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Recent Therapeutic Approaches in Treatment of Huntington's Disease

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ABSTRACT

Huntington's disease is a rare neuropsychiatric disorder. It is most common in Europe and European countries. It is an autosomal dominant genetic and progressive neurodegenerative disorder caused by abnormal expansion of CAG trinucleotide repeats within exon 1 of the Huntington gene (HTT). CAG is a trinucleotide, the building stone of DNA. CAG is the codon for the amino acid glutamic. This disorder passes within families from generation to generation and is characterized by unwanted Choreatic movements, dementia, behaviour and psychiatric disturbances. Symptoms show at the age of 35 and 50. For the diagnosis of Huntington's Disease genetic test, prenatal test, computed tomography, magnetic resonance imaging such tests are used. Clozapine and olanzapine are atypical neuroleptics are used in treatment of Huntington's disease. Pridopadine hydrochloride Mardepodect Latrepirdine dihydrochloride Selisistat, PBT-2 and RG-6042 are drugs in clinical trial used for Huntington's disease may be used in future for treatment of Huntington's disease.

INTRODUCTION:

Huntington disease (HD) is an autosomal dominant genetic and progressive neurodegenerative disorder caused by abnormal expansion of CAG trinucleotide repeats within exon 1 of Huntington gene (HTT) (9). CAG is a trinucleotide the building stone of DNA. CAG is the codon for the amino acid glutamic. (1) Individuals with one HTT allele containing 40 or more CAG repeats are invariably affected by disease while individuals with fewer than 36 CAG repeats on both alleles do not manifest the disease (7). According to technical standards and guidelines for Huntington Disease testing allele sizes of ≤26 CAG repeats have never been associated with a Huntington Disease phenotype. Allele sizes of 27-35 CAG repeats are rare and have not been convincingly associated with Huntington Disease Phenotype. However, allele sizes of 36-39 CAG repeats have been reported in both clinically affected and clinically unaffected individuals. Alleles with more than 40 CAGs present 100% penetrance for Huntington Disease (6). This CAG expanded repeats are translated into a long pathogenic polyglutamine (poly Q) tract that renders the Huntington protein more prone to aggregate. This autosomal dominant mutation results in an abnormal Polyglutamine expansion in Huntington protein with toxic effects. mutant HTT (mHTT) protein forms nuclear & cytoplasmic inclusion that interfere with almost all aspects of cell physiology. (8) The disease which gets worse over time, attacks motor control regions of brain as well as other areas. People with Huntington Disease develop problems with behaviour, emotion, thinking personality along with uncontrollable dance- like movement (Chorea) and abnormal body posture. (10) This approaches the recent therapeutic treatment of Huntington Disease which includes the use of some recent drugs like pridopadine hydrochloride, dihydrochloride, selisistat.

EPIDEMIOLOGY

Huntington's disease is a rare neuropsychiatric disorder. In the Caucasian population it has a prevalence of 5-10 per 100,000 (1). The prevalence of Huntington's disease ranges from 10.6 to 13.7 per 100,000 western populations. Japan, Taiwan and Hong Kong have a much lower incidence of HD, with a prevalence of 1-7 per million people. In South Africa, lower rates are found in black populations compared to white and mixed populations. Differences in disease prevalence among ethnic groups are related to genetic differences in the Htt gene. Huntington's disease is most common in Europe and European countries. The lowest frequencies are recorded in Africa, China, Japan and Finland. The prevalence for most

European countries ranges from 1.63 to 9.95 per 100,000 populations. Studies on the distribution of CAG repeats in the general population suggest a high prevalence of HD in India, similar to that observed in Western Europe (5). In general, Huntington's disease is a devastating and progressive disease that causes death within 15–20 years of its onset (4).

