Review

Future NEUROLOGY

New directions in therapeutics for Huntington disease

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Huntington disease (HD) is an autosomal dominantly inherited neurodegenerative disease that affects motor, cognitive and psychiatric functions, and ultimately leads to death. The pathology of the disease is based on an expansion of CAG repeats in exon 1 of the *huntingtin* gene on chromosome 4, which produces a mutant huntingtin protein (mHtt). This protein is involved in neurotoxicity and brain atrophy, and can form β-sheets and abnormal mHtt aggregates. Currently, there are no approved effective treatments for HD, although tetrabenazine (Xenazine™) and deutetrabenazine (AUSTEDO™) have been approved for treatment of the motor symptom chorea in HD. This literature review aims to address the latest research on promising therapeutics based on influencing the hypothesized pathological mechanisms.

First draft submitted: 14 November 2017; Accepted for publication: 6 March 2018; Published online: 29 May 2018

Keywords: ASO • chorea • drug therapies • Huntington disease • mHtt • RNAi • VMAT2

Huntington disease (HD) is a dominantly inherited neurodegenerative disease that is ultimately fatal. It is caused by an abnormal expansion of CAG trinucleotide repeats in exon 1 of the *huntingtin* gene (Htt) on chromosome 4, leading to a mutated huntingtin protein (mHtt) [1,2]. Motor, cognitive and psychiatric symptoms all occur in HD. 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 [3,4]. Identification of novel biomarkers of disease progression can aid in the development of new treatments and treatment strategies.

HD is unique in that due to its single gene autosomal dominant genetics, HD can be accurately identified in patients prior to the onset of any symptoms, while still considered 'premanifest'. Because of this, HD lends itself to the possibility of a disease-modifying therapy in order to delay onset or slow down the progression of the disease. In order to develop these therapeutics, it is crucial to identify a biomarker that can accurately map disease progression. There already exists a biomarker of HD – that is, a stable measure that predicts the likelihood for developing a disease – the presence of the CAG expansion in *Htt*, which strongly correlates with disease onset and severity. There is an inverse correlation between CAG expansion length and age of onset. That is, the longer the CAG expansion length, the earlier the age of onset. However, despite this strong correlation, there is considerable variability in the timing of onset of symptoms, even with those individuals who have the same number of repeats, implying that other factors are involved.

What most of the current biomarker research efforts have been focused on is identifying a marker of disease progression. A useful biomarker should reflect a change in response to disease progression, as well as to modification by treatment. It is also important to more accurately identify and measure subtler symptoms (e.g., cognitive, mood, sleep disorders and brain atrophy) while the patients are still in the prodromal stage, before overt motor symptoms have begun [5–7].

Effective cures and disease-modifying treatments unfortunately do not currently exist for HD. The current therapeutics are symptomatic only, and do not change the course of disease. Tetrabenazine (TBZ; Xenazine™) was US FDA-approved for the treatment of chorea in HD in 2008. Additionally, the deuterated version of TBZ, deutetrabenazine (AUSTEDO™), has an improved pharmacokinetic profile and was recently approved by the FDA for treatment of chorea associated with HD, as well as for tardive dyskinesia. Several other promising symptomatic treatments are in Phases I–III [8]. Many putative treatments have shown promise in rodent models of HD. The

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Table 1. Current status of Huntington disease drug therapy – human trials.

Drug	Primary target	Status	Current US FDA approval	Ref.
Deutetrabenazine (SD809; Austedo™)	Dopamine pathway (VMAT2 inhibitor)	FDA-approved for treatment of chorea in HD	HD (chorea) TD	[9]
Tetrabenazine (Xenazine™)	Dopamine pathway (VMAT2 inhibitor)	FDA-approved for treatment of chorea in HD	HD (chorea)	[10–12]
Memantine (Namenda™)	Excitotoxicity (NMDA receptor inhibitor)	Demonstrated efficacy in human trials	AD	[13,14]
Amantadine (Symmetrel™)	Excitotoxicity (NMDA receptor inhibitor, dopamine agonist)	Demonstrated efficacy in human trials	PD; antiviral	[15–17]
Lamotrigine (Lamictal)	Excitotoxicity (voltage-gated sodium channel inhibitor)	Demonstrated efficacy in human trials	Depression	[8,18]
Remacemide (Ecovia™)	Excitotoxicity (NMDA receptor inhibitor)	Demonstrated efficacy in human trials		[19,20]
Pridopidine (ACR16; Huntexil™)	Dopamine pathway (Dopamine receptor antagonist)	Demonstrated efficacy in human trials		[21–23]
Selisistat	Aggregation (SirT1 inhibitor)	Demonstrated efficacy in human trials		[24]
PBT2	Aggregation (metal chelator)	Demonstrated efficacy in human trials		[25]
Cysteamine	Aggregation (Transglutaminase inhibitor)	Demonstrated efficacy in human trials	Cystinosis	[26,27]
Antisense oligonucleotides	Blocks translation of *mHtt*	Demonstrated efficacy in human trials		[28,29]
Triheptanoin	Mitochondria dysfunction	Demonstrated efficacy in human trials		[30,31]
Eicosapentaenoic acid (n-3 fatty acid)	Mitochondria dysfunction	Mixed picture of positive and negative trials	Hypertriglyceridemia and dietary supplement	[32,33]
Resveratrol	Mitochondrial dysfunction	Currently being tested in human trials	Dietary supplement	[34]
Tauroursodeoxycholic acid	Mitochondrial dysfunction	Currently being tested in human trials		[35]
VX15	Neurodegeneration antibody against SEMA4D	Currently being tested in human trials; given Orphan Drug Designation by the FDA		[36–39]
WVE-120101 and WVE-120102	Blocks translation of *mHtt*	Currently being tested in human trials		[29]
BN82451	Excitotoxicity (sodium channel inhibitor)	Demonstrated efficacy in rodent models; currently being tested in human trials		[40,41]
Laquinimod	Caspase inhibition	Demonstrated efficacy in rodent models; currently being tested in human trials		[42,43]
Epigallocatechin-3-gallate	Aggregation	Demonstrated efficacy in fly models; currently being tested in human trials		[44]
Creatine	Mitochondrial dysfunction	Reached futility in human trials		[45]
Coenzyme Q10	Mitochondrial dysfunction	Reached futility in human trials	Dietary supplement	[46]
Riluzole (Rilutek™)	Excitotoxicity (Glutamate release inhibitor)	Failed to show efficacy in human trials	ALS	[47]
Mavoglurant (AFQ056)	Excitotoxicity (glutamate receptor 5 antagonist)	Failed to show efficacy in human trials		[48]
Latrepirdine (Dimebon)	Mitochondrial dysfunction	Failed to show efficacy in human trials	Antihistamine	[49]

AD: Alzheimer disease; ALS: Amyotrophic lateral sclerosis; HD: Huntington disease; PD: Parkinson disease; TD: Tardive dyskinesia.

current therapeutic investigations target different aspects of HD pathology. We have chosen to organize this review of HD therapeutics based on the HD pathology and how putative agents may interact with that pathology (see Tables 1 & Table 2). Under each HD pathological section we discuss drugs approved for symptomatic treatment of HD, drugs with some demonstrated efficacy in clinical trials and drugs with demonstrated efficacy in rodent, fly or yeast HD models (see Table 3 for descriptions on animal and cell models). Many of the drugs listed under 'demonstrated efficacy in clinical trials' are of interest; however, robust efficacy has rarely been demonstrated. Search terms for HD treatments and various pathological-based terms were employed in internet searches on clinicaltrials.gov.

mHtt plays a crucial role in HD pathology. Targeting the mHtt production, processing, folding and removal (e.g., autophagy) seems to have the greatest therapeutic potential for disease modification, including blocking its

Table 2. Current status of Huntington disease drug therapy – rodent models.

