

Migraine and Headache Red Flags

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THE STORY IN ONE SENTENCE

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“Migraine is a brain alarm that fires too easily — treat the attack, prevent the next one, and always rule out the life-threatening causes hiding behind any new or weird headache.”

Normal anatomy — the body's job

Normally, your brain's nerve cells fire in smooth, organized patterns, and the blood vessels wrapped around the outside of your brain stay steady and quiet. The trigeminal nerve — the big pain nerve that covers your face, forehead, and the coverings of your brain (the meninges) — sits silent unless there is real danger. This balance keeps your head pain-free and your senses comfortable.

BODY'S JOB

The brain's job is to send electrical signals in calm, orderly waves so you can think, see, and move without interference. Blood vessels bring oxygen and fuel to brain tissue. The trigeminal nerve's job is to alert you to real threats — like a cut, infection, or dangerous pressure — by sending pain signals to your brainstem and up to your consciousness. In a healthy state, none of these systems are firing off false alarms.

1. Your brain's outer layer (the cortex) fires nerve signals in smooth, steady patterns — like a calm ocean wave rolling in.

2. Blood vessels on the surface of your brain (the meningeal arteries) stay a steady width and do not leak inflammatory chemicals.
3. The trigeminal nerve, which wraps around those blood vessels and covers the meninges (the brain's protective wrapping), stays quiet and does not send pain signals unless there is real injury.
4. Your brainstem (the stalk at the base of your brain that links your brain to your spinal cord) keeps your pain threshold normal and does not amplify every little signal into a big alarm.
5. Your senses — light, sound, smell — are processed at normal volume; nothing feels overwhelming.
6. You feel no head pain, your stomach is calm, and your vision is clear.

What breaks

In migraine, the brain's nerve cells become too excitable and fire off a slow, rolling wave of overactivity across the cortex — a process called cortical spreading depression. That wave makes the blood vessel nerves release a pain-amplifying chemical called CGRP (calcitonin gene-related peptide), which turns on the trigeminal nerve like a fire alarm. The trigeminal nerve then sends strong pain signals to the brainstem, which cranks up the volume on everything — light hurts, sound hurts, and your stomach joins in by making you feel sick. About 1 out of 3 people also see warning signs (aura) like flashing lights or zigzag lines, because the wave moves through the brain's vision center in the back before the headache hits. This is the primary breakdown in migraine: overexcitable brain waves, CGRP release, and trigeminal nerve activation — not a problem with blood vessels squeezing or opening (the old theory). However, in secondary headaches, the problem is not the brain being too sensitive — it is a real structural danger: bleeding in the brain (subarachnoid bleeding (hemorrhage)), infection (meningitis or encephalitis), stroke, a torn artery (dissection), very high blood pressure, or a growing mass like a tumor or abscess. These cause pain by stretching or irritating the meninges, raising pressure inside the skull, or directly damaging brain tissue. Red flags — like thunderclap (instant worst headache of your life), fever with stiff neck, sudden confusion or weakness, new headache in someone over 50, or vision loss with jaw pain — are the body's way of saying this is not just a migraine; something structural is breaking and needs emergency imaging or a spinal tap.

CLINICAL TERM

Primary migraine: cortical spreading depression (a slow wave of neuronal depolarization) propagates across the cortex at 2–5 mm/min, triggering release of CGRP (calcitonin gene-related peptide) and other neuropeptides from perivascular trigeminal nerve endings in the meninges. CGRP binds to receptors on meningeal nociceptors, amplifying pain signaling via the trigeminovascular pathway to the trigeminal nucleus caudalis in the brainstem. Central sensitization in the brainstem lowers the pain threshold and causes allodynia (normal stimuli like light and sound become painful). In the approximately 30% of patients with aura, the spreading depression wave crosses visual, sensory, or language cortex before reaching pain-sensitive structures, producing transient focal neurologic symptoms. Secondary headache: the pain arises from traction, inflammation, or starved blood flow (ischemia) of pain-sensitive structures (meninges, large vessels, cranial nerves, or scalp) due to subarachnoid bleeding (hemorrhage), meningitis, intracranial mass, arterial dissection, with high blood pressure (hypertensive) emergency, or giant cell arteritis. Red flags mandate urgent neuroimaging (non-contrast CT for suspected bleed, MRI/MRA for dissection or mass) and/or lumbar puncture (for infection or subarachnoid bleeding if CT negative).

How the body compensates

In a primary migraine, the body tries to protect the brain by making you shut down: you lie still in a dark, quiet room so the overexcited brain can calm down and stop the pain wave. But this compensation does not fix the underlying hyperexcitability — it just buys time until the attack passes (usually 4 to 72 hours untreated). In a secondary headache, there is no effective compensation — the body cannot stop bleeding, lower dangerously high pressure, or fight off infection on its own. Vital signs may look stable at first (normal blood pressure, normal heart rate, awake and talking) even while bleeding or infection is spreading. This stable-looking phase is the dangerous window, because teams can miss the diagnosis and lose the narrow time to intervene. Once compensatory mechanisms fail — brain swelling compresses the brainstem, infection spreads to sepsis, or bleeding raises pressure enough to herniate the brain — the patient crashes suddenly, and the window to reverse damage closes fast. The job is to recognize red flags and image or tap the spinal fluid early, before that crash, because once compensation breaks, even perfect treatment may not bring the brain back.

1. In primary migraine: the body makes you hypersensitive to light, sound, and movement (photophobia, sound sensitivity (phonophobia), osmophobia) so you naturally seek out a dark, quiet room and lie still. This lowers sensory input and helps the overexcited brainstem calm down.

