STM JOURNALS

International Journal of
Cell Biology and Cellular Functions

Volume 1, Issue 1, 2023
DOI (Journal): 10.37591/IJCBCF

https://journals.stmjournals.com/ijcbcf

Research IJCBCF

The Current State of Huntington's Disease Treatment: An Overview of Palliative Care and Symptom Management

Richa Sanyal*

Abstract

Huntington's disease (HD) is a neurodegenerative ailment that adversely affects the basal ganglia and the cortex of the brain. Although there is no recognized cure for HD, symptomatic relief and therapeutic management of the condition have improved over the course of time. This review paper provides an up-to-date overview of the current treatment options and symptom management strategies utilized in the care of HD patients. Additionally, it highlights the existing research strategies being employed to develop new treatments or technologies for managing the disease. Finally, the paper examines potential future prospects, including gene therapies and other novel approaches to treating HD. The article concludes that while there is still much work to be done to find a cure for HD, current treatment options and research strategies offer hope for a better quality of life for HD patients and their families.

Keywords: Huntington's disease, chorea, CAG trinucleotides, tetrabenazine, ASO therapies, RNA interference therapy, stem cell therapy, zinc-finger therapies

INTRODUCTION

A genetic neurological ailment called Huntington's disease (HD), often termed Huntington's chorea, is primarily categorized by neuropsychiatric symptoms, movement disorders (most commonly chorea-like symptoms), and cognitive decline [2]. Early prognostics are oftentimes self-deprecating complications with temperament and cognitive function [3]. The result is often an overall stint of coordination and unstable gait [4]. As the ailment advances, the uncoordinated and uncontrolled physiological motions associated with chorea get increasingly pronounced [3]. Physical performance eventually deteriorates to the point of difficulty maintaining coordination and loss of speech [3, 4]. Dementia usually leads to poor mental performance [5]. The exact symptoms are somewhat distinguishable within individuals [3]. It can manifest at any age, but typically symptoms begin surfacing in the age groups belonging to 30 and 50 [5, 6]. In each subsequent generation, we can see the state progressing rapidly [3]. Juvenile HD, which accounts for approximately 8% of cases occurring before age 20, often manifests as slowness of Parkinson's disease, and not chorea [5].

***Author for Correspondence**
Richa Sanyal
E-mail: richasanyal12@gmail.com

Student, Department of Biotechnology, University Institute of Biotechnology, Chandigarh University, India

Received Date: April 13, 2023
Accepted Date: May 03, 2023
Published Date: May 17, 2023

Citation: Richa Sanyal. The Current State of Huntington's Disease Treatment: An Overview of Palliative Care and Symptom Management. International Journal of Cell Biology and Cellular Functions. 2023; 1(1): 35–52p.

Traditionally, HD is a parent-inherited condition with a huntingtin gene mutation (HTT) [6]. However, novel mutations may account for up to 10% of cases [3]. The genetic information for said huntingtin protein is provided by the huntingtin gene (Htt) [3]. Aberrant mutant proteins (mHtt) are generated when the CAG (cytosine-adenine-guanine) repetitions (sometimes called trinucleotide repeat expansions) within that gene that codes for the huntingtin protein are enlarged [7]. This protein ultimately destroys brain cells in various ways [7]. Genetic testing can always be used to diagnose the

condition, regardless of whether symptoms are apparent [8]. The age at which a person is considered mature enough to choose a test, whether parents have the right to have their children examined, and also how secrecy and dissemination of examination findings are managed, affect the ethics that these facts entail. These are just a few of the technical problems [4].

The increased CAG repetition length within the huntingtin genetic factor is usually utilized to confirm an assessment in patients with clinical manifestations belonging to the disease [2]. Although unusual symptoms may occur, the diagnosis is usually straightforward and it can be difficult to determine when an asymptomatic carrier has progressed to the disease state [2]. This has gained importance due to the recent participation in clinical trials of various potential disease-modifying treatments [2]. An increasing number of diseases, including abnormal genetic causes, may mimic HD when HD genetic testing is negative [2]. For genetic testing, patients are best cared for in specialized multidisciplinary clinics [2]. The majority of current treatments are symptomatic and focus on chorea and neurobehavioral problems, although supporting research data may be lacking [2].

End-stage HD requires full-time care and currently has no recognized treatment [4]. Some treatments can reduce symptoms, while others can improve quality of life [5]. Tetrabenazine has the best track record in treating movement disorders [5]. Approximately 4 to 15 people of European descent have Huntington's disease [3, 5]. It is rare in Japan, but it is not known how common it is in Africa [5]. Both male and female genders are equally impacted by the malady [5]. The average lifespan is shortened by abnormalities like pneumonia, cardiovascular disease, and bodily injuries from falls [5]. About 9% of deaths are due to suicide [5]. He usually dies 15 to 20 years after the disease is first diagnosed [6].

BACKGROUND

George Huntington, a doctor from Long Island, New York, who died on March 3, 1916, provided the diagnostic characterization of the condition that bears his name, Huntington's disease [1]. His article "On Chorea," initially featured in the Surgical and Medical Reporter of Philadelphia in 1872, has drawn a great deal of attention from the medical and scientific communities during the past century and a half [1].

His own family was instrumental in defining the sickness, but so too were the relatives of others who were affected [1]. The oldest documented medical description of hereditary chorea is found in George Huntington's article, which also contributed to the definition of the distinct clinical entity known as "Huntington's chorea," the pathology of chorea [1]. He was aware of the interest from the medical community and in contact with distinguished physicians, but due to the unclear pathology of chorea, he decided against conducting his own investigation [1].

SYMPTOMS

HD often grounds motor, behavioral, and neuropsychological/psychiatric disorders, and its warning signs and symptom manifestations can diverge widely (as shown in Table 1) [9]. This fluctuates greatly from individual to individual and symptoms start to emerge early on [9]. Certain indicators might seem more obvious or affect function more than others, but may change during the period of the condition [9].