Drug	Primary target	Status	Current US FDA approval	Ref.
Rolipram	Dopamine pathway (phosphodiesterase type IV inhibitor)	Demonstrated efficacy in rodent models		[50–52]
Cystamine	Aggregation transglutaminase inhibitor	Demonstrated efficacy in rodent models		[53,54]
Congo Red	Aggregation	Demonstrated efficacy in rodent models		[55]
Disaccharide Trehalose	Aggregation	Demonstrated efficacy in rodent models		[56]
Compound C2–8	Aggregation	Demonstrated efficacy in rodent models		[57]
Rapamycin (Sirolimus)	Aggregation mTOR inhibitor	Demonstrated efficacy in rodent models	Lymphangioleiomyomatosis prevents organ transplant rejection	[58,59]
Ubiquilin (UBQLN1)	Aggregation	Demonstrated efficacy in rodent models		[60,61]
Chaperonins	Aggregation	Demonstrated efficacy in rodent models		[62,63]
Cystamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine blockers	Mitochondrial dysfunction	Demonstrated efficacy in rodent models		[64]
Suberoylanilide hydroxamic acid (Vorinostat, Zolinza™)	Transcriptional deregulation histone deacetylase inhibitor	Demonstrated efficacy in rodent models	Cutaneous T-cell lymphoma	[65]
Sodium phenylbutyrate (BUPHENYL™)	Transcriptional deregulation histone deacetylase inhibitor	Demonstrated efficacy in rodent models	Urea cycle disorders	[66]
HDACi4b	Transcriptional deregulation histone deacetylase inhibitor	Demonstrated efficacy in rodent models		[67]
Mithramycin (Plicamycin)	Transcriptional deregulation G-C-rich DNA binding antibiotic	Demonstrated efficacy in rodent models	Antitumor agent	[68]
Happ1	*Htt* antibody	Demonstrated efficacy in rodent models		[69]
RNAi	Blocks transcription of *mHtt*	Demonstrated efficacy in rodent models		[3]
Tetrahydrocannabinol and cannabidiol	Cannabinoid receptors	Demonstrated efficacy in rodent models	Marinol, Syndros, Cesamet for appetite and weight loss and nausea associate with cancer treatment	[70]
VY-HTT01	Blocks production of *mHtt* mRNA	Demonstrated efficacy in rodent models		[71]
AMT-130	Blocks translation of *mHtt*	Demonstrated efficacy in rodent models		[72]
V(L)12.3	*Htt* antibody	Demonstrated mixed results in rodent models		[69]
Meclizine (Bonine™, Dramamine II™)	Mitochondrial dysfunction	Demonstrated efficacy in fly models	Antihistamine motion sickness	[73]
Kynurenine inhibitors	Neurodegeneration	Demonstrated efficacy in mouse models		[74,75]

synthesis by antisense oligonucleotides or its removal with antibodies. Normal Htt has important roles in normal cell function, and effective treatments need to avoid targeting normal Htt. Many of these therapies have shown promise in mouse models with the advantage of not targeting the normal Htt. However, sufficient safety studies need to be conducted for many of these drugs. Ionis Pharmaceuticals has completed sufficient human safety data to support the randomized placebo controlled trial of antisense oligonucleotides (ASOs).

Therapeutics

Effective disease-modifying treatments unfortunately do not currently exist for HD. The current approved therapeutics are symptomatic only, and do not change the course of disease. There are approved symptomatic treatments for chorea. TBZ (Xenazine™) was FDA-approved for the treatment of chorea in HD in 2008. Several other promising symptomatic treatments are in Phases I–III testing [8]. Additionally, other putative treatments show promise in rodent models. The following discussion of treatments is grouped based on their proposed mechanism of action. Within each mechanistic group, FDA-approved treatments are listed first (A), followed by those that show promise in human trials (B), followed by those that failed in human trials (C), and last, treatments with compelling data in rodent or cell models (D).

Table 3. Overview of Huntington disease mouse models.

Model	Onset of clasping phenotype[†]	Other symptoms	Cell loss	Brain atrophy
R6/1 (~110Q)	5 months [76]	Tremors and abnormal gait, learning deficit, hypokinesis [76]	Cortical, striatal and cerebellar Purkinje cells at late stage [76]	Overall brain atrophy [76]
R6/2 (~150Q)	2 months [76]	Tremors and abnormal gait, learning deficit, hypokinesis [76]	Cortical, striatal and cerebellar Purkinje cells at late stage [76]	Overall brain atrophy [76]
N171-82Q	5 months [76]	Tremors and abnormal gait, hypokinesis, weight loss, early death [76]	Striatum [76]	Striatum [76]
YAC128	3 months [77]	Motor abnormalities from 3 to 12 months [77]	Striatum and then cortex [78]	Striatum and cortex [78]
BAC (97Q)	Not reported	Motor deficits at 2 months [79]	Striatum [79]	Striatum and forebrain [79]
Knock-In (111, 92, 50Q)	Phenotype not observed [80]	Motor deficits at 9 months or 2 years (conflicting reports) [80,81]	Striatum [80]	Striatum [80]
Knock-In (150Q)	60 weeks [76]	Clasping gait deficit at 25 weeks [76]	None observed [76]	Glial fibrillary acid protein positive cells [76]
Knock-In (Q175F)	Not reported	Late-onset motor deficits (later than 2 months) [82]	Loss of white matter [82]	Forebrain [82]
Knock-In (Q175FDN)	Not reported	Late-onset motor deficits (later than 2 months); anxiety-like and depressive-like changes [82]	Loss of white matter [82]	Forebrain [82]
Humanized (Hu97/18)	Not reported	Learning motor deficit at 2 months; motor abnormalities; anxiety-like and depressive-like changes [83]	Loss of white matter; cortical shrinking [83]	Forebrain, striatum, corpus callosum [83]

[†] Mice show abnormal clasping of their hind limbs when suspended.

Drugs targeting excitotoxicity

Excessive increase in glutamate release can cause excitotoxicity and neuronal death. Promising treatments involve glutamate: blocking glutamatergic receptors or glutamate release.

