ABSTRACT

Huntington’s disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person’s physical and mental abilities during their prime working years and has no cure. The disease is caused by an autosomal dominant mutation in either of an individual's two copies of a gene called Huntingtin. HD is known as the quintessential family disease because every child of a parent with HD has a 50/50 chance of carrying the faulty gene. Symptoms usually appear between the ages of 30 to 50, and worsen over a 10 to 25 year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Over time, HD affects the individual’s ability to reason, walk and speak. There is no cure for HD. Full-time care is required in the later stages of the disease. Treatments can relieve some symptoms and in some improve quality of life. The best evidence for treatment of the movement problems is with tetrabenazine.

INTRODUCTION

It is a neurodegenerative disorder passing within families from generation to generation with onset in middle age and characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia resulting in death within 15 to 20 years after diagnosis (Roos, 2010; Dayalu and Albin, 2015). One of the most recognized motor sign in HD is chorea, which is characterized by unwanted muscle contractions that are progressive over time and interfere in activities of daily living. Typically, onset of symptoms is in middle-age after affected individuals have had children, but the disorder can manifest at any time between infancy and senescence (Walker, 2007). Men and women are equally at risk. Median age of diagnosis approximates 40 years, with a wide range in age of onset. Onset before age
20 years or after age 65 years is rare (Dayalu and Albin, 2015). HD is caused by a cytosine-
adine-guanine (CAG) trinucleotide repeat expansion in the huntingtin protein located on
chromosome 4p16.3. The mutant huntingtin accumulates within brain cells, causing cell
toxicity and dysfunction of neurons throughout the brain when the disease progresses.
Neuropathological alterations are found widely throughout the brain, but the primary focus of
atrophy is located in the striatum and cerebral cortex. The distinct striatal atrophy is caused
by extensive loss of striatal medium-sized spiny neurons that is suggested to result in the
choreiform movements seen in HD (Coppen and Roos, 2017). The gene for HD is larger than
normal. If an affected parent has one normal-sized copy of the gene and one larger-sized
copy, there is a 50% chance of the child getting half of the large-sized genetic material. Thus,
every pregnancy has a 50:50 chance or “1 in 2 chances” of developing this disease. If one has
the faulty gene they will at some stage develop the disease. However, if one inherits the
“good” gene, they will not develop the disease and will not pass the effective gene to their
children. If one parent has one normal copy of the gene and another a large-sized copy, there
is a 50:50 (or 50%) chance to get HD each time a child is born. Although the gene is present,
the symptoms of HD appear in the 2nd or 3rd decade and sometimes, even later in life
(Muthane, 2011). Symptoms in juvenile HD can differ substantially from those with adult-
onset of HD. Although there is no cure of HD and management is limited, motor and
psychiatric symptoms often respond to pharmacotherapy, and nonpharmacological
approaches as well as supportive care are essential (Schiefer et al., 2015).

HUNTINGTON’S DISEASE: A BRIEF HISTORY

In 1872 Huntington’s disease was first identified and described in a paper by George
Huntington, granting a model for the disease’s phenotypes. His patients had a common
lineage – all had family members which had emigrated from Suffolk, England in the mid-
1600s. Before him, his father and grandfather also studied the same group of patients. It is
believed the occurrence of Huntington’s disease was seen in the 1600s, but was
misunderstood as a “dancing disorder” and was viewed as witchcraft. Although it is believed
that previous characterizations of people with Huntington’s disease were recorded, the credit
for the development of the disease characterization is still granted to George Huntington.
Even after his paper was published, it was over 100 years before the gene associated with
Huntington’s disease was discovered. In order to isolate this unknown gene, researchers used
the DNA samples of families in Venezuela, where Huntington’s disease and consanguinity
are highly prevalent. In 1983, a linkage on chromosome 4 was established the gene for HD
and in 1993 the gene for HD was found. In 1993, the researchers discovered a trinucleotide repeat which was unstable when expanded and which they believed was strongly linked to Huntington’s disease (Bonilla, 2000). That period marked a tremendous increase in interest in HD and neurogenetic disorders. For the first time, actual premanifest diagnoses could be made and as more diseases involving trinucleotide repeats of CAG were found, HD served as a model for many studies in medicine. CAG (cytosine (C), adenine (A), and guanine (G)), is a trinucleotide, the building stone of DNA. CAG is the codon for the amino acid glutamic. Finding the gene opened new research lines, new models and for the first time a real rationale on the way to treat this devastating disease. Many symptomatic treatments are now available, but there is a need for better, modifying drugs (Roos, 2010).

ONSET OF HD
Huntington’s Disease manifests as a triad of motor, cognitive, and psychiatric symptoms which begin insidiously and progress over many years, until the death of the individual (Rosenblatt et al., 2011). A hallmark of HD is onset of mood changes, psychosis, and suicidal thoughts prior to the presentation of the movement disorder. Due to local social conventions, it is possible that these patients and their families would not recognize, or would minimize, reports of mood changes, depression, or suicidal thoughts. Presentation and care of a family with Huntington disease in a resource-limited community (Charles et al., 2017). Age of onset varies markedly, typically occurring between the ages of 35 and 50 but varying from early childhood to ≥80. The course is relentlessly progressive, with death usually 15–20 years after disease onset (Margolis and Roos, 2003). The progression of the disease leads to more dependency in daily life and finally death. The most common cause of death is pneumonia, followed by suicide (Roos, 2010).

![Figure 1: Huntington’s disease onset ages (Richard, 2004).](image-url)
TYPES OF HUNTINGTON'S DISEASE

Huntington's disease has two subtypes:

**Adult-onset Huntington's disease:** This is the most common form of Huntington's disease. People with adult-onset Huntington's disease usually develop symptoms in their mid-40s and 50s (Nance and Myers, 2001).

**Juvenile Huntington's disease:** If the first symptoms and signs start before the age of 20 years, the disease is called Juvenile Huntington’s disease (JHD). Behaviour disturbances and learning difficulties at school are often the first signs. Motor behaviour is often hypokinetic and bradykinetic with dystonic components. Chorea is seldom seen in the first decade and only appears in the second decade. Epileptic fits are frequently seen. The CAG repeat length is over 55 in most cases. In 75% of the juveniles the father is the affected parent (Roos, 2010). Children and teenagers have this form of Huntington's disease, which is very rare. Children with Huntington's disease often have symptoms similar to Parkinson's disease. They may also develop problems with schoolwork (Nance and Myers, 2001).

