

Major Depressive Disorder (MDD)

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.

THE ONE-LINE TRUTH

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 chain — how it unfolds

1. Reward shutdown feeds behavioral shutdown. — why: 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. — why: 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. — why: 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. — why: 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. — why: 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.

Spot it — what you see, 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.

Red flags — act now

- 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.

Treat it — in this order

1. 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.
2. 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.

3. 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.
4. 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.
5. 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.

Your top priorities at the bedside

1. Assess suicide risk directly at every encounter — ideation, plan, means, intent — why: 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 — why: 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 — why: A missed bipolar history plus antidepressant monotherapy can launch a manic switch.