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# A Comprehensive Perspective of Huntington's Disease

[1]Mohammad Shaheen; [2]Tejomurtula Hari Chandana; [3]Guddanti Hema; [4*]Gayathri Paturi Assistant Professor
[1,2]Department of Pharmaceutical Engineering, BV Raju Institute of Technology, Naraspur, - 502313
[3]Department of Pharmacology, Vishnu Institute of Pharmaceutical Education and Research, (VIPER), Naraspur - 502313

Corresponding Author:- [4*]Gayathri Paturi,

**Abstract:- Huntington's disease (HD) is a severe genetic illness caused by a CAG expansion on chromosome 4 in the huntingtin gene. This results in an excessively long polyglutamine tract, which has negative consequences. The normal huntingtin protein serves important tasks, however the mutant version causes a variety of detrimental effects. Disruptions in cellular processes such as autophagy, decreased mitochondrial activity, lysosomal dysfunction, and others are involved in the etiology of HD. Inflammation, oxidative stress, and transcriptional alterations all contribute to neurodegeneration. Despite great progress in understanding the genetic basis of HD, there is currently no cure. The current approach to management focuses on symptomatic control, but as our understanding of genetics advances, targeted medicines might become available. Although HD is still a difficult condition to treat, there is optimism for future advancements in research. Clinical techniques mostly focus on symptom management, with genetic testing assisting in diagnosis. Promising research looks on potential disease-modifying therapies, such as ways to reduce mutant huntingtin levels and improve clearance. Ongoing clinical research provide promise for future treatments, bringing hope to HD patients and their families.**

***Keywords:-*** *Huntington's Illness, Diagnosis, Treatment, Inflammation.*

## I. INTRODUCTION

A uncommon, hereditary neurological disease called Huntington's Disease (HD) is marked by problems with movement, cognitive impairment, and psychiatric symptoms. It usually appears in middle age, while a juvenile version can also appear in early childhood[1]. It was first discovered in 1842 and was subsequently named Huntington's chorea in 1872. Increased research and the capacity to diagnose patients before symptoms appeared were prompted by the 1993 identification of the HD gene. Numerous symptomatic therapies were developed as a result of the gene, which is characterized by CAG repeats[2]. Even with current alternatives, there is an urgent need for more effective medications that modulate illness. HD patients and their families suffer greatly because the disease is still incurable.

- *Epidemology:*

A genetic condition known as Huntington's Disease (HD) varies in frequency among various populations. It is less common in Asian and African populations and more common in persons of European origin, especially those with British ancestry. The prevalence is 2.71 per 100,000 worldwide; North America, Europe, and Australia have greater rates than Asia (0.40 per 100,000), with 5.70 per 100,000). The prevalence varies by nation; in the US, it ranges from 4.1 to 8.4 per 100,000, while in Europe, it ranges from 1.63 to 9.95 per 100,000.

Between the third and fifth decades of life, at an average age of about forty, is when HD usually first manifests[3]. After onset, the usual survival period is between 15 and 20 years. The age of onset may vary among populations due to genetic modifications and environmental variables. In comparison to Americans and Canadians, Venezuelan relatives exhibit a mean age of onset that is earlier.

Genetic variants in the HTT gene are connected to the variances in prevalence across ethnic groups[4]. Asian people have shorter average CAG repeats (16.9–17.4) in the gene, whereas populations with higher prevalence, such as those of European descent, have longer average CAG repeats (18.4–18.7). In many populations outside of the developed world, the prevalence is still lower and has received less research.

- *Etiology and genetics:*

It being mapped to chromosome 4 in 1983, the Huntington's disease (HD) gene was extracted and found at location 4p16.3 a decade later. Expanding trinucleotide repeats (CAG) in the first exon of the huntingtin (HTT) gene is the etiology of Huntington's disease (HD). This enlargement results in a toxic mutant huntingtin protein that affects corticostriatal circuits and the striatum in particular, causing synaptic dysfunction and cell death[5]. An important factor in the development of HD is the length of the CAG repeat in HTT, which is inversely connected with the age of onset. When there are 40 or more CAG repeats, a sign of strong penetrance, HD is diagnosed. People that have 36–39 repeats show partial penetrance and are classified as carriers.