2. You feel nauseous and may vomit — your body slows digestion (via the vagus nerve) so all energy can go to protecting the brain. Lying still and resting also lowers the risk of making the pain worse.
3. Some people feel very tired or fall asleep after the headache ends (postdrome phase) — this is the brain recovering and resetting its electrical balance.
4. But these compensations do not fix the root problem: your brain is still wired to be hyperexcitable. Without acute treatment (triptans, NSAIDs, antiemetics) or prevention (daily meds, CGRP blockers, lifestyle changes), the migraine just runs its full 4 to 72 hour course and will likely come back.
5. In secondary (red-flag) headache: there is no effective compensation. If you are bleeding into the space around your brain (subarachnoid bleeding (hemorrhage)), your body cannot stop the leak or clear the blood on its own. If you have bacterial meningitis, your immune system cannot sterilize the cerebrospinal fluid without antibiotics. If an artery in your neck is torn (dissection), your body cannot re-seal the vessel wall — it can only try to clot off the tear, which may cause a stroke.
6. Vital signs can look deceptively normal in the early phase: blood pressure stable, heart rate steady, patient awake and talking. This is the dangerous middle — the body is working hard to keep oxygen flowing to the brain (by raising blood pressure a little, shunting blood away from the gut, releasing stress hormones like cortisol and adrenaline), but it is buying time, not fixing the leak, infection, or rising pressure.
7. The crash point: once blood fills the brain's ventricles or pushes the brainstem down through the skull opening (herniation), or once infection spreads to the bloodstream (sepsis), or once an artery clots off and causes a stroke, the body's compensation fails suddenly. Blood pressure may spike or drop, consciousness fades, pupils may dilate and stop responding to light, breathing becomes irregular, and the window to reverse damage closes fast.
8. The key is to catch the red flag early — before compensation fails — because once the brain herniates, even emergency surgery may not bring the patient back. Look at the pattern and trajectory, not just one set of vital signs: new, sudden, worst-ever headache (thunderclap) means image the brain now. Headache plus fever plus stiff neck means do a lumbar puncture and start antibiotics now. New headache in someone over 50 plus vision changes plus jaw pain means check inflammatory markers (ESR, CRP) and start steroids for possible giant cell arteritis now, because waiting can cause permanent blindness in hours to days.

Domino effect

1. A trigger (stress, lack of sleep, skipped meals, hormone drop, weather change, alcohol, or strong smells) lowers the brain's threshold for overexcitation. — Your genes already make your brain more excitable than average (migraine runs in families about 60% of the time). The trigger tips the balance, and nerve cells in your cortex start firing in a slow, rolling wave instead of staying calm.
2. Cortical spreading depression: a wave of abnormal electrical activity rolls across the surface of your brain at 2 to 5 millimeters per minute. — This is like a power brownout spreading block by block. Nerve cells depolarize (lose their normal charge), fire all at once, then go silent. The wave moves forward, leaving a trail of temporarily shut-down brain tissue behind it.
3. The spreading wave reaches the blood vessels wrapped around your brain (meningeal arteries) and the trigeminal nerve endings that surround those vessels. — When the wave hits, those nerve endings release CGRP (calcitonin gene-related peptide), a chemical messenger that cranks up pain signaling and makes blood vessels swell and leak inflammatory molecules into the meninges (the protective layers around your brain).
4. CGRP activates the trigeminal nerve — the main pain highway for your face, forehead, and the coverings of your brain. — CGRP binds to receptors on the trigeminal nerve like a key in a lock, turning the nerve on high. Pain signals flood into the trigeminal nucleus caudalis (a pain-processing station in your brainstem), and you start to feel throbbing, pulsing pain, usually on one side of your head (because the wave and CGRP release often start on one side).
5. The brainstem amplifies the pain signals and lowers your pain threshold (central sensitization), so even normal things like light, sound, or touch feel painful. — Your brainstem is trying to protect you by making everything feel worse, forcing you to lie still and avoid anything that could stress your brain further. This is why light hurts your eyes (photophobia), sounds feel too loud (phonophobia), and even brushing your hair or wearing a ponytail can hurt (allodynia).
6. The brainstem also talks to the vagus nerve, which controls your stomach and gut, so you feel nauseous and may throw up. — The brainstem is saying, 'Stop everything — don't eat, don't move, just rest,' so it shuts down your digestion. This is not a separate problem; it is part of the same survival response to give your brain a break.

7. In about 1 out of 3 people, the spreading wave crosses the visual cortex (the back of your brain that processes what you see) before it reaches the pain-sensitive structures, so you get an aura: flashing lights, zigzag lines, blind spots, or shimmering waves in your vision. — The wave temporarily shuts down the vision cells as it passes, so you see weird patterns or lose part of your visual field. The aura usually lasts 5 to 60 minutes, then fades as the wave moves on and the headache begins. Some people get sensory aura (tingling or numbness in the hand or face) or even speech aura (trouble finding words) if the wave crosses those brain areas.
8. The pain peaks and lasts 4 to 72 hours if untreated, then slowly fades as the brain's chemistry resets and CGRP levels drop. — Your body is not broken — it is working hard to recover. The cortical spreading depression wave stops spreading, CGRP breaks down, the trigeminal nerve calms down, and the brainstem lowers the alarm. You enter the postdrome phase: tired, drained, foggy, but the pain is gone. This is the brain healing and rebalancing.
9. Red-flag secondary headaches break this pattern with new danger: sudden thunderclap (worst headache of your life in seconds means suspect bleeding from a ruptured aneurysm), headache plus fever plus stiff neck (suspect meningitis), headache plus sudden weakness or speech trouble (suspect stroke or dissection), new headache in someone over 50 plus vision loss or jaw pain (suspect giant cell arteritis), or headache that wakes you at night or gets worse lying down (suspect rising pressure from a tumor or bleed). — These red flags mean the pain is not from overexcitable brain waves — it is from something structural breaking: blood leaking into the space around your brain, bacteria or viruses inflaming the meninges, a blood vessel tearing, a clot blocking blood flow, or pressure building inside your skull. The body cannot compensate for these on its own. You need emergency imaging (CT or MRI) or a lumbar puncture (spinal tap to check the fluid around your brain and spinal cord) right away, because the window to treat — drain the bleed, give antibiotics, dissolve the clot, or start steroids — is measured in hours, not days. Once the brain swells or herniates (pushes down through the skull opening), even perfect treatment may not bring you back.

