

Review

Therapeutics Advancement for Huntington Disease

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Abstract: Huntington disease (HD) is a progressive neurological disease that is inherited in an autosomal fashion. The cause of disease pathology is an expansion of CAG repeats within the huntingtin gene (*HTT*) on chromosome 4 (4p16.3), which codes huntingtin protein (mHTT). The common symptoms of HD include motor and cognitive impairment with psychiatric functions. Patients exhibit a representative phenotype of involuntary movement (chorea) of limb, impaired cognition, and severe psychiatric disturbances (mood swings, depression, and personality changes). A variety of symptomatic treatments (which target glutamate and dopamine pathway, caspases, inhibition of aggregation, mitochondrial dysfunction, transcriptional dysregulation, and fetal neural transplants, etc.) are available and some are in pipeline. Advancement in novel therapeutic approaches includes targeting mutant huntingtin (mHTT) protein and the *HTT* gene. Good gene-editing techniques will reduce the CAG repeats. Good phenomenology and instant tractable treatment goals coupled with advances analytical tools will help to assay the clinical outcome in HD treatment. It will not only improve the quality of life and life span of HD patients but also provide a beneficial role in other inherited and neurological disorders. In this review, we aim to discuss current therapeutic research approaches and their possible uses in HD.

Keywords: Huntington disease; CAG repeat; Mutant huntingtin (mHTT); Therapeutics; Neurodegeneration

1. Introduction:

Huntington disease (HD) is genetically inherited in an autosomal dominant fashion. It is a fatal neurodegenerative disease, caused by an abnormal triplet repeats expansion of CAG (cytosine-adenine-guanine) within the huntingtin (*HTT*) gene on chromosome 4p16.3, causing a mutated huntingtin protein (mHTT) [1-5]. HD is predominantly characterized by adult-onset, progressive motor dysfunction, cognitive impairment and psychiatric (depression, anxiety, obsessive-compulsive disorder, and psychosis) symptoms. Chorea, incoordination, and rigidity are common motor symptoms due to neurotoxicity of mHTT, leading to brain atrophy of the striatum, thalamus, cerebellum, brain stem and the cortex [6-9]. Clinically, HD includes juvenile HD (onset less than 21 years, and a mark clinical symptoms), and late-onset HD (after the age 60 years) [10-13]. Alcohol, drug, and tobacco abuse were associated with earlier onset of HD and hasten motor onset in women. These abuses have a significant association in female than male [14,15]. Children with CAG repeats ≥ 39 , had significantly lower measures of head circumference, weight, and body mass index [16-18]. Disrupted sleep, tics, pain, itching, and psychosis are the common symptoms of juvenile Huntington's disease [19].

Presently there is no remedy for HD, and the disease progresses manifests with a presumed continuation of 15–20 years after the existence of the first symptom [20,21]. The identification of novel biomarkers involves the development of new treatment strategies. The current therapeutics are symptomatic only and do not change the course of the disease. Tetrabenazine (TBZ; Xenazine™) was approved for the remedy of chorea in HD by the US FDA. Additionally, the deuterated version of TBZ, deutetabenazine (AUSTEDO™), has an improved pharmacokinetic profile and was recently approved by the FDA for the treatment of Huntington chorea. In the last review [22], we had discussed different promising agents in the treatment of HD and their phases under clinical trial. Here we are describing updates related to these promising agents which will cure HD.

2. Pathogenesis of the HD:

HD is a monogenic disease with prevalence is about 1 in 7,500 individuals in the general population [23,24]. The normal allele has less than 27 CAG repeats and intermediate alleles have 27-35. CAG repeat sizes of 36-39 will develop HD with less penetrance. Individuals who have 40 or more CAG repeats will develop HD with full penetrance. It is also reported that higher the CAG expansion, the earlier the onset and increased disease severity [20,25-28]. Kremer et al. reported the largest expansion of 121 trinucleotides [29]. CAG codon encoded glutamine α -amino acid (symbol Gln or Q). Glutamine ($C_5H_{10}N_2O_3$) is synthesized from glutamate and ammonia by the enzyme glutamine synthetase. It is mainly produced in muscle, lungs, and brain and acts as a precursor to the neurotransmitter glutamate [30]. CAG has glutamine amino acids within the *HTT* gene and it is not toxic in itself. However, the polyglutamine expansion involves the formation of aggregate and ultimately become toxic. It is the principal factor for the manifestation of HD because aggregates are never remarked in the brain of normal subjects [31,32]. Aggregates formation are accountable for secondary problems, like inflammatory responses (altered cytokine and nitric oxide level), mitochondrial dysfunction (imbalanced level of free radicals and oxidative stress markers), nuclear cleavage, apoptosis, excitotoxicity, transcriptional altered regulation, and at last responsible for altered neuropathological features (cause of cell death/damage) (Fig. 1). Approximately 70% variation of the disease is owing to expanded CAG repeats and polymorphism in the *GRIK2* gene responsible for 13% variation of the disease [33]. This depicts the importance of secondary factors that affect disease onset, its severity, and possible output.