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Although they are not linked to HD, hose with 27 to 35 repeats run the risk of growing during transmission. A decrease in the age of onset in subsequent generations is a sign of genetic anticipation, which is shown in cases with youthful onset and is frequently associated with significant increases in repeat length during paternal transmission[6]. The remaining variable in age of onset is attributed to a combination of genetic and environmental factors, however the length of the CAG repeat explains approximately 70% of the variation in this age. The average age of onset is between 21 and 50 years, and varied allele lengths (40–58 CAG repeats) correlate with different onset ages. The majority of repeat sizes, which are between 40 and 50 CAG repeats, can cause symptoms at any age, although late-onset people, who start showing symptoms around 51 years old,typically have repeat lengths ranging from 40 to 45 CAGs[7].

➢ *Pathophysiology:*

The loss of neurons in the striatum and cortex is the primary cause of neurological abnormalities in Huntington's disease (HD), while there are also effects in the thalamus, substantia nigra, cerebellum, and hypothalamic lateral tuberalnucleus[8]. These consequences, however, are not as noticeable as the substantial reduction in the Putamen and the Caudate nucleus.

One of the main areas of interest in HD neuropathology is the basal ganglia, an important subcortical structure in the brain. The predominant neuron type in the neostriatum, which makes up the majority of the basal ganglia, is GABAergic[9]. One progressive feature of HD is the degradation of GABAergic Medium-Sized Spiny neurons (MSNs) in the striatum. It is believed that MSNs on the indirect pathway are impacted by the disease more quickly than MSNs on the direct pathway. An imbalance results from the disruption of the basal ganglia circuitry caused by the degeneration of these neurons. Due to this imbalance, the subthalamic nucleus becomes inhibited. The thalamus then relieves inhibition, which leads to an excess of glutamate activity in the cortex and hyperkinetic movements.

Research has revealed that HD patients had different firing rates in the internal and external Globus Pallidus (GPi and GPE, respectively)[10]. Abnormal motions could be caused by higher firing rates in GPe and lower firing rates in GPi. Some HD patients' aberrant motions have been observed to improve with deep brain stimulation of the GPi.

➢ *Aetiology:*

An hereditary genetic mutation in the huntingtin (HTT) gene on chromosome 4 is the cause of Huntington's disease. A mutant huntingtin (mHTT) protein with an exceptionally long polyglutamine repeat is produced as a result of this mutation. While those with 36 to 39 repeats may have lower penetrance, which means that not everyone in this range would certainly exhibit symptoms, those with more than 39 repeats are guaranteed to acquire the condition[11]. Especially when inherited from the male, anticipation, where the gene grows in the next generations, is shown because sperm tend to be larger and have more repeat variability than other tissues.

