Chorea Associated with Huntington's Disease

Disease State Overview

NEUROCRINE® BIOSCIENCES

MED-MSL-HD-US-0002_v4

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Huntington’s Disease Background

Huntington's Disease is a Hereditary Neurodegenerative Disorder[1,2]

Characterized by a **progressive neurodegeneration** in the **cortex and striatum**

Inherited in an **autosomal-dominant** manner

Typically diagnosed between **30-50 years**[2,3]

Triad of symptoms:

Motor | **Cognitive** | **Psychiatric**

Currently no cure; treatment goals are to manage symptoms and improve QoL

HD, Huntington's disease; HTT, huntingtin; QoL, quality of life.

1. Roos RA. *Orphanet J Rare Dis*. 2010;5:40. 2. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America; 2011. 3. Solberg OK, et al. *J Huntingtons Dis*. 2018;7(1):77-86.

The Triad of Symptoms in Huntington's Disease[1,2]

Motor

Involuntary movements (chorea) and impaired voluntary movements

Chorea is the most recognized motor symptom in HD, but dystonia, bradykinesia, myoclonus and tremor can also be present

Cognitive

Reduced speed and flexibility in mental processing and executive function*

Learning and memory issues begin early in the disease, with subclinical cognitive changes that can occur 15 years before diagnosis

Psychiatric

Personality and behavioral changes (depression, irritability, psychosis)

Anxiety, apathy, obsessive compulsive disorder, and agitation may also be present

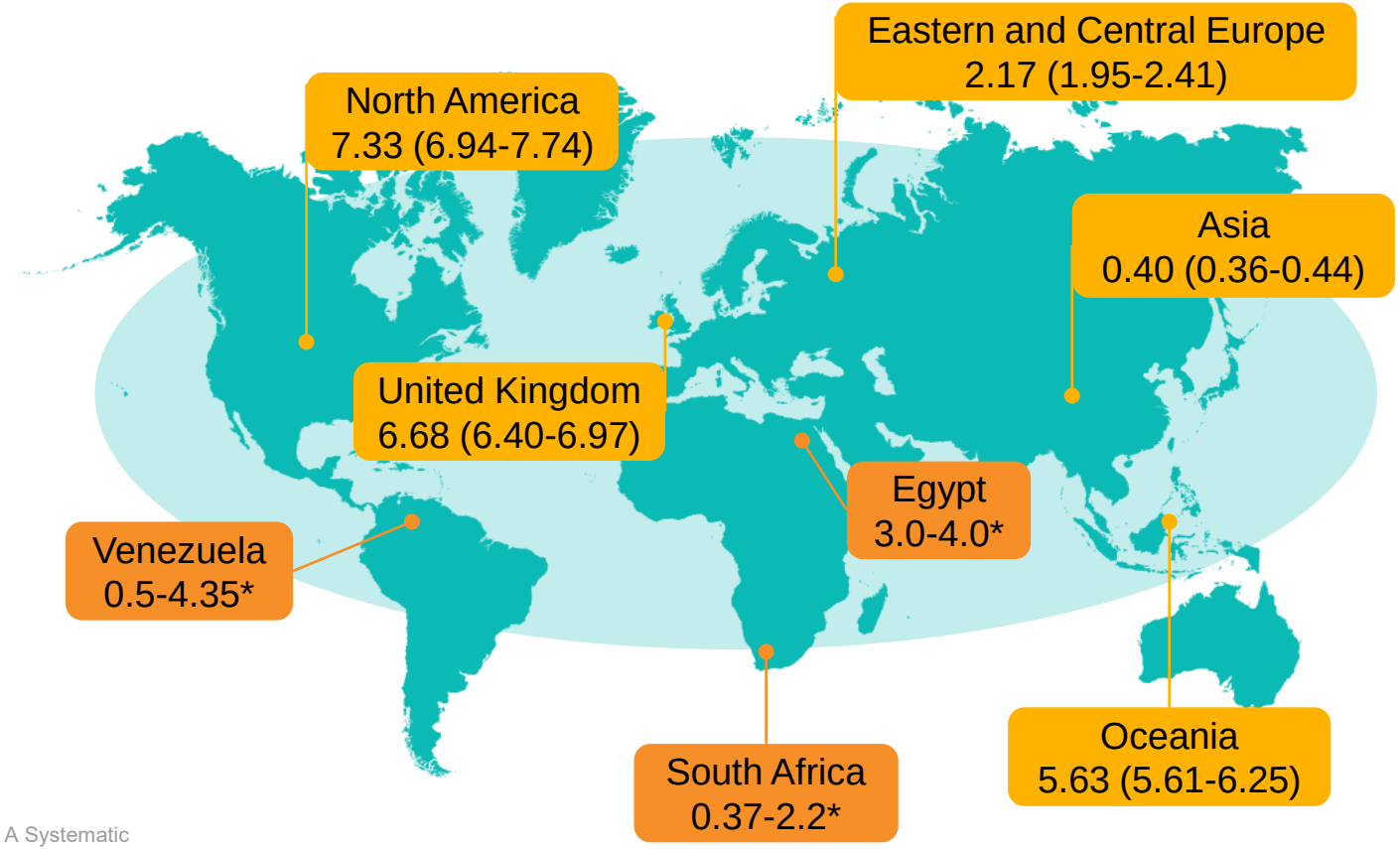
*Executive functions include high-order cognitive abilities such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem solving.[3] HD, Huntington's disease.

1. Roos RA. *Orphanet J Rare Dis*. 2010;5:40. 2. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America. 2011.

HD Epidemiology Suggests Variable Prevalence Worldwide[1,2]

Approximately **41,000 Americans** have manifest HD, with **>200,000** at risk of inheriting the disease[1,2]

Both incidence and prevalence of HD are **higher in individuals of Caucasian descent**



