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MOVEMENT DISORDERS (S FOX, SECTION EDITOR)

Huntington's Disease—Update on Treatments

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Abstract Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline, ending in death. Despite the discovery of the underlying genetic mutation more than 20 years ago, treatment remains focused on symptomatic management. Chorea, the most recognizable symptom, responds to medication that reduces dopaminergic neurotransmission. Psychiatric symptoms such as depression and anxiety may also respond well to symptomatic therapies. Unfortunately, many other symptoms do not respond to current treatments. Furthermore, high-quality evidence for treatment of HD in general remains limited. To date, there has been minimal success with identifying a disease-modifying therapy based upon molecular models. However, one of the emerging gene silencing techniques may provide a breakthrough in treating this devastating disease.

Keywords Huntington · Neurodegeneration · Chorea · Behavioral · Cognitive · Treatment

Introduction

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease characterized by progressive motor, behavioral, and cognitive decline. The disease results from a trinucleotide repeat expansion in the huntingtin gene (HTT) on chromosome 4 [1]. The gene product, huntingtin protein, is widely expressed and has many functions in human neurons. In the general population, there is an average of 17–20 CAG repeats in the HTT gene. With 40 or more CAG repeats, HD emerges with 100% penetrance. The typical age of disease onset is between 20 and 65 years; the disease progresses inexorably over an average of 20 years and is ultimately fatal. Management options at this time are limited, and there is still no therapy to slow the neurodegeneration or the overall rate of function loss. However, over the past decade, there have been many more clinical trials for symptomatic and potentially neuroprotective treatments. In addition, early human trials of gene silencing techniques are now underway. This paper reviews the current treatment landscape for HD, with an emphasis on recent clinical trials literature and on future directions.

HD is best understood as a combination of motor, cognitive, and psychiatric derangements. We consider each domain in turn, summarizing the typical symptomatic manifestations before exploring relevant treatments and trials.

Motor Symptoms

Although chorea is only a small part of motor dysfunction in HD, it is its most recognizable and treatable feature. Chorea often begins as fleeting, suppressible, random fidgety movements, seen best in the distal extremities. With time, chorea may involve more proximal muscles and even become ballistic. Severe chorea may result in exhaustion or falls. HD comprises many other motor phenomena, however. As the disease advances, chorea can actually "burn out" only to give way to motor phenomena that are more disabling and harder to treat. These include bradykinesia (slowness and reduced scaling of movement), dystonia (posturing and twisting), rigidity, and

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ataxia. Dysphagia contributes to weight loss and aspiration. Postural instability leads to falls, and serious injuries become increasingly common. Progressive motor failure is a major cause of life-ending complications.

Treatment of Motor Symptoms

Chorea

Many patients with chorea are neither aware of, nor impaired by, the involuntary movements. In these cases, reassurance and education (especially of family members) is important. Chorea only requires treatment when it impairs the patient's quality of life, function, or safety.

The predominance of chorea in early HD is explained by early preferential loss of striato-GPe neurons, key components of the indirect pathway. This initial dysfunction of the indirect pathway results in inhibition of the subthalamic nucleus, resulting in a hyperkinetic state [2, 3]. Reducing dopamine neurotransmission, either via presynaptic depletion or via D2 receptor blockade, has the net effect of reducing excessive movement. This is the key idea behind existing pharmacotherapy for chorea.

Tetrabenazine (TBZ) is the only medication currently FDA-approved for treatment of chorea in HD. TBZ reversibly inhibits the vesicular monoamine transporter 2 (VMAT-2) in the central nervous system. Since VMAT-2 packages serotonin, dopamine, and norepinephrine from the cytoplasm into presynaptic vesicles, its inhibition leads to premature degradation of these monoamines [4]. The resulting depletion of dopamine reduces chorea, while depletion of serotonin and norepinephrine may worsen depression and anxiety. Dosing TBZ can be tricky as some patients respond to small doses and others to much larger doses. Most of the studies start with 12.5 mg per day and up-titrate to a max dose of 300 mg per day or less; however, the degree of benefit is usually limited by side effects. Because of its short half-life, TBZ is dosed three times a day [5]. TBZ is metabolized hepatically via the CYP2D6 system, which is induced by fluoxetine and paroxetine. It is recommended that patients receiving more than 50 mg of TBZ per day be genotyped for CYP2D6, to enable dosage adjustments that minimize side effects. However, a retrospective review questioned the validity of this recommendation [6].

