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# DRUG THERAPIES IN PIPELINE FOR THE MANAGEMENT OF HUNTINGTON'S DISEASE

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## ABSTRACT

Huntington's disease (HD) is an inherited neurodegenerative disease caused by an expansion of a repeating CAG triplet series in the huntingtin gene on chromosome 4, resulting in a protein with a tremendously long polyglutamine sequence. Huntington's disease belongs to a large variety of polyglutamine repeat diseases, all of which are neurodegenerative diseases. It is inherited in an autosomal dominant manner so that every child from an affected parent has a 50% chance of developing the disease. The HD gene was identified in 1993. It contains a repeating sequence of three base pairs called a trinucleotide repeat. An excessive number of CAG repeats in the gene results in a protein that contains an excessive number of glutamine units. The normal function of huntingtin is unknown, but the extended polyglutamine sequence in the huntingtin protein is in some ways toxic to brain cells. Just like other polyglutamine expansion disorders, certain neurons appear to be more prone to damage in Huntington's disease. The pathophysiology of Huntington's disease and the cellular mechanisms underlying it are obscure and complicated, making it difficult for clinicians, doctors, neurologists, and researchers to diagnose the disease and devise the approach to developing new drug candidates for the disorder. There is currently no cure or treatment that can stop, slow, or reverse the progression of the disease, but still, researchers are conducting observational studies and clinical trials in order to development-

modifying drugs to cure HD patients and increase the survival rate of HD patients. In this review we try to collect information regarding the various interventions which are under the clinical trials for the management of HD.

**Keywords: Huntington's disease, huntingtin gene, chorea, tetrabenazine**

## 1. INTRODUCTION

Huntington's disease (HD) refers to an autosomal disease that is caused by a mutation in a single gene that leads to progressive neurological disorder caused by protein misfolding **[1]**. The mutation codes for an expanded polyglutamine tract within the Huntingtin gene (HTT) **[2]**, leading to neuronal loss through a pathological cascade of events. HD is caused by a DNA trinucleotide repeat expansion of equal to or greater than 40 CAG repeats within the gene Huntingtin[1]. Repeat numbers vary from 9 to 35 in the non- HD population[2]. Less than 27 repeats, indicates that there is no manifestation of HD, and repeat lengths between 27 to 35 also don't cause the evolution of HD but there is a chance of expansion upon transmission, since the mutant genes may give rise to the occurrence of genetic disorders symptoms at the early stage of HD. At the longer repeat range greater than 35 (i.e., 36 to 39) or more **[2]**, there is an expansion of transmission rate, and it mostly affects the Male population **[3]**.

Huntington's disease was formerly known as Huntington's chorea. On February 15, 1872, Dr. George Huntington wrote his dissertation on chorea in which he mentioned that the name chorea was given because of the tendency to dance in those affected, and it was a very apt name **[1, 4]**. He also found that the most noticeable and distinctive feature is a clonic spasm affecting the voluntary muscles **[1]**. The disease generally manifests itself in middle age and exhibits both physical and psychological symptoms, and the average life expectancy for Huntington's disease is relatively long compared to other neurodegenerative diseases. HD patients can live up to 15 years from diagnosis to death. Huntington's disease is therefore divided into five stages, which include preclinical, early, intermediate, late, and end-of-life (death) stages. Symptoms vary at each stage **[4]**.

The clinical diagnosis of Huntington's disease is possible by observing the characteristics of involuntary movements in HD patients with a family background (for instance over the past decade, observational findings of the early stages have shown an early onset of symptoms before HD motor symptoms begin **[5]**. Early indicators of

cognitive impairment were seen in around half of those investigated, and in more than 70% of those on the borderline of an HD diagnosis. Studies have shown that cognitive impairments and psychiatric disorders are major causes of dysfunction in the brain than a motor disorder in people with HD **[6]**.

