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HUNTINGTON'S DISEASE (HD): A BRIEF REVIEW

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Abstract:
Huntington's disease (HD) is an incurable lethal inherited neurological disorder of brain cells caused by increased CAG repeats in the huntingtin gene. It is the disease of mind and body which causes uncontrolled movements, loss of intellectual faculties, and emotional disturbance leading to eventual death. HD is incurable, but treatment is available for the symptoms of this disease. Latest technologies and techniques are used to diagnose HD. Neuroimaging and genetic testing are two important diagnoses techniques are available to measure the progress of the disease at any later stage. Drastic research is underway to control the disease with neuro-transplantation and neuro-surgery as a potential treatment in future to cure HD. The advancements in science and technologies and research on HD have indicated bright chances of cure. In the future, this disease seems to become curable Huntington's disease.

Keywords: Huntington's disease, diagnosis, symptoms and treatment

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1. Introduction

Huntington's disease, known as (HD), is an incurable hereditary progressive neurodegenerative disorder of brain cells affecting a person's behaviour, particularly in thinking, reasoning, and movement. The medical dictionary defines Huntington's disease as "*a rare inherited disease of the central nervous system (CNS) characterised by progressive dementia, abnormal posture, and involuntary movements*." HD damages nerve cells (called neurons) in parts of the brain to gradually break down and die.

HD gets worse over time and attacks motor control regions of the brain (those involved with movement) and other areas. As a result, patients with HD develop behavioural, emotional, thinking, and personality problems, along with uncontrollable dance-like movements (called chorea) and abnormal body postures.

The typical age of onset is between "30 and 50 years". The mean age of onset for HD is 35 to 44 years [Bates et al., 2002]. Inherited diseases are transferred from parent to offspring through genes.

Genes control cells by producing proteins; each gene is a recipe for making a specific protein. Genes are usually attached to a chromosome (a strand of Deoxyribonucleic acid-DNA containing many different genes). A chromosome is the structure housing DNA in a cell. Chromosomes are structurally quite sophisticated, containing elements necessary for processes such as replication and segregation. Each human cell contains around 25,000 genes, and most have 23 pairs of chromosomes. Twenty-two of these pairs, called autosomes, look the same in both males and females. However, the 23rd pair, the sex chromosomes, differs between males and females, X and Y. Each parent contributes one chromosome of each pair to an offspring.

HD is a monogenic neurological disorder [Fisher & Hayden, 2014] resulting from modifying a single gene. More than 10,000 monogenic diseases have been documented worldwide, with neurological disorders accounting for roughly 17% of the total, encompassing a wide range of brain abnormalities [Chen et al., 2020]. Monogenic neurological disorders, in particular, are thought to account for up to 40% of the burden in hospital paediatrics, with over 1% of children affected from birth [Scott et al., 2016].

Monogenic neurological illnesses are linked to a wide range of brain impairments. These include birth defects (e.g., fragile X syndrome, Huntington's disease, or monogenic autism), a degenerative neuronal deficiency that manifests later in life (e.g., some forms of Parkinson's disease or amyotrophic lateral sclerosis), and early or late onset of abnormal functioning in people with structurally normal brains (e.g. Dystonia) [Chen et al., 2020].

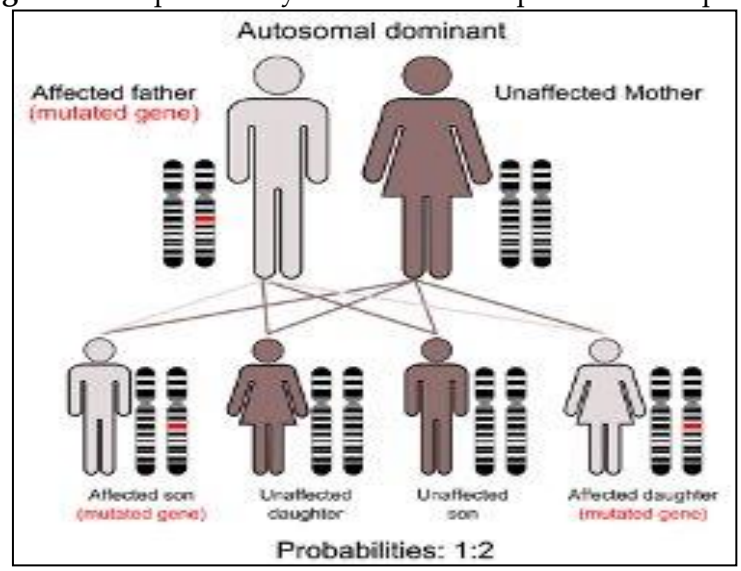
The offspring gets the same copy of genetic material as of the parents. The brain is one of the most important organs of the human body which not only responsible for thinking, planning, storing information but also monitor, regulate, coordinate and control conscious and unconscious body processes such as breathing, digestion and body movements. HD occurs due to cytosine, adenine, and guanine (CAG) trinucleotide repeats on the short arm of the chromosome (pair 4) 4p16.3 in the Huntingtin (HTT) gene.

This mutation leads to an abnormally long expansion of the polyglutamine in the HTT protein, which leads to neurodegeneration.

The neurological disorder in HD is caused by transferring a single defective Huntingtin gene from parent to offspring, which does not produce a normal functional protein, instead produces a defective misfolded protein with an excessive amount of the amino acids glutamine. This defective misfolded protein causes the degeneration of nerve cells leading to the death of these cells. Affected people lose their mental and physical abilities. They find difficulties in walking, talking, remembering, and becoming depressed; therefore, the cost of care for this disease is very high compared to other diseases. Patients need a wide range of experts and professionals, including doctors, neurologists, psychologists, speech and physical therapists, social workers and carers to look after them.

