

Huntington Disease

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THE STORY IN ONE SENTENCE

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“Huntington disease is a genetic condition where a faulty gene makes an abnormal protein that slowly destroys brain cells. The disease causes uncontrolled movements, memory loss, and mood changes that worsen over time. It usually begins in mid-life and is passed from parent to child.”

Normal anatomy — the body's job

The brain uses specialized regions called the basal ganglia (clusters of nerve cells deep in the brain) to coordinate smooth, purposeful movement and support thinking and emotion. The striatum (the largest part of the basal ganglia) receives signals from the cortex (the brain's outer layer) and sends refined instructions to other brain areas to control movement precision and suppress unwanted motions. Neurons (nerve cells) in the striatum use chemical messengers called neurotransmitters (brain chemicals that carry signals between nerve cells) to communicate. Healthy huntingtin protein supports neuron survival, helps transport materials inside cells, and regulates gene activity in the nucleus (the cell's control center).

BODY'S JOB

The striatum works like a traffic controller at a busy intersection, deciding which movements to allow through and which to stop, ensuring your body moves smoothly and your thoughts stay organized.

1. The cortex generates movement plans and sends signals to the striatum
2. Striatum neurons receive these signals and use neurotransmitters like dopamine and GABA to process them

3. Striatum refines the signals by filtering out unnecessary movements and amplifying intended actions
4. Processed signals travel to the thalamus (a relay station deep in the brain) and other basal ganglia structures
5. Thalamus sends the refined instructions back to the motor cortex (the brain area that controls voluntary movement)
6. Motor cortex executes smooth, coordinated movements while normal huntingtin protein supports neuron health throughout the process

What breaks

In Huntington disease, a gene mutation adds extra DNA building blocks to the huntingtin gene, creating an abnormally long stretch of repeating code. This mutation causes cells to make a misshapen huntingtin protein that clumps together inside neurons and becomes toxic. The mutant protein damages the cell's power plants, disrupts gene control, and triggers the cell's self-destruct program, slowly killing neurons in the striatum and other brain regions over decades.

CLINICAL TERM

The HTT gene on chromosome 4 contains an expanded CAG trinucleotide repeat (a stretch of three DNA letters—cytosine, adenine, guanine—repeated too many times), with 40 or more repeats causing disease compared to the normal 10 to 35 repeats. This expansion results in a mutant huntingtin protein with an elongated polyglutamine tract (a long chain of the amino acid glutamine) that misfolds and forms toxic aggregates (clumps) inside neurons. The mutant protein impairs mitochondrial function (energy production in cells), disrupts axonal transport (movement of materials along nerve fibers), and triggers apoptosis (programmed cell death), causing preferential loss of GABAergic medium spiny neurons (the main nerve cells in the striatum that use GABA as their neurotransmitter) in the caudate and putamen (the two parts of the striatum).

How the body compensates

The brain initially compensates by increasing activity in remaining neurons and recruiting alternative neural circuits to maintain function. However, these compensatory mechanisms eventually fail as neuron loss accelerates, because the brain cannot regenerate the specialized striatal neurons or replace the critical circuit connections. Unlike conditions with reversible

injury, the ongoing production of toxic huntingtin protein ensures continuous neuronal damage that overwhelms any adaptive response.

1. {'step': 'Remaining striatal neurons increase neurotransmitter production and receptor sensitivity', 'detail': 'Surviving neurons work harder to maintain signal strength, but this increased metabolic demand makes them more vulnerable to the toxic effects of mutant huntingtin'}
2. {'step': 'Alternative motor pathways in cerebellum and cortex attempt to bypass damaged striatal circuits', 'detail': 'Other brain regions try to take over movement control, but they lack the striatum's specialized ability to fine-tune and inhibit movements, resulting in less precise control'}
3. {'step': 'Glial cells (support cells in the brain) initially increase to protect neurons and clear debris', 'detail': 'Astrocytes and microglia (two types of brain support cells) multiply and become activated, but chronic activation leads to inflammation that further damages neurons'}
4. {'step': 'Unaffected brain regions show increased activity on functional imaging', 'detail': 'Brain scans reveal that areas not primarily damaged by huntingtin try to compensate, but this extra work cannot replace the lost striatal function'}
5. {'step': 'Synaptic plasticity (the brain's ability to form new connections) attempts to rewire circuits', 'detail': 'Remaining neurons try to form new connections to work around damaged pathways, but mutant huntingtin interferes with the molecular machinery needed for plasticity'}
6. {'step': 'Compensatory mechanisms progressively fail as neuron loss exceeds 50-60% in the striatum', 'detail': 'Once more than half the striatal neurons are dead, no amount of compensation can maintain function, and symptoms become severe and irreversible'}

