

Bipolar Disorder

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THE STORY IN ONE SENTENCE

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“Bipolar disorder means the brain's mood-control circuits swing wildly between dangerously high energy (so high you can't sleep, you take huge risks, and you may lose touch with reality) and dangerously low energy (so low you can't feel joy, can barely move, and may think about ending your life)—all because dopamine, serotonin, and norepinephrine levels surge and crash instead of staying steady.”

Normal anatomy — the body's job

In a healthy brain, the prefrontal cortex (the front planning and impulse-control center), the limbic system (deep emotion center including the amygdala, which flags danger, and hippocampus, which stores memories and regulates stress), and the striatum (reward and motivation hub) talk constantly using balanced levels of dopamine (the reward and drive messenger), serotonin (the mood-steadying messenger), and norepinephrine (the alertness and energy messenger). These circuits work like a thermostat, adjusting mood and energy up when you need motivation—like waking up to tackle a challenge—and down when you need rest, but always keeping everything inside a predictable, livable range.

BODY'S JOB

This system lets you feel happy when good things happen and sad when bad things happen, gives you energy to work and play during the day and lets you sleep deeply at night, and keeps your thoughts organized and your decisions safe—so you can hold a job, care for people you love, and respond to the world in a way that makes sense.

1. The prefrontal cortex (front of the brain) constantly monitors signals from the limbic system (emotion center) and decides whether to speed up or slow down your mood and behavior, like a conductor leading an orchestra.
2. When something good happens, dopamine rises in the striatum (reward hub, especially the nucleus accumbens), making you feel motivated and pleased, but the prefrontal cortex keeps it from going too high so you don't lose your judgment.
3. Serotonin from the raphe nuclei (a cluster of cells in the brainstem) flows to the limbic system and prefrontal cortex, steadying your baseline mood so you don't swing wildly in response to small events.
4. Norepinephrine from the locus coeruleus (another brainstem cluster that controls alertness) raises energy and focus when you need to react or work, then drops at night so you can fall asleep and stay asleep through normal sleep stages.
5. This balanced back-and-forth keeps your mood predictable, your sleep regular, your thoughts clear, and your decisions safe—day after day, year after year.

What breaks

In bipolar disorder, the brain circuits that regulate mood and energy lose their ability to keep dopamine, serotonin, and norepinephrine inside a healthy range. Levels swing too high—flooding the striatum and prefrontal cortex and causing mania or hypomania (extreme energy, no need for sleep, risky behavior)—or crash too low, starving the same circuits and causing major depression (no energy, no joy, no motivation, sometimes thoughts of suicide). These swings happen without any reasonable outside cause, or a tiny trigger (like one sleepless night or a stressful week) sets off a huge mood change that lasts days to months.

CLINICAL TERM

Bipolar disorder (formerly called manic-depressive illness) is a chronic mood disorder caused by dysregulation—meaning loss of normal control—of monoaminergic neurotransmission (the signaling systems that use dopamine, serotonin, and norepinephrine) in prefrontal-limbic-striatal circuits. Genetic variants (especially in genes controlling dopamine receptors, serotonin transporters, calcium channels like CACNA1C, and circadian rhythm proteins like CLOCK) make these circuits hypersensitive to stress, sleep deprivation, seasonal light changes, and substances. Chronic stress, sleep loss, alcohol, stimulants (cocaine, methamphetamine), corticosteroids, and antidepressants without a mood stabilizer all destabilize these circuits further and can trigger or worsen episodes. Bipolar I disorder is defined by at least one full manic episode (lasting ≥ 7 days or requiring hospitalization); Bipolar II disorder is defined by at least one major depressive episode and at least one hypomanic episode (≥ 4 days of elevated mood and energy, but not severe enough to cause major impairment or psychosis). Cyclothymic disorder describes chronic, milder mood swings that never meet full criteria for mania or major depression but last for years.

How the body compensates

Early in a manic or hypomanic episode, you and the people around you may think you are just 'doing really well'—feeling confident, sleeping less but getting more done, full of ideas—so the brain's malfunction is mistaken for success or motivation. Early in depression, you may force yourself to keep working, put on a smile in public, and hide the exhaustion and loss of joy, so others don't realize how bad things are. But these workarounds always fail: hypomania escalates into full mania with psychosis and destroyed relationships, depression deepens into immobility and suicidal crisis, and mixed episodes bring the worst of both worlds—agitation plus hopelessness, the single most dangerous combination.

1. ****Hypomania feels good at first****: Increased dopamine in the striatum makes you feel confident, creative, energetic, and social—you sleep four hours and wake up refreshed, you start new projects, you reconnect with old friends, you feel like the best version of yourself—so you, your family, and even some doctors may think this is just normal happiness or finally 'coming out of depression,' completely missing that the brain's thermostat is broken and the mood is climbing out of the safe range.
2. ****Mania removes insight****: As dopamine keeps rising and the prefrontal cortex shuts down, you lose the ability to see that anything is wrong—this is called anosognosia (lack of awareness of illness)—so when family or friends worry about your nonstop talking, risky behavior, or lack of sleep, you feel annoyed or betrayed, convinced they are trying to hold you back from your 'great ideas,' making it nearly impossible to get you into treatment voluntarily.

