Neurocrine Biosciences: Overview of Valbenazine and Related Disease States

NEUROCRINE® BIOSCIENCES

MED-MSL-VBZ-US-0013_v1

Table of Contents

About Neurocrine Biosciences

For three decades, Neurocrine Biosciences, headquartered in San Diego, CA, has been dedicated to discovering and developing life-changing treatments for patients with under-addressed neurological, neuroendocrine and neuropsychiatric disorders.

Our Purpose

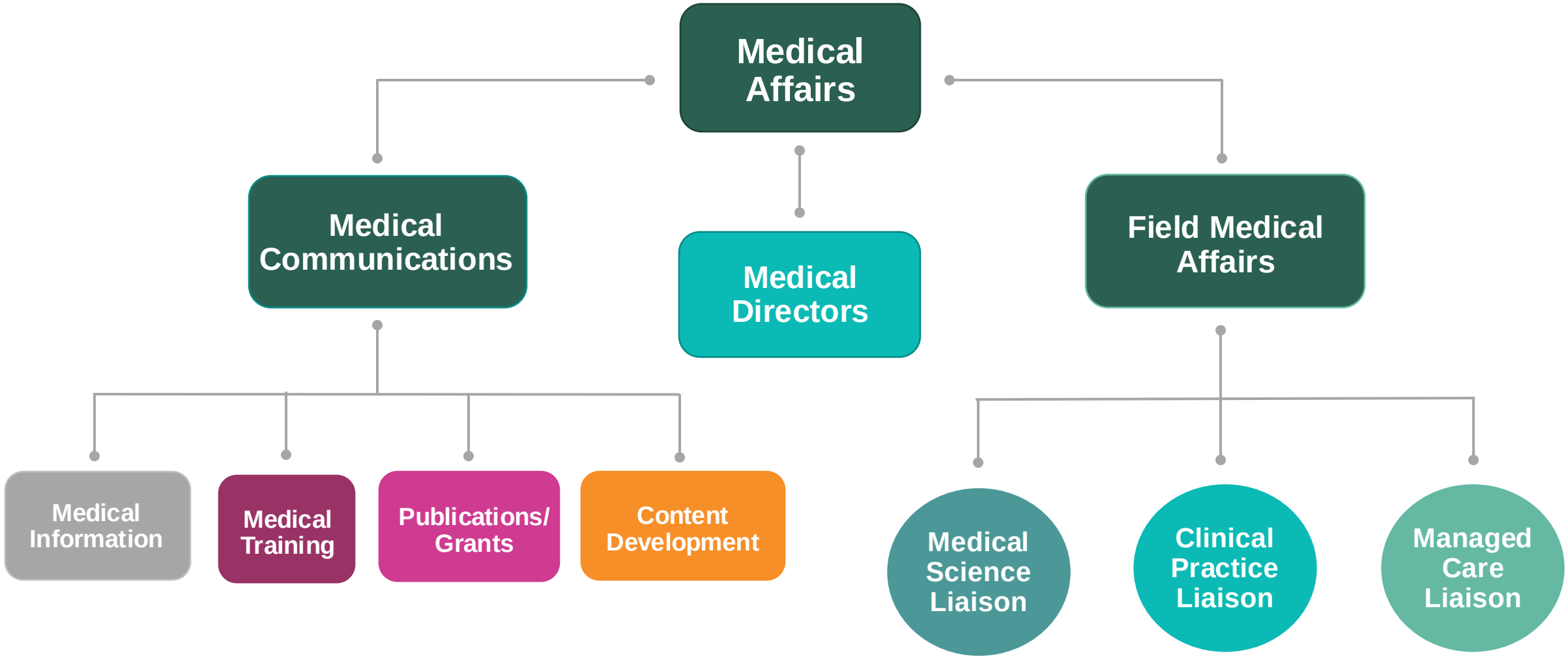
To relieve suffering for people with great needs, but few options