Symptoms · what the patient feels, and why

- Throbbing or pounding pain on one side of the head: Blood vessels around the brain swell and press on pain-sensing nerves wrapped around them. The trigeminal nerve (the big face nerve that carries pain signals) sends alarm signals into the brain, creating that pounding feeling that often beats with your heartbeat.
- Pain that gets worse with movement, bright light, or loud noise: The brainstem (the control tower where your brain meets your spine) becomes extra-sensitive during a migraine. Normal things like walking, bright screens, or sounds now feel like they are turning up the pain dial because your brain's filters are overloaded.

- Nausea or throwing up: Migraine turns on the vagus nerve (a big nerve that runs from your brain down through your stomach). This same nerve is why your stomach churns when you are nervous. When it fires too hard during a migraine, your stomach slows down and you feel sick.
- Seeing flashing lights, zigzag lines, or blind spots (aura): A wave of electrical silence called cortical spreading depression creeps slowly across the visual cortex (the back of your brain that builds what you see). As brain cells fire and then go quiet in that wave, you see sparkles, lines, or dark patches for 5 to 60 minutes before or during the headache.
- Trouble thinking clearly or finding words: When the electrical wave reaches language and thinking areas in the cortex (the outer layer of the brain), those brain cells pause their work. You might mix up words, forget names, or feel foggy until the wave passes and blood flow returns to normal.
- Numbness or tingling, usually on one side of the face or hand: The same slow electrical wave can sweep across the sensory cortex (the strip of brain that reads touch and position). As it moves, it shuts down feeling in the matching body part—usually face, hand, or arm—for a few minutes, then the feeling comes back.
- Sudden, explosive 'thunderclap' headache that peaks in seconds: This can mean a blood vessel in or around the brain has torn or burst (subarachnoid bleeding (hemorrhage)), or a vessel has suddenly narrowed or swollen dangerously. It is NOT a typical migraine pattern and needs emergency imaging right away.
- Headache with fever, stiff neck, confusion, or rash: Infection (meningitis or encephalitis) may be inflaming the protective layers around the brain and spinal cord. Bacteria, viruses, or fungi release toxins that irritate the meninges (the brain's wrapping) and trigger immune cells to flood in, raising pressure and causing pain, fever, and neck stiffness.
- New headache after age 50, or a clear change in your usual headache pattern: A brand-new headache in an older adult raises concern for giant cell arteritis (inflamed arteries in the head) or a growing mass. A sudden shift in a long-standing migraine pattern can signal a structural problem like a bleed, clot, or tumor that was not there before.
- Headache that starts or worsens with coughing, straining, or lying flat: Anything that raises pressure inside the skull—like a tumor, blockage of spinal fluid (hydrocephalus), or too much fluid around the brain (idiopathic intracranial high blood pressure (hypertension))—gets squeezed harder when you cough, bear down, or lie down, ramping up the pain quickly.

Focused exam

- One-sided throbbing head pain: This is the main signal in migraine — waves of electrical activity spread across one side of your brain, and nerves around blood vessels fire up, making them throb. If the pain is steady and squeezing instead of throbbing, or if it is on both sides, think about tension headache. If the pain is sudden and the worst ever, think about bleeding around the brain.
- Light and sound make the pain worse (photophobia and sound sensitivity (phonophobia)): When the electrical waves spread in migraine, the thalamus (the brain's relay station for what you see and hear) gets overexcited and makes every light and sound feel louder and sharper. This tells you the nervous system is stuck in overdrive, not that the person is being picky.
- Nausea or vomiting: Migraine spreads signals through the brainstem (the part at the base of your brain that controls your stomach and breathing), so nausea is common. If there is no nausea in a severe headache plus fever or confusion, ask: could this be meningitis (infection around the brain) or bleeding?
- Aura — vision changes (zigzag lines, blind spots, flickering lights), tingling, numbness, or trouble speaking before the pain starts: Aura happens when the electrical wave spreads slowly across the occipital cortex (the back of your brain that handles what you see) or the sensory cortex (the strip that handles touch). It usually lasts 5 to 60 minutes and then fades. This is classic migraine with aura, not a stroke. But if aura is brand new, lasts longer than an hour, or includes weakness that does not go away, that is a red flag — think stroke or complicated migraine and get imaging.
- No fever, no stiff neck, no confusion, no lasting weakness or numbness: Migraine does not cause fever, a stiff neck, confusion, or permanent weak spots. If the person has any of these, you are not looking at migraine — think meningitis (infection around the brain), encephalitis (infection inside the brain), or subarachnoid bleeding (hemorrhage) (bleeding around the brain).
- Red flags: worst headache of life (thunderclap onset, reaching peak pain in seconds to minutes), new headache pattern in someone over 50, headache that wakes you from sleep, or scalp tenderness: These findings point to subarachnoid bleeding (hemorrhage) (bleeding around the brain), giant cell arteritis (inflamed arteries in the head and temples, especially over age 50), or a brain tumor — not migraine. Stop and get imaging (CT or MRI) or blood work (ESR and CRP for arteritis) right away.

