Therapeutic Approaches for the Treatment of Chorea in Huntington's Disease

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Huntington's disease (HD) is a complex condition that involves both motor and non-motor symptoms. The hallmark motor symptom is chorea, which can be suppressed with treatment. However, the potential benefits of treatment must be carefully weighed against the risks. Currently, three US Food and Drug Administration-approved medications are available for treating HD-related chorea: tetrabenazine, deutetrabenazine and valbenazine. While these medications can be effective in suppressing chorea, they have limitations. As a result, alternative classes of medications, such as antipsychotics, may also be considered when treatment of chorea is necessary, especially in the context of troublesome psychiatric symptoms. In this article, we review the literature supporting pharmacological and non-pharmacological therapies for HD. While chorea is only one of many symptoms in HD, effective suppression of troublesome chorea can reduce the burden on those affected by HD.

Keywords

Antipsychotics, chorea, dopamine, Huntington's disease, treatment, vesicular monoamine transporter 2 (VMAT2) inhibitors

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Huntington's disease (HD) is a neurodegenerative disease inherited in an autosomal dominant manner. It is caused by an expansion of cytosine, adenine, guanine (CAG) repeats within the huntingtin (*HTT*) gene, which is located on chromosome 4. This pathological expansion of CAG repeats results in the production of a mutant huntingtin protein with an abnormally long polyglutamine sequence.[1,2] CAG repeats ranging from 36 to 39 result in incomplete penetrance, while 40 or more repeats lead to complete penetrance of the disease.[3] The mechanisms linking the elongated mutant HTT protein to neurodegeneration in HD are not yet fully understood. However, several mechanisms have been proposed, including glutamatergic-induced excitotoxicity, dopaminergic dysfunction, mitochondrial dysfunction, oxidative stress, autophagy dysregulation and decreased trophic support.[4,5]

Dopaminergic transmission plays a key role in movement control. Within the striatum, the largest subcortical brain structure of the basal ganglia, dopaminergic communication takes place through two pathways: 'direct pathway' and 'indirect pathway'. These pathways function in opposition to each other to assist in evaluating and selecting motor movements. In simple terms, dopaminergic neurons expressing D1-like receptors are excitatory, while those expressing D2-like receptors are inhibitory. Neurons expressing D1-like receptors form the direct pathway by projecting to the globus pallidus internus (GPi)/substantia nigra pars reticulata. Conversely, neurons expressing D2-like receptors are part of the indirect pathway by projecting to the globus pallidus externus (GPe). Activation of the direct pathway facilitates or 'disinhibits' motor movement, while the indirect pathway suppresses motor activity.[6]

Pathologically, HD is marked by neurodegeneration of the striatum, particularly the loss of gamma-aminobutyric acidergic medium spiny neurons (MSNs), which project to either the GPi (direct pathway) or the GPe (indirect pathway). The loss of MSNs appears to follow a biphasic pattern. Initially, there is involvement of the indirect pathway, leading to hyperkinetic symptoms (e.g. chorea). This is followed by the involvement of the direct pathway, resulting in hypokinetic symptoms (e.g. bradykinesia).[7,8] With disease progression, the grey matter loss extends beyond the striatum.[7] These pathological changes lead to the clinical manifestations of HD, which is characterized by a classic triad of motor, cognitive and psychiatric symptoms.[9]

Motor symptoms

Motor symptoms in HD are characterized by involuntary movements and impaired voluntary movements. The hallmark motor symptom is chorea, which refers to involuntary movements that flow from one body region to another in an irregular pattern. Chorea can affect various body regions, including limbs, trunk, neck, face and tongue. Initially, subtle chorea may appear as fidgety movements. However, over time, chorea can evolve and increase in severity.[10,11] Previous studies have shown that chorea tends to increase during the early stages of HD, followed by a plateau and

possibly a decrease over time. However, there are limited longitudinal data on chorea severity across different stages of HD. A recent study found that chorea severity did not decrease over time at any stage of HD; instead, there was an increase in chorea severity during the early stages of HD, which plateaued in the middle and late stages.[12] As HD progresses, voluntary motor impairment becomes more pronounced, especially in the later stages.[13] Additional motor findings include bradykinesia, dystonia rigidity, gait impairment and postural instability, leading to an increased risk of falls.[2,14] Rigidity is frequently associated with dystonia in the limbs or trunk.[5]

Cognitive symptoms

Cognitive impairment is a prominent feature of HD. The deficits are primarily subcortical, with impairments in executive functioning such as organizing, planning, checking or adapting, and restrict the acquisition of new motor abilities with slowing of thought processing.[15,16] HD has been historically diagnosed according to motor criteria, i.e. the 'unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g. chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD'.[17] However, it is not uncommon that individuals with HD present with cognitive impairment prior to the onset of movement disorders.[18] Accordingly, a task force commissioned by the Movement Disorder Society to address research and clinical diagnostic issues in HD recommended that cognitive impairment should be considered in the clinical diagnosis of HD in addition to the movement disorder. In addition, the task force recommended the use of standardized *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*)-based criteria to diagnose neurocognitive disorder in HD and emphasized the importance of longitudinal ascertainment of cognitive disorder in HD.[19]

Cognitive difficulties in prodromal HD seem to become more prominent in individuals who are relatively close to motor diagnosis.[20] A comprehensive analysis of the Enroll-HD data set revealed a high prevalence of *DSM-5*-defined neurocognitive disorders (mild and major) in various stages of HD, which tended to worsen as individuals approached the predicted diagnosis. For premanifest HD that is far from the predicted diagnosis (>7.6 years), the rate was 29.5%, while for premanifest HD that is near the predicted diagnosis (<7.6 years), the rate was 60.6%. By the manifest stage, 82.9% of individuals with HD met the *DSM-5* criteria for neurocognitive disorder.[21]

