

# Treatment Of Huntingtons Disease

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## **Abstract**

*Huntington's disorder is an incurable genetic neurodegenerative disorder that affects many people's day-to-day lives, and in the United Kingdom alone, affects an estimated 8,000 people (Balogun et al., 2022). Its prevalence worldwide depends on the lineage of those afflicted – for example, 10 people of European descent per 100,000 are affected, whereas it is rarer in those of Japanese descent (Frank, 2013). Symptoms include those that are psychological, such as difficulties with concentration and memory, mood swings, and those that are physical, such as chorea, dysphagia, speaking impairment, sluggishness, and breathing problems to name a few. Patients with late-stage Huntington's disorder may require full-time nursing care because of the severity of these symptoms. Research is ongoing into the biochemistry of Huntington's disorder as well as possible treatment pathways. In 2020-21 alone, the National Institute for Health and Care Research dedicated £77 million of its £1.2 billion budget towards the research into neurodegenerative disorders such as Huntington's (Balogun et al., 2022; NIHR, 2022), which shows how these disorders are a research hot spot. This analysis aims to present and explore the main topics – What Huntington's disease is, its symptoms, its treatment and their side effects as well as why therapy is the best treatment for Huntington Disease*

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Date of Submission: 26-07-2024

Date of Acceptance: 06-08-2024

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## **I. Background Of The Study**

Huntington's disease (HD) is a hereditary, neurodegenerative disorder that affects the brain, leading to progressive deterioration in motor control, cognitive function, and emotional regulation (Pringsheim et al., 2015). This debilitating condition, caused by a mutation in the HTT gene, has no cure. However, various treatments and management strategies exist to alleviate symptoms, improve quality of life, and slow disease progression. The disease, which gets worse over time, attacks motor control regions of the brain (those involved with movement), as well as other areas. People with HD develop problems with behavior, emotion, thinking, and personality, along with uncontrollable dance-like movements (called chorea) and abnormal body postures (Rodrigues et al., 2017). The gene mutation that causes HD is present from birth. Symptoms of HD typically appear in middle age (adult HD), and in rare cases they appear in children (juvenile HD). The duration of the illness generally ranges from 10 to 30 years. HD is not fatal. The most common causes of death are infection (most often pneumonia) and injuries related to falls. There is no cure for HD, but treatments are available to help manage its symptoms.

HD is passed from parent to child through a mutation in a gene. The gene responsible for HD lies on chromosome four. (Chromosomes contain a person's genetic material.) When a parent has HD, each child has a 50% chance of inheriting the copy of chromosome four that carries the HD mutation (CDC, 2019). If a child does not inherit the HD mutation, he or she will not develop the disease and cannot pass it to subsequent generations. People with HD have an abnormal, repetitive, greatly expanded three-letter code (or triplet) in the DNA sequence that is found in genes. DNA uses a triplet to prescribe the order and identity of amino acids—a protein's building blocks. This three-base repeat—called a triplet repeat expansion—causes dozens of other neurological diseases, but in HD the triplet involves the excessive repeat of cytosine, adenine, and guanine (called CAG). Most people have fewer than 27 CAG repeats in the HD gene and are not at risk for the disease. Individuals with the disease may have 36 or more repeats. People who have repeats in the intermediate range (27-35) are unlikely to develop the disease, but they could pass it on to future generations (Alzheimer's Society, 2020).

## **Causes of Huntington's Disease**

Huntington's disease (HD) is a devastating neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms (Nopoulos, 2016). Understanding why people develop Huntington's disease involves delving into the genetic, molecular, and biological mechanisms underlying this condition (Die-Smulders et al., 2013) **Genetic Basis of Huntington's Disease**

### **Inheritance Pattern**

Huntington's disease is inherited in an autosomal dominant pattern, meaning that a person only needs to inherit one copy of the mutated gene to develop the disease. The gene responsible for HD is called HTT (huntingtin), located on chromosome 4. Every child of a parent with Huntington's disease has a 50% chance of inheriting the mutated gene (CDC, 2019).

