

Peripheral Neuropathy

The long wires that carry messages from your brain to your toes and fingers are breaking down.

THE STORY IN ONE SENTENCE

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“Peripheral neuropathy: find what is hurting the nerve, stop it, and treat the symptoms while the nerve tries to heal.”

Normal anatomy — the body's job

Peripheral nerves are long cables that run from your spinal cord out to every muscle, patch of skin, and organ. Each nerve has a center wire called the axon (the part that carries the electrical signal), wrapped in a fatty insulation called myelin that speeds the message up to 100 times faster and protects it. Schwann cells build and repair the myelin. Tiny blood vessels feed the axon with oxygen and glucose. Sensory axons carry touch, pain, temperature, and position signals from your skin and joints back to the spinal cord. Motor axons carry command signals from the spinal cord out to muscles. Autonomic axons control blood pressure, heart rate, digestion, and sweating without you thinking about it.

BODY'S JOB

When the system works, you feel a pebble in your shoe instantly, know where your foot is in the dark, move your toes on command, and keep your blood pressure steady when you stand up. The myelin wrap lets signals zip along at up to 120 meters per second instead of crawling at 1 meter per second. The longest nerves — to your toes — can be over three feet long, so keeping them fed and insulated is hard work.

1. The dorsal root ganglion (a cluster of sensory nerve cell bodies next to the spinal cord) sends a long axon out to the skin of your big toe.
2. Schwann cells wrap the axon in myelin, segment by segment, like beads on a string.
3. Tiny blood vessels run alongside the nerve and deliver oxygen and glucose to the axon and Schwann cells.

4. Motor axons from the spinal cord run out to muscle fibers in your foot, carrying the 'contract now' signal.
5. Autonomic axons branch to blood vessels, sweat glands, and the gut, running the automatic systems.

What breaks

Peripheral neuropathy happens when either the axon itself is starving and dying (axonal neuropathy) or the myelin insulation is being stripped away (demyelinating neuropathy). The longest nerves fail first because they are hardest to feed and farthest from the cell body.

CLINICAL TERM

Axonal degeneration (the axon dies back from the tip toward the cell body) is caused by metabolic starvation — uncontrolled diabetes (high glucose damages the tiny blood vessels feeding the nerve), vitamin B12 deficiency (B12 is needed to build the axon skeleton), chronic alcohol use (alcohol is toxic to axons and depletes thiamine), chemotherapy drugs (especially platinum-based, taxanes, and vinca alkaloids that poison the axon transport system), or severe waste buildup in the blood (uremia) (waste products in kidney failure poison the nerve). Demyelinating neuropathies strip the myelin coat while the axon stays intact — Guillain-Barré syndrome (GBS, where the immune system attacks myelin after an infection), chronic inflammatory demyelinating polyneuropathy (CIDP, the chronic version of GBS), or hereditary neuropathies like Charcot-Marie-Tooth disease (faulty genes build defective myelin). Some conditions (diabetes, vasculitis) attack the nerve cell body itself or the blood vessels feeding the nerve. The longest axons — to the toes — fail first because they are over three feet from the cell body and need the most energy and building materials to stay alive.

How the body compensates

The body cannot fix a dying nerve quickly — axons regrow at only about 1 millimeter per day, so recovering sensation in a three-foot nerve from toe to spinal cord would take years if the axon fully died. In the meantime, the nervous system tries to cope by rerouting signals and triggering protective reflexes, but this compensation is limited and can mask how bad things really are until a sudden crash (like respiratory failure in GBS or a painless foot ulcer turning into gangrene in diabetic neuropathy).

1. {'step': 'Neighboring intact nerve fibers try to sprout new branches to re-supply the skin or muscle that lost its nerve.', 'why': 'This can restore some sensation or movement over months, but the new branches are thin and slow, and they cannot fully replace the original network.'}