Diagnostics · every test answers a question

- Non-contrast head CT (computed tomography scan) → Is there bleeding in or around the brain, or a mass pushing on brain tissue?

- Brain MRI with and without gadolinium contrast → Is there a tumor, stroke, demyelinating disease (like multiple sclerosis), or vascular malformation that CT might miss?
- Lumbar puncture (spinal tap) with opening pressure and cerebrospinal fluid (CSF) analysis → Is there infection (meningitis or encephalitis) or blood in the cerebrospinal fluid that CT missed?
- Red blood cell (Erythrocyte) sedimentation rate (ESR) and C-reactive protein (CRP) → Is there giant cell arteritis (inflamed arteries in the head and temples), especially in someone over 50 with new headache, jaw pain, or scalp tenderness?
- Magnetic resonance angiography (MRA) or CT angiography (CTA) of the head and neck → Is there a vessel blockage, aneurysm (balloon in a blood vessel), or arterial dissection (tear in the artery wall)?
- Complete blood count (CBC) with differential → Is there infection (high white count), anemia (low red cells that can trigger headache), or a blood disorder?
- Basic metabolic panel (BMP) → Is there dehydration (high sodium or low kidney function) or electrolyte imbalance that can worsen headache?
- Fundoscopic exam (looking at the back of the eye with an ophthalmoscope) → Is there swelling of the optic nerve (papilledema) (swelling of the optic disc where the nerve enters the eye), which means increased pressure inside the skull?

Treatment logic

- Triptan (sumatriptan 50–100 mg by mouth or 6 mg subcutaneous, rizatriptan 10 mg, or zolmitriptan 2.5–5 mg) → Triptans grab onto serotonin 1B and 1D receptors (docking spots for serotonin, a brain messenger) on blood vessels and squeeze them tighter, stopping them from swelling. They also block CGRP (calcitonin gene-related peptide, a chemical that turns up pain signals) from the trigeminal nerve (the main nerve that carries face and head pain). They work best if you take them in the first hour of the migraine.
- NSAID (ibuprofen 400–800 mg, naproxen 500–550 mg, or ketorolac 30 mg IV) → NSAIDs block COX-1 and COX-2 enzymes (proteins that make prostaglandins, chemicals that turn up inflammation and pain). This turns down the swelling and throbbing around nerves in the meninges (the layers covering the brain) that are sending pain signals.
- Anti-nausea medicine (metoclopramide 10 mg IV or by mouth, ondansetron 4–8 mg, or prochlorperazine 10 mg IV or 25 mg rectal) → Metoclopramide blocks dopamine D2 receptors (docking spots for dopamine, a brain messenger) in the area postrema (the brainstem's vomiting center), so your stomach calms down and you can keep food and other medicines down. Ondansetron blocks serotonin 5-HT3 receptors in the same area. Prochlorperazine works on dopamine receptors and also helps headache pain a little.

- Preventive medicine taken every day: beta-blocker (propranolol 80–240 mg or metoprolol 100–200 mg), antiepileptic (topiramate 50–200 mg or valproate 500–1000 mg), or tricyclic antidepressant (amitriptyline 25–100 mg at bedtime) → Daily preventive medicine steadies the balance of serotonin, norepinephrine (another brain messenger), and electrical activity in your cortex (the outer layer of your brain) so the spreading waves are less likely to start in the first place. Propranolol calms overactive adrenergic (adrenaline-related) nerve signals, topiramate quiets voltage-gated sodium and calcium channels (gates that control electrical firing), and amitriptyline raises serotonin and norepinephrine and blocks pain pathways.
- CGRP monoclonal antibody (erenumab 70–140 mg monthly, fremanezumab 225 mg monthly or 675 mg quarterly, galcanezumab 240 mg first dose then 120 mg monthly, or eptinezumab 100 mg IV every 3 months) → These shots or infusions are antibodies (proteins your immune system makes) designed to grab CGRP (calcitonin gene-related peptide) or its receptor before CGRP can amplify pain signals in the trigeminal nerve (the main nerve that carries face and head pain). This lowers how many migraines happen and how bad they get each month.
- Gepant (rimegepant 75 mg or ubrogepant 50–100 mg by mouth for acute migraine; atogepant 60 mg daily or rimegepant 75 mg every other day for prevention) → Gepants are small molecules (not antibodies) that block the CGRP receptor directly. They work like triptans but do not tighten blood vessels, so they are safe in people with heart disease or stroke history. For acute treatment, they stop pain and nausea. For prevention, they lower migraine frequency.
- Healthy habits: regular sleep schedule (same bedtime and wake time every day, 7–9 hours), drink 8 glasses of water daily, manage stress (deep breathing, exercise, cognitive behavioral therapy), avoid overusing pain medicine (no more than 2 days per week) → Regular sleep keeps your brain's serotonin and melatonin (the sleep hormone) balanced in the suprachiasmatic nucleus (the brain's clock) so electrical activity does not tip into migraine mode. Water keeps blood volume steady so vessels do not swell. Limiting pain medicine prevents medication overuse headache (rebound headache), where your brain gets used to the medicine and starts hurting when it wears off.

Medications

Ibuprofen (or naproxen) · NSAID (non-steroidal anti-inflammatory drug)

NSAIDs block an enzyme called cyclooxygenase (COX) that makes prostaglandins—chemicals that tell blood vessels to swell and nerves to shout pain louder. By turning down prostaglandin production, ibuprofen shrinks the throbbing inflammation around blood vessels in the

meninges (the brain's protective wrapping) and quiets the pain signals traveling up the trigeminal nerve (the main face-and-head pain highway).