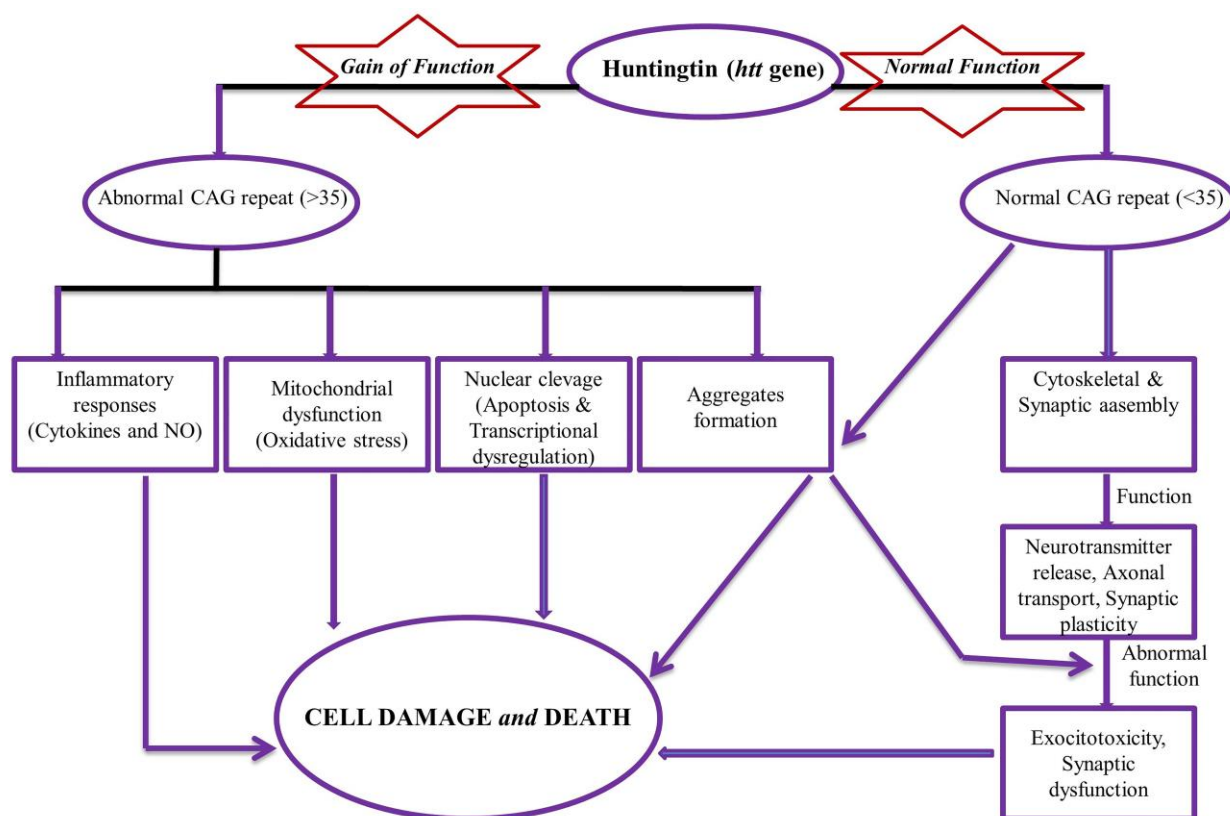


Figure 1: Mechanism of Toxicity of Huntingtin (*HTT*) gene. NO = Nitric Oxide.

3. Therapeutics update

(1) Drug against excitotoxicity

1.1. Riluzole and Memantine drug:

Riluzole is a glutamate inhibitor that reduces abnormal movements in amyotrophic lateral sclerosis (ALS) patients [22,34,35]. In a double-blinded trial, it did not decrease symptoms of HD nor it was neuroprotective [36] (Table 1 & Fig. 2).

Memantine is an antagonist of extrasynaptic NMDA receptors and used for the treatment of moderate-severe dementia in Alzheimer's disease (AD). It diminishes striatal cell death, hinders disease progression and improves cognitive function related to disease [22,37,38]. The combination of memantine and risperidone prevented the expected progression of motor symptoms, cognitive decline, and psychosis over a 6-month study period [39]. However, memantine dosing may be critical, as rodents on low-dose memantine had decreased pathology, while high-dose memantine worsened rodent outcomes and possibly promoted cell death [40-42] (Table 1 & Fig. 2).

1.2. Tetrabenazine (TBZ) and Deutetabenazine :

TBZ inhibits the dopamine pathway by inhibiting vesicular monoamine transporter (VMAT) type 2 and consequently decreasing available dopamine in synapse and its interactions with postsynaptic dopamine receptors [43-47]. Deutetabenazine contains deuterium atoms and is a novel inhibitor of VMAT2. In an indirect treatment comparison study, deutetabenazine has found to be a favorable tolerability profile compared to tetrabenazine [48]. In mice models, TBZ ameliorated chorea and other motor symptoms, and reduced striatal neuronal cell loss [43] (Table 1 & Fig. 2).