3. ****Psychotic features emerge in severe mania****: Extremely high dopamine in the mesolimbic pathway (the brain's reality-testing circuit, running from the midbrain to the limbic system) causes delusions (fixed false beliefs, like believing you have special powers, are on a divine mission, or are a celebrity) and sometimes hallucinations (hearing voices or seeing things that are not there), identical to what happens in schizophrenia but triggered by mood instability instead of primary psychosis.
4. ****You burn through money, relationships, and safety****: During mania, you may max out credit cards, give away money, quit your job impulsively, drive recklessly at high speed, have unprotected sex with strangers, or use dangerous drugs—none of which you would do when stable—so by the time the episode ends, your life is often badly damaged.
5. ****Depressive compensation is invisible and exhausting****: In early or mild depression, you force yourself to show up at work or school, fake smiles in social situations, and hide the anhedonia (inability to feel pleasure) and fatigue, so people think you are fine—but inside, every task feels like moving through mud, nothing brings joy, and you are barely holding on; this masking drains the last of your energy and accelerates the slide into severe, immobilizing depression.
6. ****Suicidal thoughts become plans****: As serotonin and dopamine drop further, hopelessness deepens, and thoughts shift from 'I wish I weren't here' to detailed plans and means—stockpiling pills, researching methods, writing goodbye notes—and in major depression the fatigue may paradoxically protect you (you are too exhausted to act), but if energy rises even slightly (early recovery, or switching into a mixed state), the risk of completed suicide skyrockets.
7. ****Mixed episodes are the highest-risk state****: When norepinephrine and dopamine stay high enough to cause agitation, racing thoughts, and motor restlessness, but serotonin stays low enough to cause hopelessness and suicidal thoughts, you have the despair of depression plus the energy and impulsivity to act on it—this combination is why mixed episodes have the highest suicide completion rate of any bipolar state, far higher than pure depression or pure mania.
8. ****Rapid cycling shortens the window for intervention****: When episodes start coming every few months or even every few weeks (rapid cycling, defined as four or more mood episodes per year), you spend almost all your time either manic, depressed, or recovering, leaving almost no stable time to build coping skills, repair relationships, or hold a job—this pattern is especially common in Bipolar II, in women, and in people who were given antidepressants without a mood stabilizer.

9. ****Medication non-adherence restarts the cycle****: Lithium, valproate (also called divalproex or valproic acid), and other mood stabilizers take weeks to work, require regular blood tests to check levels and monitor kidney and thyroid function, and cause side effects (weight gain, tremor, thirst, acne), so many people stop taking them once they feel better—but within weeks to months, the next episode hits, often worse than the last, because the brain's kindling effect has lowered the threshold for relapse.

Domino effect

1. Genetic vulnerability and early-life stress prime mood circuits for instability. — You inherit variants in genes controlling dopamine receptors (DRD2, DRD4), serotonin transporter (5-HTTLPR short allele, which reduces serotonin signaling), calcium channels (CACNA1C, which control how neurons fire), and circadian rhythm proteins (CLOCK and ARNTL, which regulate daily sleep-wake cycles), which make prefrontal-limbic-striatal circuits hypersensitive to stress, sleep loss, and seasonal light changes. Childhood trauma, abuse, or chronic stress further remodels these circuits by raising baseline cortisol (the body's main stress hormone, made by the adrenal glands) and lowering the threshold for mood swings, so by adolescence or early adulthood, the system is primed to break with even moderate triggers.
2. A trigger—stress, sleep deprivation, substance use, or sometimes no clear cause—destabilizes the mood thermostat. — Sleep loss (even one or two nights of less than six hours) disrupts circadian rhythm genes in the suprachiasmatic nucleus (the brain's master clock, located in the hypothalamus), which directly controls dopamine and serotonin release. Chronic stress floods the brain with cortisol, which damages hippocampal neurons (memory and emotion-regulation cells) and dysregulates the hypothalamic-pituitary-adrenal (HPA) axis (the body's main stress-response system). Stimulants (cocaine, methamphetamine, even prescription amphetamines) dump dopamine into the striatum. Alcohol disrupts GABA (the brain's main calming messenger) and glutamate (the main excitatory messenger) balance. Antidepressants raise serotonin but can overshoot and trigger mania if no mood stabilizer is on board. Any of these pushes the unstable system past its breaking point.

3. Dopamine and norepinephrine surge in the striatum, thalamus, and prefrontal cortex, launching mania or hypomania. — Dopamine floods the nucleus accumbens (reward center in the ventral striatum), making everything feel intensely pleasurable and meaningful—so starting ten projects at once, spending your entire paycheck in one night, or having sex with a stranger all feel like brilliant ideas. Excess dopamine in the dorsal striatum (movement and habit center) speeds up movement and speech (you talk so fast others cannot get a word in). Norepinephrine overwhelms the locus coeruleus (alertness center in the brainstem), so you feel wide awake and energized after only two or three hours of sleep. Racing thoughts (flight of ideas) happen because the prefrontal cortex, flooded with dopamine and norepinephrine, jumps from idea to idea faster than you can speak, and every idea feels urgent and profound.
4. The ventromedial and dorsolateral prefrontal cortex shut down, erasing impulse control and judgment. — Extremely high dopamine silences the prefrontal regions that normally put the brakes on risky behavior, foresee consequences, and keep you socially appropriate. You lose insight (anosognosia)—you cannot see that anything is wrong—so when loved ones worry, you feel angry or misunderstood. You make decisions you would never make when stable: draining your savings, driving 100 mph, quitting your job without a plan, having unprotected sex, using dangerous drugs. If dopamine climbs even higher in the mesolimbic pathway (running from the ventral tegmental area in the midbrain to the limbic system), delusions form—believing you have superpowers, are destined for greatness, or are receiving special messages from God or the universe—and sometimes hallucinations (hearing voices, seeing things) appear, identical to schizophrenia but driven by mood instability.
5. Sleep architecture collapses during mania, fueling the upward spiral. — Hyperactive orexin (also called hypocretin, a wakefulness chemical) neurons in the lateral hypothalamus (sleep-wake control center) and suppressed melatonin (the sleep hormone from the pineal gland) block deep NREM (non-REM, or slow-wave) sleep, the stage that restores the body and stabilizes mood. You feel fully rested after two or three hours because high norepinephrine creates a false sense of alertness, but your brain never gets the deep sleep it needs to reset dopamine and serotonin systems—so the mania accelerates. Each night of lost sleep makes the next day worse, creating a self-reinforcing upward spiral until you crash, are hospitalized, or the episode burns out after days to weeks.