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Memantine

Memantine is an antagonist of extrasynaptic NMDA receptors. It is approved for treatment of moderate-to-severe dementia in Alzheimer's disease. In rat models, it reduces striatal cell death, slows disease progression and improves cognitive function [8,13]. In a case report, the combination of memantine and risperidone prevented the expected progression of motor symptoms, cognitive decline and psychosis over a 6-month study period [84]. A similar finding using fluorodeoxyglucose (FDG)-PET (a measure of brain metabolic activity) was consistent with a lack of expected deterioration [85]. 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 [86–88]. In a 2-year open-label trial, at doses up to 30 mg/day (a dose used to treat Alzheimer's disease), memantine appeared to slow disease progression. Disease progression was evaluated based on motor and psychometric tests, and measures of activities of daily living [14]. A Phase IIb, double-blind study evaluating memantine in prodromal and early-stage HD is listed in clinicaltrials.gov (NCT01458470); however, the results have not been published.

Amantadine

Amantadine is a weak NMDA receptor blocker [15], and also indirectly increases dopamine release [16]. Verhagen Metman *et al.* reviewed amantadine clinical trials and concluded that amantadine ameliorates dyskinesias common in HD, without inducing parkinsonism [89]. In a study of nine patients, participants received intravenous amantadine for 2 h, followed by oral amantadine for 1 year. Both administrative methods decreased dyskinesia scores [17].

However, a study by O'suilleabhain and Dewey, using the same amantadine dose, did not show an improvement in chorea in a 2-week crossover study [90].

Lamotrigine

Lamotrigine, an antiepileptic drug, decreases glutamate release by blocking voltage-gated sodium channels [8,91]. There are case reports of lamotrigine improving motor and mood symptoms in HD [92]. In a 30-month, double-blind study, more patients reported symptomatic improvement on lamotrigine (53.6 vs 14.8% on placebo), although there was no evidence of slowing progression in patients with early stage HD [18]. Stanford's Huntington's Outreach Project for Education suggests that based on an open-label study by Higgins *et al.*, there may measurable cognitive improvement, in terms of processing speed [93].

Remacemide

Remacemide blocks glutamate release by noncompetitively inhibiting NMDA receptors. In R6/2 mice, remacemide was more efficacious when combined with coenzyme Q10 (see coenzyme Q10 section), than when either drug was used alone [8,19]. In a large clinical trial of early HD (n = 347) patients were randomized to coenzyme Q10 (at 300 mg two-times a day), remacemide (at 200 mg three-times a daily), or combination, or placebo for 30 months. Those receiving remacemide showed reduced chorea throughout the study; however, the treatment had no impact on functional decline. The authors note that the failure to affect functional decline may have been due to dosage or stage of disease of the subjects [20].

Drugs in clinical trials, but failed to show efficacy

Riluzole

Riluzole is glutamate release inhibitor that reduces abnormal movements in patients with amyotrophic lateral sclerosis [8,94–95]. In a double-blinded trial it did not decrease symptoms of HD nor it was neuroprotective [47]. However, Squitieri *et al.* found that brain glucose metabolism and gray matter volume were preserved in those HD patients taking riluzole. The authors also found an increase in serum brain-derived neurotrophic factor (BDNF) and TGFβ-1 in patients taking riluzole, which may explain the preservation of brain metabolism and volume [96]. However, caution is warranted, as measuring BDNF in the peripheral blood may not be reliable [97].

AFQ056 (mavoglurant)

AFQ056 is a selective metabotropic glutamate receptor 5 antagonist. It failed to improve chorea in a 32-day randomized, double-blind clinical trial [48].

Drugs only tested in HD rodent or cell models

BN82451

BN82451 decreases glutamate release by blocking Na+ channels. It also protects the mitochondria, inhibits cyclooxygenases and provides antioxidant, anti-inflammatory and neuroprotective effects [40]. In R6/2 mice models, it improved motor function and survival, as well as decreased brain atrophy, neuronal atrophy and neuronal mHtt inclusions [41]. A Phase II clinical trial in male HD patients has been completed, however, according to clinicaltrials.gov (NCT02231580), no results have been published.

Conclusion on drugs targeting excitotoxicity

Converging data suggest that blocking glutamate release or NMDA receptors decreases some of the expected brain metabolic decline and atrophy. However, there is a lack of sufficient human data showing that progression is altered and functionality is improved.

Drugs targeting the dopamine pathway

Chorea is a ubiquitous symptom of HD that is hypothesized to be due to a hyperactive dopaminergic system.

Drugs approved for symptomatic treatment of HD

Tetrabenazine

TBZ inhibits the dopamine pathway by inhibiting vesicular monoamine transporter (VMAT) type 2, and consequently decreasing available dopamine in the synapse and its interactions with postsynaptic dopamine receptors. TBZ therefore has antichoreic properties. In mice models, TBZ ameliorated chorea and other motor symptoms, and reduced striatal neuronal cells loss [98]. TBZ has been approved by the FDA for treatment of chorea in HD.

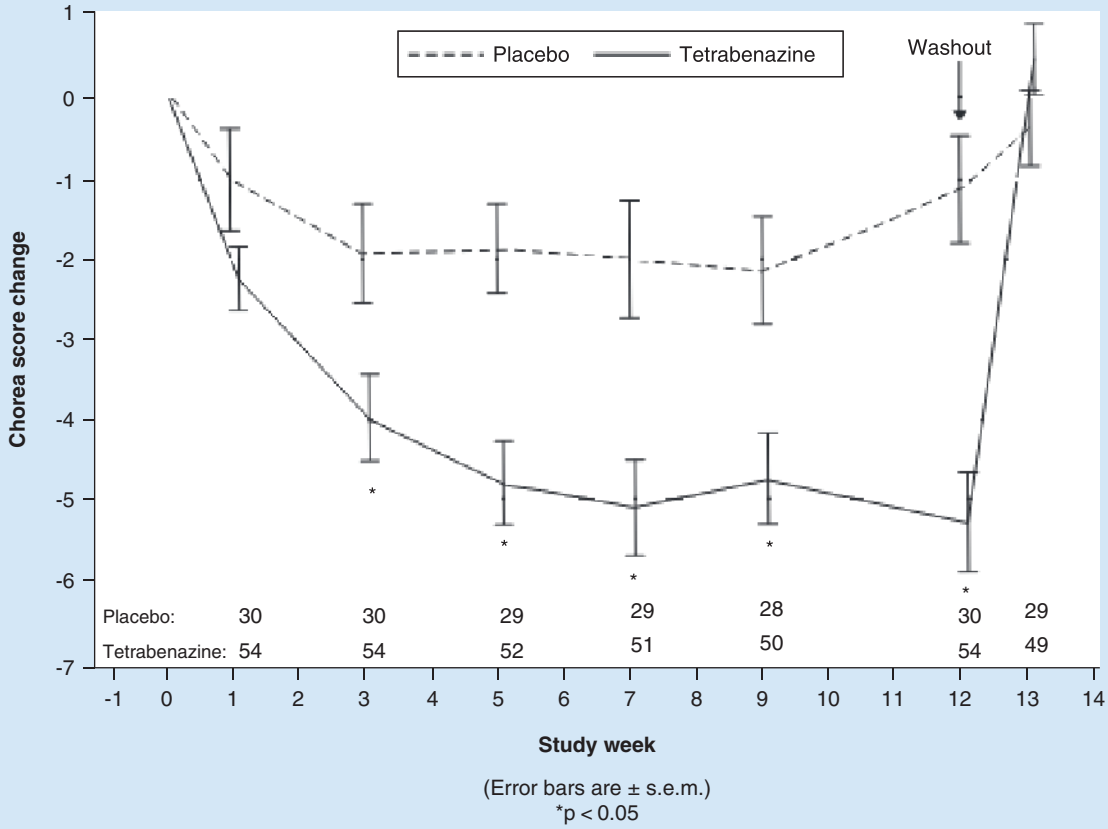

Figure 1. Chorea score change in Huntington disease patients treated with tetrabenazine as compared with placebo.
s.e.m.: Standard error of the mean.
Data taken from [136].