Doctor George Huntington was the first person who discovered Huntington's disease in 1872 when he observed abnormal behaviour in a family living in Long Island, New York. The disease was given Huntington's name in recognition of his invaluable research. HD equally affects both males and females across all cultures and ethnic groups. The chances of getting HD are 50:50 from HD parents to children [Passarge, 2001, Sapiro 2015].

Figure 1: HD probability of transfer from parents to offspring



Source: Wikimedia Commons.

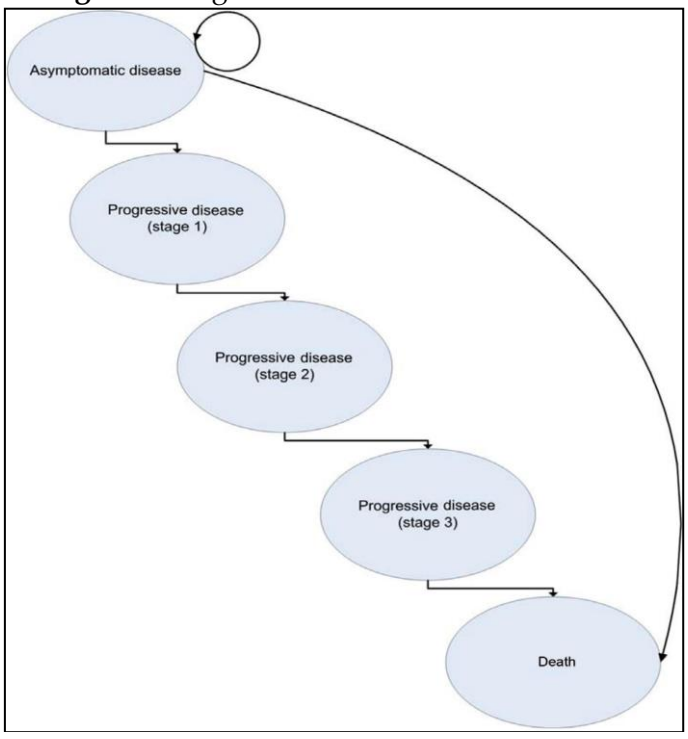
There is continuous deterioration over 10 to 25 years, gradually moving towards death. According to Huntington's disease society of America, HD has affected more than 30,000 individuals and expected additional 200,000 people at are risk of developing this disease in the United States of America. According to The Huntington's Disease Association, there are between 6,500 and 8,000 HD patients in the UK. HD is more common in western countries, and 10 per 100,000 people are affected by HD. It appears less in Asian and African countries. The frequency of HD was found lowest in Japan at between 0.1 and 0.38 per 100,000, and the highest in Venezuela 700 per 100,000 of the

population The prevalence of HD exceeds 15 per 100,000 in some populations. (Bates et al. 2002). The variations in the distribution of HD are at least partially explained by the distribution of predisposing alleles in the normal population of these ethnic groups [Kremer et al., 1994, Squitieri et al., 1994, Almqvist et al., 1995, Watkins et al., 1995]. The most common alleles in all populations contain 15 to 20 CAG repeats; in western European populations, the distribution is skewed towards longer alleles within the normal range, whereas these longer alleles are less common in African and Asian populations [Squitieri et al., 1994, Watkins et al., 1995, Rubinsztein et al., 1996], suggesting that the expanded alleles in the disease range arise from long normal alleles, which are more prevalent in western European populations.

2. Opportunities for Treatment

The HD is incurable but treatable; there is a difference between cure and treatment. HD is incurable means there are no such medicines that can change the defective misfolded protein into normal functional protein or stop the neurological degeneration of nerve cells. However, a treatment can slow the process of neurological degeneration or ease the symptoms such as depression, aggression, anxiety, and emotional instability. Therefore, the Markov model can best explain the stages of progressive disease such as HD.

Figure 2: Stages of diseases in Markov Model



Source: Briggs and Sculpher (1998).

HD being a progressive disease, it is not possible that the patient moves from severe to moderate and from moderate to mild. In HD condition the patient has to pass through all stages of the Markov model. Early diagnosis of HD remains at the mild stage

for 3 to 5 years and gradually moves to the moderate stage and then severe stage completing all these three stages within 10 to 20 years. HD effective and on-time treatment can increase the time span of each stage.

2.1 Symptoms at Mild Stage

According to Walker, the early symptoms are subtle and only physical symptoms can be noticed but not the psychiatric symptoms.

1) Agitation,
2) Anxiety,
3) Mild tremor,
4) Clumsiness,
5) Lack of concentration and irritability,
6) Difficulty in remembering complex things,
7) Easily mood changes,
8) Depression.

HD patients exhibit similar physical symptoms but slight variations in psychiatric symptoms, depending on the individual, Kremer (2002). Individuals can usually perform most of their ordinary activities and continue work [Bates et al. 2002]. In addition, a patient shows minor involuntary movements and irritation, which are sometimes considered normal behaviour of an individual. The age range is between 30 to 40 when a patient passes through this stage.

2.2 Symptoms at Moderate Stage

- **Physical Changes**
  - Unsteady gait,
  - Speech problems,
  - Chorea, twisting and writhing motions, jerks, staggering, swaying, disjointed gait,
  - Dystopia (prolonged muscle contractions); face, neck, and back,
  - Lack of coordination,
  - Slow reaction time,
  - General weakness,
  - Weight loss,
  - Appearance of dementia.
- **Emotional Changes**
  - Aggressive antisocial behaviour,
  - Annoyance,
  - Lack of interest,
  - Stubbornness,
  - Frequent disappointment.
- **Cognitive Changes**
  - Loss of orientation,
  - Difficulties in multitasking,

- Lack of creativity.