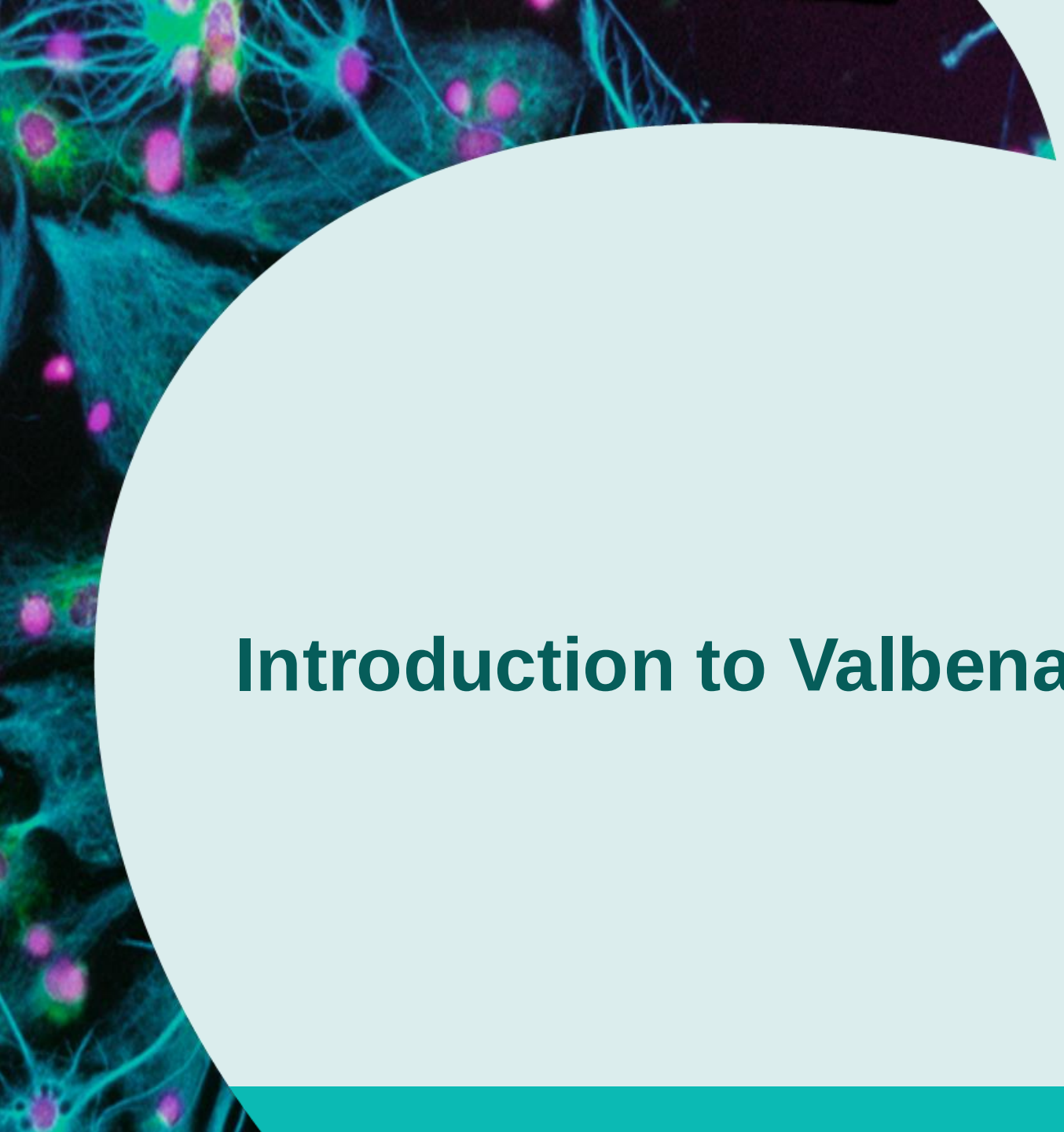
Our Values

Passion
Integrity
Collaboration
Innovation
Tenacity

Neurocrine Biosciences is dedicated to advancing science through research and development