2. {'step': 'The brain remaps sensation — areas of cortex that used to process signals from numb toes may start responding to input from the ankle or leg.', 'why': 'This helps you notice touch higher up the leg, but it does not restore fine sensation in the toes and can cause phantom tingling or pain.'}
3. {'step': 'You walk more carefully, watch your feet, and grip harder to compensate for lost position sense and weak muscles.', 'why': 'Conscious attention replaces automatic balance and strength, but it is exhausting, slow, and fails in the dark or when distracted — leading to falls.'}
4. {'step': 'Autonomic nerves try to maintain blood pressure by constricting blood vessels higher up when the leg vessels cannot respond.', 'why': 'This keeps you from fainting when you stand, but it is fragile; severe autonomic neuropathy causes dangerous drops in blood pressure (orthostatic low blood pressure (hypotension)) and fainting.'}
5. {'step': 'In demyelinating neuropathies, Schwann cells try to rebuild myelin around the axon, forming layers (remyelination).', 'why': 'This can restore some conduction speed and strength, but the new myelin is thinner and slower than the original; repeated cycles of damage and repair (as in CIDP) create thick onion-bulb layers that slow signals even more.'}
6. {'step': 'Pain signals fire randomly from damaged nerve fibers, creating burning or electric-shock sensations (neuropathic pain).', 'why': 'Bare or dying axons become hyperexcitable and misfire; the brain interprets this noise as pain, even though there is no injury to the skin — this is the nerve crying for help, not a useful compensation.'}
7. {'step': 'Watch for the crash point in Guillain-Barré syndrome: forced vital capacity (FVC, the amount of air you can blow out in one breath) dropping below 20 milliliters per kilogram, shallow breathing, or inability to cough.', 'why': 'GBS paralysis ascends and can hit the diaphragm (the main breathing muscle) within hours; falling FVC means get the patient to the ICU and prepare for intubation before they stop breathing, because once respiratory arrest happens, brain damage starts in minutes.'}
8. {'step': 'Watch for the crash point in diabetic neuropathy: a painless red spot or blister on the sole of the foot.', 'why': 'Numb feet do not feel injuries, so a small blister or cut goes unnoticed, gets infected, and can tunnel to bone (osteomyelitis) or turn gangrenous, requiring amputation; inspect feet daily and treat any wound immediately.'}
9. {'step': 'Stable exam today does not mean stable trajectory — a patient with GBS whose weakness has climbed from toes to knees in 24 hours is on a path to respiratory failure even if they look comfortable right now.', 'why': 'Progression speed predicts the crash; ascending paralysis moving more than one spinal segment per day means close ICU monitoring, because the compensation (accessory breathing muscles working harder) runs out suddenly when the diaphragm fails.'}

Domino effect

1. The longest sensory axons — from your toes to your spinal cord — start dying from the tip backward, because they are farthest from the cell body and hardest to feed. — Diabetic damage to tiny blood vessels, B12 deficiency, alcohol toxicity, or chemotherapy poison all nerves, but the three-foot nerve to your big toe needs the most oxygen and building materials, so it fails first while shorter nerves to your knee are still fine.
2. You lose sensation in both feet in a symmetric stocking pattern — numbness, tingling, or a dead feeling that starts at the toes and creeps up toward the knee over months to years. — The tips of the longest sensory axons die first, so the skin of the toes stops sending touch, pain, and temperature signals to the brain; as more axon dies back, the numb zone climbs higher, like a stocking being pulled on.
3. You lose proprioception (position sense) from your feet, so you cannot feel where your feet are unless you look at them. — Specialized sensory axons from joint and muscle receptors carry the 'where-am-I' map to the brain; when these die, the brain loses the map, and you walk like you are on a boat in the dark — unsteady, wide-based, and at high risk for falls.
4. Neuropathic pain starts — burning, stabbing, electric-shock, or pins-and-needles sensations in the feet and hands, often worse at night. — Dying or demyelinated axons become hyperexcitable and fire randomly; the brain interprets this electrical noise as intense pain even though nothing is touching the skin. Bare nerve endings sprout pain receptors (nociceptors) to try to detect danger, worsening the pain.
5. Motor axons to foot and ankle muscles die, causing weakness — foot drop (cannot lift the front of the foot), trouble standing on tiptoes, and a slapping gait. — Motor neurons in the spinal cord send long axons to command the tibialis anterior (lifts the foot) and gastrocnemius (points the foot down); when those motor axons die from the tip backward, muscles stop receiving signals, weaken, and shrink (atrophy).
6. Deep tendon reflexes disappear — tapping the Achilles tendon or patellar tendon produces no ankle jerk or knee jerk. — The reflex arc requires a sensory axon to carry the stretch signal from the muscle spindle to the spinal cord and a motor axon to carry the 'contract' signal back to the muscle; if either axon is dead or demyelinated, the loop is broken and the reflex is gone (areflexia).
7. If the neuropathy is severe or affects autonomic nerves, you may get orthostatic low blood pressure (hypotension) (blood pressure drops when you stand, causing dizziness or fainting), gastroparesis (stomach empties slowly, causing nausea and bloating), or loss of sweating in the feet. — Autonomic axons control blood vessel constriction, gut movement, and sweat glands; when they die, blood pools in the legs when you stand (causing fainting), the stomach does not push food into the intestines (causing nausea), and feet stop sweating (causing dry, cracked skin that is prone to infection).

8. In demyelinating neuropathies like Guillain-Barré syndrome, weakness ascends rapidly from legs to arms to face and breathing muscles over days. — Antibodies strip myelin from nerves throughout the body, blocking signals; the longest nerves (legs) fail first, then arms, then cranial nerves (causing double vision, trouble swallowing) and phrenic nerves to the diaphragm, leading to respiratory failure and death if not treated with IVIG or plasmapheresis in the ICU.
9. In diabetes, numb feet lead to unnoticed injuries — blisters from tight shoes, cuts from stepping on glass, burns from bath water — that become infected ulcers and can progress to gangrene and amputation. — Pain is the alarm that tells you to stop walking on a blister; when sensory axons are dead, the alarm is silent, so the blister ruptures, bacteria enter, and infection spreads to bone (osteomyelitis) before you notice, requiring surgical removal of dead tissue or amputation to save the leg.