PATHOPHYSIOLOGY:

Mutated Huntingtin Leads to Neuronal Dysfunction and Death through some mechanism. This includes Mhtt fragment exon 1, Mhtt formation propensity abnormal aggregates and effects on cellular protein homeostasis, axonal transport, transcription and translation, mitochondria and synaptic function of central spiny neurons (MSNs) [25]. The striatum is selectively susceptible to Mhtt [26]. Or Indirect Route MSN Selective Vulnerability Causes Unknown. However, dopamine D2 receptors may be a factor They are represented through MSNs indirectly rather than directly. It is involved in the etiology of Huntington's disease [27]. Other hypotheses include Loss of brain-derived neurotrophic factor, glutamate excitotoxicity of cortico-striatal projections and repetitive toxic effects Associated non-ATG translated proteins [28].HTT is a very large protein, mainly Repeating units of about 50 amino acids called HEAT repeats. These repeats are Spiral hairpin shape that gathers in a super spiral structure with a continuous hydrophobic core [29]. Most available Dominant genetic transmission, including evidence, exists abnormal aggregated proteins and biochemical findings, cells and mouse model studies suggest that HD predominates Acquisition of toxic functions from anomalous conformations of mutant HTT.

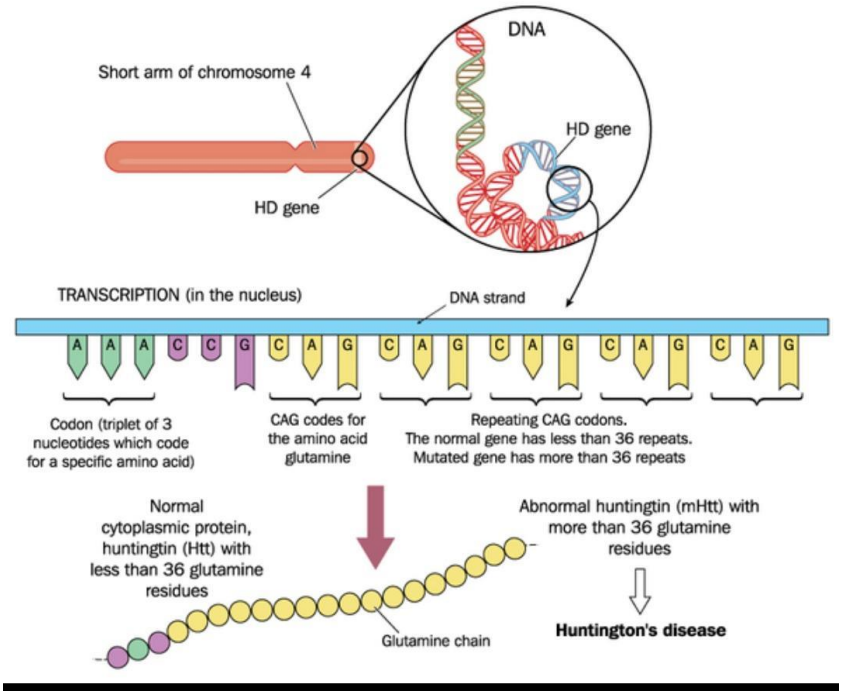


Fig No -01 Pathophysiology of Huntington Disease

SYMPTOMS: - The symptoms of Huntington's disease are summarised in table no 01

Table No 1 Symptoms of Huntington's Disease

Motor symptoms	Psychiatric symptoms	Secondary symptoms
Changes in fingers, toes also in small facial muscles	Depression	**Behavioural changes:**
Eyebrows lifted	Weight loss	Activity issues
Problem during talking and swallowing	Difficulty in organising and prioritizing	loss of antecedently learned educational or physical skills
Tongue is protruded with lips pouting	Inactivity in Huntington Disease	fast and vital drop by overall performance.
Eye closed	Apathy	**Physical changes:**
Head is bent	Lack of flexibility	Changes in fine motor skills
Bradykinesia	Lack of impulse	Seizures
Dystonia Abnormal posture	Difficulty in learning new information	Narrowed and rigid muscles that have a effect on gait

PREVALENCE:

The prevalence of Huntington Disease varies more than ten times between different geographical regions. In Asian population there is lower incidence but in Australia, North America and in Western Europe prevalence has increased over the years.(15).