6. Dopamine, serotonin, and norepinephrine collapse, flipping the brain into major depression.
— After days or weeks of mania (or sometimes without any preceding mania, especially in Bipolar II), the same circuits that surged now crash. Dopamine drops far below normal in the nucleus accumbens, so nothing brings pleasure—food tastes like cardboard, music sounds flat, being with loved ones feels empty (anhedonia). Serotonin drops in the raphe nuclei (brainstem serotonin factory) and limbic system, causing overwhelming sadness, guilt, worthlessness, hopelessness, and suicidal thoughts. Norepinephrine drops in the locus coeruleus and prefrontal cortex, causing crushing fatigue, psychomotor retardation (thinking and moving in slow motion), inability to concentrate, and early-morning awakening (waking at 3 or 4 a.m. and unable to fall back asleep). You may sleep ten or twelve hours and still wake up exhausted because REM (rapid eye movement) sleep is fragmented and non-restorative.
7. Mixed episodes combine high motor activity with depressive cognition—the most lethal state. — Sometimes dopamine and norepinephrine stay partially elevated—enough to cause agitation, racing thoughts, pressured speech, and motor restlessness—while serotonin stays low, so you feel hopeless, irritable, worthless, and suicidal at the same time. You have the despair and suicidal thoughts of depression plus the energy and impulsivity to act on them, which is why mixed episodes have the highest rate of suicide attempts and completions of any bipolar state, far higher than pure mania or pure depression. This state is agonizing—you feel trapped in your own revved-up, miserable mind—and it is often missed or mistaken for severe depression or agitated depression, delaying the right treatment.
8. Without mood stabilizers, each episode remodels the brain, shortening cycles and worsening outcomes (kindling effect). — Every manic or depressive episode causes measurable changes in brain structure: hippocampal volume shrinks (the memory center, which also regulates the HPA stress axis), prefrontal cortex gray matter thins (worsening impulse control and planning), and synaptic connections between neurons are pruned or strengthened in ways that make the next episode easier to trigger and harder to stop. This is called kindling (borrowed from epilepsy research): just as repeated small electrical stimuli can eventually cause a seizure, repeated mood episodes lower the threshold for future episodes, so over time smaller stressors—or no stressor at all—can launch full mania or depression. Early, continuous treatment with lithium or other mood stabilizers prevents kindling, protects brain structure, and dramatically improves long-term outcomes.

Symptoms · what the patient feels, and why

- Mania: sky-high mood or explosive anger lasting at least one week, bad enough to wreck work or land you in the hospital: Too much dopamine (a brain chemical that drives pleasure and action) floods the limbic system (the brain's emotion center) and weakens the prefrontal cortex (the front part that normally pumps the brakes on big feelings), making the person feel unstoppably happy or furiously angry when things don't go their way.

- **Hypomania:** noticeably higher mood and energy lasting at least four days—people see the change but you can still function: A moderate bump in dopamine and norepinephrine (a brain chemical that revs up alertness and drive) boosts energy, confidence, and get-up-and-go without destroying judgment—this marks Bipolar II, not Bipolar I.
- **Barely needing sleep—feeling fully rested after only two or three hours:** High norepinephrine keeps the locus coeruleus (the brain's wake-up alarm in the brainstem) firing nonstop, blocking the normal signal that says it's time to sleep.
- **Pressured speech:** talking fast, loud, and nonstop so it's almost impossible to interrupt: Too much dopamine speeds up how fast thoughts form—faster than the mouth can keep up—and the loss of prefrontal cortex brakes removes the normal social filter on talking.
- **Flight of ideas or racing thoughts—your mind jumps from topic to topic without finishing any one idea:** Dopamine overactivity in the thinking centers fires connections between ideas too fast, so thoughts leap from one thing to another before finishing the first.
- **Grandiosity:** blown-up self-esteem, believing you have special powers, are famous, or can do impossible things: Dopamine flooding the reward pathways (the ventral striatum and nucleus accumbens, deep brain circuits that tag things as important or pleasurable) creates false confidence and a distorted self-view, sometimes reaching delusional intensity—a fixed false belief that cannot be shaken even by proof.
- **Risky behavior:** wild spending sprees, hypersexuality, reckless driving, or drug and alcohol binges: The prefrontal cortex (the brain's impulse-control center) fails while dopamine exaggerates the pleasure signal in the reward system, so immediate reward crushes long-term thinking and consequences disappear.
- **Major depressive episodes:** no pleasure in anything (anhedonia), crushing fatigue, feelings of worthlessness, and suicidal thoughts: Dopamine, serotonin (a brain messenger that steadies mood, sleep, and appetite), and norepinephrine all drop too low in mood and reward circuits, causing loss of motivation, energy, pleasure, and hope.
- **Psychotic symptoms during mania:** delusions like 'I can fly' or 'I am God,' or hallucinations (seeing or hearing things that aren't there): Severe dopamine excess in the mesolimbic pathways (deep dopamine circuits running from the midbrain to the limbic system) distorts reality testing—the same mechanism seen in schizophrenia.
- **Mixed features:** motor restlessness, racing thoughts, and suicidal thinking all at the same time: High norepinephrine creates motor agitation and energy while low serotonin maintains hopelessness, giving the person the dangerous combination of energy to act on suicidal thoughts plus the despair to want to.

Focused exam

- Sleep pattern: needs much less sleep but does not feel tired (mania) OR sleeps 12+ hours and still feels exhausted (depression): Sleep change is the earliest and most reliable sign that the mood circuits in bipolar disorder are shifting. The suprachiasmatic nucleus (the master clock in the brain that keeps your body on a 24-hour schedule) breaks in this condition. When that clock breaks, sleep breaks first. During mania, the clock speeds up so the person needs almost no sleep — sometimes only 2 or 3 hours a night — but feels full of energy. During depression, the clock slows down so even 12 hours of sleep leaves the person exhausted. Watching sleep is like checking the engine light on a car — it tells you the system is off-track before other problems become obvious.
- Speech rate and pressure: talking very fast, jumping topics, hard to interrupt (mania) OR quiet, slow, long pauses (depression): The prefrontal cortex (the front part of the brain that controls how fast you think and organize your thoughts) is not working properly in bipolar disorder. Pressured speech — talking so fast others cannot get a word in, jumping from idea to idea without finishing — means the mood-thinking circuit is running too hot, like a car engine revving out of control. During depression, that same circuit slows to a crawl, so speech becomes quiet and slow with long pauses because thoughts move sluggishly. Both extremes come from the same broken circuit, just swinging in opposite directions.
- Energy and goal-setting: taking big risks (excessive spending, starting many new projects at once, risky sexual behavior, reckless driving) OR no energy to get out of bed: Bipolar disorder breaks the brain's reward and impulse-control circuits. These circuits involve dopamine (the brain messenger that drives pleasure, energy, and motivation) and the ventral striatum (the brain's reward center). During mania, the brakes fail — the person cannot stop themselves from taking risks they would normally avoid, like spending the rent money on sudden plans or starting five new projects at once. During depression, the engine shuts down completely — there is no drive or motivation at all, even for things the person usually loves. Both extremes come from the same broken circuit, just swinging in opposite directions.
- Mood baseline over time: asks 'How long have these mood episodes lasted?' Answer is days to weeks, not hours. Pattern repeats over time.: Bipolar disorder is defined by episodes that last for days or weeks and then repeat. One bad day is not bipolar disorder. Distinct episodes of mania lasting at least 4 days (called hypomania if mild) or 7 days (full mania if severe), plus episodes of depression lasting at least 2 weeks, establish the diagnosis. The pattern over time — up, then down, then up again — is the signature of this condition. Normal mood swings last hours and are tied to events. Bipolar episodes last weeks and often have no clear trigger.