Symptoms · what the patient feels, and why

- Tingling or burning in the hands and feet: The outer coating (myelin sheath) or the long wire part (axon) of the nerve is damaged, so the nerve sends mixed-up signals that the brain reads as tingling or burning even though nothing is actually hot or poking the skin.
- Numbness starting in the toes and fingers and slowly moving up: The longest nerves (the ones reaching the feet and hands) run out of fuel or get poisoned first, so they stop sending touch signals back to the brain. It creeps up because shorter nerves higher up the limb are healthier longer.
- Weakness in the feet or hands, such as trouble lifting the toes or gripping: The motor nerves (the wires that tell muscles to move) are damaged, so the signal from the brain doesn't reach the muscle strongly enough to make it contract.
- Sharp, shooting, or electric-shock pains: Damaged nerve fibers fire off spontaneous bursts of electricity like a frayed wire sparking, and the brain interprets those random bursts as sudden stabs of pain.
- Loss of balance or feeling unsteady when walking: The sensory nerves in the feet normally tell the brain where the ground is and how the body is positioned (proprioception). When those signals are lost, the brain can't adjust balance well, especially in the dark or on uneven ground.
- Extreme sensitivity to light touch (allodynia): Injured nerves can become hyperexcitable, meaning even a gentle touch (like bedsheets) is read by the damaged nerve as a much stronger, painful signal.
- Sudden weakness in one limb or on one side of the body: A single nerve or a group of nerves on one side is being squeezed, starved of blood (ischemia, not enough blood reaching the tissue to feed it), or inflamed, rather than the slow, even damage seen in metabolic causes like diabetes.

- Rapid worsening over days to weeks: Fast progression suggests an acute cause such as inflammation (like Guillain-Barré syndrome), infection, a toxin, or a blood vessel blockage, rather than the slow burn of chronic metabolic or vitamin problems.
- Trouble breathing, swallowing, or speaking: The nerves controlling the diaphragm (the main breathing muscle), throat, and vocal cords are being attacked or compressed, which can quickly become life-threatening.

Focused exam

- Numbness in toes and fingers that moves up the legs and arms in a stocking-and-glove pattern: This is the hallmark of peripheral neuropathy. The longest nerve fibers — the ones that stretch from the spine all the way down to the toes — are the farthest from their food supply in the spine, so they fail first. That is why numbness starts at the tips and creeps upward. If numbness is patchy or random instead, think about inflammation (like vasculitis) or a pinched nerve.
- Loss of vibration sense (tested with a tuning fork on the ankle bone) and position sense (the patient cannot tell if you move their big toe up or down): The large nerve fibers that carry vibration and position information are wrapped in thick myelin coats and need a lot of energy to stay alive. In peripheral neuropathy, they die before the pain fibers do. If the patient cannot feel the tuning fork buzz on their ankle, it tells you the axon is starving or the myelin coat is stripped off.
- Weak foot and ankle muscles, with calf muscles that are smaller and softer than normal: Motor nerve fibers (the ones that tell muscles to contract) follow the same starvation pattern as sensory fibers. Weakness starts at the feet and moves up. The muscles shrink because the nerve is not sending the 'stay strong' signal anymore. If weakness is only on one side or jumps around, think about a stroke or a pinched nerve root instead.
- Absent or very faint ankle reflexes (tested by tapping the Achilles tendon): The reflex arc is a loop: tap the tendon, the signal runs up the sensory nerve to the spinal cord, then down the motor nerve to make the calf muscle jerk. In peripheral neuropathy, the distal sensory and motor nerves are dead, so the signal never completes the loop. This is real nerve damage, not a brain problem.
- Falling or stumbling during walking, especially in the dark or with eyes closed (positive Romberg test): Position sense tells your brain where your feet are in space. When those nerves die, your brain loses the map. You can stay balanced only if you watch your feet — close your eyes and you fall. This is sensory loss of coordination (ataxia) (unsteady walking from lost feedback), not muscle weakness.

- Painless sores, ulcers, or blisters on the feet that the patient did not notice: Peripheral neuropathy kills pain nerves, so you cannot feel when your shoe is rubbing a blister or when you step on something sharp. In diabetes especially, these ulcers can get infected, spread to the bone (osteomyelitis), and lead to amputation. This is the single most dangerous consequence of neuropathy.