Mobility Ailments

The first physical sign to be noticed is chorea, which is spastic, unpredictable, and uncontrollable movements [10]. Many people impede or are unaware of their involuntary movements [10]. General restlessness, carelessly initiated or incomplete small movements, poor coordination, or slow saccadic eye movements may be the earliest signs of chorea [11]. As the disease worsens, signs such as stiffness, twisted movements, or abnormal posture become more evident [11]. This indicates that brain motor control mechanisms are affected [12]. All behaviors related to muscle control are affected by the progressive deterioration of psychomotor function [12]. Gradual decline in psychomotor function

impairs all behaviors related to muscle control. Dystonia is a term used to describe problems with muscle control, such as stiffness or muscle contractions [12]. A neurological condition known as dystonia causes twisting or repetitive movements similar to tremors [11]. Bodily disequilibrium, imbalance, peculiar facial expressions, and problems with speech, gulping, and chewing are common consequences [11]. Weight loss and sleep problems are other related symptoms [13]. Eating problems often lead to emaciation and can lead to malnourishment [14]. Individuals with HD often lose weight, consequently, their condition worsens over time. Westphalian variants with slow movements, stiffness, and spasms are more common among adolescent HD patients, as so are the convulsions. Adolescent HD often progresses more rapidly to more severe cognitive impairment, with occasional chorea [11, 13].

Table 1. Overview of symptoms of huntington's disease.

Symptoms of Huntington's Disease		
Movement Disorders	Cognitive Impairment	Psychiatric disorders
Chorea Dystonia Poor coordination Stiffness Poor posture Anorexia Bradykinesia	Loss of memory Executive incompetence Unable to concentrate Lack of impulsivity Unawareness Rigidity	OCD BPD Insomnia

Cognitive Impairment

Cognitive abilities progressively worsen and become progressively impaired with dementia [5]. Executive skills, such as decision-making, impulse control, conceptual thought, pattern memorization, commencing acceptable behaviors, and ceasing unsuitable ones, are particularly impaired. Various cognitive deficits include being unable to concentrate, being rigid, lacking in impulsivity, being unaware concerning personal own actions, plus talents, and also having trouble acquiring and comprehending relevant knowledge [12]. As the condition worsens, memory issues generally appear. There are reports of deficits in working memory, procedural memory, and episodic memory (memory for life), as well as problems with short-term and long-term memory [12].

Psychiatric Disorders

Anxiety, despair, a lack of emotional expression, egocentrism, hostility, and compulsive behavior are among the reported neuropsychiatric symptoms (as shown in Table 1) [15]. The latter can lead to or exacerbate an addiction, including drunkenness, gambling, and hypersexuality [15]. Manic, sleeplessness, bipolar disorder, and OCD (obsessive-compulsive disorder) are some of the more common mental conditions [12]. It has also been observed that people struggle to read unfavorable facial expressions of others [12]. The lifetime incidence of psychological problems is estimated to range between 33% and 76%, and the prevalence of these conditions varies widely between studies [15]. These symptoms are among the most unpleasant signs of the disease for many patients and their families [15]. It often interferes with daily life and becomes a factor in hospitalization [15]. mHtt is articulated all across the body, and this development outside the brain is directly related to abnormalities in peripheral organs. These problems include testicular atrophy, weight loss, osteoporosis, decreased glucose tolerance, and muscle wasting [16].

ETIOLOGY OF HD

Genetic Mutation

A rise in the CAG repetitions within the HD encoding gene results in HD, "trinucleotide repeat" state [17]. The HTT gene can be found at 4p16.3 on the short arm of chromosome 4 [11]. A trinucleotide repeating, or HTT, is a pattern or string of the nucleotides cytosine (C), adenine(A), and guanine(G), (CAG) DNA bases repeated many times (i.e., CAGCAGCAGCAG...) [11]. These chains create repeat regions of the gene known as polyglutamine tracks (or poly-Q tracks), amino acid glutamine chains, and poly-Q regions [18]. The amino acid, glutamine’s 3-letter genetic code is CAG. [18].

PolyQ regions usually contain less than 36 repeats of glutamine, leading to the synthesis of the intracellular huntingtin protein. Though, more than 36 glutamine sequences result in proteins with different properties [11]. Known as mutated huntingtin (mHtt), this altered form accelerates the degree of degeneration of particular types of neurons [11]. Diverse brain parts are affected because they depend to varying degrees on specific types of neurons [11].

Table 2. Correlation of CAG repetitions and disorder status.

CAG repetition rate	Categorization	Does it have an effect?	Threat to the next generation?
Less than 27	Standard	None	None
27 to 35	Intermediary	None	Yes, but less than 50 percent
35 to 39	Penetration is less	Might have an effect	Fifty percent
40 and more	Complete penetration occurs	Yes	Fifty percent

Environmental and other genes that alter HD mechanisms are responsible for the remaining variation [11]. 40 or more repetitions are allied with ailment manifestations, although a repetition number of 26 or less is considered ordinary [17]. Intermediary repeat counts from 27 to 35 are not linked with disease countenance, though it might increase when transmitted from the father, leading to disease in the offspring [17]. Repeats 36-39 are associated with lower penetrance, which causes some people to get Huntington's disease and others not (as shown in Table 2) [17]. Sometimes the onset is so late that no one notices the symptoms [11]. Adolescent HD can begin before the age of 20 with a very high relapse rate (60 years of age and older) [19, 20]. The Westphalian form of adolescent HD is often characterized by slow movements, rigidity, and tremors. About 7% of HD operators fall into this category [19, 20].

Inheritance

Genetic mutations in one gene are the main cause of HD [9]. Due to HD being an autosomal dominant disease (as illustrated in Figure 1), you just need a single duplicate of the abnormal gene to get Huntington's disease [9]. Except for genes upon the allosomes, every gene is transferred two times, once from each parent [9]. A normal copy or an atypical duplicate of a gene can be acquired from either of the parents with a faulty gene [9]. Therefore, every offspring in the family has a 50% chance of acquiring the gene responsible for causing the hereditary disorder [9].

