarily.
2. The reward pathway keeps pleasure and motivation available.
3. The HPA axis spikes cortisol and then resets when the stressor passes.
4. Sleep and appetite stay regulated.
5. Mood recovers; thinking and self-worth remain intact.

What breaks

In a major depressive episode the whole mood-reward-vegetative system fails together. For at least two weeks, nearly every day, at least five of nine defined symptoms are present — and at least one of them must be depressed mood or anhedonia (losing interest or pleasure in things that used to matter). The reward pathway stops paying out, so nothing feels worth doing. The HPA stress axis runs stuck-on-high, flooding the body with cortisol. Sleep architecture breaks — waking at 3 a.m. unable to fall back, or sleeping half the day. Appetite and weight shift. Thinking slows, guilt inflates beyond reason, and in the darkest version, the brain begins to argue that death is a solution. This is a system state, not just a feeling.

CLINICAL TERM

Major depressive episode (DSM-5-TR): five or more of nine symptoms during the same two-week period, nearly every day, representing a change from previous functioning, with at least one being depressed mood or anhedonia; causing clinically significant distress or impairment; not attributable to a substance or medical condition; no lifetime manic or hypomanic episode (which would recode to bipolar disorder).

How the body compensates

The person compensates by spending their shrinking energy on appearances: showing up to work on willpower, smiling on schedule, cancelling everything optional. Caffeine props up mornings; alcohol quiets nights. The mask costs more energy than it saves, and when it finally slips — missed work, missed hygiene, a frightening statement — the episode is usually months old.

1. Willpower substitutes for motivation — everything optional gets cancelled first (social plans, hobbies, exercise).
2. Caffeine props mornings; alcohol or over-the-counter sleep aids patch nights.
3. Social 'masking' continues at rising energy cost — forcing a smile, performing small talk.
4. Work and hygiene finally slip as reserves empty — missing deadlines, skipping showers.
5. Hopeless arithmetic begins — 'everyone would be better off without me' — the point of maximum danger.

Domino effect

1. Reward shutdown feeds behavioral shutdown. — Anhedonia removes the payoff for activity, so activity stops. That leads to deconditioning (losing fitness and routine) and isolation, which deepen the depression. This loop is why behavioral activation (structured return to pleasant and necessary tasks) works as treatment.

2. Sleep and appetite disruption erode biology. — Broken sleep amplifies emotional reactivity (the amygdala, the brain's alarm center, fires hotter) and cognitive impairment (the prefrontal cortex struggles to focus and decide). Weight swings alter energy and self-image.
3. Cognitive distortion hardens: worthlessness, guilt, hopelessness. — The depressed brain generates evidence against itself — filtering memories, catastrophizing the future. Untreated, these distortions become the person's operating beliefs and block help-seeking.
4. Function collapses: work, school, relationships. — Concentration and decision-making fail at the exact moment life demands recovery effort. Missed work or school piles up. Relationships fray under withdrawal and irritability.
5. Suicide risk peaks — including early in treatment. — Energy sometimes returns before hope does. The weeks after starting an antidepressant (especially in people under 25) need the closest monitoring. As the paralysis lifts but despair remains, the person may gain just enough activation to act on suicidal thoughts.

Symptoms · what the patient feels, and why

- Sad, empty, or hopeless mood almost all day, nearly every day (or grouchy, angry mood in kids and teens): The mood-control circuits deep in the brain—especially the prefrontal cortex (the brain's planning and braking center) and the limbic system (the emotion engine)—lose their steady rhythm. Levels of serotonin, norepinephrine, and dopamine (the brain's main messenger chemicals that balance mood, energy, and pleasure) drop or stop working smoothly, so the person gets stuck in a low, dark feeling that won't lift on its own. In kids and teens, this broken mood system often shows up as irritability and anger instead of tears.
- Loss of interest or pleasure in almost everything you used to enjoy (anhedonia): The brain's reward circuit—especially the ventral striatum and nucleus accumbens, powered by dopamine (the 'this feels good' messenger)—goes offline. Things that once felt fun or satisfying now feel flat, pointless, or hollow. At least one of your five-or-more symptoms must be either this or the sad mood above; one of these two is the core of depression.
- Big change in weight or appetite (gain or loss of more than 5% of your body weight in a month, or not gaining weight as expected in a growing child): The hypothalamus (the brain's control tower for hunger and metabolism) gets scrambled by the mood disorder. Some people stop feeling hungry and lose weight; others crave comfort and gain. Either direction counts as a symptom.
- Trouble sleeping or sleeping way too much, almost every night: The brain's sleep architecture—controlled by serotonin, norepinephrine, and the circadian clock in the suprachiasmatic nucleus—breaks down. Classic pattern: you wake up at 3 or 4 a.m. and can't get back to sleep (early-morning waking). Or the opposite: you escape into sleep for ten or twelve hours and still wake up exhausted (hypersomnia).