Diagnostics · every test answers a question

- Fasting blood glucose and hemoglobin A1c → Is high blood sugar starving the nerve fibers?
- Vitamin B12 level and methylmalonic acid (MMA) → Is the nerve starving for B12, which it needs to build myelin and keep the axon alive?
- Thyroid-stimulating hormone (TSH) → Is low thyroid hormone slowing down nerve metabolism?
- Comprehensive metabolic panel (CMP) with creatinine and estimated glomerular filtration rate (eGFR) → Are the kidneys failing and letting toxins build up in the blood?
- Serum protein electrophoresis (SPEP) and immunofixation → Is there a rogue antibody attacking the nerve, or a cancer making abnormal proteins?
- HIV antibody and viral load (if risk factors present) → Is HIV itself — or the drugs used to treat it — damaging the nerves?
- Nerve conduction study (NCS) and electromyography (EMG) → Is the problem in the axon (the wire) or the myelin (the insulation), and how severe is the damage?
- Red blood cell (Erythrocyte) sedimentation rate (ESR) and C-reactive protein (CRP) → Is inflammation attacking the blood vessels that feed the nerves?

Treatment logic

- Identify and treat the root cause: control blood sugar in diabetes (target A1c < 7%), replace vitamin B12 (1000 mcg intramuscular weekly for deficiency), stop alcohol, adjust or stop neurotoxic chemotherapy, treat hypothyroidism, or manage severe waste buildup in the blood (uremia) with dialysis → Stops the upstream break. If the axon is starving for glucose control or B12, fixing that halts the damage so nerves stop dying. If a toxin (alcohol, chemo drug, uremic waste) is poisoning the nerve, removing it stops further injury. This is the only intervention that can prevent progression.

- Duloxetine (30–60 mg daily) or gabapentin (300–3600 mg daily in divided doses) or pregabalin (150–300 mg daily in divided doses) for neuropathic pain → These drugs quiet the pain signals in the dorsal horn of the spinal cord and in the brain. Damaged nerves misfire and send pain messages even when nothing is hurting you. Duloxetine raises serotonin and norepinephrine (brain chemicals that turn down pain volume). Gabapentin and pregabalin block calcium channels on nerve endings so they stop firing randomly. This makes the burning, tingling, and stabbing pain feel less loud.
- Intravenous immunoglobulin (IVIG, 2 g/kg over 2–5 days) or plasmapheresis (plasma exchange, 5 sessions over 10–14 days) for acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) or chronic inflammatory demyelinating polyneuropathy (CIDP) → IVIG floods the bloodstream with normal antibodies that distract and block the rogue antibodies attacking myelin. Plasmapheresis physically filters out the bad antibodies from the blood. Both stop the immune attack on the myelin coat so the nerve signal highway stays intact. This prevents paralysis and can reverse weakness if started early (within 2 weeks of symptom onset for Guillain-Barré).
- Daily foot inspection, properly fitted shoes, fall prevention (remove rugs, use a cane or walker, install grab bars), balance training, and physical therapy to keep muscles strong → Prevents the catastrophic complications of neuropathy: foot ulcers, infections, amputations, and fractures from falls. Physical therapy teaches you to use vision and upper-body strength to compensate for lost position sense and keeps leg muscles from shrinking even when the nerve signal is weak.
- Topical lidocaine 5% patches or capsaicin 8% patches applied to painful skin areas → Lidocaine numbs the nerve endings in the skin so pain signals from that spot stop reaching the brain. Capsaicin (the chemical in hot peppers) exhausts substance P (the pain messenger stored in nerve endings) so the nerve runs out of ammunition to send pain signals. Both work only on the skin surface where you apply them.

Medications

Gabapentin (Neurontin) · Anticonvulsant (nerve-calming medicine originally made to stop seizures)

Gabapentin quiets pain signals traveling up damaged nerves by blocking voltage-gated calcium channels (gates on nerve endings that normally let calcium rush in and fire off pain messages). When these gates stay more closed, the nerve can't shout 'pain!' as loudly, even though the nerve itself is still damaged.

1. Gabapentin locks onto the alpha-2-delta subunit (a docking spot) on voltage-gated calcium channels at nerve terminals.
2. This binding makes it harder for calcium to rush into the nerve when it tries to fire.

3. With less calcium inside, the nerve releases fewer excitatory neurotransmitters like glutamate (the brain's main 'go!' signal).
4. Fewer pain signals climb the spinal cord to the brain, so the burning, shooting, or electric sensations quiet down.
5. The drug does NOT repair the axon, regrow myelin, or fix whatever originally hurt the nerve—it only turns down the volume on the pain alarm.

SAFETY WATCH

Dizziness and drowsiness are very common, especially in the first few weeks; do not drive or climb ladders until you know how it affects you. · Can cause swelling in the ankles and legs (peripheral swelling (edema)). · Rarely triggers mood changes—some people feel more anxious, sad, or have suicidal thoughts; tell your doctor right away if your mood shifts. · Stopping suddenly after weeks of use can trigger withdrawal (anxiety, sweating, trouble sleeping); taper the dose slowly under your doctor's guidance. · Kidney dose adjustment required—if your kidneys are weak, the drug builds up and raises the risk of side effects; your doctor will lower the dose based on creatinine clearance.

Pregabalin (Lyrica) · Anticonvulsant (nerve-calming medicine, chemically similar to gabapentin but stronger)

Pregabalin works almost identically to gabapentin—it binds to the same alpha-2-delta calcium-channel subunit on nerve terminals and blocks calcium from rushing in. This quiets the release of pain neurotransmitters. Pregabalin is absorbed more predictably and reaches steady levels faster, so it often works at lower doses.