At this stage, chorea becomes more prominent, and individuals find difficulties in walking and talking and are compelled to quit work and start becoming dependent on others for help. However, they are still independent to some extend and try to maintain personal independence. Individuals show aggressive behaviours and noticeable abnormalities in actions. They have chorea, gait disturbances, and dysphagia. Patients tend to have a lower body mass index (BMI) than controls [Pratley et al., 2000, Stoy & McKay, 2000, Djousse et al., 2002, Robbins et al., 2006]. This is the transition stage, which totally makes them dependent on the third stage.

2.3 Symptoms at Severe Stage

- **Physical Changes**
  - Severe chorea (less common),
  - Serious weight loss,
  - Inability to move,
  - Increased risk of falls,
  - Inability to speak,
  - Swallowing problems, danger of choking.
- **Emotional and Cognitive Changes**
  - Confusion and screaming,
  - Mental incapability,
  - Memory loss.

The symptoms become severe at this stage of HD, and the patient becomes mute. They depend on others who need total support for all necessities to maintain life from professional nursing care. After onset, the median survival time is 15 to 18 years (range: 5 to >25 years). The average age at death is 54 to 55 years [Harper, 1996, Harper, 2005].

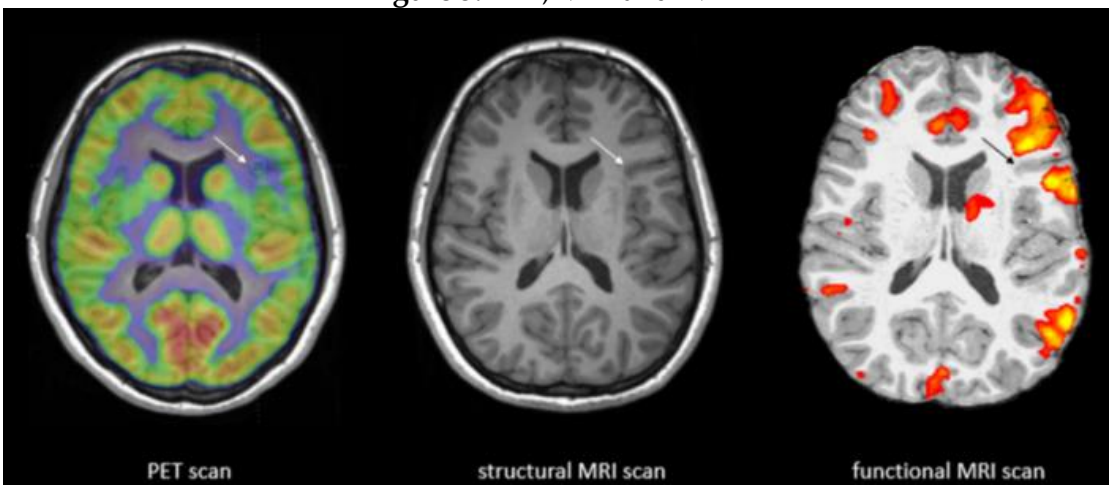
2.4 Diagnosis

Various laboratory and clinical tests are available for the diagnosis, such as Neurological, Psychological, Brain function and Genetic tests.

Schneider, Walker, Bhatia (2007) say observational diagnoses of HD symptoms are easy to recognise, and it is correct as a genetic test if the individual has a family history of HD. An individual begins to show HD symptoms that cannot be doubted with any other illness. A family history of HD is often the only clue valid to the possibility of developing the disease. If there is no family history of HD, then now individuals can go for a blood test to determine whether an individual has the HD gene. However, the blood test cannot predict when symptoms will begin to appear. Clinical methods of computerised tomography (CT scan) and magnetic resonance imaging (MRI) are used to show the visible brain in the later stage of the disease. Rao et al. (2009) say the recent advancements have made it possible to measure the progress of the disease at an advanced stage. The neuroimaging techniques such as Functional magnetic resonance imaging (fMRI) and Positron emission tomography (PET) can show brain activities and

processes. The former shows and measures the blood flow through the brain, and lateral measures and monitors the oxygen contents of the blood.

Figure 3: PET, MRI and fMRI



Source: Google Images.

The significant advantage of fMRI is that it does not use radiation like X-rays, computerised tomography (CT) and positron emission tomography (PET) scans. As a result, it can evaluate brain function safely, non-invasively and effectively.

HD gene was discovered in 1993 which is responsible for the misfolded protein. Human beings have 23 pairs of chromosomes; this gene HTT was located at chromosome number 4.9dna HTT contains a sequence of three Deoxyribonucleic acid (DNA) bases — cytosine-adenine-guanine (CAG) known as a trinucleotide repeat.

Gene is a section of DNA that encodes for a specific trait, while an allele is a variant form of a gene.

Alleles in the HD gene are classified as normal, intermediate, or HD- causing depending on the number of CAG repeats. Therefore, the classification of the trinucleotide repeat, and resulting disease status, depends on the number of CAG repeats.

Table 1: Repeat count, classification and disease status

Repeat count	Classification	Disease status
<27	Normal	Unaffected
28–35	Intermediate	Unaffected
36–39	Reduced Penetrance	I+/- Affected
>40	Full Penetrance	Affected

Source: Walker F., Huntington's disease The Lancet, Volume 369, Issue 9557

2.5 CAG Repeat Sizes

The number of CAG repeats in the HTT gene determines whether or not someone will develop HD during their lifetime. Every person carries two copies of the HTT gene, one from their father and mother. Therefore, the CAG repeat size in both HTT genes of a person is measured using DNA acquired from a blood sample in HD testing.