(2) Targeting caspase activities and huntingtin proteolysis:

2.1. Minocycline:

Minocycline is a tetracycline analog and can cross the blood-brain barrier (BBB) and inhibits the expression of caspase-3 and caspase-1[49,50]. Treatment with minocycline proved to be neuroprotective and to improve the disease phenotype [35,49,51]. A human trial observed motor [Unified HD Rating Scale (UHDRS)], and cognitive [Mini-Mental State Examination (MMSE)] improvement in 14 HD patients, taking 100 mg of minocycline for 6 months [50]. This study was continued for another 18 months, finding that the MMSE, the TMS, the total functional capacity (TFC) and Independence Scale were all stabilized after treatment, not showing the expected decline in these measures. There was also a decrease in psychiatric symptoms at 24 months, which was not apparent after 6 months of treatment [51]. In a pilot study, Thomas et al. found improvement in MMSE, UHDRS, and Abnormal Involuntary Movements Scale (AIMS), in 30 patients with HD who were given minocycline for 6-month [52]. (Table 1 & Fig. 2).

(3) Targeting HTT aggregation & clearance:

3.1. Congo red and Trehalose:

Congo red dye binds preferably to β -sheets with amyloid fibrils. When it was injected into HD mice, it preserved normal protein synthesis and degradation and improved motor functions. This dye promotes clearance of expanded polyQ repeats and inhibits polyglutamine oligomer formation through the disruption of preformed oligomers. Congo red dye also prevented ATP depletion and caspase activation [53-55] (Table 1 & Fig. 2).

Trehalose disaccharide inhibited the formation of nuclear inclusion, improved motor altered function and high rate of survival in R6/2 mice without causing harmful side effects [56-58] (Table 1 & Fig. 2).

3.2. Compound C2-8:

Compound C2-8 inhibits polyglutamine aggregates in brain slices and cell cultures. It improved motor function, decreased the amount of neuronal atrophy and decreased the size of the mHTT aggregates in R6/2 mice [59,60] (Table 1 & Fig. 2). There are no ongoing human trials are currently listed on clinicaltrials.gov.

3.3. Rapamycin:

mTOR is a protein kinase that phosphorylates many proteins and playing a key role in various cellular functions (like autophagy and transcription). mTOR interacts with mHTT and localizes to these polyglutamine aggregates and thus sequestration of mTOR reduces mTOR's activity, resulting in a decrease in autophagy and a decrease in the clearance of mHTT. mTOR phosphorylates S6K1 (a key regulator of cell volume), therefore mHTT-related impairment of mTOR may account for the brain atrophy in HD. Rapamycin (which inhibits mTOR and consequently induces autophagy) decreased mHTT aggregates and improved neuronal survival in *Drosophila* HD models. Rapamycin also improved motor performance and decreased striatal neuropathology in mice Huntington models [61-64] (Table 1 & Fig. 2).

Table 1. Recent status of Huntington disease drug therapy.

Drug/Reagents	Primary target (Mechanism of action)	Status and Principal results	Ref.
(1) Drug against excitotoxicity			
Riluzole	Glutamate release inhibitor	Do not show efficacy in human trails	[36]
Memantine	NMDA receptor inhibitor	Demonstrated efficacy in human trials	[37,38]
Tetrabenazine	Dopamine pathway	Approved by FDA for	[43-46]