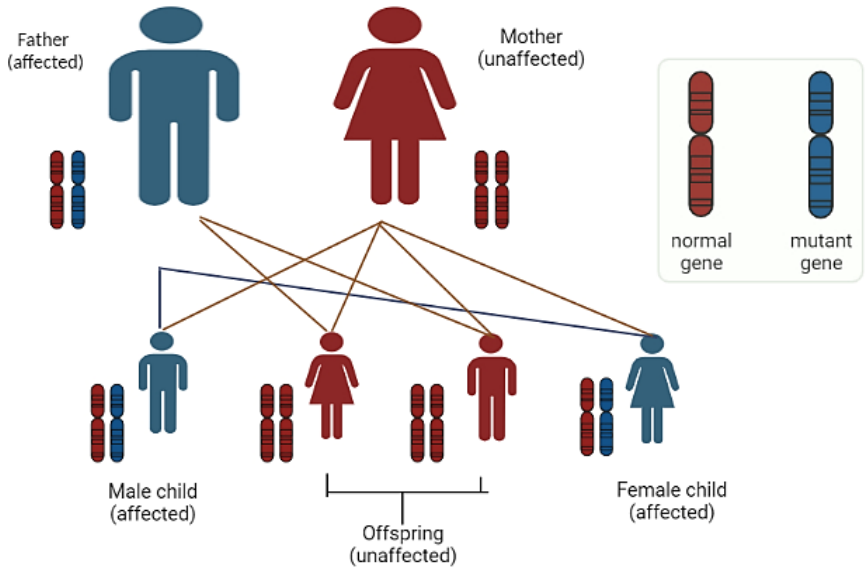

Figure 1. Autosomal Dominant Inheritance of HD [21].

Usually, one affected parent passes the mutated gene on to the affected child (as illustrated in Figure 1) [21]. Rarely, none of the parents of people with Huntington's disease have the disease [21]. CAG

trinucleotide repeats often increase in number when the mHtt gene is transmitted between generations (as shown in Table 2) [21]. Early development of signs and symptoms is usually associated with more repetitions. Anticipation is the term for this phenomenon [21].

MECHANISM OF PATHOGENESIS

The huntingtin protein appears to have a variety of activities and interrelates with more than 100 distinct proteins [22]. Granting the activity of the transformed protein (mHtt) remains not fully understood, the situation is harmful towards some cell categories, predominantly brain cells [11]. As this disease progresses, other fragments of the brain, like the cerebral cortex, are correspondingly damaged [11]. The subcortical basal ganglia, the first in the striatum, show early lesions [11]. Early symptoms such as motor control, mood regulation, and higher cognitive functions are caused by connections between the striatum and cortical functions [11]. HD also appears to alter DNA methylation [23].

Huntingtin Activity

All cells express Htt, but the brain and testes have the highest levels, while the liver, heart, and lungs express Htt only to a lower extent [24]. Although its exact role is unknown, it networks with proteins participating in intracellular transport, cellular communication, and transcription [24]. Htt serves multiple purposes in transgenic animals with HD [25]. Htt is vital for embryogenesis since its exclusion is associated with prenatal lethality in these animals [25]. The mutant gene is believed to activate caspases, enzymes involved in the catalysis of cell death, by interfering with the ubiquitin-protease system [25].

This moreover serves as an anti-apoptotic mediator, regulating the overall synthesis of the neurologically trophic element, a polypeptide that shields synapse and modulates development throughout neurogenesis, and prevents programmed cell death [25]. Htt also regulates neuronal gene transcription and aids in synaptic vesicle transport and synaptic transmission [25]. When Htt expression is reduced, subsequent symptoms more closely resemble those perceived in the incidence of mutated Htt, but increased Htt expression improves cellular survival of the brain and reduces the mHtt impacts [25].

Cellular Abnormalities

HD pathology may be produced by the toxic action of mHtt through a variety of cellular alterations [26]. The peptide is further susceptible to denaturation when it is within its mutant (polyglutamine-extended) construct, which results in petite residues with polyglutamine advancement [26]. These polypeptide residues are prone to misfolding as well as accumulation, resulting in fibrillar integrates that contain hydrogen bonds that hold non-native polyglutamine threads from various proteins combined [7]. Similar cross-beta amyloid geometry is shared by these aggregates and other protein deposition disorders [27]. Throughout the period, the particles build up inside cells to create inclusion bodies, which ultimately disrupt neural function [26].

The cellular nucleus and plasma, both have been found to contain inclusion bodies [26]. The initial pathological alterations are the development of inclusion bodies in brain cells [26]. While some studies have found that inclusion bodies can be toxic to cells, other studies suggest that inclusion bodies may evolve as defense mechanisms for cells to defend themselves [26].

Macroscopic Alterations

The hinder striatum belonging to the subcortical basal ganglia is considered as the primary area of the brain that is initially damaged, and subsequently, all areas of the cortex are involved [28]. Basal ganglia, divided into the striatum and pallidum, are major pathological sites of Huntington's disease [29]. Intermediate neurons and projection neurons are the two main types of nerve cells found within the striatum, while projection nerve cells predominate inside globus pallidus [29]. Although most striatal interneuron types are extremely resistant to HD, this must be emphasized that the damage to

striatal nerve cells in HD mainly affects projections neurons [29]. The striatal basal ganglia are a major site of neuronal loss in HD, and striatal projection neurons lose almost all function in the late stages of HD [29]. Loss of cortical neurons and early dysfunction is evident [29]. Deterioration in cognitive and motor function results from progressive neuronal loss over time and usually leads to death in adults 20 years after the onset of the disease [29].

Disruption of Transcription

The transcriptional co-regulator CBP (CREB-binding protein) is crucial to cellular function since it is the co-activator of the transcription of corresponding survival pathway genetic factors on a significant number of promoters [30]. HTT is linked to the acetyltransferase domain of CBP via a polyglutamine-containing domain [31]. Similarly, autopsies of the brains of HD patients have found very low levels of CBP [32]. Moreover, overexpression of CBP reduces polyglutamine-induced mortality, supporting the notion that CBP is important for overall neurological health and the recovery of HD [30].