Significant cognitive impairment or dementia is an important predictor of HD progression.[22] Even mild cognitive impairment (MCI) can predict HD onset, as indicated by motor diagnosis, even after adjusting for known predictors, i.e. the CAG-Age-Product and total motor scores. In addition to its predictive validity for age at motor onset and dementia in HD, MCI is also associated with brain atrophy of the striatum and, therefore, has been proposed as a clinically important early landmark event in the course of HD.[18]

Behavioural and psychiatric symptoms

Psychiatric symptoms are an integral part of HD. Psychiatric features are more variable than motor and cognitive disorders in HD.[23] A wide range of neuropsychiatric symptoms occur in HD, including depression, apathy, anxiety, irritability, obsessive-compulsive behaviour and psychosis.[24] These psychiatric symptoms may appear years before motor symptoms; however, they are not present in all cases and can vary over time.[25] Although HD gene carriers may not experience all neuropsychiatric symptoms, the majority are likely to encounter at least one of these symptoms throughout the disease course.[26]

Pharmacological treatments for Huntington's disease-associated chorea

The treatment of chorea may not be indicated in all individuals with HD. To facilitate informed decision-making, it is crucial to collect a thorough history of how chorea affects an individual's functioning, incorporating consultations with both the person living with HD and their care partner, given the frequency of anosognosia in HD.[27] When deemed necessary, chorea suppression can potentially improve balance, indirectly reduce the risk of falls, improve speech, preserve self-care abilities and maintain employment, ultimately improving the quality of life.[28,29] It is important to note that in cases where chorea is not causing significant distress, the potential side effects of currently available medications (e.g. depression, parkinsonism, suicidal thoughts, cognitive decline, sedation and agitation) may outweigh the benefits.[28,29] Therefore, it is vital to provide tailored treatment that addresses the specific needs of each individual.

In this section, we delve into the key medications employed to manage chorea, including vesicular monoamine transporter 2 (VMAT2) inhibitors and antipsychotics. These medications exert their antichorea effects mainly through antidopaminergic mechanisms. In addition, we explore alternative medications with varied non-dopaminergic mechanisms. *Table 1* presents the clinical trials assessing the efficacy of pharmacological treatments for chorea associated with HD.[30–57]

Vesicular monoamine transporter 2 inhibitors

VMAT2 is a transporter protein for monoamines (e.g. dopamine, serotonin and norepinephrine) responsible for the presynaptic vesicular packaging, storage and subsequent exocytotic release.[58,59] Inhibiting VMAT2 leads to a synaptic depletion of serotonin, norepinephrine and, particularly, dopamine. Dopamine dysfunction has been identified as a key mechanism contributing to chorea in HD.[9,60,61]

Three VMAT2 inhibitors are approved by the US Food and Drug Administration (FDA) for the treatment of HD-associated chorea, including tetrabenazine (TBZ), deutetrabenazine (DTBZ) and valbenazine (VBZ).[62–64] In 2008, TBZ became the first FDA-approved drug for HD-associated chorea.[62] This approval followed a randomized controlled trial (RCT): A Randomized, Double-blind, Placebo-controlled Study of Tetrabenazine for the Treatment of Huntington's Chorea (ClinicalTrials.gov identifier: NCT00219804), also known as the TETRA-HD study.[30] This study compared the progressive titration of TBZ, up to a maximum dose of 100 mg/day over 7 weeks or until chorea was controlled, against a placebo. The results revealed a significant reduction in the severity of chorea as measured by the Unified Huntington's Disease Rating Scale (UHDRS).[30] An additional study demonstrated the re-emergence of chorea 5 days after the withdrawal of TBZ treatment.[65] Finally, an open-label extension of the TETRA-HD study confirmed the long-term effectiveness of TBZ for up to 80 weeks with a mean daily dosage of 63.4 mg (range, 12.5–175 mg).[31]

The typical starting dose for TBZ is 12.5 mg once daily, followed by an increase to 12.5 mg BID and subsequently three times daily. The daily dose is then increased weekly by 12.5 mg until an effective dose is reached that suppresses chorea without unwanted side effects. The maximum recommended daily dose is 100 mg. If the medication is discontinued for more than 5 days, it should be reintroduced with gradual titration starting from the initial dose.[66] If a daily dose of TBZ over 50 mg is required, patients should undergo genotyping for cytochrome P450 family 2 subfamily D member 6 (CYP2D6) before initiating treatment.

Table 1: Clinical trials assessing the efficacy of pharmacological treatments for chorea associated with Huntington's disease[30–57]