In a discontinuation and reinstitution study, patients on TBZ for 1 month without significant side effects were discontinued from TBZ and then had TBZ reinstituted. TBZ improved scores on the Unified Huntington's Disease Rating Scale (UHDRS) motor test, the Tinetti Mobility Test total and balance subscale scores, and the Five Times Sit-to-Stand test. However, spatiotemporal gait measures, Six Condition Romberg test, and UHDRS measures for hand and forearm functions did not change with TBZ. Documented side effects of TBZ have included parkinsonism, depression and akathisia. However, in this recent human study, there was no parkinsonian gait observed, although it is important to note that the inclusion criterion for this study required that patients be on TBZ for 1 month without significant side effects. Many HD patients experience side effects on TBZ (including parkinsonism), a limitation in this treatment [8,10–12]. The Huntington Study Group (2006)'s study on TBZ led to FDA approval. This double-blind placebo-controlled study, increased TBZ dosage over 7 weeks (up to 100 mg/day). There was a reduction of 5 units in chorea severity scores, as compared with 1.5 units in the placebo group [11] (see Figure 1).

Deutetrabenazine (aka SD809)

One drawback of TBZ is that it is subject to variable metabolism and has to be administered three-times daily because of its short half-life. Some of the side effects, such as anxiety, fatigue and akathisia, may be due to peak blood concentrations related to its pK profile including its short half-life and failure to reach steady state. Deuterium is a heavier, nontoxic, form of hydrogen that forms a stronger bond with carbon, therefore requiring more energy to be broken. Consequentially, it is not as easily metabolized, which creates a longer half-life and can be given at lower doses and less frequently (i.e., twice a day). A recent study tested deutetrabenazine in ninety manifest HD patients [9]. There was a significant improvement in chorea following treatment, to a similar degree as TBZ. Also, there was an improvement in total motor scores and in dystonia, which was not seen with TBZ. In this

deutetrabenazine study, depression and parkinsonism side effects were not seen. This is important, given that VMAT inhibition depletes dopamine. A side effect of TBZ is depression, a serious concern given the high suicide rate in HD patients [99]. The lack of depression could be due to the advantages of deutetrabenazine being given at a lower dose, although this needs to be replicated over a longer time period, as this study was conducted over 12 weeks. In 2017, deutetrabenazine was FDA-approved for the treatment of chorea associated with HD.

Drugs with some demonstrated efficacy in clinical trials

Pridopidine/ACR16

Pridopidine (aka ACR16) is part of a class of dopidines, 'dopamine stabilizers', and targets and modulates the σ-1 receptor. Pridopidine is a dopamine receptor antagonist, but differs from classic dopamine receptor antagonists in several ways. Pridopidine has lower affinity for and disassociates more rapidly from D2 receptors, than standard dopamine receptor antagonists [21,100].

Pridopidine increased in BDNF, reduced the size of mHtt aggregates and improved motor performance in R6/2 mice [101]. However, in a 400-subject Phase II double blind study, pridopidine did not show an improvement compared with placebo. Unfortunately, there was an unusually high placebo effect, confounding interpretation of the data. In a subgroup of those with early stage HD, there was an improvement in the total motor score (TMS), as well as some evidence of modification of disease progression [22–23,101–102].

Antipsychotic drugs

Antipsychotic drugs are used to treat chorea symptoms because they block or modulate dopamine receptors. However, many antipsychotic drugs, especially typical antipsychotics, produce Parkinson motor side effects and akathisia. Currently, a Phase III trial comparing TBZ with olanzapine and tiapridal (a benzamide, similar to amisulpride) is underway.

Drugs in clinical trials, but failed to show efficacy

None.

Drugs only tested in HD rodent or cell models

Rolipram

Rolipram is a phosphodiesterase type IV inhibitor that has been proposed to affect the second-messenger dopamine cascade, and thereby decreasing the effects of dopamine [50]. Rolipram also decreases inflammation and increases the activity of proteasomes, thereby decreasing the cellular burden of aggregates [51]. Rolipram was neuroprotective when given to R6/2 mice. These mice had an increased survival and less severe neurological deficits. Interestingly, these mice also had an increase of BDNF in the striatal spiny neurons and less striatal spiny neuron loss [52]. It may be that the lack of BDNF transport from the cortex to the striatum is responsible for the atrophy of the striatum, commonly seen in HD. It has not yet been tried in HD patients, but was ineffective in multiple sclerosis studies [103].

Conclusion on drugs targeting dopamine pathways

Blocking dopamine by decreasing its release (e.g., VMAT2 inhibition) or its interaction with D2 dopamine receptors (antipsychotics) is effective in decreasing chorea but has little effect on the cognitive and psychiatric symptoms of HD or its progression. Additionally, these dopamine-targeted treatments have their own side effects, such as akathisia, fatigue and other Parkinson-related symptoms.

Antiapoptotic drugs

Caspase cleavage of mHtt occurs in HD, leaving toxic mHtt protein fragments that accumulate in the pathologic HD brain. A key player in this mHtt cleavage is caspase-3 [104]. Mutating the caspase cleavage sites on mHtt leads to neuroprotection and prevents neurodegeneration in yeast artificial chromosome (YAC) mice that express mHtt. Mice that were modified to be caspase-3 and -6 resistant did not develop HD neurodegeneration, suggesting that cleavage at these caspase sites may play an important role in HD neurodegeneration [105].

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Laquinimod

Laquinimod reduces the expression of Bax – a molecule that causes cytochrome C to be released from the mitochondria and caspases to be activated, leading to apoptosis and a buildup of toxic mHtt fragments [42]. In YAC128 mice models, treatment with laquinimod for 6 months reduced striatal, cortical and corpus callosal atrophy. Diffusion tensor imaging showed improvement in white matter microstructure abnormalities in the corpus callosum. The drug also showed motor function improvements and less depressive-like behaviors in the mice [43]. Laquinimod decreases the amount of white and gray matter damage present in human MS patients. It is currently undergoing a Phase II clinical trial in human HD patients [42].

Drugs in clinical trials, but failed to show efficacy

Minocycline

Minocycline, an antibiotic, inhibits both caspase-dependent and -independent neurodegeneration pathways in R6/2 mice. Treatment with minocycline proved to be neuroprotective and to improve the disease phenotype [8]. Specifically, minocycline inhibits caspase-1 and -3 mRNA upregulation, and decreases inducible NO synthetase activity [106]. A human therapeutic minocycline trial observed motor performance (measured by UHDRS) and cognitive performance (measured by the Mini-Mental State Examination) improvement in 14 HD patients taking 100 mg of minocycline for 6 months [107]. This study was continued for another 18 months, finding that the Mini-Mental State Examination, 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 [108]. However, a futility analysis was conducted with a threshold of 25% or more reduction in progression (as measured by the TFC score). Futility was reached, and therefore did not support the value of conducting a larger Phase III trial [109].