THE CURRENT TREATMENT AND MANAGEMENT OF HD

Huntington's disease has no known treatment that can reverse its progression [33]. However, some symptoms of psychological and motor disorders can be reduced with medication (as shown in Table 3) [33]. Clinicians can use symptom management and education to communicate effectively with HD patients and their families [34]. Additionally, just during a brief length of time, numerous therapies are available to help you adapt to changes in technology (as illustrated in Figure 2) [33].

Therapy

Those with Huntington's disease may benefit from a mix of psychoanalysis, behavioral therapy, physical rehabilitation, and assistive help to retain movement as well as enhance functional abilities (as illustrated in Figure 2) [33]. Psychotherapy can assist with behavior issues, the development of coping mechanisms, the management of prospects over the course of the disease, and the facilitation of family member communication [33]. Although physiotherapy might help with exercises to increase resistance and strength, fluidity, stability, and co-ordination, speaking therapy can help patients speak more effectively or utilize communication aids [33]. A person with weak fine motor skills may benefit from assistive equipment for tasks like washing and dressing as well as eating and drinking utensils [33]. Occupational therapy provides help for tasks like washing and grooming, and apparatus for food and drinks modified for people with restricted fine mobility skills [33].

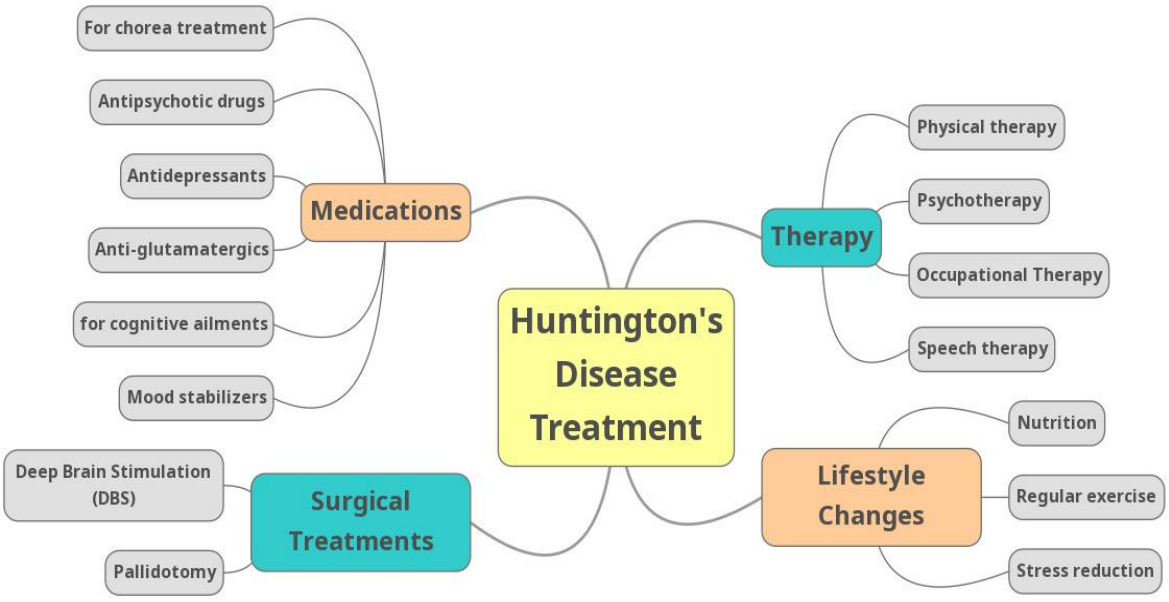

Figure 2. Overview of The Current Management and Treatment of Huntington's Disease [35].

Medications

Huntington's disease has no known therapies that can change its progression. Yet, certain symptoms of psychological and motor problems can be minimized by medication (as shown in Table 3) [33]. Depending on the general objectives of the treatment, medications will probably change as the disease progresses. Pharmaceuticals that alleviate one set of symptoms could also have unintended side effects that make other symptoms worse. Priorities for treatment will be revised and evaluated on a regular basis [33].

For Chorea Treatment

Tetrabenazine

The first medication authorized to treat chorea linked to Huntington's disease is tetrabenazine (TBZ) [35]. Despite potentially harmful side effects, this dopamine-depleting medication may be one of the most targeted treatments for chorea [17]. The two methods that TBZ decreases dopamine levels in the brain allow it to have anti-choreic effects [36]. The first and more well-known method is by limiting dopamine release from vesicles and obstructing monoamine uptake [36]. The movement of neurotransmitters into the vesicles is mediated by specialized proteins known as vesicular monoamine transporters (VMATs) [36]. The VMATs get bound to TBZ and are unable to carry out this function. Dopamine, for example, cannot enter the synapse since it is not kept in vesicles [36]. The putamen, caudate nucleus, and nucleus accumbens, which are known to be the sites of the greatest pathology in HD, have the highest binding densities for TBZ [36].

Deutetrabenazine

The second pharmaceutical for the treatment of HD chorea to receive FDA approval is deutetrabenazine [37]. In comparison to TBZ, which it is a deuterated version of it, it has an enhanced risk-benefit profile attributable to an extended half-life, substantially lower concentrations, and an unaltered medicinal target impact [37]. These factors collectively lead to a reduced dosage and recurrence demand and a generally reduced incidence of negative side effects, such as depression [37].

Antipsychotic Drugs

Antipsychotic drugs are hypothesized to effectively reduce chorea by inhibiting D2 receptors, which diminishes the hypersensitivity of the striatal dopamine receptors brought on by the depletion of MSNs [38].