CLINICAL PRESENTATION OF HD

HD onset is defined by the beginning of motor symptoms, and most often the initial complaint that leads patients to seek medical attention is “clumsiness”, “tremor”, “balance trouble”, or “jerkingness”. The primary involuntary movement abnormality, and often the earliest symptom, is chorea or choreoathetosis, continuous and irregular writhing and jerking movements. The limbs and trunk are most prominently affected, but respiratory, laryngeal, pharyngeal, oral, and nasal musculature may also be involved. Abnormalities of voluntary movement, although usually less striking than chorea, are more associated with functional disability. Frequent findings include impaired visual tracking; slow, poorly coordinated, arrhythmic fine motor movements; dysarthria and dysphagia; rigidity; and ataxia (Margolis and Ross, 2003).

Cognitive abnormalities usually begin at about the same time as movement abnormalities and progress in tandem with the loss of voluntary movement capacity. As in other subcortical dementias, aphasia and agnosia are less evident than in Alzheimer disease, whereas cognitive speed and efficiency are relatively impaired. However, as the disease progresses, the dementia becomes more global. As many as 80% of HD patients develop some form of non-cognitive psychiatric disorder within 10–15 years of disease onset. Mood disorders and
personality changes (often manifest as irritability or apathy) are common, and the suicide rate may be as high as 5%. Fortunately, the psychiatric manifestations of HD are responsive to treatment (Margolis and Ross, 2003).

![Symptoms of HD](image)

**Figure 2: Symptoms of HD.**

**Behavior and psychiatric signs and symptoms**

Psychiatric symptoms are very frequently present in the early stage of the disease, often prior to the onset of motor symptoms. Because of their impact on daily life, these symptoms and signs usually have a highly negative impact on functioning and on the family (Wheelock *et al.*, 2003). The most frequently occurring sign is depression. The diagnosis is difficult because weight loss, apathy and inactivity also occur in HD. Usually there is low self esteem, feelings of guilt and anxiety. Apathy is related to disease stage, whereas anxiety and depression are not. Suicide occurs more frequently in early symptomatic individuals and also in pre manifest gene carriers. Around the time of the gene test and the stage when independence diminishes are the most risky periods for suicide. Anxiety also occurs frequently (34-61%), sometimes in relation to uncertainty about the start and or the course of the disease. Obsessions and compulsions can disturb the patient’s life and also lead to irritability and aggression. Irritability is often the very first sign, in retrospect, but in fact occurs during all stages of the disease. Apathy is one of the most common behavioural symptoms of HD characterized by indifference or lethargy (Slanghter and martens, 2001). The way irritability is expressed varies enormously from serious disputes to physical aggression. A loss of interest and increasing passive behaviour are seen as part of the apathy syndrome. It can be difficult to discriminate apathy from depression. Psychosis may appear, mainly in the later stages of the
disease. In most cases this goes together with cognitive decline. The complete clinical is comparable to schizophrenia with paranoid and acoustic hallucinations. Apathy occurs mainly due to the disconnection between the caudate to the frontal lobes and limbic system which mainly control “emotions” of the brain. Depression is often dismissed as an understandable reaction being diagnosed with HD. While a saddened mood is an understandable response to the life changes and loss of abilities resulting from HD. Depression occurs in HD due to alteration in neurotransmitters, the chemicals in brain that regulate moods (Naarding et al., 2001). Hallucinations, delusions and mania are very rare behavioural symptoms of HD. Hallucinations involve seeing, hearing or experiencing things that are not real such as feeling bugs crawling on you, hearing voices etc. Delusions are defined as thoughts about unreal situations (Hoffman et al., 1999). A very common behavioural symptom of HD is altered sexuality. Possible cause is that the delicate balance of hormones in the brain is disrupted by the progression of HD causing changes in behaviours regulated by hormone levels. Most commonly, people with HD suffer from a decreased sex drive. Increased sex drive and inappropriate sexual behaviour are less that involve knowing, thinking, remembering, organizing and judging. Certain changes in cognitive abilities are characteristic of HD and can significantly impact the lives of individuals with this disease (Kumar et al., 2015).

**Dementia**

Cognitive decline is the other main sign of HD and can be present long before the first motor symptoms appear, but can also be very mild in far advanced stages of the disease. The cognitive changes are particularly in relation to executive functions. In normal conditions cognitive and motor behaviour is goals directed and planned. Normally individuals are able to distinguish what is relevant and what can be ignored, but patients with HD lose this capability. The patients are no longer able to organise their life or to plan things which in the past simple. They lose flexibility of mind, and can no longer make mental adjustments. Misjudgements lead to complicated situations, with patients no longer reacting as they did in the past or in a way that the environment expects. Language is relatively spared. Memory certainly becomes impaired, although the semantic memory can be spared to a certain extent. All psychomotor processes become severely retarded (Walker, 2007).
Motor Symptoms

Chorea
In adults, chorea is the most prevalent motor dysfunction in the beginning of symptom manifestation in HD. Involuntary movements of the facial muscles and the distal extremities – fingers and toes in particular – occur predominantly. These movements are nonrepetitive, arrhythmic, and jerky. In the beginning, they are small and get integrated into voluntary movements unknowingly. Thus they may be misinterpreted as agitation or nervousness. Since the choreatic movements cannot be suppressed voluntarily and are associated with motor impersistence, chorea best can be observed if the subject is asked to absolutely rest or highly concentrated on a given (eg, cognitive) task. Surprisingly, unawareness of chorea by the patients themselves can last for quite a long time and still is present in almost 50%, even if the symptoms cannot be ignored by outsiders any longer. Motor impersistence also leads to the phenomenon that sustained tongue protrusion out of the wide-open mouth cannot be performed adequately. With disease progression, chorea often worsens. Proximal muscle groups and the axial trunk muscles are affected consecutively, while both the intensity and amplitude of the uncontrolled movements increase. Secondary problems result, which can lead to severe problems in everyday life, such as, for example, progressing imbalance, unstable walking, and frequent risk of falling. Involvement of the diaphragm and muscles located in larynx and pharynx leads to breathing disturbances, dysphagia, dysarthria, and involuntary vocalization interrupting the speech melody. In advanced stages of HD, chorea may plateau or decline and is replaced by rigidity and parkinsonian-like features eventually (Walker, 2007).