The best evidence for safety and efficacy of TBZ for HD-associated chorea is the TETRA-HD study and its open-label extension. TETRA-HD was the first randomized controlled trial (RCT) that showed a benefit for TBZ for HD chorea. Eighty-four patients with HD were randomized 2:1 to TBZ or placebo. The primary outcome was change in the Universal Huntington's Disease Rating Scale (UHDRS) chorea score after 12 weeks. A clinically significant mean difference of 5 points on the chorea score was identified between the groups. Adverse events in this study were notable for one suicide, increased suicidal ideation, and depression [7]. In the open-label extension study over 80 weeks, there was a high attrition rate, with only 45 of 75 participants completing. While significant chorea benefits were still seen, there was also a subsequent increase in extrapyramidal symptoms including parkinsonism and dysphagia (though the latter was generally mild). The most common side effect was sedation; but depression, anxiety, insomnia, and akathisia were also commonly reported. Three of the participants withdrew from the study as a result of neuropsychiatric symptoms including depression, delusions with associated suicidal behavior, and vocal tics [8].

Another long-term study of the efficacy and safety of TBZ followed 68 patients for an average of 3 years. The overall effectiveness of TBZ on chorea declined with longitudinal follow-up, despite a 60% increase in the mean dose. Drowsiness and depression were still the most commonly reported side effects, but overall TBZ was well tolerated with only 2 participants withdrawing due to severe side effects [9]. Kenney et al. also demonstrated that TBZ had long-term tolerability and efficacy in a diverse population with hyperkinetic movement disorders. In this study, all adverse effects were felt to be dose-related and decreased with dose reduction [6]. Discontinuation of TBZ has also been shown to be safe, but might worsen chorea [8, 10]. Another study of 98 patients with HD chorea treated with TBZ followed for a mean of 3.1 years reported three study participants with suicidal ideation and attempted suicide [11].

The above-mentioned results, in conjunction with the known depletion of serotonin and norepinephrine resulting from TBZ, prompted a black box warning for increased risk of depression and suicidality with this drug. While at least one subsequent observational study did not find an increased risk in TBZ-exposed patients [12], this drug should be avoided in patients with uncontrolled depression or with a history of suicidality. We note that depression and suicide are already common in the HD population and are often a much bigger problem than the involuntary movements. This, and the extreme cost of tetrabenazine in the USA at this time, argue against recommending TBZ as the first line for HD chorea.

Recently, a randomized, double-blind, placebo-controlled trial was published about the effect of deutetrabenazine (SD-809) on chorea in patients with HD. This is a novel molecule containing six deuterium atoms, or "heavy hydrogen", in place of typical hydrogen. Deuterium-carbon bonds require more energy for cleavage. This increases the half-life of the active metabolite so that fewer and lower doses are needed to obtain the same benefit. The hope is to decrease the unwanted side effects of sedation and akathisia that occur at peak doses and to optimize dosing for control of chorea. The study showed a significant decrease in the UHDRS chorea score and UHDRS total motor score in patients taking twice a day

deutetrabenazine when compared to those of placebo. There was no increase in depression, suicidal ideation, or sedation compared to that of placebo [13••]. While it is not surprising that this molecule could successfully suppress chorea, a head-to-head study versus standard TBZ is needed to demonstrate additional value of the deuterated form; for example, a meaningful decrease in side effects.

