

Neurocognitive Disorders

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THE STORY IN ONE SENTENCE

In neurocognitive disorders, the team that spots early memory loss, asks one good screen question, and checks for reversible causes outperforms the team that assumes it's just old age.

“Neurocognitive disorders: when the brain loses its ability to remember, plan, or think clearly—because cells die, connections break, or chemistry goes wrong.”

Normal anatomy — the body's job

The brain runs on networks of nerve cells that talk through chemical messengers (neurotransmitters like acetylcholine, dopamine, and glutamate). The hippocampus (a seahorse-shaped part deep in the brain) files new memories, the prefrontal cortex (the front of the brain) handles planning and decisions, and the parietal and temporal lobes (sides and back) store words, faces, and skills. At rest you have reserve—extra connections—so losing a few cells doesn't show; under stress or as cells die off that cushion disappears and symptoms appear.

BODY'S JOB

Your brain's job is to take in the world (sight, sound, touch), make sense of it (recognize your daughter's face, understand her words), store it as memory, then use all that to plan and act (choose lunch, button a shirt, drive home). Neurotransmitters ferry signals: acetylcholine helps lock in memories, dopamine coordinates smooth movement and motivation, serotonin steadies mood, and glutamate excites cells to learn. When cells and messengers work, thinking feels automatic; when they fail, every step—memory, language, reasoning—becomes hard or impossible.

1. Information flows IN: your eyes see a grandchild's face, ears hear her voice, nose smells her perfume—sensory signals race to the back of the brain.

2. The brain RECOGNIZES: the temporal lobe matches the face to stored memories ('That's Emma'), the hippocampus time-stamps the moment ('She visited today'), and language areas in the left hemisphere decode her words.
3. The brain DECIDES and PLANS: the prefrontal cortex weighs options ('I'll hug her, then offer tea') and sequences the steps in order.
4. Signals flow OUT: motor cortex (the strip across the top of the brain) sends commands down the spinal cord to muscles, so you stand, smile, reach out, and speak her name.
5. Feedback ADJUSTS: as you move, the cerebellum (the mini-brain at the back) fine-tunes balance, and sensory nerves report 'Emma hugged back,' closing the loop so you know the plan worked.

What breaks

In neurocognitive disorders, brain cells die or their connections fray because plaques and tangles clog them (Alzheimer), tiny strokes cut off blood (vascular dementia), protein clumps jam the machinery (Lewy body or frontotemporal dementia), repeated head hits scar tissue (chronic traumatic encephalopathy), infections inflame and kill cells (HIV dementia, prion disease), or poisons and nutrient shortages starve cells (alcohol, B12 deficiency). The hippocampus shrinks so new memories never stick, the prefrontal cortex thins so planning falls apart, and neurotransmitter factories slow down—especially acetylcholine (the memory messenger) and dopamine (the movement and motivation messenger)—leaving the brain without enough signal to think, remember, or move smoothly.

CLINICAL TERM

Neurocognitive disorder is acquired, progressive decline in one or more cognitive domains (memory, executive function, language, visuospatial, social cognition) that interferes with independence, caused by Alzheimer pathology (amyloid- β plaques and tau tangles), cerebrovascular disease (ischemic or bleeding-driven (hemorrhagic) injury), Lewy body disease (α -synuclein aggregates), frontotemporal lobar degeneration (tau or TDP-43 inclusions), traumatic brain injury, Parkinson disease, HIV, prion disease, or reversible etiologies such as vitamin deficiency, hypothyroidism, medication toxicity, or normal-pressure hydrocephalus.

How the body compensates

At first the brain reroutes signals through surviving cells and you work harder—writing lists, asking people to repeat—to hide the gaps. As more cells die those workarounds max out,

symptoms break through, and the extra effort itself exhausts you and worsens confusion (like revving an engine low on oil).