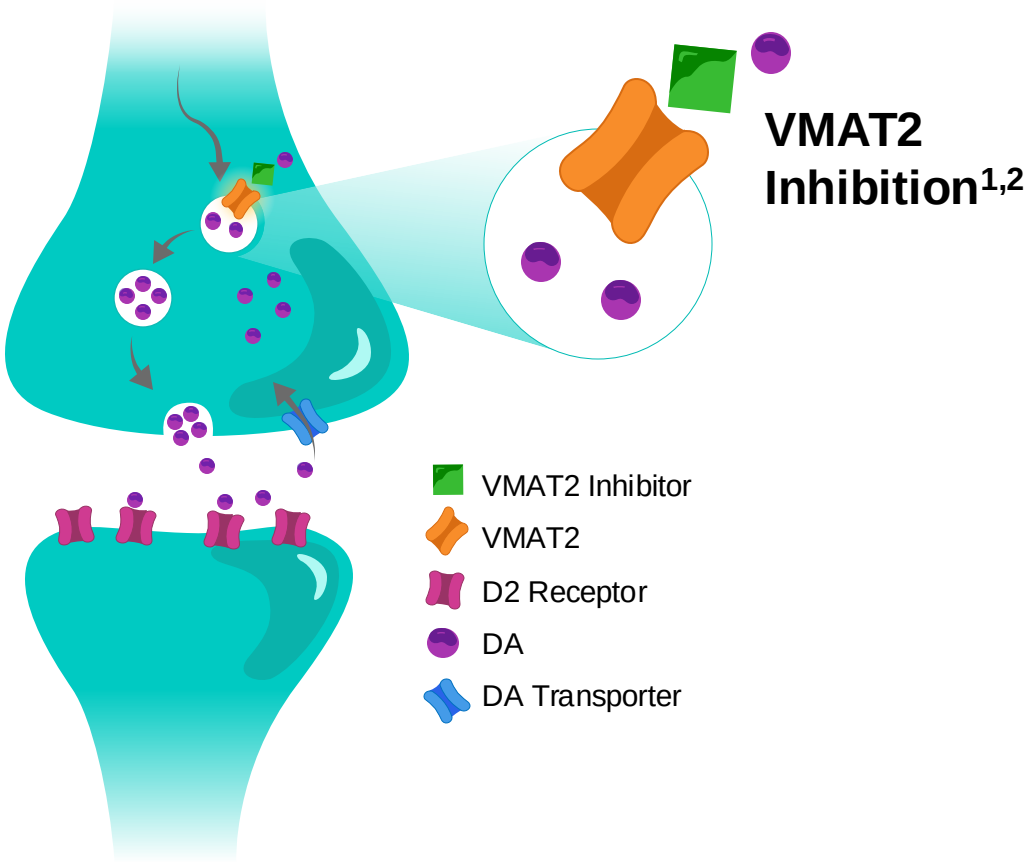
Groups Within Neurocrine Medical Affairs





Introduction to Valbenazine

Valbenazine Mechanism of Action



Valbenazine is FDA-approved for the treatment of adults with:

- Tardive dyskinesia (TD)
- Chorea associated with Huntington's disease (HD)

The mechanism of action of valbenazine for the treatment of TD and chorea associated with HD is unclear, but is thought to be mediated through the reversible inhibition of VMAT2[1]

Valbenazine Mechanism of Action Video

FDA, Food and Drug Administration; HD, Huntington's disease; PI, Prescribing Information; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

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

Valbenazine Overview

Valbenazine[1]

