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REVIEW

Treatment of Huntington's Disease

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Abstract Huntington's disease (HD) is a dominantly inherited progressive neurological disease characterized by chorea, an involuntary brief movement that tends to flow between body regions. HD is typically diagnosed based on clinical findings in the setting of a family history and may be confirmed with genetic testing. Predictive testing is available to family members at risk, but only experienced clinicians should perform the counseling and testing. Multiple areas of the brain degenerate, mainly involving the neurotransmitters dopamine, glutamate, and γ-aminobutyric acid. Although pharmacotherapies theoretically target these neurotransmitters, few well-conducted trials for symptomatic interventions have yielded positive results and current treatments have focused on the motor aspects of HD. Tetrabenazine is a dopamine-depleting agent that may be one of the more effective agents for reducing chorea, although it has a risk of potentially serious adverse effects. Some newer neuroleptic agents, such as olanzapine and aripiprazole, may have adequate efficacy with a more favorable adverse effect profile than older neuroleptic agents for treating chorea and psychosis. There are no current treatments to change the course of HD, but education and symptomatic therapies can be effective tools for clinicians to use with patients and families affected by HD.

Key Words Huntington's disease · Chorea · Tetrabenazine · CAG repeat disorders · Movement disorders · Subcortical dementia

Introduction

Huntington's disease (HD) is a hereditary, progressive neurodegenerative disease clinically characterized by abnormal involuntary movements, behavioral disturbance, cognitive dysfunction, and psychiatric disease. The disease is caused by a CAG (glutamine) trinucleotide expansion in exon 1 of the huntingtin (*htt*) gene at the location 4p16.9 [1]. The normal function of *htt* is not known, but it may be involved in internal cell signaling, maintenance of cyclic adenosine monophosphate response element binding protein, and preventing neuronal toxicity [2]. Early evidence suggests that the binding of the Ras homologue enriched in striatum protein to mutant *htt* (*mhtt*) may be necessary to cause cellular toxicity [3]. However, why the protein causes cellular toxicity in adulthood is not well understood. There is evidence suggesting that the interaction of the group 1 metabotropic glutamate receptors and *mhtt* protein may be at the root of delayed onset [4].

Although there is no established treatment to delay the onset or forestall the progression of HD, symptomatic treatment of chorea based on the neurochemical pathology known may be beneficial in some individuals, as it may have a favorable effect on motor function, quality of life, and safety [5–7]. Clinicians may also consider treatment for dystonia, other movement disorders, and non-motor aspects of HD.

Pathologically, HD is associated with diffuse loss of neurons, particularly involving the cortex and the striatum. Medium spiny neurons in the striatum that contain γ-aminobutyric acid and enkephalin are affected early in the disease, and are the primary neurons targeted in HD. These neurons typically project into the lateral globus pallidus. Over time, the degenerative process progresses to involve the remainder of the basal ganglia with subsequent dissemination, including cortex and substantia nigra. Intranuclear and cyoplasmic inclusions of the *mhtt* aggregate can be demonstrated microscopically. Huntingtin is cross-linked with other soluble *mhtt* to form the inclusion bodies in neurons. It is not known if the accumulation of *mhtt* conglomerate results in cell death, or if the soluble form of the protein is the toxic form [8, 9]. Dopamine, glutamate, and γ-aminobutyric acid are thought to be the most affected neurotransmitters in HD and are currently the focus of pharmacotherapy (Table 1) [10–23].

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Table 1 Neurotransmitters involved in the pathogenesis of Huntington's disease

Receptor	Location	Stage of disease
Adenosine A2A	Striatum, GPe	Preclinical to advanced
Cannabinoid	Striatum, GPe	Preclinical to advanced
Dopamine D_1	Striatum, substantia nigra	Clinical diagnosis to advanced
Dopamine D_2	Caudate, putamen	Prodromal
Dynorphin	Striatum	Emergence of dystonia
Enkephalin	Striatum	Emergence of chorea
GABA	Striatum	Advanced
Glutamate	Cortical	Preclinical to advanced
Substance P	Striatum	Emergence of dystonia

GPe = globus pallidus externa; GABA = γ-aminobutyric acid.

There are multiple theories on the pathogenesis of HD. It is likely that more than one process may be occurring at once, but there is evidence to support multiple individual mechanisms, including toxic neuronal aggregates, transcriptional dysregulation, excitotoxicity, mitochondrial dysfunction with altered energy metabolism, and changes in axonal transport and synaptic dysfunction (Table 2) [24–30].