1. You swallow the pill; it enters your bloodstream within 20–30 minutes.
2. The drug reaches inflamed blood vessels and nerve endings in the meninges.
3. It blocks COX enzymes, so fewer prostaglandins are made.
4. With less prostaglandin, blood vessels constrict slightly and nerve endings stop firing as many pain messages.
5. Pain fades over 30–60 minutes if the migraine is caught early (within the first hour or two of onset).

SAFETY WATCH

Can irritate the stomach lining and cause ulcers or bleeding, especially if taken daily or on an empty stomach; take with food. · Long-term or high-dose use can harm the kidneys or raise blood pressure. · Avoid if you have a history of stomach ulcers, kidney disease, heart failure, or allergic reactions to aspirin or NSAIDs. · Do not use more than 10 days per month—overuse triggers medication-overuse headache (rebound headaches that come back as soon as the medicine wears off).

Sumatriptan (or other triptans: rizatriptan, eletriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan) · Triptan (serotonin 5-HT_{1B/1D} receptor agonist)

Triptans turn on special serotonin docking sites—5-HT_{1B} receptors on blood vessels and 5-HT_{1D} receptors on trigeminal nerve endings. Flipping the 5-HT_{1B} switch causes swollen vessels in the meninges to narrow. Flipping the 5-HT_{1D} switch stops the nerve from releasing CGRP (calcitonin gene-related peptide, a powerful pain messenger that fans the flames of migraine). This directly interrupts the migraine cascade.

1. You take the pill, nasal spray, or injection; it reaches peak levels in 30 minutes to 2 hours (subcutaneous injection is fastest, around 10–15 minutes).
2. The drug travels to the meninges and binds to 5-HT_{1B} receptors on dilated blood vessels, causing them to constrict.
3. It also binds to 5-HT_{1D} receptors on trigeminal nerve endings, blocking release of CGRP and substance P.
4. With less CGRP and narrower vessels, the pain signal weakens and the throbbing stops.
5. Many people feel relief within 1–2 hours (sooner with nasal spray or injection).

SAFETY WATCH

Can cause temporary tightness in the chest, throat, neck, or jaw (usually harmless muscle tightness, not heart-related, but scary; stop and call your doctor if severe or accompanied by shortness of breath). · Should not be used if you have uncontrolled high blood pressure, coronary artery disease, history of heart attack or stroke, or peripheral vascular disease, because they constrict blood vessels. · Do not combine with ergotamines (e.g., dihydroergotamine) or use within 24 hours of another triptan (risk of prolonged blood vessel constriction). · Overuse (more than 10 days per month) causes medication-overuse headache. · Common mild side effects: tingling (paresthesia), dizziness, fatigue, warm or flushed feeling, drowsiness. · Rare but serious: serotonin syndrome if combined with SSRIs, SNRIs, or MAOIs (symptoms include agitation, confusion, rapid heart rate, muscle twitching, sweating, fever).

Ubrogepant or rimegepant · Gepant (CGRP receptor antagonist)

Gepants block the receptor (docking station) for CGRP on blood vessels and trigeminal nerves. CGRP is a powerful pain messenger released during a migraine; when it locks onto its receptor, it causes blood vessels to swell and nerves to shout pain signals. Gepants sit in that receptor and plug it, so CGRP cannot land. This stops the pain cascade without constricting blood vessels the way triptans do.

1. You swallow the orally disintegrating tablet or regular tablet; it is absorbed quickly (peak levels in 1-2 hours).
2. The drug circulates to the meninges and brainstem.
3. It sits on CGRP receptors, physically blocking CGRP molecules from attaching.
4. With CGRP locked out, blood vessels stay calmer and pain signals weaken.
5. Headache relief typically begins within 1-2 hours.

SAFETY WATCH

Generally well tolerated; main side effect is nausea (usually mild). · Avoid in severe liver disease (both drugs are metabolized by the liver). · Can be used safely in people with cardiovascular disease, high blood pressure, or previous stroke (unlike triptans, they do not constrict blood vessels). · Do not overuse (keep under 10 days per month to avoid medication-overuse headache). · Pregnancy category not fully established; discuss with your doctor.

Lasmiditan · Ditan (serotonin 5-HT_{1F} receptor agonist)

Lasmiditan activates a different serotonin switch—the 5-HT_{1F} receptor—found on trigeminal nerve endings and brainstem pain-relay neurons in the trigeminal nucleus caudalis. Turning on

this receptor calms the nerve, stopping it from firing pain signals. Unlike triptans, lasmiditan does not touch the 5-HT_{1B} receptors on blood vessels, so it does not cause vasoconstriction (narrowing), making it safe for people with heart disease.

1. You take the pill; it is absorbed within 1–2 hours.
2. The drug reaches trigeminal nerves and brainstem pain-relay centers.
3. It binds to 5-HT_{1F} receptors on pain neurons, dampening their excitability.
4. Pain signals weaken; the migraine fades over 1–2 hours.
5. No effect on blood vessels means no chest tightness or cardiovascular risk.

SAFETY WATCH

Causes dizziness, fatigue, and sedation (sleepiness) in many people—do not drive or operate machinery for at least 8 hours after taking it. · Avoid alcohol (increases drowsiness and dizziness). · Safe for people with heart disease, high blood pressure, or previous stroke (does not affect blood vessels). · Not a controlled substance, but the driving restriction limits its use for many people. · Rare: serotonin syndrome if combined with other serotonin drugs (SSRIs, SNRIs, MAOIs, triptans)—though risk is lower than with triptans.