(TBZ)	(VMAT2 inhibitor)	treatment of chorea in HD	
(2) Targeting Caspase & huntingtin (HTT) proteolysis			
Minocycline	Caspase-dependent and independent neurodegenerative pathways	Inhibits caspase-1 and -3 mRNA upregulation, and decreases inducible NO synthetase activity	[49,51,52]
(3) Targeting HTT aggregation & clearance			
Congo red and Trehalose	Aggregation	Showed efficacy in rodent models	[53,56]
Compound C2-8	Aggregation	Showed efficacy in rodent models	[60]
Rapamycin	Aggregation mTOR inhibitor	Showed efficacy in rodent models	[61,62]
(4) Targeting mitochondrial dysfunction			
Creatine	Mitochondrial dysfunction	Attained futility in human trials	[65]
CoQ10	Mitochondrial dysfunction	Attained futility in human trials	[66]
Eicosapentaenoic acid (EPA)	Mitochondria dysfunction	A mixed scenario of positive and negative trials	[67]
Cystamine and MPTP blockers	Mitochondrial dysfunction	Showed efficacy in rodent models	[68]
Meclizine drug	Mitochondrial dysfunction	Showed efficacy in fly models	[69]
(5) Targeting transcriptional dysregulation			
Sodium phenylbutyrate	Transcriptional deregulation histone deacetylase inhibitor	Showed efficacy in rodent models	[70]
HDACi4b	Transcriptional deregulation histone deacetylase inhibitor	Showed efficacy in rodent models	[71]
SAHA	Transcriptional deregulation histone deacetylase inhibitor	Showed efficacy in rodent models	[72]
Mithramycin & chromomycin	Transcriptional deregulation G-C-rich DNA binding antibiotic	Showed efficacy in rodent models	[73]
(6) Targeting mutant huntingtin(mHTT)			
RNAi and ASO	Blocks transcription of mHTT	Showed efficacy in rodent models	[6]
Artificial peptides and intrabodies	Targeting proline-rich domain of HTT	Showed efficacy in rodent models	[74]
(7) Therapies targeting Nucleic acid			
Zinc finger protein	Reduced mutant protein expression	Showed efficacy in a rodent model	[75]
CRISPR-Cas9	Excision of CAG repeat and, reduction of mutant HTT	Showed efficacy in a rodent model	[76,77]
ASO approach ((IONIS-HTTRX, Peptide conjugated ASOs)	Reduction in HTT mRNA and protein	Showed efficacy in a rodent model	[78,79]
RNAi approach (siRNA, shRNA, and miRNA)	Improves motor and neuropathological abnormalities, silencing of <i>HTT</i> ,	Showed efficacy in a rodent model	[6,80]
Novel Viral Vectors (AAV1, AAV5, AAV9, AAV-PHP.B, CREATE)	Widespread transduction of cells	Showed efficacy in primates and rodents	[81,82]

Small molecules (RG7800, RG7916)	-	-	-
(8) Other therapeutics			
Fetal Neural transplant	Striatal degeneration	Not efficacious	[83-85]
Ubiquilin	Reduces mHTT aggregation	Showned efficacy in rodent models	[86,87]
miRNA	Silence HTT	Testing in rodents and nonhuman primates	[6,80]
Chaperonins	Decrease mHTT aggregation	Showned efficacy in rodent models	[88,89]
AFQ056	The antagonist for glutamate receptor 5	Showned no improvement in Chorea in a clinical trial	[90]
BN82451	Decreases glutamate release by blocking Na ⁺ channels	Showned efficacy in a rodent model	[91,92]
Antipsychotic drug	Block or modulate dopamine receptors	Under Phase III trial	-
Antiapoptotic drug	Cleave mHTT	Effective in mice model	[93,94]
Diet	Delay onset of disease	Effective result but require further evaluation	[95]