- Suicidal or self-harm thoughts: especially in mixed episodes when depressive and manic symptoms happen at the same time: Mixed episodes — depression plus agitation and high energy at the same time — carry the highest suicide risk in bipolar disorder. The person has the dark, hopeless thoughts of depression plus the energy and impulsivity to act on them. This combination is extremely dangerous. The brain is stuck in two opposite states at once: the limbic system (the emotion center) is flooded with despair while the motor circuits (the action centers) are revved up. This is a psychiatric emergency and requires immediate safety planning.
- Substance use: asks about stimulants (cocaine, methamphetamine), alcohol, cannabis, or mood episodes that started after beginning or stopping substances: Stimulants flood the brain with dopamine (the messenger that drives reward and energy), which can trigger manic episodes in people with bipolar disorder. Alcohol disrupts the balance of GABA (the brain's main calming signal) and glutamate (the brain's main exciting signal), destabilizing mood circuits. Cannabis affects cannabinoid receptors that regulate mood and perception. A mood episode caused by substances requires different treatment than primary bipolar disorder. The timeline — did the substance come first or did the mood episode come first — is critical to get the diagnosis right.

Diagnostics · every test answers a question

- Complete metabolic panel (CMP) including electrolytes (sodium, potassium, calcium), kidney function (creatinine, blood urea nitrogen BUN), liver enzymes (ALT, AST) → Are the kidneys and liver healthy enough to safely clear mood-stabilizing medications like lithium and valproate? Are electrolytes balanced so seizure risk is low?
- Complete blood count (CBC) with differential → Is the bone marrow making enough blood cells, and are there any signs of infection or blood disorder that would make certain mood stabilizers unsafe?
- Thyroid-stimulating hormone (TSH) and free thyroxine (free T4) → Is the thyroid gland working properly, or is thyroid disease causing symptoms that look like mania or depression?
- Urine drug screen (UDS) for amphetamines, cocaine, cannabis, opioids, and benzodiazepines → Are substances causing or contributing to the mood symptoms, or is this primary bipolar disorder?
- Pregnancy test (urine or serum β -hCG) in all people who could become pregnant → Is the person pregnant? Pregnancy changes which mood stabilizers are safe to use.
- Electrocardiogram (ECG) if planning to start lithium or certain antipsychotics → Is the heart's electrical system normal, or are there rhythm problems that make certain mood stabilizers unsafe?

- Vitamin B12 and folate levels if there are signs of anemia or cognitive slowing → Is a vitamin deficiency causing symptoms that look like depression (fatigue, poor concentration, low mood)?
- HIV and hepatitis C screening if there is history of injection drug use or high-risk behavior → Is there a chronic infection that affects the brain and contributes to mood symptoms?

Treatment logic

- Lithium started as mood stabilizer for acute mania or maintenance treatment to prevent future episodes → Lithium enters brain cells and changes the signaling pathways that control how excitable neurons are. Specifically, it blocks enzymes called inositol monophosphatase and glycogen synthase kinase-3 (GSK-3), which stabilizes the circuits that swing between mania and depression. By blocking GSK-3, lithium strengthens connections between brain cells (neurons) and protects them from stress damage. Over weeks to months, lithium prevents extreme mood swings in both directions. It also reduces suicide risk more than any other mood stabilizer — studies show up to 80% reduction in suicide attempts. Think of lithium as resetting the brain's thermostat so it does not overheat (mania) or freeze (depression).
- Valproate (divalproex) started as mood stabilizer for acute mania or maintenance treatment → Valproate increases the amount of GABA (gamma-aminobutyric acid, the brain's main calming chemical) by blocking the enzyme GABA transaminase (which breaks GABA down) and by increasing the enzyme glutamic acid decarboxylase (which makes GABA). More GABA means the overactive circuits in mania are calmed. Valproate works faster than lithium for acute mania (within 1 to 2 weeks). It is especially effective for mixed episodes (depression plus mania at the same time) and rapid cycling (four or more episodes per year), which lithium may not control as well.
- Second-generation antipsychotic (such as quetiapine, lurasidone, olanzapine, aripiprazole, or cariprazine) for acute mania or bipolar depression → These medications block dopamine D2 receptors in the mesolimbic pathway (the brain's reward circuit), which reduces the euphoria, grandiosity, impulsivity, and racing thoughts of mania by turning down excess dopamine signaling. Some (quetiapine, lurasidone) also block serotonin 5-HT_{2A} receptors, which improves depressive symptoms by rebalancing serotonin (a brain messenger that steadies mood). They work fast — within days to a week — so they are used to calm acute agitation, psychotic features (delusions like believing you have special powers, hallucinations like hearing voices), and severe mania. Think of antipsychotics as turning down the volume on an overloaded circuit.