Metoclopramide or prochlorperazine · Anti-nausea medicine (dopamine D₂ receptor antagonist and prokinetic agent)

These drugs block dopamine D₂ receptors in two key spots: the chemoreceptor trigger zone (the brain's vomit sensor, located in the area postrema of the brainstem) and the stomach wall. Blocking dopamine in the chemoreceptor trigger zone calms the nausea signal. Blocking dopamine in the stomach restores normal muscle squeezing (motility), which slows down during a migraine, so food and pills move along again. This helps oral migraine medicines get absorbed faster.

1. You take the pill, dissolving tablet, or injection (IV or intramuscular); it enters the bloodstream quickly.
2. The drug crosses into the brainstem and blocks dopamine D₂ receptors in the chemoreceptor trigger zone, turning off the nausea signal.
3. It also blocks dopamine receptors in the stomach wall, which speeds up gastric emptying (the stomach starts pushing food into the intestine again).
4. Nausea fades within 15–30 minutes (faster with IV).
5. The stomach begins moving food and pills again, so other migraine drugs (like triptans or NSAIDs) get absorbed and start working.

SAFETY WATCH

Can cause drowsiness and fatigue. · Can cause restlessness (akathisia—a jittery, uncomfortable feeling that you cannot sit still), especially within the first few hours. · Can cause involuntary muscle spasms (acute dystonia), especially of the face, neck, and tongue; happens more often in young people and women; treat with diphenhydramine (Benadryl) if it occurs. · Rare but serious: with long-term use (months to years), can cause tardive dyskinesia—permanent repetitive movements of the face, tongue, or limbs; risk increases with cumulative dose. · Metoclopramide carries a black-box FDA warning for tardive dyskinesia; use the lowest dose for the shortest time; prochlorperazine is often preferred for repeated use. · Avoid in people with Parkinson disease (worsens symptoms), bowel obstruction, or seizure disorder (lowers seizure threshold slightly).

Propranolol or metoprolol · Beta-blocker (β_1 and β_2 adrenergic receptor antagonist)

Beta-blockers block receptors for adrenaline (epinephrine) and noradrenaline (norepinephrine) on neurons in the brain and on blood vessels. This steadies the nervous system, reduces overexcitability in neurons in the cerebral cortex (which can trigger cortical spreading depression—the slow electrical wave that starts a migraine), and keeps blood vessels from dilating too easily. Over weeks, this raises the brain's threshold for migraine attacks, so they happen less often.

1. You take a daily pill (usually once or twice a day; extended-release forms are once daily).
2. The drug circulates continuously, blocking adrenaline and noradrenaline receptors throughout the body and brain.
3. Neurons in the cortex become less excitable, making the brain less likely to generate cortical spreading depression.
4. Blood vessels stay more stable—less prone to the dilation-and-inflammation cycle that drives migraine pain.
5. After 4–8 weeks of daily use, migraine frequency drops by about 50% in many people (some benefit seen as early as 2–4 weeks).

SAFETY WATCH

Can cause fatigue, cold hands and feet, dizziness (especially when standing up), and vivid dreams or nightmares. · Lowers heart rate and blood pressure—monitor both regularly; avoid if you have severe a slow heart rate (bradycardia) (slow heart rate below 50), heart block (electrical conduction problem in the heart), or very low blood pressure. · Avoid in people with asthma or severe chronic obstructive pulmonary disease (COPD)—beta-blockers can tighten airways (bronchospasm); metoprolol (more β_1 -selective) is safer than propranolol if a beta-blocker is necessary. · May mask symptoms of low blood sugar (hypoglycemia) in people with diabetes—check blood sugar more often. · Can cause or worsen depression in some people. · Do not stop suddenly—can cause rebound high blood pressure, rapid heart rate, or even angina (chest pain); taper off slowly under doctor supervision.

Topiramate · Anti-seizure medicine (broad-spectrum: enhances GABA activity, blocks voltage-gated sodium channels, antagonizes glutamate receptors, inhibits carbonic anhydrase)

Topiramate calms the brain's electrical activity in several ways at once: it boosts GABA (gamma-aminobutyric acid, the brain's main calming signal) by enhancing GABA-A receptors, blocks voltage-gated sodium channels (which neurons use to fire rapidly), blocks AMPA and kainate glutamate receptors (glutamate is the brain's main excitatory messenger), and weakly inhibits carbonic anhydrase (an enzyme). Together, these actions quiet overactive neurons in the cerebral cortex, making it much harder for cortical spreading depression (the electrical wave that starts a migraine) to ignite and spread.

1. You take a daily pill, starting at a low dose (usually 25 mg once or twice daily) and slowly increasing over 4–8 weeks to the target dose (50–100 mg twice daily for migraine prevention).
2. The drug builds up in your system and continuously modulates brain excitability.
3. GABA activity rises (more inhibition), sodium channel activity falls (less rapid firing), glutamate activity falls (less excitation).
4. The cortex becomes less prone to the electrical storm (cortical spreading depression) that launches a migraine.
5. After 1–2 months at the target dose, migraine frequency typically drops by 50% or more.

SAFETY WATCH

Common: tingling in fingers and toes (paresthesia), weight loss, loss of appetite, altered taste (especially carbonated drinks taste flat). · Cognitive side effects: word-finding trouble ('tip-of-the-tongue' moments), slowed thinking, memory problems, difficulty concentrating (patients sometimes call it 'dopamax'); these are dose-related and often improve if dose is lowered. · Rare but serious: kidney stones (topiramate reduces urinary citrate—drink plenty of water to dilute urine and lower risk), acute angle-closure glaucoma (sudden severe eye pain, blurred vision, red eye—stop drug immediately and see a doctor), metabolic acidosis (acid building up in the blood) (too much acid in the blood—can cause fatigue, rapid breathing; rare). · Can cause birth defects, especially cleft lip and cleft palate (Category D in pregnancy); avoid in pregnancy or use highly reliable birth control; discuss risks with your doctor. · Start low (25 mg/day), go slow (increase by 25 mg every 1–2 weeks) to minimize side effects and improve tolerability.