Dystonia
Dystonia can be also one of the early symptoms in JHD and is seen in advanced stages of HD almost regularly. Dystonia is accompanied by increased muscle tone of defined muscle groups, thus leading to abnormal posture of single limbs or the trunk and slowing of voluntary and involuntary movements. Dystonia can be completely absent while sitting and talking, but suddenly springs into attention if the subject is asked to walk. Thus, a slight abnormal finger posture of one hand or a sustained slightly supinated posture of one foot while walking can be subtle clinical signs of ongoing dystonia. With disease progression, dystonia will get more and more predominant not only by visible abnormal postures of trunk, head, and limbs but also by the increased muscle tone one will feel impressively when flexing/bending the extremities (Walker, 2007).
Bradykinesia
Bradykinesia is uncontrollable slowing of voluntary and involuntary movements, typically is combined with dystonia and increased muscle tone. Whereas both dystonia and bradykinesia contribute to the ever-increasing risk of falling, the latter causes a particular accident hazard due to the retarded ability to react in dangerous situations. The inability to start a certain movement is called akinesia. This situation is even worsened since motor dysfunction usually is accompanied by additional symptoms such as deficits in postural control, generalized slowing of cognitive functions, and defined neuropsychiatric deficits (Schiefer et al., 2015).

Eye movements
Pathological findings of eye movements can be the first symptoms in early stages of HD and also have been described in premanifest HD gene carriers. Therefore, special attention should be paid to the examination of eye movements during the neurological investigation in premanifest and young people in particular. The clinical examination can be complemented by vestibulooculography, which can objectify subtle findings and depict subclinical alterations. One of the first findings in early stages of HD can be an incomplete suppression of the optokineticnystagmus. Slowing of saccade velocity and a delay in initiating volitional saccades is found additionally. In contrast, smooth pursuit is not altered in early stages. With disease progression, all mentioned functions are altered including refixation (Schiefer et al., 2015).

Suicide risk
Patients with Huntington’s disease are more likely than members of the general population to commit suicide according to a meta-analysis of studies that reported mortality associated with mental disorders. Suicidal ideation was highest in gene carriers who were nearing the threshold of being diagnosed with manifest disease (those with soft motor signs of Huntington’s disease), and in those who were beginning to lose their functional ability and independence (those with stage 2 disease). Risk factors for suicide in Huntington’s disease include depression and impulsivity. Some people with the disease also have suicidal thoughts in the absence of depression, for some, thoughts of suicide seem to be a rational response to their imminent loss of independence (Novak and Tabrizi, 2010).

Secondary symptoms and signs
From early on, an unintended weight loss has been reported in all patients. As more attention is now paid to this phenomenon, the loss seems to be a little less severe, the cause being
diverse. Although it seems logical to think that chorea should play the main role in weight loss, it has been shown that there is no relation between weight loss and chorea or other movement disorders. A relation with the length of the CAG repeat has been described. More practical issues, such as slower functioning, decreased appetite, difficulty handling food and swallowing certainly play a role. But hypothalamic neuronal loss is also a causative factor. Attention has only recently been focused on sleep and circadian rhythm disturbances of patients with HD. Autonomic disturbances can result in attacks of profuse sweating (Roos, 2010).

![Figure 3: Symptoms of HD (Aylward et al., 2012).](image)

**EPIDEMIOLOGY OF HD**

Huntington’s disease has a population frequency of about 7-10 per 100,000 population and usually starting in adult life-fourth or fifth decade (Aggarwal et al., 2004). Huntington’s disease is a rare neuropsychiatric disorder with a prevalence of 5-10 per 100,000 in the Caucasian population (Wallker, 2007). Great geographic differences were seen in HD prevalence. The overall prevalence of HD in Asian was 0.40/100,000, much lower comparing with that of 5.70/100,000 in European, North American, and Australia. Recently, an epidemiologic study of HD in Taiwan (China) showed that the average annual incidence rate was 0.1/100,000, much lower than those of Caucasians (5–10/100,000) (Xu and Wu, 2015). There are varying rates of prevalence in different racial groups. The highest frequencies of HD are found in Africa, China, Japan, and Finland. In Western populations HD has a prevalence of 10.6-13.7 individuals per 100,000 (Albanese et al., 2013).

A few isolated populations of western European origin have an unusually high prevalence of HD. These include the Lake Maracaibo region in Venezuela (700 per 100,000 people), the is
Huntington's disease (HD) is an Autosomal Dominant Disease having a varying age at onset. There is no epidemiologic data on the prevalence of HD in India. However, among immigrants from the Indian subcontinent to Britain, there were 22 patients with HD in a population of 1.26 million, giving an age-adjusted prevalence rate of 1.75 per 100,000 population. In a study of genetically confirmed HD patients from India, adult onset HD was found to be more common than Juvenile HD (below 20 years). HD commonly presents as chorea (88.5%) or with psychiatric symptoms (11.5%) (Muthane, 2011).

**STAGES OF HD**

Although symptoms of HD vary from person to person, even within the same family, the progression of the disease can be roughly divided into three stages.

**Early stage HD**

In early stage HD, individuals are largely functional and may continue to work, drive, handle money, and live independently. Symptoms may include minor involuntary movements, subtle loss of coordination, difficulty thinking through complex problems, and perhaps some depression, irritability, or disinhibition (Rosenblatt et al., 2011).

**Middle stage HD**

In middle stage HD, individuals lose the ability to work or drive and may no longer be able to manage their own finances or perform their own household chores, but will be able to eat, dress, and attend to personal hygiene with assistance. Chorea may be prominent, and people with HD have increasing difficulty with voluntary motor tasks. There may be problems with swallowing, balance, falls, and weight loss. Problem solving becomes more difficult because individuals cannot sequence, organize, or prioritize information (Rosenblatt et al., 2011).

**Late stage HD or Advanced HD**

In late stage HD, individuals require assistance in all activities of daily living.
Although they are often nonverbal and bedridden in the end stages which can result in agitation and frustration, it is important to note that people with HD seem to retain some comprehension. Chorea may be severe, but more often it is replaced by rigidity, dystonia, and bradykinesia. Psychiatric symptoms may occur at any point in the course of the disease, but are harder to recognize and treat late in the disease because of communication difficulties. By the time patients have end stage disease they are profoundly disabled. Huntington’s disease does not cause global dementia, however, and the ability to recognise and interact with people is often preserved. Huntington’s disease is a catabolic condition, and this, combined with marked dysphagia, means that it can be difficult to provide sufficient nutrition to maintain a patient’s weight (Novak and Tabrizi, 2010; Rosenblatt et al., 2011).

In all stages of HD, weight loss can be an important complication that can correspond with worsening symptoms and should be countered by adjusting the diet and maintaining appetite.