Drug therapies for the treatment of HD are not yet available, but the progression of HD is controlled by FDA-approved drugs for symptomatic reliefs of motor, cognitive and psychological disorders **[7]**. These are antipsychotics, neuroleptics, anti-depressants, deep brain stimulation. Pharmacological therapies should be started in the scope of formal education, moral support, and environmental control, rather than in isolation **[6]**. Symptomatic therapy for HD should be treated in the same way as any other medical illness. The physician should note down the symptom's characteristics, onset, and duration and its conditions, which should include causative, aggravating, and relieving aspects. Non-pharmacological therapies should be reviewed, and the physician should be able to identify if treatment goals are being fulfilled and should be ready with an emergency plan if therapy fails.

The US government, pharmaceutical corporations, and private financing organizations have made efforts to perform HD clinical research to overcome this problem by encouraging the researchers to conduct further research on drugs and conduct clinical trials to develop a new drug therapy for long-term disease prevention **[6]**.

## 2. Etiology

An expanded CAG repeats on chromosome 4 causes the neurodegenerative condition and detects the pathogenetic agent i.e., a mutant variant of the versatile protein huntingtin[3,8,9]. These results in the mHTT protein, which has an exceedingly long polyglutamine repeat **[3]** that correlates to the CAG expansion, the toxic properties of the protein causes degeneration of neurons **[8]**. Unaffected populations typically have 17 to 20 CAG repeats across countries; however, CAG tracts with 36 or more repeats are in the affected range **[10]**. The size of the CAG tract is inversely associated with the age of disease onset, with longer tracts signifying earlier initial stages. The CAG repeats are susceptible to expansion, especially when paternal alleles are transmitted down **[10]**. When a gene is passed from father to child, a father with an intermediate range of CAG repeat lengths is likely to have children with lengthy pathogenic repeats. This is because male sperm possesses a greater repeat genetic variation and larger repeat size than somatic

tissues **[3]**. Alleles with between 27 to 35 CAG repeats, known as intermediate alleles (IAs), are capable of causing de novo expansions during transmission **[10]**. In individuals with IAs, HD is unlikely to develop, but their descendants may inherit an enlarged CAG tract and become pathogenic **[10]**. Although the length of the CAG tract is associated with the age of onset, resulting in instability, there is tremendous phenotypic variation among individuals with identical repeat lengths **[9]**. The striatum's medium spiny neurons are highly susceptible to mutant huntingtin-induced damage. Due to the hereditary nature of the disease, genetic testing can be used to diagnose and monitor it. A prodromal phase is characterized by motor, cognitive, and psychological impairments that occur frequently up to 15 years before a full clinical diagnosis of motor onset after a variable premanifest interval **[5]**. Once clinical signs appear, they progress inevitably throughout an illness, that's always fatal, with a typical lifespan of 18 years from motor onset, except for late-onset individuals who suffer from many other causes which may lead to death8.

## 3. Epidemiology

The current epidemiological scale of Huntington's disease is marked by the genetic confirmation of the CAG repeat expansion **[8]**. Prevalence studies including both genetic and clinical diagnostic characteristics in the Western population show that 10.6 to 13.7 people per 100,000, or one in every 7,300, are affected **[3, 8]**.

Huntington's disease is seen in many ethnicities; however, it is far more prevalent in Europeans. HD is diagnosed in just 17 individuals per million in Japan, Hong Kong, and Taiwan, about a tenth of the prevalence in Europe and North America. Black individuals in South Africa also present themselves at lower rates than white and mixed subpopulations. These differences are ethnically specific, as indicated by the fact that HD is far more frequent among individuals of European ancestry (17.2 per 100,000) than in the ethnically diversified general population in British Columbia, Canada (2.1 per 100,000).