In an HTT gene, the number of CAG repeats can range from less than 10 to more than 120. However, the average CAG repeats number is around 17.

- **Normal Alleles: 27 or fewer CAG Repeats**

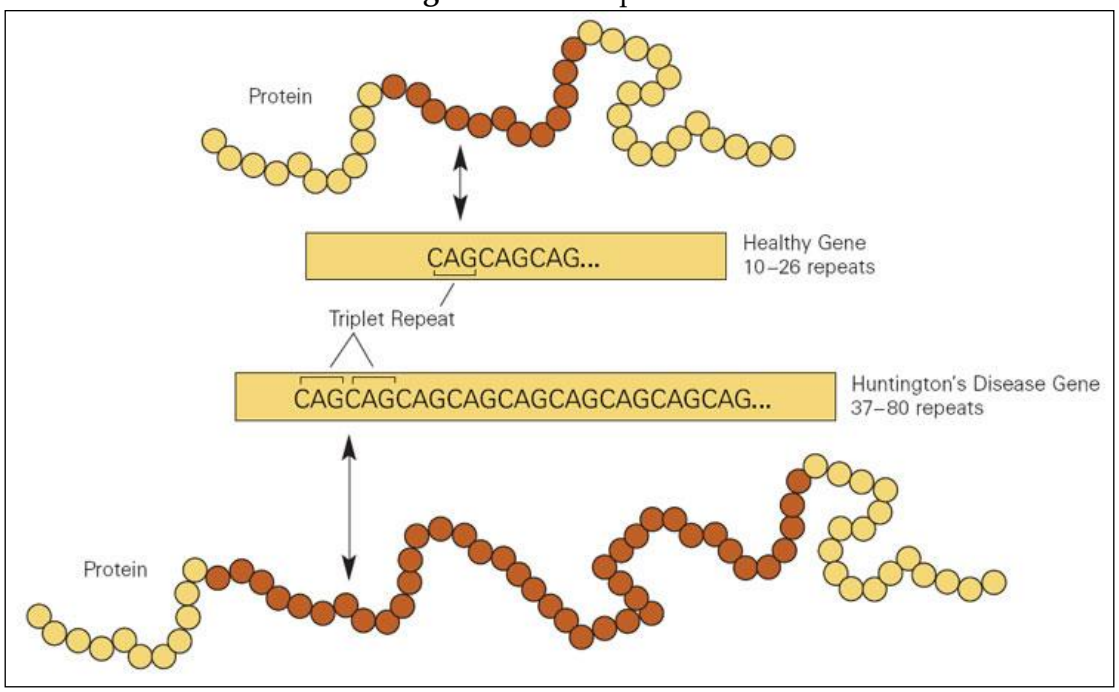
People with 27 or lower CAG repeats will not develop the signs and symptoms of Huntington's disease. In addition, with less than 27 repeats, a normal repeat has never been associated with an HD phenotype, nor has it shown instability resulting in an HD allele in offspring.

- **Intermediate Alleles: 28-35 CAG Repeats**

An individual with an allele in this range is not at risk of developing HD symptoms, but because of instability in the CAG tract, may be at risk of having a child with an allele in the HD-causing range [Semaka et al., 2006]. Alleles in the intermediate range have also been described as "*mutable alleles*" [Potter et al., 2004]. There is a chance that offspring of an intermediate allele carrier may inherit more than 26 repeats, as well as a minor chance that transmission will result in an HD allele with or without penetrance.

The figure shows the excessive repetitions of the cytosine-adenine-guanine (CAG) nucleotide sequence in a gene from a Huntington's disease patient (bottom) compared to a gene from a person without the neurodegenerative disorder (top).

Figure 4: CAG repetition



Source: Wikimedia (National Institute of General Medical Sciences, National Institutes of Health.

- **HD-causing Alleles: 36 to 39 CAG Repeats**

Persons who have an HD- causing allele are considered at risk for developing HD in their lifetime. A CAG repeat of the Huntingtin gene (HTT) greater than 35 trinucleotides designates an allele capable of causing the HD phenotype, with reduced penetrance at

36–39 CAG repeats. However, the HD phenotype is not always penetrant, with increasing penetrance possibly associated with increasing repeat length [Brinkman et al., 1997].

- **HD-causing Alleles: 40 or More CAG Repeats**

With 40 or more CAG repeats, which is called a full penetrance gene. A disease is then associated with Huntington pathology. In addition, higher repeat CAG sizes are associated with a younger age at onset [Brinkman et al., 1997].

An individual with an allele in this range is at risk for HD but may not develop symptoms. In rare cases, elderly asymptomatic individuals have been found with CAG repeats in this range [Rubinsztein et al., 1996, McNeil et al., 1997, Langbehn et al., 2004]. If people have less than 36 CAG repeated, this is a clear indication of normal people. If people have more than 36 CAG repeated means they are affected; anything between 36 to 44 CAG repeated indicated affected people. The variation in CAG repeats is related to how progressive the disease concerning age factors is 60%, and other remaining 40% variation is related to environment and other genes that affect the mechanism of HD. In any appropriate pharmaceutical form, the fatty acid eicosapentaenoic acid (EPA) can be used to treat HD. Genetic screening is one of the crucial areas that has developed recently with mapping the human genome. Researchers see genetic screening as the future hope of disease prevention. In addition, genetic screening can be used for diagnostic testing to confirm or exclude a suspected genetic disorder.