Most European populations show a prevalence rate of 4–8 cases per 100,000 [31–33]. HD is notably rare in Finland and Japan, but data for Eastern Asia, Africa and Black Americans are inadequate [34]. There are well-known large populations of patients with HD in Scotland and the Lake Maracaibo region of Venezuela [35, 36]. There have been no widespread epidemiologic studies of HD in the USA since genetic testing became widely available in 1993, but it is estimated that approximately 25,000–30,000 individuals have manifest HD and a further 150,000–250,000 individuals are at risk for HD [37].

Table 2 Potential pathways for pathogenesis of Huntington's disease (HD)

Neuronal aggregates
Neuronal intracytoplasmic and intranuclear inclusions containing mutant huntingtin, truncated N-terminal mutant and wild-type fragment, and chaperones and components of the proteolytic pathway are characteristic of HD neuropathology
Accumulation of mutant protein aggregates may be a result of impairment of the ubiquitin–proteosome pathway
Autophagic mechanisms are implicated in the clearance of protein aggregates
Transcriptional dysregulation
Aberrant nuclear localization of mutant toxic huntingtin fragments and their association with transcription factors
Dysregulation related to entrapment of transcriptional factors in protein aggregates
Excitotoxicity
Excitotoxic neuron death in HD could result from a combination of increased glutamate and glutamate agonist release from cortical afferents
Mitochondrial dysfunction and altered energy metabolism
Selective inhibitors of complex II of the mitochondrial electron transport chain, 3- nitropropionic acid, and malonate, cause selective striatal neuronal loss similar to that seen in patients with HD
Multitude of bioenergetic defects have been reported in patients with HD
Changes in axonal transport and synaptic dysfunction
Normal huntingtin plays a role in axonal trafficking
Disruption of axonal transport contributes to pathologic process in HD

Men and women are affected equally, and typically become symptomatic in the third and fourth decades of life. The symptoms of HD can start at any age ranging from 1 to 90 years. Approximately 5–10 % of cases are classified as juvenile onset, with symptoms starting before the age of 20 years. The vast majority of juvenile cases are inherited paternally, and instead of chorea patients may exhibit more parkinsonian signs of bradykinesia, dystonia, tremors, and cognitive deficit [38]. When patients exhibit more hypokinetic features (bradykinesia and dystonia) than hyperkinetic features (chorea), they are said to have the Westphal variant of HD.

HD is diagnosed based on the presence of typical motor findings commonly in the setting of a family history of the disease. There may be other manifestations of HD at the time of presentation or prior to diagnosis based on personality changes or behavioral and cognitive symptoms. A DNA test showing abnormal CAG expansion in the *htt* gene can be used to confirm the diagnosis in symptomatic individuals. With proper genetic counseling and at the patient's request, DNA analysis can be performed in individuals at risk for developing HD under the care of experienced clinicians.

The course of the disease is typically 15–20 years, with dementia, mutism, dystonia, and bradykinesia predominating in advanced disease. Patients with more dystonia and swallowing issues may experience accelerated complications and, therefore, shorter lifespan. Chorea may become a safety issue with larger amplitude movements causing injury or poor positioning. Frequent movements may result in skin injuries, infections, or even fractures and head trauma. Cause of death is typically related to complications of immobility, such as skin breakdown, pneumonia, cardiac disease, or infection. However, 25 % of patients attempt suicide, which is a cause of death in 8–9 % of patients [39].

Behavioral dyscontrol can be a severely disabling symptom of HD causing distress to the patient, family, and caregivers. Environmental approaches and cognitive interventions are the mainstay of treatments, but pharmacological agents can augment addressing disruptive behaviors. Depression, anxiety, aggressive, impulsive, and obsessive–compulsive behaviors are also frequently treated pharmacologically and require behavioral intervention, but caution should be used to avoid oversedation and apathy, already common in patients with HD. Although not well-studied, cognitive approaches to

treat behavior may be more effective than pharmacotherapy for some aspects of the disease [40]. There have been few clinical trials to examine the effect of agents for cognition in HD such as donepezil, rivastigmine, and atomoxetine. None of the trials to date have demonstrated significant improvement [41–43]. Recent advances in the cognitive aspect of HD have focused on finding improved methods of diagnosing and tracking changes over time [44].