1. Pregabalin binds tightly to the alpha-2-delta subunit on voltage-gated calcium channels at nerve endings.
2. Calcium entry into the nerve terminal drops.
3. Less calcium means the nerve releases less glutamate and substance P (two chemicals that shout 'pain!' to the next nerve in line).
4. Fewer pain messages reach the brain, so burning, stabbing, and tingling sensations ease.
5. The underlying nerve damage—whether from diabetes, chemotherapy, or another cause—remains; pregabalin only dials down the pain alarm, it does not repair the nerve.

SAFETY WATCH

Dizziness, drowsiness, and trouble with balance are common, especially in the first two weeks; avoid driving or operating heavy machinery until you adjust. · Can cause weight gain and swelling in the hands, feet, or ankles. · Rarely triggers blurry vision or trouble focusing. · Mood changes—anxiety, depression, or suicidal thoughts—can occur; report any mood shift to your doctor immediately. · Stopping abruptly can cause withdrawal (sweating, headache, nausea, trouble sleeping); taper slowly under supervision. · Kidney dose adjustment required—pregabalin is cleared by the kidneys; reduced doses are necessary if creatinine clearance is low. · Controlled substance (Schedule V in the U.S.)—small risk of misuse or dependence, especially in people with a history of substance use disorder.

Duloxetine (Cymbalta) · Serotonin-norepinephrine reuptake inhibitor (SNRI—an antidepressant that also calms nerve pain)

Duloxetine blocks the brain and spinal cord from sucking serotonin and norepinephrine (two chemical messengers) back into nerve cells after they're released. When these messengers stay in the gaps between nerves longer, they strengthen the body's natural pain-dampening pathways that run from the brainstem down the spinal cord, turning down the volume on pain signals climbing up from damaged peripheral nerves.

1. Duloxetine blocks the serotonin transporter (SERT) and norepinephrine transporter (NET)—these are pumps that normally vacuum serotonin and norepinephrine back into the nerve that released them.
2. With the pumps blocked, serotonin and norepinephrine linger longer in the synapse.
3. Higher levels of these messengers activate descending inhibitory pathways from the brainstem (especially the periaqueductal gray and rostral ventromedial medulla) that project down the spinal cord.
4. These pathways release more serotonin and norepinephrine at the dorsal horn (the spinal relay station), which suppresses the forward transmission of pain signals.
5. Peripheral pain messages—burning, tingling, shooting—are filtered out more effectively before they reach the brain.
6. The drug does NOT repair the damaged nerve or reverse the neuropathy; it only strengthens the brain's own pain-dampening system.

SAFETY WATCH

Nausea is very common in the first one to two weeks; taking it with food can help. · Can cause dry mouth, constipation, drowsiness, or trouble sleeping. · May raise blood pressure slightly; monitor BP, especially if you already have high blood pressure (hypertension). · Rarely triggers liver enzyme elevation; your doctor may check liver function tests, especially if you drink alcohol or have liver disease. · Do NOT stop suddenly—abrupt discontinuation causes withdrawal (dizziness, electric-shock sensations, nausea, irritability); taper slowly over weeks. · Serotonin syndrome risk if combined with other serotonergic drugs (SSRIs, MAOIs, tramadol, triptans)—watch for confusion, rapid heart rate, muscle rigidity, fever, sweating; seek emergency care if these appear. · Black-box warning (FDA): may increase suicidal thoughts or behavior in children, adolescents, and young adults under 25, especially in the first few months; all patients should be monitored closely for mood changes.

Amitriptyline (Elavil) · Tricyclic antidepressant (TCA—an older antidepressant that is also a strong nerve-pain reliever)

Amitriptyline blocks the reuptake of serotonin and norepinephrine (just like duloxetine, but less selectively), boosting the brain's descending pain-control pathways. It also blocks sodium channels on nerve membranes, which directly quiets overactive pain-signaling nerves. Finally, it has anticholinergic effects (blocks acetylcholine receptors), which contribute to side effects but may add a small pain-dampening effect.

1. Amitriptyline blocks the serotonin and norepinephrine transporters, raising levels of these messengers in brain and spinal-cord synapses.
2. Higher serotonin and norepinephrine strengthen the descending inhibitory pathways that dampen pain transmission in the dorsal horn of the spinal cord.
3. The drug also blocks voltage-gated sodium channels on nerve membranes, making it harder for damaged nerves to fire repetitive pain signals (similar to how local anesthetics work).
4. These combined actions reduce the intensity of burning, stabbing, and shooting neuropathic pain.
5. Amitriptyline does NOT repair the nerve or reverse the underlying neuropathy; it only turns down the pain alarm.

