

Valproate Toxicity

Valproate blocks the liver's ammonia-cleaning system, so ammonia backs up into the brain and shuts down thinking.

THE ONE-LINE TRUTH

Valproate can poison the liver, raise ammonia to dangerous levels, damage the pancreas, and slow the brain—even at normal doses.

The chain — how it unfolds

1. Valproate blocks the liver's urea cycle and uses up carnitine, so ammonia starts to build in the blood instead of being cleared. — why: The enzyme carbamoyl phosphate synthetase I needs carnitine and a clear mitochondrial pathway to turn ammonia into urea. Valproate shuts down both, so ammonia accumulates like trash piling up when the garbage truck stops coming.
2. Rising ammonia crosses the blood-brain barrier and floods into astrocytes and neurons, especially in the cerebral cortex and brainstem. — why: Ammonia is small and uncharged enough to slip through the barrier. Once inside the brain, it disrupts glutamate recycling and mimics GABA's calming effect, over-sedating the circuits that keep you awake and thinking.
3. The person becomes unusually tired, confused, and clumsy. Speech may slur, hands may tremble, and they may vomit or stop eating. — why: The cerebral cortex (the outer brain layer responsible for reasoning and coordination) is slowing down because neurons are drowning in ammonia. The reticular activating system in the brainstem, which keeps you alert, is also suppressed, so the person feels like they are in a fog or falling asleep.
4. Astrocytes swell as they try to convert ammonia into glutamine; this swelling presses on surrounding neurons and blood vessels, raising pressure inside the skull. — why: Glutamine is osmotically active—it pulls water into astrocytes, making them balloon. This is the beginning of cerebral swelling (edema), which in severe cases can crush the brainstem and cause brain herniation (the brain gets pushed down through the skull opening, cutting off its own blood supply).

5. At the same time, valproate inflames the pancreas, causing severe upper belly pain, nausea, and vomiting. Pancreatic enzymes (lipase, amylase) spike in the blood. — why: The pancreas is digesting itself because enzymes meant for the intestine are activated too early. The pain and vomiting make the person even sicker, and they may stop taking fluids, worsening dehydration and ammonia buildup.
6. Liver cells begin dying from mitochondrial poisoning. Liver enzymes (ALT, AST) and bilirubin rise. The liver can no longer make clotting factors, so the person bruises easily or bleeds. — why: Valproate's breakdown products generate reactive oxygen species that kill hepatocytes. Without enough healthy liver tissue, the body cannot clot blood (because clotting factors are made in the liver), cannot regulate blood sugar, and cannot clear even more ammonia—so the spiral accelerates.
7. If valproate is not stopped, ammonia climbs even higher, the person slips into stupor or coma, and multi-organ failure begins (liver, brain, sometimes kidneys and heart). — why: The liver is no longer clearing toxins, the brain is swelling and shutting down, and the pancreas may leak enzymes that trigger body-wide inflammation. At this stage, only intensive care—stopping the drug, giving intravenous fluids, lactulose or rifaximin to lower ammonia, dialysis if needed, and sometimes a liver transplant—can save the person.
8. Early recognition and stopping valproate allows the liver to regenerate, ammonia to drop, and the brain to wake up, usually with full recovery. — why: The liver is one of the few organs that can regrow itself. Once the poison is removed, surviving hepatocytes divide, the urea cycle restarts, ammonia clears, astrocyte swelling resolves, and mental clarity returns—often within days to weeks.

Spot it — what you see, and why

- Nausea and vomiting: Valproate irritates the stomach lining directly and also triggers the brain's vomiting center (called the chemoreceptor trigger zone), making the person feel sick and throw up.
- Confusion or drowsiness: Too much valproate slows down the brain's normal electrical activity by boosting GABA (the brain's main calming signal) too much, making the person foggy, sleepy, or hard to wake up.
- Tremor (shaking hands): High valproate levels disrupt the signals between nerves and muscles, especially in the hands, causing fine shaking that the person cannot control.
- Fast breathing (hyperventilation): Valproate can build up ammonia (a waste chemical) in the blood, which the brain senses as dangerous, triggering faster, deeper breathing to try to blow off carbon dioxide and balance the blood.
- Low blood pressure: Valproate can relax blood vessel walls and slow the heart, so blood pressure drops because the vessels are wider and the pump is weaker.

