Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease

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Abstract: Huntington 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 those 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 or neuroprotective interventions yielded positive results. Tetrabenazine (TBZ) 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 antipsychotic agents, such as olanzapine and aripiprazole, may have adequate efficacy with a more favorable adverse-effect profile than older antipsychotic agents for treating chorea and psychosis. This review will address the epidemiology and diagnosis of HD as background for understanding potential pharmacological treatment options. Because TBZ is the only US Food and Drug Administration-approved medication in the United States for HD, the focus of this review will be on its pharmacology, efficacy, safety, and practical uses. 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.

Keywords: dopamine-depleting agent, neuroleptics, tetrabenazine

Introduction

Huntington 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 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 evidences suggest that the binding of the Ras homologue enriched in striatum (Rhes) protein to *htt* may be necessary to cause cellular toxicity.[3] However, why the protein causes cellular toxicity in adulthood is not well understood. Recent evidence suggests that the interaction of the group 1 metabotropic glutamate receptors and *htt* 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 may be beneficial in some individuals, as it may have a favorable effect on motor function, quality of life, and safety.[5–7]

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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 (GABA) and enkephalin are impacted early in the disease, and are the primary neurons targeted in HD. These neurons typically project into the lateral globus pallidus. Then, there is progression to the remainder of the basal ganglia with subsequent dissemination, including cortex and substantia nigra. There are intranuclear and cytoplasmic inclusions of the *htt* aggregate. Huntingtin is cross-linked with other soluble *htt* to form the inclusion bodies in neurons. It is not known if the accumulation of *htt* conglomerate results in cell death, or if the soluble form of the protein is the toxic form.[8,9] Dopamine, glutamate, and GABA are thought to be the most involved neurotransmitters in HD and are targeted for treatment (Table 1).[10–23]

There are multiple theories on the pathogenesis of HD. It is likely that more than 1 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).[24–30,31]

Epidemiology

Most European populations show a prevalence rate of 4–8 cases per 100,000, and HD may be frequently seen in India and parts of Central Asia.[32] More recent studies in other European nations have confirmed this prevalence rate.[33,34] HD is notably rare in Finland and Japan, but data for Eastern Asia and Africa are inadequate. Outside of Venezuela, there are little epidemiological studies of HD in Hispanic populations. A recent study found a slightly higher prevalence rate than expected and higher proportion of juvenile cases in Mexico.[35] There are also well-known large populations of

Table I Neurotransmitters involved in the pathogenesis of Huntington 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

Abbreviations: GPe, globus pallidus externa; GABA, γ-aminobutyric acid.

Table 2 Potential pathways for pathogenesis of Huntington disease

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-NP 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

Abbreviations: HD, Huntington disease; NP, nitropropionic acid.

patients with HD in Scotland and the Lake Maracaibo region of Venezuela.[36,37] The disorder may be underestimated in the Black American population. There have been no widespread epidemiological studies of HD in the United States since the wide availability of genetic testing, 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.[38]

Men and women are affected equally and typically become symptomatic in the third and fourth decades. 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.[39] When patients exhibit more hypokinetic features (bradykinesia and dystonia) vs hyperkinetic features (chorea), they are said to have the Westphal variant of HD.

Diagnosis

HD is diagnosed based on the presence of typical motor findings as measured by the Unified Huntington's Disease

Rating Scale 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 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. There are many reasons why patients request presymptomatic testing, including financial planning, family planning, insurance decisions, and the need to know. Some people at risk for HD are reluctant to undergo testing and are brought into the clinic by future spouse, family, or others who believe testing should be performed. Under these circumstances or if the at-risk individual is likely to harm themselves or others based on the outcome of the test, genetic testing should be reconsidered.

There are ongoing studies to examine individuals who are gene positive but not yet symptomatic by motor criteria (TRACK-HD, Neurobiological Predictors of Huntington's Disease Trial [PREDICT-HD], Prospective Huntington at Risk Observational Study [PHAROS]).[40–43] There is also a study currently enrolling subjects with HD and their affected and unaffected family members to further understand biomarkers of disease and signs of onset (Cooperative Huntington's Observational Research Trial [COHORT]).[44] The focus of the COHORT study is not neuroimaging and anatomical measures but rather clinical measures and biological samples.