SAFETY WATCH

Anticholinergic side effects are very common: dry mouth, blurry vision, constipation, urinary retention, confusion (especially in older adults)—use the lowest effective dose and monitor closely. · Sedation and drowsiness—usually taken at bedtime; do not drive or operate machinery the next morning if you feel groggy. · Can cause weight gain. · Lowers the seizure threshold slightly—use cautiously in people with epilepsy. · Cardiac effects: can prolong the QTc interval (a heart-rhythm measurement on EKG) and cause arrhythmias; avoid in patients with recent heart attack, heart block, or QTc prolongation; baseline EKG recommended in older adults or those with heart disease. · Orthostatic low blood pressure (hypotension) (dizziness when standing up quickly) is common; rise slowly from sitting or lying down. · Do NOT stop suddenly—taper slowly to avoid withdrawal (nausea, headache, a run-down, unwell feeling (malaise)). · Black-box warning (FDA): may increase suicidal thoughts or behavior in children, adolescents, and young adults under 25; monitor mood closely, especially in the first weeks. · Overdose is dangerous—tricyclics are toxic to the heart and brain in overdose; keep pills secure and out of reach of children.

Intravenous immunoglobulin (IVIG) · Immunomodulatory therapy (pooled human antibodies given through a vein to calm the immune system)

IVIG delivers a concentrated mixture of antibodies collected from thousands of healthy donors. These antibodies flood the immune system and shift it away from attacking the body's own myelin (the insulating coat around nerves). The exact mechanism is not fully understood, but IVIG blocks harmful autoantibodies, saturates Fc receptors on immune cells (so they can't latch onto myelin as easily), and releases anti-inflammatory signals that quiet the immune attack. Over weeks to months, this allows the myelin sheath to stop being stripped away and—in some cases—begin to repair.

1. IVIG is infused into a vein and spreads throughout the bloodstream.
2. The donor antibodies bind to and neutralize pathogenic autoantibodies (the rogue antibodies attacking myelin or nerve components).
3. IVIG saturates Fc receptors on immune cells, blocking these cells from binding to antibody-coated myelin and stripping it away.
4. The infusion delivers anti-inflammatory cytokines and other immune-modulating signals that calm overactive T cells and B cells.
5. With the immune attack dampened, demyelination (myelin stripping) slows or stops.
6. In Guillain-Barré syndrome (GBS), this halts the acute paralysis and allows recovery to begin; in chronic inflammatory demyelinating polyneuropathy (CIDP), it stabilizes or improves chronic weakness and numbness.

7. IVIG does NOT work for neuropathies caused by metabolic injury (diabetes, B12 deficiency, alcohol, chemotherapy)—it only helps immune-mediated demyelinating neuropathies.

SAFETY WATCH

Infusion reactions are common: headache, chills, fever, nausea, muscle aches during or within hours of the infusion—slow the rate and premedicate with acetaminophen or antihistamines to reduce these. · Aseptic meningitis (sterile inflammation of the brain lining) can occur, causing severe headache, stiff neck, and fever 6–24 hours after infusion; usually resolves on its own but may require supportive care. · Thrombotic events (blood clots—stroke, heart attack, a clot in a deep leg vein (deep vein thrombosis), pulmonary embolism (a clot lodging in a lung artery)) are rare but serious, especially in older adults, people with clotting disorders, or those with cardiovascular disease; use the lowest effective dose and infuse slowly. · Acute kidney injury can occur, especially with sucrose-containing IVIG products or in patients with preexisting kidney disease or diabetes; monitor creatinine and urine output; ensure adequate hydration. · Red blood cell destruction (Hemolysis) (red blood cell breakdown) can happen if the IVIG contains antibodies against your blood type; watch for dark urine, fatigue, or yellowing of the skin and eyes (jaundice); check hematocrit and LDH before and after infusion. · Transfusion-related acute lung injury (TRALI)—rare but life-threatening—causes sudden shortness of breath and low oxygen during or within 6 hours of infusion; stop the infusion immediately and provide respiratory support. · Allergic reactions, including anaphylaxis (severe allergic shock), are rare; patients with IgA deficiency are at higher risk; check IgA level before first infusion if the patient has a history of anaphylaxis to blood products. · Infectious risk is extremely low (IVIG is screened and treated to inactivate viruses), but transmission of blood-borne pathogens is theoretically possible.

Plasmapheresis (Plasma exchange, PLEX) · Extracorporeal immunomodulation (a procedure, not a drug—blood is removed, filtered to take out harmful antibodies, and returned)

Plasmapheresis physically removes the liquid part of your blood (plasma), which contains the autoantibodies and inflammatory proteins attacking your nerves. The red and white blood cells are separated out, mixed with clean donor plasma or albumin (a replacement fluid), and pumped back into your body. Each session removes roughly 60–70% of circulating autoantibodies; after 5–6 sessions over 10–14 days, the level of harmful antibodies drops enough to stop or slow the immune assault on myelin, allowing the nerves to begin recovering.

1. Blood is drawn from a large vein (usually in the arm or through a central line).
2. A cell separator (apheresis machine) spins or filters the blood to separate plasma (the liquid carrying antibodies and clotting factors) from red cells, white cells, and platelets.