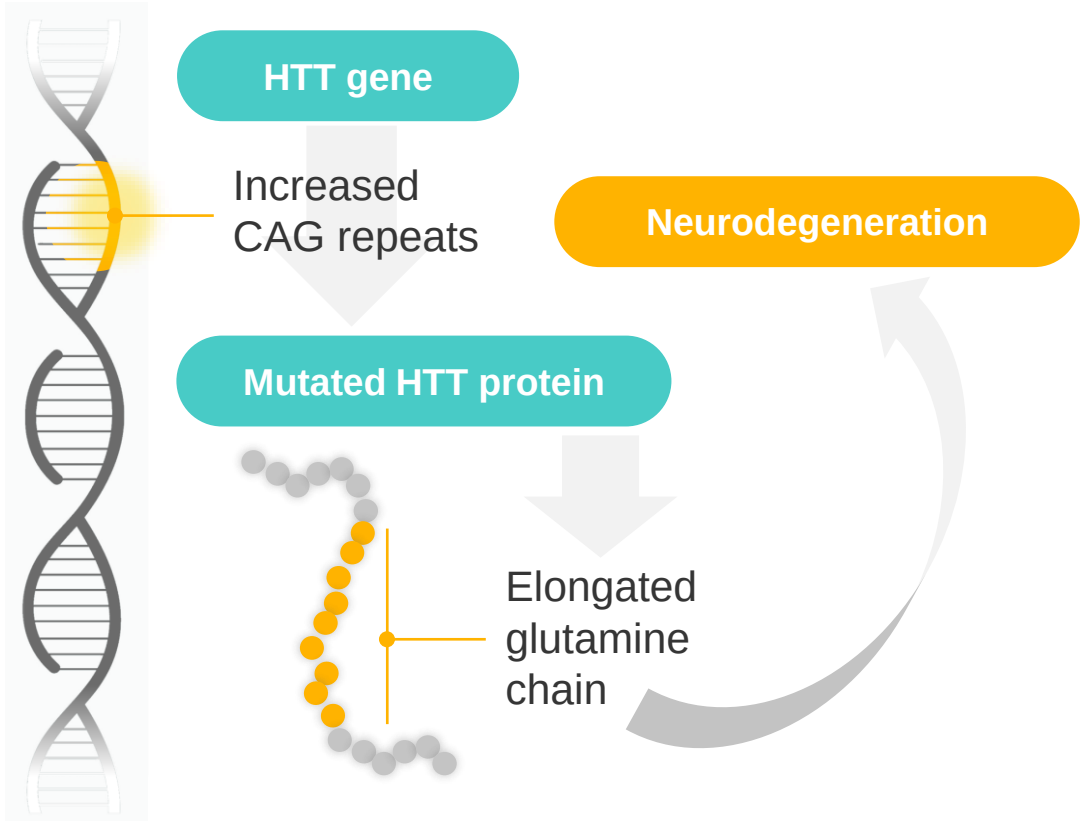
*Region dependant[2,3,4,5]

1. Pringsheim T, Wiltshire K, Day L, et al. The Incidence and Prevalence of Huntington's Disease: A Systematic Review and Meta-analysis. 2012. Movement Disorders 27(9):1083-91. | 2. Rawlins MD, Wexler NS, Wexler AR, et al. The Prevalence of Huntington's Disease Neuroepidemiology 2016;46:144-53. | 3. The U.S.–Venezuela Collaborative Research Project* and Nancy S. Wexler. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. *PNAS.* 2004;101(10):3498-503. | 4. Scrimgeour EM. Huntington Disease (Chorea) in the Middle East. *Sultan Qaboos Univ Med J*. 2009;9(1):16–23. | 5. Lekoubou A, Echouffo-Tcheugui JB, Kengne AP. Epidemiology of neurodegenerative diseases in sub-Saharan Africa: a systematic review. *BMC Public Health.* 2014;14:653.

*Increased prevalence due to founder effect

Huntington's Disease is Caused by a Mutation in the Huntingtin Gene (HTT)

CAG repeats within HTT are associated with penetrance of HD and timing of onset, with larger CAG repeats associated with younger disease onset[1]



Significance of CAG repeats in the huntingtin gene[1]

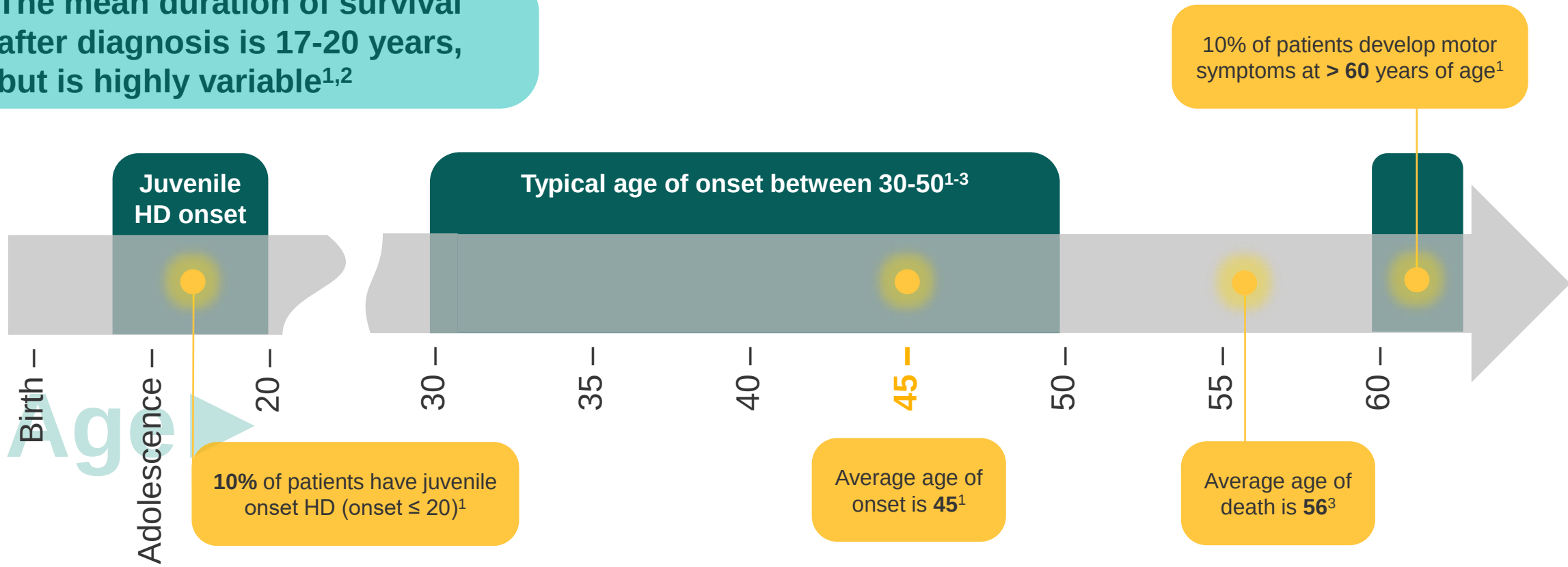
CAG Repeat Length	Interpretation	
< 27	Normal	Normal
27 - 35	Intermediate	**Not at risk of developing HD symptoms** but due to instability of CAG repeats, potential risk of having a child with expanded CAG repeats
36 - 39	Reduced penetrance	**May or may not develop symptoms of HD**. Unstable CAG repeats → future generations at risk
≥ 40	Affected	Development of HD symptoms

CAG, cytosine, adenine, and guanine; HD, Huntington's disease. HTT; huntingtin gene; Htt, huntingtin protein.

Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition*. Huntington's Disease Society of America. 2011.

No Current Treatments Alter Disease Progression

The mean duration of survival after diagnosis is 17-20 years, but is highly variable[1,2]



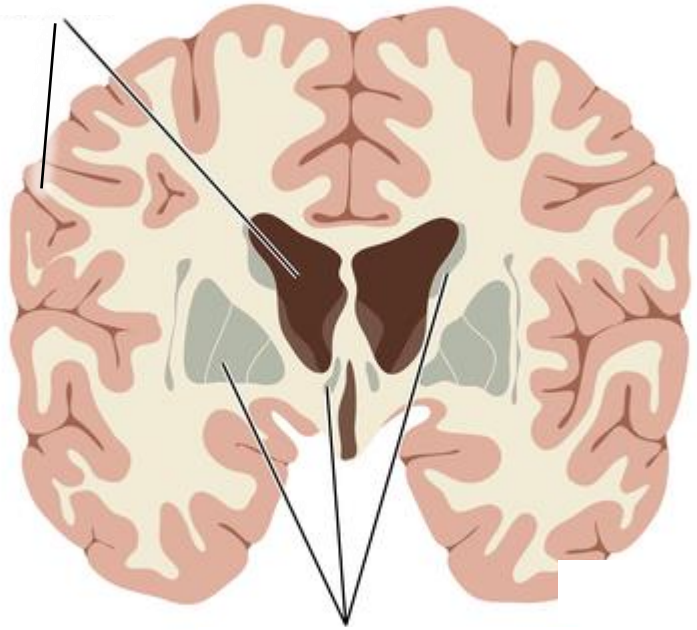
The leading cause of death in patients with HD is pneumonia followed by suicide[2,3]

1. Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011. 2. Roos RA. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010 Dec 20;5:40. 3. Solberg OK, Filkukov P, Billaud Fergen KJ. Age at Death and Causes of Death in Patients with Huntington Disease in Norway in 1986–2015. J Huntingtons Dis. 2018;7(1):77-86

HD is Associated with Diffuse Loss of Neurons in the Cortex and Striatum[1,2]

Unaffected brain

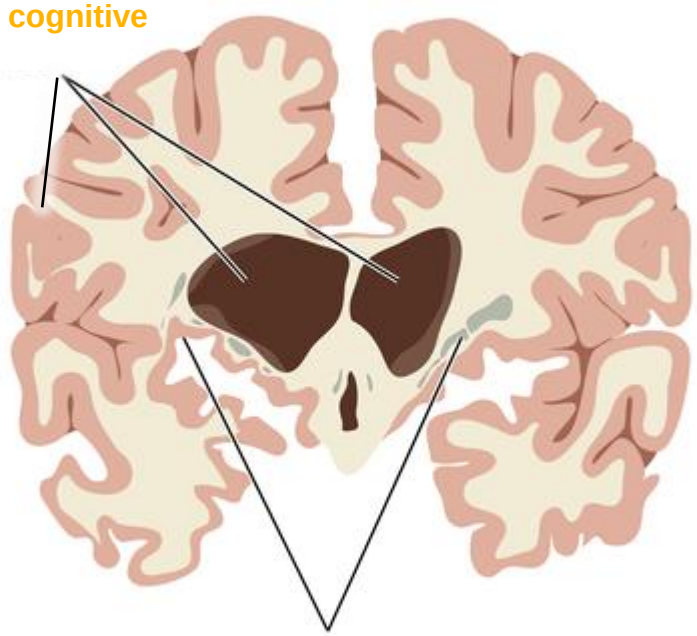
Normal ventricles; intact cortex



The striatum is a component of the basal ganglia primarily involved in **planning and controlling movement**

Huntington's Disease

Degradation of the cortex contributing to **cognitive deterioration**



Atrophy of the basal ganglia (striatum) leads to movement disturbances and eventually progressive global decline

Image courtesy of The Huntington's Disease Association[3]

1. Frank S. Treatment of Huntington's Disease. Neurotherapeutics. 2014;11(1):153-60. 2. HD History. The European Huntington's Disease Network. Available at http://www.ehdn.org/about-hd/. Accessed July 7, 2021. 3. Huntington's Disease Association. Huntington's Disease: A guide for social workers. 2020. Available at https://www.hda.org.uk/media/2597/social-worker-guide.pdf. Accessed January 27, 2020.

HD Symptoms Fluctuate and Worsen Throughout the Disease Course

Early Stage

Symptoms

- Minor involuntary movements
- Subtle loss of coordination
- Difficulty thinking through complex problems
- Possible depression, irritability, disinhibition

Level of Care

- Largely functional and independent
- Can perform activities of daily living (ADLs) without assistance

Middle Stage

Symptoms

- Chorea may be prominent
- Increasing difficulty with voluntary motor tasks; issues with swallowing, balance, falls, weight loss
- Problem solving becomes difficult

Level of Care

- Loss of ability to work or drive
- Difficulty managing finances
- Able to attend to ADLs with assistance

Late Stage

Symptoms

- Chorea may be severe or replaced with rigidity, dystonia, and bradykinesia
- Dementia; psychiatric symptoms appear and/or worsen
- Often nonverbal and bedridden in end stages

Level of Care

- Assistance required with most or all ADLs

Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011.

HD Symptoms are Patient-Specific and Require Individualized Treatment[1]

Motor

- Chorea
- Myoclonus
- Dystonia
- Rigidity
- Bradykinesia
- Tics

Psychiatric

- Major depression
- Sexual disorders
- Obsessive compulsive disorder (OCD)
- Mania
- Delirium
- Suicidal ideation

Cognitive

- Implicit memory impairment
- Loss in executive function
- Perceptual problems

Other

- Loss of self-esteem
- Weight loss
- Urinary and fecal incontinence
- Loss of sex drive
- Loss of appetite

This list is not exhaustive; HD symptoms are extensive and varied in appearance and severity

Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011

HD Treatment Goal is Symptom Management and Improved QoL[1,2]

Pharmacological

- Address hyperkinetic movements
- Consider psychiatric risks/benefits of medications

Quality of Life (QoL) Measures

- Regular monitoring of treatment efficacy and disease progression
- UHDRS TFC scales

Symptom Management

Integrated Care Team

- Address hyperkinetic movements
- Consider psychiatric risks/benefits of medications

Family/Social Support

- Involvement of care partners
- Leverage patient/caregiver support and advocacy groups

AIMS, Abnormal Involuntary Movements Scale; TFS, Total Functional Capacity; UHDRS, Unified Huntington's Disease Ratings Scale

1. Frank S. Treatment of Huntington's Disease. Neurotherapeutics. 2014;11(1):153-60. 2. Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011