Several high-frequency areas have been identified, the most prominent of which is in the Venezuelan city of Maracaibo, where hundreds of associated cases may be traced down to a single founder. Huntington's disease is considered to have lineage-specific prevalence rates attributed to genetic variations at the HTT gene. CAG repeats are greater among groups with a high frequency of the disease, ranging from 18.3–18.8 repeats in Europeans but only 17.5–17.7

repeats in Asian people and 16.9–17.4 repeats in Africans **[8]**. This genetic pattern toward longer CAG repeats is based on particular haplotypes with long CAG repeats seen only in European populations. Intermediate alleles with (27 to 35) CAG repeats leading to Huntington's disease are predominantly found on these haplotypes, implying CAG expansion events in certain chromosomes are more likely to be transmitted to the next generation. The frequency of intermediate alleles increases with the length of CAG repeats in the genome, which suggests that longer CAG repeat lengths may cause greater CAG expansion rates and increased Huntington's disease prevalence. In contrast, enlarged CAG repeats are unusual in fewer populations and occur with a bunch of local haplotypes, indicating a lower mutation rate **[10]**.

## 4. Pathogenesis of HD

### Neuropathology of HD

HD is a neurogenic disorder that involves gradual atrophy of the brain. The major site of pathology is the neostriatum, enclosing basal ganglion which includes the caudate nucleus and putamen **[11]**. Approximately 50 to 60% of the cross-sectional area in advanced HD is lost due to neurodegeneration of the caudate nucleus (CN) and putamen of the neostriatum **[12, 13]**. The globus pallidus (GP), thalamus, and amygdala are also affected by brain atrophy, but to a lesser extent. In addition, the frontal, anterior parietal, anterior temporal, and posterior temporal areas lose around 20% to 30% of their cross-sectional area, damaging white matter **[12]**. The pathological changes in the neostriatum process begin from the caudal-rostral axes, extending to the dorsal-ventral axes and further towards medial-lateral axes **[12]**.

The mutant huntingtin protein has a toxic effect that leads to neuronal death, The most exposed region in the striatum **[14]**. Medium spiny neurons are at high risk when exposed to that. In striatal pathology, a biphasic process occurs. The loss of MSNs from the indirect route initially results in a hyperkinetic phenotype followed by the loss of MSNs from the direct pathway causing a hypokinetic state **[3]**. Affected earlier ones are the indirect pathway neurons that express both proenkephalin and dopamine D2 receptors, as opposed to direct pathway neurons that express preprotachykinin and dopamine D1 receptors **[12]**. Brain atrophy usually occurs during illness, in which functional and morphological connections between the striatum and other brain regions are lost.