**Table 1: Clinical Signs in HD.**

<table>
<thead>
<tr>
<th>Early stage HD</th>
<th>Middle Stage HD</th>
<th>Late stage HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clumsiness</td>
<td>Dystonia</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Agitation</td>
<td>Involuntary movements</td>
<td>Bradykinesia (difficulty initiating and continuing movements)</td>
</tr>
<tr>
<td>Irritability</td>
<td>Trouble with balance and walking</td>
<td>Severe chorea (less common)</td>
</tr>
<tr>
<td>Apathy</td>
<td>Chorea, twisting and writhing motions, jerks, staggering, swaying, disjointed gait (can seem like intoxication)</td>
<td>Serious weight loss</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Trouble with activities that require manual dexterity</td>
<td>Inability to walk</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Slow voluntary movements, difficulty initiating movement</td>
<td>Inability to speak</td>
</tr>
<tr>
<td>Delusions</td>
<td>Inability to control speed and force of movement</td>
<td>Swallowing problems, danger of choking</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Slow reaction time</td>
<td></td>
</tr>
<tr>
<td>Abnormal eye movements</td>
<td>General weakness</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Olfactory dysfunction</td>
<td>Speech difficulties</td>
<td></td>
</tr>
<tr>
<td>Stubbornness</td>
<td>Speech difficulties</td>
<td></td>
</tr>
</tbody>
</table>

**RISK FACTORS FOR HD**

Three major categories of risk factors for onset of HD were identified:

a. CAG repeat length in the huntingtin gene

b. CAG instability
c. genetic modifiers

Of these, CAG repeat length in the huntingtin gene is the most important risk factor. For the progression of HD: genetic, demographic, past medical/clinical and environmental risk factors have been studied. Of these factors, genetic factors appear to play the most important role in the progression of HD. Among the potential risk factors, CAG repeat length in the mutant allele was found to be a relatively consistent and significant risk factor for the progression of HD, especially in motor, cognitive, and other neurological symptom deterioration (Rahman and Rhim, 2017).

DIAGNOSIS

Diagnosis of Huntington’s disease generally occurs after the development of motor system problems, as well as language issues. MRIs and other forms of neuroimaging are integral tool in diagnosing patients, verifying atrophy of areas of the brain due to the condition. Genetic testing may also be used to confirm the presence of the disease (Dunn, 2016).

PATHOGENESIS

The pathogenesis of HD is still not elucidated. Many possible mechanisms are being explored. In particular, factors promoting apoptosis, phenomena causing the toxic aggregation of proteins, the blockage of trophic factors, mitochondrial dysfunction, and excitotoxicity have been studied (Xu and Wu, 2015).

HD Genetics

The gene for huntingtin is comprised of 67 exons in humans. It is located between the markers D4S127 and D4S180 on chromosome 4p16.3. The gene spans a genomic region of over 200kb. Huntingtin is a 350kDa protein with no strong homology to known proteins. In normal huntingtin, the number of CAG repeats ranges from 6 to 35, whereas with individuals with the dominant HD mutation, the repeat length varies from 36 to 121.

The age of onset of HD is inversely correlated with CAG repeat length. Adult onset generally occurs with repeat lengths of 36-50, while juvenile onset is often seen with greater than 60 repeats (McMurray, 2001).

HD is one of nine disorders, all neurodegenerative diseases, caused by CAG repeat expansions that give rise to protein products with expanded polyglutamine tracts. Each disease in this group is caused by an expansion in a different gene, and the genes have little in
common with each other except for the presence of the CAG repeat. In the case of HD, the repeat is in exon 1 of a gene termed huntingtin (originally known as IT-15) located on chromosome 4p16.3 (Margolis and Ross, 2001). The range of repeat length in the unaffected population is 6–35 triplets. Repeats longer than 35 are considered expanded, and no individual with a repeat length ≤ 36 triplets has been convincingly diagnosed with HD. Although repeats ≤ 27 triplets in length are transmitted stably during meiosis, repeats in the range of 27–35 triplets will rarely expand to the disease range. Repeats 36–39 triplets in length are considered variably penetrant, such that the probability of developing the disease by late-life is not 100% and may be ≈ 50% for repeats of 36 or 37 triplets. Once in the disease range, repeat length is unstable during vertical transmission. The bias is toward longer repeats, at times markedly longer, in paternal transmission. Concomitantly, the age of disease onset is inversely correlated with repeat length. Together, these two factors explain the phenomenon of anticipation, in which age of onset tends to decrease in successive generations; on average, affected children will develop the disease ≈ 8 years earlier than their affected father (Margolis and Ross, 2001).

**Neurotransmission in HD**

In the normal human brain, the striatum comprises up to 95% of medium spiny neurons. These projection neurons are involved in the feedback loop that suppresses involuntary movements. In HD, atrophy of the striatum is the pathological hallmark of the disease and the medium spiny neurons are the most affected cells (Levine et al., 2014). Loss of medium spiny neurons causes abnormal neurotransmission of the dopamine, glutamate, and gamma-aminobutyric acid (GABA) systems and is therefore the main focus of pharmacotherapy in HD (Frank, 2014).

Dopamine is a major neurotransmitter that is involved in movement control, cognition, motivation, reward processing, and emotion modulation. Specific dopamine receptors are widely expressed throughout the central nervous system and are activated by dopamine on pre- and post-synaptic neurons. Free, unbound dopamine can be transported to the pre-synaptic terminal via the high affinity dopamine transporter (DAT). Here, it is re-packaged into vesicles by the vesicular monoamine transporter type 2 (VMAT2) or broken down into inactive metabolites by enzymes such as monoamine oxidase. The neurodegenerative processes in HD cause mainly postsynaptic dopaminergic dysfunction of dopaminergic type 1 (D1) and type 2 (D2) receptors in the striatum (Schwab et al., 2015).
Dopaminergic dysfunction is found in both pre manifest and manifest HD, where manifest patients show a greater loss of striatal D1 and D2 receptor binding. In PET studies, this decrease in dopamine receptor binding seems to be correlated with clinical motor assessment, functional capacity scores, and assessments that measure executive dysfunction. As it is hypothesized that chorei form movements in HD are related to overstimulation of dopamine receptors, pharmacological agents that modify the activity of the dopaminergic system have been of specific interest. Still, the glutamate neurotransmitter system is already affected in early disease stages and it is suggested that increased glutamatergic neurotransmission in the thalamocortical pathways also contributes to hyperkinetic movements (Coppen and Roos, 2017).

**Structural changes in HD**

![Figure 4: Major areas of brain affected in HD.](image)

HD affects the whole brain, but certain areas are more vulnerable than others. Pictured above are the basal ganglia - a group of nerves cell clusters, called nuclei. These nuclei play a key role in movement and behavior control and are the parts of the brain most prominently affected in early HD.