Haloperidol

Antipsychotic medication haloperidol inhibits dopamine in the limbic region of the brain and lessens psychotic symptoms in HD patients [39]. Movement suppression, mood swings, breast growth, unpredictable menstrual cycles, and decreased enthusiasm for sexual activity are some of this medication's adverse effects [39].

Olanzapine

Olanzapine has been shown to assist HD patients with a variety of neuromuscular and psychiatric symptoms [38]. Moreover, especially in contrast with risperidone, aripiprazole, and olanzapine presents a larger potential for weight gain in the broader population and can produce insomnia [38]. This is most likely caused by higher H1 receptor affinity and its well-known antagonistic 5HT2A and D2 receptor interactions [38]. Olanzapine's acceptability and use in HD may be constrained by side effects such as excess weight gain and drowsiness [38]. Nonetheless, doctors frequently recommend this medicine to some HD patients in an effort to raise their BMI. Most significantly, the tranquil effects of this drug can enhance sleep, which may offer patients relief [38].

Risperidone

Risperidone is an adjunct to conventional antipsychotics offered to patients with HD [35]. Risperidone, commonly used in the treatment of schizophrenia, exhibits antagonistic properties similar

to those of olanzapine and specifically inhibits serotonin-S2 (5-HT) and dopamine-D2 receptors [35]. An atypical antipsychotic is a risperidone [35]. An atypical antipsychotic is a drug that binds more strongly to 5-HT receptors (like olanzapine), whereas typical antipsychotics bind more strongly to D2 receptors [35]. Risperidone is an atypical antipsychotic, but it is important to remember that it binds to 5-HT2 and D2 receptors [35].

Drugs Targeting Glutamate Excitotoxicity

According to the excitotoxic theory of HD, the overproduction of glutamate or overactivation of glutamate receptors (most likely NMDA receptors) leads to neurodegeneration of the striatum [40]. Clinical trials have been conducted with anti-glutamatergic drugs (also called receptor antagonists or release blockers), including ketamine, amantadine, Remacemide, and Riluzole. While some of these drugs improved chorea and motor scores, most also had side effects [40].

Remacemide, a nonselective NMDA receptor antagonist, exhibited a trend towards improvement in chorea but had side effects such as mental problems, gastrointestinal distress, and dizziness and had no effect on the functional decline [40]. In three-year research conducted in Europe, the glutamate release inhibitor riluzole had no appreciable impact on the chorea, behavioral, cognitive, independent, or functional scores. Ketamine, an NMDA blocker, caused declines in the UHDRS total motor score and eye movements [40].

For Depression

Neurodegenerative disorders such as Huntington's disease are more likely to lead to depression than the general population [41]. Antidepressants have been shown to be effective in treating depression in the general population; a recent meta-analysis showed superior efficacy of mirtazapine, tricyclic antidepressants, and selective serotonin reuptake inhibitors compared to other antidepressants [41]. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants are the three main classes of antidepressants commonly used to treat depressive symptoms in patients with Huntington's disease [42].

Selective serotonin reuptake inhibitors (SSRIs) make up the majority of antidepressants used to treat HD-induced depression. SSRIs preferentially inhibit 5-HT reuptake in presynaptic nerve terminals [35]. Increasing the amount of 5-HT that can bind to postsynaptic cleft receptors, increases the concentration of 5-HT in the extracellular environment and desensitizes the receptors [35]. The therapeutic effects of SSRIs can be attributed to the desensitization of serotonin receptors, which may explain why users of these drugs develop a tolerance to their acute negative effects [35]. SSRIs cause strong but slow disinhibition of 5-HT neurotransmission. 5-HT2 receptors are also downregulated by antidepressant treatment [35].

Neurons get more serotonin because SSRIs prevent the reabsorption of serotonin (nerve cells). Zoloft (sertraline), Celexa (citalopram), Paxil (paroxetine), Lexapro (escitalopram) and Prozac are some examples of SSRIs (fluoxetine) [42].

In addition to serotonin, SNRIs prevent the recycling of norepinephrine. Examples of SNRIs include Cymbalta and Effexor (venlafaxine) (duloxetine) [42].

Drugs known as atypical antidepressants do not exactly fall under the SSRI or SNRI groups. An example of this is Wellbutrin (bupropion), which prevents the reuptake of dopamine and norepinephrine. Remeron (mirtazapine) is another option that increases serotonin and norepinephrine levels [42].

Drugs for Mood Regulation

HD patients with behavioral symptoms may also have symptoms of OCD, aggression, and bipolar disorder [35]. Patients may be prescribed a variety of anticonvulsants, including valproate, lantranin,

and carbamazepine, to stabilize various mood disorders. Several studies have shown that anticonvulsants can help reduce the intensity of these symptoms [35].

Lamotrigine is used as a mood stabilizer in HD, but its inhibition of excitatory neurotransmitters may reduce neuronal excitotoxicity [35]. The mechanism of action of Carbamazepine relies entirely on the blockade of voltage-gated sodium ion channels, but the exact pharmacodynamics of the drug has not been fully elucidated [35]. Anticonvulsants have many side effects such as hypersensitivity, blood dyscrasias, dizziness, gastrointestinal disturbances, depression, and hyponatremia, as well as serious skin conditions such as Stevens-Johnson syndrome or necrolysis epidermal [35].

Table 3. Medications for Symptoms Management and their side effects.