NCT number	Status	Study title	Drug	Sample size	Main outcomes	Relevant side effects	References
VMAT2 inhibitors							
NCT00219804	Completed	A Randomized, Double-blind, Placebo-controlled Study of Tetrabenazine for the Treatment of Huntington's Chorea (TETRA-HD)	TBZ	n=84 for the randomized, placebo-controlled trial; n=75 for the open-label continuation	TBZ treatment at adjusted dosages of up to 100 mg/day resulted in a reduction of 5.0 units in chorea severity (TMC) compared with a reduction of 1.5 units on placebo treatment (p<0.0001) Open-label continuation study: at week 80, chorea had significantly improved from baseline with a mean reduction in the TMC score of 4.6 (SD 5.5) units; the mean dosage at week 80 was 63.4 mg (range 12.5–175 mg)	Drowsiness, insomnia, depressed mood, anxiety, akathisia, parkinsonism, dystonia, dysphagia and suicide ideation	Huntington Study Group (2006)[30]; Frank (2009)[31]
NCT01795859	Completed	First Time Use of SD-809 in Huntington Disease (First-HD)	DTBZ	n=90 for the randomized, placebo-controlled trial;	DTBZ treatment at adjusted dosages of up to 48 mg/day (or 36 mg for participants with impaired CYP2D6 function) resulted in a reduction of 4.4 units in chorea severity compared with a reduction of 1.9 units on placebo treatment (p<0.001)	Somnolence, dry mouth, diarrhoea, irritability, insomnia, fatigue and parkinsonism	Huntington Study Group (2006)[30]; Frank et al. (2016)[32]; Frank et al. (2022)[33]
NCT01897896		Alternatives for Reducing Chorea in Huntington Disease (ARC-HD)		n=119 for the open label extension study	Open-label continuation: adverse events observed with long-term DTBZ exposure were consistent with previous studies Reductions in chorea persisted over time DTBZ was proven to be an effective therapeutic treatment option for chorea in HD, with a more favourable adverse effect profile than TBZ	Despite the lack of statistical worsening of depression and suicidality and a side effect profile that is overall similar to placebo, DTBZ still has a boxed warning for depression and suicidality	
NCT04102579	Completed	Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease (KINECT-HD)	VBZ	n=127	VBZ treatment at adjusted dosages (as tolerated) of up to 80 mg/day resulted in a total motor score reduction of 4.6 points for VBZ and 1.4 for placebo (p<0.001)	Somnolence, fatigue, falls, urticaria, rash, insomnia and nausea; there was no worsening in akathisia, parkinsonism, depression or anxiety; participants treated with VBZ did not report any suicidal behaviour or worsening of suicidal ideation	Furr Stimming et al. (2023)[34]
NCT04400331	Active, not recruiting	Open-label Rollover Study for Continuing Valbenazine Administration for the Treatment of Chorea Associated with Huntington Disease (KINECT-HD2)					
NCT06312189	Enrolling by invitation	Long-term Study to Evaluate Safety and Tolerability of Valbenazine in Participants with Chorea Associated with Huntington Disease in Canada					
NCT05475483	Completed	Efficacy and Safety on SOM3355 in Huntington's Disease Chorea	Bevantolol hydrochloride	n=140 (actual)	No results have been reported yet	No results have been reported yet	No results have been reported yet[54]
Antipsychotics							
NCT00632645	Completed	Neuroleptic and Huntington Disease Comparison of: Olanzapine, la Tetrabenazine and Tiapride	Olanzapine, TBZ and tiapride	n=180	No results have been reported yet	No results have been reported yet	No results have been reported yet[55]
NCT04071639	Recruiting	Symptomatic Therapy for Patients with Huntington's Disease	Haloperidol, risperidone, sertraline, idebenone and DTBZ	n=60 (estimated)	No results have been reported yet	No results have been reported yet	No results have been reported yet[56]
NCT04201834	Completed	Risperidone for the Treatment of Huntington's Disease Involuntary Movements	Risperidone	n=5 (actual)	No results have been reported yet	No results have been reported yet	No results have been reported yet[57]
Not registered on ClinicalTrials.gov	Completed	Olanzapine for Huntington's Disease: An Open Label Study	Olanzapine	n=9	In this open-label trial, olanzapine (average=15.6 mg/day; range 5–30 mg/day) significantly reduced chorea scores from 13.4 to 6.9 (p=0.017)	Sedation, weight gain, metabolic syndrome and dry mouth	Bonelli et al. (2002)[35]