Gross pathology of HD is limited to the brain, with atrophy most prominent in the caudate, putamen, and cerebral cortex. Brain weight may be reduced by as much as 25–30% in advanced cases. The basal ganglia atrophy is readily visible by magnetic resonance imaging scan and progresses over time. Gross cortical atrophy is also readily detectable on magnetic resonance imaging, and increasingly sophisticated volumetric analysis has demonstrated early and progressive changes in the cortex (Rosas *et al.*, 2002). Microscopically, selective neuronal vulnerability is even more prominent, with loss of medium spiny neurons in the caudate and putamen and large neurons in layers III, IV, and V of the cortex (Hedreen *et al*,
An especially intriguing finding is the presence of intranuclear inclusion bodies, consisting of amyloid-like fibrils that contain mutant huntingtin, ubiquitin, synuclein, and other proteins (Becher et al., 1998).

The expanded CAG repeat generates an elongated polyglutamine tail on the huntingtin protein, which leads to cleavage and the generation of toxic fragments of this abnormal protein. The polyglutamine composition of the toxic fragments predisposes them to cross-link, forming aggregates that resist degradation and interfere with a variety of normal cellular functions, particularly mitochondrial energy metabolism. However, these aggregates also interfere with the regulation of transcription, axonal and vesicular transport, apoptosis, proteasome function, and cell-cell interactions. Haplo-insufficiency, the reduction in levels of wild-type huntingtin, does not cause disease. However, it may contribute to the adverse effects of aggregates. Therapeutic interventions designed to improve mitochondrial function, block huntingtin cleavage at sites that generate toxic fragments, prevent expression of mutant huntingtin, improve cell-cell interactions, enhance autophagic consumption of mutant proteins, and retard apoptosis are under active investigation (Raymond et al., 2011).

Huntington's disease primarily affects the striatum, and most clinical features are directly attributable to damage in this area, including cognitive impairment, behavioural changes, and loss of coordination. However, pathological changes occur in multiple cortical and subcortical structures as well (Raymond et al., 2011).

Chorea, the most striking feature of Huntington's disease, results from striatal dysfunction. Neuropathologically, HD is primarily characterized by neuronal loss in the striatum and cortex. However, many other nuclei including the globus pallidus (GP), thalamus, hypothalamus, subthalamic nucleus, substantia nigra (SN), and cerebellum are also affected (Raymond et al., 2011).

**Striatum**

Medium-sized spiny neurons (MSNs) constitute 90–95% of all striatal neurons and utilize γ-aminobutyric acid (GABA) as their principal neurotransmitter, as well as co-localizing specific neuropeptides. The dorsal striatum receives parallel sets of diffuse glutamatergic inputs from almost all neocortical areas and several thalamic nuclei. These inputs primarily synapse onto spines of MSNs. The striatum also contains a number of modulatory components including dopamine (DA) projections from the SN pars compacta (SNC) and
cholinergic or GABAergic inputs from striatal interneurons. These elements constitute the basic striatal microcircuit, a circuit that is severely disrupted in HD. In the striatum, GABAergic MSNs are most affected and degeneration of these neurons occurs progressively. The large spiny cholinergic interneurons and the numerous other interneuronal GABAergic populations are relatively spared from degeneration. Striatal output is largely segregated into two populations of MSNs (the direct and indirect pathways) with distinct projections, as well as DA receptor and neuropeptide expression, although some overlap exists. The direct pathway consists of MSNs that predominantly express D1 DA receptors as well as substance P (SP) and dynorphin and project to the SN and the internal segment of the GP (GPi). The indirect pathway is comprised of MSNs that express predominantly D2 receptors, met-enkephalin or neurotensin and project to the external segment of the GP (GPe) (Raymond et al., 2011).

This segregation is important in the context of HD, as there is evidence during disease progression for a time-dependent, differential loss of the two populations of striatal projection neurons. MSNs of the indirect pathway appear to be particularly vulnerable in HD and markers for these neurons and their projections, such as enkephalin, are lost in postmortem brains of fully symptomatic patients, in early symptomatic and presymptomatic brains and in genetic mouse models. In contrast, MSNs of the direct pathway are relatively spared in the early stages, although the SP-containing projections to the SN pars reticulata (SNr) are more severely affected than the SP-containing projections to the GPi and SNc. These results are consistent with the hypothesis that chorea results from preferential dysfunction and ultimate loss of indirect pathway MSNs and possibly that akinesia and dystonia which occur later in HD are a consequence of the additional dysfunction and loss of direct pathway MSNs (Raymond et al., 2011).

Another organizational feature of the striatum is the separation into a patch (striosome) and a matrix compartment, based on neurochemical markers such as opioid receptors and acetylcholinesterase staining, as well as input-output organization. Corticostriatal neurons in deep layer V and VI project to the striatal patch compartment, whereas superficial layer V and layers II–III neurons project to the matrix. Afferents to the striosomes originate in the SNc, prefrontal cortex and limbic system, whereas afferents to the matrix originate in the motor and somatosensory cortices, and in the parietal, occipital and frontal cortices. In terms of striatal outputs, neurons from the patch compartment provide inputs to the DA neurons of
the SNc, whereas matrix neurons provide inputs to the GABAergic neurons of the SNr. During the early phase of HD (grades 0 and 1), discrete islands of neuronal loss and astrocytosis appear selective mostly to the patch compartment, whereas in later stages cell loss increasingly involves the matrix compartment. As MSNs from patches project to the SNc it may be that early degeneration of these neurons produces hyperactivity of the nigrostriatal DA pathway, contributing to chorea and other early clinical manifestations of HD (Raymond et al., 2011).