Subtle motor abnormalities have been associated with a smaller striatal volume and higher probability of disease diagnosis.[40] Lower scores on the Hopkins Verbal Learning Test-Revised were associated with closer proximity to diagnosis and smaller striatal volumes.[44] Subjects with an expanded repeat and preclinical diagnosis of HD also had less accurate recognition of negative emotions.[45] In addition, motor exam score, striatal volume, speeded finger tapping, self-timed finger tapping, word-list learning, and odor identifications in subjects in the PREDICT-HD study were all associated with the predicted time to diagnosis.[46] Expansion-positive individuals reported more psychiatric symptoms (depression, anxiety, obsessive–compulsiveness) than expansion-negative individuals.[47] The TRACK-HD study has confirmed some and expanded upon findings in PREDICT-HD in that presymptomatic subjects had significant changes in whole-brain volume, regional grey and white matter differences, impairment in a range of motor tasks, oculomotor findings, and cognitive and neuropsychiatric dysfunctions. The various motor and nonmotor measures on the neurological examination used to diagnose and track HD are included in the Unified Huntington's Disease Rating Scale.[48] The scale is divided into 6 sections: motor, cognitive, behavioral, and 3 functional scales (total functional capacity, functional checklist, and the independence scale).

Based on the guidelines published by the American College of Genetics, patients with 40 or more repeats have 100% penetrance.[49] In other words, if patients have 40 or more copies of the gene, they will inevitably express the disease clinically. In patients with a CAG repeat length in the range of 36–39, there is reduced penetrance with increased likelihood of expression occurring with longer length of repeats and with longer lifespan of the patient. Although there are case reports of patients who manifest HD in this range, patients with fewer than 36 repeats will generally not develop clinical disease.[50,51] Patients with an allele repeat size of 27–35 have demonstrated meiotic instability, particularly in sperm, indicating that the following generation is at higher risk of inheriting an expanded number of repeats, increasing the risk of clinical disease. The length of repeat size correlates generally with the age of onset, but not necessarily with the severity or duration of disease.[52]

The course of the disease is typically 15–20 years, with dementia, mutism, dystonia, and bradykinesia predominating in end-stages. 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.[53]

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.[54]

Pharmacological treatment options

Many agents and surgical procedures have been evaluated in HD for their efficacy on 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.[55–58] Pharmacological interventions typically address the hyperkinetic movement disorders that may be associated with HD, such as chorea, dystonia, ballism, myoclonus, and tics. With regards to choose the agent, providers need to consider if there will be a positive or negative impact of the agent on psychiatric issues associated with HD, such as irritability, depression, anxiety, mania, apathy, obsessive–compulsive disorder, or cognitive decline associated with HD. 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.

Several excellent reviews have summarized the symptomatic treatment of HD.[55–67] 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.[61] A Cochrane review of studies for the symptomatic treatment of HD examined 22 trials that involved 1,254 different participants.[62] 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 tetrabenazine (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".

Tetrabenazine

TBZ is the only US Food and Drug Administration (FDA)-approved drug for HD, indicated for the treatment of chorea associated with HD. In addition to the United States and Canada, TBZ is marketed in Australia, Denmark, France, Germany, Ireland, Israel, Italy, New Zealand, Portugal, Spain, Switzerland, and United Kingdom. An excellent review of the chemistry, pharmacodynamics, pharmacokinetics, and mechanism of action is available in a previous issue of this journal.[68] By reversibly inhibiting the central vesicular monoamine transporter type 2 (VMAT2), TBZ more selectively depletes dopamine than norepinephrine.[69,70] The highest binding density for TBZ is in the caudate nucleus, putamen, and nucleus accumbens, areas known to bear the brunt of pathology in HD.[71,72] VMAT2 binding and monoamine depletion by TBZ are reversible, last hours, and are not modified by long-term treatment.[73,74] These features of the drug differentiate it from the other dopamine-depleting agent, reserpine. Reserpine binds to both VMAT1 and VMAT2. While VMAT2 is located solely in the central nervous system, VMAT1 is localized to the peripheral nervous system, accounting for some of the peripheral adverse effects, such as orthostatic hypotension and diarrhea. In contrast to TBZ, reserpine binds irreversibly to VMAT1 and VMAT2, making the duration of action considerably longer (hours vs days). In addition to TBZ, the 2 active metabolites, α- and β-dihydrotetrabenazine, have longer half-lives and are more highly bound to proteins than the parent compound.[75–77]