Drug Classification	Drug Name	Mode of action	Potential side effects
Movement Control	Tetrabenazine (Xenazine) Deutetrabenazine	Chorea treatment	Drowsiness, restlessness, and despair
Antipsychotic drugs	Haloperidol Olanzapine Risperidone Fluphenazine Quetiapine	minimize irrational behavior, irritability, and several other symptoms of psychosis or behavior problems	Dystonia escalation, restlessness or can cause other movement issues
Antidepressants	Fluoxetine Citalopram Sertraline	To treat anxiety. depression, and obsessive-compulsive disorder	Dizziness, nausea. appetite loss, hypotension
Mood Regulators	Lamotrigine Carbamazepine	For bipolar disorder, mood swings, aggression, OCD	Hypersensitivity, dizziness
Cognitive impairment	Rivastigmine galantamine	To treat the cognitive ailment	Anorexia, fatigue
Anti-glutamatergic drugs	Amantadine Remacemide Riluzole Ketamine	Targets glutamate excitotoxicity, chorea	Weight gain, aggression, uneasiness

For Cognitive Impairment

Acetylcholinesterase Inhibitors

ACh (acetylcholinesterase) amounts in the brain can be raised and the intelligence quotient can be enhanced by (ACh) enzyme antagonists such as rivastigmine and galantamine [39]. These medications have been linked to adverse effects like fatigue, disorientation, decreased appetite, and anorexia [39]. Galanthus nivalis bulbs and flowers contain the primary component galantamine, a fundamental isoquinoline alkaloid that provides galantamine its neuroprotective properties [39]. It is a carbamates AChE reversible inhibitor. It can activate nicotinic receptors, which further enhances cognitive abilities and memory [39]. The medication boosts the action of ACh on cholinergic cells by allosterically regulating nicotinic sensors of ACh, especially variants α7 and α3β4 [39].

Education

Families and the general public to have acquired or being at risk of getting HD have dealt with the condition for generations, but they might not be aware of current advances in medical knowledge or the accessibility of genetic examining [43]. The benefits of genetic counseling for these people include updating their knowledge, attempting to debunk any erroneous views they may have, and assisting them in thinking through their alternatives and future goals [43]. To assist in educating family members, carers, and those who have been diagnosed with Huntington's disease, the “Patient Education Program for Huntington's Disease” was established [43].

Lifestyle Changes and Adaptations

Individuals with HD can manage their symptoms and enhance their quality of life by implementing lifestyle modifications (as shown in Table 4). A thorough treatment strategy for Huntington's disease

should include occupational therapy, regular exercise, a balanced diet, stress management, and socialization (under a doctor's or specialist's guidance) [44, 45].

Table 4. Lifestyle Adaptations necessary for HD patients.

Lifestyle Changes	Purpose
Regular Exercise	HD causes coordination issues and muscular weakness. In addition to releasing endorphins that lessen melancholy and anxiety, regular exercise can assist preserve physical strength and balance.
Balanced Diet	HD patients can maintain a healthy weight and prevent nutritional deficits by eating a balanced diet. Essential nutrients may be provided and general health can be enhanced by eating a diet high in fruits, vegetables, whole grains, lean protein, and healthy fats.
Stress Management	Anxiety and stress can make HD symptoms worse. Deep breathing, meditation, and yoga are examples of relaxation practices that can reduce stress and elevate mood.
Socialization	HD patients frequently experience social isolation. Participating in social activities can help people feel more emotionally supported and less lonely and depressed.
Occupational Therapy	People with HD can benefit from occupational therapy by learning new ways to handle daily tasks including cooking, dressing, and grooming.

RESEARCH STRATEGIES AND FUTURE THERAPEUTIC PROSPECTS OF HD

HD is a neurodegenerative disorder that is autosomal dominant with no disease-modifying intervention [46]. It is caused by full-length expansion of huntingtin and somatic expansion of N-terminal strand of protein, huntingtin, aberrant intron-1 splicing, and CAG repeats [46]. Remedies directed to huntingtin nucleic acids (DNA/RNA), Htt protein ablation, DNA restoration pathways, and additional therapies aiming towards inflammation and cellular turnover are potential approaches for treating Huntington's disease [46].

Reducing the Huntingtin Production

Therapies targeting mutant huntingtin DNA, mRNA, and protein have a chance of becoming the first disease-modifying treatments for Huntington's disease [47]. Trials using antisense oligonucleotide technology to reduce huntingtin levels in Huntington's disease (HD) are ongoing [48]. These advances reflect the tremendous advances in genetic engineering over the past few decades and are the result of intense basic science work and major registry studies around the world [48]. Several therapeutic strategies are currently being explored, ranging from genome editing to stimulation of proteolysis [48].

A recent study highlighted the importance of huntingtin RNA in disease pathogenesis, making the reduction of huntingtin RNA by RNA interference a particularly promising strategy and this approach is on the verge of a clinical trial period [47].

Increasing the rate at which cells can clear mutant huntingtin is another way to reduce its concentration. Pharmacological and genetic inducers of autophagy have been studied in various models of Huntington's disease. Many of them have been found to lower mHtt levels and reduce toxicity [49].

Stem Cell Therapy

Another potential candidate for future treatment for HD is stem cell therapy [35]. Its ability to replace neurons destroyed by HD disease, promote regeneration, and provide factors that promote survival is a major benefit [35]. Additionally, integrating stem cells into a patient's brain microenvironment has the potential to sustain long-term benefits [35].

Huntington's disease causes cellular degeneration in cells other than neurons; Glial cells, including oligodendrocytes and astrocytes, appear to be affected from the earliest stages of the disease, making glial cell replacement an attractive new treatment option [50]. Human glial progenitor cells (GPCs) are widely migratory cells that also give rise to oligodendrocytes and astrocytes [50]. In particular, astrocytes affected by Huntington's disease appear to be responsible for much of the synaptic pathology, 12-14 and their replacement with transplanted healthy GPCs successfully rescued at-risk GPCs in a mouse model of the disease. Combinations of certain as yet undefined GPCs with MSN progenitors or

MSN-biased neural stem (or progenitor) cells may be more effective in achieving structural repair and functional salvage of diseased striatum in Huntington's disease [50]. Indeed, GPC cannot recover a lost MSN [50]. Therefore, we have not yet determined the composition, developmental potential and molecular composition of an "ideal" donor cell for stem cell therapy in Huntington's disease [50].

Presently, Cellavita HD is the most advanced stem cell treatment for HD. It is an intravenous injection-based mesenchymal stem cell treatment [35].