2.6 Current Treatments

The HD treatment is composed of three main categories drugs to control symptoms such as depression and anxiety, food supplements to maintain weight and a healthy lifestyle and therapies including physical, cognitive and occupational to keep physical movement and speech at the right level. This treatment does not focus on the cause of the disease. HD drugs include psychotropic agents to manage and control movement disorders. Quality-adjusted life-year (QALY) takes into account both the quantity (duration of life) and quality (condition) of life generated by healthcare interventions. This explains the intervention to disease through an appropriate on-time treatment, which gives a greater number of years to life. QALYs indicate that the patients who receive the treatment extend the life span and improve the quality of life. HD symptoms can be classified into three main categories: physical symptoms, cognitive symptoms, and Psychiatric symptoms. Physical symptoms include jerky involuntary movements of body parts with difficulties in speaking, walking, moving, and swallowing. Psychiatric symptoms include anxiety; depression, and aggression, while cognitive symptoms include lack of concentration, enthusiasm, initiative and, of course, ignorance, negligence, not remembering essential things, and a lack of planning and organising skills. As already explained, there is currently no cure for HD but there are some effective drugs to treat and ease symptoms to make patients comfortable to some extent to spend a normal life for some period. HD is a progressive disease that eventually leads to death within 10 to 20 years.

Tetrabenazine (Xenazine) is the only medication FDA approved for HD. However, many other drugs approved for other symptoms (depression, psychosis, Parkinson's

disease, Alzheimer's disease) have been tried and may be used for HD. This usage is called off-label prescribing.

Table 2: Symptoms and medication

Treatment for psychiatric problems	
Medicines	**Symptoms /Treatment /Effects**
Antidepressants	Anti-depressants, mainly selective serotonin re-uptake inhibitors like Lexapro, Prozac, and Zoloft, are frequently used to treat Huntington's patients' depression. They can also alleviate some symptoms of obsessive-compulsive disorder.
Benzodiazepine known as tranquilizers.	It acts on the central nervous system, produces sedation and muscle relaxation, and lower anxiety levels. The most common side effects are drowsiness, light-headedness, confusion, dizziness, slurred speech, muscle weakness.
Clonazepam Brand name (Klonopin®)	It belongs to a group of medicines called benzodiazepines. It works by decreasing abnormal electrical activity in the brain. Possible side effects are drowsiness, dizziness and unsteadiness
Alprazolam Brand name (Xanax®)	It is a fast-acting tranquilizer of medium duration in the benzodiazepine family Class. This drug works rapidly for the treatment of anxiety and insomnia, with side effects of feelings of sedation.
Diazepam Brand name (Valium®)	It is a faster-acting drug and is about 10 times stronger than alprazolam, meaning that it can rapidly cause feelings of sedation and drowsiness
Lorazepam Brand name Ativan®)	It is a benzodiazepine medication. It is used to treat anxiety disorders, trouble sleeping, severe and agitation. It gives lesser daytime drowsiness than valium. Minor side effects such as feeling sleepy, or unusually tired in the daytime. Many people reported no side effects.
Atomoxetine (Aathy) Brand name (Strattera®)	Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson's disease. Apathy is one of the most frequent behavioural disturbances in many neurodegenerative disorders and is known to have a negative impact on disease progression. Several side effects such as heartburn, nausea, vomiting, loss of appetite, weight loss, constipation, stomach pain, gas, dry mouth, excessive tiredness and dizziness.
Dextroamphetamine Brand name (Dexedrine®)	Dextroamphetamine belongs to a class of drugs known as stimulants. It affects chemicals in the brain and nerves that contribute to hyperactivity and impulse control. It is used to treat narcolepsy and attention deficit hyperactivity disorder (ADHD). Common side effects are headache, dry mouth, unpleasant taste, constipation and weight loss
Modafinil Brand name (Provigil®)	It is a medication to treat sleepiness due to narcolepsy, shift work sleep disorder, and obstructive sleep apnea. Side effect: headache and insomnia nausea, nervousness, dizziness, or difficulty sleeping may occur.
Amantadine Brand name (Symmetrel®)	It is used to treat Parkinson's disease and "Parkinson-like" symptoms such as stiffness or tremors, shaking, and repetitive uncontrolled muscle movements. Very effective slowing of disease progression in both cognitive and motor parameters. Side effects, hypertension, dizziness, confusion, headache, constipation and vomiting.

Memantine Brand name (Namenda®)	Memantine is a medication used to slow the progression of moderate-to-severe Alzheimer's disease. It is taken by mouth. Common side effects include headache, constipation, sleepiness, and dizziness. Severe side effects may include blood clots, psychosis, and heart failure.
Quetiapine Brand name (Seroquel®)	It is used to treat bipolar disorder (manic depression) in adults and children who are at least 10 years old. Side effects are sleepiness low blood pressure, restlessness, dry mouth, and weight gain.
Clozapine Brand name (Clozaril®)	Clozapine is a medication that works in the brain to treat schizophrenia. It is also known as a second-generation antipsychotic (SGA) or atypical antipsychotic. It rebalances dopamine and serotonin to improve thinking, mood, and behaviour. Low side effects
Risperidone Brand name (Risperdal®)	Risperidone is a medicine that helps with symptoms of some mental health conditions such as schizophrenia and mania symptoms of bipolar disorder, where mood changes between feeling highly excited (mania) and very low (depression) New drug, side effects are sleepiness, low blood pressure, restlessness, breast stimulation and weight gain
Olanzapine Brand name (Zyprexa®)	It is an atypical antipsychotic primarily used to treat schizophrenia and bipolar disorder. Side effects worsening of rigidity and slowness of movement. weight gain, sleepiness, restlessness, low blood pressure, dry mouth, and constipation.
Ziprasidone Brand name (Geodon®)	It is an atypical antipsychotic used to treat schizophrenia and bipolar disorder Side effects are nausea, weakness, and nasal congestion
Aripiprazole Brand name (Abilify®)	It is used to treat mania in bipolar disorder, or schizophrenia. Side effects are headache, nausea, vomiting, restlessness, tremor, and constipation
Rivastigmine Brand name (Exelon®)	Rivastigmine is a reversible cholinesterase inhibitor used to treat mild to moderate dementia caused by Alzheimer's or Parkinson's disease. Common side effects are severe or ongoing vomiting or diarrhea, loss of appetite, weight loss;
Treatment for movement problems	
Tetrabenazine (Xenazine®)	Xenazine is used to treat Huntington's chorea It provides a sustained anti-choreic effect. Side effects include sleep problems, depression, anxiety restlessness and suicidal thoughts or actions Xenazine (tetrabenazine) is the first medication the U.S. Food and Drug Administration has approved specifically for Huntington's. It helps suppress jerky involuntary movements, but it may cause serious side effects, such as worsening depression. It reduces the number of certain chemicals in the body that are overly active in people with Huntington's disease.
Deutetrabenazine Brand name (Austedo®)	It is a modified version of Tetrabenazine Austedo is used to treat involuntary muscle movements therefore significantly reduces chorea less side effects, such as depression and somnolence
Haloperidol (Haldol®)	Adverse effects include sedation, stiffness, and rigidity.