1. {'what': 'The brain uses backup connections', 'why': 'Healthy neighboring neurons sprout extra branches and take over some jobs of dead cells—like coworkers covering a missing teammate—so early memory slips stay mild and you still function day to day.'}
2. {'what': 'You lean on external aids and routines', 'why': 'You write everything down, stick to the same daily path, and let family prompt you, offloading memory work from your failing hippocampus to paper, habit, and other people.'}
3. {'what': 'The brain recruits other regions', 'why': 'Scans show that in early dementia the right hemisphere or frontal areas light up during memory tasks they normally wouldn't do—the brain is jury-rigging a fix—but this costs mental energy and only buys months.'}
4. {'what': 'Compensation maxes out and symptoms explode', 'why': 'Once cell loss crosses roughly 30–40 percent in key areas, no amount of rerouting or effort can cover the deficit—you forget you already ate lunch, wander outside at night, or cannot recognize your spouse—and the struggle itself spikes stress hormones like cortisol (the body's main alarm chemical) that poison surviving neurons faster.'}
5. {'what': 'Late-stage: the brain gives up nonessential tasks', 'why': 'To conserve energy, higher functions (language, planning, recognizing faces) shut down and only the brainstem (the stalk that runs breathing and heartbeat) keeps working, leaving the person mute, bedbound, and needing total care.'}

Domino effect

1. Protein clumps or blood-flow loss kill the first wave of neurons — In Alzheimer disease, amyloid- β plaques stack up outside cells like sticky garbage and tau tangles twist inside, choking the cell until it dies; in vascular dementia, a clot or burst vessel starves a brain patch of oxygen (ischemia) and cells die within minutes—either way, the hippocampus and cortex start to thin.
2. Dying cells dump glutamate and calcium, exciting neighbors to death — Ruptured neurons spill glutamate (the brain's go-go messenger) into the space between cells; too much glutamate forces calcium flood-gates open in nearby neurons, and calcium overload is like revving an engine until it seizes—the cell burns out and dies, spreading the damage in a wave (excitotoxicity).
3. Inflammation roars as the brain's cleanup crew goes rogue — Microglia (the brain's resident immune cells, like tiny janitors) swarm to eat dead cells and plaques, but they get stuck in an angry on-mode, spraying inflammatory chemicals (cytokines like IL-1 and TNF- α) that poison healthy bystanders, widening the kill zone.

4. Neurotransmitter factories shut down, and circuits go silent — The nucleus basalis stops making acetylcholine, the substantia nigra stops making dopamine, and the raphe nuclei stop making serotonin—without these chemical couriers, the cortex, hippocampus, and basal ganglia lose their signals, so memory, movement, and mood all falter.
5. Brain volume shrinks and cerebrospinal fluid fills the empty space — As cortex and hippocampus waste away, the ventricles (fluid-filled caves inside the brain) balloon to fill the gap—visible on CT or MRI as widened dark spaces and shrunken folds—marking permanent, irreversible loss.
6. Behavior and personality shift as frontal and temporal lobes fail — The orbitofrontal cortex (underside of the front brain that reads social cues and taps the brakes on impulses) and anterior temporal lobes (that recognize faces and empathy) die off, so the person becomes disinhibited (says cruel things, shoplifts, eats trash), apathetic (sits all day, no interest), or paranoid (accuses family of theft) because the circuits that made them 'them' are gone.
7. Late cascade: breathing and swallowing centers falter, infections and starvation threaten — When degeneration reaches the brainstem (the stalk controlling automatic survival functions), swallowing becomes uncoordinated (dysphagia) so food goes into the lungs causing aspiration pneumonia (lung infection from inhaled food or spit), and eventually the medulla (the brainstem's bottom that runs heartbeat and breath) fails, leading to death from respiratory arrest or infection.
8. The final common path is immobility, total dependence, and multi-organ decline — Bedbound and mute, the person cannot shift weight so pressure sores (bedsores) open and infection (sepsis) spreads through the blood; muscles waste (sarcopenia), joints freeze (contractures), kidneys and heart weaken under the load, and the body shuts down system by system.

Symptoms · what the patient feels, and why

- Memory loss that disrupts daily life: The hippocampus (the brain's memory keeper, tucked deep in the middle of the brain) and the nearby areas that store and retrieve memories shrink or get damaged, so new information can't be filed away or old facts can't be pulled back up when you need them.
- Trouble planning or solving problems: The prefrontal cortex (the front of the brain that organizes your thoughts and plans your next steps) loses cells and connections, so tasks that need multiple steps—like following a recipe or balancing a checkbook—become confusing and slow.
- Confusion about time or place: Damage to the parietal lobes (the parts of the brain on the top and back that map where you are in space and time) and the hippocampus makes it hard to remember today's date, where you are right now, or how you got there.