- Moving or talking much slower than usual, or being so restless and fidgety that other people can see it: The motor-control loops—basal ganglia and motor cortex, driven by dopamine—slow to a crawl (psychomotor retardation) or rev up without purpose (psychomotor agitation). This must be visible to someone else watching you, not just a private feeling of being on edge or sluggish.
- Feeling exhausted or drained of energy nearly every day, even after rest: The brain's energy-management system—involving norepinephrine (the alert-and-go messenger) and mitochondria (the cell's power plants)—runs on empty. This is the single most common reason people with depression first see a doctor, often saying 'I'm tired all the time' before they ever mention feeling sad.
- Feeling worthless, or guilty in a way that's way out of proportion to anything you actually did: The prefrontal cortex (the brain's reality-checker and self-judge) twists thoughts into harsh, unfair self-attacks. You might blame yourself for things that aren't your fault, or feel like a burden or a failure when you're not. In severe cases this guilt can become a delusion—a fixed, false belief that feels absolutely real.
- Hard time concentrating, remembering things, or making even small decisions: The prefrontal cortex and hippocampus (the brain's memory and focus centers) slow down when serotonin, norepinephrine, and dopamine levels fall. Students say 'I can't study'; workers say 'I read the same email three times and still don't know what it says.' Often this shows up before the person even realizes they feel sad.
- Repeated thoughts of death, wishing you were dead, thinking about suicide, planning suicide, or trying suicide: The depressed brain—starved of serotonin (the calming, steady messenger) and with a prefrontal cortex that can't pump the brakes on dark thoughts—starts to see death as a way out of unbearable pain. These thoughts can range from passive wishes ('I wish I wouldn't wake up') to active plans with intent and means. This symptom is a medical emergency and must be asked about directly, kindly, and clearly at every visit.

Focused exam

- Psychomotor retardation: the person's speech is slow, they take a long time to answer questions, and they move less than usual: This is one of the few signs you can actually see and measure. It helps prove the episode is real and shows how severe it is.
- Weight change compared to past visits; detailed sleep history (how many hours, trouble falling asleep or staying asleep, waking too early): These are concrete facts you can measure — not just feelings. They help confirm the physical symptoms (called vegetative signs) that are part of depression.

- Direct suicide-risk questions: Are you thinking about hurting yourself? Do you have a plan? Do you have access to means (like pills or weapons)? Do you intend to act on it? What keeps you safe (like family, beliefs, future plans)? Thoughts of death or suicide are symptom number 9 in the criteria — and the most dangerous one. The answers decide whether the person goes home with a safety plan or needs an emergency psychiatric evaluation today.
- Signs of medical copycats: thyroid problems (slow heart rate under 60, dry skin, puffy face), anemia (pale skin and inside of eyelids), recent alcohol or drug use or withdrawal: Other medical problems and substance use can look exactly like depression. You must rule those out before calling it Major Depressive Disorder.
- Psychotic features: false beliefs that match the depressed mood (like 'I've ruined my family' when that's not true, or 'I'm rotting inside from a terrible disease'), or hearing voices that criticize or accuse: Depression with psychotic features is a psychiatric emergency. It needs a combination of antidepressant plus antipsychotic medication — or electroconvulsive therapy (ECT, controlled electrical pulses to the brain that reset mood circuits) — not an antidepressant alone.
- Energy level and ability to concentrate during the interview; can the person track the conversation or do they lose the thread?: Low energy and poor concentration are two of the nine core symptoms. Seeing them in real time helps confirm what the person is reporting and shows functional impact.

Diagnostics · every test answers a question

- DSM-5 criteria checklist: count 5 out of 9 symptoms, present nearly every day during the same 2-week period, and a change from how the person was before → Are at least 5 of the 9 defined symptoms present nearly every day for at least 2 weeks, with at least one being either depressed mood or loss of interest/pleasure, AND is this a clear change from baseline causing distress or problems functioning?
- PHQ-9 (Patient Health Questionnaire-9, a validated 9-question tool that maps directly to DSM criteria) → How severe is the depression right now, and is it getting better or worse with treatment?
- Lifetime mania and hypomania screen: Mood Disorder Questionnaire (MDQ) plus asking family or close friends if they ever saw the person 'revved up' — abnormally high energy, needing much less sleep, talking nonstop, taking big risks, or feeling on top of the world for days → Has this person ever had a manic episode (1+ week of extreme high energy and risky behavior) or a hypomanic episode (4+ days of milder but clear high energy)?