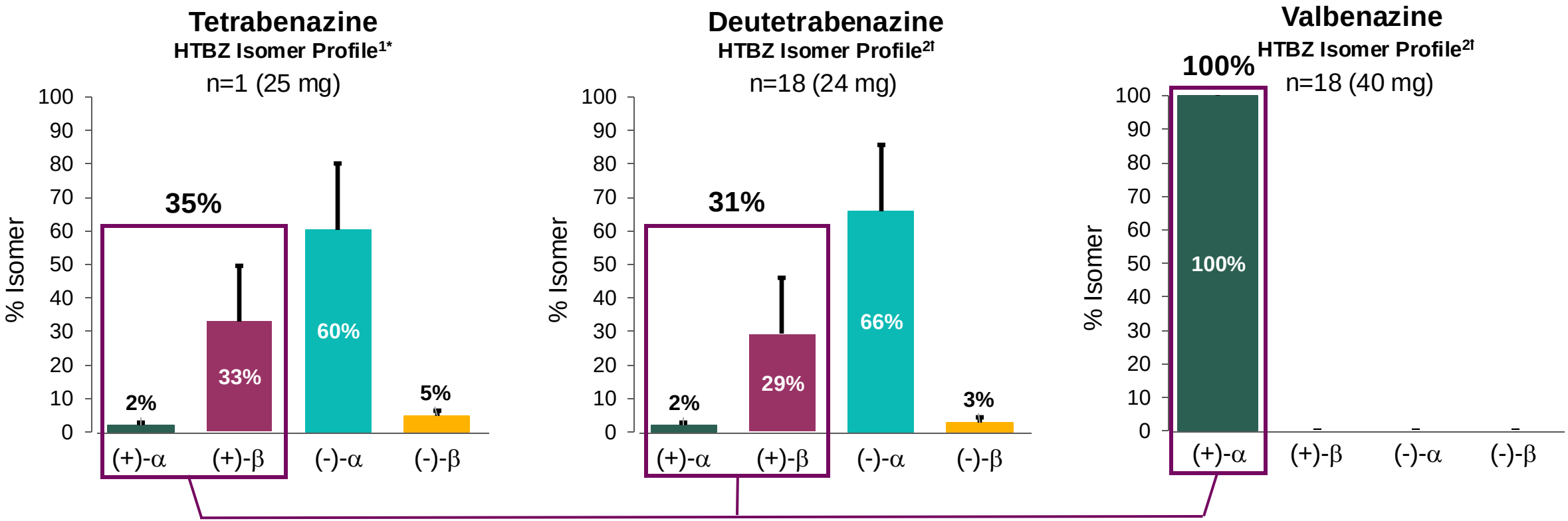
Typical dosage range	40, 60, 80 mg, 1 capsule once daily
2 Formulations	INGREZZA® INGREZZA® SPRINKLE
Renal Impairment or **Geriatric Use**	No dose adjustment
Hepatic Impairment	40mg once daily for moderate or severe hepatic impairment (Child-Pugh score 7 to 15)
Effect of Food	Taken with or with food
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]



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).

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

Additional Pharmacology Information

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.