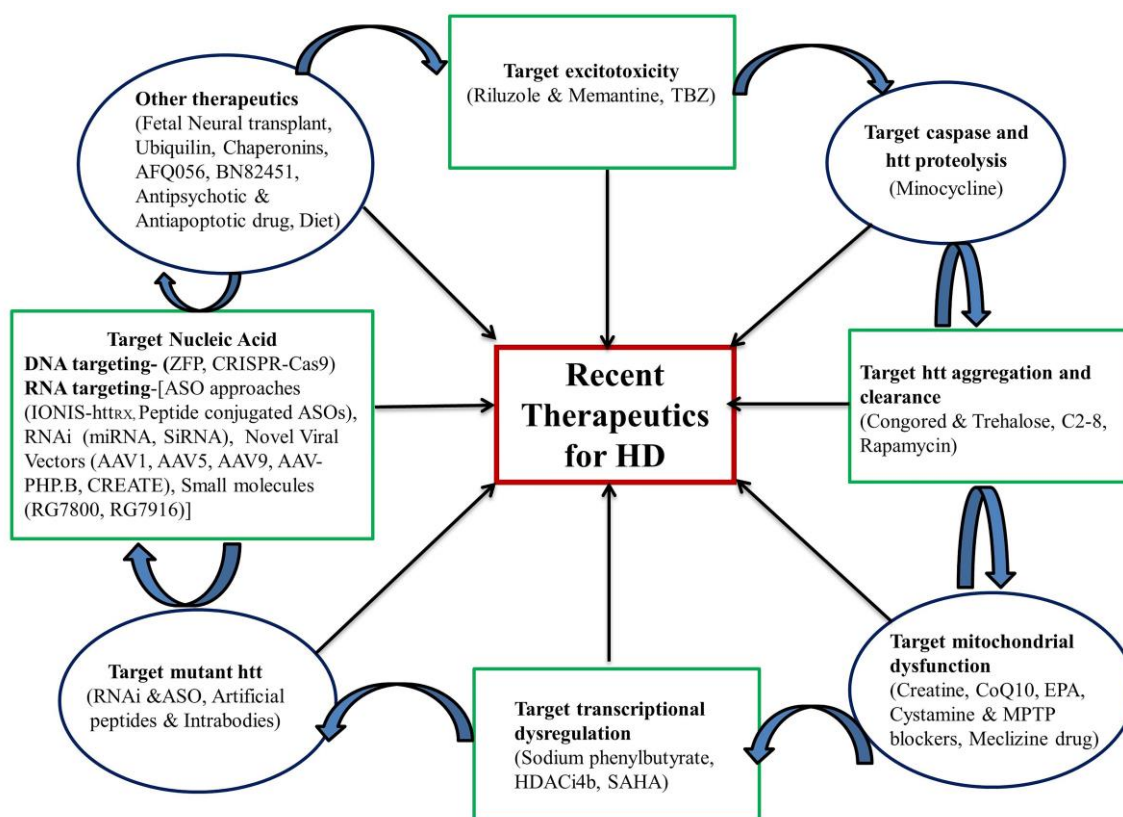


Fig 2: Recent Advancement in the therapeutics for Huntington disease. TBZ (Tetrabenazine); EPA (Eicosapentaenoic acid); MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); SAHA (Suberoylanilide hydroxamic acid); HDACi4b (Histone deacetylase inhibitors); RNAi (RNA interference); ASO (Antisense Oligonucleotide); ZFP (Zinc finger protein); CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats); miRNA (micro RNA); siRNA (Small interfering RNA).

(4) Targeting mitochondrial dysfunction:

4.1. Creatine:

Creatine (antioxidant properties) reduced serum levels of 8-hydroxy-2'-deoxyguanosine (8-OH-2'-dG) in HD patients [96,97] and safe and tolerable at a dose of 15 g twice daily [98]. In a trial study (with HD patients) receiving 8 g/day dose of creatine, it was secure and well-tolerated but produced no mark changes on the UHDRS scale [97]. At a higher dose (up to 40 g daily) randomized, a double-blind study measuring TFC, the trial was terminated early due to futility criterion being reached. The use of creatine fails to delay functional decline in an early manifestation of HD [65]. In another controlled study, creatine (5 g/day; 1 year) treatment results in better muscle function capacity in patients with neuromuscular disease but did not show improvement in neuromuscular function and cognitive status in HD patients with stage I-III [99] (Table 1 & Fig. 2).

4.2. Coenzyme Q10:

Coenzyme Q10 cofactor involved in ATP production in the electron transport chain (ETC) of mitochondria and its supplementation in HD patients may improve mitochondrial function [100]. It was neuroprotective in R6/2 mice, delaying motor deficits, atrophy, and inclusions, and extending survival [101,102]. In a Phase-III randomized clinical trial, coenzyme Q10 was not effective and the trial was stopped because of reaching the futility criteria (<http://hdsa.org/wp-content/uploads/2015/01>) [66] (Table 1 & Fig. 2).

4.3. Eicosapentaenoic acid (EPA):

Ethyl-EPA is a derivative of the n-3 polyunsaturated fatty acids EPA, which binds to peroxisome proliferator-activated receptors of mitochondria [103]. Ethyl-EPA improves the neuronal function by inhibiting caspase and reducing mitochondrial damage by reducing the activity of the JNK pathway [104,105]. Treatment with ethyl-EPA (2 g/day) showed a stable/improved motor function. However, intent-to-treat analysis shows no significant change between ethyl-EPA and placebo for Total Motor Score 4 (TMS-4) subscale in HD patients (stage III) [106]. Patients with less CAG repeat showed significant improvement in TMS-4.

In a Phase-III, double-blind randomized control trial, ethyl-EPA did not show improvement in TMS, function, cognition or global impression over 6 months. After 6 months, all participants (both those in the treatment and placebo groups) were given ethyl-EPA. Those in the original treatment group showed a better motor function (indicated by TMS scores). This suggests that ethyl-EPA needs a longer period before improvement is observed and possibly could reflect a disease modification [107]. In a recent study, no significant improvement of the treatment group over placebo was found in measures of TMS or UHDRS scores [67] (Table 1 & Fig. 2).

4.4. Cystamine and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) blockers:

Both increase the survival effects of HD cells and inhibit oxidative damage [68] (Table 1 & Fig. 2).

4.5. Meclizine drug:

Meclizine drug inhibits oxidative metabolism and inhibits apoptosis, and neuroprotective in *Drosophila* models. Energy metabolism deficits and neuronal degeneration are hallmarks of HD, treatment with meclizine is a potential strategy, especially since it crosses the BBB [22,69] (Table 1 & Fig. 2). There are no human clinical trials listed in clinicaltrials.gov.

(5) Targeting transcriptional dysregulation:

5.1. Sodium phenylbutyrate:

Administration of sodium phenylbutyrate (an HDAC inhibitor) to N171-82Q symptomatic mice showed less brain atrophy and extended survival rates. Further, increased and decreased histone acetylation and methylation respectively in the rodent brain. It also downregulated caspases involved in apoptosis [70]. A dose-finding study highlighted that sodium phenylbutyrate was safe, secure, effective and well-tolerable in HD patients [108] (Table 1 & Fig. 2).