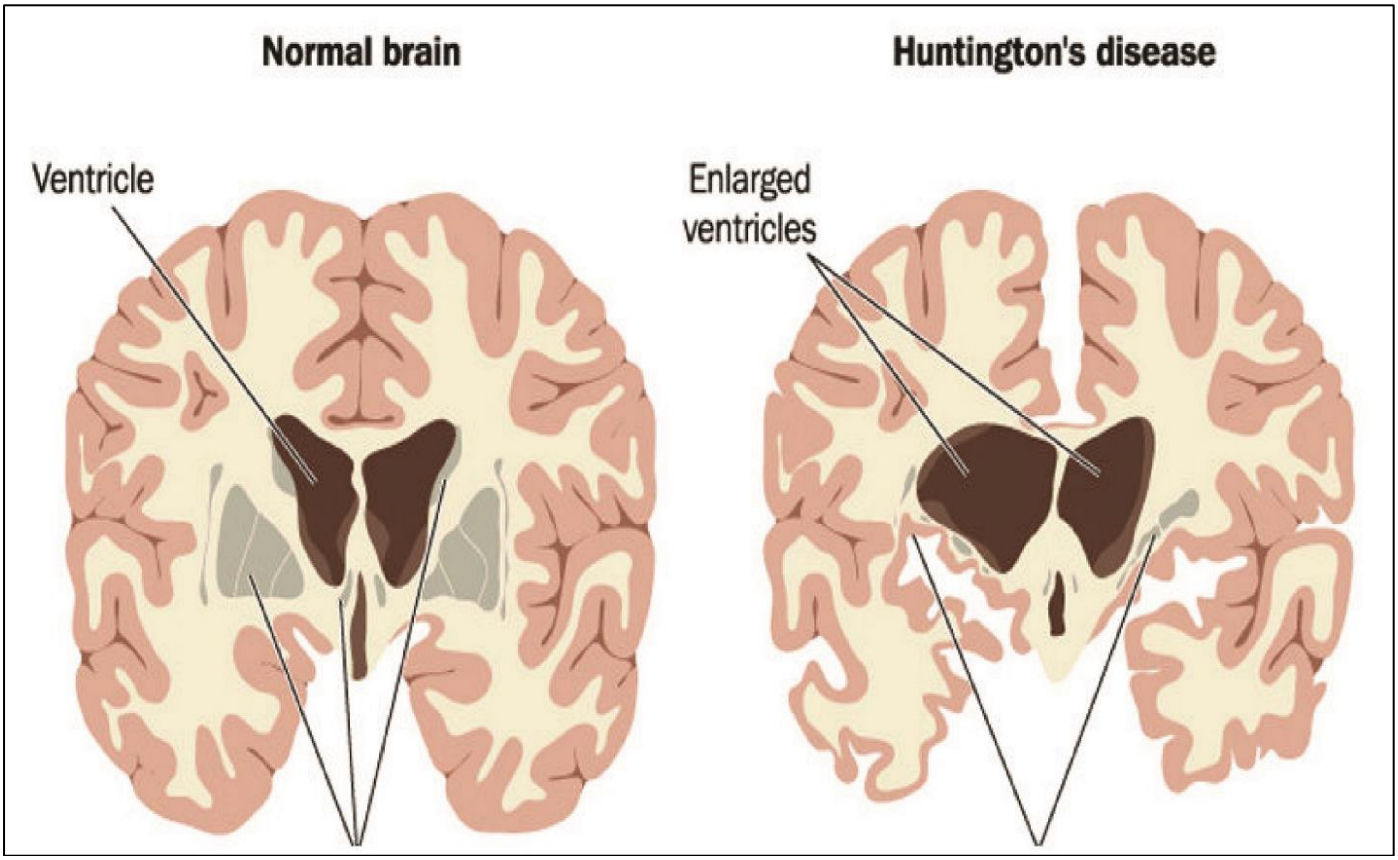


Fig 1 Huntington’s Disease

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## II. CLINICAL FEATURES

A neurodegenerative condition that impairs both motor and cognitive abilities is called Huntington's disease (HD)[12]. HD has a wide range of clinical symptoms that fall into three categories: motor, cognitive, and psychiatric problems.

➢ *Motor Signs And Symptoms*

- *Chorea:*

A defining feature of HD is jerky, involuntary movements. These motions, referred to as chorea, frequently impact the arms, legs, and face.

- *Dystonia:*

Uncontrollably contracted muscles cause unusual stances and motions.

Slowness of voluntary movements is known as bradykinesia[13].

➢ *Symptoms of Cognition:*

- *Cognitive Decline:*

Memory, attention, and executive functioning are among the cognitive processes that HD gradually degrades.

- *Impaired Judgement:*

People may have trouble organizing their thoughts and making decisions.

Cognitive rigidity is the inability to change tactics or adjust to new information.

➢ *Mental Health Symptoms:*

- **Depression:**People with HD may have lingering depressive symptoms.
- **Anxiety:**Overly concerned thoughts and agitation are typical.
- **Irritability:**There is frequently a heightened sensation of frustration and irritability.
- **Apathy:**for pursuits. A deficiency of drive or enthusiasm
- **Psychosis:**People may occasionally have delusions or hallucinations.

➢ *Behavioural Signs And Symptoms:*

- *Impulsivity:*

The inability to restrain one's urges and make thoughtful choices.

A propensity to distance oneself from social situations is known as social withdrawal.

- *Aggression:*

Aggressive conduct is exhibited by certain individuals.

➢ *Decline in Function:*

- *Loss of Independence:*

As the illness worsens, people may need help with everyday tasks.

- *Communication Issues:*

Speech and language skills may deteriorate.

It's crucial to remember that each person with HD may experience these symptoms at different times and in different ways. Every kid of an affected parent has a 50% chance of receiving the faulty gene because the condition is inherited[14]. For those who are at risk, genetic testing can be done to find out if they have the mutant gene.

A multidisciplinary strategy is usually used to manage HD, and it includes medicine, physical therapy, and support for both the patient and their family. Owing to the intricacy of Huntington's disease, patients are frequently managed by a multidisciplinary team of medical specialists, comprising genetic counsellors, neurologists, and psychiatrists.