Drugs only tested in HD rodent or cell models

None.

Conclusion on drugs targeting caspase inhibition

There are few data for drugs targeting caspase inhibition in HD. In fact, the only published human study reached futility criteria.

Drugs targeting aggregation

Preventing misfolding, and related aggregation, of mHtt in neurons of HD patients is a promising therapeutic strategy aimed at mitigating the atrophy and symptoms of HD patients as well as progression of disease. Abnormal aggregates of mHtt are hallmarks of HD pathology and the target of potential therapeutic intervention, although these aggregates under some circumstances may be protective by isolating toxic compounds from the rest of the cell [110].

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Selisistat

Selisistat is a selective SirT1 inhibitor. SirT1 is a type of deacetylase that removes acetyl groups on proteins, including mHtt. Acetylation of mHtt has been shown to increase its clearance. Therefore, blocking the deacetylation of mHtt should promote clearance. In a 14-day proof of concept study in early stage HD patients, selisistat showed an improvement in TMS, however, not in most measures of cognition, mood and functionality [24].

PBT2

Some studies suggest that the aggregation of mHtt could be partially due to interaction with metals (such as copper and iron). PBT2 is an 8-hydroxyquinoline drug that chelates metals, thereby decreasing metals to nonpathogenic levels. In R6/2 mice, PBT2 improved scores on motor tasks and increased lifespans. The treated animals had larger brains and smaller lateral ventricles [111]. In a Phase II clinical trial using PBT2 in early to mid-stage HD, patients showed that PBT was safe and generally well tolerated. Importantly, the subjects receiving the higher dose (250 mg)

showed improvement on the Trail Making Test Part B, which is a cognitive test that involves set shifting. However, neither dose of PBT2 showed improvement in the composite cognition Z score – the primary efficacy outcome – as compared with placebos. A larger and longer study is needed in HD patients, although clinicaltrials.gov does not list any ongoing HD trials [25]. This drug is also being tested in clinical trials for Alzheimer's disease.

Cysteamine

Cysteamine (a reduced form of cystamine– discussed below) is a competitive substrate of transglutaminase 2. Transglutaminase catalyzes a bond between a γ-carboxamid group of glutamine and a free amino group (including lysyl residues and polyamines). This transglutaminase-based linking forms an insoluble protein polymer that may be key in producing the insoluble aggregates of mHtt protein. Importantly, increased transglutaminase activity has been shown in the brains of HD patients [26]. Blocking these transglutaminases could prevent the formation of aggregates, and be a therapeutic strategy [26]. Even though cysteamine is not an irreversible inhibitor, prolonged treatment decreased transglutaminase activity. Jeitner *et al.* suggest that cysteamine may work by inhibiting the binding of transcription factors to transglutaminase promoters, thereby decreasing the amount of transglutaminase protein [112]. Cysteamine was tested in randomized, double-blind, Phase II/III study. The manufacturer, Raptor Pharmaceutical, reported a statically significant slowing in total motor dysfunction (as measured by TMS) for subjects treated with cysteamine in a 36-month Phase II/III trial. The improvement was noted in those regardless of whether they were also simultaneously treated with TBZ. This trial is yet to be published [27].

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is an inhibitor of the mHtt aggregation. EGCG modulates misfolding and oligomerization of mHtt *in vitro*. In yeast models, it reduces aggregation and cytotoxicity. In fly HD models, EGCG decreased photoreceptor degeneration and improved motor function. This suggests that preventing the misfolding of mHtt reduces the toxicity of these expanded repeats. EGCG is a polyphenol catechin found in green tea [8,44]. According to clinicaltrials.gov, EGCG was more recently tested in a Phase II double-blind, randomized study giving 1200 mg daily dose of EGCG to HD patients. The outcome of this trial is not listed on clinicaltrials.gov (NCT01357681), nor in publications.

Drugs in clinical trials, but failed to show efficacy

None.

Drugs only tested in HD rodent or cell models

Cystamine

Cystamine is also a transglutaminase inhibitor. Karpuj *et al.* found that cystamine improved abnormal movements, including tremor, and extended survival in mice models [53]. However, cystamine did not alter the amount or the appearance of the mHtt aggregates. Interestingly, treatment with cystamine surprisingly increased transcription of genes known to be neuroprotective in *Drosophila*, for example, the chaperone DnaJ (HDJ1 in humans, and Hsp40 in mice) [53,113]. Dedeoglu *et al.* found similar results with cystamine in R6/2 mice, with delayed onset of neuropathological observations, although this was not observed in the Karpuj *et al.* study. Cystamine normalized the elevated transglutaminase activity that is observed in untreated HD mice models [54]. No human trials are currently listed on clinicaltrials.gov.

Congo red

Congo red is a dye that binds preferentially to β-sheets with amyloid fibrils. When Congo red was injected into HD mice that already had onset of symptoms, it preserved normal cellular protein synthesis and degradation, and improved motor functions [8,55]. Congo red promotes the clearance of expanded polyQ repeats and inhibits polyglutamine oligomer formation through the disruption of preformed oligomers. Congo red also prevented ATP depletion and caspase activation. Unfortunately, Wood *et al.* were unable to replicate these Congo red results [114].

Disaccharide trehalose

Trehalose is a disaccharide sugar that prevented the formation of nuclear inclusion bodies, and improved motor function and increased survival in R6/2 mice. This drug lead to a reduction of polyglutamine aggregates in the cerebrum and liver. Tanaka *et al.* suggest that these effects could be the result of disaccharide trehalose binding to the expanded mutated protein and stabilizing this partially unfolded protein, thereby having chaperone-like

properties. There were minimal side effects in these mice models, suggesting a promising therapy. There are no ongoing human trials listed on clinicaltrials.gov [8,56].

Compound C2–8

Compound C2–8 inhibits polyglutamine aggregates in brain slices and cell cultures. In R6/2 mice, C2–8 improved motor function, decreased the amount of neuronal atrophy and decreased the size of the mHtt aggregates [8,57]. No ongoing human trials are currently listed on clinicaltrials.gov.

Rapamycin

The protein mTOR is a kinase and phosphorylates many proteins, playing a key role in cellular functions, such as autophagy and transcription [58]. mTOR interacts with mHtt, and localizes to these polyglutamine aggregates. This 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 therefore induces autophagy) decreased mHtt aggregates and improved neuronal survival in *Drosophila* HD models [8,59]. It also improved motor performance and reduced striatal neuropathology in mice HD models [59]. A rapamycin ester CCI-779, which has more favorable pharmaceutical properties, showed beneficial effects in mice [8,59]. It has been used in clinical cancer trials previously and was generally well tolerated. Interestingly, when rapamycin was combined with trehalose (see above), there was an additive effect on the clearance of these mHtt aggregates in cell models [115].