- Difficulty understanding visual images or judging distance: The occipital lobes (the back of the brain that process what you see) and the parietal lobes that make sense of space get damaged, so reading, recognizing faces, or judging how far away a car is becomes hard—even though the eyes themselves still work fine.
- Problems with words in speaking or writing: The left temporal and frontal lobes (where the brain stores word meanings and builds sentences) lose neurons, so finding the right word, following a conversation, or calling things by their correct name becomes a struggle.
- Misplacing things and losing the ability to retrace steps: The hippocampus and prefrontal cortex can't hold onto the memory of where you put your keys or glasses a few minutes ago, and the reasoning circuits that would let you work backward to find them don't fire reliably anymore.
- Decreased or poor judgment: The prefrontal cortex—which weighs risks, plans ahead, and pumps the brakes on bad ideas—shrinks and loses dopamine (a brain messenger that helps with decision-making), so choices about money, safety, or social situations become reckless or odd.
- Withdrawal from work or social activities: As memory, language, and thinking skills slip, following a conversation or keeping up at a job feels overwhelming and embarrassing, so the person quietly pulls back to avoid situations that expose the gaps.
- Changes in mood or personality: Damage to the frontal lobes and the limbic system (the emotional center deep inside the brain) disrupts serotonin, dopamine, and norepinephrine (brain messengers that steady mood), and the person may become confused, suspicious, depressed, fearful, or easily upset—especially outside their comfort zone.
- Sudden worsening of confusion or inability to stay awake: An infection (like a urinary tract infection or pneumonia), a stroke, a medication side effect, or low blood sugar can push a fragile brain over the edge, causing delirium (a sudden, severe confusion) on top of the underlying dementia—and this is a medical emergency.

Focused exam

- Mental status check: alert, oriented to person/place/time/situation, follows commands, speaks clearly: This tells you if the brain's processing center—the cerebral cortex (the thinking layer)—is working normally or if confusion, delirium, or dementia is present. New confusion means something broke recently.
- Glasgow Coma Scale: eye opening (4 points), verbal response (5 points), motor response (6 points), total out of 15: A score of 8 or less means the brain is not protecting the airway and the person may need a breathing tube. A falling score over minutes to hours signals worsening swelling, bleeding, or infection.

- Cranial nerve exam: pupils equal, round, reactive to light; eyes track smoothly in all directions; face symmetric when smiling: One blown pupil (wide and fixed) or eyes that don't move together points to pressure on the brainstem (the alarm cable connecting the brain to the body) or a stroke. This tells you WHERE the problem is.
- Motor and sensory exam: strength 5 out of 5 in all limbs, sensation intact, reflexes symmetric: Weakness on one side of the body (hemiparesis) or loss of sensation (hemianesthesia) points to stroke, bleeding, or a mass pushing on the motor strip (the brain's movement control center). Asymmetry narrows the location.
- Gait and coordination: walks steadily, touches finger to nose smoothly, stands with feet together without swaying: Trouble walking or balance problems point to the cerebellum (the brain's balance computer at the back) or to the frontal lobes (the planning and movement centers). This separates cerebellar stroke from frontal dementia.
- Signs of increased intracranial pressure: headache, vomiting without nausea, Cushing triad (high blood pressure, slow heart rate, irregular breathing): The skull is a closed box. If swelling, bleeding, or a tumor takes up space, pressure rises and squeezes the brainstem—this is a true emergency that can stop breathing and cause death within minutes.

Diagnostics · every test answers a question

- Non-contrast head CT → Is there bleeding, a stroke, swelling, a mass, or a skull fracture causing the confusion or altered mental status?
- Basic metabolic panel (BMP): sodium, potassium, chloride, CO₂, BUN, creatinine, glucose → Is confusion caused by low or high blood sugar, kidney failure, or dangerously abnormal sodium?
- Complete blood count (CBC) with differential → Is there infection, anemia (low oxygen delivery to brain), or a blood cancer affecting the brain?
- Thyroid-stimulating hormone (TSH) and vitamin B₁₂ level → Is confusion from hypothyroidism (thyroid too low, brain slows down) or B₁₂ deficiency (nerves and brain cells can't repair)?
- Urinalysis and urine culture → Is a urinary tract infection (UTI) triggering delirium, especially in an older adult?
- Lumbar puncture (spinal tap) with CSF analysis: cell count, protein, glucose, Gram stain, culture → Is meningitis or encephalitis (brain infection) causing fever, headache, and confusion?
- Electroencephalogram (EEG) → Is confusion from ongoing seizures (status epilepticus), past seizures leaving the brain tired (postictal state), or abnormal brain waves from encephalitis or metabolic crisis?

