

Review Article

# Multimodal treatment strategies in Huntington's disease

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## Abstract

Huntington's disease (HD) is an incurable neurodegenerative disease that causes involuntary movements, emotional lability, and cognitive dysfunction. HD symptoms usually develop between ages 30 and 50, but can appear as early as 2 or as late as 80 years. Currently no neuroprotective and neurorestorative interventions are available. Early multimodal intervention in HD is only possible if the genetic diagnosis is made early. Early intervention in HD is only possible if genetic diagnosis is made at the disease onset or when mild symptoms manifest. Growing evidence and understanding of HD pathomechanism has led researchers to new therapeutic targets. Here, in this article we will talk about the multimodal treatment strategies and recent advances made in this field which can be used to target the HD pathogenesis at its most proximal level.

## Introduction

HD is an inherited degenerative condition of brain cells, characterized by gradual development of involuntary movement of muscles, deterioration of cognitive processes leading to dementia, and psychiatric and psychosocial disturbances. It is caused by an expanded CAG glutamine codon repeat in exon 1 of huntingtin (HTT) gene, which encodes huntingtin [1-4]. Linkage analysis mapped the genetic defect to chromosome 4p16.3 using linkage analysis [5]. The average age of onset is 40 years followed by an unrelenting progression and average survival of 15–20 years [6].

Putative polymorphic HTT repeat is commonly seen in the normal population [7], but people who inherit >35 CAGs are prone to have HD. Rubinsztein, et al. reported >40 CAG repeats are fully penetrant within a normal lifespan [8]. Very frequently, germline instability is seen in expanded repeats in HD patients which may not have a CAG repeat length similar to their transmitting parent [9-11]. Intergenerational expansion of a normal length CAG repeat may be the reason behind sporadically generated rare de novo cases of HD in general population. [12,13].

Longer repeat lengths have been shown to lead to earlier onset disease of increased severity [14]. However, genetic modification of additional loci can influence onset and progression of the disease [15]. Meta-analyses show a worldwide prevalence of 2.7 per 100,000 with the highest rates in Western populations and lowest among Asians [16,17]. Symptomatic treatment of chorea remains the only approved

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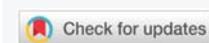
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Abbreviations: CCPs: Cell-Penetrating Peptides; RNase H1: Ribonuclease H1; mRNA: Mature Messenger Ribonucleic Acid; ZNF: Zinc Finger; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; ZFP: Zinc Finger Protein; NAD: Nicotinamide Adenine Dinucleotide; NMDAR: N-Methyl-D-Aspartate Receptor; CSF: Cerebrospinal Fluid; Mbp: Myelin basic protein; Plp1: Proteolipid protein 1; BDNF: Brain-Derived Neurotrophic Factor; Bax: BCL2-associated X protein; UHDRS: Unified Huntington's Disease Rating Scale; TMS: Total Motor Score; PARP: Poly-ADP Ribose Polymerase; 3-NP: 3-Nitropropionic acid; MN: Memantine; 3-AB: 3-aminobenzamide; IV: Intravenous; MSC: Mesenchymal Stem Cells; LER/BM-MS: Lercanidipine Bone Marrow-Derived Mesenchymal Stem Cells; NPC: Neural Progenitor/Precursor Cell; IL-1β: Interleukin 1 beta; TNF: Tumor Necrosis Factor; RIP3: Receptor-Interacting Protein; CM: Conditioned Medium; hAMSC: human Amniotic Mesenchymal Stromal Cells; GPI: Globus Pallidus internus; GPe: Globus Pallidus externus



indication in HD with drugs such as vesicular monoamine 2 transporter (VMAT-2) inhibitors or neuroleptics [18].

The role of HTT is considered as a scaffold that engages with many other proteins and cellular mechanisms [19]. Mutant HTT (mHTT) contains an expanded polyglutamine tract near the amino terminus. This leads to misfolding that triggers a cascade of pathogenic processes. These are driven by mHTT being unable to perform normal functions and the

accumulation of toxic species from various permutations of aberrant mRNA splicing, translation and subsequent mHTT proteolytic cleavage [20,21], and accumulation of toxic aggregates. However, a definitive correlation is yet to be established, as HD mouse model studies have demonstrated neuronal loss in the absence of aggregates [22] and aggregates in the absence of neuronal dysfunction [23].