➢ *Age on Set Hungtington's Disease Statistics:*

Huntington's disease (HD) can strike at any age, however most cases occur between the ages of 30 and 50. The average age of onset is approximately 40 years old. Though extreme cases outside of the usual range are less prevalent, there is a wide range, with onset occurring as late as old age or as early as childhood.

It's crucial to remember that the quantity of CAG repeats in the HTT gene significantly affects the age at which symptoms first appear[15]. Higher CAG repeat counts are associated with early onset of symptoms in most people. The variation in the age of onset of HD can also be attributed to genetic and environmental variables.

## III. DIAGONISIS

A combination of neurological examination, genetic testing, medical history assessment, and occasionally brain imaging is used to diagnose Huntington's disease. This is a synopsis of the diagnostic procedure:

➢ *Medical History and Symptom Assessment:*

When evaluating a patient's symptoms and medical history for Huntington's disease (HD), doctors carefully record the patient's family medical history, taking special note of any cases of HD or associated neurodegenerative diseases. They examine the patient's past medical history in detail, paying close attention to the beginning and development of symptoms like dysphagia, cognitive decline, and psychiatric disorders like depression or mood swings[16]. Clinicians also look into any prior exposure to environmental triggers that might have aggravated HD symptoms. This thorough assessment provides a solid basis for other diagnostic studies, such as genetic testing and neurological exams, allowing for a comprehensive understanding of the disease's expression and course in the individual.

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➢ *Neurological Examination:*

During a neurological examination for Huntington's disease (HD), medical professionals carefully consider many facets of the patient's neurological function in order to determine whether or not the disease-related symptoms are present and how severe they are. Typically, this test evaluates reflexes, motor function, coordination, and cognitive capacity[17]. Physicians keep an eye out for common abnormalities in the patient's movement, include bradykinesia (slowness of movement), dystonia (sustained muscular contractions generating twisting or repeating movements), and chorea (involuntary jerky movements). Along with evaluating muscular strength and tone, they may also search for indications of weakness or rigidity. Motor coordination deficiencies can be detected with the use of coordination tests, such as the heel-to-shin and finger-to-nose motions. Tests of reflexology are used to examine nervous system integrity, and cognitive evaluations, such as executive function, memory, and attention tests, are used to identify any signs of cognitive deterioration. Additionally, since mental symptoms like anxiety, depression, or irritability are common in HD patients, clinicians may keep an eye out for these indicators. All things considered, the neurological examination plays a critical role in the diagnosis and follow-up of Huntington's disease. It offers important information about the degree of neurological involvement and directs management and treatment plans.