Continued

Table 1: Continued

Not registered on ClinicalTrials.gov	Completed	Treatment of the Symptoms of Huntington's Disease: Preliminary Results Comparing Aripiprazole and Tetrabenazine	Aripiprazole and TBZ	n=63	In this cross-over trial, both aripiprazole (mean final daily dose=10.76 ± 4.91 mg) and TBZ (mean final daily dose=95.83 ± 33.2 mg) reduced chorea severity (5.2- and 5.4-unit reduction, respectively)	No significant difference in extrapyramidal adverse effects between the two medications; aripiprazole was associated with a lower risk of sedation compared with TBZ	Brusa et al. (2009)[36]
Not registered on ClinicalTrials.gov	Completed	Clozapine in Huntington's Chorea	Clozapine	n=5	Open-label trial: all participants reported a reduction in chorea (self-rated decrease) after 3 weeks of treatment with clozapine (150 mg/day)	No significant side effects were reported; potential side effects include orthostatic hypotension, sedation, weight gain, elevated risk of seizures and agranulocytosis	Bonuccelli et al. (1994)[37]
Not registered on ClinicalTrials.gov	Completed	Clozapine Versus Placebo in Huntington's Disease: A Double-blind Randomised Comparative Study	Clozapine	n=33	Clozapine (maximum 150 mg/day) had minimal effects in reducing chorea, although some individuals may tolerate doses high enough to reduce chorea	Potential side effects include orthostatic hypotension, sedation, weight gain, elevated risk of seizures and agranulocytosis	van Vugt et al. (1997)[38]
Not registered on ClinicalTrials.gov	Completed	The Gait Abnormality of Huntington's Disease	Haloperidol	n=13	Open-label study: a reduction in choreiform movements compared with baseline was observed with doses ranging from 2 to 80 mg	Potential adverse effects include tachycardia, hypotension, hypertension, extrapyramidal symptoms, withdrawal-emergent neurological syndrome, tardive syndromes, insomnia, restlessness, anxiety, agitation, depression, confusion, lactation, gynaecomastia, impotence, dry mouth, blurred vision and urinary retention	Koller and Trimble (1985)[39]
Not registered on ClinicalTrials.gov	Completed	Effect of Neuroleptic Treatment on Involuntary Movements and Motor Performances in Huntington's Disease	Haloperidol, pimozide and tiapride	n=18	Open-label study: pimozide and haloperidol decreased hyperkinetic movement significantly compared with baseline	Potential adverse effects include tachycardia, hypotension, hypertension, extrapyramidal symptoms, withdrawal-emergent neurological syndrome, tardive syndromes, insomnia, restlessness, anxiety, agitation, depression, confusion, lactation, gynaecomastia, impotence, dry mouth, blurred vision and urinary retention	Girotti et al. (1984)[40]
Not registered on ClinicalTrials.gov	Completed	Huntington's Disease: Tetrabenazine Compared to Haloperidol in the Reduction of Involuntary Movements	Haloperidol and TBZ	n=11	A single-blind cross-over trial: both haloperidol and TBZ decreased choreiform movement compared with baseline, but no significant difference between the two was observed	Severe depression occurred in three patients under TBZ, in one leading to attempting suicide, while tardive dyskinesia complicated haloperidol therapy in three patients	Giménez-Roldán and Mateo (1989)[41]
Not registered on ClinicalTrials.gov	Completed	Fluphenazine Decanoate in the Treatment of Chorea: A Double-blind Study	Fluphenazine	n=9	Double-blind study reported a significant decrease in chorea following treatment with fluphenazine decanoate in contrast to the placebo group	Potential side effects similar to other first-generation antipsychotics	Terrence (1976)[42]
Other medications							
Not registered on ClinicalTrials.gov	Completed	Controlled Clinical Trial of Cannabidiol in Huntington's Disease	CBD	n=15	Double-blind, randomized, placebo-controlled, cross-over study: CBD, at an average daily dose of about 700 mg/day for 6 weeks, was neither symptomatically effective nor toxic, relative to placebo, in antipsychotics-free patients with HD	Not different from placebo	Consroe et al. (1991)[43]
Not registered on ClinicalTrials.gov	Completed	A Pilot Study Using Nabilone for Symptomatic Treatment in Huntington's Disease	Nabilone	n=44	Double-blind, randomized, placebo-controlled, cross-over study: non-significant effect of nabilone on HD-related motor symptoms	Nabilone was safe and well tolerated, no psychotic episodes	Curtis et al. (2009)[44]
NCT01502046	Completed	A Double-blind, Randomized, Cross-over, Placebo-controlled, Pilot Trial with Sativex in Huntington's Disease	Sativex	n=26	Double-blind, randomized, placebo-controlled, cross-over study: Sativex had no significant effects on HD chorea	Sativex was safe and well tolerated; no significant symptomatic effects were detected at the prescribed dosage	López-Sendón Moreno et al. (2016)[45]
Not registered on ClinicalTrials.gov	Completed	Riluzole Therapy in Huntington's Disease	Riluzole	n=8	Open-label trial: compared with baseline, the chorea rating score improved by 35% on treatment (p=0.013) and worsened after discontinuation of treatment (p=0.026)	Riluzole was well tolerated	Rosas et al. (1999)[46]
Not registered on ClinicalTrials.gov	Completed	Dosage Effects of Riluzole in Huntington's Disease: A Multicenter Placebo-controlled Study	Riluzole	n=56	Riluzole 200 mg/day significantly reduced chorea (-2.2) compared with placebo (+0.7) (p=0.01)	Dizziness, elevated ALT, fatigue, muscle weakness, nausea and somnolence	Huntington Study Group (2003)[47]
Not registered on ClinicalTrials.gov	Completed	Riluzole in Huntington's Disease (HD): An Open-label Study with One-year Follow-up	Riluzole	n=9	At 3 months, the chorea score significantly improved compared with baseline; at 12 months, however, the beneficial effects were not sustained	Riluzole was well tolerated; no increase in serum liver enzymes was seen throughout the study in all but one patient showing a mild elevation	Seppi et al. (2001)[48]

Continued

Table 1: Continued

NCT00277602	Completed	Riluzole in Huntington's Disease: A 3-year, Randomized-controlled Study	Riluzole	n=379	No differences between riluzole and placebo	No unexpected adverse events were reported, and tolerability was acceptable	Landwehrmeyer et al. (2007)[49]
NCT00001930	Completed	Huntington's Disease: A Randomized-controlled Trial Using the NMDA-antagonist Amantadine	Amantadine	n=22	Double-blind, placebo-controlled cross-over study: chorea scores were lower with amantadine (usually 400 mg/day) than with placebo, with a median reduction in extremity chorea at rest of 36% (p=0.04)	There were no serious adverse events; side effects during amantadine treatment included increased forgetfulness, insomnia, hallucinations and confusion, exacerbation of preexistent morbid thoughts, dry mouth, hives, nausea and diarrhoea	Verhagen Metman et al. (2002)[50]
Not registered on ClinicalTrials.gov	Completed	A Randomized Trial of Amantadine in Huntington's Disease	Amantadine	n=24	Randomized, placebo-controlled cross-over trial: amantadine hydrochloride treatment at doses of 300 mg/day had no effect, on average, for Huntington chorea, although most patients felt subjectively better during the short course of amantadine treatment	Insomnia, agitation or anxiety, confusion, diarrhoea and sleepiness	O'Suilleabhain and Dewey (2003)[51]
Not registered on ClinicalTrials.gov	Completed	Efficacy of Levetiracetam in Huntington's Disease	Levetiracetam + olanzapine	n=22 (n=15 levetiracetam and n=7 controls)	Open-label study: a significant reduction in chorea scores and a minor improvement in functional ability were observed in comparison to the control group (i.e. people who did not receive levetiracetam)	No serious adverse events were experienced by the treated patients	de Tommaso et al. (2005)[52]
Not registered on ClinicalTrials.gov	Completed	Open-label Pilot Study of Levetiracetam (Keppra) for the Treatment of Chorea in Huntington's Disease	Levetiracetam	n=9	Open-label study: significant decrease in chorea scores compared with baseline (12.6 versus 6.7)	Three out of nine individuals developed parkinsonism and 33% left the trial due to somnolence	Zesiewicz et al. (2006)[53]

ALT = alanine transaminase; CBD = cannabidiol; CYP2D6 = cytochrome P450 family 2 subfamily D member 6; DTBZ = deutetrabenazine; HD = Huntington's disease; NMDA = N-methyl-D-aspartate; SD = standard deviation; TBZ = tetrabenazine; TMC = total maximal chorea; VBZ = valbenazine; VMAT2 = vesicular monoamine transporter 2.