### **Expansion of CAG Repeats**

The genetic mutation underlying Huntington's disease involves an expansion of a CAG trinucleotide repeat within the HTT gene. Normally, this region of the gene contains between 10 to 35 repeats of the CAG sequence. In individuals with HD, there is an abnormal expansion of these repeats, typically exceeding 36 repeats.

Normal Range: 10-35 CAG repeats

Intermediate Range: 27-35 CAG repeats (may or may not lead to HD)

Full Penetrance Range: 36 or more CAG repeats (leads to HD)

The number of CAG repeats correlates with the age of onset and severity of symptoms:

**Reduced Penetrance:** Individuals with 36 to 39 CAG repeats may or may not develop symptoms of HD, and if they do, it tends to occur later in life.

**Full Penetrance:** Individuals with 40 or more CAG repeats almost always develop Huntington's disease, with earlier onset and more severe symptoms.

### **Molecular Mechanisms of Huntington's Disease Mutant Huntingtin Protein**

The expanded CAG repeats in the HTT gene result in the production of an abnormal protein called mutant huntingtin (mHTT). This protein has toxic effects on neurons, particularly in the striatum (a region of the brain involved in motor control) and other areas of the brain affected by HD. The exact mechanisms by which mHTT causes neuronal damage are complex and multifaceted:

**Aggregation:** mHTT tends to form aggregates or clumps within neurons, disrupting normal cellular functions and causing cellular dysfunction.

**Protein Misfolding:** The abnormal structure of mHTT leads to protein misfolding, where the protein does not fold into its proper shape. This misfolding can trigger cellular stress responses and interfere with protein clearance mechanisms.

**Mitochondrial Dysfunction:** mHTT disrupts mitochondrial function, leading to impaired energy production within neurons. This energy deficit contributes to neuronal dysfunction and cell death.

**Excitotoxicity:** mHTT alters the balance of neurotransmitters in the brain, particularly increasing levels of glutamate. Excessive glutamate can overactivate receptors on neurons, leading to excitotoxicity and neuronal damage.

**Impaired Transport and Signaling:** mHTT interferes with intracellular transport mechanisms and disrupts signaling pathways essential for neuronal survival and function.

### **Neuroinflammation and Glial Activation**

In addition to neuronal dysfunction caused by mHTT, Huntington's disease is associated with neuroinflammation and activation of glial cells (such as astrocytes and microglia) in the brain. These cells play critical roles in immune responses and maintaining brain homeostasis. In HD, glial cells become activated and release inflammatory cytokines and reactive oxygen species, contributing to ongoing neurodegeneration.

### **Effects of Huntington's Disease**

Early signs of the disease vary greatly from person to person, but typically include cognitive or psychiatric symptoms, difficulties with movement, and behavioral changes. Symptoms of Huntington's disease include:

**Behavioral changes** such as mood swings, irritability, apathy, inactivity, depression, or anger. These symptoms may lessen as the disease progresses or, in some individuals, may continue and include hostile outbursts, thoughts of suicide, deep bouts of depression, and psychosis. People with HD also may avoid social interaction.

**Cognitive changes** may include issues with judgment, attention, other cognitive functions, problem-solving, or decision making. Other effects may include trouble with driving, prioritizing tasks, and organizing, learning new things, remembering a fact, putting thoughts into words, or answering a question. These cognitive problems worsen as the disease progresses and affected individuals are no longer able to work, drive, or care for themselves. When the level of cognitive impairment is significant enough to impair daily functioning, it is described as dementia. Many people with HD, however, remain aware of their environment and can express

emotions.

**Uncontrolled and difficult movement** in the fingers, feet, face, or torso. These movements, which are signs of chorea, often intensify when the person is anxious or distracted and become more pronounced and apparent over time. HD can also begin with mild clumsiness or problems with balance. Some people develop chorea-related movements such as problems walking, increasing the likelihood of falls. Some individuals with HD do not develop chorea; instead, they may become rigid and move very little, or not at all, a condition called akinesia. Others may start out with chorea but become rigid as the disease progresses. In addition to chorea, some individuals have unusual fixed postures, called dystonia. The two movement disorders can blend or alternate. Other symptoms may include tremor (unintentional rhythmic muscle movement back-and-forth) and abnormal eye movements that often occur early in the disease progression.