5.2. HDACi4b:

HDACi4b (a pimelic diphenylamide HDAC inhibitor) improves motor impairments as well as decrease neurodegeneration in mice models. Oral administration of HDACi4b to mice showed improvement in these motor deficits. These mice also showed less striatal atrophy and brain-size reduction. HDACi4b reversed hypoacetylation of the H3 histone subunit that occurs in the presence of mHTT, and mRNA expression levels were returned to normal levels [71] (Table 1 & Fig. 2).

5.3. Suberoylanilide hydroxamic acid (SAHA):

Histone acetylation in the brain increases by SAHA (by inhibiting HDAC), improves motor impairments in transgenic R6/2 mice. BBB crossed by SAHA and can be taken orally, however, this has not been tested in humans [72] (Table 1 & Fig. 2).

5.4. Mithramycin & chromomycin:

Treatment with mithramycin & chromomycin (anthracyclin derivatives) was capable to perform epigenetic histone modification in transgenic R6/2 mouse and N171-82Q cell lines, allowing the effective design of HD clinical trials [73,109,110] (Table 1 & Fig. 2).

(6) Agents targeting mutant huntingtin:

6.1. RNA Interference (RNAi) and Antisense Oligonucleotide (ASO):

ASO and RNAi execute their knockdown function by allele and nonallele-selective manner [111-113]. As an example, modified ASO (peptide nucleic acid i.e. PNA) enables the selective recognition of the mutant allele and selective inhibition of mHTT expression in human fibroblasts [114]. RNAi reduced neuropathology, better motor behavior and extending viability in HD [112,115,116] (Table 1 & Fig. 2).

6.2. Intrabodies and artificial peptides:

In a transgenic mouse model of HD like R6/2, N171-82Q, YAC128, and BACHD, treatment with intrabodies improve body weight, motor function, cognitive, and neuropathological manifestations [74,117] (Table 1 & Fig. 2).

(7) Nucleic acid-targeting therapies:

7.1. Therapies targeting DNA:

Currently, zinc finger proteins (ZFPs) and CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-CRISPR-associated system) are under investigation.

7.1.1. ZFPs:

These are one of the most abundant groups of protein and have various functions including regulation of DNA, RNA, and protein function. It can bind to specific sequences of DNA and can be used as therapeutic compounds. Zinc fingers reduced mHTT expression and do not affect the expression of other genes/wild-type *HTT* [75,118,119] (Table 1).

7.1.2. CRISPR-Cas9:

CRISPR-Cas9 are involved in bacterial defense mechanism which recognizes and destroy foreign DNA. CRISPR-Cas9 involved in the excision of CAG repeats to make harmless alleles and silencing the *mHTT* expression by insertion of stop codons/missense mutations [76,120-123]. In mouse (HD140Q-knockin mice) model, CRISPR-Cas9 involved in the reduction of mHTT, and improvement of motor function, but not increases lifespan [77]. Ekman et al. showed that CRISPR-Cas9 mediated *mHTT* editing extends survival and improves motor functions in the R6/2 mouse model of HD following its in vivo delivery to the striatum [124] (Table 1).

7.2. RNA targeting therapies:

There are mainly four methods to inhibit the function of mHTT mRNA are ASOs, RNAi compounds, Novel viral vectors, and small-molecule splicing modulators.

7.2.1. ASO approaches:

These are single-stranded DNA (ssDNA) molecules that primarily bind to a specific sequence on RNA and regulate post-transcriptional gene expression [125]. The ssDNA diffuses well in the CNS and is taken up by neurons. Therefore, the injection of ASOs into the cerebrospinal fluid (CSF) results in, ubiquitous delivery of drug and suppress the production of mHTT [78] (Table 1). However, ASO delivery has some side effects, like thrombocytopenia which was remarked in some human trials of ASOs [126]. ASO can ameliorate transcriptional dysregulation and reduced the levels of *mHTT* and improve behavior in the model of HD (YAC128, YAC18, and BACHD mouse lines) [127,128].

IONIS-HTTRx is an important ASO. It has 12-25 nucleotides and transforms phosphodiester linkages to phosphorothioate. IONIS-HTTRx dose caused a remarkable reduction in HTT mRNA and protein expression [79]. The injection of ASOs (conjugated with peptides), produced wide CNS distribution and longer life span in the spinal muscular atrophy (SMA) mouse model [129]. In a recent study of phase 1–2a trial, HTTRx lessen the concentration of mutant HTT in CSF of HD patients. Therefore, ASOs compounds not only suppress the expression of HTT mRNA and protein in CNS but also in CSF [130].

7.2.2. RNAi approaches:

RNA interference is a gene-silencing process that uses, short interfering RNA (siRNA), short hairpin RNA (shRNA), bi-functional shRNA and microRNA (miRNA). The combination of neural progenitor stem cell and RNAi therapy can ameliorate symptoms in the HD model of mice [131]. In the animal model (R6/1, R62, N171-82Q, RAT AAV-HD70^q) of HD, siRNA, shRNA and miRNA treatment have improved the neuropathological and motor function [6,80,115,132,133]. AMT-130 (adeno-associated virus vector) contains an artificial miRNA which produces a Huntingtin lowering molecule. Side effects like peripheral neuropathy observed in clinical trials of siRNA. RNAi is presently tested in rodents and the delivery system tested in nonhuman primates [134] (Table 1).