- Thyroid-stimulating hormone (TSH), complete blood count (CBC), vitamin B12 and vitamin D levels, comprehensive metabolic panel (CMP, checks kidney, liver, electrolytes, and blood sugar); urine drug screen if substance use is suspected → Is an underlying medical problem or substance causing the depressive symptoms instead of primary Major Depressive Disorder?
- Subtype specifiers: psychotic features present? Episode started during pregnancy or within 4 weeks of delivery? Pattern of fall/winter episodes and spring/summer recovery? Melancholic features (severe anhedonia, early-morning waking, worse mood in morning, marked psychomotor changes, guilt) or atypical features (mood brightens with good news, increased appetite/sleep, leaden paralysis, rejection sensitivity)? → Which subtype of Major Depressive Disorder is this — because the subtype changes the treatment plan?

Treatment logic

- Suicide risk assessment and safety planning before starting any other treatment → The answers determine where care happens. Active suicidal thoughts with a specific plan, access to means (like pills or a gun), and intent to act → emergency psychiatric evaluation today, often inpatient admission. Passive thoughts ('I wish I wouldn't wake up') without plan or intent → outpatient care with a written safety plan (remove or lock up means, list warning signs, identify people to call, crisis hotline numbers), close follow-up in 1 week, and family/friend support.
- SSRI antidepressant (sertraline, escitalopram, or fluoxetine are first choices) PLUS psychotherapy (Cognitive Behavioral Therapy or Interpersonal Therapy) → For moderate to severe depression, combining medication and therapy works better than either alone. The SSRI increases serotonin (a brain messenger chemical that steadies mood, sleep, and appetite) in the synapse (the gap between brain cells) over 4–6 weeks, lifting the biological weight. Therapy dismantles the negative thought loops ('I'm worthless', 'nothing will help') and teaches skills to handle triggers and stress.
- Optimize the dose to the maximum tolerated level, then switch medication class or add augmentation if response is inadequate after 4–8 weeks → If the first SSRI only gives partial improvement at full dose after 4–8 weeks, switch to a different class: SNRI (venlafaxine or duloxetine, which raise both serotonin and norepinephrine, another mood and energy messenger), bupropion (raises dopamine and norepinephrine, the brain's motivation and focus signals), or mirtazapine (blocks certain receptors to boost serotonin and norepinephrine and improve sleep/appetite). If switching doesn't work, augment by adding a second medication: low-dose aripiprazole or quetiapine (atypical antipsychotics that modulate dopamine and serotonin) or lithium (a mood stabilizer). The STAR*D trial showed that each step still achieves remission in some people who didn't respond to earlier steps.

- Continue antidepressant treatment for 6–12 months after full remission (all symptoms gone, back to normal functioning); if 3 or more past episodes, consider indefinite maintenance → Staying on the medication during the continuation phase (after feeling better) cuts the relapse risk in half. For people with recurrent depression (3+ lifetime episodes), long-term or lifelong maintenance treatment prevents future episodes.
- Electroconvulsive therapy (ECT) for psychotic depression, catatonia (immobility, mutism, rigid posture), severe depression with refusal to eat or drink, or imminently life-threatening suicidal intent → ECT uses controlled electrical pulses delivered under anesthesia to trigger a brief seizure that resets abnormal activity in mood-regulating brain circuits, especially the prefrontal cortex and limbic system (the emotional center deep in the brain). It has the highest remission rate of any depression treatment — often 70–90% — and works within days to weeks, much faster than medication.
- Bright light therapy (10,000 lux light box for 30 minutes each morning) for seasonal pattern depression (fall/winter onset, spring/summer remission) → Morning bright light exposure resets the circadian clock (the brain's internal day-night timer, controlled by the suprachiasmatic nucleus in the hypothalamus) and boosts serotonin production. It reduces seasonal depression symptoms, often within 1–2 weeks.

Medications

Sertraline / Escitalopram / Fluoxetine (SSRIs — first choice) · Selective serotonin reuptake inhibitor

Blocks the pump that sucks serotonin (a brain messenger that steadies mood, sleep, and appetite) back into the nerve cell. More serotonin stays in the gap between nerve cells. Over weeks, the brain adjusts its receivers and grows new connections, and the dark cloud slowly lifts.