- MRI brain with and without contrast (if CT normal but suspicion high) → Is there early stroke, small bleeds, inflammation, demyelination (loss of nerve insulation), or a tumor that CT missed?

Treatment logic

- Check airway, breathing, circulation (ABCs); give oxygen to keep $\text{SpO}_2 \geq 94\%$; place on cardiac monitor → The brain needs constant oxygen and glucose. Low oxygen (Hypoxia) (low oxygen) or low blood pressure (hypotension) (low blood pressure) kills brain cells within minutes. Oxygen and monitoring prevent secondary brain injury while you find the cause.
- Stat fingerstick glucose; if $< 60 \text{ mg/dL}$ give IV dextrose 25 g (one amp D50), then recheck in 15 minutes → Glucose is the brain's only fuel. Low blood sugar (Hypoglycemia) (low blood sugar) causes confusion, seizures, and coma within minutes. Dextrose reverses it instantly if given in time.
- If $\text{GCS} \leq 8$, focal neurologic deficit, or signs of increased ICP: elevate head of bed 30° , avoid neck flexion, give osmotic agent (mannitol 1 g/kg IV or 3% hypertonic saline 250 mL IV over 30 min), keep systolic BP 100–160 mmHg, aim PaCO_2 35–40 mmHg if intubated → Elevating the head helps venous blood drain out of the skull. Mannitol and hypertonic saline pull water out of swollen brain tissue (osmosis—water follows salt). This lowers pressure inside the skull and prevents the brainstem from getting squeezed (herniation), which stops breathing and causes death.
- If seizure witnessed or suspected: IV levetiracetam 1,500 mg load (or fosphenytoin 20 mg PE/kg if levetiracetam unavailable), protect airway, give oxygen, place on continuous EEG if available → Levetiracetam and fosphenytoin raise the threshold for neurons (brain cells) to fire. This stops the seizure cascade—repeated firing burns through oxygen and glucose, kills cells, and can lead to status epilepticus (a seizure that will not stop) (seizure lasting > 5 minutes or back-to-back seizures), which is deadly.
- If fever ($> 38^\circ\text{C}$ or 100.4°F) and concern for meningitis or encephalitis: blood cultures $\times 2$, then empiric IV antibiotics (ceftriaxone 2 g + vancomycin 15–20 mg/kg, add acyclovir 10 mg/kg if encephalitis possible) within 1 hour, then lumbar puncture after CT clears increased pressure → Bacterial meningitis kills within hours by inflaming the brain's protective layers and cutting off blood flow. Empiric antibiotics (given before culture results) cover the most common bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria*). Acyclovir stops herpes simplex virus from destroying the temporal lobes (memory and language centers).

- Correct metabolic derangements: if sodium < 120 mEq/L give 3% saline slowly (goal rise 4–6 mEq/L in 24 h, never faster to avoid osmotic demyelination); if sodium > 160 mEq/L give free water; replace thiamine 100 mg IV before dextrose if malnourished or alcohol use disorder → Severe low sodium (hyponatremia) (low sodium) causes brain swelling and seizures; slow correction prevents brain injury. High sodium (Hypernatremia) (high sodium) shrinks brain cells. Thiamine (vitamin B₁) is needed for glucose metabolism; without it, giving glucose can trigger Wernicke encephalopathy (bleeding in memory and balance centers).
- If delirium (acute confusion with fluctuating attention, agitation, hallucinations): treat underlying cause, stop or reduce offending medications (anticholinergics, benzodiazepines, opioids), reorient frequently, normalize sleep-wake cycle, mobilize early; use low-dose antipsychotic (haloperidol 0.5–1 mg IM or PO, or quetiapine 25 mg PO) only if agitation risks harm → Delirium is a symptom, not a disease. Fixing the trigger (infection, dehydration, medication, low oxygen (hypoxia)) reverses it. Reorientation and sleep hygiene calm the confused brain. Antipsychotics reduce dangerous agitation by blocking dopamine (a brain messenger that revs up movement and emotion) but do not cure delirium.

Medications

Donepezil (Aricept) · Cholinesterase inhibitor

Donepezil blocks an enzyme (a molecular scissor) called acetylcholinesterase that normally breaks down acetylcholine, a brain messenger that helps memory and thinking. By blocking that scissor, the drug lets more acetylcholine stick around in the spaces between brain cells, which can slightly slow the loss of memory and attention in Alzheimer disease.