Striatal medium spiny neurons (MSNs) are selectively vulnerable to mHTT through multiple mechanisms, including but not limited to, the loss of trophic support (in particular, the reduction in brain-derived neurotrophic factor - BDNF), immune dysregulation, synaptic dysfunction (excitotoxicity), altered cellular homeostasis and impaired mitochondrial function [6]. mHTT accumulates in glial cells leading to reactive astrocytosis and microgliosis that can accelerate atrophy [24]. Coup-TF interacting protein 2 (CTIP2), a transcription factor that is expressed abundantly by all MSNs is known to interact with mutant huntingtin and is implicated in human MSN homeostasis and striatal neurodegeneration [25].

### Therapeutic approaches

**HTT lowering:** Lowering HTT levels has become one of the most intriguing and promising emerging therapeutic options with disease modifying potential.

**RNA based approaches:** HTT pre-mRNA can be targeted using antisense oligonucleotides (ASOs) and mature ribonucleic acid (mRNA) with interfering RNA (RNAi), both of which enhance early degradation and lower levels of mHTT [26]. ASOs are single-stranded deoxyribonucleotide capable of altering mRNA expression through several mechanisms, including direct steric blockage, inhibition of 5' cap formation, ribonuclease H mediated decay of the pre-mRNA, and exon content modulation through splicing site binding on pre-mRNA. The goal of the antisense approach is to influence certain protein production. Once inside the cell, the ASO binds to the target mRNA or pre-mRNA, inducing its degradation and preventing the mRNA from being translated into a detrimental protein product [26,27].

Blood-brain barrier (BBB) is impermeable to ASOs, therefore it has to be administered directly to CNS. An animal study showed when ASOs were tagged with arginine-rich CPPs and systemically delivered, resulted in BBB crossing and got widely distributed in brain [28]. ASOs can be allele specific or non-specific. Development of RNAi-based strategies to silence or edit HTT are currently in preclinical phases. Potential modalities include employing small-interfering RNA (siRNA) or short-hairpin RNA (shRNA) [29], artificial microRNA (miRNA) [30]. Double-stranded RNA (vs. single-stranded ASOs) has low diffusion and CNS uptake thereby requiring this strategy to utilize a viral vector, such as an adeno-associated virus (AAV) containing complementary DNA, to introduce the RNAi [26,31]. The RNAi will then bind mature mRNA from the mutated gene. There have been promising preclinical results in HD models [32,33].

AAV vectors have become popular in studies of neurodegenerative disease due to their low immunogenicity, non-pathogenicity and efficient transduction of brain cells [34]. Serotype AAV9 crosses the BBB easily and is being increasingly used in treatment of neurological conditions. Presumably, this modality will allow for sustained and long-term target silencing after a single administration [35]. Less invasive, systemically administered RNAi has shown promise in HD mouse models [36] but not primates [37].

Isabel Pérez-Otaño, et al. in their study showed motor impairment and corticostriatal dysconnectivity in HD can be reversed by silencing GluN3A, which is glycine binding subunit belonging to the N-Methyl-D-aspartate (NMDA) receptor family, and thereby supported the use of RNAi-based approach for utilization of this therapeutic model [38]. Matthes, et al. in their HD cell line model study showed furamidine decreases protein level of HTT [39].

Recently, Ramos, et al. suggested intranasal administration of nanoparticles carrying siRNA as a promising therapeutic alternative for safe and effective lowering of mutant HTT expression [40]. Previously, Miniarikova, et al. has reported suppression of mutant huntingtin aggregation in neurons and neural dysfunction in a rat model of HD by using AAV5-miHTT gene therapy [41].

This gene therapy lowered HTT but no immune response was initiated due to non-activation of astrocytes or microglia. These findings may interest researchers in using gene therapy in knocking down HTT which may benefit HD individuals clinically and symptomatically [42].

Tominersen, previously known as IONIS-HTTRx and RG6042 is allele non-specific. It forms a hybridized complex that is degraded through an RNase-H1 mechanism. A very significant reductions of disease-causing mutant huntingtin protein in people with HD was seen [43,44].