1. The drug blocks SERT within hours, so serotonin piles up in the synapse (the tiny gap where nerves talk to each other).
2. Over 2 to 6 weeks, serotonin receivers on the next cell adjust their number and sensitivity, and the brain releases chemicals that help nerve cells grow and repair connections.
3. Mood, sleep, appetite, and clear thinking recover step by step — usually mood improves last.

SAFETY WATCH

BLACK BOX WARNING: In people under 25, these drugs can increase thoughts of suicide or plans to hurt oneself in the first weeks. See the patient again within 1 to 2 weeks of starting, then often until stable. · Serotonin syndrome (too much serotonin) when combined with migraine pills (triptans), tramadol, or MAOIs: restlessness, fast heart, high fever, muscle jerking, confusion. Go to the ER. · Trouble reaching orgasm or lower interest in sex, upset stomach or loose stools in the first weeks, low sodium (especially in older adults — causes confusion, falls). Never stop suddenly — taper slowly to avoid dizziness, zaps, and rebound.

Venlafaxine / Duloxetine (SNRIs) · Serotonin-norepinephrine reuptake inhibitor

Blocks the pumps for two brain messengers: serotonin (which steadies mood and sleep) and norepinephrine (which fuels energy, focus, and the body's get-up-and-go). Used when an SSRI did not work well enough, or when exhaustion and body pain are big parts of the depression.

1. Both reuptake pumps get blocked, so serotonin and norepinephrine stay longer in the synapse.
2. Norepinephrine adds a boost to energy, attention, and motivation — serotonin alone may not be enough for some people.
3. Full response unfolds over 4 to 6 weeks as the brain remodels its receivers and connections.

SAFETY WATCH

Venlafaxine can raise blood pressure in a dose-related way — check BP before starting and a few weeks in. · Stopping suddenly causes intense withdrawal (brain zaps, dizziness, nausea, mood swings) — taper very slowly. · Duloxetine can stress the liver — be cautious if the person drinks heavily or has liver disease.

Bupropion · Norepinephrine-dopamine reuptake inhibitor

Blocks the pumps for norepinephrine (which fuels alertness and drive) and dopamine (which powers motivation, pleasure, and focus). Targets the 'zombie' symptoms — no energy, no joy, foggy thinking. Does not harm sex drive like SSRIs do. Also helps people quit smoking.

1. Blocking reuptake pumps raises dopamine and norepinephrine levels in key circuits.
2. Energy, motivation, and mental sharpness lift over a few weeks.
3. Often added to an SSRI when that drug worked on sadness but left energy and interest flat, or when sex side effects are a problem.

SAFETY WATCH

Lowers the seizure threshold (the brain's resistance to a seizure) — never use in anyone with a seizure disorder or active bulimia/anorexia (low electrolytes raise seizure risk). · Can cause insomnia and restlessness — dose in the morning and early afternoon, not at night. · May suppress appetite and cause weight loss.

Mirtazapine · Noradrenergic and specific serotonergic antidepressant (alpha-2 antagonist)

Blocks the brake pedal (alpha-2 autoreceptors) on nerve cells that release norepinephrine and serotonin, so those messengers flood out. Also blocks histamine receptors (causes sleepiness) and certain serotonin receptors that trigger nausea. Perfect when depression steals sleep and appetite.

1. Alpha-2 blockade releases the brakes, so more norepinephrine and serotonin pour into synapses.
2. Histamine blockade makes you sleepy — dose at bedtime.
3. Sleep and appetite often recover in the first week or two; mood lifts more slowly over 4 to 6 weeks.

SAFETY WATCH

Expect weight gain and strong sedation — helpful if those are wanted, harmful if not. · Rare but serious: agranulocytosis (white blood cells crash). If fever, sore throat, or infection signs appear, check a complete blood count right away. · Adds to sleepiness from alcohol, benzodiazepines, or opioids — warn the patient.

Tricyclic antidepressants (amitriptyline, nortriptyline) · Tricyclic antidepressant (TCA)

Older drugs that block serotonin and norepinephrine pumps like the newer drugs do, but they also hit many other receptors — acetylcholine (causes dry mouth, blurry vision, constipation, confusion), histamine (drowsiness), alpha receptors (dizziness when standing), and heart sodium channels (dangerous in overdose). Effective but messy, so now second or third choice.

1. Blocking serotonin and norepinephrine reuptake lifts mood over several weeks, just like newer drugs.
2. The off-target receptor hits cause side effects: dry mouth, sleepiness, constipation, blurry vision, lightheadedness when standing.
3. In overdose, the drug blocks sodium channels in heart muscle — the heart's rhythm collapses and can stop. This is the lethal mechanism.