Although TBZ is FDA-approved and has better clinical trial evidence, the risk of depression is a serious concern. The neuroleptics, while off-label and less supported by trials, have a long history of use for HD chorea in the USA, and have the advantage of being adjuncts to treatment of depression and behavioral issues which are commonly seen in patients with HD. Antipsychotics have varying affinity for the D2 receptor, and thus vary in their ability to control chorea in patients with HD. It is important to recognize that they can all cause extrapyramidal side effects of parkinsonism, akathisia, and tardive movement disorders; as well as non-motor side effects like sedation, QT prolongation, and weight gain (may be beneficial in some HD patients).

The evidence for typical antipsychotics including haloperidol [14, 15], perphenazine [15], pimozide [16], and fluphenazine [17] consists of small, non-randomized studies that show mixed effect on chorea. The atypical antipsychotics have similarly poor evidence to support their use in patients with HD. A double-blind, placebo-controlled study of clozapine in 33 patients with HD showed dose-dependent improvement in chorea; but side effects were limiting and led to dose reduction and discontinuation in nearly half their participants [18]. A second, much smaller, open-label trial also showed improvement in chorea, and it was reported as being better tolerated [19]. The side effect profile including agranulocytosis and seizures is not favorable; weekly screening blood draws would be especially impractical in the HD population. Of the other atypical antipsychotics, several small, open-label trials showed a reduction in chorea with olanzapine [20–22]; and there is one-blinded, crossover study comparing aripiprazole to TBZ that showed comparable effect on chorea with less sedation [23]. Risperidone also has case reports to support improvement in involuntary movements and psychosis related to HD [24–26]; the same is true for quetiapine and ziprasidone [27, 28].

We feel that haloperidol, fluphenazine, risperidone, and olanzapine are all reasonable options. We do not recommend clozapine and quetiapine for HD chorea, for the same reason that they are less likely to worsen parkinsonism, as these drugs have the lowest affinity for D2 receptors. There is a stark absence of head-to-head studies or RCTs to otherwise help to guide their use. However, the best advice is to start low, and go slow, and switch to a different agent if problems develop.

The dopidines are a novel class of "dopamine stabilizers" in development. Their complex pharmacodynamics results in state-dependent effects on dopamine transmission. When dopaminergic tone is low, dopidines enhance transmission; when tone is high, they antagonize dopamine receptors, similar to antipsychotics [29]. The hope is that such drugs might improve other aspects of motor dysfunction in HD, instead of merely dampening chorea. One such molecule, pridopidine, has been tested with three randomized, double-blind, placebo-controlled trials. These studies showed that when dosed at 90 mg per day, there may be improvement in motor symptoms of HD, but not necessarily chorea; and there was no statistical improvement seen in functional outcomes [30, 31]. There are conflicting results regarding this drug's effect on cognition and behavioral symptoms [29–31]. This medication is well tolerated with a side effect profile similar to that of placebo, except for a potential increased risk of seizures [31]. While the antichorea effect is limited, the report of improvement in gait, balance, and dystonia is promising, as these are less responsive to other drugs. However, larger and more rigorous trials are needed to establish this drug as an advance in HD symptomatic treatment.

Other medications have been evaluated for use in treatment of HD-associated chorea, but results have been disappointing. Amantadine, an NMDA antagonist with poorly understood effects at dopaminergic synapses, has antidyskinetic properties in Parkinson disease, and thus might be expected to treat chorea in HD. There have been three small, randomized, placebo-controlled, crossover trials in addition to one open-label prospective study with varying results. There may be a potentially beneficial effect of treatment on hyperkinesia in HD [32–34], but no benefit was seen for cognition or behavior [32, 33]. Unfortunately, high doses of amantadine were required to attain symptomatic benefit for chorea, leading to intolerable side effects including hallucinations, confusion, insomnia, sleepiness, agitation, and anxiety [34, 35]. Riluzole, an antiglutamatergic drug posited to work by alleviating excitotoxicity, also failed to show improvement in chorea, behavioral and cognitive symptoms, and functional independence when compared to those of placebo in a large randomized 3-year study [36]. The Huntington Study Group looked at higher doses of riluzole and found a beneficial effect on chorea in participants receiving 200 mg per day; however, this was no longer significant when controlling for neuroleptic use. The most significant adverse effect was a dose-dependent elevation in ALT [37].