Pharmacological Treatment Options

Many agents and surgical procedures have been evaluated in HD for their efficacy in suppressing chorea, including dopamine-depleting agents, dopamine antagonists, benzodiazepines, glutamate antagonists, acetylcholinesterase inhibitors, dopamine agonists, antiseizure medications, cannabinoids, lithium, deep brain stimulation, and fetal cell transplantation [45–48]. Pharmacological interventions typically address the hyperkinetic movement disorders that may be associated with HD, such as chorea, dystonia, ballism, myoclonus, and tics. When choosing an intervention, providers should consider if there will be a positive or negative effect of the agent on psychiatric issues associated with HD, such as irritability, depression, anxiety, mania, apathy, obsessive–compulsive disorder, or cognitive decline. Adjunctive therapies, alternative and complementary therapies, behavioral plans, and cognitive interventions also may play a role in addressing the symptoms of HD and need to be considered when choosing medications.

Chorea

Several reviews have summarized the symptomatic treatment of chorea associated with HD [49–61]. Overall, there is not enough evidence available to guide long-term symptomatic treatment in HD, and double-blind and long-term studies assessing various treatment strategies in HD are needed [55]. Despite the lack of evidence, an American Academy of Neurology Guidelines publication was recently released recommending consideration of tetrabenazine (TBZ), amantadine, or riluzole if chorea requires treatment [46]. A Cochrane review of studies for the symptomatic treatment of HD examined 22 trials that involved 1254 different participants [56]. Nine trials had a crossover design and 13 were conducted in parallel. The studies examined were of relatively short duration, ranging from 2 to 80 weeks. The number of trials examining various pharmacological interventions included antidopaminergic drugs (n=5), glutamate receptor antagonists (n=5), and energy metabolites (n=5). Based on available evidence, the authors of the Cochrane review concluded that only TBZ showed clear efficacy for the control of chorea, but "no statement can be made regarding the best medical practice for the control of motor and non-motor symptoms in HD".

TBZ is the only US Food and Drug Administration-approved drug for HD, indicated for the treatment of chorea associated with HD. Previous publications have reviewed the chemistry, pharmacodynamics, pharmacokinetics, and mechanism of action [47]. There is a recent review of the development and uses of tetrabenazine [62]. By reversibly inhibiting the central vesicular monoamine transporter type 2, TBZ more selectively depletes dopamine than norepinephrine [48, 63]. The highest binding density for TBZ is in the caudate nucleus, putamen, and nucleus accumbens, areas known to be most affected in HD [64, 65]. Vesicular monoamine transporter type 2 binding and monoamine depletion by TBZ are reversible, last hours, and are not modified by long-term treatment [66, 67].

The efficacy of TBZ as an antichoreic drug was convincingly demonstrated in a double-blind, placebo-controlled trial conducted by the Huntington Study Group [68]. TBZ was titrated weekly in 12.5-mg increments to a maximum of 100 mg/day or to the development of intolerable adverse effects. Compared with baseline, TBZ treatment resulted in a reduction of 5.0 Unified Huntington Disease Rating Scale (UHDRS) total maximal chorea units compared with a reduction of 1.5 units in the placebo group. There is also evidence to suggest continuous long-term efficacy and tolerability of TBZ in patients with HD [69–72].

In the same study, the adverse events that occurred significantly more frequently in the TBZ group included drowsiness or somnolence, insomnia, depressed mood, agitation, akathisia, and hyperkinesia. However, by the conclusion of the maintenance phase, when patients were presumably on optimal dosage, there were no significant differences between TBZ and placebo. Potential side effects include akathisia, depression, dizziness, fatigue, or parkinsonism. During titration, patients may experience insomnia, somnolence, or gastrointestinal distress.

There was one completed suicide in the double-blind study in a subject taking TBZ. Depression is common in HD and can be exacerbated by TBZ. However, attempted or completed suicides in HD do not necessarily correlate with severity of depression, and other associated factors need to be considered, such as impulsiveness, obsessive–compulsive behavior, and socioeconomic factors. Nevertheless, all patients taking TBZ need to be monitored for signs of depression and suicidal ideation. In a follow-on, open-label, extension study, no new adverse effects were reported, and the drug was well tolerated, with an average chronic total daily dose of 62.5 mg.

When using TBZ in doses higher than 50 mg/day, the Xenazine product insert states that "patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer or an extensive metabolizer" [73].

However, clinically, there is little need to consider genotyping aside from the need for a longer titration in ultra-rapid metabolizers, and there are no distinguishing features of patients with various CYP2D6 genotypes [74].