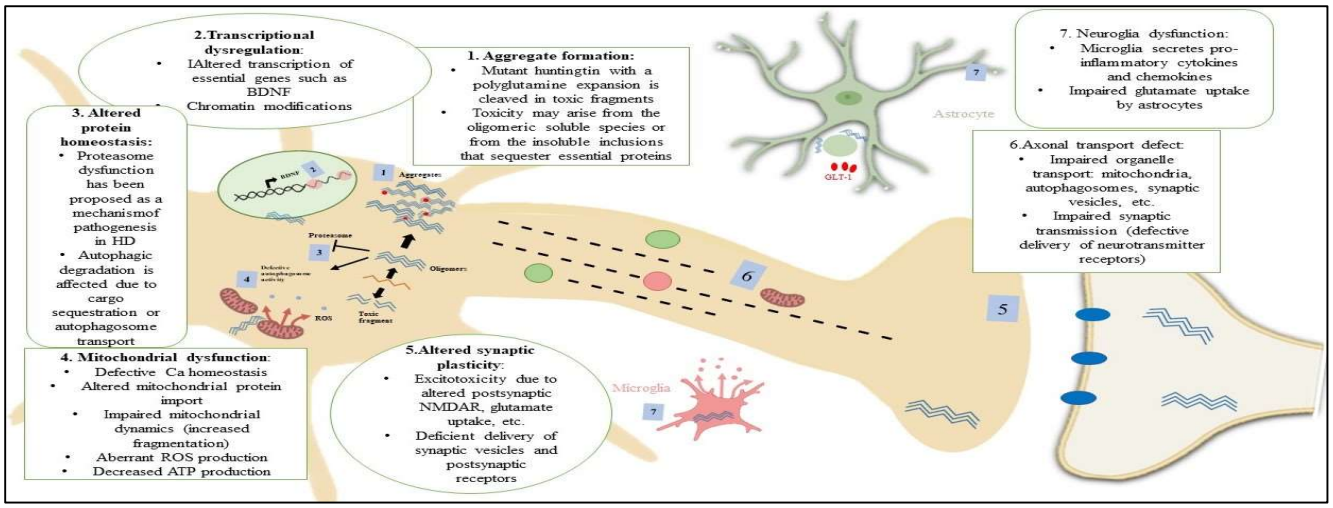


**Figure 1: Pathogenesis mechanisms of Huntington's disease [15]**

## 5. Treatment

Currently, there is no effective treatment available to prevent the advancement of Huntington's disease **[16]**. Hence, the increasing prevalence of HD has been accompanied by an increase in the research for the development of medicinal drugs to eradicate the disease and reduce the mortality rate. Therefore, the only way to control the progression of the disease is strictly based on the management of symptoms, genetic counselling, and palliative care **[16, 17]**.

Recent research has shown that because Huntington's disease is autosomal dominant and, unlike other neurogenerative diseases, does not follow the Mendelian inheritance pattern, therefore, symptoms are easily traceable before the disease progresses, making pre-symptomatic treatment a viable option **[18]**. Thus, the pharmacological activity relates to the prevention of symptomatic relief **[7]**. It played the role in treating the hyperkinetic movement disorders mainly associated with Huntington's disease, such as chorea, dystonia, as well as on psychiatric problems related to Huntington's disease such as depression, anxiety, mania, apathy, obsessive-compulsive disorder, or the cognitive decline associated with HD **[19]**.

People with HD are currently only treated symptomatically, in an attempt to improve their quality of life. There are a number of off-label medications that can be used for psychomotor symptoms, including antipsychotics, glutamine antagonists, NMDA antagonists. For choreatic dystonia (HD) treatment, the FDA currently approves only two drugs: deutetrabenazine and

tetrabenazine, which inhibit vesicular monoamine transporter 2 (VMAT2). The treatment of neuropsychiatric symptoms is often associated with neuroleptics, mood stabilizers, and antidepressants. As part of HD treatment, non-drug therapies, including occupational therapy, physiotherapy, speech therapy, psychotherapy, social services, and nutrition are also important.

The majority of pharmacotherapy used to treat motor symptoms is aimed at restoring the neurotransmitter balance most notably GABA, dopamine (DA), and glutamate **[19]**. These pharmaco-therapeutic agents include dopamine-depleting drugs such as tetrabenazine, neuroleptic agents e.g. Haloperidol, Pimozide, Fluphenazine, Thioridazine, Sulpiride, and Tiapride, glutamate antagonists e.g. Amantadine, Remacemide, Memantine, Riluzole, Lamotrigine, Acetylcholinesterase inhibitors e.g. Donepezil, Rivastigmine, Galantamine, dopamine agonists e.g. Levodopa, pramipexole, Cabergoline, antidepressants e.g. Paroxetine, Fluoxetine, Mirtazapine, deep brain stimulation e.g. TBZ, haloperidol, amantadine, and fetal cell transplantation **[19, 20]**.