- Fixed sleep-wake schedule (same bedtime and wake time every day, including weekends; dark, quiet sleep environment; no screens 1 hour before bed; no daytime naps) → The suprachiasmatic nucleus (a tiny cluster of nerve cells in the hypothalamus) is the brain's master clock that controls circadian rhythms — the 24-hour cycles that regulate sleep, body temperature, hormone release (like cortisol, the stress hormone), and mood. In bipolar disorder, this clock is unstable. A fixed sleep schedule resets the clock by giving it consistent time cues (light in the morning, darkness at night). This stabilizes the hypothalamic-pituitary-adrenal axis (the stress-response system) and reduces the frequency of mood episodes. Clinical studies show that people who keep regular sleep-wake times have up to 50% fewer relapses. A single night of missed sleep can precipitate mania in someone with bipolar disorder.
- Psychoeducation: teach the patient to identify their personal early warning signs (such as needing less sleep, increased spending, social withdrawal), understand bipolar disorder as a chronic medical condition like diabetes, and recognize the importance of medication adherence → When people recognize the early signs of a developing episode — called early-warning (prodromal) symptoms — such as sleeping only 3 hours without feeling tired, suddenly losing interest in activities they love, or feeling irritable over small things, they can contact their provider before the episode becomes severe. Early intervention with medication adjustment (raising a dose, adding a short-term medication like a benzodiazepine to restore sleep) can prevent hospitalization and shorten episode duration. Studies show that psychoeducation reduces relapse rates by up to 40%. It also reduces the stigma and shame people feel, which improves adherence (sticking with the treatment plan).
- Interpersonal and social rhythm therapy (IPSRT): structured psychotherapy that regularizes daily routines (sleep, meals, exercise, social contact) to the same times each day → External time cues — like morning sunlight, meal timing, exercise at the same hour, and regular social interaction — train the suprachiasmatic nucleus (the brain's master clock) to stay on schedule. Consistent daily rhythms stabilize the hypothalamic-pituitary-adrenal axis (the stress-response system) and reduce circadian disruption, which lowers the frequency and severity of mood episodes. Clinical trials show IPSRT reduces relapse rates when combined with medication. Think of IPSRT as building a fence around your daily schedule so the brain clock cannot drift.

- Stable housing plus substance use disorder treatment (if alcohol or drug use is present) integrated into the care plan alongside mood disorder treatment → Homelessness and housing instability create chronic stress that activates the hypothalamic-pituitary-adrenal axis (the stress-response system), raising cortisol (the stress hormone) and triggering mood episodes. Alcohol disrupts the balance of GABA (the brain's calming signal) and glutamate (the brain's exciting signal); stimulants like cocaine and methamphetamine flood the brain with dopamine, precipitating mania. Removing these stressors and substance triggers reduces the frequency of episodes and improves medication adherence and effectiveness. Integrated treatment (addressing substance use and bipolar disorder together in the same program with the same team) works better than treating them separately because both conditions affect the same brain circuits.

Medications

Lithium · Mood stabilizer (alkali metal)

Lithium is a simple metal that slips into brain cells and shifts how they handle signals. It blocks an enzyme called inositol monophosphatase (a protein that recycles a building block for signals inside the cell), which slows down a chemical relay inside nerve cells. This calms the wild electrical storms that fuel mania and steadies the brain against deep dips into depression. Think of it like a voltage regulator that keeps power steady instead of spiking high or dropping low.

1. Lithium enters nerve cells through sodium channels (gates that normally let sodium rush in to start electrical signals).
2. It blocks inositol monophosphatase, an enzyme that recycles inositol (a building block for signals inside the cell).
3. This reduces IP₃ and DAG (two messenger molecules that amplify signals inside neurons), calming overactive firing.
4. It also boosts proteins like BDNF (brain-derived neurotrophic factor, a protein that helps neurons survive and grow new connections) and increases gray matter volume (the thinking tissue of the brain) over months.
5. The net effect is fewer extreme mood swings, less mania, less depression, and better protection of brain cells.

SAFETY WATCH

Narrow therapeutic window: the safe dose is very close to the toxic dose. Blood levels must be checked every 3 to 6 months (target 0.6 to 1.2 mEq/L for keeping stable, 0.8 to 1.2 for treating active mania). · Kidney monitoring: lithium can harm the kidneys over years, causing chronic kidney disease (the kidneys slowly lose their ability to filter waste). Check creatinine (a waste product that shows kidney function) and eGFR (estimated glomerular filtration rate, which tells how well kidneys filter blood) every 6 to 12 months. · Thyroid monitoring: lithium blocks thyroid hormone release, causing hypothyroidism (low thyroid, which slows metabolism and saps energy) in 10 to 20% of patients. Check TSH (thyroid-stimulating hormone, the brain's signal that tells the thyroid to make hormone) every 6 to 12 months. · Dehydration risk: anything that lowers body water—vomiting, diarrhea, heavy sweating, or diuretics (water pills that make you pee more)—raises lithium levels and can cause toxicity. Symptoms include tremor, confusion, slurred speech, and seizures. Drink plenty of fluids and avoid sudden changes in salt intake. · Pregnancy risk: lithium causes Ebstein anomaly (a heart defect where the valve between the right chambers does not form correctly) if taken in the first three months of pregnancy. Avoid in pregnancy if possible. If essential, use the lowest dose and monitor closely with fetal ultrasounds.

Valproate (divalproex, valproic acid) · Mood stabilizer (anticonvulsant)

Valproate calms the brain by boosting GABA (gamma-aminobutyric acid, the main brake chemical that slows nerve firing) and blocking sodium channels (gates on nerve cells that spark electrical signals). More GABA means less wild firing, which stops the racing thoughts and impulsive acts of mania. It works faster than lithium for active mania, often within 5 to 7 days.

1. Valproate increases GABA levels by blocking GABA transaminase, the enzyme that breaks down GABA.
2. It also opens more GABA-making pathways, raising the amount of calming chemical available.
3. At the same time, it blocks sodium channels, stopping the rapid firing of action potentials (electrical sparks) in overexcited neurons.
4. Together, these actions reduce the hyperactivity and irritability of mania and stabilize mood over weeks.