Another possible combination treatment that has shown success in decreasing the amount of mHtt aggregates is the combination of rapamycin and lithium. Lithium induces mTOR-independent autophagy through inhibition of inositol monophosphatase, which reduces inositol and IP3 levels. However, these actions are more complex because lithium also inhibits glycogen synthase kinase-3-β (which has the opposite effect of inhibiting mTOR). That is, lithium decreases autophagy through activation of mTOR. The combination of rapamycin and lithium enhances autophagy by both the mTOR-dependent pathway (through inhibition by rapamycin) and the mTOR-independent pathway (through inositol monophosphatase inhibition by lithium) and has proven effective. This combination treatment is protective against neurodegeneration – and in HD fly models, more protective than with either rapamycin or lithium alone [116]. According to clinicaltrials.gov, this has not yet been tested in humans.

Ubiquilin

Ubiquilin (a ubiquitin-like protein) reduces mHtt aggregation in cell, *Caenorhabditis elegans* and R6/2 mouse HD models. Ubiquilin facilitates protein clearance via proteasome and autophagy pathways. In HD brains, there is a 30% decrease in ubiquilin concentrations, as the disease approaches end stage. Overexpressing ubiquilin in R6/2 mice decreased aggregation in the hippocampus and cortex, and increased lifespan. When ubiquilin levels were decreased, mHtt aggregation and cytotoxicity increased. Surprisingly, the overexpression did not change the amount of aggregates in the striatum, nor did it improve motor symptoms [60,61]. According to clinicaltrials.gov, this has not yet been tested in humans.

Chaperonins

Chaperonin complexes can decrease mHtt aggregation by preventing protein misfolding. TRiC is a chaperonin that is involved in the folding of approximately 9–15% of the normal proteins [62]. This protein is large, approximately 1 million daltons, with eight subunits (CCT1-CCT8), some of which have been shown to inhibit aggregation of mHtt [117]. The substrate-binding apical part of subunit CCT1 (ApiCCT1) is only 20 kDa. ApiCCT1 is able to enter cells following exogenous delivery and can enter through penetrating the cell membrane and localizes to the nucleus. It reduced the amount of inclusions, fibrillar oligomers and insoluble mHtt fragments. ApiCCT1 reduced toxicity in striatal cells from HD mice models [63]. There are no therapeutics using ApiCCT1 currently listed on clinicaltrials.gov.

Conclusion on drugs targeting aggregation

Misfolding of mHtt is a crucial step in HD pathology and several interventions are effective in rodent models. Preventing the misfolding of mHtt reduces the toxicity of these expanded CAG repeats in rodent models. There have been some promising results in human studies, but usually only in certain measures, while failing to show improvement in other symptomatic measures. Further well-designed human trials are needed.

Drugs targeting mitochondrial dysfunction

mHtt affects many mitochondrial functions – metabolism, motility, ATP levels and oxidative stress.

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Eicosapentaenoic acid (n-3 fatty acid)

In symptomatic YAC128 mouse models, oral delivery of ethyl-eicosapentaenoic acid (EPA), a fish oil used to treat hypertriglyceridemia, led to improvements in motor and behavioral deficits. However, there was no neuropathological improvement, for example, striatal area and volume, or number of neurons, were unchanged [8,118–119]. In a 6-month, Phase III, double-blind randomized control trial, ethyl-EPA did not improve TMS, function, cognition or global impression over 6 months. After these 6 months, all participants (both those in the treatment and placebo groups) were given ethyl-EPA. Those in the original treatment group showed an improvement of motor function, as indicated by TMS scores. This staggered-start design suggests that ethyl-EPA needs a longer period before improvement is observed and possibly could reflect a disease modification. This study needs to be replicated in longer placebo-controlled studies [32]. In a recent nonstaggered start design, no significant improvement of the treatment group over placebo was found in measures of TMS or UHDRS subscores [33].

Triheptanoin

Triheptanoin is a triglyceride that is made up of fatty acid chains that can be broken down into substrates for the Krebs cycle [30]. A hypothesis was proposed to reverse the metabolic deficits in HD by providing substrates for the Krebs cycle. In a clinical study using triheptanoin oil in HD patients, the metabolic bioenergetic profile of the HD brains (as measured by magnetic resonance spectroscopy) was corrected [31]. Motor function after 1 month of the drug therapy was also improved, but the authors caution that a placebo effect cannot be ruled out because of the open-label nature of the study [31]. Currently, a Phase II study investigating triheptanoin oil's efficacy in early phase HD patients is being conducted. This study is posted on clincialtrials.gov under #NCT02453061. No results have been published.

Tauroursodeoxycholic acid/ursodiol

Mitochondrial dysfunction in HD can lead to cell death and regional brain atrophy. Tauroursodeoxycholic acid (TUDCA) is a bile acid that has been shown to be antiapoptotic in mouse models. Mice given TUDCA showed less striatal atrophy and less striatal apoptosis. Locomotor and sensorimotor deficits improved [35]. A commercially available exogenous form of UDCA (uroursodeoxycholic acid; the precursor of TUDCA), ursodiol, has been tested in a Phase I trial, although to date not reported.

Drugs in clinical trials, but failed to show efficacy

Resveratrol

Resveratrol (RV) is an antifungal molecule produced by plant species, such as red grapes, peanuts or tea. RV is thought to activate SIRT1, which deacetylates p53 and therefore inhibits p53-dependent apoptosis. In HD, the p53 activation leads to increased mitochondrial oxidation. By activating SIRT1 (through RV), the cell can adapt to energy stress better without undergoing apoptosis [34]. A current human Phase III trial is being conducted for RV's ability to ameliorate caudate volume reduction in HD patients.

Creatine

Creatine has antioxidant properties and stimulates mitochondrial respiration. In R6/2 mice, it decreased the formation of mHtt aggregates and delayed striatal and brain atrophy [120]. Creatine also reduced levels of 8-hydroxy-2′-deoxyguanosine (8-OH-2'-dG) in the serum of HD patients, which is a marker of oxidative stress. In a double-blind, randomized, placebo-controlled study with HD patients receiving 8 g/day of creatine, it was safe and well tolerated but produced no changes on the UHDRS scale [121]. In a higher dose (up to 40 g daily) randomized, double-blind study measuring TFC, the trial was terminated early due to futility criterion being reached [45].

Coenzyme Q10

Coenzyme Q10 is a cofactor in the electron transport chain and involved in ATP production in the mitochondria. It was neuroprotective in R6/2 mice, delaying motor deficits, atrophy and inclusions, and extending survival [19].

In a large clinical trial of early HD patients (as mentioned above under remacemide), those taking coenzyme Q10 showed a trend toward a smaller decline in the TFC. This was not evident until a year after treatment, and there was no clear continuing separation between those taking coenzyme Q10 and those who were not [20]. In another large, Phase III randomized clinical trial, coenzyme Q10 was not effective and the trial was stopped because of reaching the futility criteria [46].