Datson, et al. in their study reported changes in brain anatomy and chemical milieu which led to the improvement of motor performance, suggesting that treatment with (CUG)<sub>7</sub> may ameliorate basal ganglia dysfunction in HD patients. A study done in Q175 mice using an identical (CUG)<sub>7</sub> AON dosing regimen confirmed lowering of HTT. An increase in motor activity with significant decrease in mHTT in cortex, hippocampus, and striatum lasting up to 18 weeks post last infusion was observed. The authors believe (CUG)<sub>7</sub> can be used in lowering HTT in HD individuals [45].

Keeler, et al. in their study reported lowering of mRNA expression of HTT in striatum by 50% when intrastriatal infusion of an AV9-GFP-miRHTT vector was given. The main reason behind this finding was partial reduction in the number of copies of mHTT mRNAs per cell [46].

Recently, a report suggested a distinct delay in the



differentiation of the juvenile onset HD (JHD) neural progenitor population. However, the authors think this reduction of the JHD aberrant progenitor populations can be accomplished by treating either with HTT ASOs or targeting the notch signaling pathway [47]. Therefore, in principle, a single stereotactic intrastriatal injection may be all that is needed, which although still invasive, may provide some advantage over the repeated injections in ASO-based strategies. On contrary, potential advantage of ASOs over RNAi-based modalities is that ASOs can be taken up by multiple CNS cell types with high efficiency without the need for a carrier [48].

**DNA based approaches:** Most common approaches are through naturally occurring proteins, ZNFs and genome editing tool CRISPR/Cas9 which has gained much attention recently. ZFPs are a diverse group of naturally occurring proteins that are able to interact with deoxyribonucleic acid (DNA) and modulate transcription [49]. They are engineered to bind to any DNA sequence, with preference for longer CAG repeats in the case of HD mouse models and human cells [50,51]. After delivery with an AAV, they can bind to transcriptional repressor domains and was shown to selectively suppress mHTT expression [50]. A study has reported in HD mouse models, ZFPs were able to reduce mHTT levels and an HD-like behavioral phenotype [51].

CRISPR/Cas9 edits genes by precisely cutting DNA and then letting natural DNA repair processes to take over [52,53,54]. Recent, evidence showed complete suppression of mHTT in the striatum of HD mouse models with attenuation of neuropathological changes [55]. Shin j, et al. demonstrated inactivation of the mutant allele using haplotype-specific CRISPR/Cas9 target sites in HD. They were able to completely prevent the generation of mutant mRNA and mHTT in patient-derived fibroblasts [56]. Pan, et al. observed any disturbances in DNA methylation play a critical role in mHTT induced neuronal dysfunction and death in HD. Additional preclinical studies are required to validate CRISPR-based strategies in HD before they can be developed into clinical trials [57].

### HTT modulation

**Selisistat:** Sirtuin activity modulation enhance clearance of mHTT. Sirtuins are NAD dependent deacetylases involved in metabolic regulation and neuroprotection through either overexpression or inhibition of various sirtuins [58-60]. Post-translational modification of proteins such as acetylation of mHTT promotes its clearance, clearly linking it to autophagy by the autophagic-lysosomal pathway [61].

SirT1 (silent information regulator T1) is a member of the sirtuin family. It is a NAD dependent deacetylase and removes acetyl groups from lysine residues in many histone and nonhistone proteins and other proteins including mHTT [61-63]. A study reported that inhibition of SirT1 in transgenic *Drosophila* and R6/2 mice resulted in selective decrease in mutant HTT protein levels [63]. These abovementioned

studies made researchers around the world to hypothesize that inhibition of SirT1 results in the selective clearance of mHTT without affecting normal protein levels.

Selisistat is a selective SirT1 inhibitor that inhibits recombinant human SirT1 both in vivo and vitro [64]. It exhibits neuro and cytoprotective activity against toxicity induced by mHTT in cellular and in vivo models of HD. It has been linked to increased survival rate and improvement of behavioral impairment [65].

A larger study of 125 patients randomized to 50 or 200 mg selisistat over 12 weeks also demonstrated safety and tolerability except for reversible increases in liver function tests [66]. No significant differences between selisistat and placebo groups has been observed and currently no phase III trials are ongoing, and further development appears to be on hold.