If the individual is identified as a poor metabolizer, the maximum prescribed dose should not exceed 50 mg/day.[67]

TBZ can cause various adverse effects, including drowsiness, insomnia, depressed mood, anxiety, akathisia, parkinsonism, dystonia, dysphagia and suicidal ideation.[30,31,65,66] These side effects may be reduced by lowering the dose; however, if suicidal thoughts and ideations occur, the drug should be stopped immediately with appropriate follow-up. Given the increased incidence of depression and suicidality in individuals with HD, routine screening should be performed with increased vigilance when prescribing TBZ.[24,67,68]

The pharmacokinetic and side effect profiles of TBZ led to the development of DTBZ. DTBZ is a deuterated form of TBZ with an improved pharmacokinetic profile. The substitution of hydrogen with deuterium at specific positions in the TBZ molecule results in a longer half-life and, therefore, less frequent daily dosing.[69] DTBZ became the second FDA-approved medication for HD-associated chorea after the FIRST-HD trial (First Time Use of SD-809 in Huntington Disease; ClinicalTrials.gov identifier: NCT01795859) demonstrated its efficacy compared with a placebo.[32,63] This trial showed significant improvements in mean total maximal chorea scores after 12 weeks of treatment and an increase in the proportion of individuals in the DTBZ group who showed treatment success on the Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C).[70,71] DTBZ was initiated at a dose of 6 mg/day with weekly increments of 6 mg/day until effective control of chorea was achieved, the person experienced significant adverse effects or the maximum dose was reached (48 mg/day or 36 mg for participants with an impaired CYP2D6 function).[32] DTBZ has been proven to be an effective therapeutic treatment option for HD-related chorea, with a more favourable adverse effect profile compared with TBZ.[69] The long-term safety and efficacy of DTBZ in treating HD-related chorea was demonstrated in the open-label extension study published in 2022.[33]

Adverse effects of DTBZ include somnolence, dry mouth, diarrhoea, irritability, insomnia, fatigue and parkinsonism. Noteworthy, depression and parkinsonism were not statistically associated with the treatment in the original RCT, but they showed increased incidence after starting the treatment regimen in the open-label extension study.[33] Moreover, despite the lack of statistical worsening of depression and suicidality and a side effect profile that is overall similar to placebo, DTBZ still carries a boxed warning for depression and suicidality.[69]

VBZ was the third medication approved by the FDA for the treatment of HD-associated chorea, gaining approval in August 2023 based on the results of the phase III, randomized, double-blind, placebo-controlled trial KINECT-HD (Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated with Huntington Disease; ClinicalTrials.gov identifier: NCT04102579).[34,64] VBZ is a novel VMAT2 inhibitor and was introduced as an alternative to TBZ and DTBZ. In the KINECT-HD trial, participants in the treatment group initially received 40 mg daily for 2 weeks (given as two capsules of 20 mg once daily). After this, the dose was increased as tolerated by 20 mg at the end of weeks 2, 4 and 6, reaching a maximum dose of 80 mg.[34,72] The results assessed at weeks 10 and 12 showed a marked improvement in the UHDRS total maximal chorea score (primary endpoint), CGI-C and PGI-C (secondary outcomes). An open-label rollover study is currently underway to evaluate its long-term safety and tolerability (Open-label Rollover Study for Continuing Valbenazine Administration for the Treatment of Chorea Associated with Huntington Disease, KINECT-HD2; ClinicalTrials.gov identifier: NCT04400331).[73]

In the KINECT-HD trial, the most commonly reported adverse effects were somnolence, fatigue and falls. In addition, some individuals reported urticaria, rash, insomnia and nausea. There was no worsening in akathisia, parkinsonism, depression or anxiety. Participants treated with VBZ did not report any suicidal behaviour or worsening of suicidal ideation.[34] Compared with TBZ and DTBZ, VBZ has a stronger affinity for VMAT2 and minimal off-target binding, which may result in better tolerability. In addition, VBZ and its metabolites have a long half-life (15–22 hours), allowing for once-daily dosing, easier titration and a relatively short period from initiation to achieving an effective dose.[34,72]

Bevantolol hydrochloride, a β1-antagonist with VMAT2 properties, is currently under evaluation for its potential to reduce chorea in HD (Efficacy and Safety on SOM3355 in Huntington's Disease Chorea; ClinicalTrials.gov identifier: NCT05475483).[54] In a randomized, proof-of-concept study on 32 individuals with HD, bevantolol hydrochloride with a dose of 200 mg BID was well tolerated and significantly reduced chorea compared with a placebo, while the 100 mg BID dosage did not demonstrate any significant effects.[74]

In summary, VMAT2 inhibitors – TBZ, DTBZ and VBZ – are the only FDA-approved drugs for the treatment of chorea associated with HD. They have shown efficacy in large, double-blind, placebo-controlled clinical trials.[31,32,34] However, it is important to note that these medications work by depleting monoamines, which raises concerns about their potential to cause depression and suicidal thoughts, conditions that are more common in individuals with HD. In addition, VMAT2 inhibitors may not be widely accessible due to their high cost and limited availability in some parts of the world.