Other medications that are commonly considered when treating chorea include dopamine antagonists, benzodiazepines, and glutamate antagonists. Dopamine antagonists (neuroleptics) are perhaps the most commonly considered agents in the management of chorea and psychosis in patients with HD, but few double-blind, placebo-controlled studies evaluating the efficacy and safety of these agents have been published [75–77]. None of the typical neuroleptics have been found to be effective in reducing chorea in placebo-controlled trials. However, in a study of haloperidol in 10 patients, oral doses of 1.5–10.0 mg/day corresponded with at least a 30 % reduction in chorea compared with baseline [78]. The quantity and quality of these efficacy data need to be taken into account when considering the risks of using typical neuroleptics, particularly tardive dyskinesia. Apathy and akathisia, other potential adverse effects of the dopamine receptor blockers, can be particularly problematic in patients with HD, as they may not have the insight to recognize these problems or may wrongly attribute the symptoms to HD.

Owing to their presumed improved tolerability, atypical neuroleptics have recently been evaluated in HD. Olanzapine has been used in small open-label studies to treat the motor symptoms of HD [79–83]. The range of effect on chorea has been a reduction of 0–66 %. There are no clinical trials of risperidone for HD, but a few reports suggest a positive effect on the disease with a tolerable adverse effect profile [84–87]. Quetiapine has been tried in multiple, small, uncontrolled, nonrandomized trials for HD with some success on both motor and psychiatric symptoms of HD [88–90]. Clozapine was studied in patients with HD up to a dose of 150 mg/day for up to 31 days without benefit and significant adverse events, including drowsiness, fatigue, anticholinergic symptoms, and walking difficulties [91]. The newer atypical agent with multiple mechanisms of action, aripiprazole, has been found to be beneficial in a few small trials with a reduction in chorea equivalent to that with TBZ [92–94]. Although aripiprazole may have fewer adverse effects on mood than TBZ, it may be associated with akathisia and tardive dyskinesia, similar to other typical and atypical neuroleptics.

The N-methyl D-aspartate-antagonist amantadine has been shown in controlled trials to significantly reduce chorea in patients with HD [95]. Doses in the range of 400 mg/day or higher may be required for symptomatic benefit, but even in doses used to treat influenza, amantadine may increase irritability and aggressiveness [96]. Because riluzole retards striatal glutamate release and the pathological consequences in neurotoxic animal models of HD, multiple large trials have been conducted to determine if there is a possible neuroprotective effect. Although there was no clear neuroprotective effect found, riluzole significantly reduced chorea at a dose of 200 mg/day, but not 100 mg/day [97, 98]. Benzodiazepines are also frequently used clinically in patients with HD to treat anxiety and chorea, but there is limited evidence to suggest that higher doses of clonazepam (up to 5.5 mg/day) may be needed to suppress chorea [99]. At this dose, sedation becomes a potential adverse effect. In a few short-term studies (hours), there is evidence that dopamine agonists may reduce the motor signs of HD, vaguely defined as "abnormal involuntary movements" in 2 of the studies and a reduction in the UHDRS total motor score and abnormal involuntary movement scale (AIMS) with apomorphine infusion [100–102]. Although the pharmacological rationale for using dopamine agonists in the treatment of chorea is not clear, presumably they act by activating the presynaptic dopamine receptors leading to decreased dopamine turnover. More likely, however, is that the observed symptomatic effects are related to nonspecific or sedating effects.

The goal of any treatment to reduce chorea should be discussed with the patient and family. Chorea should be reduced to a point that is acceptable to the patient rather than to eliminate chorea completely or to reduce chorea to a level that is acceptable to the caregiver or even physician treating the patient. Because HD is a progressive disease that changes over time, the dose and use of medications need to be reassessed every few months. Considerations when choosing an agent to treat chorea are outlined in Table 3.

Parkinsonism

For patients with the akinetic form of HD (Westphal variant), antiparkinsonian medications, such as levodopa, dopamine agonists, and amantadine, may be beneficial [103–106]. Botulinum toxin injections can also be considered for focal dystonia associated with HD, both typical presentation

Table 3 Considerations when treating chorea pharmacologically

If the patient has troublesome chorea with:	Consider using:
No other symptoms	Tetrabenazine, amantadine, (riluzole)
Weight loss	Olanzapine, cannibinoids
Psychosis, aggression or impulsivity	Aripiprazole, haloperidol, olanzapine, risperidone, or other neuroleptic
Anxiety	Benzodiazepines
Depression	Aripiprazole and avoid tetrabenazine
Apathy	Amantadine or stimulating medications and avoid neuroleptics
Prominent dystonia	Amantadine, benzodiazepines, focal neurotoxin injection, and avoid neuroleptics
No response to pharmacotherapy	Deep brain stimulation

and Westphal variant. Even in patients with chorea, underlying dystonia and/or bradykinesia may be present and needs to be addressed.