1. Normally, brain cells release acetylcholine (the messenger) into the gap between cells to carry signals for memory and attention.
2. An enzyme called acetylcholinesterase sits in that gap and chops acetylcholine apart within milliseconds, ending the signal.
3. In Alzheimer disease, the cells that make acetylcholine die off, so there is already less messenger available.
4. Donepezil plugs the active site of acetylcholinesterase (like jamming the blades of the scissor), so the acetylcholine that is left lasts longer.
5. The extra time the messenger stays in the gap gives the next cell a better chance to catch the signal, which can modestly improve memory, attention, and daily function for a few months to a couple of years.

SAFETY WATCH

Nausea, vomiting, and diarrhea (because acetylcholine also controls gut muscles; taking the pill with food and starting at a low dose helps). · Vivid dreams or trouble sleeping (the drug can make dreams more intense; taking it in the morning instead of bedtime often fixes this). · Slow heart rate or heart block (acetylcholine slows the heart; tell the doctor right away if you feel dizzy, faint, or notice a very slow pulse). · Muscle cramps or tremor (extra acetylcholine can make muscles twitch). · Worsening of asthma, COPD, or peptic ulcer (acetylcholine can tighten airways and increase stomach acid; use with caution if you have these conditions). · Increased risk of falls due to dizziness or muscle weakness.

Rivastigmine (Exelon) · Cholinesterase inhibitor

Rivastigmine blocks two molecular scissors—acetylcholinesterase and butyrylcholinesterase—that break down acetylcholine, the brain messenger for memory and thinking. By jamming both scissors, the drug raises acetylcholine levels in the gaps between brain cells, which can modestly slow memory loss in Alzheimer disease and dementia with Lewy bodies.

1. Brain cells release acetylcholine into the gap to carry memory and attention signals.
2. Two enzymes—acetylcholinesterase (the fast scissor) and butyrylcholinesterase (a backup scissor)—chop acetylcholine apart and end the signal.
3. In dementia, acetylcholine-making cells die off, so less messenger is available; at the same time, butyrylcholinesterase activity rises.
4. Rivastigmine binds tightly to both scissors and puts them out of action for hours.
5. The acetylcholine that remains in the gap lasts longer, giving brain cells more time to catch the signal and improving memory and daily function for a limited period.

SAFETY WATCH

Nausea, vomiting, loss of appetite, and weight loss (common, especially with pills; the skin patch causes less stomach upset). · Diarrhea and stomach cramps (acetylcholine revs up gut muscles). · Dizziness and weakness, raising fall risk. · Slow heart rate or fainting (acetylcholine slows the heart; report any chest pain, severe dizziness, or very slow pulse immediately). · Worsening of asthma, COPD, or stomach ulcers (acetylcholine tightens airways and boosts stomach acid). · Skin irritation if using the patch (rotate the patch site daily and avoid the same spot for 14 days). · Tremor or muscle twitching.

Galantamine (Razadyne) · Cholinesterase inhibitor with nicotinic receptor modulation

Galantamine blocks the enzyme acetylcholinesterase (the molecular scissor that chops up acetylcholine, a memory messenger) and also gives a boost to nicotinic receptors (the docking

ports on brain cells that catch acetylcholine). This double action raises acetylcholine levels and makes the remaining receptors work better, which can modestly slow memory and thinking decline in Alzheimer disease.

1. Brain cells release acetylcholine to carry memory signals across the gap to the next cell.
2. Acetylcholinesterase normally breaks acetylcholine apart within milliseconds, ending the signal.
3. In Alzheimer disease, fewer cells make acetylcholine, and many receptors are damaged or lost.
4. Galantamine plugs the active site of acetylcholinesterase, so the messenger lasts longer in the gap.
5. At the same time, galantamine binds to nicotinic receptors and makes them more sensitive (like turning up the volume), so the acetylcholine that is there works better.
6. Together, these actions improve the strength and duration of memory signals, slowing decline for a limited time.

SAFETY WATCH

Nausea, vomiting, diarrhea, and loss of appetite (take with food and start at a low dose to ease stomach upset). · Dizziness and headache. · Weight loss (monitor weight regularly). · Slow heart rate or heart block (acetylcholine slows the heart; call the doctor if you feel faint, have chest pain, or notice a very slow pulse). · Worsening of asthma, COPD, or peptic ulcer (acetylcholine tightens airways and increases stomach acid). · Increased fall risk due to dizziness or muscle weakness. · Severe skin reactions (rare but serious; stop the drug and get help if a rash with blisters or peeling appears).