**Physical changes** may include slurred speech and decline in vital functions, such as swallowing, eating, speaking, and especially walking. Weight loss may occur due to problems with feeding, swallowing, choking, and chest infections. Other symptoms may include insomnia, loss of energy, fatigue, and seizures. Eventually the person will be confined to a bed or wheelchair.

### **Treatment For Huntington's Disease**

There is no treatment to stop or reverse the course of the disease. Most of the medications available for HD symptoms work by modulating neurotransmitters the brain's chemical messengers that shuttle between neurons. Current treatment strategies for Huntington's disease focus on managing symptoms and enhancing the quality of life. These treatments can be broadly categorized into pharmacological and non-pharmacological interventions (Myers, 2004).

### **Symptomatic Treatment**

Symptomatic treatment targets the diverse manifestations of Huntington's disease, including motor, cognitive, and psychiatric symptoms.

### **Medications for Motor Symptoms**

Motor symptoms such as chorea (involuntary jerking movements), dystonia (muscle contractions), and bradykinesia (slowness of movement) significantly impact daily functioning. Medications used to manage motor symptoms include:

- **Tetrabenazine and Deutetrabenazine:** These drugs are specifically approved for treating chorea in Huntington's disease. They work by depleting dopamine in the brain, which helps reduce involuntary movements. However, they can have side effects such as depression, drowsiness, and parkinsonism.
- **Antipsychotics:** Medications such as risperidone, olanzapine, and quetiapine can help control chorea and other movement disorders. They also address psychiatric symptoms but can cause weight gain, sedation, and metabolic issues.

### **Medications for Psychiatric Symptoms**

Psychiatric symptoms, including depression, anxiety, irritability, and psychosis, are common in Huntington's disease. According to Huntington's Disease Association, (2015) Treatment options include:

- **Antidepressants:** Selective serotonin reuptake inhibitors (SSRIs) like sertraline and fluoxetine are commonly used to treat depression and anxiety. They help regulate mood and alleviate emotional symptoms.
- **Mood Stabilizers:** Medications such as lithium and valproate can manage mood swings and irritability, helping to stabilize emotional responses.
- **Antipsychotics:** These medications are also effective for treating psychosis and severe agitation. Commonly used antipsychotics include risperidone and aripiprazole.
- **Anticonvulsants:** Drugs like lamotrigine and carbamazepine can stabilize mood and manage irritability, offering additional options for psychiatric symptom management.

### **Non-Pharmacological Interventions**

Non-pharmacological interventions play a crucial role in the comprehensive management of Huntington's disease, addressing physical, cognitive, and functional impairments Huntington's Disease Association, (2015). Some of these are:

### **Physical Therapy**

Physical therapy is essential for maintaining mobility, balance, and strength. Physical therapists design individualized exercise programs to help patients manage motor symptoms, prevent complications like falls and contractures, and enhance overall physical function.

### **Occupational Therapy**

Occupational therapists assist patients in maintaining independence in daily activities. They recommend adaptive devices, teach energy conservation techniques, and modify the home environment to enhance safety and accessibility. Occupational therapy aims to improve the quality of life by enabling patients to perform everyday tasks with greater ease.

### **Cognitive Therapy**

Cognitive therapy helps manage cognitive decline, focusing on memory, attention, and executive function. Therapists use exercises and strategies to improve cognitive skills, enhance mental function, and compensate for cognitive deficits. This therapy is crucial for maintaining independence and mental sharpness.

### **Nutritional Support**

Nutritional support is vital for patients with Huntington's disease, who may experience weight loss and swallowing difficulties. Dietitians provide guidance on high-calorie, nutrient-dense foods and strategies to manage dysphagia. Maintaining adequate nutrition helps support overall health and energy levels.