SAFETY WATCH

Liver toxicity: rare but serious, especially in children under age 2 or patients with mitochondrial disorders (conditions where cells cannot make energy correctly). Check liver enzymes (AST and ALT, proteins that leak out when liver cells are damaged) at baseline and during the first 6 months. · Pancreatitis (inflammation of the pancreas, the organ that makes digestive juices and insulin): sudden severe belly pain, nausea, vomiting. This is an emergency. Stop the drug immediately if suspected and go to the hospital. · Weight gain and metabolic syndrome: valproate increases appetite and insulin resistance (cells stop responding well to insulin, raising blood sugar). Monitor weight, fasting glucose, and lipids (cholesterol and triglycerides, the fats in blood that can clog arteries) every 3 to 6 months. · A low platelet count (Thrombocytopenia) (low platelet count, the blood cells that clot wounds), raising bleeding risk. Check CBC (complete blood count, which measures all blood cell types) at baseline and if bruising or bleeding appears. · Pregnancy risk: valproate causes neural tube defects (spina bifida, where the spine does not close) in 1 to 2% of exposed pregnancies and fetal valproate syndrome (facial abnormalities, heart defects, developmental delays, lower IQ). Absolutely avoid in women of childbearing age unless no other option exists and reliable contraception is in place. If pregnancy occurs, stop immediately and start high-dose folic acid (a vitamin that helps prevent birth defects).

Quetiapine · Second-generation antipsychotic (atypical antipsychotic)

Quetiapine blocks dopamine D₂ receptors (which calm overactive reward and motivation circuits) and serotonin 5-HT_{2A} receptors (which smooth out mood and reduce agitation). It also blocks histamine H₁ receptors (causing drowsiness and helping sleep). Unlike older antipsychotics, it does not clamp down as hard on dopamine, so it causes fewer stiffness and movement side effects. It is FDA-approved for both bipolar mania and bipolar depression, making it very flexible.

1. Quetiapine binds loosely to dopamine D₂ receptors in the mesolimbic pathway, reducing the go-go-go drive of mania without completely shutting down dopamine (which would cause flat mood and stiffness).
2. It strongly blocks serotonin 5-HT_{2A} receptors, which lifts mood and reduces irritability.
3. The loose D₂ binding lets normal movement and motivation continue, avoiding the zombie-like state older antipsychotics can cause.
4. Its breakdown product, norquetiapine, also blocks the norepinephrine transporter (the pump that sucks norepinephrine, an alertness and mood chemical, back into nerve endings), which may help lift bipolar depression by raising norepinephrine levels.

SAFETY WATCH

Metabolic syndrome: weight gain (average 2 to 4 kilograms in the first year), high blood sugar, high cholesterol, and increased risk of type 2 diabetes. Check weight, waist circumference, fasting glucose, HbA1c (a 3-month average of blood sugar measured by looking at sugar stuck to red blood cells), and lipid panel at start, at 3 months, and every year. · Sedation: very common, especially at first. Take at bedtime. Be careful driving or using machines until you know how it affects you. · Orthostatic low blood pressure (hypotension): blood pressure drops when you stand up, causing dizziness or fainting. Stand up slowly from sitting or lying down. · Cataracts (clouding of the lens in the eye): animal studies showed this side effect. Not clearly proven in humans, but eye exams every 1 to 2 years are reasonable if used long-term. · Rare: prolonged QTc interval (electrical delay in the heart that can trigger dangerous rhythms). Get a baseline EKG (electrocardiogram, a heart tracing) if you have heart disease or take other drugs that affect the QTc.

Lurasidone · Second-generation antipsychotic (atypical antipsychotic)

Lurasidone blocks dopamine D₂ receptors (calming overactive reward circuits) and serotonin 5-HT_{2A} receptors (smoothing mood), but it also activates 5-HT_{1A} receptors (which lifts mood and reduces anxiety). This unique serotonin boost makes it especially good for bipolar depression. Think of it as turning down the too-much signals and turning up the feel-better signals at the same time.

1. Lurasidone blocks dopamine D₂ receptors, reducing the racing thoughts and impulsivity of mania.
2. It blocks serotonin 5-HT_{2A} receptors, which lowers irritability and agitation.
3. At the same time, it activates 5-HT_{1A} receptors (a different serotonin receptor), which lifts mood, reduces anxiety, and sharpens thinking and memory.
4. This balanced action treats both poles of bipolar disorder—depression and mania—without as much sedation or weight gain as other antipsychotics.

SAFETY WATCH

Metabolic effects: much lower risk of weight gain and diabetes than quetiapine or olanzapine, but still check weight, glucose, and lipids at start and yearly. · Akathisia (inner restlessness, feeling like you must keep moving): happens in 10 to 15% of patients. May need a lower dose or a beta-blocker (like propranolol, a drug that slows the heart and calms jitters) to manage. · Nausea: take with food (at least 350 calories, like a full meal or large snack) to reduce stomach upset and help the drug absorb. · Sedation: less than quetiapine, but still possible. Take at bedtime if it makes you drowsy. · Rare: extrapyramidal symptoms (stiffness, tremor, slow movement) at higher doses, though much less than older antipsychotics like haloperidol.

Lamotrigine · Mood stabilizer (anticonvulsant)

Lamotrigine blocks sodium channels on nerve cells, stopping the rapid-fire electrical bursts that trigger mood swings. It is the best medication for preventing bipolar depression (the depressive episodes in bipolar disorder) but does not work well for active mania. Think of it as a long-term shield against down swings, not a fast rescue for up swings.

1. Lamotrigine binds to sodium channels when they are in their inactive state, keeping them closed longer.
2. This stops the rapid, repetitive firing of neurons that destabilizes mood.
3. It also reduces the release of glutamate (an excitatory neurotransmitter that makes neurons fire), preventing overexcitement and protecting cells from damage.
4. Over weeks to months, this stabilizes baseline mood and reduces how often and how deep depressive episodes hit.