Memantine (Namenda) · NMDA receptor antagonist

Memantine blocks NMDA receptors (docking gates on brain cells that let calcium rush in when glutamate, an excitatory messenger, arrives). In Alzheimer disease, these gates get stuck partly open, letting too much calcium leak in all the time, which poisons and kills the cell. Memantine plugs the gate just enough to stop the toxic leak but still lets normal bursts of calcium through when a real signal arrives, protecting cells from slow death while preserving learning.

1. Glutamate is the brain's main 'go' messenger; it docks onto NMDA receptors and opens a gate that lets calcium ions flood into the cell.
2. A quick calcium burst is normal and needed for memory formation, but the gate is supposed to close right after.
3. In Alzheimer disease, plaques and tangles cause a constant low-level release of glutamate, keeping NMDA receptors partly open all the time.

4. The constant calcium leak overloads the cell's cleanup systems and triggers a death program (excitotoxicity).
5. Memantine sits in the NMDA receptor channel and blocks it when glutamate levels are abnormally high or steady.
6. When a real learning signal arrives (a strong, brief glutamate burst), memantine pops out of the way, letting the gate open normally.
7. This selective block stops the toxic leak without interfering with real memory signals, slowing cell death and preserving function.

SAFETY WATCH

Dizziness and headache (common, especially in the first few weeks). · Confusion or worsening agitation (rare; the drug usually calms, but in some people it can increase restlessness—report this right away). · Constipation (memantine can slow the gut; drink plenty of water and stay active). · High blood pressure (check blood pressure regularly). · Hallucinations or unusual thoughts (uncommon but possible; tell the doctor if you see or hear things that are not there). · Use with caution if kidney function is low (the drug is cleared by the kidneys; dose may need adjustment).

Aducanumab (Aduhelm) · Monoclonal antibody targeting amyloid-beta

Aducanumab is a laboratory-made antibody (a protein that tags enemies for cleanup) designed to stick to clumps of amyloid-beta protein (the sticky plaques that build up in Alzheimer disease). Once tagged, the brain's immune cells (microglia) recognize the antibody flag and sweep the plaques away. Clearing plaques may slow the underlying disease process, though the clinical benefit remains uncertain and the drug is highly controversial.

1. In Alzheimer disease, the protein amyloid-beta misfolds and clumps together into sticky plaques between brain cells.
2. Plaques trigger inflammation and damage nearby neurons, contributing to memory loss and cognitive decline.
3. Aducanumab is given as an intravenous infusion (into a vein) every four weeks.
4. The antibody travels into the brain and binds tightly to aggregated (clumped) amyloid-beta.
5. Microglia recognize the antibody tag on the plaque and move in to engulf and break down the amyloid.
6. Over months, imaging shows that plaques shrink, though whether this translates into meaningful slowing of memory loss is still debated.

SAFETY WATCH

ARIA (amyloid-related imaging abnormalities): brain swelling or microbleeds seen on MRI, which can cause headache, confusion, vision changes, or (rarely) seizures. MRI monitoring is required before and during treatment. · Infusion reactions: fever, chills, flushing, or nausea during or shortly after the IV infusion. · Headache and dizziness. · Falls (due to dizziness or confusion). · High cost and uncertain insurance coverage (the drug is very expensive and many insurers do not cover it). · Not recommended if you carry two copies of the APOE ε4 gene (a genetic risk factor for Alzheimer disease) because the risk of brain swelling is much higher. · Requires regular MRI scans to watch for brain swelling and bleeding. · Controversial approval: the FDA granted accelerated approval based on plaque reduction, but clinical trials showed conflicting results on whether memory and thinking actually improve. Many major medical centers do not offer this drug.

Lecanemab (Leqembi) · Monoclonal antibody targeting amyloid-beta protofibrils

Lecanemab is a laboratory-made antibody that sticks to soluble amyloid-beta protofibrils (early, toxic clumps of the amyloid protein before they harden into full plaques). By tagging these early clumps, the antibody flags them for the brain's cleanup cells (microglia) to remove. Clearing protofibrils may slow the toxic cascade that damages neurons in Alzheimer disease, and clinical trials show a modest slowing of decline in early-stage patients.