Amitriptyline · Tricyclic antidepressant (TCA)

Amitriptyline blocks the reuptake pumps (recycling machinery) for serotonin and norepinephrine on neurons in the brainstem, so these two brain messengers stay in the synapse (the gap between nerve cells) longer. More serotonin and norepinephrine in the periaqueductal gray, raphe nuclei, and locus coeruleus (brainstem pain-control centers) strengthens the brain's natural descending pain-modulation pathways—nerve highways that run from the brainstem down the spinal cord and tell pain-relay neurons to quiet down. Over time, this reduces how easily the trigeminal nucleus fires pain signals and lowers migraine frequency and intensity.

1. You take a daily pill at bedtime (it causes drowsiness, so nighttime dosing turns the side effect into a benefit).
2. The drug blocks serotonin and norepinephrine reuptake pumps, so these messengers stay in synapses longer.
3. Brainstem pain-control circuits (especially the periaqueductal gray and raphe nuclei) become more active, sending inhibitory signals down to pain-relay neurons in the trigeminal nucleus.
4. The trigeminal nucleus becomes less sensitive to incoming pain messages from the meninges.
5. After 4–6 weeks of daily use, migraine frequency and intensity drop.

SAFETY WATCH

Common: dry mouth, constipation, weight gain (increased appetite), drowsiness (take at bedtime), blurred vision (pupils dilate slightly), urinary hesitancy (harder to start urinating). · Can lower the seizure threshold slightly (use caution in people with epilepsy). · Rare but serious: heart rhythm changes (prolonged QT interval on EKG, which can lead to dangerous arrhythmias)—get a baseline EKG before starting if you have heart disease or a family history of sudden cardiac death. · Avoid in people with narrow-angle glaucoma (can raise eye pressure) or urinary retention (makes it worse). · Overdose is dangerous and can be fatal (affects heart rhythm and causes seizures); keep out of reach, especially if depression or suicidal thoughts are present. · Can cause orthostatic low blood pressure (hypotension) (dizziness when standing up due to blood pressure drop)—rise slowly from sitting or lying down. · May interact with other serotonin-boosting drugs (SSRIs, SNRIs, MAOIs, triptans)—risk of serotonin syndrome (confusion, agitation, rapid heart rate, muscle twitching, fever, sweating); use caution and monitor. · Anticholinergic effects (dry mouth, constipation, blurred vision, confusion) are worse in older adults—use lower doses or choose a different preventive.

OnabotulinumtoxinA (Botox) · Botulinum toxin type A (neuromuscular blocker and neuropeptide release inhibitor)

Botox blocks the release of acetylcholine (the chemical messenger that makes muscles contract) at neuromuscular junctions, relaxing chronically tight muscles in the head and neck. More importantly for migraine, it also blocks the release of CGRP (calcitonin gene-related peptide), substance P, and glutamate from peripheral trigeminal nerve endings in the skin and muscles of the head. By stopping these pain chemicals from reaching blood vessels in the meninges and the trigeminal nucleus in the brainstem, Botox interrupts the migraine pain pathway before it fully activates.

1. A trained doctor injects small amounts of Botox into 31–39 specific sites (5 units per site, total 155–195 units) across your forehead (frontalis muscle), temples (corrugator, procerus), back of the head (occipitalis), neck (trapezius, cervical paraspinal), and shoulders (trapezius).
2. The toxin enters nerve endings and cleaves SNAP-25 (a SNARE protein needed for vesicle fusion), so neurotransmitters and neuropeptides cannot be released.
3. Muscle tone drops; tight 'trigger points' (areas of muscle tension that can feed into migraine pain) relax.
4. Peripheral trigeminal nerves stop sending as much CGRP, substance P, and glutamate toward the meninges and brainstem.
5. Over 2–4 weeks, migraine frequency and severity decrease (some people notice benefit sooner, but peak effect is usually 4 weeks post-injection).

6. Effects last about 12 weeks; repeat injections every 3 months to maintain benefit.

SAFETY WATCH

Injection-site pain, bruising, or temporary neck stiffness or soreness (common and mild). · Rare: drooping eyelid (ptosis) or drooping eyebrow if toxin spreads from injection sites near the eyes (resolves on its own in 2–4 weeks as the toxin wears off). · Very rare: botulism-like symptoms if toxin spreads beyond injection sites (muscle weakness, trouble swallowing, trouble breathing, blurred or double vision)—seek emergency care immediately; more common with higher doses or off-label use. · Avoid if you are pregnant, breastfeeding, or have a neuromuscular disease (myasthenia gravis, Lambert-Eaton syndrome, ALS), because Botox can worsen muscle weakness. · Must be administered by a trained, certified provider (neurologist, headache specialist, or trained injector); improper technique or incorrect injection sites reduce effectiveness and increase risk of side effects. · Usually takes 2–3 treatment cycles (6–9 months) to see full benefit; do not stop after one round if response is partial.

Erenumab, fremanezumab, galcanezumab, or eptinezumab · CGRP monoclonal antibody (mAb)

These are lab-made antibodies—large Y-shaped proteins designed to hunt down and bind to either CGRP (the pain molecule itself) or the CGRP receptor (the docking station on cells). Erenumab binds the CGRP receptor and blocks it; fremanezumab, galcanezumab, and eptinezumab bind CGRP itself and trap it in the bloodstream. Either way, CGRP cannot activate pain pathways, dilate blood vessels in the meninges, or sensitize trigeminal nerves. Because these antibodies are large proteins, they stay in the bloodstream and tissue fluid for weeks, providing continuous CGRP blockade and preventing migraines before they start.