**Hydroxyquinoline (PBT2):** It is considered as a metal chaperone [67]. PBT2 is a moderate-affinity 8-hydroxyquinoline transition metal-ligand that acts as a synthetic chaperone, redistributing copper, zinc, and iron from locations where they are abundant to subcellular locations where they might be deficient. Delivery of copper and zinc by PBT-2 into the cytoplasm deactivates the kinase glycogen synthase kinase 3 $\beta$  and the phosphatase calcineurin both potential targets for HD.

PBT2 is able to protect against glutamate-induced neural excitotoxicity mediated through NMDARs. This phenomenon is attributed to PBT2 inducing Zn<sup>2+</sup>-dependent increases in intracellular Ca<sup>2+</sup> levels resulting in preconditioning of neurons and inhibition of Ca<sup>2+</sup>-induced neurotoxic signaling cascade involving calpain-activated cleavage of calcineurin. [68]. PBT2 was considered safe and well tolerated, however, the FDA issued a Partial Clinical Hold in 2015 (in effect) due to safety concerns of the 250 mg dose and require more data for this to be lifted [69,70].

### Immunomodulation

Plasma levels of a specific cytokine, interleukin 6 (IL-6) have been shown to correlate with disease progression in premanifest HD individuals. Increased microglial activation in the brain also leads to abnormal proinflammatory profiles that correlate with progression and can predict disease onset. Several proinflammatory cytokines are present in the CSF of HD patients in addition to abnormal blood chemokine profiles [71]. These chronic state of neuroinflammation likely stems from a reactive response to mHTT-induced neurodegeneration as well as the cellular dysfunction associated with mHTT expression itself [72].

**Laquinimod:** Laquinimod is an immunomodulatory agent under clinical development for HD. In the YAC128 HD mouse model, behavioral improvements along with prevention of



shrinking of the white matter rich corpus callosum was seen. Laquinimod was able to preserve myelin in the posterior region of corpus callosum, thereby increasing myelin sheath thickness and rescuing myelin basic protein mRNA and other important protein deficits.

Furthermore, the levels of the Mbp and Plp1 transcripts were also increased in the striatum which shows that role of laquinimod on myelin-related gene expression was not region-specific. The authors believe HD-related demyelination in YAC128 HD mice did not depend on the immunomodulatory effect of laquinimod [73].

Laquinimod might influence BDNF-dependent pathways in HD. However, mild changes are seen in striatal histopathology and motor functionality [74]. A recent study on YAC128 model of HD reported modest behavioral improvements and preservation of cortical, striatal, and white matter [75].

Post DNA damage, Laquinimod reduces the basal expression of Bax in primary neurons and reduces neuronal caspase-6 activation. Laquinimod have direct effect on astrocytes and microglia and can halt axonal degeneration by downregulating neuronal apoptosis and may provide some clinical benefit [76].

**Semaphorin 4AD:** Semaphorin 4AD (SEMA4D) is also known as Cluster of Differentiation 100 (CD100). It is a protein of semaphorin family and is encoded by the SEMA4D gene. It is an axon guidance molecule which is secreted by oligodendrocytes and induces growth cone collapse in the central nervous system [122]. It is responsible for chronic inflammation in brain, halts neural development, apoptosis, breakdown of BBB, and neurodegeneration.

VX15/2503 is an antibody developed by Vaccinex, which prevents brain inflammation by blocking the activity of SEMA4D. This antibody is responsible for maturation of specific cells which in turn repairs myelin loss. Several preclinical studies in animal models have showed the efficacy of this antibody against brain atrophy. It is also known to prevent spatial memory loss and suppress anxiety.

A 12-month intravenous treatment with VX15/2503 was safe and a follow-up of three months did not show any undesired side effects and was well tolerated. Patients treated with this antibody stabilized Huntington's related brain atrophy and showed improvement in metabolic activity over placebo [77,78,79].

### Synaptic modulation

Synaptic dysfunction is a well-defined mechanism of HD pathogenesis. Excitotoxicity through synaptic connections with striatal MSNs may be mediated through various neurotransmitter receptor pathways thereby offering themselves as potential therapeutic targets [80].