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

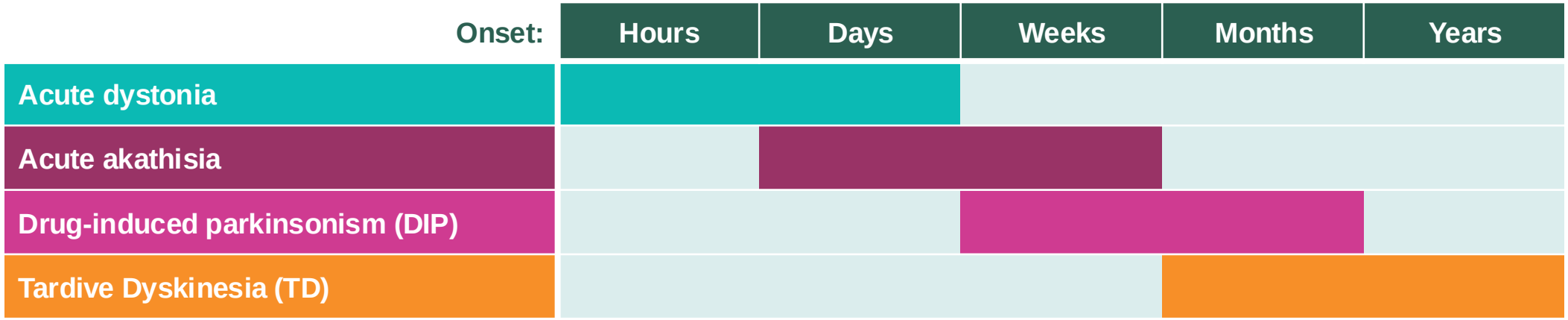
Tardive Dyskinesia and Valbenazine

DRBA-induced Movement Disorders

- DRBA-induced movement disorders are associated with medications commonly used to **manage psychiatric disorders or GI problems**, such as **antipsychotics and metoclopramide**[1,2]
- DRBA-induced movement disorders can include acute presentations or may present after prolonged use of DRBAs (i.e., tardive)[1,2,3]

"Extrapyramidal symptoms" (EPS) is an **obsolete umbrella term** that has been used to describe a collection of DRBA-induced movement disorders[4]

- Classification of these under EPS may be problematic as **each syndrome has its own pathophysiology, presentation, and treatment**[5]

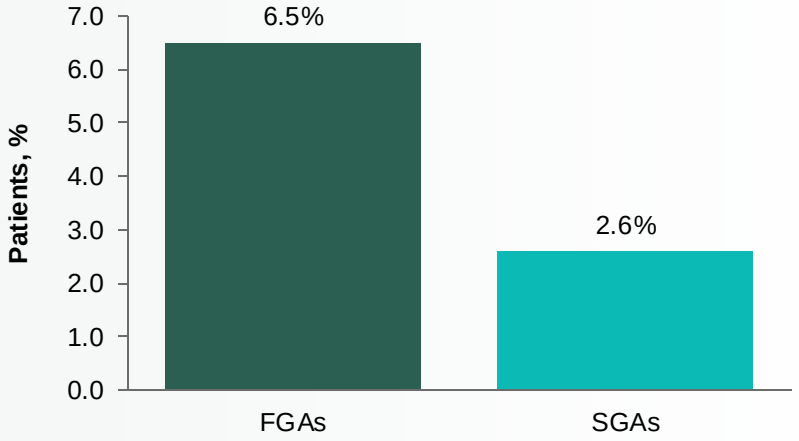


DRBA, dopamine receptor–blocking agent; EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.

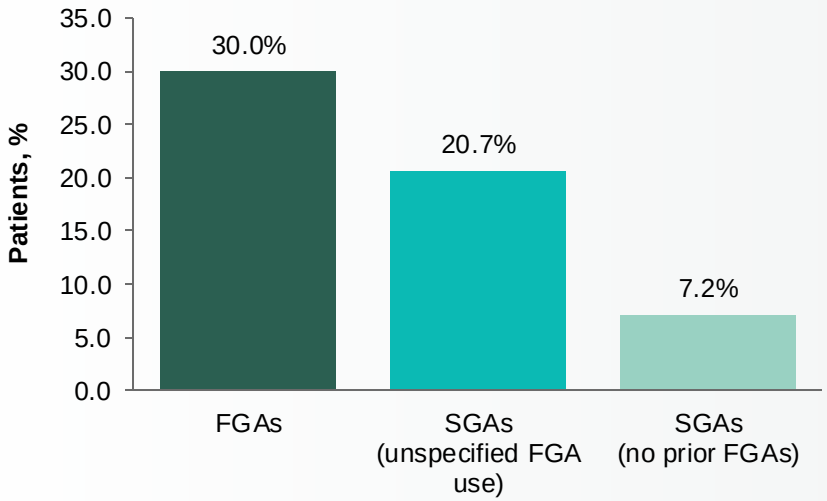
1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.* American Psychiatric Association; 2013. 2. Fahn S, et al. *Principles and Practice of Movement Disorders*. 2nd ed. Elsevier Inc.; 2011. 3. Hauser RA, et al. *CNS Spectrums*. 2020:1-10. 4. Mehta SH and Sethi KD. Drug-induced movement disorders. In: Poewe W, Jankovic J, eds. *Movement Disorders in Neurologic and Systemic Disease*. Cambridge University Press; 2014:203-219. 5. Caroff SN, Campbell EC. *Psychiatr Clin North Am*. 2016;39(3):391-411.