**Table 1: A summary of the available drugs which are currently used for symptomatic relief of Huntington's disease**

| Drugs | Class | Mechanism of action | Indication | Doses | Side-effects | Ref |
|---|---|---|---|---|---|---|
| Tetrabenazine (TBZ) | Dopamine depleting agent | TBZ inhibits vesicular monoamine transporter (VMAT2) of the central nervous system | Chorea Tardive dyskinesia Spinal myoclonus Dystonia | 12.5-200 mg/day | parkinsonism depression, anxiety, acute dystonia, orthostatic hypotension, hallucination. | [19,21–23] |
| Risperidone | Atypical Antipsychotic | Inhibiting the action of both dopaminergic and serotonergic receptors | Chorea Tremor Depression Apathy | 2-20 mg/day | Prolonged QT interval, postural hypotension, tardive dyskinesia, parkinsonism, fatigue, | [24–26] |
| Olanzapine | Antipsychotic agent 5-HT2 and D2 receptor antagonist | It blocks the D1, D2, D4, 5HT2A, 5HT2C, 5 HT3, receptors | Chorea Dystonia Weight loss Depression | 10-20 mg/day | Agranulocytosis fatigue, hepatitis, | [25,27–29] |
| Haloperidol | Anti-psychotic, typical neuroleptic agent, D2 antagonist | Inhibiting the D2 receptors | Chorea, Psychosis, depression | 2-80 mg/day | extrapyramidal symptoms, withdrawal neurological syndrome, lactation, gynecomastia, impotence | [30–32] |
| Fluphenazine | Antipsychotic drug, D2 receptor antagonist, | It antagonizes postsynaptic dopamine-2 receptors in mesolimbic nerve tracts | Chorea Depression | 1-40 mg/day | akathisia, gait, acute dystonic reactions, oculogyric crises, opisthotonos | [33–35] |
| Pimozide | D2 antagonist | It selectively blocks D1–D2 receptors along with calcium ion channels. | Chorea OCD Depression | 13.8 mg/day | constipation, tardive dyskinesia, malignant syndrome. | [7,36,37] |
| Sulpiride | D2/D3 antagonist | It blocks D2-D3 receptors | Chorea | 300-1200 mg/day | parkinsonism, neuroleptic malignant syndrome. | [7,38,39] |
| Amantadine | NMDA Receptor Antagonists | It prevents dopamine reuptake. | Chorea | 100-400 mg/day | anorexia, ataxia, livedo reticularis, peripheral edema, somnolence, agitation | [40–43] |
| Remacemide | NMDA antagonist | It inhibits the binding | Chorea | 200-600 | Dizziness, | [44] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **of glutamate to NMDA receptors** | | **mg/day** | **gastrointestinal disturbances** | |
| **Memantine** | **NMDA antagonist** | **It Inhibits the pathway to excessive NMDA activation and nerve cell death.** | **Chorea swallowing function, lip dyskinesia, dystonia** | **5-20 mg/day** | **constipation, confusion, cough, hypertension.** | **[37,45–47]** |
| **Riluzole** | **NMDA antagonist** | **It inhibits the release of glutamate due to the inactivation of voltage-dependent sodium channels** | **Chorea** | **50-200 mg/day** | **increase in the levels of the aminotransferase enzyme** | **[48–52]** |
| **Lamotrigine** | **NMDA antagonist** | **Inhibits the release of glutamate by interfering with sodium channels via prolonging the inactive refractory period** | **Chorea Depression Mood swings High risk of suicidal attempts** | **25-300 mg/day** | **Nausea, skin rash, insomnia, and severe depression** | **[48,53,54]** |
| **Donepezil** | **Acetylcholinesterase inhibitors** | **It inhibits the hydrolysis of acetylcholine** | **Chorea Dementia** | **5-10 mg/day** | **Bradycardia edema, EKG abnormalities, rhabdomyolysis.** | **[55,56]** |
| **Rivastigmine** | **Acetylcholinesterase inhibitor** | **Inhibits the hydrolysis of acetylcholine** | **Chorea Cognitive dysfunction** | **3-6 mg/day** | **Nausea, dyspepsia, bradycardia, and hallucinations.** | **[37,57–60]** |
| **Galantamine** | **Allosteric modulator of nAchR** | **Allosteric modulation of nicotinic acetylcholine receptors (nAchR)** | **Dementia Chorea Cognitive disorders** | **24 mg/day** | **seizures, collapse, chest pain irregular heartbeat.** | **[61–64]** |
| **Levodopa** | **Dopa agonist** | **Lowering the sensitivity of postsynaptic dopamine receptors** | **Chorea Gaits Postural instability Dystonia** | **250 mg/day-6g/day** | **Impaired speech, Hallucinations** | **[65–67]** |
| **Paroxetine** | **Selective serotonin reuptake inhibitors (SSRI)** | **block serotonin reabsorption** | **Depression Anxiety Psychiatric disorders** | **20-60 mg/day** | **Sexual dysfunction, insomnia, weight loss, and restlessness.** | **[68–70]** |