AGE AFFECTED

Table No 02- Age Affected in Huntingtins Disease

Sr No	Age group	Population affected
1	Toddlers (3-5 years):	extremely rare
2	Children (6-13 years):	extremely rare
3	Teenagers (14-18 years):	Very rare
4	Young adults (19-40 years):	rare
5	Adults (41-60 years):	rare
6	Seniors	rare

DIAGNOSIS:

Diagnosis of Huntington Disease is generally based on findings from neurological Psychological and genetic testing. (10) It is also based on clinical symptoms and signs in a person with a parent with proven Huntington Disease.(1). Neurological exam and patient history: A neurologist will conduct an in depth interview to obtain the medical history to rule out other conditions. Neurological and physical exams may review reflexes, balance movement, muscle tone, hearing, walking and mental status. (10)

DIAGNOSTIC IMAGING:

In some cases, especially if a person's family history and genetic testing are inconclusive, the physician may recommend brain imaging such as computed tomography (okCT) or magnetic resonance imaging (MRI). As the disease progresses, these Scans typically reveal shrinkage in parts of the brain and enlargement of fluid- filled cavities within the brain called ventricles. (10)

GENETIC TESTS:

The most effective and accurate method of testing for Huntington Disease called the direct genetic test- counts the number of CAG repeats in Huntington gene using DNA taken from a blood sample. The presence of 36 or more repeats supports diagnosis of Huntington Disease. Older genetic test called 'linkage testing' required sample of DNA from a closely related affected relative, preferably a parent. (10) The genetic test does not confirm the diagnosis. These Phenocopies are defined by clinical diagnosis of Huntington Disease with choreo, psychiatric and cognitive signs and an autosomal dominant pattern of inheritance or family history (1). Prenat testing is an option for people who have a family history of Huntington Disease. (10) As the test can be performed on any cell with a nucleus containing DNA prenatal diagnosis is also possible. The procedure is embarked on with the intension of ending the pregnancy if the Huntington Disease gene is found in embryo. (1)

TREATMENT:

The most commonly used drugs for depression and aggression are listed in Table 3. Clozapine and olanzapine are atypical neuroleptics. Both have an antichoreatic effect. Clozapine requires white cell Control in the blood and is, therefore, less practical, Making olanzapine the preferred drug. The most frequently reported side effects are weight increase and Anti-depressive effects.(1). The most commonly used therapies in HD patients are Symptomatic drug therapies and no therapies has been developed that effectively modifies disease progression. Even though the pathogenesis of HD has still not been resolved and a cure is not available, many therapeutic options are available for treating symptoms and signs with a view to improving quality of life. Treatment consists of drug prescription and non-medication Advice [5]. There is presently no cure for Huntington's illness and no thanks to slow stop the brain changes it causes. Current treatments concentrate on managing symptoms. The subsequent treatments area unit used as first-line methods for 3 of the disorder's most worrisome Symptoms.

• Chorea (involuntary movements)

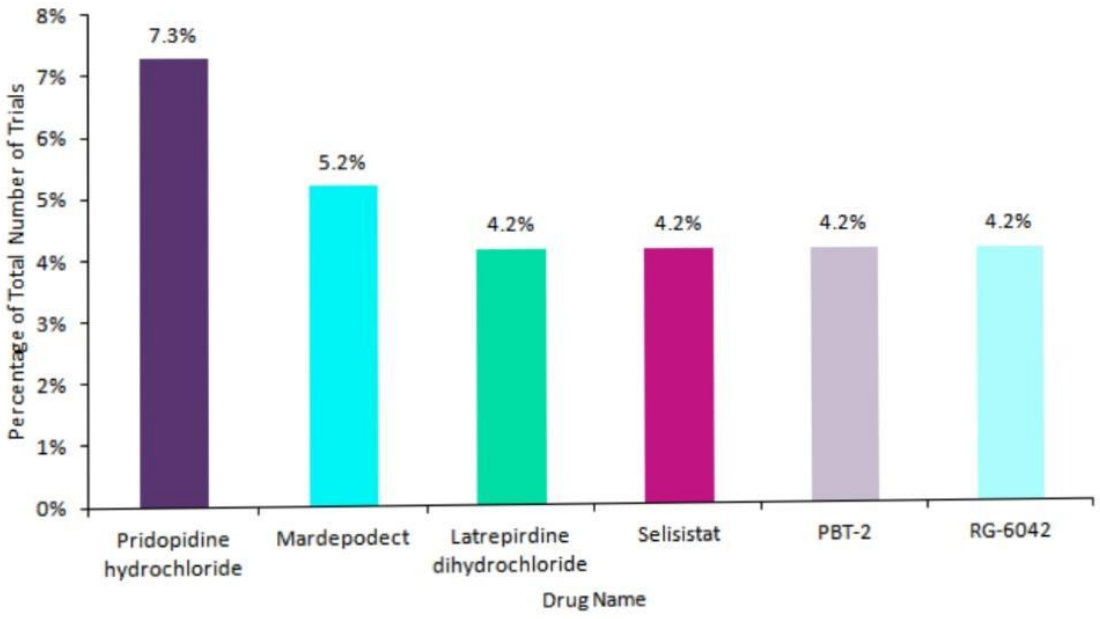
• Irritability: For severe anger and threatening behavior, Neurotic thoughts and actions: specialists conjointly suggest SSRIs because the customary treatment for these symptoms. Abundant analysis on HD is concentrated on however mutant Huntingtin causes toxicity in cell-based and model organisms.(4)