SAFETY WATCH

LETHAL IN OVERDOSE: Blocks heart conduction (wide QRS on ECG), causes dangerous rhythms and sudden death. Never prescribe to someone at high suicide risk, or give only a few days' worth at a time. · Anticholinergic overload in older adults: can't pee (urinary retention), worsens glaucoma, causes confusion and delirium. · Orthostatic low blood pressure (hypotension) (blood pressure drops when you stand) — leads to falls, especially in the elderly.

MAOIs (phenelzine, tranylcypromine) — specialist use only · Monoamine oxidase inhibitor

Blocks monoamine oxidase, the enzyme that breaks down serotonin, norepinephrine, and dopamine inside nerve cells and in the gut and liver. All three messengers build up. Very powerful for depression that has not responded to anything else, but comes with strict food and drug rules because the gut enzyme that normally destroys tyramine (a chemical in aged foods) is also blocked.

1. Enzyme blockade stops the breakdown of serotonin, norepinephrine, and dopamine — levels of all three climb.
2. Mood lifts in people who did not respond to SSRIs, SNRIs, or other drugs.
3. Because gut MAO is blocked, tyramine from food is not destroyed — it gets absorbed, floods into the blood, and can trigger a blood pressure spike (hypertensive crisis).

SAFETY WATCH

With high blood pressure (Hypertensive) crisis (sudden dangerous blood pressure spike) if you eat tyramine-rich foods: aged cheese, cured or fermented meats (salami, pepperoni), sauerkraut, soy sauce, tap beer, red wine. Causes severe headache, chest pain, stroke. Go to the ER immediately. · Serotonin syndrome when combined with SSRIs, SNRIs, tramadol, meperidine (Demerol), dextromethorphan (cough syrup), or St. John's wort. · Orthostatic low blood pressure (hypotension) (dizziness when standing) — falls are common.

Red flags

- Suicidal thoughts with a specific plan, intent to act, or access to a gun, pills, or other lethal means — needs emergency evaluation the same day, usually in an ER or crisis center
- Psychotic features — delusions (false beliefs, like 'I'm rotting inside' or 'I've lost all my money when I haven't') or hallucinations (hearing voices, often cruel ones) — requires combined medication and therapy or electroconvulsive therapy (ECT), and urgent psychiatry referral

- Refusing to eat or drink, or catatonia (frozen, unresponsive, or bizarre posturing) — medical emergency that can be life-threatening; ECT is often the fastest, most effective treatment
- Any history of a manic or hypomanic episode (days of sky-high mood, racing thoughts, risky behavior, little need for sleep) — STOP: this is bipolar disorder, not simple depression. Giving an antidepressant alone can flip the person into mania. Must treat with a mood stabilizer first.
- New or worse suicidal thoughts in the first few weeks after starting an antidepressant, especially in anyone under 25 — FDA black-box warning: the medicine can briefly increase suicide risk before it helps. Needs close follow-up.
- Started right after having a baby, with scary intrusive thoughts about harming the infant — same-day assessment to rule out postpartum psychosis, which is a psychiatric emergency

Nursing priorities

1. Assess suicide risk directly at every encounter — ideation, plan, means, intent — Criterion 9 is the fatal one; asking does not plant the idea, and risk changes visit to visit — including upward in early treatment.
2. Teach the 4–6 week medication timeline and book follow-up within 1–2 weeks of starting — Side effects come first, benefits later — unprepared patients quit; under-25s need early black-box monitoring.
3. Screen every depressed patient for lifetime mania/hypomania BEFORE antidepressants — A missed bipolar history plus antidepressant monotherapy can launch a manic switch.
4. Mobilize behavioral activation early: small scheduled activities, sleep regularity, daylight — Reversing the anhedonia-inactivity loop is evidence-based treatment, not politeness.
5. Involve family/supports in the safety plan and means restriction — Locking up medications and firearms is one of the highest-yield suicide-prevention moves available.
6. Never stop antidepressants abruptly; plan continuation 6–12 months past remission — Discontinuation syndrome punishes abrupt stops, and early withdrawal of treatment is the classic relapse trigger.

Sources

- American Psychiatric Association DSM-5-TR (2022)
- NIMH Major Depression fact sheet
- FDA black-box warning on antidepressants and suicidality
- Rush et al. STAR*D trial (NEJM 2006)

Last reviewed: 2026-06-01