The Burden of Huntington's Disease

The Individual

Early awareness of HD risk leads to anticipatory stress, anxiety and hopelessness[1]

-

Fear of lost independence and symptom progression creates a psychological burden[2]

-

Prominent chorea is associated with higher levels of anxiety and stigma[2]

-

Social stigma is associated with decreased confidence and social interaction[2]

The Caregiver

An HD diagnosis impacts the extended genetic family[3]

-

HD impacts patients during their prime working years[3]

-

Psychological aspects of patient care may overwhelm caregivers as HD progresses[1]

-

Caregivers both observe and are heavily impacted by the behavioral and psychiatric symptoms of HD

-

Stigma associated with visible motor symptoms extends to caregivers[2]

1. Ready RE, Mathews M, Leserman, et al. Patient and Caregiver Quality of Life in HD. Movement Disorders. 2008;23(5):721-6. 2. Thorley EM, Iyer RG, Carlozzi NE, et al. Understanding How Chorea Affects Health-Related Quality of Life in Huntington Disease: An Online Survey of Patients and Caregivers in the United States. Patient. 2018:11(5):547-59. 3. Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011

HD Overview – Key Takeaways

HD is a rare hereditary and ultimately fatal neurodegenerative disorder

Average age of onset is 45, and average age of death is 56

HD is associated with neuronal loss in the cortex and striatum

HD disease manifestation is dependent on CAG repeats in the HTT gene

Symptoms typically grouped into motor, cognitive, and psychiatric

Symptoms evolve over course of disease, requiring variable levels of care

No cure; symptom management and improved QoL are goals of treatment

HD, Huntington Disease; HTT, Huntingtin gene; QoL, quality of life; UHDRS, Unified Huntington's Disease Ratings Scale

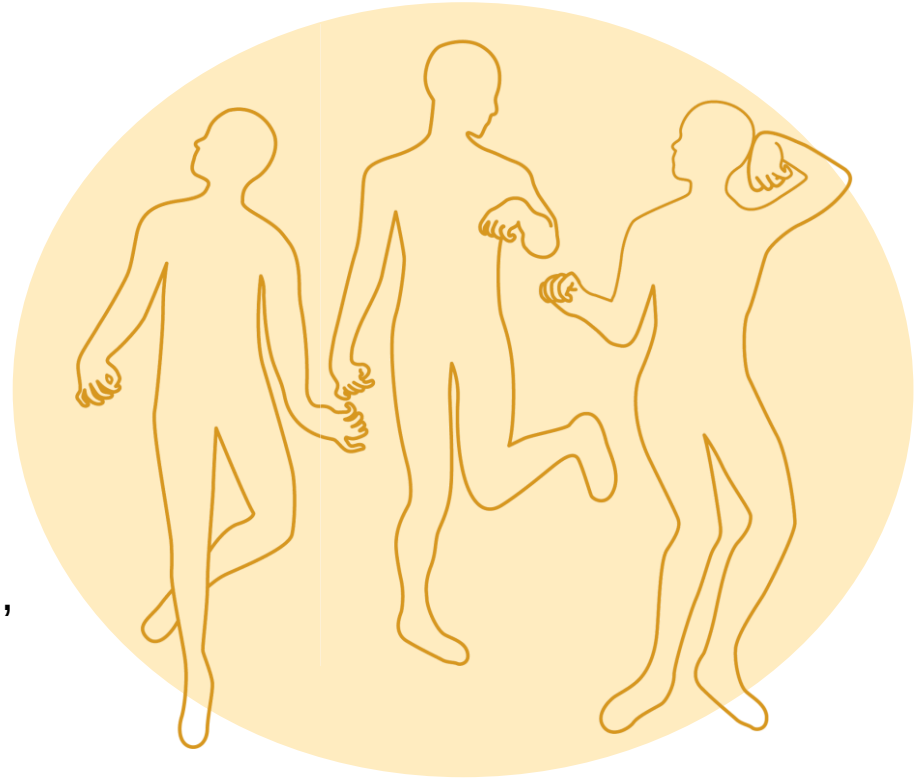
Huntington’s Disease Chorea

Chorea is a Hallmark Symptom of HD

~90% of people with HD experience chorea[1]

Chorea is typically the symptom leading to diagnosis of HD[2]

- Increases in **intensity and affected body regions** over time, starting at the extremities and progressing to the face, neck, shoulder and trunk[1-3]
- The evolution of chorea **varies for each patient**[1]



Chorea is characterized by sudden, irregular, unpredictable, involuntary movements[2,3]

HD, Huntington's disease; OBL, oral-buccal-lingual.

1. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition.* Huntington's Disease Society of America; 2011. 2. Frank S. *Neurotherapeutics*. 2014;11(1):153-160. 3. Cubo E, et al. Accessed July 7, 2021. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Chorea--Huntingtons-Disease.htm.

Impact of Chorea

Physical/Functional Impact[1-3]

- Speaking and swallowing
- Walking, frequent falls and injuries
- Getting in and out of bed
- Cooking/eating, taking medication
- Getting dressed/washed
- Using the restroom
- Stop working due to worsening symptoms
- Assistance with daily activities from caregivers

Social/Emotional Impact[1,3,4]

- Anxiety and stress
- Require emotional support from caregivers
- Embarrassment
- Isolation
- Social stigma (often mistaken for drunkenness)

Most patients and caregivers consider **managing chorea as "very important"[1]***