Domino effect

1. Mutant huntingtin protein begins accumulating in striatal neurons during childhood or young adulthood — The inherited CAG expansion causes lifelong production of toxic protein, but it takes years of accumulation before enough damage occurs to cause symptoms
2. Medium spiny neurons in the striatum start dying, initially without symptoms (presymptomatic phase) — The brain's compensatory reserve masks early neuron loss, and functional imaging shows changes 10-15 years before symptoms appear
3. Chorea (involuntary, jerky, dance-like movements) emerges as striatal inhibition fails — Loss of GABAergic neurons removes the brake on unwanted movements, allowing excessive motor activity from intact dopamine pathways to cause uncontrolled motions

4. Cognitive decline begins with executive dysfunction (trouble planning, organizing, and multitasking) — Striatal-frontal circuits that coordinate thinking and decision-making degenerate, and cortical neurons in frontal lobes also accumulate mutant huntingtin
5. Psychiatric symptoms including depression, irritability, apathy, and impulsivity worsen — Loss of neurons in limbic circuits (brain pathways controlling emotion) and disrupted serotonin and dopamine signaling alter mood regulation
6. Motor symptoms progress to bradykinesia (slow movement), rigidity, and dystonia (sustained muscle contractions) — As striatal degeneration becomes severe, the motor system loses both the ability to suppress unwanted movements and to initiate desired movements smoothly
7. Severe dementia develops with profound loss of memory, language, and self-care ability — Progressive cortical atrophy (brain shrinkage) affects multiple lobes, destroying the neural networks needed for higher cognitive functions
8. Death occurs 15-20 years after symptom onset, typically from aspiration pneumonia, fall injuries, or malnutrition — Complete loss of motor control and swallowing coordination, combined with severe immobility and cognitive impairment, leads to life-threatening complications that cannot be prevented once neurodegeneration is advanced

Symptoms · what the patient feels, and why

- Chorea (involuntary jerky movements): Loss of striatal neurons (nerve cells in the basal ganglia that control movement) removes inhibition of unwanted movements
- Difficulty walking and frequent falls: Damage to basal ganglia (deep brain structures) impairs coordination, balance, and smooth motor control
- Depression and apathy: Degeneration of frontal cortex (front brain region) and striatum disrupts circuits that regulate mood and motivation
- Difficulty swallowing (dysphagia): Chorea and incoordination affect throat muscles, impairing safe passage of food and liquid
- Irritability and angry outbursts: Frontal lobe atrophy (shrinkage) disrupts impulse control and emotional regulation pathways
- Memory problems and slowed thinking: Loss of striatal-frontal connections impairs working memory and processing speed
- Weight loss despite adequate food intake: Constant involuntary movements increase calorie expenditure; hypothalamic dysfunction may alter metabolism
- Suicidal thoughts or attempts: High depression rates plus awareness of progressive decline create significant suicide risk

Focused exam

- Chorea: random, brief, irregular movements of face, trunk, and limbs: Hallmark motor sign; severity correlates with functional impairment and guides symptomatic treatment decisions
- Dystonia (sustained muscle contractions causing twisting postures): Common in later stages; can cause pain and contractures (permanent joint stiffness) requiring physical therapy
- Impaired saccades (fast eye movements are slow or require head thrust): Early oculomotor sign that supports diagnosis before chorea becomes obvious
- Slurred speech (Dysarthria) (slurred, irregular speech): Affects communication and swallowing; may need speech therapy and swallow evaluation
- Abnormal gait: wide-based, unsteady, dance-like quality: High fall risk; triggers need for assistive device, home safety evaluation, and physical therapy
- Cognitive testing showing executive dysfunction (poor planning, judgment, abstract thinking): Impairs decision-making capacity; guides discussions about advance directives and caregiver roles

Diagnostics · every test answers a question

- Genetic testing for HTT gene CAG repeat expansion → Does the patient have the mutation that causes Huntington disease?
- Brain MRI → Is there caudate atrophy (shrinkage of striatal structures) typical of Huntington disease?
- Complete blood count (CBC) → Are there other causes of abnormal movements like anemia or infection?
- Comprehensive metabolic panel (CMP) → Are electrolytes, kidney function, and liver function normal?
- Thyroid-stimulating hormone (TSH) → Could thyroid disease explain psychiatric or motor symptoms?
- Ceruloplasmin level → Could this be Wilson disease instead (treatable copper disorder)?
- Depression screening (PHQ-9 or similar tool) → How severe is depression, and is there suicide risk?
- Swallow study (videofluoroscopy or fiberoptic endoscopic evaluation) → Is the patient aspirating food or liquid into the lungs?