Drug treatment for Huntington's chorea.

Table No 03 – Drug treatment for Huntington's disease

Sr No	Drug name	Dose (mg)
1	Tiapride	600
2	Olanzapine	20
3	Tetrabenazine	200
4	Pimozide	6
5	Risperidone	16
6	Fluphenazine	10

Analysis of drugs used in clinical trails:-



Top six drugs used in Huntington's disease clinical trial

Table No:- 04 Drugs in clinical trials

Sr.no.	Drug in clinical trials
1	Pridopadine hydrochloride
2	Mardepodect
3	Latrepirdine dihydrochloride
4	Selisistat
5	PBT-2
6	RG-6042

Pridopadine hydrochloride

In stage 3, a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of pridopidine 45 mg BID in patients with early stage HD. Eligible patients who completed the main study (65 to 78 weeks) will have the option to enrol in an open-label extension. (1)

Mardepodect (PF-2545920)

Is a potent, orally active and selective PDE10A inhibitor with an IC50 of 0.37 nM and >1000-fold selectivity over other PDEs. Mardepodect can cross the blood-brain barrier. (2)

Latrepirdine

Short-term administration of latrepirdine is well tolerated in patients with HD and may have a beneficial effect on cognition. Further investigation of latrepirdine is warranted in this population with HD.Latrepirdine, 20 mg three times daily, has been studied in a randomized, double-blind, placebo-controlled trial in patients with mild to moderate Alzheimer's disease (AD) and demonstrated significant improvement compared with placebo in cognitive, behavioral, and functional scores at 6 and 12 months. 5 An earlier open-label, dose-escalation study in patients with HD suggested dosages up to 20 mg 3 times daily would be tolerated in this population. 6 We studied the safety and tolerability of latrepirdine, 20 mg 3 times daily, and explored its effects on symptoms in patients with mild to moderate HD. (3)

Selisistat

The 10 mg dose level (125 nm) was found to be safe and well tolerated, and systemic exposure parameters showed that the average steady-state plasma concentration achieved at

the 10 mg dose level (125 nm) was comparable to the IC50 for SirT1 inhibition. No adverse effects on motor, cognitive, or functional readouts were recorded. While circulating levels of soluble huntingtin were not affected by selisistat in this study, the biological samples collected have allowed the development of assay technology for use in future studies. No effects on innate immune markers were seen. (4)

PBT2-203

The study will evaluate how safe and well tolerated PBT2 is at a dose of 100 mg or 250 mg a day administered as oral daily capsules compared to a placebo over a six-month treatment period. The trial will also measure whether there is an effect on cognitive abilities as well as other HD symptoms, including motor and overall functioning of individuals with HD. (5)

BP40410

Study BP40410 is an open-label, adaptive multiple-dose clinical study designed to characterise the PK of RO7234292 (RG6042) in plasma and CSF as well as the acute time course and recovery profile of CSF mHTT lowering in response to RO7234292 (RG6042) treatment after intrathecal (IT) administration of RO7234292 (RG6042) to patients with manifest Huntington's disease (HD). (6)

CONCLUSION-

Huntington's disease is a rare neuropsychiatric disorder. In review article discuss about diagnosis of Huntington's Disease such as genetic test, prenatal test, computed tomography, and magnetic resonance imaging. Clozapine and olanzapine are atypical neuroleptics are used in treatment of Huntington's disease. And about recent drugs used in treatment of Huntington's disease such as Pridopadine hydrochloride, Mardepodect Latrepirdine, dihydrochloride, Selisistat, PBT-2 and RG-6042 which may be used as new therapeutic approaches in treatment of Huntington's disease.

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