1. In Alzheimer disease, the protein amyloid-beta misfolds and begins clumping into soluble protofibrils (small, mobile toxic clusters) before hardening into large plaques.
2. Protofibrils are thought to be more toxic to neurons than mature plaques because they move around and damage cell membranes and synapses (the connection points between neurons).
3. Lecanemab is given as an intravenous infusion every two weeks.
4. The antibody enters the brain and binds tightly to protofibrils.
5. Microglia see the antibody flag, engulf the tagged protofibrils, and break them down.
6. Over months, imaging shows reduced amyloid burden, and clinical trials show a small but measurable slowing of memory and thinking decline (about 27% slower decline over 18 months compared to placebo).

SAFETY WATCH

ARIA (amyloid-related imaging abnormalities): brain swelling or small bleeds seen on MRI. Most cases are mild and cause no symptoms, but some cause headache, confusion, vision changes, nausea, or (rarely) seizures. MRI monitoring is required at baseline and regularly during treatment. · Infusion reactions: chills, fever, flushing, shortness of breath, or nausea during or within 24 hours of the infusion (slowing the infusion rate often helps). · Headache. · Falls and dizziness. · Higher risk of ARIA if you carry one or two copies of the APOE ε4 gene (a common Alzheimer risk gene); genetic testing is recommended before starting treatment. · Not safe if you are on blood thinners (anticoagulants) because the risk of brain bleeding is higher. · Requires MRI scans before treatment and at regular intervals (every few infusions) to check for brain swelling and bleeding. · High cost and limited availability; not all insurance plans cover it and not all centers offer it.

Red flags

- Sudden, rapid confusion or change in alertness over hours to days—may signal delirium from infection, stroke, or medication toxicity
- New trouble walking, severe headache, or one-sided weakness—may mean a stroke or bleeding in the brain
- Weight loss, not eating or drinking, or signs of neglect or abuse—the person may no longer be safe at home
- Thoughts of harming themselves or others, severe agitation, or hallucinations that are frightening—needs urgent psychiatric and medical evaluation

Nursing priorities

1. Assess and document Glasgow Coma Scale score every 1 to 2 hours, notifying provider immediately if score drops 2 or more points — Declining GCS means worsening brain function from swelling, bleeding, or herniation (brain squeezing through skull); early detection allows intervention before respiratory arrest
2. Check blood glucose with fingerstick immediately on arrival and repeat every 4 hours if abnormal — Low blood sugar (Hypoglycemia) below 60 causes confusion identical to stroke but reverses in minutes with glucose; missing this delays real treatment and risks permanent brain damage from prolonged low sugar
3. Position head of bed at 30 degrees and keep head midline, avoiding neck flexion or rotation — Elevation and midline alignment promote venous drainage (blood flow out of brain) and reduce intracranial pressure (ICP); neck twisting kinks jugular veins and traps blood inside the skull

4. Monitor pupil size, shape, and reaction to light every 2 hours, reporting unequal pupils or new sluggish response — Pupil changes signal brainstem compression from rising ICP or herniation; unilateral dilated pupil means immediate danger needing emergency imaging and neurosurgery consult
5. Maintain oxygen saturation above 94% with supplemental oxygen, and ensure patent airway with suction at bedside — Low oxygen (Hypoxia) (low oxygen) worsens brain swelling and confusion; patients with altered mental status cannot protect their airway from aspiration (breathing in saliva or vomit)
6. Perform fall-risk precautions with bed alarm, padded rails, and frequent reorientation without physical restraints — Confused patients do not remember they are weak or impaired and will attempt to stand; restraints increase agitation and injury risk while reorientation and safe environment prevent trauma
7. Review medication administration record and hold anticholinergic, sedating, or opioid medications until provider reassesses — Many routine medications worsen delirium by blocking acetylcholine (a brain chemical) or depressing the central nervous system; stopping the culprit drug often clears confusion within 24 hours
8. Monitor intake and output strictly, assess for urinary retention, and check for constipation or fecal impaction — Full bladder, impacted stool, dehydration, and urinary tract infection are reversible delirium causes in elderly patients; correcting these prevents unnecessary sedation and hospital complications

Sources

- American Academy of Neurology (AAN) practice guideline on mild cognitive impairment and dementia
- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)
- Alzheimer's Association clinical criteria
- UpToDate: Evaluation of cognitive impairment and dementia

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