Antipsychotics

Given the association between hyperdopaminergic states and hyperkinetic movement disorders, therapeutic strategies for chorea have primarily centred around dopamine modifications. Unlike VMAT2 inhibitors, which achieve their antidopaminergic effect by inhibiting presynaptic monoamine release, antipsychotics exert their influence through antagonism of postsynaptic dopamine receptors.[75] While none of the antipsychotic medications are FDA-approved for treating chorea in HD, they are often used off-label when treating concurrent psychiatric symptoms and chorea in HD.[75] VMAT2 inhibitors are generally avoided in individuals with uncontrolled depression or suicidality.[75,76]

The complex pharmacological mechanisms of antipsychotics impact various neurotransmitter systems, primarily targeting dopamine and serotonin, with weaker muscarinic, histaminergic and adrenergic activity. Antipsychotics can be classified based on their affinity for receptors. First-generation antipsychotics exhibit a higher affinity for dopamine receptors, while second-generation antipsychotics have a preference for serotonin receptors.[77] Antipsychotics are frequently employed as an off-label medication in the treatment of chorea, particularly when there is concurrent psychosis or other psychiatric and behavioural problems, as seen in HD.[65,78] This might be attributed to a body of evidence supporting the use of antipsychotics and, more importantly, the availability and lower cost of antipsychotics compared with VMAT2 inhibitors.[75] However, high-quality evidence is still lacking regarding the efficacy of antipsychotics in treating chorea.[78,79] Second-generation antipsychotics are generally preferred because of their lower risk of extrapyramidal adverse events (e.g. parkinsonism, akathisia, dystonia and tardive dyskinesia) compared

with first-generation antipsychotics.[77] It is important to note that second-generation antipsychotics pose a significant risk of endocrine and metabolic adverse events.[77]

Antipsychotics can be particularly helpful in managing chorea co-existing with neuropsychiatric symptoms in individuals with HD. According to expert-based recommendations, antipsychotics can be used to treat acute or chronic agitation, anxiety and, especially, psychosis in HD. Side effect profiles of antipsychotics should be considered when choosing an antipsychotic drug in HD. A second-generation antipsychotic is preferred, but a first-generation alternative can be considered.[80]

Second-generation antipsychotics

Some case reports have emphasized the potential effectiveness of risperidone in treating chorea and psychiatric symptoms in HD.[81–84] In one case, where a patient with HD presented with psychosis and affective symptoms, clozapine alone effectively reduced psychotic symptoms (but not chorea). When risperidone was added to the regimen (0.5 mg/day, gradually increased to 6 mg/day over 6 weeks), there was a marked improvement in chorea and further improvement in psychosis.[84] A retrospective study employing a chart review of 17 individuals with HD undergoing treatment with risperidone at an average daily dose of 2.5 mg confirmed its positive impact on psychiatric symptoms. In addition, they reported stabilization of motor decline compared with 12 individuals who were not receiving any antipsychotic treatment over 14.8 months.[85] It is important to note that, according to a survey of HD experts worldwide, 43% of specialists consider risperidone to be the preferred antipsychotic for treating chorea.[78] Adverse effects seen commonly with risperidone treatment include hyperprolactinaemia, weight gain and parkinsonism.[78]

An observational study used the Enroll-HD database to compare two antipsychotics (risperidone and olanzapine) with a VMAT2 inhibitor (TBZ) for controlling chorea associated with HD.[86] The study found that both risperidone and olanzapine were as effective as TBZ in controlling chorea; however, olanzapine led to a significantly higher weight gain and body mass index (BMI increased compared with TBZ and risperidone).[86]

Olanzapine was originally approved by the FDA in 1996 for treating symptoms of psychotic disorders and later in 2000 for manic disorders.[87] It has a strong affinity for a wide range of receptors, including the dopamine receptors D1, D2, D4; the serotonin receptors (5HT)2A, 5HT2C and 5HT3; and the α-1-adrenergic, H1 and muscarinic receptors.[88] In an open-label trial, olanzapine was found to significantly improve chorea, with scores reducing from 13.4 to 6.9.[35] Five of the seven UHDRS sub-scores, including oculomotor function, orolingual function, fine motor skills, chorea and statics and gait, showed significant improvement. The average dosage used was 15.6 mg/day, with a range of 5–30 mg/day, and no adverse effects were noted.[35] It is worth mentioning that the common side effects of olanzapine include sedation, weight gain, metabolic syndrome and dry mouth.[78]

Another antipsychotic showing promising effects on HD-associated chorea is aripiprazole. It has a partial agonist effect on dopaminergic and serotonergic receptors, stabilizing the dopamine receptor and improving symptoms.[89,90] A small cross-over trial involving six individuals with HD compared the effects of aripiprazole and TBZ on chorea.[36] Both medications showed positive effects, with reductions in chorea severity of 5.2 and 5.4 units, respectively. The trial found no significant difference in extrapyramidal side effects between the two drugs. Aripiprazole, at a mean dose of 10.76 (±4.91) mg/day, was associated with a lower risk of sedation compared with TBZ.[36] Due to its unique profile (partial D2 and 5HT1A agonism and 5HT2A antagonism), aripiprazole has a lower risk of inducing extrapyramidal and metabolic side effects compared with other second-generation antipsychotics.[89] RCTs are needed to further establish the effect of aripiprazole on chorea and to provide more comprehensive comparisons with other medications.