- Coma or very deep sleepiness: At very high levels, valproate shuts down so much brain activity that the person stops responding and may need a breathing machine; the brain is too suppressed to wake up or protect the airway.

Red flags — act now

- Coma or cannot wake the person up
- Yellow skin or eyes (jaundice), which means the liver is failing
- Very fast breathing or gasping, which may signal high ammonia or acid in the blood
- Seizures that keep happening or will not stop
- Bleeding that will not stop (valproate can lower platelets, the blood cells that form clots)

Treat it — in this order

1. Stop valproate immediately → Removes the ongoing source of toxicity. Valproate has a half-life of 9–16 hours, so blood levels will fall by half each day once you stop the dose. Ammonia and liver enzyme levels can start to improve within 24–48 hours if the damage is not too severe.
2. Give intravenous L-carnitine 100 mg/kg (max 6 g) loading dose, then 15 mg/kg every 4 hours until ammonia normalizes → L-carnitine is a helper molecule that shuttles fatty acids into mitochondria for energy. Valproate depletes carnitine and blocks the enzyme that clears ammonia. Giving carnitine back helps the liver restart the urea cycle (the ammonia-cleaning assembly line) and lowers blood ammonia within hours.
3. Hemodialysis if serum valproate > 850 mg/L, ammonia stays very high despite L-carnitine, or the patient is in a coma or has severe liver failure → Dialysis physically pulls valproate and ammonia out of the bloodstream through a filter, bypassing the damaged liver. It can drop valproate levels by 50% or more in 4–6 hours and rapidly lower ammonia when the body cannot do it on its own.
4. Activated charcoal 50 g by mouth or nasogastric tube if ingestion was within 1–2 hours and the patient can protect their airway → Charcoal binds valproate in the stomach and intestines before it absorbs into the blood, reducing the total dose that enters the body. Most effective when given early.
5. Supportive care for liver failure: IV fluids, correct low blood sugar (dextrose if glucose < 70 mg/dL), give vitamin K 10 mg IV if INR > 1.5, monitor for encephalopathy, and stop all other potentially liver-toxic drugs → Keeps vital functions stable while the liver tries to regenerate. The liver has enormous healing capacity if you remove the toxin and support the patient through the critical window. IV fluids prevent dehydration from vomiting; dextrose prevents brain damage from low sugar; vitamin K helps clotting if the liver can still use it.

Your top priorities at the bedside

1. Check level of consciousness every 15 to 30 minutes using the Glasgow Coma Scale (a scoring system that measures eye opening, speech, and movement) and immediately notify the provider if the score drops or the patient cannot be awakened. — why: High ammonia (a waste product that builds up when the liver fails) crosses into the brain and causes encephalopathy (brain poisoning), leading to confusion, then coma, so catching worsening sleepiness early allows time to give L-carnitine (a medicine that lowers ammonia) and start hemodialysis before brain swelling becomes irreversible.
2. Start two large-bore intravenous lines (IV catheters size 18 gauge or bigger) immediately and prepare to infuse L-carnitine 100 mg per kilogram (maximum 6 grams) over 30 minutes as ordered. — why: L-carnitine helps the body break down ammonia and protects liver cells from valproate damage, and giving the loading dose quickly through large IVs prevents veins from getting irritated and ensures the drug reaches the liver and brain fast.
3. Draw blood for ammonia level, complete blood count (a test that counts red cells, white cells, and platelets), liver enzymes (ALT and AST, which leak out when liver cells die), bilirubin (a yellow waste product that builds up in liver failure), and serum valproate level before giving any treatment. — why: Ammonia above 80 micromoles per liter and valproate above 850 milligrams per liter are thresholds for hemodialysis, and low platelets or high bilirubin tell us the liver is failing and bleeding risk is high, so these baseline labs guide all treatment decisions.