71%
of caregivers

59%
of patients

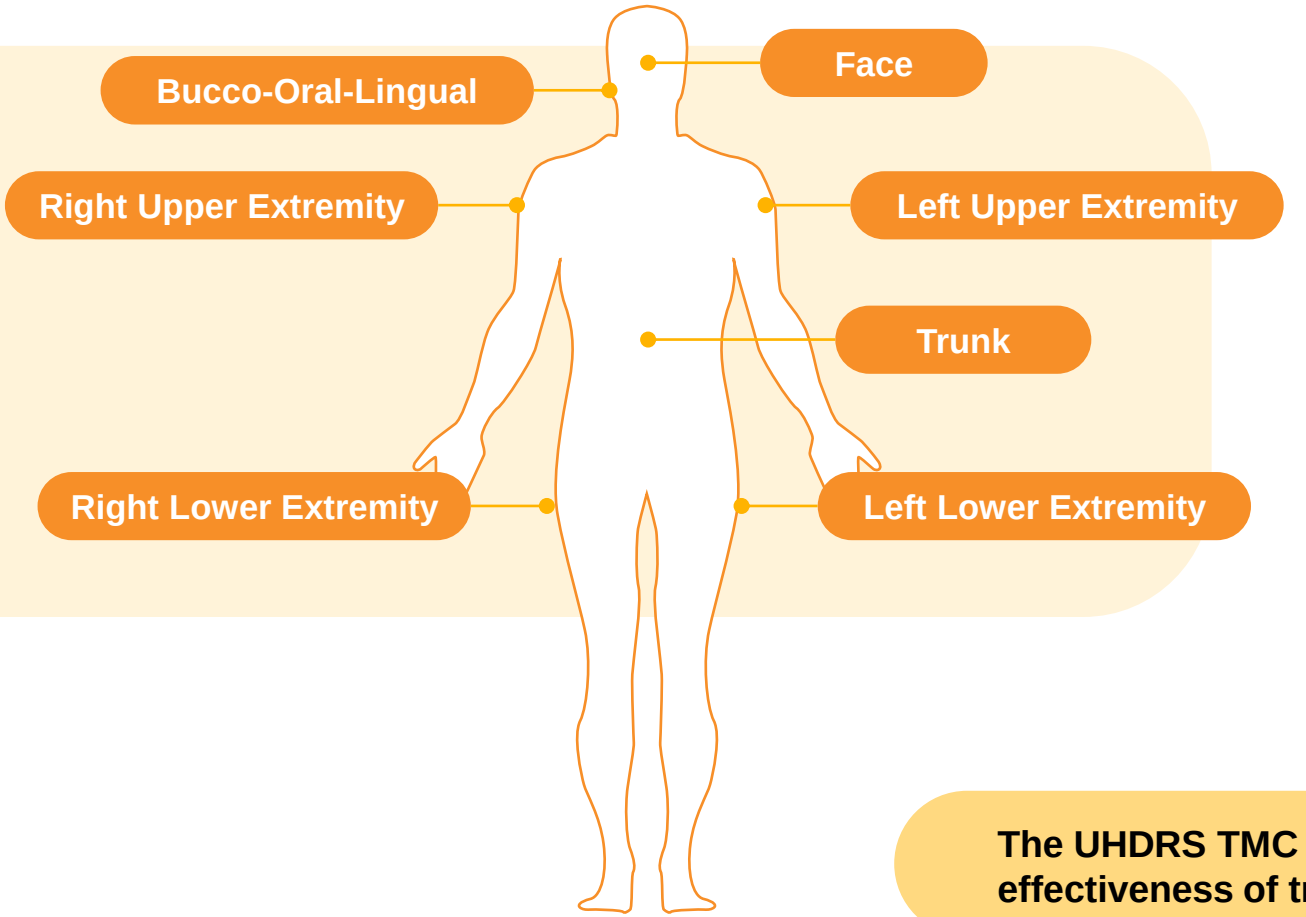
Top reasons why patients indicated chorea management was important[1]*

- Loss of independence (18%)
- Unpredictability/uncontrollability (18%)
- Fear or chorea getting worse (15%)
- Fear of falling (15%)
- Painful/harmful (15%)
- Impact on family life (13%)

*In a survey assessing the impact of chorea on overall functioning and health-related quality of life; Survey was a 4-point Likert scale; question "How important is it to you to control of manage your chorea?"[1]

1. Thorley EM, et al. *Patient.* 2018;11(5):547-559. 2. Simpson JA, et al. *J Huntingtons Dis*. 2016;5(4):395-403. 3. Claassen DO, et al. *J Health Econ Outcomes Res.* 2021;8(1):99-105. 4. Sherman CW. *Neuropsychol Rehabil.* 2020;30(6):1150-1168.

Chorea is Assessed Using the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) Score



UHDRS Motor Assessment Chorea Scale	
Severity	
0	Absent
1	Slight/intermittent
2	Mild/common or moderate/intermittent
3	Moderate/common
4	Marked/prolonged

TMC score is the sum of the severity scores for each body region and ranges from **0 to 28**

The UHDRS TMC score is often used to assess the appropriateness and effectiveness of treatment interventions

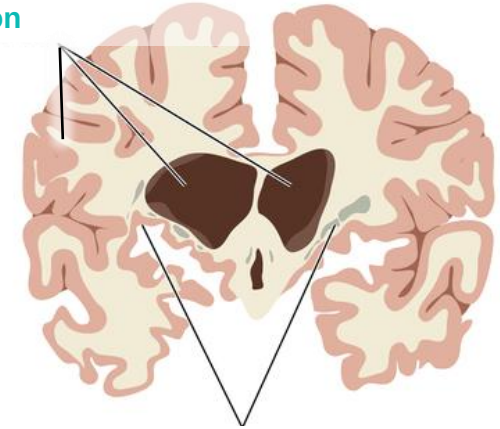
TMC, total maximal chorea; UHRDS, Unified Huntington's Disease Rating Scale.

Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition.* Huntington's Disease Society of America. 2011.

Dopamine Dysfunction in HD Chorea[1-3]

HD

Degeneration of the cortex leads to ventricle enlargement, contributing to **cognitive deterioration**



Atrophy of the basal ganglia (**striatum**) leads to movement disturbances and eventually progressive global decline