### **Emerging Therapies and Research**

Research is ongoing to develop new treatments that target the underlying causes of Huntington's disease, offering hope for more effective therapies and, ultimately, a cure

### **Gene Silencing Therapies**

Gene silencing aims to reduce or eliminate the production of the mutant huntingtin protein. Techniques include:

- **Antisense Oligonucleotides (ASOs):** These short DNA or RNA sequences bind to the mutant HTT mRNA, preventing the production of the toxic protein. Clinical trials for ASOs, such as tominersen, are underway and show promise in reducing disease progression.
- **RNA Interference (RNAi):** This approach uses small RNA molecules to degrade HTT mRNA, reducing protein levels. RNAi therapies are being explored for their potential to target the root cause of Huntington's disease.

### **Stem Cell Therapy**

Stem cell therapy involves transplanting healthy cells into the brain to replace damaged neurons. While still in the experimental stages, this approach has shown promise in preclinical studies and early-phase clinical trials. Stem cell therapy aims to restore lost neural function and slow disease progression.

### **Neuroprotective Strategies**

Neuroprotective strategies aim to prevent or slow neuronal damage. Potential approaches include:

- **Small Molecule Drugs:** Compounds that enhance neuronal survival and function are being investigated for their potential to protect brain cells from degeneration.
- **Growth Factors:** Proteins that promote neuron health and repair, such as brain-derived neurotrophic factor (BDNF), are under study for their neuroprotective effects.

### **CRISPR and Gene Editing**

CRISPR technology offers the potential to correct the genetic mutation responsible for Huntington's disease. Research is ongoing to refine these techniques and ensure their safety and efficacy in humans. Gene editing could provide a permanent solution by directly addressing the genetic cause of the disease.

### **Lifestyle and Management Strategies**

In addition to medical treatments, lifestyle and management strategies play a crucial role in managing Huntington's disease.

### **Exercise and Physical Activity**

Regular exercise helps maintain physical function, improve mood, and reduce the risk of comorbid conditions. Activities like walking, swimming, and yoga can be beneficial. Exercise programs should be tailored to individual capabilities and preferences.

### **Diet and Nutrition**

A balanced diet supports overall health and addresses specific nutritional needs. High-calorie, high-protein foods can help manage weight loss, while soft or pureed foods may be necessary for those with swallowing difficulties. Proper nutrition helps sustain energy levels and overall well-being.

### **Mental Health and Emotional Support**

Psychological support is vital for patients and their families. Counseling, support groups, and stress-reduction techniques can help manage the emotional challenges associated with Huntington's disease (Walker, 2019). Mental health professionals can provide valuable support and coping strategies.

### **Caregiving and Family Support**

Caregivers play a critical role in managing Huntington's disease. Education, respite care, and support services can help alleviate the burden on caregivers and improve the quality of care for patients. Caregiver support is essential for maintaining their well-being and ability to provide effective care.

### **Community and Social Engagement**

Maintaining social connections and engaging in community activities can enhance quality of life and provide emotional support. Support groups and advocacy organizations offer valuable resources and opportunities for connection. Social engagement helps reduce isolation and fosters a sense of belonging.

### **Side Effects of Treatments for Huntington's Disease**

Huntington's disease (HD) is a progressive neurodegenerative disorder that profoundly impacts motor function, cognition, and psychiatric health (CDC, 2019). While there is no cure for HD, various treatments exist to manage symptoms and improve quality of life. However, these treatments can come with a range of side effects that may complicate the overall management of the disease. This article delves into the side effects of the primary treatments for Huntington's disease, covering both pharmacological and non-pharmacological interventions, and explores strategies to mitigate these adverse effects.

### **Pharmacological Treatments and Their Side Effects**

According to Franklas (2013), Pharmacological treatments for Huntington's disease focus on alleviating motor, cognitive, and psychiatric symptoms. These treatments include medications specifically approved for HD as well as those used off-label to manage symptoms. Each medication comes with potential side effects that patients and healthcare providers must carefully consider.