The efficacy of TBZ as an antichoreic drug was convincingly demonstrated in a double-blind, placebo-controlled trial conducted by the Huntington Study Group (HSG).[78] Subjects were randomized to receive either TBZ (n = 54) or placebo (n = 30). TBZ was titrated weekly in 12.5 mg increments to a maximum of 100 mg/d or to the development of intolerable adverse effects. The primary efficacy outcome was the change from baseline in the total maximal chorea score of the Unified Huntington's Disease Rating Scale.[48] On this scale, chorea is graded from 0 to 4 (with 0 representing no chorea) for 7 body regions for a range in total scores from 0 to 28. Compared with baseline, TBZ treatment resulted in a reduction of 5.0 units in chorea compared with a reduction of 1.5 units in the placebo group. About 50% of TBZ-treated subjects had a 6-point or greater improvement compared with 7% of placebo recipients. There is also evidence to suggest continuous long-term efficacy and tolerability of TBZ in patients with HD.[79–82]

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 subjects were presumably on optimal dosage, there were no significant differences between TBZ and placebo. Among subjects completing the study, the most common adverse event at the end of TBZ exposure was fatigue, reported by 7 subjects on TBZ (14.3%) and 2 on placebo (6.9%). There was 1 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 may be related to associated impulsiveness, obsessive–compulsive behavior, and a variety of socioeconomic factors. Nevertheless, all patients taking TBZ need to be monitored for signs of depression and suicidal ideation. Cognition in the TBZ group, as assessed by the Unified Huntington's Disease Rating Scale, did not differ from that in the placebo group statistically, although both groups declined as expected over the course of the study. There were no HD-related quality-of-life measures included in the published TBZ studies.

The same group of study participants was given the opportunity to participate in an open-label extension study.[82] Seventy-five subjects were elected to participate initially, and at the end of the 3 phases of the extension study, 45 subjects had completed 80 additional weeks of treatment with TBZ. In the extension study, no new adverse effects were reported, and the drug was well tolerated, despite the attrition rate in the study (mostly for logistical reasons). There are a number of older open-label studies, primarily out of the Baylor College of Medicine database.[80] The side effects and doses reported were fairly consistent with the double-blind study with the exception of insomnia. Chronic doses of the Baylor group were comparable with that in the long-term HSG study of 62.5-mg total daily dose.

The safety of TBZ was evaluated in these studies, and in an additional study, the safety of sudden withdrawal after long-term use was assessed. The side effects are consistent among studies, and once the drug is titrated slowly to effect, the drug is well tolerated. Potential side effects include akathisia, depression, dizziness, fatigue, or parkinsonism (Table 3). During titration, patients may experience insomnia,

Table 3 Treatment-emergent side effects to monitor for when using tetrabenazine

During titration
Insomnia
Somnolence
Gastrointestinal distress
During chronic therapy
Sedation
Depressed mood (and suicidality)
Anxiety
Insomnia
Akathisia
Fatigue
Agitation
Falls
Dysphagia
Dysarthria

somnolence, or gastrointestinal distress. If at any time side effects do occur, the dose can be lowered to the previously well-tolerated dose. Since the half-life is short, side effects tend to wane quickly. Withdrawal of TBZ results in a recurrence of chorea, not worse than before starting the drug.[83] There are no particular characteristics that may predispose patients to experience 1 or more side effects, but patients with a history of depression should be more closely monitored for changes in mood or impulsivity. Although it is listed in the product information sheet, TBZ does not cause and in fact may be an excellent treatment for tardive dyskinesia.