TD Is Associated With Prolonged DRBA Treatment

TD Annual Incidence[1]*



TD Prevalence[2]†



~5 million patients in the US are treated with antipsychotics[3]
≥600,000 patients may have TD[3,4]‡

*2018 meta-analysis of 57 randomized controlled trials (FGA-SGA studies, N=10,706; SGA-SGA studies, N=9153). †2017 meta-analysis of 41 studies (N=11,493).
‡Estimate from a 2014 analysis of prescriptions and incidence rates.
DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.

1. Carbon M, et al. *World Psychiatry*. 2018;17(3):330-340. 2. Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278. 3. Cloud LJ, et al. *Neurotherapeutics*. 2014;11:166-176. 4. Data on file. Neurocrine Biosciences.

Trends in Antipsychotic Prescribing

TD is a Clinically Distinct, Delayed DRBA-induced Movement Disorder[1]

Defined as abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with medications that block postsynaptic dopamine receptors

TD movements may be:*

Choreiform	Rapid, jerky, nonrepetitive
Athetoid	Slow, sinuous, continual
Semirhythmic	E.g., stereotypies

DRBAs can include:

- FGAs
- SGAs
- Gastrointestinal medications, such as metoclopramide

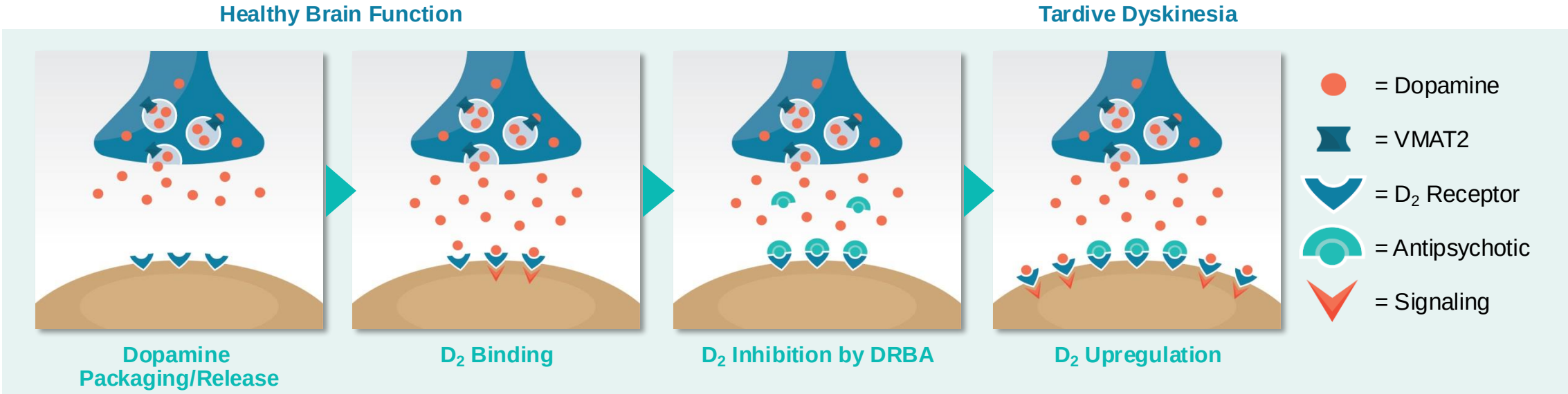
Jaw, Tongue, Neck → **OBL and Legs** → **Jaw, Hand, Face** → **Leg, Shoulder, Face**

DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; OBL, oral-buccal-lingual; SGA, second-generation antipsychotic; TD, tardive dyskinesia.
*Movements are distinctly different from the rhythmic tremors (3–6 Hz) commonly seen in drug-induced parkinsonism.[1]

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision.* American Psychiatric Association; 2022.