Striatal atrophy

↓

Disruption in **DA, GABA,** and **Glu** pathways

↓

Overstimulation of **DA receptors**

↓

Choreiform movement

The HD DA Synapse

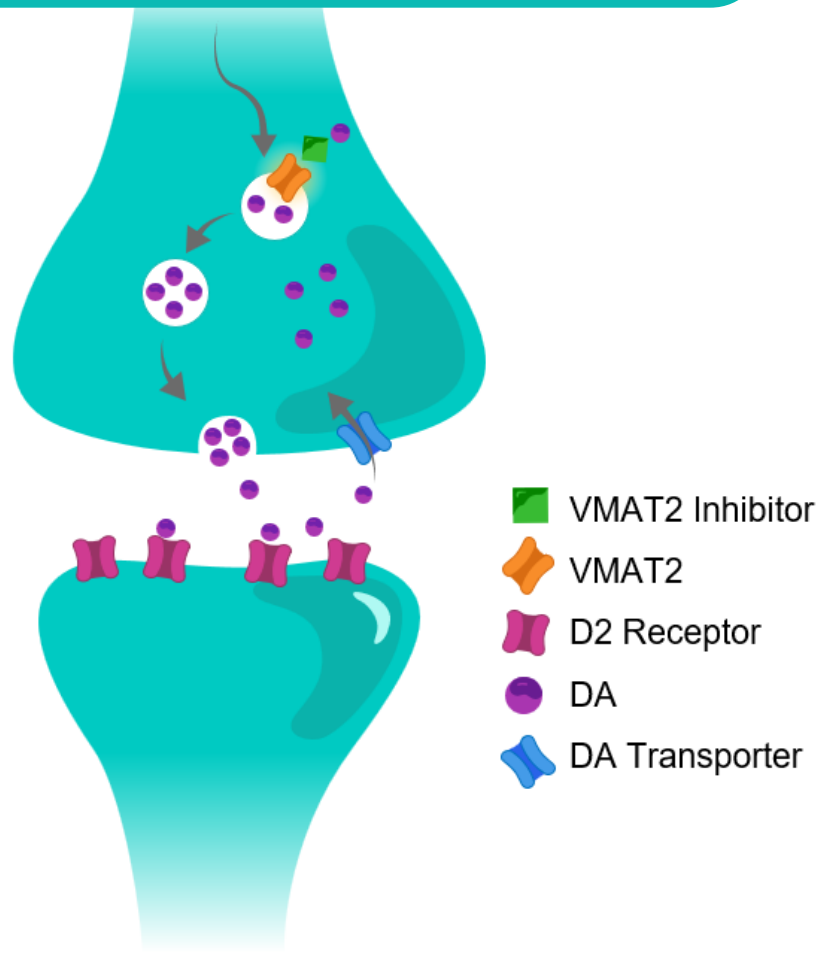


Image courtesy of The Huntington's Disease Association[3]

DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2.

1. Coppen EM, Roos RA. *Drugs*. 2017;77(1):29-46. 2. The European Huntington's Disease Network. Accessed July 7, 2021. http://www.ehdn.org/about-hd/. 3. Huntington's Disease Association. Accessed August 2, 2023. https://www.hda.org.uk/seecmsfile/?id=110

FDA-Approved Treatments

Three VMAT2 inhibitors are FDA-approved for chorea associated with HD:

Valbenazine

The highly selective VMAT2 inhibitor, approved in 2023[1,5*]

Deutetrabenazine

A deuterated version of tetrabenazine, approved in 2017[2]

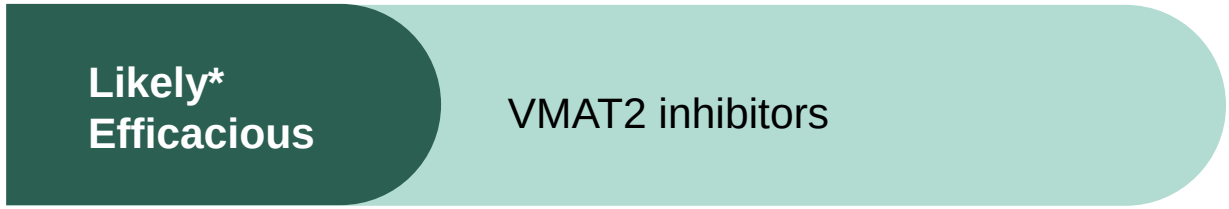
Tetrabenazine

Approved in 2008[3]

International Parkinson and Movement Disorder Society (MDS) –

Evidence-Based Review on Treatments in HD 2022[4]

Symptomatic Interventions for Chorea



Conclusion:

Data are limited and only support the use of VMAT2 inhibitors for symptomatic treatment of chorea[4]

Valbenazine was not approved at the time of this analysis, therefore was not included in the review

*From in vitro studies. ‡Based on moderate level of evidence; no direct comparisons have been conducted.

FDA, Food and Drug Administration; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2. 1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.2. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.3. XENAZINE [package insert]. Washington, DC: Prestwick Pharmaceuticals Inc. 4. Ferreira JJ, et al. Movement Disorders. 2022. 37(1):25-35. 5. Brar S, et al. Clin Pharmacol Drug Dev. 2023;12(4):447-456.

HD Chorea – Key Takeaways

Chorea is a hallmark symptom of HD

HD-related chorea is a movement disorder resulting from neurodegeneration of striatum

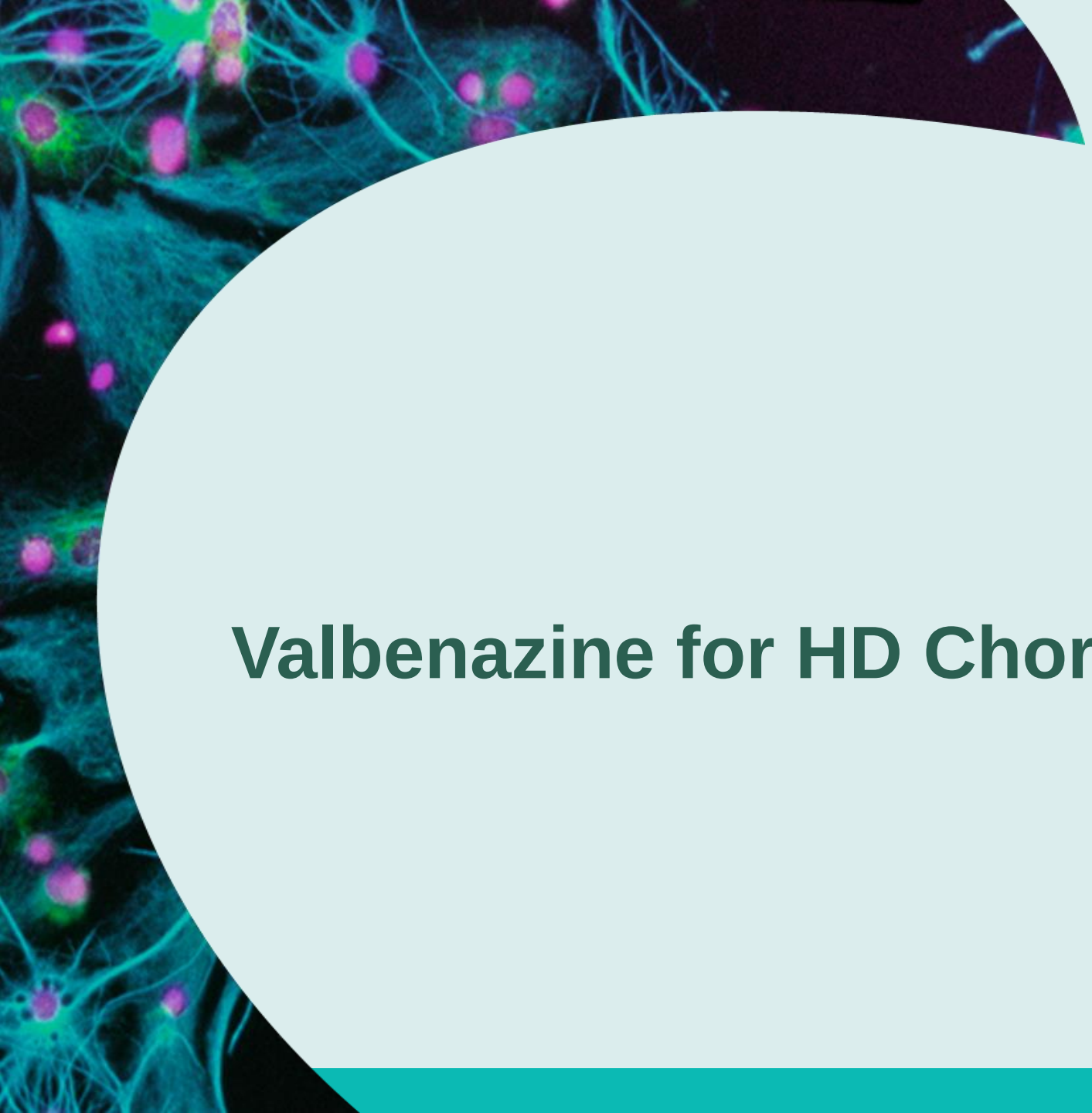
Measured using the UDHRS Motor Assessment Chorea Scale