Source: Authors' compilation.

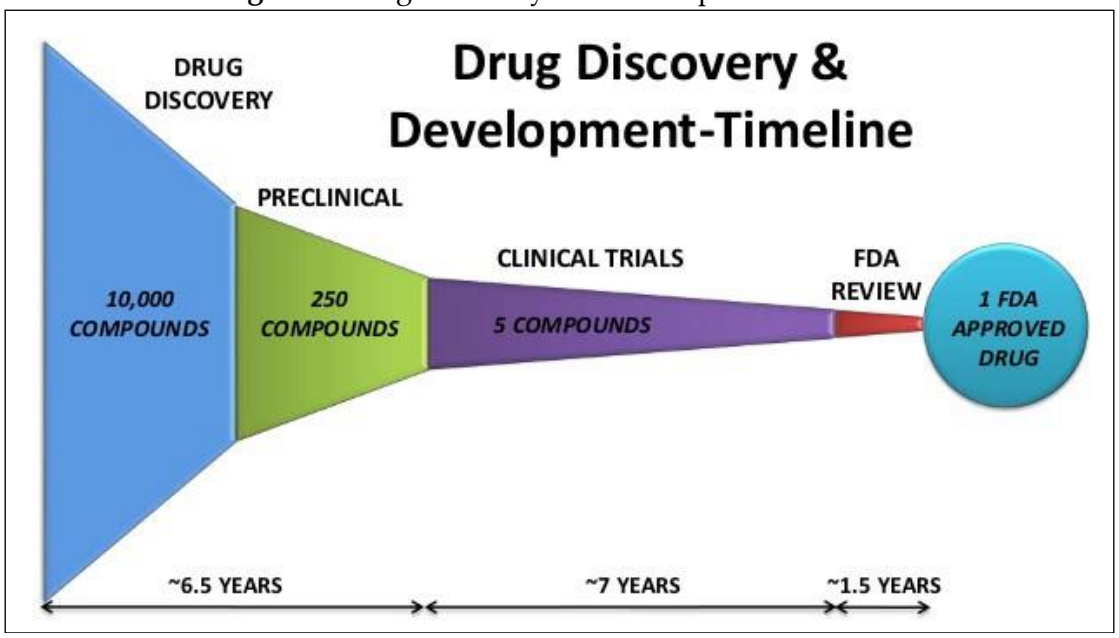
Tetrabenazine (TBZ) is a safe and effective medicine for a wide range of hyperkinetic movement disorders and it is highly effective for Huntington's disease This is the first medicine approved by the Food and Drug Administration (FDA) for the treatment of the signs or symptoms of HD. TBZ is quite effective in reducing the jerky, involuntary movements with possible side effects such as dizziness, insomnia, and restlessness. TBZ is not used as a cure for hyperkinetic movement disorders but for treatment. Tetrabenazine is sold under the trade name of Nitoman® in Canada and Xenazine® in New Zealand and in some parts of Europe and the USA Xenazine® from Cambridge Laboratories Group Limited. Tranquilisers such as clonazepam (Klonopin) and antipsychotic drugs such as haloperidol and clozapine (Clozaril) can help control movements, violent outbursts and hallucinations. While these medications can be helpful, a common side effect is a sedation, and in some cases, these medications may cause additional stiffness and rigidity. Various medications, including fluoxetine (Prozac, Sarafem), sertraline (Zoloft) and nortriptyline (Pamelor), can help control depression and the obsessive-compulsive rituals that some people with Huntington's disease develop. Medications such as lithium (Eskalith, Lithobid) can help control extreme emotions and mood swings. Side effects from many of the drugs used to treat the symptoms of Huntington's disease may include hyperexcitability, fatigue and restlessness. Speech therapy Huntington's disease impairs speech and confined patients to express only simple and straightforward thoughts. The patient cannot express complicated thoughts. The speech therapist can help to ease this problem. Physical and occupational therapy patients find difficulties in walking and moving, physical therapy can help to keep muscles functional and stronger. Occupational therapy can assist the patient in eating, dressing, and personal hygiene. There is no cure for HD but the above-mentioned drugs along with supportive care can ease and relieve many symptoms of HD and help patients to lead a normal life as possible. Therapies can help improve speech and swallowing problems. High-calorie food supplements can help maintain weight and behavioural problems.

2.7 New Developments

Developing a new drug for any disease is not an easy task. The process of developing a new drug consists of many steps from basic research in a science laboratory to a successful availability to people is complex, costly, and time-consuming. This complex process is often known as Research and Development, or short the R&D pipeline. The figure below states the steps that interact and feedback to one another.