7.2.3. Small molecule approach:

Small Molecules like RG7800 showed ocular complications in the $\Delta 7$ mice model of spinal muscular atrophy (SMA) [135] while phase I trial of the molecule RG7916 (**risdiplam**) was recently completed (NCT02633709). **RG7800 and RG7916 are splicing modifier, they change the way the pre-mRNA is spliced so that it contains all the information necessary to make a functional protein. They promote the production of a full-length and functional protein from the gene. RG7800 increases the survival motor neuron (SMN) protein level by modifying the splicing of the SMN2 mRNA. RG7800 is shown to promote the inclusion of exon 7 in SMN2 mRNA, generating full-length mRNA using fibroblasts from an SMA type I patient. In SMA mouse model, the treatment of RG7800 shows a dose-dependent increase in SMN protein levels [136]. RG7800 oral administration in SMA**

patients increased the functional SMN protein level up to two-fold from baseline [137]. (Table 1, Fig. 2 & 3). The journey of such work is now underway to identify these molecules and their possible role in lowering of mutant HTT gene and protein expression [119,138].

(8) *Other therapeutics advancements:*

8.1. *Fetal cell neural transplant:*

Different scientists found that after fetal neural transplant, not all patients initially benefited, even those benefited, had a progressive decline 4–6 years after surgery [83-85]. Probably it is due to mHTT spread from the diseased brain into the normal fetal striatal grafts [85] (Table 1 & Fig. 2).

8.2. *Ubiquilin:*

Ubiquilin overexpression in R6/2 mice decreased aggregation in the hippocampus and cortex and increased lifespan. However, its overexpression did not improve motor symptoms and not change the aggregates amount in the striatum [86,87] (Table 1 & Fig. 2).

8.3. *Chaperonins:*

TRiC (CCT1-CCT8 subunit) is an example of chaperonin which is involved in the folding of about 9–15% of the normal proteins [88] and inhibits aggregation of mHTT [89]. It reduced the number of inclusions, fibrillar oligomers and insoluble mHTT fragments (Table 1 & Fig. 2).

8.4. *AFQ056:*

It can't improve chorea in a randomized, double-blind clinical trial [90] (Table 1 & Fig. 2).

8.5. *BN82451:*

It inhibits cyclooxygenases and provides antioxidant, anti-inflammatory and neuroprotective effects [91]. It also improved motor function and survival, decreased brain atrophy, neuronal atrophy, and neuronal mHTT inclusions in R6/2 mice models [92] (Table 1 & Fig. 2). Recently a Phase II clinical trial has been completed in male HD patients. As per clinicaltrials.gov (NCT02231580), no results have been published.

8.6. *Antipsychotic drug:*

It is used to treat chorea associated symptoms because they block or modulate dopamine receptors. Though of its utility, many antipsychotic drugs (especially typical antipsychotics) produce Parkinson's disease (PD) motor side effects (Table 1 & Fig. 2). Currently, a Phase III trial comparing TBZ with olanzapine and tiapridal is under evaluation [44].

8.7. *Antiapoptotic drug:*

Caspase cleavage (mainly caspase-3 and 6) occur in mHTT [94]. After mutating the caspase cleavage sites on mHTT leads to neuroprotection and prevents neurodegeneration in yeast artificial chromosome (YAC) mice that express mHTT. Caspase-3 and -6 resistant mice did not develop HD neurodegeneration, indicates that cleavage at these caspase sites plays an important role in neurodegeneration of Huntington [93,139,140] (Table 1 & Fig. 2).

8.8. *Diet:*

Various studies indicate that the Mediterranean-type diet may delay the onset of other neurodegenerative diseases, like AD, PD, dementia and cognitive impairment [141]. Recently a study highlighted that a Mediterranean-type diet affects time to HD phenoconversion. In fact, eating high amounts of dairy products was associated with an increased risk of phenoconversion. This may

be due to a lower level of urate, which leads to a faster progression and manifestation of HD. These types of diet-related studies need further investigation [95,118,142]. (Table 1 & Fig. 2). Intermittent fasting promotes autophagy and cleared the mHTT [143].

9. Some promising clinical trials:

9.1. Cysteamine (CYST):

It controls the reduced level of oxidation through increasing concentration of glutathione, activation of protein catabolism through the hindrance of transglutaminase and induction of heat shock proteins (HSPs) effects [144]. Inhibition of transglutaminase supposed as the primary mode of action and observed in R6/2 and zQ175 knock out HD mouse models [145]. The Cysteamine-HD phase II/III trial indicated that delay release of cysteamine in HD patients.