Treatment logic

- Genetic counseling before and after testing → Helps patient and family understand inheritance pattern, recurrence risk (50 percent for each child), and implications for life planning
- Antidepressant therapy (SSRI or SNRI) → Reduces depression, anxiety, and irritability by increasing brain serotonin and/or norepinephrine (mood-regulating chemicals)
- Physical therapy and fall prevention → Improves balance, strengthens muscles, teaches safe mobility strategies, and delays need for wheelchair
- High-calorie diet (1.5 to 2 times normal calorie needs) → Prevents malnutrition and weight loss by compensating for hypermetabolism (increased calorie burning) from constant movements
- Speech and swallow therapy → Teaches safe swallowing techniques, diet modifications (thickened liquids, soft foods), and communication strategies
- Advance care planning and legal support → Establishes healthcare proxy, living will, and financial power of attorney while patient has decision-making capacity

Medications

Tetrabenazine · Vesicular monoamine transporter 2 (VMAT2) inhibitor

Tetrabenazine blocks VMAT2 proteins inside nerve cells. VMAT2 normally packages dopamine (a movement-controlling chemical) into storage bubbles. Blocking VMAT2 reduces dopamine release, which decreases excessive involuntary movements.

1. Tetrabenazine enters dopamine-releasing nerve terminals in the striatum
2. Drug binds to VMAT2 transporter proteins on synaptic vesicle membranes
3. VMAT2 blockade prevents dopamine from entering storage vesicles
4. Free dopamine in nerve terminal is broken down by MAO enzymes (chemical scissors)
5. Less dopamine is released into synapse, reducing overstimulation of movement pathways and decreasing chorea

SAFETY WATCH

Can cause or worsen depression and suicidal thoughts; screen mood before each dose increase · May cause drowsiness, Parkinsonism (stiffness and slowness), and akathisia (restless urge to move) · Requires slow titration (gradual dose increase) to minimize side effects · Contraindicated in patients with active suicidal ideation or untreated depression

Deutetrabenazine · Vesicular monoamine transporter 2 (VMAT2) inhibitor (deuterated form)

Deutetrabenazine works exactly like tetrabenazine to block dopamine storage in nerve cells. The deuterium (heavy hydrogen) substitution slows drug breakdown in the liver, allowing twice-daily dosing instead of three times daily and causing fewer peak-related side effects.

1. Deutetrabenazine enters dopamine nerve terminals in the basal ganglia
2. Drug binds to and blocks VMAT2 transporter proteins
3. Dopamine cannot enter storage vesicles and is degraded by MAO enzymes
4. Reduced dopamine release into synapse decreases overactivity in motor pathways
5. Chorea severity decreases; deuterium substitution provides steadier drug levels throughout the day

SAFETY WATCH

Lower risk of depression compared to tetrabenazine but still requires mood monitoring · May cause sedation, Parkinsonism, and diarrhea · Avoid in patients taking MAO inhibitors or reserpine (risk of severe dopamine depletion) · Requires dose adjustment in patients taking strong CYP2D6 inhibitors

Sertraline or citalopram · Selective serotonin reuptake inhibitor (SSRI)

SSRIs block the pump that pulls serotonin (a mood-regulating chemical) back into nerve cells after release. This leaves more serotonin in the space between nerve cells, strengthening mood-control signals in the brain. Over weeks, this lifts depression and reduces anxiety and irritability.

1. SSRI enters brain and binds to serotonin transporter (SERT) proteins
2. SERT blockade prevents serotonin from being pulled back into the nerve cell
3. Serotonin accumulates in the synapse (gap between nerve cells)
4. Increased serotonin stimulates postsynaptic receptors on receiving nerve cells
5. Enhanced serotonin signaling in mood circuits gradually improves depression, anxiety, and irritability over 4 to 6 weeks

SAFETY WATCH

Takes 4 to 6 weeks for full antidepressant effect; early follow-up needed · May initially increase anxiety or agitation in first 2 weeks · Can cause sexual dysfunction, GI upset, and sleep changes · Monitor for worsening suicidal thoughts, especially in first month of treatment

Olanzapine or risperidone · Atypical antipsychotic

These drugs block dopamine receptors (landing sites for dopamine) in multiple brain areas. In the striatum, dopamine blockade reduces chorea. In frontal and limbic areas, the drugs calm agitation, psychosis, and severe irritability by dampening overactive dopamine and serotonin signals.

1. Antipsychotic enters brain and binds to dopamine D2 receptors on nerve cells
2. Receptor blockade prevents dopamine from activating these cells
3. In striatum, reduced dopamine signaling decreases involuntary movements
4. In frontal and limbic regions, dopamine and serotonin blockade calms agitation and irritability
5. Behavioral symptoms and chorea improve within days to weeks

SAFETY WATCH

Can cause sedation, weight gain, metabolic syndrome (high blood sugar, cholesterol, triglycerides) · Risk of Parkinsonism, tardive dyskinesia (late-onset involuntary movements), and akathisia · Monitor fasting glucose, lipids, and weight every 3 months · Use lowest effective dose to minimize side effects

Percutaneous endoscopic gastrostomy (PEG) tube feeding · Enteral nutrition support (not a drug but included as critical non-drug intervention)

A PEG tube is a flexible tube inserted through the abdominal wall into the stomach. It allows direct delivery of liquid nutrition when swallowing becomes too dangerous. This prevents aspiration pneumonia (lung infection from inhaling food) and provides consistent calories to maintain weight and hydration.