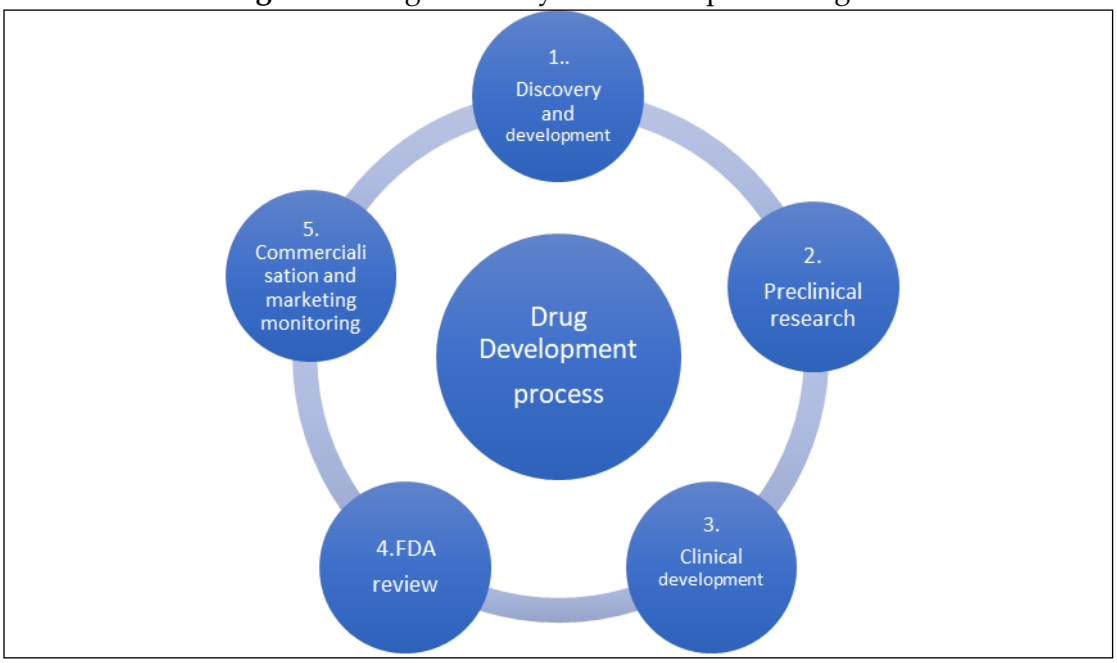
A new drug to be designed, developed, and approved takes approximately 12-15 years for use in patients. The figure below shows that the drug discovery and development process can broadly be broken down into two stages. Early-stage and later-stage, the early stage is where the researchers find the treatment for a disease. The later stage determines the efficacy and effectiveness of the drug.

Figure 5: Drug discovery and development timeline



Over the last 40 years, the complexity of drug development has skyrocketed, requiring preclinical testing, investigational new drug (IND) applications, and completed clinical testing before marketing & commercialisation approval from the FDA.

Figure 6: Drug discovery and development stages



Stage 1: Discovery and development,
Stage 2: Preclinical research,
Stage 3: Clinical development,
Stage 4: FDA review,
Stage 5: Commercialisation and marketing monitoring.

uniQure is developing gene therapy for HD, candidate AMT-130 to carry an artificial micro-RNA specifically tailored to silence the huntingtin gene. The therapeutic goal is to inhibit mutant protein production (mHTT).

uniQure's gene therapy candidate for Huntington's disease is differentiated in that:

- AMT-130 targets the deep brain structures known for the disease pathology onset.
- AMT-130 silences mutant huntingtin protein at levels not demonstrated in other studies.
- AMT-130 targets the accumulation of the exon 1 HTT fragment, the most toxic source of abnormal protein aggregation in Huntington's disease (Source: uniQure 2022).

AMT-130 will be delivered by brain surgery to spread the treatment throughout the brain. The treatment targets the genetic messages of both the harmful and normal huntingtin protein, lowering both.

Recently uniQure announced plenty of essential updates about AMT-130. Firstly, they have dosed the first cohort of ten participants in their Phase I/II safety trial in the USA. Despite all of the challenges of conducting a study during a worldwide epidemic, this was completed ahead of time.

Scientists have developed anti-sense oligonucleotides (ASOs) targeting huntingtin's genetic message, mRNA. This message gives cells the instructions to make the huntingtin protein, so if instructions are unreadable using an ASO, the huntingtin protein levels will go down. One downside of ASOs is that because they are big and bulky molecules requiring repeated dosing, they must be given a spinal injection.

A new analysis of clinical trial data indicates that therapy with pridopidine can slow the decline in total functional capacity in people with Huntington's disease.

The findings were published in the Journal of Huntington's Disease in two studies: "Effects of Pridopidine on Functional Capacity in Early-Stage Participants from the PRIDE-HD Study" and "Additional Safety and Exploratory Efficacy Data at 48 and 60 Months from Open-HART, an Open-Label Extension Study of Pridopidine in Huntington Disease."

Pridopidine is a tiny molecule that activates the sigma-1 receptor, producing biological effects that protect nerve cells from damage. The medication was developed initially as a potential treatment to improve motor functions; however, emerging biological data has indicated it could have other effects. The therapy is currently being developed by Prilenia Therapeutics, which acquired it from Teva Pharmaceuticals in 2018. Prilenia is presently executing a Phase 3 trial, PROOF-HD (NCT04556656), to additionally assess the effects of pridopidine.

The drug pipeline comprises eight clinical (Phase I-III) development programmes: Huntexil® (pridopidine) for Huntington's disease (Phase III), The Huntexilr® now pridopidine (note that pridopidine is no longer called Huntexil) will be ready in couple of years.