Cerebral Cortex

In the cortex, pyramidal neurons of layers III, V, and VI ultimately degenerate. Whereas striatal neuronal death may underlie many symptoms in late stage HD, early deficits, which are apparent years before the overt movement disorder, are more likely associated with cellular and synaptic dysfunction in the cortex (Backman and Farde, 2001; Rosas et al., 2008). Advances in neuroimaging techniques have contributed greatly contributed to a better understanding of HD pathology, providing correlations between morphological brain changes and the development of cognitive deficits in attention, working memory, and executive functions (Bohanna et al., 2008; Rosas et al., 2004). Magnetic resonance imaging (MRI)-based morphometric analyses have shown that subjects carrying the HD mutation have significant volume reductions in the cortex and such changes occur before the onset of motor symptoms. In manifest HD, differential involvement of specific cortical areas might help explain much of the clinical heterogeneity and complexity of the disease, as specific regional cortical pathology correlates well with the nature of symptoms. For example, motor dysfunction correlates with the extent of cell loss in the primary motor cortex whereas mood changes are associated with cell loss in the cingulate cortex (Rosas et al., 2005; Rosas et al., 2006; Thu et al., 2010). Among the earliest prodromal changes in HD are alterations in cognitive function and sensory integration. In sensory tests that do not involve motor components, sensory-evoked brain activation is reduced in cortical (somatosensory and frontal) and subcortical (basal ganglia) areas. Cognitive deficits have been shown in HD mutation carriers decades before motor diagnosis. These cognitive changes affect functional skills and work performance, and include deficits in attentional set shifting and semantic verbal fluency. Performance on the self-timed finger-tapping task, reflecting skilled motor learning, begins to decline more than 20 years prior to predicted age of HD onset. Moreover, the decline in a variety of other cognitive and motor tasks begins approximately 10–15 years prior to HD onset and correlates well with a sharply progressive reduction in tissue volume in
the striatum and cortical white matter as assessed by MRI (Beglinger et al., 2010; Paulsen et al., 2008).

The striatum begins to degenerate before other brain areas, and altered activity at corticostratial synapses contributes to an imbalance in survival versus death signaling pathways in this brain region. Striatal projection neurons of the indirect pathway are most vulnerable, and their dysfunction contributes to motor symptoms at early stages of the disease. Mutant Htt expression changes striatal excitatory synaptic activity by decreasing glutamate uptake and increasing signaling at N-methyl-d-aspartate receptors (NMDAR). A variety of studies indicate that reduced brain-derived neurotrophic factor (BDNF) transcription, transport and signaling contribute importantly to striatal neuronal dysfunction and degeneration in HD. Striatal dopamine and endo-cannabinoid signaling are also altered and progressively become dysfunctional. Changes at striatal neurons vary with the stage of disease and clinical symptoms (Sepers and Raymond, 2014).

MANAGEMENT OF HD

Despite the fact that the pathogenesis of HD has still not been fully resolved, effective pharmacological treatment to stop the pathophysiological process underlying HD is unfortunately not available. Pharmacological treatment is therefore focused on improving daily functioning by reducing symptom severity (Frank, 2014). Although many potential effective pharmacological options for the treatment of chorea are available, only few randomized controlled studies have been performed that assess the effects on symptom reduction. To date, practice based studies showed that among HD experts, there is a wide variety in preferred drugs to treat chorea (Priller et al., 2008).

The most commonly used therapies in HD patients are symptomatic drug therapies and no therapy has been developed that effectively modifies disease progression. Despite the fact that 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. Although many signs and symptoms can be treated, it is not always necessary to do so. The patient’s limitations in daily life determine whether or not drugs are required. Very little evidence is available about the drug or the dosage to prescribe for any signs and symptoms. Drug treatment is, therefore, individualized and based on expert opinion and daily practice Treatment consists of drug prescription and non-medication advice (Sharma et al., 2012). Surgical treatment does not play an important role in HD (Roos, 2010).
Non-Pharmacological Treatment of Chorea in HD

Non-pharmacological treatment approaches to reduce chorea are currently also under investigation. For example, pallidal deep brain stimulation (DBS) has been shown to be a safe treatment option. The effects of DBS on motor symptoms are currently under examination in a larger follow-up study (Wojtecki et al., 2015).

Pharmacological Treatment of Chorea in HD

Hyperkinesia, or chorea, is treated with dopamine B2 receptor locking or depleting agents. Most commonly used drugs for chorea are typical or atypical neuroleptics (dopamine receptor blocking) and tetrabenazine (dopamine depleting). The drugs prescribed differ per country. 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 (Roos, 2010).

Tetrabenazine

Tetrabenazine was synthesized in 1956 and first introduced in the 1970s for the management of hyperkinetic movement. Tetrabenazine is a reversible dopamine-depleting drug that selectively binds to the central VMAT2 and depletes monoamines by inhibiting their transport into presynaptic vesicles. Tetrabenazine is rapidly metabolized into two metabolites, alpha- and beta-dihydrotetrabenazine via CYP2D6, a hepatic isoenzyme, with maximum concentrations reached in 1.5 h after dosing. Elimination of tetrabenazine and its metabolites is primarily renal. As the half-life of the metabolites is between 2 and 8 hr. Nevertheless, depression and suicidal behavior can be exacerbated by tetrabenazine, especially in patients with a history of depressive mood. Tetrabenazine is therefore contraindicated in patients who are actively suicidal and in patients with inadequately treated depression. Furthermore, concomitant treatment with antidepressant drugs that have strong CYP2D6 inhibiting effects (such as fluoxetine and paroxetine) can lead to increased levels of the active metabolite due to a prolonged half-life. In case of concomitant use of CYP2D6 inhibitors, a 50% reduction of the daily tetrabenazine dose is recommended (Coppen and Roos, 2017).

Dopamine antagonists

Tiapride

Tiapride is a first-generation D2 receptor antagonist that is only available in European countries. Although tiapride is a classic antipsychotic drug, it is a frequent choice for the
treatment of chorea by HD experts. Tiapride has an oral bioavailability of about 75%, with peak plasma concentrations reached in 1 h after oral Pharmacological Treatment of Chorea in HD 35 administration, a half-life of 2.6–4 h, and is eliminated mostly by urinary excretion (Roos, 2010).

Besides the potential positive effects on choreatic symptoms, dopamine antagonists are known to cause adverse effects due to dopamine D2 receptor blockage. Adverse effects include dyskinesias, rigidity, cognitive impairment, hypotension, and sedative effects (Coppen and Roos, 2017).

**Neuroleptics**

**Clozapine**

Clozapine is an atypical neuroleptic drug commonly used in the treatment of schizophrenia. Since clozapine has a low incidence of extrapyramidal side effects, it is also suggested to be a suitable symptomatic drug for chorea. Clozapine has a relatively high affinity for dopamine D1 and D4 receptors and relatively low D2 dopaminergic antagonistic properties in contrast to typical neuroleptic drugs. Clozapine is eliminated by hepatic cytochrome isoenzymes with an elimination half-life of 14 h. Sertraline, paroxetine, and fluoxetine have been reported to increase plasma concentrations of clozapine, whereas coadministration with carbamazepine or rifampin reduced clozapine plasma concentrations (Roos, 2010). Clozapine was only effective in reducing dyskinesias in patients that had no prior exposure to neuroleptics. Higher doses were required for reasonable effectiveness and these high doses were poorly tolerated in most patients. Evidence from small open label series supports the use of other atypical antipsychotics in HD. These include olanzapine, risperidone, aripiprazole. It also prevents dopamine signaling by blocking postsynaptic dopamine receptors. Drowsiness, depressed mood, parkinsonism, and akathisia were the most commonly reported.