The last evidence-based medicine guidelines published in 2012 by the American Academy of Neurology for treatment of chorea in Huntington's disease cite strong evidence to support the use of TBZ in patients with HD, and weaker evidence for the use of amantadine and riluzole [38]. As mentioned earlier, we have other reasons to favor the use of antipsychotics for HD chorea. If antipsychotics and TBZ are not an option or have failed, then we would consider amantadine, followed by riluzole.

Deep brain stimulation (DBS) might be an option for some patients with medically refractory HD chorea. There are now multiple case reports and series in the literature demonstrating short- and long-term benefit of deep brain stimulation with bilateral internal globus pallidi (GPi) stimulation. The major side effects of stimulation are dystonia and bradykinesia; that may result from progression of the underlying disease or as a result of stimulation [39, 40•, 41, 42]. While chorea shows a significant and durable response to DBS, dystonia does not; so phenomenology should be carefully evaluated prior to surgery [39, 43, 44]. There are variable reports of functional improvement, but quality of life seems to improve with treatment [45]. In patients with medically intractable chorea with significant quality-of-life impairment, bilateral GPi DBS may be considered. However, recommendation for the neurosurgical treatment of HD patients should not be taken lightly. Chorea is the predominant phenotype for only part of the disease process, and over time the bradykinesia and dystonia predominate. Adequate education about the disease process for the patient and family member cannot be understated given the risks associated with brain surgery, especially in a population where the target is actively degenerating, and the potential benefit has a limited duration.

Other Motor Manifestations

HD encompasses many more motor problems than chorea. Unfortunately, treatment options for the rest of the motor disorder are limited and based on low-quality evidence.

Patients with onset of HD before the age of 20 are more likely to present with an akinetic-rigid syndrome known as Westphal variant HD. This presentation is relatively rare in adults, but several cases have been reported [46, 47]. In childhood, 65–85% of patients present with this phenotype, and it can be seen in up to 55% of those presenting as young adults. The predominant phenomenology is parkinsonism with dystonia. Treatment with levodopa [40•, 48, 49] and dopamine agonists [47, 50, 51] has shown a variable benefit in case reports. We favor levodopa over dopamine agonists in this population given the generally higher likelihood of behavioral side effects with the latter. Surgical management with bilateral GPi pallidotomy and DBS in this population has been tried with minimal and non-sustained effect [52, 53].

Cortical myoclonus is another uncommon phenomenon seen in juvenile more than adult onset HD. The myoclonus is stimulus- and action-sensitive; abnormalities may be seen on EEG. The speculated mechanism is due to deficiency in GABA, so these patients may respond to valproic acid or benzodiazepines [54–56]. Dystonia is common in HD, but no trials have assessed its treatment specifically in this context. Botulinum toxin might be useful for patients with severe or disabling focal or segmental dystonia.

Given the limited drug treatment options, exercise-based therapies might be of value in HD. Physical therapy (PT) can be very helpful in the earlier stages to evaluate and address gait impairment, imbalance, and falls. Occupational therapists (OT) can assist when motor dysfunction begins to interfere with activities of daily living. Therapists and social workers can recommend assistive devices and home modifications (e.g., grab bars, shower chairs) to enhance independence and safety. In addition to PT and OT for motor symptoms, speech pathologists can help at all stages of the disease process, with dysarthria and dysphagia. We recommend speech and swallow therapy before the onset of significant dysphagia, so that behavior and diet can be modified to reduce aspiration risk.