According to Sarah Tabrizi, Professor of Clinical Neurology at Huntington's Disease Multidisciplinary Clinic of the National Hospital for Neurology and

Neurosurgery, said Clinical research in HD is entering into a revolutionary era to cure the disease. Many clinical trials on animals (Mice) have been effective and successful to slow down progression of the disorder. These new treatments are in waiting to be applied to HD patients The chances are bright HD to become completely curable disease.

2.8 Neurotransplantation

Neurotransplantation is going under drastic research to fix defective brain cells. Human fetal striatal transplantation (HFST) is an experimental stereotactic intervention in the treatment of Huntington's disease (HD). This procedure has proved feasible, safe, well-tolerated and it offers a potential strategy for brain repair in HD patients. Dopamine is one of the important neurotransmitter chemicals, which is responsible for normal brain function. Transplantation of dopamine-containing cells has been attempted to treat HD at a few neuro research centres in the world. The results are unclear and further research needs to be undertaken to make the neurotransplantaion successful. Mouse Model Cure Dr. Michael Hayden and colleagues discovered that by preventing the cleavage of the mutant huntingtin protein responsible for Huntington's disease (HD) in a mouse model, the degenerative symptoms underlying the illness do not appear and the mouse displays normal brain function. This is the first time that a cure for HD in mice has been successfully achieved. Researchers also found that the drug Memantine, which is approved to treat Alzheimer's disease, successfully treated Huntington's disease in a mouse model by preserving normal synaptic electrical activity and suppressing excessive extrasynaptic electrical activity. Neuro Surgery (Sept. 15, 2009) Milestone research was conducted at the University of Kentucky College of Medicine relating to significant cure for Huntington's disease Dr. Zhiming Zhang, UK associate professor of anatomy and neurobiology with his associates have performed experimental neurosurgery focused on site-specific delivery of therapeutic drugs into the brain with a purpose of treating a certain number of neurological disorders caused by the defective protein. This technology is known as RNA interference with aims to decrease a toxic protein produced by the mutant huntingtin gene, which causes Huntington's disease.

2.9 HD No More Mystery

A research team from John Hopkins University reports at the 24th annual convention on June 5th - 7th, 2009 in Phoenix, Arizona solved a long-awaited mystery, why HD patients with misfolded protein in their genes destroy only certain brain cells not all. Until now, researchers were perplexed as to the cause of the brain damage in HD patients and why only certain cells die although the faulty protein is found in all cells. The answer lies in a little-known molecule known as "Rhes", which mixes with mutated Huntington's protein and sparks a chemical reaction that damages the brain cells. The discovery provides what scientists are calling a "promising avenue" for researchers throughout the world who are seeking a definite cure for HD and related brain diseases.

RNA Silencing Treating symptoms of HD is no cure but a temporary treatment. To cure the disease, it is better to remove the root cause of the disease. The root cause for HD is misfolded protein; this defective misfolded protein can eliminate or removed from

the gene by targeting mutant huntingtin as explained by Heredity Disease Foundation's (HDF) ex Executive Director for Science Carl Johnson. The options for achieving this goal by targeting Huntington messenger RNA (mRNA) using RNA silencing techniques or targeting the huntingtin protein using antihuntingtin intrabodies. This silencing technique has to be implemented in human beings, but researchers fully understand and conceptualise it.

2.10 Stem Cells

Currently, there are no approved stem cell therapies for HD at this time. Although neural stem cell transplants have been studied in the treatment of HD patients, they still need to go through rigorous clinical trials to prove that they are safe and effective.

Stem cells are the essential building blocks of life and play a crucial role in the genesis and development of all higher organisms. The development of stem cell-based therapies for HD aims to replace lost neurons and/or to prevent cell death.

Due to neuronal cell death caused by the mutated huntingtin (mHTT) protein accumulation, it is unlikely that such brain damage can be treated solely by drug-based therapies. Therefore, stem cell-based therapies are essential in order to reconstruct damaged brain areas in HD patients.

Dr.Cohen and Researchers at Tel Aviv University have introduced mesenchymal stem cells to fix defective brain cells in a neurotoxin rat model of Huntington's Disease.

2.11 Impact of New Development

The impact of new development is very optimistic; it gives researchers a hope to cure this disease in near future. Pharmaceutical companies are spending lavishly such as NeuroSearch to build drugs to treat HD. These companies also see potential market opportunities for Neurodegeneratives drugs. This market is growing

3. Conclusion

Huntington's disease is a fatal inherited neurodegenerative disease associated with gene located on chromosome number 4 which produces a misfolded protein that damages the nerve cells in certain areas of the brain. HD is caused by a mutation in HTT gene on chromosome number 4. Mutations in the HTT gene are responsible for Huntington's disease. The genetic mutation for HD is unlike other mutations, i.e. instead of substitution or deletion of the gene, there is copying default, and i.e. an area within the gene gets copied too many times. The HTT gene consists of CAG trinucleotide repeats (cytosine, adenine, and guanine). The symptoms appear in middle age and the disease is incurable but symptoms can be treated to some extent.

Medications and therapies are recommended for the control of symptoms of HD which provide relief from some physical and mental problems.

Physical therapy helps to refine balance and co-ordination and occupational therapy helps the patient to deal with concentration and memory-related issues.

Till today there is no definite cure for HD but research on mice has been very successful which gives the hope for a future cure for HD. There is a potential market for Neurodegenerative drugs in the world with continuous growth.

The Neurodegenerative Disease market was valued at approximately USD 39. 09 billion in 2021 and is expected to grow with a CAGR of 3.24% over the forecast period (Mordor intelligence, 2022).

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