Severity varies by patient and disease progression

MDS Guidelines only support use of VMAT2 inhibitors for HD chorea

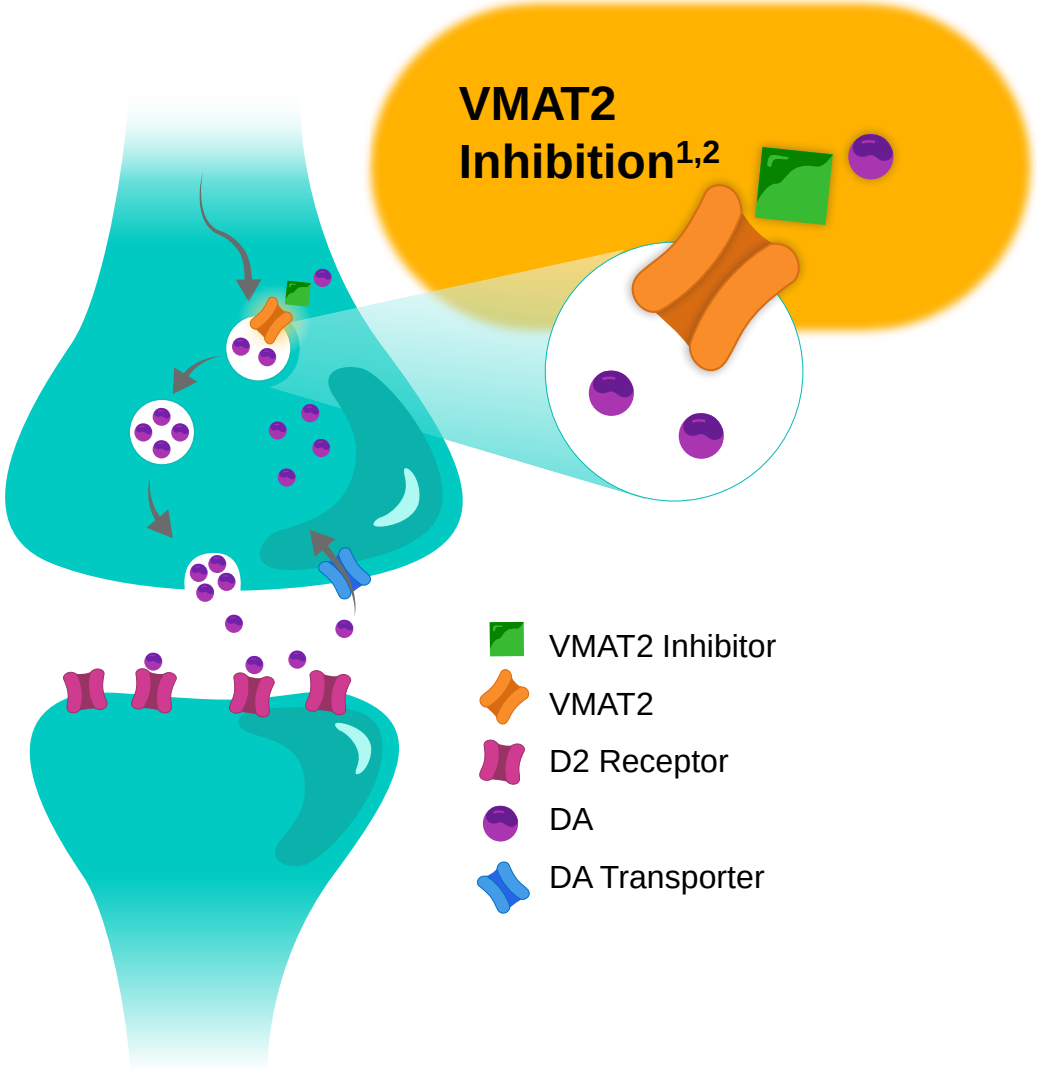
**Deutetrabenazine was approved for the treatment of HD-related chorea by the US Food and Drug Administration in 2017*

HD, Huntington disease; MSN, medium-sized spiny neurons; UHDRS, Unified Huntington's Disease Ratings Scale



Valbenazine for HD Chorea

Valbenazine Mechanism of Action



Valbenazine is FDA-approved for the treatment of adults with chorea associated with Huntington's disease[3]

The mechanism of action of valbenazine for the treatment of chorea associated with HD is unclear, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release[3]

DA, dopamine; FDA, Food and Drug Administration; HD, Huntington's disease; VMAT2, vesicular monoamine transporter 2.

1. Coppen EM, Roos RAC. Drugs. 2017:77;29-46. 2. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed July 7, 2021. https://www.ncbi.nlm.nih.gov/books/NBK548187/?report=reader. 3. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Overview

	Valbenazine[1]
Typical dosage range	40, 60, 80 mg, 1 capsule once daily
2 Formulations	INGREZZA® and INGREZZA® SPRINKLE
Renal Impairment or **Geriatric Use**	No dose adjustment
Hepatic Impairment	Maximum 40mg daily
Effect of Food	Taken with or with food
Single Active Metabolite	[+]-α-HTBZ Selective for VMAT2 only, with no appreciable binding affinity for dopaminergic, serotonergic, adrenergic, or histaminergic receptors[2]
Elimination half-life	15–22 hours