**Olanzapine**

In the UK, olanzapine is the most commonly prescribed dopamine antagonist for the treatment of motor and behavioral symptoms in HD. Olanzapine is an atypical antipsychotic drug with a broad pharmacokinetic profile with high affinity for serotonergic (5HT2A, 5HT2C, 5HT3) receptors, but antagonizes dopamine (D2) receptors. Olanzapine has a oral bioavailability of 60%, as 40% is inactivated by first-pass hepatic metabolism. Olanzapine reaches a maximum plasma concentration within 5–8 h and has a mean half-life in healthy individuals of approximately 33 h. Fluvoxamine or estrogens (CYP1A2 inhibitors) have been
shown to increase plasma concentrations of olanzapine, whereas carbamazepine, omeprazole, and rifampin (CYP3A4 inducers) may reduce olanzapine plasma concentrations (Mauri et al., 2014).

Risperidone
Risperidone acts as a 5-HT2A and D2 receptor antagonist and is generally used in the treatment of schizophrenia and the acute manic phase of bipolar disorders. Although risperidone is an atypical antipsychotic drug, it behaves more as a typical antipsychotic drug, as there is a relatively high risk of developing tardive dyskinesia and other extrapyramidal effects compared to other second-generation antipsychotics. Risperidone has a good oral bioavailability of 70–85%, with peak plasma concentrations reached in 1 h and a mean half-life of 22 h of the active metabolite. As risperidone is metabolized via CYP2D6 in the liver, simultaneous use of CYP2D6 inhibitors (such as fluoxetine and paroxetine) can increase the plasma concentration of risperidone (Mauri et al., 2014).

The use of risperidone for the treatment of chorea in HD is not investigated in clinical trials. Several case-reports on risperidone describe a reduction in motor symptoms and improvement of psychiatric symptoms. Risperidone also showed a trend toward stabilizing motor decline, as the total motor scores did not change over time. Among HD experts, risperidone was reported by 43% of the respondents as the first choice antipsychotic drug for the treatment of chorea. Current clinical reports suggest that risperidone might improve motor symptoms in HD, specifically when psychiatric symptoms are present (Cankurtaran et al., 2006).

Anti-Glutamatergic Drugs
Amantadine
Amantadine is a noncompetitive N-methyl-D-aspartic acid (NMDA) receptor antagonist and is commonly used in the treatment of extrapyramidal symptoms in Parkinson’s disease (PD). Amantadine reaches peak plasma concentrations after 1–4 h, is poorly metabolized in humans via renal secretion (90% can be recovered unchanged in urine), and has a relatively short half-life of 12 h in young adults. Although amantadine is recommended as an alternative for tetrabenazine by the AAN guidelines for the treatment of chorea in HD, there is limited evidence about the efficacy and safety of amantadine in patients with HD (Armstrong and Miyasaki, 2012).
Riluzole

Riluzole is a glutamate release inhibitor that displays anti excitotoxic characteristics. Therefore, riluzole is proposed as a potential neuro protective agent for treatment in HD. Peak plasma concentrations are reached in 14 h, with a bioavailability of 60%. Riluzole is eliminated via urinary excretion for 85–95% in the first 24 h after administration. clinicians prescribe riluzole (200 mg/day) to treat chorea (Mauri et al., 2014).

Other Pharmacological Preferences

Benzodiazepines (such as clonazepam and diazepam), haloperidol, and sulpiride are also frequently prescribed drugs to reduce chorea in daily clinical practice. Although it is suggested that benzodiazepines have a beneficial effect on motor signs, no clinical trials have investigated this effect on chorea. Among HD experts, clonazepam is only used as an adjunctive therapy. Haloperidol and sulpiride are both classic first-generation antipsychotics drugs that were previously in favor for the treatment of choreiform movements in HD (Burgunder et al., 2011).

Potential New Treatment Options

Promising treatment options are deutetrabenazine and pridopidine, which are being developed to target motor symptoms in HD.

Deutetrabenazine

SD-809 or deutetrabenazine is a newly developed VMAT2 inhibitor that is structurally related to tetrabenazine in a deuterated form. Deuterium is a naturally occurring, nontoxic form of hydrogen and can create stronger bonds with carbon than with hydrogen. The specific sites of deuterium placement in deutetrabenazine are thought to increase the half-life of active circulating metabolites compared to tetrabenazine without changing its target pharmacology. Deutetrabenazine has been found to significantly reduce chorea in patients with HD and also significantly improved overall motor function (Stamler et al., 2013).

Pridopidine

Pridopidine (formerly known as ACR-16) is a recently developed drug that belongs to a new class of pharmacological agents known as dopidines, which act as dopamine stabilizers. By binding to striatal dopamine D2 receptors, pridopidine can reverse and improve behavioral states by modulating hyperactivity or hypoactivity of the dopaminergic system, without having major effects on normal psychomotor function. Pridopidine is orally administered and
has a rapid absorption, with peak plasma concentrations within 0.5–4 h and an elimination half-life between 10 and 14 h, with elimination partly by urinary excretion and partly by hepatic metabolism (Ponten et al., 2010).

Drug treatment for hypokinesia has been tried using antiparkinsonian drugs, but almost always with very disappointing results. Deep brain stimulation has a place in other movement disorders such as Parkinson disease. In Alzheimer’s disease, anticholinesterase drugs are in use. In Huntington’s disease no clinical trials with Rivastigmine or donepezil are available (Roos, 2010).

**Psychiatric signs**

As depression and aggressive behaviour are the most devastating to family life, the majority of drugs are prescribed for these signs. It is important to find the right therapy for the right person at the right time. Medical and non-medical treatment must be individually tailored, as the symptoms and signs differ by person and over time tremendously. Non-medical interventions available are: physiotherapy, occupational therapy, speech therapy, dietician, psychologist, social worker, and nurse (Roos, 2010).

There is no single preferred antidepressant for treating depression in HD. The treating physician should bear in mind that people with HD are sensitive to the cognitive side effects of some antidepressants and are easily made delirious, as if they were much older than their chronological age. Therefore the older agents such as tricyclic antidepressants and monoamine oxidase inhibitors should generally be avoided, or at least not considered first line. Generallyselective serotonin reuptake inhibitor (SSRI), such as fluoxetine, sertraline, paroxetine, citalopram, or escitalopramarepreferredfor reasons of safety and tolerability. Other popular choices include bupropion, venlafaxine, duloxetine and desvenlafaxine (Paulsen et al., 2007).