SAFETY WATCH

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): rare but life-threatening skin reactions where the skin blisters and peels like a severe burn. Risk is about 1 in 1,000, higher if you raise the dose too fast or combine lamotrigine with valproate (which doubles lamotrigine blood levels). ANY new rash in the first 8 weeks: STOP the drug immediately and call your doctor. Do not wait. · Slow dose increase required: start at 25 mg per day, increase every 2 weeks. Go even slower if on valproate; go faster if on carbamazepine (which speeds up breakdown of lamotrigine). · Aseptic meningitis (inflammation of the lining around the brain and spinal cord without infection): rare—severe headache, stiff neck, fever, nausea. Stop the drug and go to the emergency room. · Benign rash: 10% of patients get a mild, harmless rash. Hard to tell apart from early SJS, so any rash needs immediate medical evaluation. · Pregnancy: safer than valproate or lithium, but still linked to a small increase in cleft lip and palate (a gap in the roof of the mouth or upper lip). Discuss risks and benefits. Take folic acid (at least 0.4 to 1 mg daily) before and during pregnancy to lower the risk.

Olanzapine · Second-generation antipsychotic (atypical antipsychotic)

Olanzapine blocks dopamine D₂ receptors (calming overactive emotion and thought circuits) and serotonin 5-HT_{2A} receptors (smoothing mood and reducing agitation). It is one of the most powerful drugs for active mania, often calming symptoms within 3 to 5 days. However, it has the highest risk of weight gain and metabolic problems of any antipsychotic, so doctors usually save it for severe mania or when other drugs fail.

1. Olanzapine blocks dopamine D₂ receptors in the mesolimbic pathway, reducing the euphoria, racing thoughts, and impulsive acts of mania.
2. It blocks serotonin 5-HT_{2A} receptors, which lowers irritability and aggression.
3. It also blocks histamine H₁ receptors (causing drowsiness and increased hunger) and muscarinic M₁ receptors (causing dry mouth, constipation, and some dulling of thinking).
4. The strong blockade across many receptors makes it very effective for mania but also causes more side effects than newer antipsychotics.

SAFETY WATCH

Metabolic syndrome: the highest risk of any antipsychotic. Average weight gain is 5 to 10 kilograms in the first year. Raises risk of type 2 diabetes, high cholesterol, high triglycerides, and heart disease. Check weight, waist size, fasting glucose, HbA1c, and lipid panel at start, at 1 month, at 3 months, and every 3 to 6 months after that. · Sedation: very common, especially at first. Take at bedtime. · Orthostatic low blood pressure (hypotension): blood pressure drops when you stand, causing dizziness or fainting. Stand up slowly. · Anticholinergic effects: dry mouth, constipation, blurred vision, trouble peeing. Older adults are especially vulnerable and may get confused. · Rare: prolonged QTc interval (electrical delay in the heart that can cause dangerous rhythms); neuroleptic malignant syndrome (fever, muscle rigidity, confusion—a medical emergency—call 911); tardive dyskinesia (involuntary tongue and lip movements after years of use, which may not go away even after stopping).

Carbamazepine · Mood stabilizer (anticonvulsant)

Carbamazepine blocks sodium channels on nerve cells, stopping the rapid firing that triggers mood swings and seizures. It is an older mood stabilizer, effective for mania but less used now because of drug interactions and side effects. It speeds up the liver's breakdown of many other drugs (including birth control pills and other psych meds), making dosing tricky.

1. Carbamazepine binds to sodium channels, keeping them in the inactive state longer.
2. This prevents the rapid, repetitive firing of neurons that can escalate into mania.
3. It also reduces the release of glutamate, calming overactive brain circuits.
4. Over weeks, it stabilizes mood and lowers the frequency of manic episodes.

SAFETY WATCH

Enzyme inducer: carbamazepine speeds up liver enzymes (CYP3A4, CYP2C9, and others), lowering blood levels of many drugs. This includes hormonal birth control (risk of unintended pregnancy—use barrier methods or non-hormonal IUD), lamotrigine, antipsychotics, and warfarin (a blood thinner). Always check for interactions before starting any new medication. · Low sodium (Hyponatremia) (low sodium in the blood): causes confusion, headache, nausea, and seizures. More common in older adults. Check sodium at baseline and if symptoms appear. · Aplastic anemia and agranulocytosis: rare but serious drops in red blood cells or white blood cells, raising risk of infection and bleeding. Check CBC (complete blood count) at baseline and if fever, sore throat, easy bruising, or unusual fatigue occurs. · Stevens-Johnson syndrome (SJS): rare life-threatening rash where skin blisters and peels. Risk is much higher in people with the HLA-B*1502 gene variant (common in people of Asian descent, especially Han Chinese, Thai, and Filipino). Genetic testing is recommended before starting in at-risk populations. ANY new rash: stop the drug and see a doctor immediately. · Pregnancy risk: carbamazepine causes neural tube defects (like spina bifida) and craniofacial abnormalities (face and skull malformations). Avoid in pregnancy. Use effective non-hormonal contraception if taking carbamazepine.

Aripiprazole · Second-generation antipsychotic (atypical antipsychotic)

Aripiprazole is a partial agonist at dopamine D₂ receptors, which means it acts like a dimmer switch instead of an on/off switch. When dopamine is too high (like in mania), it blocks some of the signal, calming you down. When dopamine is too low (like in depression or flat mood), it gently boosts the signal. It also partially activates serotonin 5-HT_{1A} receptors (which lifts mood) and blocks 5-HT_{2A} receptors (which reduces agitation). This balancing act treats mania without completely flattening motivation or emotion.

1. Aripiprazole partially activates dopamine D₂ receptors. If dopamine activity is too high (mania), it acts as a brake by blocking some of the excess signal. If activity is too low, it gently pushes the pedal by adding a small boost.
2. It also partially activates serotonin 5-HT_{1A} receptors, which lifts mood and reduces anxiety.
3. At the same time, it blocks serotonin 5-HT_{2A} receptors, smoothing irritability and agitation.
4. This flexible action stabilizes mood in both directions—calming mania without causing the flat, numb feeling of older antipsychotics.