Cognitive Symptoms

Progressive cognitive disturbance is inevitable in HD. A large-scale prospective observational analysis of premanifest persons with HD showed that cognitive impairment can be measured before the motor manifestations, and the rate of decline increases as patients near motor onset of their disease [57], and eventually progresses to frank dementia. The cognitive effects of HD are underappreciated, as the dementia is subcortical with deficits in processing speed, attention, problem-solving, and memory retrieval; unlike the more striking defects of memory encoding, language, and visuospatial dysfunction seen in cortical dementias like Alzheimer's disease [58]. Therefore, traditional screening measures such as the Folstein Mini-Mental State Examination (MMSE) are less useful in HD. Patients tend to have poor insight into their deficits due to dysfunction of the frontal striatal connections [59], compounding safety concerns and family distress. Cognitive dysfunction in HD disrupts social and occupational function in the prime of these patients' lives, and we lack good treatment options for it at this time.

Treatment of Cognitive Symptoms

Despite their use in other dementias, there is little evidence to support the use of cholinesterase inhibitors or memantine in this population. Of the cholinesterase inhibitors, rivastigmine is possibly the best option. There are three small open-label studies which suggest improvement in cognitive testing after treatment with short- and long-term treatment with rivastigmine [60–62]. However, there has been criticism of these studies, because the MMSE is not felt to adequately capture the impairments in processing speed and frontal dysfunction that are common in patients with HD. There is one small, randomized, placebo-controlled trial with more rigorous cognitive testing that demonstrated a trend toward improvement in the recognition of verbal information in HD

patients on rivastigmine at 6 months [62]. There is even less evidence to support the use of donepezil [63].

The striatum receives a massive glutamatergic input from the cortex and thalamus, and thus it is postulated that at least part of the neurodegeneration in HD may occur as a result of excitotoxic damage. Memantine is a non-competitive glutamate receptor antagonist that stabilizes glutamatergic tone [64]. Despite its use in Alzheimer's dementia, there are no studies designed to assess memantine for cognition in HD. One small, open-label study suggested a potential neuroprotective effect following long-term treatment [65]; however, this finding has yet to be replicated.

Given the lack of good evidence for any of these drugs, we cannot recommend their routine use to enhance cognition in HD. Supportive measures, such as providing cues, minimizing multitasking, and allowing adequate time for cognitive tasks, should be emphasized.

Psychiatric Symptoms

Psychiatric disease is the third cardinal feature of HD and can also be the most bothersome for patients and their families. Dysfunction can manifest as a wide range of disorders from depression to psychosis. Depression, OCD, and other problems with emotion and behavior are likely related to degeneration in striatal circuits involving the frontal lobe and ventral anterior and medial dorsal nuclei of the thalamus [66]. Disinhibition and apathy in particular, might be due to dysregulation of the medial prefrontal, anterior cingulate, and anterior temporal paralimbic cortices [67].

As seen with cognitive symptoms, behavioral manifestations can start before the diagnosis of HD, and are invariably present in nearly all patients throughout the course of the disease, independent of motor and cognitive symptoms [66]. The exact prevalence of psychiatric symptoms is difficult to assess due to the small studies and variable definitions among studies. As with cognitive symptoms, the behavioral manifestations of HD become more prominent around the time of clinical diagnosis [68]. However, unlike cognitive symptoms, they are more amenable to treatment. It is important to recognize and treat behavioral manifestations of the disease, because the presence of psychiatric symptoms has been shown to be negatively correlated with daily functioning [68, 69].

Treatment of Psychiatric Disease

Depression and Suicide

In our experience, depression can be exquisitely responsive to treatment, yet it remains an undertreated component of the illness. In a review of the European HD cohort (REGISTRY) of 1,993 patients, only half of patients reporting moderate to severe depression were on medications for their symptoms [70]. Depression is the most common psychiatric symptom and occurs in 33–70% of patients with HD [70, 71]. This is most prevalent as these patients begin to lose independence, but then slowly decreases as the disease progresses.