## 6. Clinical Trials

Clinical trials include both long-term studies aimed at slowing the progression of Huntington's disease and short-term studies aimed at improving symptoms. Scientists speculated that HD could be treated and was determined to find therapies for in vitro HD models, such as healthy transgenic mice **[6]**.

HDSA has provided grants to a large number of basic science researchers. significant contributions were made by other organizations to HD research. In 1968, Milton Wexler, MD, founded the renowned Hereditary Disease Foundation (HDF). A team of more than 100 scientists led by HDF worked together to study thousands of blood samples and pedigrees collected from volunteers in Venezuela, a country with a high prevalence of HD **[6]**. There is no cure for HD yet so the development of effective and novel HD therapies remains a priority since the current treatments focus mainly on managing the symptoms. Several clinical trials are currently underway to evaluate the potential effectiveness of various treatment modalities for HD **[17]**.

**Table 2: A summary of each intervention and its potential mechanism of action of phase I are listed below [72]**

| Sr. No. | Intervention/class of drug | CT identifier ID | Sponsor | Status | Location | Start date | Expected end date |
|---|---|---|---|---|---|---|---|
| 1 | Nilotinib (Kinase inhibitors) | NCT03764215 | Georgetown University | Recruiting | United States | November 15, 2018 | November 30, 2020 |
| 2 | Rolipram (PDE4 inhibitor) | NCT01602900 | GlaxoSmithKline | completed | United Kingdom | May 21, 2012 | June 20, 2017 |
| 3 | Cellavita (Stem cell therapy) | NCT02728115 | Azidus Brasil | Active not recruiting | Brazil | April 5, 2016 | June 23, 2021 |
| 4 | SAGE-718 Oral Solution (NMDA modulator) | NCT03787758 | Sage Therapeutics | Completed | United States | December 26, 2018 | November 19, 2019 |
| 5 | Pridopidine (Sigma-1 Receptor (S1R) agonist) | NCT03019289 | Prilenia | completed | Germany | January 12, 2017 | November 19, 2021 |
| 6 | RO7234292 (RG6042) Mtt lowering | NCT04000594 | Hoffmann-La Roche | Recruiting | Netherlands, United Kingdom | June 27, 2019 | November 3, 2021 |
| 7 | CKD-504 (HDAC inhibitor) | NCT03713892 | Chong Kun Dang Pharmaceutical | Recruiting | Korea | October 22, 2018 | December 2020 |