TD Pathophysiology

- The mechanism underlying TD is complex, and the exact cause has not been fully elucidated[1-4]
- A leading theory is the upregulation and subsequent hypersensitivity of brain dopamine D_2 receptors following prolonged exposure to DRBAs[1]
- Additional hypotheses include DRBA-induced:
  - Oxidative stress from free radical formation[2]
  - Dysfunction of GABA and/or serotonin pathways[3,4]



TD Mechanism of Disease Video

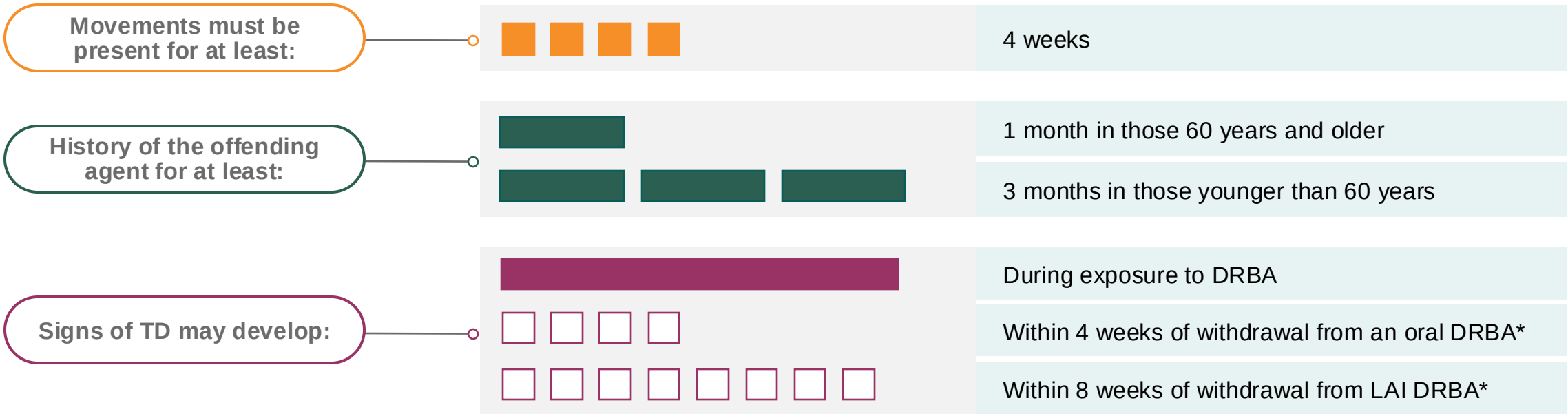
Valbenazine MOA in TD

DRBA, dopamine receptor–blocking agent; GABA, gamma-aminobutyric acid; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2.

1. Klawans H, et al. *Acta Neurol Scand*. 1970;46(4):409-441. 2. Pai BN, et al. *Biol Psychiatry*. 1994;36(7):489-491. 3. Segman RH, et al. *Mol Psychiatry*. 2001;6(2):225-229. 4. Gittis AH, et al. *J Neurosci*. 2011;31(44):15727-15731.

Diagnosis of TD

- Health care providers use clinical evaluation and medical history to diagnose TD
- TD may appear in patients also experiencing other DRBA-induced movement disorders



Screening Guidelines

Scoring AIMS

DRBA, dopamine receptor–blocking agent; TD, tardive dyskinesia; LAI, long-acting injectable.
*Dyskinesia may remit with continued withdrawal. A diagnosis of TD may be warranted if the dyskinesia persists for at least 4 weeks.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*. American Psychiatric Publishing; 2022.