3. The plasma—along with the pathogenic autoantibodies and inflammatory proteins—is discarded.
4. The cells are mixed with replacement fluid (donor plasma, albumin, or saline) and returned to your body.
5. Each session removes a significant fraction of circulating autoantibodies, complement proteins, and cytokines fueling the immune attack.
6. After several sessions, the concentration of these harmful molecules drops low enough that demyelination slows or stops.
7. In Guillain-Barré syndrome (GBS), this halts the acute paralysis and speeds recovery; in chronic inflammatory demyelinating polyneuropathy (CIDP) or other antibody-mediated neuropathies, it stabilizes or improves symptoms.
8. Plasmapheresis does NOT repair dead axons, reverse long-standing damage, or treat metabolic, toxic, or hereditary neuropathies—it only works when circulating autoantibodies or immune complexes are driving the nerve injury.

SAFETY WATCH

Vascular access complications—requires large-bore IV or central venous catheter; risk of bleeding, infection, or clot at the catheter site. · Low calcium (Hypocalcemia) (low calcium)—citrate (an anticoagulant used during the procedure) binds calcium; causes tingling around the mouth, muscle cramps, or rarely tetany (muscle spasms); calcium is given orally or IV during or after the session. · Low blood pressure (Hypotension) (low blood pressure) during the procedure—especially if too much fluid is removed at once; managed by slowing the exchange and giving IV saline. · Infection risk—any time blood leaves and re-enters the body, there is a small risk of bacterial contamination; strict sterile technique is essential. · Depletion of clotting factors and immunoglobulins—plasma contains albumin, clotting factors, and antibodies; replacing with albumin alone can leave you temporarily more prone to bleeding or infection; fresh frozen plasma is sometimes used to replace clotting factors. · Allergic reactions to replacement fluids (donor plasma or albumin) are rare but possible. · Not suitable for patients with severe heart failure or very low blood pressure—removing and replacing large volumes of fluid can destabilize the cardiovascular system.

Capsaicin 8% patch (Qutenza) or 0.025-0.075% cream · Topical analgesic (a cream or patch made from chili peppers that numbs nerve endings in the skin)

Capsaicin is the chemical that makes chili peppers hot. When applied to the skin, it binds to TRPV1 receptors (heat and pain sensors) on the tiny nerve endings in the skin. At first, this causes a burning sensation as the nerves fire intensely. But with repeated or high-dose exposure (as with the 8% patch), the nerve endings become exhausted—they release all their

substance P (a pain chemical) and then go quiet for weeks to months. This creates a localized numbing effect, reducing burning, stabbing, or tingling pain in that one spot.

1. Capsaicin penetrates the skin and binds to TRPV1 (transient receptor potential vanilloid 1) channels on nerve terminals.
2. TRPV1 channels open, allowing calcium to flood into the nerve ending.
3. The nerve fires rapidly, releasing substance P and CGRP (calcitonin gene-related peptide)—chemicals that signal pain and inflammation.
4. This causes an initial intense burning or stinging sensation (which is why the first application can be uncomfortable).
5. With continued exposure (low-dose cream) or one high-dose application (8% patch), the nerve endings deplete their substance P and become desensitized (they stop responding to pain signals).
6. The numbed nerve endings can no longer send pain messages to the spinal cord, so localized burning, shooting, or tingling pain fades for weeks to months.
7. Capsaicin does NOT repair the underlying nerve damage or reverse neuropathy; it only silences the pain alarm in the treated area.

SAFETY WATCH

Burning, stinging, or intense warmth at the application site is expected, especially in the first few minutes to hours; this usually fades but can be distressing. · Wash hands thoroughly after applying cream (or wear gloves)—accidental contact with eyes, mouth, or mucous membranes causes severe burning. · Do NOT apply to broken, irritated, or recently shaved skin—this intensifies burning and can cause blistering. · The 8% patch is applied only by a healthcare provider (requires local anesthetic pretreatment and careful monitoring); do not apply at home. · Rare systemic effects if large areas are covered or if you use too much: elevated blood pressure, rapid heart rate—use only the recommended amount and area. · Not recommended during pregnancy or breastfeeding—safety data are limited.

Lidocaine 5% patch (Lidoderm) · Topical local anesthetic (a sticky patch that numbs nerve endings in the skin)

Lidocaine is a local anesthetic that blocks sodium channels on nerve membranes. When applied to the skin as a patch, it soaks into the top layers and prevents the small pain-sensing nerve endings (C-fibers and A-delta fibers) from firing. Sodium channels are the gates that let sodium rush into a nerve cell to create an electrical pain signal; when lidocaine locks these gates shut,

the nerve can't send pain messages to the spinal cord. The effect is localized to the patch area and lasts as long as the patch is on (up to 12 hours per day).