**Pridopidine:** It has much higher affinity for the sigma-1

receptor (SIG1R) [81], and various other mechanism of action [82]. This chaperone function has been shown to be abnormal in HD models [83]. Subsequently, when a SIG1R agonist (PRE084) was used in neuronal cells expressing mHTT, it demonstrated improved survival [84]. Raymond, et al. reported on the disruption in homeostatic synaptic plasticity, known to enable new learning and cognitive flexibility. This disruption was restored by stimulation of SIG1R, which should be studied for developing treatment strategy to alleviate cognitive impairment in HD [85].

The neuroprotection exerted by pridopidine in HD cell models is SIG1R dependent. Pridopidine and S1R agonists can act as neuroprotective agents in HD which should be studied in large trials [86].

Pridopidine was shown to restore transcriptomic disturbances in the striatum, increase transcription across synapses, and activating neuroprotective pathways affected in HD [87]. Marta, et al. showed pridopidine if taken in early stages in HD exerts beneficial effects at the transcriptional level and improvement in behaviour [88].

Unfortunately, pridopidine did not significantly change the UHDRS-TMS at 26 weeks compared to placebo at any dose in PRIDE-HD trial. Serious adverse events like aspiration pneumonia, head injury, falls etc. occurred in the pridopidine group only. A phase III study has been considered. Teva Pharmaceuticals has announced a halt to further development at this time however its future is uncertain at this moment [89].

**Phosphodiesterase 10A inhibitors:** PDE10A inhibitors are known to have antipsychotic property and are also thought to be neuroprotective [90]. PDE10A is abundant in striatum and is a key regulator of basal ganglia circuitry modulating cortical motor activity. Diggle, et al. reported two families comprising of eight individuals with germline PDE10A mutations affected with hyperkinetic movements due to homozygous mutations [91].

TAK-063, a novel PDE10A inhibitor, halts neurodegeneration in striatum and improves behavioral deficits in the R6/2 mouse model of HD. It ameliorated deficits in procedural learning, but was ineffective for deficits in contextual memory [92].

Early chronic PDE10 inhibition rather than acute administration after onset of symptoms in Q175 mice showed drastic response in the form of partial reversal of striatal deregulated transcripts and prevention of occurrence of neurophysiological deficits [93].

**Memantine:** Coordinated structural and functional connectivity is disrupted by hyper-excitability in HD. Memantine as a NMDA antagonist can reduce the excitotoxicity and normalize the brain connectivity [94]. Chidambaram, et al. reported simultaneous blockade of NMDAR and

suppression of PARP activity is necessary to ameliorate immune-excitotoxicity and improve bioenergetics in 3-NP induced neurodegeneration. Treatment with MN+3-AB can be an efficient regimen in the symptomatic management of HD [95].

Loss of synapse and death of SPNs in HD has been linked to age-inappropriate expression of juvenile NMDARs containing GLuN3A subunits. GLuN3A promotes NMDA spiking by enhancing transmission across synapses in HD models [96].

### Other medical therapies

**Cysteamine:** In a nuclear condensation cell toxicity assay, cysteamine exhibits a strong neuroprotective effect against toxicity caused by mHTT. It was also shown to safeguard mitochondrial structures harmful to mHTT. Neuroprotection by cysteamine is not mediated by cysteine metabolism. Certain metabolites of cysteamine like taurine and hypotaurine are neuroprotective against toxicity caused by HTT.

Cysteamine is known to activate secretion of BDNF. However, BDNF pathway antagonists could not protect cysteamine. The authors think more studies are required in this field to determine neuroprotective pathways [97]. Cysteamine has been demonstrated in numerous animal models of HD as potentially safe and effective [98].

A recent trial comprising of 96 patients with early-stage HD receiving 1200 mg delayed-release cysteamine bitartrate or placebo daily for 18 months was conducted. At the end of the study, the treatment effect was not statistically significant but less mean deterioration from baseline for the treated group as compared to placebo. The authors could not determine the efficacy of cysteamine in the studied population with HD but post hoc analyses indicated the need for future studies in large population subset [99].

### Stem cell therapy

In HD, replacement of the degenerated striatal MSNs and reconstruction of damaged neural circuitry is the main aim to reverse the disease or modify progression [100]. Modulation of glymphatic activity using IV-MS-C can be a novel strategy for improving the potency of ASOs in the treatment of HD as delivering of ASOs to deeper brain structures is very difficult [101]. Recently Elbaz, et al. suggested combining LER/BM-MS-C therapy seems to be superior to cell therapy alone in inhibiting 3-NP-induced neurological insults. This is mediated by modulation of two main signaling pathways i.e. Ca/Ca<sub>N</sub>/NFATc4 and Wnt/ $\beta$ -catenin [102].