A recent systematic review showed a lack of sufficient evidence to guide pharmacotherapy of depression in HD [72]. Three studies suggested a benefit of the SSRIs and the SNRI venlafaxine in this population. Of the SSRIs, fluoxetine and citalopram showed a trend toward improvement in the Hamilton Depression Rating Scale (HDRS), despite the samples comprising non-depressed individuals [73, 74]. Venlafaxine XR improved depressive symptoms after 4 weeks of treatment [75]; however, this study was uncontrolled and of short duration compared to that of typical trials in depression.

Despite this lack of published evidence, a common experience is that HD patients usually respond to standard treatments of depression, notably SSRIs. For refractory depression, atypical antipsychotics including olanzapine [21, 22], risperidone [76], aripiprazole [23, 77], and clozapine [78] have shown benefit in case reports and small open-label case series. In cases where adherence is an issue, one case series suggests that long-acting injections of risperidone are safe and may be effective [79]. ECT has also been shown to be effective in refractory HD depression [80–82].

Suicidality in the HD population is a serious problem. Patients with prior or current depression are more likely to attempt suicide. About 20% of HD patients in a very large cohort endorsed suicidal ideation, and the rate of attempted suicide might be as high as 10% [70, 83]. Compared to those of the general population, patients with HD have a 4–8 fold increased risk of completed suicide [84, 85]. This risk increases at motor symptom onset and when independence begins to decline [83]. Risk factors include lack of offspring, being single/divorced, living alone, suicide in other family members, no contact with other individuals with HD, and depression [85]. Anxiety, aggression/irritability, and prior alcohol abuse are also associated with higher risk of suicidal ideation [86]. As such, aggressive treatment of behavioral symptoms and support groups should be encouraged especially in patients who are isolated.

Other Behavioral Symptoms

Apathy is the lack of motivation with a decrease in goal-directed behavior that is separate from depressive symptoms. It is most prevalent in the advanced stages of the disease [70]. While less common than depression, it has been reported in about 50% of large cohort studies [66, 71]. There are no known effective treatments for apathy in HD. Medications that have been tried include bupropion, bromocriptine, and amoxetine, all without significant improvement [87]. As the

disease advances, if chorea is less a problem, we recommend considering a reduction in the dose of tetrabenazine or neuroleptics, as these drugs can blunt motivation.

Obsessive and/or compulsive symptoms can be seen in 10–50% of patients with HD [71], but information to guide treatment is only based upon case reports and expert opinion [88–90]. In a survey of HD experts, SSRIs and clomipramine were most frequently mentioned as the first-line therapies. Cognitive behavioral therapy was felt to be an option, but only for patients with mild or no cognitive dysfunction. For adjunctive therapy, the respondents most favored antipyschotics and mood-stabilizing antiepileptic drugs (AEDs), such as valproate, carbamazepine, lamotrigine, and topiramate [90].

Irritability and agitation occur in 38–73% of patients [71], and this wide range has been supported by other studies [66, 70]. Again, at this time, there are only case reports [91] and surveyed expert opinions to guide treatment. In milder cases without aggression, education of families and caregivers on trigger identification and behavioral strategies to avoid outbursts is key. In these cases, SSRIs may help. When there is coexistent impulsivity, aggression, or hypersexuality, then treatment with atypical antipsychotics and mood-stabilizing AEDs is recommended over that of SSRIs [92].

Psychosis and delusions are less common in HD and have been reported in 3–11% of patients [71] with a higher prevalence in later stages [70]. Atypical antipsychotics are recommended in these patients, but care should be taken to monitor for side effects [25, 93–95] as hypokinesia can intensify later in the disease.