In the pursuit of effective treatments for HD-associated chorea, it becomes evident that not all antipsychotics have demonstrated favourable outcomes. A noticeable example is clozapine. Some improvements in abnormal involuntary movements in individuals with HD have been demonstrated in small trials at various doses of clozapine, ranging from 50 to 500 mg/day.[37,91] A randomized, double-blind trial of 33 individuals with HD found minimal beneficial effects for clozapine in reducing chorea.[38] A non-significant minor reduction in chorea (0.7 units) was observed on the UHDRS total chorea score. The authors indicated that while some individuals may experience benefits from clozapine, they would need to tolerate doses high enough to effectively alleviate chorea.[38] In addition to the limited benefits, consideration should be given to the potential side effects of this medication, including orthostatic hypotension, sedation, weight gain and an elevated risk of seizures. Some of these side effects, such as agranulocytosis (or severe neutropaenia), can be life-threatening.[38,92]

Quetiapine is recognized for its lower D2 antagonism compared with other second-generation antipsychotics. There is limited evidence supporting its efficacy in reducing chorea in HD.[93,94]

First-generation antipsychotics

The use of first-generation antipsychotics to manage HD-associated chorea is less common due to the higher risk of adverse effects such as sedation, dystonia, parkinsonism, hypotension or akathisia. However, their higher potency may justify consideration after treatment failure with VMAT2 inhibitors and second-generation antipsychotics.[95]

Tiapride has been commonly used for the treatment of HD chorea in Europe (but is unavailable in the USA), mostly due to its low cost, high availability and additional effectiveness in addressing behavioural, sleep and motor function disturbances.[78,96] An RCT in 1982 treated 22 individuals with HD with tiapride 300 mg/day for 2 weeks.[97] Compared with placebo, tiapride did not show any significant improvement in choreiform movements.[97] Another double-blind, cross-over trial conducted in 1984 compared 3,000 mg/day of tiapride with a placebo in 29 individuals with HD.[98] Choreiform movements were significantly reduced in four of the five body regions (head, trunk, upper limbs and lower limbs) following tiapride therapy.[98] However, these results should be interpreted with caution, as the study's cross-over design lacked a wash-out period between the treatments and did not analyse the potential carry-over effect.[99]

Haloperidol is also another first-generation antipsychotic that was commonly used to treat HD-associated chorea.[78] Its effect was studied in the early 1980s in two open-label studies: in the first study involving 13 individuals, a reduction in choreiform movements compared with baseline was observed with doses ranging from 2 to 80 mg.[39] In the second study, 18 subjects received treatment with one or more of haloperidol, pimozide and tiapride.[40] In cases where more than one treatment was administered, they were given individually and sequentially, with a 15-day wash-out period between treatments.[40] The pharmacological trial spanned 1 month for each medication. Nine individuals had taken haloperidol (dosage range: 6–9 mg/day). Pimozide and haloperidol significantly decreased hyperkinetic movement compared with baseline.

No improvement was reported after the tiapride trial.[40] A single-blind cross-over trial involving 11 subjects with HD was conducted to evaluate the efficacy of haloperidol and TBZ. Both medications showed a decrease in choreiform movements compared with baseline, but no significant difference between the two was observed.[41]

Fluphenazine is commonly employed for prolonged therapy in psychotic disorders and is administered as a long-acting injectable and an off-label medication for the management of tics and Tourette syndrome.[100–102] In 1976, a double-blind study involving nine individuals with HD reported a significant decrease in chorea over a 4-week observation period following treatment with fluphenazine decanoate, in contrast to the placebo group.[42]

Other medications

Minimal research has been performed on the effectiveness of benzodiazepines in reducing chorea. Benzodiazepines have been used as adjunctive treatment for chorea, and clonazepam has been the preferred benzodiazepine for this purpose.[78] Only two case reports have found clonazepam to be beneficial.[103,104] Generally, prolonged use of benzodiazepines or their use as monotherapy is not recommended for individuals with HD.[78,80] Benzodiazepines may be used to treat anxiety in HD. However, the doses required for treating chorea are typically higher, which increases the risk of side effects such as dependence, misuse, risk of falls and possible cognitive decline, especially in the elderly.[105–107]

Cannabinoids have been the subject of investigation in a few clinical trials. In a double-blind, cross-over RCT, cannabidiol was found to be ineffective for the treatment of chorea when compared with the placebo.[43] Nabilone, a synthetic analogue of delta-9-tetrahydrocannabinol, was investigated in a double-blind, randomized, placebo-controlled, cross-over trial of 44 individuals with HD with non-significant results.[44] Another double-blind, randomized, cross-over, placebo-controlled trial involving 26 participants examined the effects of a botanical extract that comprises an equimolecular combination of delta-9-tetrahydrocannabinol and cannabidiol.[45] Both the drug and placebo were administered in oral sprays. Although the study's primary aim was to assess the safety and adverse effects, no significant benefits were detected on motor scores, including chorea.[45]

Riluzole is an antiglutaminergic medication used to treat amyotrophic lateral sclerosis and has also been studied as a potential treatment for reducing chorea in HD. Its beneficial effects on neurodegeneration are attributed to its ability to reduce glutamate excitotoxicity.[108,109] Studies on its effects on HD have produced conflicting results, with some showing improvements in chorea compared with baseline or placebo treatment.[46,47] However, these effects were not sustained in long-term and larger trials, and the evidence and clinical utility of the use of riluzole in treating HD-associated chorea are considered limited. It is worth mentioning that the American Academy of Neurology (AAN) initially recommended riluzole as a treatment option for chorea in HD in their 2012 guidelines.[48,49,110] However, these guidelines were retired in 2022.