1. PEG tube is placed endoscopically through abdominal wall into stomach under sedation
2. Liquid formula is delivered directly into stomach several times daily
3. Nutrition bypasses oral and pharyngeal phases of swallowing where aspiration risk is highest
4. Stomach empties formula into small intestine for normal absorption
5. Patient maintains weight, hydration, and medication administration without choking risk

SAFETY WATCH

Insertion carries risks of bleeding, infection, and perforation · Tube site requires daily cleaning to prevent skin infection · Requires careful discussion of goals of care; may prolong life without improving comfort in late-stage disease · Aspiration can still occur from saliva or reflux even with tube feeding

Amantadine · NMDA receptor antagonist and dopamine modulator

Amantadine blocks NMDA receptors (glutamate-activated channels) on nerve cells and increases dopamine release and blocks dopamine reuptake. This dual action can reduce chorea in some patients, though the exact mechanism in Huntington disease is not fully understood. It may also improve rigidity if present.

1. Amantadine enters brain and binds to NMDA receptors on nerve cells
2. NMDA receptor blockade reduces excitatory glutamate signaling that may contribute to chorea
3. Drug also increases dopamine release and blocks dopamine reuptake pumps
4. Net effect balances excitatory and inhibitory signals in basal ganglia circuits
5. Chorea and rigidity may decrease in responsive patients

SAFETY WATCH

Can cause livedo reticularis (purple skin mottling), ankle swelling, and dizziness · May worsen confusion or hallucinations, especially in patients with cognitive impairment · Requires dose reduction in kidney disease (drug is renally cleared) · Abrupt discontinuation can cause neuroleptic malignant syndrome-like symptoms in rare cases

Red flags

- New or worsening suicidal thoughts (suicide risk is 4 to 6 times higher than general population)
- Choking episodes or recurrent pneumonia (suggests aspiration and need for swallow evaluation and feeding tube discussion)
- Rapid weight loss despite adequate intake (signals disease progression and increased metabolic demands)
- Severe agitation, aggression, or psychosis (requires urgent psychiatric evaluation and medication adjustment)

Nursing priorities

1. Monitor for chorea (involuntary jerky movements) and fall risk — Huntington disease causes progressive motor dysfunction with unpredictable movements that increase fall and injury risk, requiring environmental safety modifications and supervision.

2. Assess swallowing ability and aspiration risk at every meal — Trouble swallowing (Dysphagia) (trouble swallowing) worsens as the disease progresses, leading to aspiration pneumonia, malnutrition, and choking, which are leading causes of death in Huntington disease.
3. Screen for depression, suicidal ideation, and psychiatric symptoms daily — Huntington disease causes psychiatric changes including depression, irritability, and psychosis; suicide risk is 4 to 6 times higher than the general population, often occurring early in the disease.
4. Coordinate speech therapy for communication strategies as slurred speech (dysarthria) (slurred speech) progresses — Speech becomes increasingly impaired, isolating patients socially and emotionally; early intervention with alternative communication methods preserves dignity and reduces frustration.
5. Ensure adequate caloric intake and monitor weight weekly — Patients have markedly increased metabolic demands from involuntary movements and often lose weight despite eating normally; cachexia (severe weight loss) accelerates functional decline.
6. Provide family education about genetic inheritance and testing options — Huntington disease is autosomal dominant (50% chance each child inherits the mutation); families need genetic counseling for family planning and presymptomatic testing decisions.
7. Assess and manage medication side effects, especially from antipsychotics and dopamine-blocking agents — Drugs used to control chorea and psychiatric symptoms can worsen parkinsonism (stiffness and slow movement), cause sedation, or trigger neuroleptic malignant syndrome (life-threatening reaction).
8. Support advance care planning early in the disease course — Cognitive decline (loss of thinking ability) and dementia develop predictably; discussing goals of care, feeding tubes, and end-of-life wishes while the patient has decision-making capacity honors autonomy.

Sources

- Huntington Study Group and European Huntington Disease Network guidelines on clinical management of Huntington disease (2020)
- American Academy of Neurology practice guideline on genetic testing and counseling for Huntington disease (2019)
- National Institute of Neurological Disorders and Stroke (NINDS) Huntington Disease Information Page (2023)
- Huntington Disease Society of America nursing and care management recommendations for Huntington disease patients and families (2021)

Last reviewed: 2026-08-29