1. You inject the medicine under the skin (subcutaneous) once a month (erenumab 70 or 140 mg, galcanezumab 120 mg after a 240 mg loading dose, fremanezumab 225 mg monthly or 675 mg quarterly), or receive an IV infusion every 3 months (eptinezumab 100 or 300 mg).
2. The antibodies circulate in your blood and tissue fluid for weeks.
3. When CGRP is released from trigeminal nerves or other cells, the antibody binds it (or its receptor) immediately, stopping CGRP from causing blood vessel dilation, neurogenic inflammation, and pain signaling.
4. Blood vessels in the meninges stay calm; trigeminal nerves stay quiet; the threshold for migraine rises.
5. Over 1–3 months (some people respond within days, especially with eptinezumab IV; most see full effect by month 3), migraine days per month drop by 50% or more in about half of people; some have even greater reductions.

6. The antibody slowly breaks down (half-life is about 4 weeks); repeat injections or infusions maintain the effect.

SAFETY WATCH

Very well tolerated overall; most common side effect is injection-site reactions (redness, itching, swelling, bruising at the injection site). · Constipation, especially with erenumab (CGRP receptors are in the gut and help move stool along; blocking them can slow things down—drink water, eat fiber, use stool softener if needed). · Rare: high blood pressure (hypertension) (high blood pressure), especially with erenumab; monitor blood pressure, especially if you already have high blood pressure. · Rare: hypersensitivity reactions (rash, hives, swelling; very rare anaphylaxis—severe allergic reaction with trouble breathing and low blood pressure; if this happens, stop the drug and seek emergency care). · Long-term safety still being studied (drugs approved 2018–2020); so far, no major long-term risks have emerged in post-market surveillance. · Expensive (often \$575–700 per month wholesale; out-of-pocket cost varies by insurance); most insurers require documented failure of at least 2–3 other preventive medicines (e.g., beta-blocker, topiramate, amitriptyline) before approving. · Safe for people with cardiovascular disease, stroke history, or uncontrolled high blood pressure (hypertension) (unlike triptans, they do not constrict blood vessels). · Pregnancy and breastfeeding: limited data; these large proteins likely do not cross the placenta much in early pregnancy and probably enter breast milk in small amounts; discuss risks and benefits with your doctor.

Red flags

- Thunderclap headache (worst headache of your life, peaking in less than one minute)
- Headache with fever, stiff neck, confusion, or skin rash
- New headache after age 50, or a sudden change in your usual headache pattern
- Headache that gets worse with coughing, sneezing, straining, or lying down
- Headache plus weakness, vision loss, slurred speech, or trouble walking

Nursing priorities

1. Check blood pressure, temperature, and perform a quick neurologic exam (pupil size and reaction, arm strength, speech, neck stiffness) immediately — High blood pressure can cause with high blood pressure (hypertensive) emergency (dangerously high pressure damaging organs), fever with neck stiffness suggests meningitis, and abnormal pupils or weakness suggest stroke or brain bleed needing emergency care

2. Place the patient in a quiet, dark room and reduce noise, bright lights, and strong smells — Migraine causes light sensitivity (photophobia) (light sensitivity), sound sensitivity (phonophobia) (sound sensitivity), and osmophobia (smell sensitivity) because the trigeminal nerve (face and head nerve) becomes hyperexcitable, and reducing stimulation calms nerve firing
3. Give prescribed triptan medicine (sumatriptan, rizatriptan) or NSAID (naproxen, ibuprofen) as soon as possible when headache starts — Triptans work by narrowing swollen blood vessels and blocking pain signals in the trigeminal nerve; early treatment stops central sensitization (the brain amplifying pain signals) and prevents the headache from becoming severe
4. Administer anti-nausea medicine (metoclopramide, ondansetron) before or with the headache medicine, even if the patient is not vomiting yet — Migraine causes gastroparesis (slow stomach emptying) from autonomic nervous system changes, so oral medicine may not absorb well; anti-nausea medicine restarts stomach movement and prevents vomiting that worsens dehydration
5. Start an IV line and give normal saline fluids if the patient is vomiting or cannot drink — Dehydration worsens migraine pain by lowering blood volume and triggering more nerve sensitivity; IV fluids restore volume, help medicine work, and can reduce headache intensity
6. Ask about and document all headache medicines used in the past month, including over-the-counter pills and caffeine — Medication overuse headache develops when pain relievers are used more than 10 days per month, causing rebound pain from down-regulation (reduced response) of pain-control receptors in the brain
7. Teach the patient to track headache frequency, triggers, and medicine use in a headache diary or phone app — Pattern recognition helps identify modifiable triggers (sleep schedule, skipped meals, dehydration, hormonal changes) and determines if preventive daily medicine (propranolol, topiramate, CGRP antibody) is needed for chronic migraine (15 or more headache days per month)
8. Educate the patient that sudden vision changes, worst headache of life, fever with headache, or headache after head injury require immediate emergency care — These red-flag symptoms suggest life-threatening conditions (subarachnoid bleeding (hemorrhage), meningitis, subdural a pooled collection of blood (hematoma), stroke) that mimic migraine but need emergency CT scan, lumbar puncture (spinal fluid test), or neurosurgery, not outpatient migraine treatment

Sources

- American Headache Society
- American Academy of Neurology (AAN) 2021 migraine guideline

- CDC
- Cochrane

Last reviewed: 2026-07-07