Finally, cognitive and behavioral features of the disease may respond to a supportive, structured environment with routines and cues, whether or not medications are also used. HD affects young families and has a major impact on caregivers, so it is important to recognize and address caregiver burden early. Social workers are invaluable in helping these families and in identifying resources such as care assistance, respite, counselors, and financial sources of support.

Disease-Modifying Therapies in Huntington's Disease

Non-genetic Approaches

In the 20 plus years since the discovery of the Huntington's disease gene, there have been many attempts at disease modification based on likely functions of huntingtin and on theories of neuronal injury. Ideas have ranged from metabolic interventions to protect neurons, to gene silencing therapies. There is also an ongoing work looking for genetic modifiers that determine symptom onset [96, 97].

One obstacle is that we do not yet know the most important functions of the huntingtin protein (htt), or exactly how mutant huntingtin protein (mhtt) causes disease. Htt is important in embryonic development and survival, but after early development, its role is less clear [98]. There is evidence for a role in internal cell signaling, prevention of apoptosis, brain-derived neurotrophic factor (BDNF) production, and intra and intercellular transport [99]. Mhtt is thought to cause damage in HD through toxic gain-of-function mechanisms, and there is evidence that it causes transcriptional interference, cytoskeletal disruption, synaptic dysfunction, mitochondrial damage, excitotoxicity, accumulation of toxic aggregates, loss of BDNF, and changes in axonal transport [99, 100]. Several of these have already been pursued as targets for disease-modifying therapy, with mostly disappointing results and the recent human trials are summarized in Table 1. Neuronal dysfunction and death in HD are likely the end results of a complex combination of both gain and loss of these functions [100].

Genetic Approaches

Mutant huntingtin has so many complex pathologic effects that any single post-translational therapeutic approach, as described, is likely to be insufficient. The most exciting developments in the search for a disease-modifying treatment are those targeting the abnormal gene itself. Gene silencing techniques are now in active development in HD. These include down regulating or completely turning off transcription or preventing translation of the mutant gene. The most promising techniques for HD use antisense oligonucleotides or RNA interference (RNAi) mechanisms. These could mitigate the disease at the source, suppressing mutant mRNA prior to translation, reducing expression of the protein. However, it would be important to spare the normal allele, as wild-type huntingtin has important functions in development and cellular function, as discussed earlier.

Antisense oligonucleotides (ASOs) are small single-stranded molecules synthesized with a sequence complimentary to a particular disease-causing pre-messenger RNA (mRNA) or mRNA. One kind of ASO acts in the nucleus to bind pre-mRNAs, activating RNase H, an enzyme which degrades the message before it can be processed for translation. The ASO in this instance is not degraded, but is left free to bind subsequent pre-mRNAs. Other techniques involve ASO binding to mRNA in the cytoplasm and interfering with ribosomal translation via steric hindrance and other mechanisms [112]. Regardless, the idea is straightforward—if production of the abnormal protein can be curtailed, neurodegeneration might be slowed or arrested. In HD, it is possible to target an ASO to the CAG repeat, single nucleotide polypmorphisms (SNPs), or introns on the pre-mRNA [113, 114•]. Recent studies using ASO showed reduced mhtt production in human

Table 1 Non-genetic approaches to Huntington's disease-modifying treatment trials

Mechanism	Treatments	Results
Decrease reactive oxygen species	Creatine (mitochondrial function)	No effect in large human trial [101]
	Coenzyme Q10 (mitochondrial function)	No effect in large human trial [102]
	PBT2 (prevention of copper and zinc aggregation)	Failed phase II, safe, improved trials B subscore [103]
Increase mhtt clearance	Selistat (SirT1 inhibitor)	No cognitive or motor effect, slowed increase of soluble *mhtt* [104, 105]
	Cysteamine (transglutaminase inhibitor)	Unpublished human data, trend toward slower motor decline [106]
Increase BDNF	Glatiramer	Increased BDNF in mice, human trials ongoing [107]
	Resveratrol	Conflicting animal results [99, 108, 109]
Decrease neuronal excitotoxicity	Lamotrigine	No effect on progression, symptomatic improvement in chorea [110]
	Riluzole	No effect over 3 years [36]
Mitochondrial protection	Minocycline	No effect in futility trial [111]

fibroblasts [115, 116] and improved HD-like pathology and motor symptoms in mouse models [117–119]. These targeted both intronic and exonic SNPs that were generally very selective to the mutant allele and had little effect on the wild-type htt production. Several of these experiments also noted continued decrease in mhtt production even months after the last treatment.