Cell Survival and Gene Inhibition

Increasing the ability of cells to withstand deleterious effects and replace damaged neurons is an additional strategy [51]. One of the strategies to reduce the production of the mutant protein is to inhibit gene activity [51]. A single dominant gene encoding mHtt is designed to prevent its expression [51]. Symptomatic relief was observed with mHtt inhibition in mouse models and gene inhibition has now been shown to be safe in primates [51].

Antisense Oligonucleotide (ASO) Therapies

Several ASOs are currently undergoing clinical studies and ASO therapy is highly regarded as a possible treatment for HD [35]. A phosphate backbone and a sugar ring attached to one of the four bases form a synthetic single-stranded DNA sequence called ASO [52]. The DNA sequence of the target messenger RNA is complementary to it [52]. The messenger RNA target contacts pre-mRNA in the nucleus through Watson-Crick base pairing and marks the mRNA sequence for degradation by RNase H endonuclease, thereby reducing translation of the target gene. Stephenson and Zamecnik initially applied them to block viral RNA translation in Rous sarcoma [52].

They can act through a variety of mechanisms, such as RNA degradation, translational repression and splicing manipulations 124, ultimately altering protein expression [35]. They bind to pre-mRNA or mRNA [35]. ASOs can be allele-specific, indicating that they specifically target mHTT, or non-allele-specific, indicating that they target both wild-type HTT (wtHTT) and mHTT [35]. There are now 3 ASO (Allele non-specific ASO), WVE-120101 and WVE-120102, in clinical studies for HD (allele-specific ASO) [35].

Tominersen, WVE-120101 and WVE-120102 induce RNase H1-mediated killing by complementary base pairing to target pre-mRNAs [35]. They reduce the amount of mHTT mRNA, which reduces the production of mHTT protein [35]. A lumbar puncture is used to administer medications, including intrathecal injections into the cerebrospinal fluid (CSF) for distribution into the central nervous system [35].

RNA Interference Therapy

To silence genes, RNA interference molecules (RNAi) directly cleave perfectly complementary RNAs or block translation and cause transcriptional degradation when the structure is not fully complementary [52]. These molecules can be classified into small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs) and microRNAs (miRNAs) based on their sequence and structural features [52].

The only gene therapy for HD currently in clinical development is AMT-130. It has a gene that produces a miRNA that is administered as an injectable using the adeno-associated viral vector serotype 5 (AAV5) [52]. AMT-130 has been shown to be safe in non-human primate models of HD and in cultured neurons obtained from HD patients. It also caused a significant and long-lasting decrease in mHtt protein and mRNA levels [52].

VY-HTT01 miRNA delivered by adeno-associated virus serotype 1 (AAV1) vector induced mHtt mRNA degradation and resulted in a significant reduction of mHtt protein and improved motor and

behavioral functions in mice, and AAV1-delivered shRNA also produced positive preclinical results are among other preclinically tested RNAi therapies [52].

Small Molecule Therapies that Target RNA

An attractive approach to treating HD is a small, orally available chemical that crosses the BBB and alters the splicing of the HTT pre-mRNA [53]. Splicing regulators have been shown to reduce HTT levels in skin cells and neurons derived from HD patients, and they caused a 50% reduction in CSF HTT in two fully humanized mouse models of HD [53]. An independent program intends to conduct the first human trials [54].

Zinc-Finger Proteins

ZFPs, which can be linked to transcriptional repressors or nuclease effector domains to cleave DNA, have been engineered to precisely target the extended CAG repeat of the HTT gene [54]. ZFPs have been used as transcriptional repressors in HD [54]. According to preclinical studies, ZFP can reduce mHTT levels, and HTT protein aggregation and reverse HD-like behaviors in mice. Similar results were found in patient fibroblasts highly selective for the mutated HTT gene and derived from human stem cells [54]. This study is part of an ongoing drug development pipeline that has not yet reached the clinical stage [54]. Therapeutic administration of ZFP requires the use of viral vectors and intracranial administration, much like the RNAi approach. Another potential downside of ZFP therapy is exogenous protein synthesis, which can lead to inflammation and immune responses [54].

Transcription Activator-like Effector Nuclease (TALEN) Therapy

TALENs are DNA-binding domains that contain repeating peptides that bind to DNA nucleotides [35]. They are in the preclinical or drug discovery stage and have not been studied in animal models of HD [35]. However, they succeeded in knocking out CAG repeats grown in yeast cells by inducing double-strand breaks, leading to gene transformation. In fibroblasts derived from HD patients, TALEN- and SNP-specific transcriptional activator-like effectors (TALE-SNPs) prevented mHTT gene transcription by targeting their associated SNPs, thereby preserving wtHTT (wild huntingtin) gene expression [35]. The results showed that certain TALE-SNPs can reduce mHTT expression by up to 20% without altering normal HTT expression, suggesting proof of concept [35].

CRISPR/ Cas9 Therapies

The CRISPR/Cas9 system is a gene editing technology that involves very precise recognition of double-stranded DNA sequences by the CRISPR system, followed by the destruction and excision of the DNA sequences by a nuclease guided by RNA (Cas9 protein) [35]. In the gene replacement approach applicable to HD, a protospacer flanking motif sequence is required to enable specific recognition sites in the SNP allele of the mutant HTT gene [35]. The mHTT gene could theoretically be deleted using the CRISPR/Cas9 system and replaced with the wild-type allele, or the mutated allele could be deleted by inserting a missense mutation, or transcription of the HTT gene could be reduced in a non-allele-specific manner, for example by epigenetic regulation [35]. Several proof-of-concept experiments in cell cultures of HD patients have shown that technology based on the CRISPR/Cas9 system, in the early stages of therapeutic development, can suppress the mutant allele and stop the production of the mHTT protein [54].

In cell lines, the efficiency of CRISPR/Cas9 has been evaluated [35]. In three different fibroblast cell lines from HD patients, a paired Cas9 nickase approach successfully knocked out the extended CAG repeat in exon 1 of the HTT gene, thereby inactivating HTT [35]. Due to their greater specificity, nickases create single-strand breaks that reduce target impact. There was a different CAG repeat length in each cell line treated with Cas9 nickase, and the amount of HTT protein was reduced by approximately 70% [35].