1. Lidocaine is released from the adhesive patch and penetrates the skin.
2. It diffuses into the membranes of small nerve endings (C-fibers and A-delta fibers) that sense pain and temperature.
3. Lidocaine binds to the inside of voltage-gated sodium channels, locking them in an inactive (closed) state.
4. With sodium channels blocked, the nerve cannot generate an action potential (the electrical spike that carries a pain signal).
5. Pain signals—burning, stabbing, tingling—are silenced in the patch area.
6. The effect is purely local; the patch does NOT numb pain elsewhere in the body, heal the nerve, or reverse neuropathy.

SAFETY WATCH

Skin irritation, redness, or rash at the patch site can occur; rotate patch location each day and give the skin a break. · Do NOT apply to broken, infected, or severely inflamed skin. · Do NOT use more than 3 patches at once or wear them longer than 12 hours in 24 hours—excessive use can raise blood lidocaine levels and cause toxicity (dizziness, ringing in the ears, seizures, heart arrhythmias), though this is rare with proper use. · Allergic reactions to lidocaine or the adhesive are uncommon but possible—stop use if you develop hives, swelling, or trouble breathing. · Safe in pregnancy and breastfeeding when used as directed (minimal systemic absorption). · Keep patches out of reach of children and pets—ingestion or chewing a used patch can cause lidocaine poisoning.

Red flags

- Sudden weakness in one arm or leg, or weakness that affects only one side of the body
- Trouble breathing, swallowing, or talking
- Symptoms that get much worse over days to weeks instead of months to years
- Loss of bowel or bladder control
- Severe pain that does not respond to usual pain medicines

Nursing priorities

1. Assess respiratory effort, oxygen saturation, and ability to cough every four hours if patient has new or worsening weakness — GBS and CIDP (chronic inflammatory demyelinating polyneuropathy) can ascend to the phrenic nerve (nerve controlling the diaphragm). Fifteen to thirty percent of GBS patients need mechanical ventilation (breathing machine). Early detection of shallow breathing or falling vital capacity (lung volume) prevents respiratory arrest.
2. Inspect both feet daily for skin breaks, redness, blisters, or foreign objects; ensure patient or family demonstrates proper foot checks — Sensory loss means patients cannot feel cuts, pressure sores, or penetrating objects. Minor trauma becomes a portal for bacteria. Daily inspection catches early cellulitis (skin infection) or ulcers before they extend to bone or require amputation.
3. Implement fall precautions including non-skid footwear, bedside commode, call bell within reach, and physical therapy consult for gait training — Loss of proprioception (position sense) and muscle weakness impair balance. Peripheral neuropathy triples fall risk. Hip fractures and head injuries increase mortality in older adults. Strengthening exercises and assistive devices reduce falls by forty percent.
4. Administer duloxetine, gabapentin, or pregabalin as prescribed for neuropathic pain; assess pain using a numeric scale before and one hour after dosing — Damaged nerves fire spontaneously, creating burning or shooting pain that does not respond to NSAIDs (non-steroidal anti-inflammatory drugs) or opioids. Duloxetine (an SNRI, serotonin-norepinephrine reuptake inhibitor), gabapentin, and pregabalin modulate nerve signals in the dorsal horn (spinal cord pain center). Pain control improves sleep and function.
5. Monitor blood glucose before meals and at bedtime if patient has diabetes; report sustained readings above 180 mg/dL or HbA1c above seven percent to provider — Chronic high blood sugar (hyperglycemia) (high blood sugar) activates the polyol pathway (a metabolic route that makes sorbitol, a sugar alcohol, inside nerve cells). Sorbitol accumulation draws water into nerves and causes swelling, starving axons of oxygen. Keeping HbA1c below seven percent slows neuropathy progression by sixty percent over five years.
6. Teach patient to test water temperature with elbow before bathing and to never use heating pads or hot water bottles on numb areas — Loss of temperature sensation allows burns from water above 120 degrees Fahrenheit or direct heat. Burn wounds in neuropathic limbs heal slowly due to poor microvascular (small blood vessel) circulation, often leading to infection and tissue death (necrosis) (death).

7. Coordinate with pharmacy to review all current medications for neurotoxic agents; question orders for metronidazole courses longer than fourteen days or new fluoroquinolones — Medication-induced neuropathy is often reversible if the drug is stopped early. Cumulative doses of metronidazole above 42 grams or prolonged fluoroquinolone use cause irreversible axonal damage. Identifying culprit drugs and finding alternatives prevents permanent disability.
8. Ensure referral to physical and occupational therapy for ankle-foot orthotics fitting if patient has foot drop (inability to lift the front of the foot) — Foot drop from peroneal nerve (nerve controlling ankle lifting muscles) damage causes tripping and falls. An AFO (ankle-foot orthosis, a plastic brace) holds the foot at ninety degrees during swing phase of gait, preventing toe drag and improving walking speed and safety by fifty percent.

Sources

- American Academy of Neurology (AAN) neuropathy guideline 2021
- ADA Standards of Care in Diabetes 2024
- Cochrane systematic reviews on neuropathy
- NEJM clinical practice reviews

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