Latrepirdine (Dimebon)

Latrepirdine (originally used as an antihistamine) was found to stabilize mitochondrial membranes and improve mitochondrial function. A 90-day trial of latrepirdine showed improvement in the Mini-Mental State Examination scores in mild to moderate HD patients [122]. However, a longer (26-week) trial was conducted and latrepirdine did not improve cognitive or global function [49]. There are 13 clinical trials of latrepirdine listed as either ongoing or completed on clinicaltrials.gov (NCT00497159, NCT01085266, NCT00920946, NCT00387270, NCT00988624, NCT00827034, NCT00990613, NCT00824590, NCT00931073, NCT00831506, NCT00788047, NCT00825084), however, the only published reports are these referred to above.

Drugs only tested in HD rodent or cell models

Cystamine & 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine blockers

Cystamine prevents depolarization of mitochondria, and therefore cell death, in cell cultures derived from rodent HD models. Cystamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine blockers inhibit oxidative damage, as well as increase survival of HD-derived cells [8,64]. According to clinicaltrials.gov, there are currently no human studies testing this drug.

Meclizine

Meclizine, a drug that silences oxidative metabolism and suppresses apoptosis, has shown to be neuroprotective in *Drosophila* models. Since energy metabolism deficits and neuronal degeneration are hallmarks of HD, treatment with meclizine is a potential strategy, especially since it crosses the blood–brain barrier [8,73]. There are no human clinical trials listed in clinicaltrials.gov.

Conclusion on drugs targeting mitochondrial dysfunction

Many of the drugs targeting mitochondrial function have shown success in mice HD models, but minimal promise in human trials, possibly related to dosing issues, trial length or failure to demonstrate target engagement. Human trials to date have been disappointing.

Drugs targeting transcriptional dysregulation

Transcriptional dysregulation is characteristic of HD pathology, and occurs relatively early in the disease. mHtt interacts with transcription factors and decreases histone acetylation and increases histone methylation [66]. Targeting these transcriptional changes can be achieved by interacting with either histone deacetylase (HDACs) or DNA directly, with a potential therapeutic benefit [8,123].

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

None.

Drugs in clinical trials, but failed to show efficacy

Lithium & valproate

The mood stabilizers valproate and lithium have shown to be beneficial in HD mouse models. Lithium and valproate have neuroprotective effects and inhibit glycogen synthase kinase 3 and HDACs, respectively. Lithium and valproate improved motor dysfunction and anxiety-related behaviors in N171-82Q and YAC128 mice models. The drugs also increased striatal and cortical BDNF and Hsp70 and extended survival. The drugs were most effective in these measures when given together [124]. There have been human studies investigating the use of lithium and valproate individually in HD. These studies have mixed results as to whether these drugs improved

motor behavior in HD patients. Scheuing *et al.* highlighted the limitations of these studies as having an absence of a control group, small sample sizes, short treatment duration, being unblinded and confounded by concurrent drug therapies [125]. A Phase II trial has been conducted using a combination of lithium and valproate to determine if they increase cerebrospinal fluid (CSF) BDNF in HD patients. No outcomes have been reported.

Drugs only tested in HD rodent or cell models

Suberoylanilide Hydroxamic Acid

Suberoylanilide hydroxamic acid (SAHA) increases histone acetylation in the brain (by inhibiting HDAC). SAHA improves motor impairments in R6/2 mice. Since SAHA crosses the blood–brain barrier and can be taken orally, it has therapeutic potential; however, this has not been tested in humans [65].

Sodium phenylbutyrate

Similarly, sodium phenylbutyrate is also an HDAC inhibitor. Administration of sodium phenylbutyrate to N171-82Q symptomatic mice showed less brain atrophy and extended survival rates. Sodium phenylbutyrate increased histone acetylation and decreased histone methylation in the rodent brain. Additionally, it downregulated caspases involved in apoptosis [66]. A dose-finding study was completed and sodium phenylbutyrate was determined to be safe and well tolerated in human HD subjects [126].

HDACi4b

HDACi4b (a pimelic diphenylamide HDAC inhibitor) has also been shown to improve motor impairments, as well as decrease neurodegeneration in mice models. Oral administration of HDACi4b to mice after the onset of motor symptoms 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 has been seen in the presence of mHtt, and mRNA expression levels were returned to normal levels [67]. There are no documented trials on clinicaltrials.gov.

Mithramycin

Mithramycin is a clinically approved G-C-rich DNA-binding antitumor antibiotic. It binds to Sp family transcription factors. Sp family transcription factors (1 and 3) activate the eta-related gene (ERG)-associated protein with suppressor of variegation, enhancer of zest and trithorax (SET) domain (ESET) promoter that mediates histone methylation. ESET expression is increased in HD patients. By binding to the Sp family, mithramycin is able to suppress the ESET promoter activity, in a dose-dependent manner. When combined with cystamine (see above), mithramycin decreased behavioral abnormalities and neuropathology in R6/2 mice. It extended the survival by over 40% [68]. Similar results were also found using chromomycin, a different type of anthracycline. Both mithramycin and chromomycin were seen to restore the balance between methylation and acetylation in HD mice models, increasing gene transcription [123]. There are no clinical trials listed on clinicaltrials.gov.

Conclusion on drugs targeting transcriptional deregulation

Several of these drugs focused on DNA modification via methylation and acetylation have demonstrated efficacy in rodent and fly HD models. Unfortunately, well-designed clinical trials are lacking.

Drugs targeting mHtt production

mHtt can be suppressed by targeting the *mHtt* mRNA by three potential mechanisms: RNAi (which cleaves *mHtt* mRNA); ASO (which blocks *mHtt* translation or induces RNase-H-dependent degradation of the *Htt* transcript); targeting the protein product with synthetic peptides or antibodies for mHtt [127].

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Antisense oligonucleotides

ASOs can be delivered to the brain *in vivo*. As reported in a press release from Ionis Pharmaceuticals on 11 December 2017, a Phase I/IIA dose-dependent clinical trial of early stage HD patients with intrathecal injection of ASOs has been completed. The safety results support continued development of this drug. Ionis reports the study showed a dose-dependent reduction in mHtt in the CSF of HD patients, although the complete results have not been

published [128]. It is possible that mHtt can be reduced without altering normal *Htt* mRNA, by exploiting differences in RNA sequence between normal and mutant *Htt*. This can be done through ASOs and other RNA interacting drugs (e.g., locked nucleic acids) [129,130]. Kordasiewicz *et al.* suggest that in rodent and nonhuman primate models *mHtt* RNA can be reduced independently of changes in wild type *Htt* RNA. Importantly, ASO-mediated disease reversal persists for longer than suppression of the Htt protein [28].

WVE-120101 and WVE-120102 bind *mHtt* mRNA, thereby decreasing its production. WAVE Life Sciences has been able to identify pure stereoisomers, which may have additional benefits, as compared with a mixture of stereoisomers. It is not currently clear how pure stereoisomers differ from mixed stereoisomers in their efficacy or delivery. WAVE Life Sciences is investigating whether certain genotypes of early manifest HD patients will respond differently to these ASO compounds. Ongoing Phase I safety trials are being conducted [29].

Drugs in clinical trials, but failed to show efficacy

None.