Also under research is a PAM-altering, mHTT related SNP based CRISPR/Cas9 method. This drug inactivates the mHTT allele while leaving the wtHTT allele intact. Excision of CAG repeats associated with the mHTT allele has been successful in cell lines obtained from HD patients [35].

Antibody Therapy Approach

In addition to being investigated as potential treatments for various tauopathies and synucleinopathies, antibody-based therapies have also shown promise for the treatment of monogenic CNS disorders such as HD [35].

ANX005 Monoclonal antibody ANX005 was obtained from Annexon, Inc. Prevents initiation of the classical complement cascade by targeting C1q [35]. While neuronal stress has been implicated in the pathogenesis of HD, the role of C1q in synaptic pruning may be compromised, which may affect synapse loss, neurodegeneration, and neuroinflammation [35]. ANX005 is thought to slow neurodegeneration and synapse loss by inhibiting C1q. ANX005 was previously designed to treat Guillain-Barré syndrome (GBS) and Alzheimer's disease (AD) [35].

NOTE: LIMITATIONS OF CURRENT MANAGEMENT THERAPY AND THE ADVERSE EFFECTS ON THE NEUROPSYCHIATRY

The neurodegenerative condition Huntington's disease (HD), which is infrequent and inheritable, distorts mental faculties and hinders both cognitive and motor capabilities. There are presently limited HD therapy options available, and these alternatives do not deal with the disease's underlying determinants. Furthermore, these therapies prevalently have negative effects on the neuropsychiatric system (as shown in Table 3), which renders the patient's quality of life even worse.

Tetrabenazine, a drug that diminishes dopamine, is one of the main therapeutic interventions for HD [35]. Unfortunately, the medication commonly affects individuals to experience despair and suicidal ideation [55]. Riluzole, a distinct medication used to treat amyotrophic lateral sclerosis, has shown very sporadic effectiveness in treating HD symptoms in people while having some neuroprotective benefits in animal models [35, 56].

Antipsychotic medications including haloperidol, risperidone, and olanzapine are widely recommended to treat the mental symptoms of HD, but they can also exacerbate motor symptoms and lead to lethargy, weight gain, and cognitive decline [35].

Moreover, there is presently no cure for HD and a dearth of therapies that can cease the disease's progression [34]. Gene and stem cell therapies are potential forms of treatment, but further studies are required to assess their safety as well as efficacy [35].

Adverse Effects of the Current Therapies

HD medications may have a number of negative consequences on the neurological system and psychiatry (as shown in Table 3). One or more of the negative outcomes might be:

Disorders of movement: drugs prescribed for HD have been linked to movement ailments including akathisia, dystonia, and tardive dyskinesia. These conditions generate spontaneous actions, anxiety, and impairment in commencing movement [17].

Cognitive deficits: Certain drugs have the possibility of triggering cognitive decline, which comprises memory lapses, disorientation, and poor concentration [17].

Depression and anxiety: Although most treatments for Huntington's disease are intended to treat the physical symptoms, some of them can also have an adverse effect on a person's psychological well-being, resulting in anxiety and depressive disorders [17, 35].

Sleep disturbances: Drugs can lead to sleep difficulties including insomnia, trouble getting to sleep and staying asleep, or apathy during the day [17,35].

Psychosis: The rare but potential adverse effect of treatments for Huntington's disease is psychosis. Hallucinations, delusional beliefs, and muddled thinking are its hallmarks [57].

Sexual dysfunction: In conjunction with decreased libido and difficulty getting or retaining an erection, certain patients may also have sexual dysfunction brought on by medication [58].

Despite the fact that drugs can be useful in treating the symptoms and indications of HD patients should be warned of any potential risks and adverse reactions before receiving them [59]. Any improvements in their symptoms, alongside any possible adverse effects, should be discussed with their healthcare professional. And therefore, it is challenging to effectively control HD due to the limits of the available therapeutic choices. Further exploration might lead to the development of novel therapies that enhance HD patients' quality of life while reducing negative impacts on the neuropsychiatric network [35].

CONCLUSION

Both patient care and knowledge of illnesses have significantly improved during the previous 20 years [60]. The search for biomarkers and pathogeneses is the main topic of fundamental research [60]. A deeper comprehension of pathogenesis and progression could assuredly contribute to novel therapeutics generation that disturbs the sick mechanism [60]. The hunt for effective, simple-to-identify, and clinically important markers suggesting the start of the disease's terminal phase is ongoing, as is the search for medications capable to suspend, postpone, or cease the disease's onset [60]. Given the intricacy of HD care caused by its varied and fluctuating symptom presentations, minimal progress has been made in this area throughout the years [35]. There is no medication or cure for HD, but clinicians are receiving more guidance on how to treat the condition [35]. Owing to certain adverse effects, many advisories, drug-drug correlations, and the fact that those same HD medications exacerbate related conditions, HD therapy needs a customized strategy [35]. Along with successfully treating the symptoms of HD, clinicians also need to navigate these obstacles.

In conclusion, despite the fact that there is still no cure for Huntington's disease, there are some potential therapeutic options that can help control symptoms and enhance the quality of life for people who are affected. The efficacy of present treatments is constrained, and they do not go after the disease's root causes. As a result, ongoing research into novel approaches is essential to creating better medications and, ultimately, discovering a solution for this crippling ailment [35]. We may strive towards a point in time where Huntington's disease is not a fatal condition but a treatable disorder that can be managed via coordination between patients, families, research scientists, and clinicians.

Abbreviations

HD	Huntington’s Disease
PD	Parkinson’s Disease
JHD	Juvenile Huntington’s Disease
HTT	Huntingtin
mHtt	Mutated huntingtin
ASO	Antisense Oligonucleotide
RNAi	RNA interference
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CBP	CREB-binding protein
OCD	Obsessive Compulsive Disorder

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