Other antichorea medications

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.[84–86] 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 subjects, oral doses of 1.5–10 mg/d corresponded with at least a 30% reduction in chorea compared with baseline.[87] 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 better tolerability, atypical antipsychotics have recently been evaluated in HD. Olanzapine has been used in small open-label studies to treat the motor symptoms of HD.[88–92] The range of effect on chorea has been 0%–66% reduction. 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.[93–97] Quetiapine has been tried in multiple, small, uncontrolled, nonrandomized trials for HD with some success on both motor and psychiatric symptoms of HD.[97–99] Clozapine was studied in patients with HD up to a dose of 150 mg/d for up to 31 days, but many adverse events, such as drowsiness, fatigue, anticholinergic symptoms, and walking difficulties, occurred without beneficial effects.[100] 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.[101–103]

Although aripiprazole may have fewer adverse effects on mood than TBZ, it is associated with 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.[104] Doses in the range of 400 mg/d or higher may be required for symptomatic benefit, but even in doses used to treat influenza, amantadine may increase irritability and aggressiveness.[105] 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. Riluzole was found to reduce chorea at a dose of 200 mg/d, but not 100 mg/d.[106,107] Benzodiazepines are also frequently used clinically in patients with HD to treat anxiety and chorea, and there is limited evidence to suggest that higher doses of clonazepam (up to 5.5 mg/d) may be needed to suppress chorea.[108] 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.[109–111] 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.

For patients with the akinetic form of HD (Westphal variant), antiparkinsonian medications, such as levodopa, dopamine agonists, and amantadine, may be beneficial.[112–115] Botulinum toxin injections can also be considered for focal dystonia associated with HD.

Practical uses of TBZ

TBZ is formulated in 12.5- and 25-mg tablets. The medication is not available at local pharmacies but must be ordered through a central distribution center. Prescription information can be found through the company's Web site, including prescribing information and obtaining the prescription form.[116] Clinicians should note on the form that patients (or their guardian) must sign the release of information for the pharmacy to be able to communicate with the patient's insurance company.

TBZ should be started at 12.5 mg/d, and every week, the dose should be increased by 12.5 mg/d, distributing the drug in 3-times daily dosing. Once patients reach twice-daily dose of 12.5 mg and daily dose of 25 mg (total daily dose of 50 mg), as per the prescribing information, "before patients are given a daily dose of greater than 50 mg, they should be

tested for the *CYP2D6* gene to determine whether they are poor, extensive, or intermediate metabolizers". This test can be costly (up to $3,000) and may or may not be covered by insurance. In addition, the drug is titrated to clinical effect, and the genotyping has no impact on the clinical assessment of the patient on the drug. Ultimately, it is up to the discretion of the provider with the patient to determine if this test should be performed.

The goal of the effect of TBZ is to reduce chorea to a point that is acceptable to the patient. The goal should not be to eliminate chorea completely or to reduce chorea to a level that is acceptable to the caregiver or even physician treating the patient. The most common scenario is the titration of the drug to a side effect and then reducing the daily dose to a tolerated dose. Because HD is a progressive disease that changes over time, the dose of TBZ needs to be reassessed frequently (every 2–3 months). TBZ interacts with other CYP2D6 inhibitors, such as paroxetine. There is no evidence if TBZ can be used safely or effectively with neuroleptics or other commonly used medications for chorea.

Conclusion

Until clear neuroprotective strategies are found, clinicians can address the symptoms of patients with this devastating disease. The most and best evidence for treating troublesome chorea leads toward TBZ, but other abnormal involuntary movements, cognition, affective disorders, and behavioral dyscontrol all need to be considered when choosing therapies for patients. Further studies to determine interactions and combination therapy of TBZ need to be completed, as most patients need multiple medications to adequately address symptoms. Other issues related to HD also need to be studied more closely when treating patient with TBZ. Although there is one FDA-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 with this invariably fatal disease.

Disclosure

The author reports no conflicts of interest in this work.

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