**Neuroprotective Therapies**

Neuroprotective strategies are designed to modify disease progression based on the concept of neuronal preservation. It is likely that disease-modifying strategies will ultimately be a more powerful approach relative to symptomatic treatments. These therapies attempt to attenuate or delay the onset of symptoms by preventing cell death and preserving neuronal circuitry in vulnerable brain regions. Neuro protective therapies can be delivered in a
systemic fashion (when they are capable of crossing the blood–brain barrier) or applied directly to the brain via neurosurgical procedures.

**Coenzyme Q10**
Coenzyme Q10 is a molecule in the electron transport chain that carries electrons from complex I and II to complex III. By keeping electrons with the enzymes in the mitochondrial membrane, coenzyme Q10 reduces formation of reactive oxidative species and oxidative stress. Mitochondrial energy impairments plague brain cells in HD, resulting in neuronal death and dysfunction. Targeting enzymes or cofactors that play a role in energy production theoretically could help reduce cell death (Kidd, 2005).

**Creatine**
Creatine has been hypothesized to be effective as a therapy for HD because it is capable of buffering ATP levels in cells. Mitochondrial enzymes, and therefore ATP production, are disrupted in HD brains. When creatine is ingested it is converted into phosphocreatine and stored. In the face of an energy deficit, phosphocreatine can donate its phosphate to ADP in the presence of creatine kinase, producing the high energy ATP molecule (Ramaswamy et al., 2007).

**Trophic Factors**
Development of neurodegenerative diseases like PD, amyotrophic lateral sclerosis (ALS), and Alzheimer’s disease (AD) resulted from a deficiency in a growth factor that was stored in the targets of the affected neurons. BDNF is a neurotrophic factor that is produced by cortical neurons and is essential for survival of striatal neurons. BDNF is transported in vesicles along microtubules with the help of wild-type huntingtin protein. Either a reduction in wild-type huntingtin or the expression of mutant huntingtin disrupts transport of BDNF, resulting in a loss of trophic support to striatal neurons. Additionally, in striatal neurons, wild-type huntingtin protein enhances the expression BDNF and expression of mutanthuntingtin reduces BDNF levels and this effect is toxic to neurons. There is strong evidence to suggest that restoration of BDNF levels in striatal neurons will attenuate the cell death seen in HD (Gauthier et al., 2004).

**Ciliary Neurotrophic Factor (CNTF)**
CNTF is the first trophic factor to enter clinical trials in HD. CNTF is a differentiating cytokine that has trophic effects on striatal neurons (Ramaswamy et al., 2007).
Glial Cell Line-Derived Neurotrophic Factor (GDNF) Family of Ligands (GFLs)
Members of the GDNF family of ligands (GFLs) include GDNF, neurturin (NTN), artemin, and persephin. GDNF and NTN are two members of this family that have been extensively studied in HD. Traditionally, GFLs have been used in clinical trials for PD. In HD research, GFLs are recognized for their important role in the growth, development, and trophic support of striatal neurons. Treatment of GABAergic neurons in ventral mesencephalic cultures with GDNF or NTN promotes cell density and neurite outgrowth (Ducray et al., 2006).

THERAPEUTIC ADVANCES IN THE TREATMENT OF HD
Huntington’s disease is a devastating neurological disorder without effective treatment. There is an urgent need for developing effective therapies for HD. Researchers are actively investigating possible effective therapies based on current understanding of the molecular pathology of HD. Much attention has been focused on screening for drugs that prevent aggregation of huntingtin with expanded polyglutamine tract. The other approach is to use recent advances in molecular biology of neurotrophic factors, neuronal tissue transplantation and cell engineering in HD therapeutic developments with the aim of retarding or reversing HD pathology. Additionally, which increase survival of huntingtin’s gene. Until the discovery of one therapy that can address the myriad of concerns in HD, combinations of factors that target individual aspects of the disease may have to be considered (Sharma et al., 2012).

![Figure 5: Therapeutic targets for HD.](image)

Agents That Inhibit Mutant Huntingtin Aggregation
- **Transglutaminase inhibitors**: Transglutaminase (TGase) can use huntingtin as a substrate to cross-link huntingtin molecules. T Gase activity was found to have increased
in HD postmortem brains. T Gase provides an additional mechanism for the formation of aggregation of mutant huntingtin. This suggests that T Gase might play a role in HD pathogenesis therefore, is a potential therapeutic target.

- **Protease inhibitor**: Huntingtin can be cleared by proteases, including caspases, calpain, and aspartyl protease. Caspase and calpain-mediated partial cleavage of mutant huntingtin promotes huntingtin aggregation and cellular toxicity, inhibitors of huntingtin partial cleavage might have therapeutic values. Caspase inhibitors, z-VAD-fmk and z-DEVD-fmk, can prevent cleavage of huntingtin by caspases and reduce cytotoxicity caused by expanded polyglutamine tract. Protease inhibitors could reduce N-htt fragments and in turn, prevent or delay disease.

**Others**

- **Fetal neural transplantation**: Selection of appropriate fetal tissue is essential for optimal therapeutic benefit, and isolation of tissue destined to a striatal fate is ideal for transplantation therapies.

- **RNA interference (RNAi)**: A recently developed therapy that has come to the forefront in HD is RNAi. This therapy attempts to use short interfering RNA (siRNA), short hairpin RNA (shRNA), or microRNA (miRNA) molecules to shut down the production of the mutant huntingtin protein.

- **Stem Cells**: Practical concerns associated with procurement of large numbers of fetal human tissue have pushed transplantation research towards more modern donor tissue: stem cells. Important characteristics of stem cells for use in HD are the capability to differentiate into neurons, the capability to attain a GABAergic phenotype, and the ability to reestablish lost circuitry (Albanese et al., 2013; Kumar et al., 2015).

- **Antisense oligonucleotide therapy**

**CONCLUSION**

Huntington’s disease is a devastating neurological disorder without effective treatment. There is an urgent need for developing effective therapies for HD. Researchers are actively investigating possible effective therapies based on current understanding of the molecular pathology of HD. Much attention has been focused on screening for drugs that prevent aggregation of huntingtin with expanded polyglutamine tract. The other approach is to use recent advances in molecular biology of neurotrophic factors, neuronal tissue transplantation and cell engineering in HD therapeutic developments with the aim of retarding or reversing
HD pathology. However, no therapy has been shown to combat all of the symptoms associated with the disease: cognitive, motor, and psychiatric. Until the discovery of one therapy that can address the myriad of concerns in HD, combinations of factors that target individual aspects of the disease may have to be considered.

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