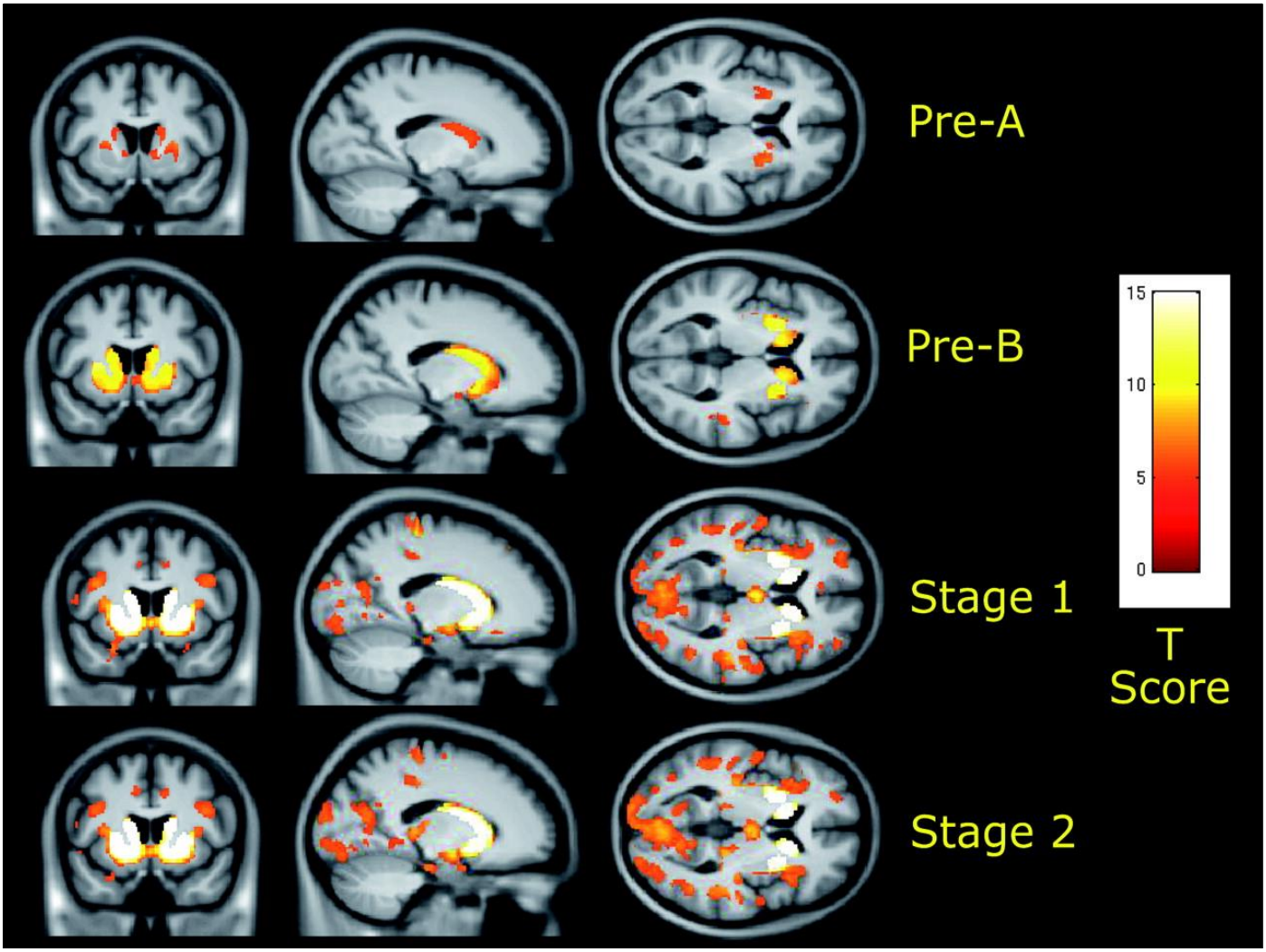


Fig 2 Stages of Huntington's Disease

➢ *Genetic Testing:*

To determine whether a mutation in the HTT gene exists or not, a person's DNA is analyzed, usually using a blood sample, as part of a genetic test for Huntington's disease. Huntington's disease is brought on by this mutation. The procedure starts with genetic counselling to go over the possible consequences of testing. Next, a sample is collected, and DNA is analyzed in a lab setting using methods including DNA sequencing and polymerase chain reaction (PCR). When genetic counsellors or medical professionals analyze the results, they can determine with certainty if a person contains the faulty gene linked to Huntington's disease[18]. While negative results mean that the person has not inherited the mutation, positive results indicate an increased risk of developing the disorder. In order to diagnose Huntington's disease, make informed healthcare decisions, and enable proper medical management and counselling for patients and their families, genetic testing is essential.

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➢ *Brain Imaging:*

Brain imaging methods provide important insights into the anatomical and functional alterations in the brain linked to Huntington's disease (HD), making them useful tools for both diagnosis and treatment. MRIs are frequently used to see anatomical anomalies, including progressive atrophy, in particular brain regions, like the white matter tracts, cortex, and basal ganglia. The degree of physical, cognitive, and psychological symptoms in HD patients may be correlated with these alterations. Furthermore, data regarding brain metabolism, blood flow, and neural activity patterns are provided by functional imaging modalities including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which contribute to our understanding of the etiology and course of the disease[19]. These imaging modalities are essential for tracking the advancement of the disease and assessing the effectiveness of treatment interventions, in addition to aiding in the diagnosis process by helping to distinguish HD from other neurodegenerative conditions.

➢ *Psychiatric Evaluation:*

In order to identify the neuropsychiatric symptoms that are frequently connected to Huntington's disease (HD), a thorough assessment of the patient's mental and emotional health is part of a psychiatric evaluation. The quality of life for people with HD can be greatly impacted by symptoms like despair, anxiety, irritability, apathy, impulsivity, and psychotic characteristics, which are examined by clinicians. A detailed discussion of the patient's past mental health issues, present symptoms, and how they affect day-to-day functioning are usually included in the evaluation. The degree of cognitive impairment and psychiatric symptoms may also be measured using neuropsychological tests and standardized rating scales. A complete treatment plan that addresses both the neurodegenerative process underlying HD and its psychiatric symptoms frequently requires collaborative participation from psychiatrists, neurologists, and other mental health experts. To reduce upsetting symptoms and improve general well-being, treatment approaches may include medication, psychotherapy, supportive counselling, and lifestyle modifications catered to the needs of the patient. For those suffering with Huntington's disease, routine psychological follow-up is crucial for tracking the development of symptoms, assessing the effectiveness of treatments, and modifying therapies as needed to provide comprehensive care.