### **Tetrabenazine (Xenazine) and Deutetrabenazine (Austedo)**

Tetrabenazine and deutetrabenazine are primarily used to manage chorea, the involuntary jerking movements characteristic of HD. These medications work by depleting dopamine levels in the brain, thereby reducing abnormal movements. However, their use is associated with several side effects:

- **Depression and Suicidality:** Both tetrabenazine and deutetrabenazine can increase the risk of depression and suicidal thoughts, particularly in patients with a history of depression.
- **Drowsiness and Sedation:** These medications often cause drowsiness, which can affect daily functioning and quality of life.
- **Parkinsonism:** Symptoms resembling Parkinson's disease, such as rigidity and bradykinesia (slowed movement), may develop.
- **Insomnia:** Sleep disturbances, including insomnia, are also reported.

## **II. Antipsychotics**

Antipsychotic medications like risperidone, olanzapine, and quetiapine are used to control chorea and other movement disorders, as well as psychiatric symptoms such as psychosis and severe agitation (Dayalu et al, 2015). However, they come with a broad range of side effects:

- **Weight Gain and Metabolic Syndrome:** Significant weight gain and an increased risk of metabolic syndrome, including diabetes and cardiovascular disease, are common with antipsychotic use.
- **Sedation:** Sedation and drowsiness can impact alertness and daily activities.
- **Extrapyramidal Symptoms (EPS):** These include tremors, rigidity, and bradykinesia, which can worsen motor symptoms in HD.
- **Tardive Dyskinesia:** A condition characterized by repetitive, involuntary movements, particularly of the face and mouth, which can become permanent.
- **Orthostatic Hypotension:** A sudden drop in blood pressure upon standing, leading to dizziness and the risk of falls.

### **Medications for Psychiatric Symptoms**

#### **Antidepressants**

Selective serotonin reuptake inhibitors (SSRIs) like sertraline and fluoxetine are commonly

prescribed to manage depression and anxiety in HD patients. While generally well-tolerated, SSRIs have side effects that can be problematic:

- ❑ **Gastrointestinal Issues:** Nausea, diarrhea, and constipation are common gastrointestinal side effects.
- ❑ **Sexual Dysfunction:** Reduced libido, erectile dysfunction, and difficulty achieving orgasm are frequently reported.
- ❑ **Weight Gain:** Some patients experience weight gain with long-term use.
- ❑ **Insomnia or Somnolence:** SSRIs can either cause insomnia or excessive sleepiness, depending on the individual.

### **Mood Stabilizers**

Mood stabilizers like lithium and valproate are used to manage mood swings and irritability. These medications require careful monitoring due to their potential side effects:

- ❑ **Lithium Toxicity:** Symptoms of lithium toxicity include tremors, nausea, vomiting, diarrhea, and confusion. Regular blood tests are required to monitor lithium levels.
- ❑ **Weight Gain:** Both lithium and valproate can cause significant weight gain.
- ❑ **Thyroid and Kidney Dysfunction:** Long-term lithium use can affect thyroid and kidney function, necessitating regular monitoring.
- ❑ **Gastrointestinal Distress:** Nausea, vomiting, and diarrhea are common with valproate.

### **Non-Pharmacological Interventions and Their Side Effects**

Non-pharmacological interventions are crucial in managing Huntington's disease and often complement pharmacological treatments (Roos, 2010). While generally considered safer, these interventions can also have side effects or complications.

#### ❑ **Physical Therapy**

- ❑ Physical therapy aims to maintain mobility, strength, and balance. While beneficial, certain aspects of physical therapy can pose risks:
- ❑ **Falls and Injuries:** Exercises aimed at improving balance and coordination can sometimes lead to falls and injuries, especially in patients with severe motor impairments.
- ❑ **Fatigue:** Intensive physical therapy sessions can cause fatigue, which may exacerbate other symptoms of HD.

### **Occupational Therapy**

Occupational therapy helps patients maintain independence in daily activities through adaptive strategies and devices (Balogun et. al, 2022). Potential side effects include:

**Frustration and Anxiety:** Learning new techniques and using adaptive devices can be frustrating and anxiety-inducing for some patients, particularly if they struggle with cognitive impairments.