Amantadine was originally approved as an antiviral medication but has been repurposed to treat levodopa-induced dyskinesias in people with Parkinson's disease. While the exact pharmacological effects of amantadine are not fully understood, its complex mechanisms of action include acting as a non-competitive antagonist of the *N*-methyl-D-aspartate glutamate receptor, regulating dopamine transmissions by increasing dopamine synthesis and release and inhibiting dopamine re-uptake. Amantadine's effects on dopaminergic regulation also seem to occur through its agonism of sigma-1 receptors.[111] The first reports of using amantadine to treat chorea associated with HD date to the 1970s.[112–114] Since then, the results have been conflicting. For example, in a case series of five patients with HD, amantadine alone had no effect in three out of four patients but had marked benefit in the fifth patient, who was also receiving haloperidol and reserpine.[112,115] The controversy remained 30 years later when randomized studies yielded positive, mixed or non-significant results.[50,51,116,117] In 2012, the currently retired evidence-based guidelines of the AAN listed amantadine (300–400 mg/day) as an option for the pharmacological treatment of chorea associated with HD (level B, degree of benefit unknown).[110]

Among the anticonvulsants, levetiracetam has been tested for HD chorea in two small open-label studies: in one study, 15 HD individuals were given levetiracetam as an adjunct treatment to olanzapine.[52] Levetiracetam was initially administered at 500 mg BID for the first 2 months, with a subsequent dosage escalation to 1,000 mg BID over the following 4 months. A significant reduction in chorea scores and a minor improvement in functional ability were observed compared with the control group, which consisted of seven HD gender- and age-matched individuals. Notably, no side effects were reported.[52] In a separate open-label study, nine individuals with HD were administered levetiracetam. The treatment was initiated at 250 mg/day, with increments of 250 mg every 4 days, reaching a maximum of 3,000 mg/day over a span of up to 48 days. Although there was no statistically significant change in UHDRS total motor scores, the study indicated a noteworthy improvement in the mean UHDRS chorea score, showing a decrease from 12.6 to 6.7.[53] Three out of nine individuals developed parkinsonism, and 33% of the participants left the trial due to somnolence.[53]

Novel treatments for Huntington's disease-associated chorea

Deep brain stimulation (DBS) is an invasive therapy approved for common movement disorders, including Parkinson's disease, essential tremor and dystonia (through a humanitarian device exemption). DBS delivers high-frequency stimulation, with the most common targets being the GPi, the subthalamic nucleus and the ventral intermediate thalamic nucleus for the indications mentioned here.[118] DBS is not approved for HD-related chorea. However, its efficacy has been evaluated for intractable chorea with the GPi as the target.[118] Several case studies and one prospective open-label trial have suggested the positive effects of DBS in reducing pharmacologically resistant chorea in individuals with HD.[119] Although the current literature supports the use of DBS as a palliative option in individuals with intractable chorea, the adverse effects should be considered, including the worsening of cognitive dysfunction and psychiatric/behavioural disorders, in addition to the risks associated with the surgical procedure itself.[119–124]

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive brain modulation modality currently approved for the treatment of Parkinson's disease and essential tremor.[125,126] The utilization of MRgFUS is currently being explored as a potential option for individuals with treatment-refractory symptoms associated with movement disorders (e.g. chorea, dystonia, myoclonus and dyskinesia). In an on-going open-label clinical trial (A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-refractory Movement Disorders; ClinicalTrials.gov identifier: NCT02252380) researchers are investigating the application of MRgFUS to induce a targeted unilateral lesion in the GPi with the goal of alleviating symptoms associated with treatment-refractory chorea in individuals with HD.[127] Beyond the treatment of chorea, MRgFUS is

being evaluated for the non-invasive disruption of blood–brain barrier to enhance the delivery of therapeutic molecules, including drugs, genes, stem cells and antibodies.[125] As an investigational treatment option, it is currently in the initial stages of exploration and development.

Lifestyle and rehabilitation for Huntington's disease-associated chorea

Unintended weight loss and decreased BMI are common in HD individuals, primarily attributable to metabolic disturbances.[128] In addition, chorea can contribute to weight loss, highlighting the need for nutrition consultations to ensure sufficient caloric consumption.[128,129] While nutritional supplements (e.g. triheptanoin, L-acetyl-carnitine and creatine) have not shown significant benefits for HD motor symptoms, certain dietary modifications, such as the Mediterranean diet, may provide motor and cognitive benefits to individuals living with HD.[130] However, their impact on chorea in particular warrants further investigations.

Multi-disciplinary rehabilitation and physical therapy have been proven to offer significant benefits to individuals with HD, particularly in terms of motor function, gait speed and balance.[131,132] An RCT found a significant positive effect on chorea and postural stability with multi-disciplinary rehabilitation, featuring individualized clinical and home-based exercise programmes.[133] It is imperative to mention that chorea itself might serve as a barrier to engaging in gym- or group-based exercises, necessitating flexibility in the choice of location to overcome this challenge, such as opting for home-based exercise.[134] A personalized rehabilitation plan, incorporating tailor-made exercise details and regular assessments, is essential to avoid excessive or inappropriate training that may worsen symptoms.[135]

Final remarks

HD is a multifaceted disease encompassing motor and non-motor symptoms. Among the many motor symptoms, chorea is one of the most common and can be suppressed with treatment. However, the potential benefits of treatment need to be carefully weighed against the risks. There are three FDA-approved medications for treating HD-related chorea: TBZ, DTBZ and VBZ. While these medications can be effective, they have limitations such as psychiatric side effects, limited availability and cost. Therefore, alternative classes of medications, such as antipsychotics, should also be considered when treatment of chorea is warranted, especially in the context of troublesome psychiatric symptoms.

Effective suppression of troublesome chorea can improve mobility, reduce the risk of falls, improve quality of life and reduce the burden on individuals living with HD.[28,29] Determining when and if chorea needs to be treated can be challenging, and it is therefore recommended that a detailed history be collected, not only from the patient but also from the care partner, given the high incidence of anosognosia in HD.

Finally, it is important to acknowledge that symptomatic treatments can make a positive impact on individuals living with HD and that, even in the face of a fatal, hereditary neurodegenerative disease, the impact of compassionate, multi-disciplinary care should not be underestimated. ❑

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