There are potential stumbling blocks. ASOs directed at the HD CAG repeat may suppress other genes with similar repeats, especially if the pathogenic allele contains less than 40 repeats. Multiple ASOs targeting SNPs would need to be used to adequately target the abnormal allele and still would only cover approximately 80% of patients [113]. Another possibility is personalized ASOs based on the patient's specific mutation and SNPs, although an FDA protocol for this type of personalized treatment is not fully in place. Additionally, ASOs do not cross the blood-brain barrier in their current formulations and need to be administered intrathecally. They do enter the neurons and their nuclei without a vector [98, 113]; but it is uncertain how much can reach the human striatum if given via lumbar puncture [120]. There is precedent for this delivery method in humans for SOD1-associated ALS [121]. There is an ongoing early phase trial of an intrathecal *htt*-directed ASO by Ionis pharmaceuticals that has not reported results yet [122].

RNA interference uses small interfering RNA (siRNA) or micro RNA (miRNA) molecules to target mRNA for degradation prior to translation by activating the RNA-silencing complex and cleaving the target. As these are short sequences, they cannot reliably degrade only mutant mRNA. However, they can target single nucleotide polymorphisms found in some Western and European HD populations [123•, 124]. Combinations of several siRNAs would be needed to selectively target mutant *htt* without those polymorphisms. Single-stranded RNA (ssRNA) can work in a similar fashion to siRNA and is longer and more stable, but may only work with very long CAG repeats (over 100 in mouse models), not found in human populations. In the YAD128 HD mouse model, intrastriatal injection of an adeno-associated virus vector with HTT-silencing miRNA produced a 50% reduction in HTT mRNA and protein, transduced approximately 80% of the striatum, and improved motor performance [125]. A major current limitation of RNAi is that they cannot enter cells in a naked state; hence the need for a viral vector. Currently, the technique requires injection to both striata, and it is uncertain how far they can diffuse within the living human brain parenchyma. They are broken down much quicker than ASOs, which could reduce the potential for harm, but also require repeated treatments. There have been two human trials using this approach already, for other diseases [126, 127].

Two other approaches of genetic modification have been proposed but not tested in humans. The first, zinc finger proteins (ZFPs), can be targeted to the CAG repeats in HD suppressing its expression. By virtue of the repeat's proximity to the 5′ end of the HTT gene, the ZFPs are selective to HTT without cross-suppressing other poly-CAG-containing genes [120]. In R6/2 mouse models, it decreased production of both the mutant protein and mRNA by 95 and 78%, respectively [128]. However, this protein would also need to be virally delivered into target cells. The other approach uses the relatively recent development of CRISPR-Cas 9 to edit out the mutation at the genome level, completely silencing the gene. However, neither of these approaches have been clinically attempted [123•].

Conclusions

Despite the discovery of the underlying genetic mutation of Huntington's disease more than 20 years ago, we are still limited to treatments that only address the symptoms and not the illness. Furthermore, existing symptomatic therapies are woefully insufficient. Chorea clearly responds to drug therapy, but other motor problems do not. Some psychiatric symptoms respond well to drug therapy, but dementia does not. There are many promising avenues to treatment on the horizon, such as gene silencing techniques. Hopefully, within the next 20 years,

we will have discovered an effective way to modify or cure this devastating illness.

Compliance with Ethical Standards

Conflict of Interest Andrew J. Ridder declares no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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