## IV. TREATMENT

Huntington's disease (HD) has no known cure or slowing down of the disease's course. The primary goals of therapy are to enhance quality of life by supporting patients and treating their symptoms. Treatment is administered for movement disorders such as chorea if they cause pain, substantially impair daily functioning, or result in falls. Tetrabenazine helps with chorea and dystonia and has FDA approval for HD[20]. To treat chorea and mood swings, some people turn to antipsychotic medications like olanzapine. Although their effectiveness is unknown, other drugs such amantadine, benzodiazepines, or baclofen may also be attempted. Standard therapy are usually used to treat psychiatric problems, while medication may not always be helpful. Because citalopram has soothing properties, antidepressants like it are used to treat depression. With few options, treatment often concentrates on managing symptoms and enhancing quality of life.

Table 1 Therapy of Huntington’s Disease

| Symptom | Drug | Dose | Main Side Effects |
|---|---|---|---|
| Chorea | Tetrabenazine | 12.5 - 200 mg/day | Sedation, depression |
| | Olanzapine | 2.5 - 20 mg | Sedation, tardive dyskinesia, parkinsonism, neuroleptic malignant syndrome, raised triglycerides, weight gain. |
| | Amantadine | 100 - 300 mg | Sedation, drowsiness, gastrointestinal disturbances, hallucination, swollen ankles, confusion, livedo reticularis, nightmares |
| Dystonia | Clonazepam | 0.5 - 5 mg | Daytime sedation, increased risk of falls, cognitive impairment, drowsiness, confusion |
| | Tetrabenazine | 12.5 - 200 mg/day | Sedation, depression |
| | Baclofen | 10 - 30 mg | Sedation, drowsiness, gastrointestinal disturbances, confusion, hypotension |
| Akinetic-rigid Parkinsonism | Levodopa | 100 - 1200 mg | Dyskinesias, gastrointestinal disturbance, postural hypotension, insomnia, agitation, increased chorea, psychiatric symptoms |
| Spasticity | Baclofen | 10 - 30 mg | Sedation, drowsiness, gastrointestinal disturbances, confusion, hypotension |
| | Tizanidine | 2 - 24 mg | Bruxism, dystonia |
| | Botulinum toxin | 6 - 12 mg/day | Muscle weakness |
| Psychosis,Irritability | Olanzapine | 2.5 - 20 mg | Sedation, depression |
| | Quetiapine | 25 - 100 mg/day | Sedation, depression |
| | Tiapride | 50 - 1000 mg/day | Sedation, depression |
| | Risperidone | 1 - 6 mg/day | Sedation, depression |
| | Haloperidol | 5 - 20 mg/day | Sedation, depression |

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| | | | |
|---|---|---|---|
| | Clozapine | 12.5 - 300 mg/day | Sedation, depression |
| | Aripiprazole | Dose varies | Sedation, depression |
| Depression/anxiety | SSRIs | Varying doses | Sedation, depression |
| Cognitive impairment | Rivastigmine | 6 - 12 mg/day | Sedation, depression |
| Circadian rhythm disturbances | Zolpidem | 5 - 10 mg/day | Drowsiness, confusion, memory disturbance, gastrointestinal disturbance |

## V. CONCLUSION

Huntington's disease (HD) is a severe condition for which there is no known treatment that frequently results in early death. On the other hand, with comprehensive care, it's also an essential field for creating biomarkers and refining symptomatic therapies, substantially improving the lives of patients and caregivers.e treatments available now control symptoms, international clinical studies hold out hope for future discoveries that may lead to cures or improved treatments. It's important to concentrate on accurate dosage and investigate cutting-edge therapies like gene therapy. Enhancing embryo screening could stop HD from being passed down, giving hope to coming generations.Despite the unknowns, people with HD can find hope and resilience by being optimistic and participating in research. To combat this difficult illness in a more efficient manner, scientific community collaboration is essential.

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