SAFETY WATCH

Akathisia (inner restlessness, feeling like you must pace or move): very common, especially in the first weeks. May need dose reduction, switching times of day, or adding a beta-blocker like propranolol. · Metabolic effects: lower risk than olanzapine or quetiapine, but weight gain and glucose/lipid changes can still happen. Monitor weight, fasting glucose, HbA1c, and lipids at baseline and yearly. · Insomnia or activation: some people feel jittery or have trouble sleeping, especially at first. Taking the dose in the morning instead of bedtime may help. · Nausea and headache: common in the first week, usually fade over time. · Rare: prolonged QTc interval; neuroleptic malignant syndrome (fever, muscle rigidity, confusion—call 911); tardive dyskinesia (involuntary movements after long-term use); and compulsive behaviors (gambling, shopping, eating, sex) in a small number of patients—stop the drug if these appear.

Asenapine · Second-generation antipsychotic (atypical antipsychotic)

Asenapine blocks dopamine D₂ receptors (calming mania) and serotonin 5-HT_{2A} receptors (smoothing mood and irritability). It is given under the tongue (sublingual tablet) because it is poorly absorbed if swallowed. It works for acute mania and mixed episodes (mania and depression at the same time). It has a lower risk of weight gain than olanzapine but can cause mouth numbness and an unpleasant taste.

1. Asenapine blocks dopamine D₂ receptors in the mesolimbic pathway, reducing the racing thoughts, euphoria, and impulsivity of mania.
2. It blocks serotonin 5-HT_{2A} receptors, which lowers irritability and smooths mood swings.
3. It also has some activity at other serotonin and histamine receptors, contributing to mood stabilization and mild sedation.
4. The sublingual route delivers the drug directly into the bloodstream through the tissue under the tongue, bypassing the stomach (where most would be destroyed).

SAFETY WATCH

Sublingual dosing: the tablet must dissolve under the tongue for 10 minutes. Do not eat or drink for 10 minutes after. If swallowed, blood levels drop by 90% and the drug will not work. · Oral numbness and bad taste: very common. Usually fades after a few minutes but can be unpleasant enough that some people stop the medication. · Metabolic effects: moderate risk of weight gain and glucose/lipid changes. Monitor weight, fasting glucose, HbA1c, and lipids at baseline, 3 months, and yearly. · Sedation: common, especially at first. Take at bedtime. · Orthostatic low blood pressure (hypotension): dizziness when standing up. Rise slowly. · Rare: extrapyramidal symptoms (stiffness, tremor), prolonged QTc interval, neuroleptic malignant syndrome, tardive dyskinesia, and severe allergic reactions (tongue or throat swelling—seek emergency care immediately).

Red flags

- Suicidal thoughts or behavior, especially during mixed episodes or in the first weeks of starting an antidepressant
- Psychotic symptoms—delusions or hallucinations—during mania
- Severe insomnia (no sleep for three or more days) or complete loss of insight (the person cannot recognize they are sick)
- Lithium toxicity signs: coarse hand tremor, confusion, slurred speech, muscle twitching, or seizures
- Rapid cycling—four or more mood episodes in one year—signaling treatment resistance and worse long-term outcome

Nursing priorities

1. Screen for suicide risk every shift using a validated tool and ask directly about intent, plan, and access to means; escalate immediately if any positive answer — Bipolar disorder carries 20 to 30 times higher suicide risk than the general population, peaking during mixed episodes, depressive phases, and the first weeks after starting treatment when energy returns before mood lifts, giving the patient the drive to act on suicidal thoughts
2. Monitor lithium level, creatinine (kidney function test), and thyroid-stimulating hormone (TSH, a measure of thyroid gland activity) per protocol—typically every 3 to 6 months for stable patients or sooner if vomiting, diarrhea, fever, or new medications — Lithium is cleared only by the kidneys and even small changes in hydration, kidney function, or salt balance can push levels from therapeutic to toxic; lithium also damages the thyroid gland over time, causing hypothyroidism (low thyroid hormone) in up to 20 percent of patients, which worsens depression

3. Enforce a fixed sleep-wake schedule with the same bedtime and wake time every day, even on weekends, and limit daytime naps to 20 minutes or less — The brain circuits that control circadian rhythm (the body's 24-hour clock) and mood regulation overlap heavily; even one night of sleep loss can trigger mania in vulnerable patients, and irregular sleep is one of the most common triggers for both manic and depressive episodes
4. Teach the patient and family to recognize early warning signs of mania—such as sleeping less than four hours for two nights in a row, racing thoughts, or starting multiple projects—and to call the provider immediately when these appear — Mania builds over days, not hours, and early intervention with a short course of extra medication or a few days of enforced sleep can abort a full manic episode and prevent hospitalization, job loss, financial ruin, or dangerous behavior
5. Assess for metabolic side effects—weight, waist circumference, fasting glucose (blood sugar), and lipid panel (cholesterol tests)—at baseline, 3 months, and then yearly for patients on second-generation antipsychotics — Second-generation antipsychotics—especially olanzapine, quetiapine, and clozapine—cause insulin resistance (the body's cells stop responding to insulin) and weight gain, roughly doubling the risk of metabolic syndrome and Type 2 diabetes, which are already elevated in bipolar disorder
6. Hold lithium and notify the provider immediately if the patient develops vomiting, diarrhea, fever, or confusion, or if creatinine rises above baseline — Anything that causes dehydration or reduces kidney blood flow—vomiting, diarrhea, fever, NSAIDs, ACE inhibitors, or diuretics—can cause lithium to build up to toxic levels within 24 to 48 hours, leading to tremor, confusion, seizures, coma, and permanent brain or kidney damage if not caught early
7. Coordinate contraception counseling and preconception planning for all patients of childbearing potential, because lithium, valproate, and carbamazepine are teratogens (substances that cause birth defects) — Valproate causes neural tube defects (spina bifida, a birth defect where the spinal cord does not close) in 10 percent of exposures in the first trimester and lowers infant IQ; lithium causes Ebstein anomaly (a heart defect) in roughly 1 percent; unplanned pregnancy is common, so counseling must happen before conception
8. Teach the patient to avoid alcohol and all recreational drugs, especially stimulants such as cocaine or methamphetamine, because these can trigger mania or interfere with mood stabilizers — Stimulants directly activate the same dopamine pathways that are already overactive in mania and can cause a manic episode even in patients who are stable on medication; alcohol disrupts sleep and medication adherence and worsens depression, roughly doubling the risk of suicide attempts

Sources

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