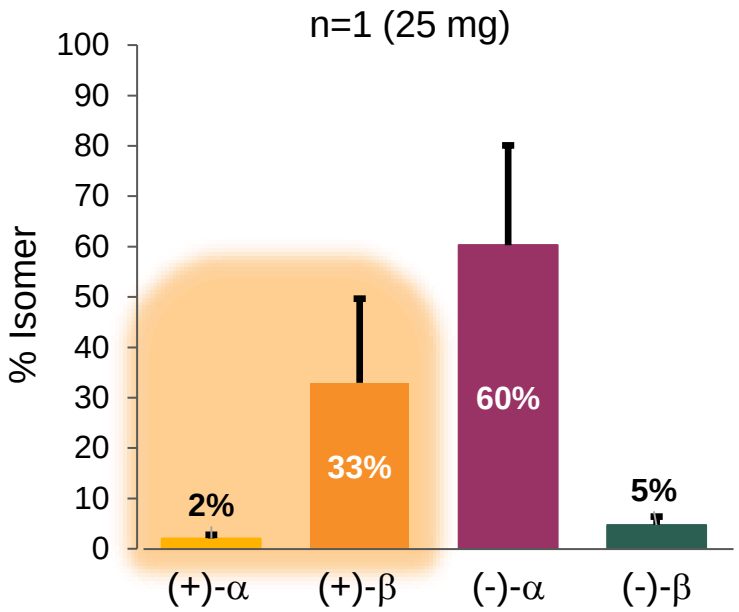
HTBZ, dihydrotetrabenazine; VBZ, valbenazine; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

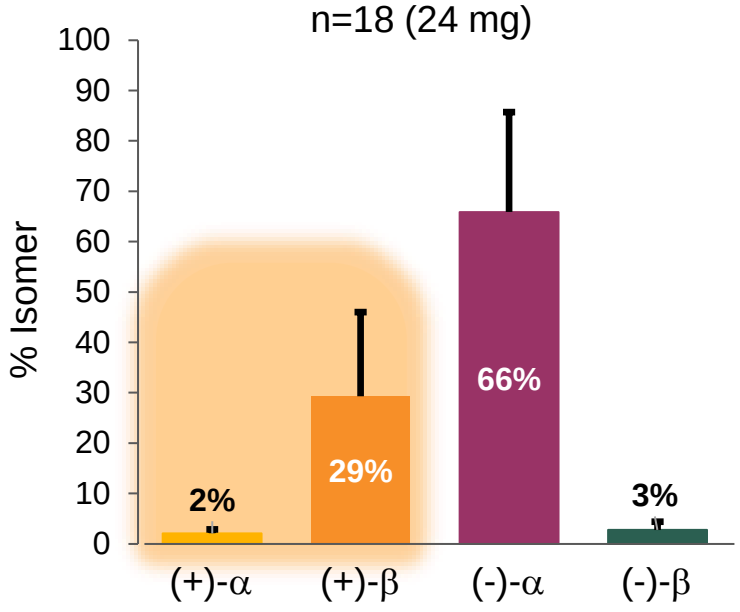
Valbenazine Delivers a Unique Metabolite Profile and Pharmacology Inhibiting VMAT2[1]

(+) isomers have a high affinity for VMAT2 with no appreciable affinity for off-target receptors (e.g., DA, 5-HT, NE)[1,2]

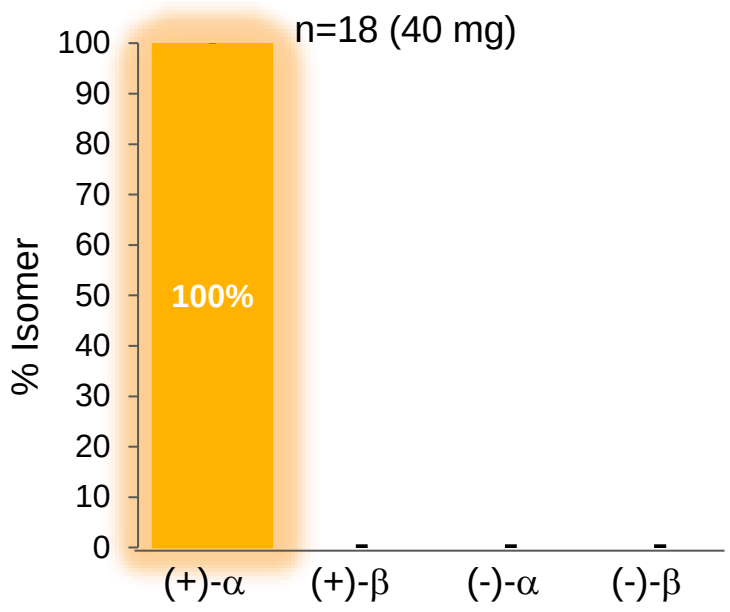
Tetrabenazine
HTBZ Isomer Profile[1]



Deutetrabenazine
HTBZ Isomer Profile[2†]



Valbenazine
HTBZ Isomer Profile[2†]



High binding affinity to VMAT2

*Concentrations of HTBZ isomers were determined in a serum sample, from 1 patient taking tetrabenazine 25 mg, that was purchased from a commercial specimen bank. †The pharmacokinetics of valbenazine and its [+]-a-HTBZ metabolite, and each of the 4 deutetrabenazine metabolites, were assessed in 18 male subjects randomized to receive single-dose valbenazine 40 mg and deutetrabenazine 24 mg (two 12 mg tablets). In this phase 1, open-label, crossover study, blood samples were obtained predose and at multiple intervals postdose. Graphs represent % isomer of area under the curve from time 0 to infinity. High binding affinity defined as relatively lower K_i (<1000 nM).

VMAT2, vesicular monoamine transporter 2; HTBZ, dihydrotetrabenazine; K_i, inhibitory constant; nM, nanomolar.

1. Skor H, et al. *Drugs* R D. 2017;17(3):339-359 2. Brar S, et al. *Clin Pharmacol Drug Dev*. 2023 Apr;12(4):447-456.

These data do not imply superiority of any compound. Head-to-head trials comparing tetrabenazine, deutetrabenazine, or valbenazine have not been conducted.

INGREZZA and INGREZZA SPRINKLE Important Safety Information

Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

CONTRAINDICATIONS

INGREZZA and INGREZZA SPRINKLE are contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA or INGREZZA SPRINKLE.

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA or INGREZZA SPRINKLE.

Somnolence and Sedation: INGREZZA and INGREZZA SPRINKLE can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA or INGREZZA SPRINKLE.

TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

INGREZZA and INGREZZA SPRINKLE Important Safety Information

QT Prolongation: INGREZZA and INGREZZA SPRINKLE may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA and INGREZZA SPRINKLE should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA or INGREZZA SPRINKLE, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism: INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

The most common adverse reaction in patients with tardive dyskinesia (≥5% and twice the rate of placebo) is somnolence. The most common adverse reactions in patients with chorea associated with Huntington's disease (≥5% and twice the rate of placebo) are somnolence/lethargy/sedation, urticaria, rash, and insomnia.

NMS, neuroleptic malignant syndrome; VMAT2, vesicular monoamine transporter 2.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.