Drugs only tested in HD rodent or cell models

RNAi

RNAi directly reduces abnormal, diseased gene expression, that is, *mHtt*. In cell culture and HD mouse model brains, RNAi (targeted for *mHtt*) decreased *mHtt* RNA and protein. Behavior was improved, and neuropathology lessened. One potential drawback for RNAi therapy is that RNAi can target both the *mHtt* mRNA and the normal *Htt*, which is required for normal function [3].

Antibodies

Happ1, an intracellular antibody (intrabody) that recognizes the proline-rich domain of *Htt* and targets it with high specificity and affinity. Happ1 improves motor function, cognitive impairments and neuropathological symptoms in several mouse models (e.g., R6/2, N171–82Q, YAC128 and BACHD). Another intrabody, V(L)12.3, that recognizes the N terminus of *Htt*, had less beneficial results and did not work in all mouse models [69].

Proprietary trans-gene

VY-HTT01 is a proprietary trans-gene delivered directly into the brain by adeno-associated virus that reduces the production of *mHtt* mRNA. It has shown to be effective in animal models [71].

miRNA

AMT-130 is an adeno-associated virus vector that contains an artificial miRNA that silences *Htt*. This has been tested in rodents and the delivery system tested in nonhuman primates [72].

Conclusion on drugs targeting mHtt production

RNAi and ASOs are both exciting and promising new directions for targeting mHtt production. Further studies are needed to determine the efficacy of these treatments in humans.

Drugs targeting neuroinflammation

mHtt alters processes in the microglia and astrocytes, leading to chronic inflammation. This may contribute to the loss of neurons seen in HD pathology [131].

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

Anti- 4D (SEMA4D)/VX15/2503

SEMA4D is a transmembrane-signaling molecule that is involved in modulation of neurodegeneration, neuronal outgrowth cone collapse, differentiation and neuroinflammation. By blocking this molecule, CNS inflammation may be decreased and neuronal growth increased [36]. An antibody against SEMA4D, VX15/2503 targets inflammation and is currently in Phase II clinical trials in late prodromal and early manifest HD patients [37]. The encouraging preliminary results have been reported in *Huntington's Disease News* (April 2017) and a press release by Vaccinex, Inc. (April 2017). This randomized double-blind placebo-controlled clinical trial showed that

VX15/2503 treatment prevented the expected decrease in brain volume seen in the placebo group [38,39]. However, there are no published results indicating outcome measures or statistical significance of these initial findings.

Drugs in clinical trials, but failed to show efficacy

None.

Drugs only tested in HD rodent or cell models

Kynurenine inhibitors

A potential therapeutic target is kynurenine inhibitors. 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 hand, kynurenine also can be metabolized into kynurenic acid, which is neuroprotective. In HD, the normal balance between the neurotoxic products and neuroprotective products may be disrupted. Targeting the rate-limiting step of IDO1 could potentially shift the balance toward neuroprotective [74]. 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 significantly lower 3-HK levels in R6/2 mice microglia than in the vehicle-treated cells [75].

Conclusion on drugs targeting neurodegeneration

Many of the drugs targeting neurodegeneration are still in a hypothesis stage and need to be tested in rodents and humans. VX15 has shown some initial promise in human trials, but results still have not been published.

Drugs targeting cannabinoid receptors

Cannabinoid receptors (CBR) are usually present in high quantities in the striatum. In HD, CBRs are decreased early in the disease, even before the widespread atrophy of the striatum occurs.

Drugs approved for symptomatic treatment of HD

None.

Drugs with some demonstrated efficacy in clinical trials

None.

Drugs in clinical trials, but failed to show efficacy

Tetrahydrocannabinol & cannabidiol

R6/2 mice with CBR knockouts have accelerated development of clinical symptoms and brain inclusions. Cannabinoids improved symptoms, decreased brain atrophy and increased BDNF levels. A Phase II study investigating the safety and efficacy of δ-9-tetrahydrocannabinol and cannabidiol was conducted and found both products to be safe; however, no clinical or biomarker improvement was found. The authors suggest that higher doses or different ratios of tetrahydrocannabinol to cannabidiol merit study [70].

Drugs only tested in HD rodent or cell models

None.

Conclusion on drugs targeting cannabinoid receptors

The value of cannabinoid receptor-targeting drugs has not been adequately tested in rodents and humans.

Alternative, nondrug therapies

Fetal neural transplants

Given the marked striatal degeneration in HD, there have been attempts to transplant human fetal striatal neuroblasts into the striata of HD patients. Bachoud-Levi *et al.* found that not all patients initially benefited from the transplant, and even those that did, had a progressive decline 4–6 years after surgery [8,132–133]. Perhaps even more concerning, is that Cicchetti *et al.* found that the mHtt spread from the diseased brain into the normal fetal striatal grafts [134].

Diet

Studies have shown that the Mediterranean-type diet may delay onset of other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. A study recently investigated if the Mediterranean-type diet affects time to HD phenoconversion. The Mediterranean-type diet did not have an effect on phenoconversion. In fact, eating high amounts of dairy products was associated with a twofold increased risk of phenoconversation (after being adjusted for age and CAG repeat length). This may be due to lower urate levels, which have been shown to lead to a faster progression of manifest HD. These types of diet studies need further investigation [135].

Conclusion

HD is a dominantly inherited neurodegenerative disease that is ultimately fatal. It is caused by an abnormal expansion of CAG trinucleotide repeats in exon 1 of the *Htt* gene on chromosome 4. Motor, cognitive and psychiatric symptoms all occur in HD. Chorea and incoordination and rigidity are common motor symptoms due to neurotoxicity of the mHtt leading to brain atrophy of the striatum, thalamus, cerebellum, brain stem and the cortex. Identification of several novel biomarkers of disease progression allows for determination of the efficacy of new treatment strategies.

The current therapeutic investigations target different aspects of HD pathology and mainly aim to target excitotoxicity, the dopamine pathway, caspases, aggregation, mitochondrial dysfunction, transcriptional dysregulation, mHtt, neurodegeneration, fetal neural transplants, cannabinoid receptors and diet. Targeting the mHtt production, processing, folding and removal (e.g., autophagy) seems to have the greatest therapeutic potential for disease modification, including blocking its synthesis by ASOs or its removal with antibodies. These therapies have shown promise in mouse models with the advantage of not targeting the normal Htt. In fact, ASOs have shown to lower mHtt levels in the CSF in preliminary human studies.

Future perspective

Targeted therapeutics for HD based on a detailed understanding of HD pathophysiology are rapidly evolving. Combined with biomarkers that predict illness stage and progression, approved treatments for the motor, cognitive and psychiatric symptoms are anticipated. The most promising drugs are those that target the production of mHtt protein and its key role in HD pathophysiology.

Acknowledgements

The authors thank J Jankovic for his very helpful comments.

Financial & competing interests disclosure

KT Potkin received speaking honoraria from the National Institute of Neurological Disorders & Stroke and Teva Pharmaceuticals. This effort was in part funded by the US NIH through the following grants: Center for Protein Folding Machinery grant 5PN2EY016525 (SG Potkin), 5U24RR021992 (SG Potkin), the Undergraduate Research Fellowship (KT Potkin). The authors have no other 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 apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical considerations

This review included publically available data. The human studies referenced in the article all obtained appropriate institutional review board approval prior to initiating the studies.

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