**Table 3: Summary of each intervention and its potential mechanism of action of phase II are listed below**

| Sr. No. | Intervention/ class of drug | CT identifier ID | Sponsor | Status | Location | Start date | Expected end date |
|---|---|---|---|---|---|---|---|
| 1 | Memantine (NMDA antagonist) | NCT01458470 | University of British Columbia | completed | Canada | October 24, 2011 | January 13, 2020 |
| 2 | WVE-003 (Stereo pure antisense oligonucleotide (ASO)) | NCT05032196 | Wave Life Sciences Ltd. | Recruiting | Australia Canada Denmark France Germany Poland United Kingdom | November 1, 2021 | December 2022 |
| 3 | Deutetrabenazine (Dopaminergic modulation) | NCT04713982 | Vanderbilt University Medical Center | Recruiting | United States | November 22, 2021 | July 30, 2023 |
| 4 | Fenofibrate (Antilipemic drug) | NCT03515213 | University of California, Irvine | Active, not recruiting | United States | April 19, 2021 | August 2021 |
| 5 | Risperidone (Dopaminergic modulation) | NCT04201834 | University of Rochester | Recruiting | United States | November 3, 2021 | December 30, 2022 |
| 6 | Laquinimod (immunomodulator) | NCT02215616 | Teva Branded Pharmaceutical Products R&D, Inc. | completed | Canada Czechia Germany Italy Netherlands Portugal Russia Spain United Kingdom United States | August 13, 2014 | May 4, 2020 |
| 7 | Pridopidine (Sigma-1 Receptor agonist) | NCT02006472 | Prilenia | completed | Australia Austria Canada Denmark France Germany Italy Netherlands United Kingdom United States | December 10, 2013 | July 19, 2021 |
| 8 | RO7234292 (mHtt lowering) | NCT03342053 | Hoffmann-La Roche | completed | Canada Germany UK | November 14, 2017 | January 19, 2021 |
| 9 | ANX005 Anti-anemic, monoclonal antibodies | NCT04514367 | Annexon, Inc. | Active, not recruiting | United States | November 23, 2021 | January 2022 |
| 10 | AMT-130 Gene silencing | NCT04120493 | UniQure Biopharma B.V. | Recruiting | United States | October 1, 2021 | December 2022 |

Table 4: A summary of each intervention and its potential mechanism of action of phase III is listed below

| Sr. No. | Intervention/ class of drug | CT identifier | Sponsor | Status | Location | Start date | Expected end date |
|---|---|---|---|---|---|---|---|
| 1 | Valbenazine (VMAT2 inhibitor) | NCT04102579 | Neurocrine Biosciences | Active, not recruiting | Canada, United States | November 2019– | September 2021 |
| 2 | Dextromethorp-han (Glutamatergic modulation) | NCT03854019 | The University of Texas Health Science Center, Houston | Recruiting | United States | August 5, 2019 | December 31, 2021 |
| 3 | Pridopidine (Sigma-1 Receptor agonist) | NCT03019289 | Prilenia | Completed | Germany | January 12, 2017 | November 19, 2021 |
| 4 | RO7234292 (RG6042) (Antisense therapy) | NCT03842969 | Hoffmann-La Roche | Recruiting | Australia Austria Canada Chile Germany Italy Japan Spain United Kingdom United States | November 3, 2021 | June 20, 2024 |
| 5 | Metformin (AMPK activator) | NCT04826692 | Instituto de Investigation Sanitaria La Fe | Not yet recruiting | Unprovided | July 21, 2021 | August 2024 |

Table 5: A summary of each intervention and its potential mechanism of action of phase IV is listed below

| Sr. No. | Intervention/treatment | CT identifier | Status | Sponsor | Location | Start date | Expected end date |
|---|---|---|---|---|---|---|---|
| 1. | Tetrabenazine Dopaminergic modulator | NCT02509793 | Recruiting | William Ondo, MD | United States | September 19, 2019 | July 1, 2023 |
| 2 | Memantine NMDA antagonist | NCT00652457 | Completed | Jody Corey-Bloom, MD, PhD | United States | April 3, 2008 | January 5, 2021 |

## 7. CONCLUSION

Huntington's disease is a progressive neurodegenerative disease caused by an elongated CAG repeat length of the HTT gene, which codes for an important protein in brain cells called huntingtin. It manifests itself with motor, cognitive, and psychological clinical features, which are mainly characterized by involuntary movement, e.g., Chorea. HD occurs in both juveniles and adults. No treatment is currently available to cure the disease, but Huntington's disease symptoms are controlled by taking some medications, such as antipsychotics, neuroleptics, and antidepressants. In addition, clinicians, doctors, neurologists, and psychiatrists play important roles in diagnosing symptoms at each stage of Huntington's disease. They are done through genetic and predictive tests to detect the changes in the brain and report the changes in CAG repeats through this relevant data It helps the researcher to plan observational studies like PREDICT-HD, TRACK-HD, COHORT studies, to conduct the clinical trials to develop the new effective drug to treat the disease instead of preventing it.

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