9.2. Pridopidine:

It is a modulator of the dopamine 2 receptor [146] and activates the sigma-1 receptor [147]. In the most recent trials of pridopidine, highlighted no improvement in motor symptoms (Unified Huntington's Disease Rating Scale -total motor score [UHDRS-TMS]) with placebo [148-150]. High level of pridopidine is found in brain-derived neurotrophic factor (BDNF) and diminished mHTT aggregates size and surpassed motor performance in R6/2 mice [151,152]. In an early-stage HD, improvement in the total motor score (TMS) was observed [152,153].

9.3. Triheptanoin:

It is a triglyceride that reverses the metabolic defects in HD by supplying substrates to the Krebs cycle. In a clinical trial of triheptanoin, the metabolic bioenergetic side view of the HD brains was rectified [154]. Recently, a Phase II study triheptanoin trial efficacy was conducted in the early phase of HD patients (listed at clinicaltrials.gov under #NCT02453061).

9.4. Latrepirdine (Dimebon):

Latrepirdine stabilize and surpass mitochondrial membranes and functions. In a short duration trail, latrepirdine caused cognitive improvement (MMSE) in mild to moderate HD patients [13,155]. Till today, total 13 clinical trials of latrepirdine reported on clinicaltrials.gov (NCT00497159, NCT01085266, NCT00920946, NCT00387270, NCT00988624, NCT00827034, NCT00990613, NCT00824590, NCT00931073, NCT00831506, NCT00788047, NCT00825084).

9.5. Amantadine:

It is a weak NMDA receptor blocker [156] and increases dopamine release [157]. Amantadine deteriorates dyskinesias in HD, without provoking parkinsonism [158].

9.6. Lamotrigine:

It is an antiepileptic drug and decreases glutamate release by blocking voltage-gated sodium channels [159-161]. It surpassing motor and mood symptoms in HD [162].

9.7. Selisistat:

It is a selective SirT1 inhibitor and removes acetyl groups on proteins, including mHTT. Therefore, blocking the deacetylation of mHTT should activate clearance. In early-stage HD patients, selisistat showed an improvement in TMS, but not in most measures of cognition, mood, and functionality [163,164].

9.8. *Tauroursodeoxycholic acid/ursodiol:*

Tauroursodeoxycholic acid (TUDCA) is a bile acid and has antiapoptotic properties in mouse models. Mice provided TUDCA doses showed less striatal atrophy, apoptosis, and improved locomotor and sensory-motor defects [165]. A commercially available ursodeoxycholic acid precursor ursodiol has been examined in a Phase I trial, but to date not reported.

9.9. *Laquinimod:*

It reduces the expression of Bax, responsible for the release of cytochrome C from mitochondria and activation of caspases, causing apoptosis and makeup of toxic mHTT fragments. This drug improves motor function and less depressive behaviors in mice. It is recently undergoing a Phase II clinical trial in human HD patients [166]. Laquinimod ameliorate myelination deficiency and behavioral improvement in the YAC128 mouse model of HD [167,168].

9.10. *Kynurenine inhibitors:*

The enzyme Indoleamine 2,3 dioxygenase (IDO1) catalyzes the conversion of tryptophan into kynurenine. Kynurenine is then metabolized into 3-hydroxykynurenine (3-HK) and quinolinic acid, both of which are neurotoxic and are increased in HD. On the other direction, kynurenine also metabolized into kynurenic acid, which is neuroprotective. In HD, there was unbalance observed in between the neurotoxic products and neuroprotective products and targeting the rate-limiting step of IDO1 could effectively shift the balance toward neuroprotective [169]. Kynurenine 3-monooxygenase is the enzyme that catalyzes the conversion of kynurenine into 3-HK. Treating R6/2 mice microglial cells with a kynurenine 3-monooxygenase inhibitor (Ro 61-8048) showed a remarkably lower level of 3-HK in R6/2 mice microglial cells than in the vector containing cells [170].

4. Conclusion and Future perspectives:

The current therapeutic investigations mainly focus on excitotoxicity, dopamine pathway, caspases, mHTT aggregation, mitochondrial dysfunction, transcriptional dysregulation, fetal neural transplants, and diet. The application of robust molecular, imaging and digital biomarkers may provide a valuable therapeutic efficacy which boosts the current clinical trial design. Additionally, the increased openness of regulatory agencies for effectiveness will also promote the development of clinical trials. The advancement of modern technologies and the availability of various promising agents/molecules enable us for the development of such therapies which further improve the quality of research and outcome of HD patients. The most promising drugs are those that target the production of mHTT protein and block its actions.

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Abbreviation:

Alzheimer's disease (AD);
Cerebrospinal fluid (CSF);
Huntington disease (HD);
Mutant huntingtin (mHTT);
RNA Interference (RNAi);
Antisense Oligonucleotide (ASO);
CRISPR-Cas9 (Clustered regularly interspaced short palindromic repeats-CRISPR-associated system);
Parkinson's disease (PD);

Zinc finger proteins (ZFPs)

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