Yu, et al. demonstrated significantly ameliorated phenotypes of R6/2 mice after MSCs administration intranasally, suggesting this method can be effective delivering route of cells to the brain for HD therapy [103].

Cho, et al. demonstrated longer lifespans and improvement

of motor function in HD mice (compared to a sham-injection group) that were grafted with NPCs derived from wild-type and HD monkeys plus NPCs expressing shRNA against HTT [104].

Eskandari, et al. implanted dental pulp stem cells (DPSCs) in 3-NP rat models of HD. The authors reported that DPSCs were able to survive and there was significant augmentation of muscle activity and motor skills. They also found out by histological analysis that treatment with DPSCs halted the shrinkage of striatum and in addition also inhibited gliosis and microgliosis in the striatum of 3-NP rat models. It was also shown that there was downregulation of caspase-3 and proinflammatory cytokines like IL-1 $\beta$  and TNF upon DPSCs grafting. The authors strongly believe that by grafting DPSCs two things can be achieved a) repairing of motor-skill impairment b) neurogenesis induction through secretion of neurotrophic factors and proper modulation of proinflammatory response [105].

Bayat, et al. in their study investigated the role of olfactory ecto-mesenchymal stem cells (OE-MS-C) secretome in motor deficits caused by HD in a rat model. Bilateral intra-striatal implantation of OE-MS-Cs in the 3-NP + Cell group was done post 3-NP intraperitoneal injections. They found out striatal transplants of OE-MS-Cs reduced microglial inflammatory factor, TNF $\alpha$  in the 3-NP + Cell group, with a significant reduction in RIP3, the markers of necroptosis in striatum. There was a remarkable recovery of intrastriatal volume post grafting and the motor activities were enhanced in the 3-NP + cell group compared to the 3-NP + vehicle group [106].

Yoon, et al. investigated the therapeutic effects of NPCs derived from a human iPSC line (1231A3-NPCs) in the quinolinic acid (QA)-lesioned rat model of HD. 1231A3-NPCs were transplanted into the ipsilateral striatum 1 week after QA lesioning. They found out transplanted animals showed significant behavioral improvements for up to 12 weeks. Histological analysis showed transplanted 1231A3-NPCs also partially replaced the lost neurons in the striatum, enhanced endogenous neurogenesis, reduced inflammatory responses, and reconstituted the damaged neuronal connections [107].

Bessuso, et al. in their study showed in-vitro-differentiated human striatal progenitors undergo successful maturation and integrate into host circuits upon intra-striatal transplantation in a rat model of HD. The authors reported that the implanted grafts can directly communicate through synaptic contact with structures like globus pallidus, subthalamic nucleus, and substantia nigra. The transplanted subjects showed improvement of motor sensory tasks for up to 8 weeks post-transplant [108].

Carmela, et al. in their study used conditioned medium (CM-hAMSC) to treat R6/2 mouse model for HD. They found out those treated showed less severe signs of neurological dysfunction. Reduction in striatal atrophy and the formation



of striatal neuronal intranuclear inclusion body was observed with a significant amelioration of brain pathology. Furthermore, BDNF levels was not significantly increased, along with decreased microglial activation, and inducible nitric oxide synthase levels. CM-hAMSC can act by modulating microglia and other inflammatory cells [109].

Recent study has reported that transplantation of 3D-derived striatal progenitors into a transgenic mouse model of HD slowed disease progression, improved motor coordination, and increased survival. The transplanted cells developed into a MSN like phenotype and synaptic connections was formed with the host cells [110].