Behavioral and Psychiatric Disturbance

There is a wide variety of behavioral and psychiatric issues that may be seen in HD, such as aggression, irritability, impulsiveness, depression, anxiety, apathy, mania, substance abuse, sexual dysfunction, and psychosis. Management outside of pharmacotherapy should be considered when possible, including environmental changes [40]. Although commonly used in HD for depression, anxiety, obsessive–compulsive disorder symptoms and apathy, there is no convincing evidence for the use of selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, or tricyclic or atypical antidepressant therapies in HD. Similar to other non-motor aspects of HD, treatment recommendations for irritability and obsessive–compulsive behaviors exist only as a paper-based opinion survey [107, 108]. Until better means of diagnosing cognitive issues in early HD can be established, it will be difficult to develop effective treatments for the cognitive aspect of HD.

Potential New Treatments

As of 2013, there are a number of ongoing or recently completed studies in HD (http://www.clinicaltrials.gov [109]). However, there continues to be a need for symptomatic agents, and no agent has been proven to change the course of disease. In addition, advanced HD continues to be understudied with a lack of efficacious treatment options. Recently completed studies that showed no to little benefit for cognitive or motor symptoms include latrepirdine (previously called dimebon) and ethyl-eicosapentaenoic acid [110, 111]. The dopamine-stabilizing agent pridopidine has been studied, and although there was not a statistically significant change in the Modified Motor Score, a subset of the UHDRS Total Motor Score, further studies are underway to determine if the compound may have a positive effect on overall motor function. Pilot studies to evaluate the safety and dosing of memantine and sodium phenylbutyrate have been completed (although not yet published), and larger studies to evaluate safety and efficacy are ongoing.

Currently under study is the compound PBT2, a metal chaperone compound that affects copper interactions with abnormal proteins. PBT2 is a drug designed to interrupt interactions between biological metals and target proteins in the brain, to prevent deterioration of brain cells. It has been shown in animal models, as well as in a small group of patients with Alzheimer's disease, that PBT2 may improve cognition. There is some indication in animal models of HD that the drug may improve motor function and control, and reduce the amount of brain cell degeneration. For symptomatic treatment, a deuterated form of TBZ, SD-809, is being studied to determine if there may be reduced peak dose side effects while delivering improved reduction in chorea.

Although beyond the scope of this review, the key to HD is to find an intervention that will delay onset (motor, cognitive, and other), slow progression, or reverse ongoing disease. To date, there are no effective interventions to do so. However, there are ongoing studies to evaluate supplements that may affect metabolism or mitochondrial function implicated in HD to potentially change the course of disease. The largest include the 5-year study of coenzyme Q10 (2CARE) and the 3-year study of creatine (CREST-E). The green tea extract polyphenon (2)-epigallocatechin-3-gallate is under study for its effect on cognition in patients with HD over a period of 12 months. With the introduction of medical cannabis in some states in the USA, research on this "supplement" should be considered as there is some evidence for cannabinoids in the treatment of chorea and irritability in HD [112].

There are a number of non-pharmacological interventions that are also being more formally evaluated. They may be considered adjunctive to pharmacotherapy, but may, nonetheless, be important as patients and families may have more control, and the interventions are already being used without supporting evidence. In addition, they are generally low-cost, low-risk, and easily accessible in most communities or at home. Some of the interventions include the use of music therapy, exercise, dance, or video game-playing, and most are examining the effect on gait and balance. On the other spectrum of interventions under study is the use of RNA interference to reduce the expression of *mhtt*. RNA interference may be delivered using a viral vector or through direct infusion into the basal ganglia, and both systems are under study, although not yet in humans.

In addition to treating those with manifest disease, if there are means of slowing the progression of disease, then patients who are gene-positive, but not yet manifest, may also benefit with a delay in the onset of disease. Currently, there are safety studies to evaluate the use of coenzyme Q10 (PREQUEL) and creatine (Pre-CREST) in a prodromal or premanifest population. It is likely that other studies will follow if an intervention that slows the progression of disease can be identified.

Conclusion

Until clear neuroprotective strategies are found, clinicians can address the symptoms of patients with this devastating disease. The most reliable evidence for treating troublesome chorea supports the use of TBZ; however, individual patients may respond to other drugs, and selection should be individualized. The presence of other motor dysfunction, cognitive

impairment, and behavioral symptoms all need to be considered when choosing therapies for patients. There is also some evidence for the use of riluzole and amantadine. Non-motor issues need to be studied further and treatment options need to be developed. Although there is one Food and Drug Administration-approved option at this time and other medications, hopefully, soon to be available, there are not enough effective, safe interventions that can be offered to our patients and their families at any stage during the course of this illness.

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