### **Speech Therapy**

Speech therapy addresses communication difficulties and dysphagia (swallowing problems). While generally safe, there are a few considerations:

**Aspiration Risk:** Exercises and techniques for managing dysphagia must be carefully monitored to avoid aspiration, which can lead to pneumonia.

### **Cognitive Therapy**

Cognitive therapy focuses on improving memory, attention, and executive function. Possible side effects include:

**Mental Fatigue:** Cognitive exercises can be mentally exhausting, potentially leading to increased fatigue and frustration.

### **Emerging Therapies and Their Potential Side Effects**

Research into new treatments for Huntington's disease is ongoing, with several promising approaches under investigation. However, these emerging therapies also come with potential risks and side effects.

### **Gene Silencing Therapies**

Gene silencing aims to reduce or eliminate the production of the mutant Huntington protein. Techniques include antisense oligonucleotides (ASOs) and RNA interference (RNAi). Potential side effects include:

**Inflammatory Reactions:** Injections of ASOs can cause localized inflammatory reactions at the injection site.

**Off-Target Effects:** Gene silencing therapies might unintentionally affect other genes, leading to unforeseen

side effects.

**Neurological Symptoms:** Given the central role of the Huntington protein in the brain, altering its expression could lead to new neurological symptoms or exacerbate existing ones.

### **Stem Cell Therapy**

Stem cell therapy involves transplanting healthy cells into the brain to replace damaged neurons. Potential risks include:

**Immune Rejection:** The body might reject transplanted cells, leading to an immune response.

**Tumor Formation:** There is a risk that transplanted stem cells could proliferate uncontrollably, leading to tumor formation.

**Infection:** The invasive procedures required for stem cell transplantation carry a risk of infection.

### **Neuroprotective Strategies**

Neuroprotective strategies aim to prevent or slow neuronal damage. Potential side effects depend on the specific approach but might include:

**Small Molecule Drugs:** These compounds can have various side effects depending on their mechanisms of action, such as gastrointestinal issues, cardiovascular effects, or interactions with other medications.

**Growth Factors:** Proteins like brain-derived neurotrophic factor (BDNF) can have off-target effects, potentially affecting other systems in the body.

### **CRISPR and Gene Editing**

CRISPR technology offers the potential to correct the genetic mutation responsible for Huntington's disease. Potential risks include:

**Off-Target Mutations:** CRISPR could unintentionally edit other parts of the genome, leading to unforeseen consequences.

**Immune Response:** The introduction of CRISPR components could trigger an immune response, potentially leading to inflammation or other immune-mediated side effects.

### **Why Therapy is Considered the Best Treatment For Huntingtons Disease**

Therapy is considered the best approach for treating Huntington's disease (HD) due to its multifaceted nature and the ability to address the complex and varied symptoms of this neurodegenerative disorder (Tanzi, 2019). Huntington's disease is characterized by a combination of motor, cognitive, and psychiatric symptoms, which progressively worsen over time. While there is currently no cure for HD, therapy can significantly improve the quality of life for patients and their families by managing symptoms, enhancing functional abilities, and providing psychological support (Rodrigues et al., 2017). This discussion will explore the various forms of therapy used in treating Huntington's disease, including pharmacological treatments, physical therapy, occupational therapy, speech therapy, and psychological interventions. Additionally, it will examine the benefits and challenges of these therapeutic approaches.

### **III. Conclusion**

Therapy is the best approach for treating Huntington's disease due to its comprehensive and multidimensional nature. By addressing the motor, cognitive, and psychiatric symptoms of the disease, therapy can significantly improve the quality of life for patients and their families. Pharmacological treatments, physical therapy, occupational therapy, speech therapy, and psychological interventions each play a vital role in managing the diverse and complex symptoms of HD. An integrated care approach that combines the expertise of various healthcare professionals ensures that patients receive holistic and personalized care. While challenges remain, continued research, improved access to care, and increased support for patients and caregivers hold promise for the future of Huntington's disease treatment.