Ebrahimi, et al. evaluated the *in vitro* and *in vivo* efficacy of umbilical cord matrix stem cells (UCMSCs) and their paracrine effect against oxidative stress with a specific focus on HD subjects. Initially, PC12 cells were exposed to superoxide in the presence of conditioned media (CM) collected from UCMSC (UCMSC-CM) and cell viability plus neuritogenesis were measured. After that bilateral striatal transplantation of UCMSC in 3-nitropropionic acid (3-NP) lesioned rat models was done, and post-graft analysis was performed after 1 month. They reported CM of UCMSC protected PC12 cells against oxidative stress and considerably enhanced neurite outgrowth and cell viability. Furthermore, transplanted UCMSC survived, gliosis was decreased, and amelioration of motor-coordination and muscle activity was seen, along with an increase in striatal volume as well as in dendritic length of the striatum in HD rats [111].

### Deep brain stimulation

Deep brain stimulation (DBS) of the GPi shows good clinical efficacy in HD individuals as pathophysiologic disease mechanism in HD is related to the output from the GPi. Chorea-dominant HD and other subtypes such as dystonia may differ in spectral patterns in GPi. Elevated high-beta and gamma band activities are more likely to chorea specific. LFP (Local field potential) measures may help us to understand the abnormalities in basal ganglia signaling which may underlie HD symptoms. This could be considered as an useful biomarker for setting adaptive DBS parameters [112].

However, Ferrea and colleagues reported Gp-DBS in jHD is not generally recommended because no significant motor improvement was found when patients were followed up for 12 months [113].

Zittel and colleagues, prospectively evaluated the effects of bilateral DBS of GPi over one year in six severely affected HD subjects with chorea refractory to standard treatment in an advanced stage of the disease. They also evaluated the effects of GPi-DBS on the motor part of UHDRS, dystonia, bradykinesia, cognitive and psychiatric symptoms, and functional impairment hampering quality of life. The chorea sub-score significantly reduced postoperatively at 6 and 12

months, whereas UDHRS total motor score was significantly reduced at 6 months postoperatively, but overall effects did not sustain over 12 months. Pallidal DBS did not improve functional impairment or other motor symptoms. No effect was seen in psychiatric and cognitive symptoms. Three patients also developed severe spasticity during the follow up period. The authors suggest pallidal DBS could be a treatment option for HD patients with severe pharmacologically refractory chorea [114].

Gonzalez, et al. performed a prospective, open-label study of seven HD patients who underwent GPi DBS with median 3 year follow up. Results revealed a significant reduction of chorea (but not bradykinesia or dystonia) with off-stimulation evaluations confirming a persistent therapeutic effect of DBS [115].

A prospective, randomized, controlled, double-blind study evaluated six HD patients (including two juvenile HD) for equivalence of GPi and GPe stimulation. This study also had an open-label, 6-month follow up to assess chronic treatment effects. Chorea, quality-of-life, and disability scores improved significantly. However, there was no improvement in dystonia, and cognition remained stable. Both GPi and GPe were equal in terms of overall efficacy [116].

A meta-analysis by Yin, et al. found out GPi-DBS significantly improved the UHDRS-motor score in < 3 months, 3-9 months, and 9-12 months but did not continue in the later follow-up period. Clinically significant improvement in the UDHRS-chorea was seen in patients who were followed up for > 30 months. However, functional assessment did not improve 12 months post-operatively. The Westphal variant of HD (W-HD) did not show any motor benefits 6 months postoperatively. The authors also found out the only risk factor for DBS efficacy was the Westphal variant. The rate of stimulation-associated adverse events was quite high [117].

Sanrey, et al. looked at cognitive progression in HD patients with Continuous Electrical Neuromodulation (CEN) of the GPi with a follow up period of 5 years. Global cognitive profile of HD subjects treated with CEN was stable during the first 3 years of treatment. They also reported that chorea decreased post-operatively with a mean improvement of only 56% despite progression of the disease over time [118].

### New developments

Lee, et al. in their study used exosomes as a messenger during heterochromic parabiosis for improvement of HD symptoms in R6/2 mice model [119]. Drew, et al. designed a cohort of minimum 18 patients in which 5 eligible patients will be randomly selected to undergo transplantation of 12-22 million foetal cells in a dose escalation paradigm. This delivery will enable the safety, acceptability, feasibility, and cost-effectiveness in foetal cell transplants in people with HD [120].



## Conclusion

In summary, there has been extensive research on HD in recent years. Several methods and therapies are currently in development and lot of trials are ongoing in preclinical and human model side by side to address the etiology, pathophysiologic mechanisms, and modes of progression of this disease.

## Disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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