2020 APA Guideline: TD Recommendations

2018 Systematic Review[1]

Intervention	Category	Conclusion
VBZ	LEVEL A	Recommended as **first-line treatment**
Deutetrabenazine	LEVEL A	Recommended as **first-line treatment**

2020 APA Guideline Recommendations[2]

Intervention	Category	Conclusion
Reversible VMAT2 inhibitor for treatment of TD	1B	**Recommended in moderate to severe, or disabling TD**
	N/A*	**Can be considered in mild TD** based on factors such as patient preference, associated impairment, or effect on psychosocial functioning

VMAT2 inhibitors are recommended and/or considered in the full severity spectrum of TD

2018 Review Treatment Algorithm

AAN, American Academy of Neurology; APA, American Psychiatric Association; DRBA, dopamine receptor–blocking agent; N/A, not available; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2; VBZ, valbenazine. 2013 AAN guidelines were published before available treatments were approved for adults with TD. 2018 systematic review aimed to update the evidence-based recommendations and provide a practical algorithm for treatment of TD.
*GRADE ratings were only assigned for primary guideline statements.

1. Bhidayasiri R, et al. *J Neurol Sci*. 2018;389:67-75. 2. American Psychiatric Association. Clinical practice guidelines for treatment of patients with schizophrenia. Accessed on March 8, 2023. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841.

Huntington’s Disease Chorea and Valbenazine

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

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

Inherited in an **autosomal-dominant** manner

HTT gene

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

Triad of symptoms: motor, cognitive, and psychiatric

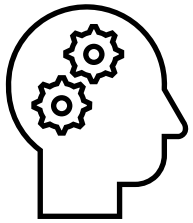
Currently no cure; treatment goals are to manage symptoms and improve QoL

HD, Huntington's disease; 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 HD

Individuals with HD exhibit a wide range of symptoms in 3 key areas:[1,2]



Motor Symptoms

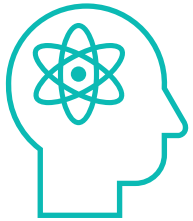
Involuntary movements (chorea) and impaired voluntary movements

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

Cognitive Symptoms

Reduced speed and flexibility in mental processing and executive function[3*]

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



Psychiatric Symptoms

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.
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. 3. Cristofori I, et al. Executive functions. *Handb Clin Neurol.* 2019;163:197-219.

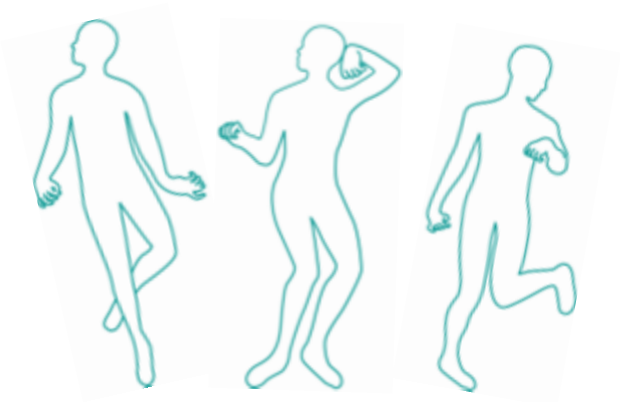
Chorea is a Hallmark Symptom of HD

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

~90% of people with HD have chorea[3]

Chorea is typically, the symptom leading to **diagnosis of HD**[4]

- Chorea is characterized by sudden, irregular, unpredictable, involuntary movements[4,5]
- Increases in **intensity and affected body regions** over time, starting at the extremities and progressing to the face, neck, shoulder and trunk[3-5]
- The evolution of chorea **varies for each patient**[3]



Face and OBL → **Trunk** → **Extremities** → **Gait**

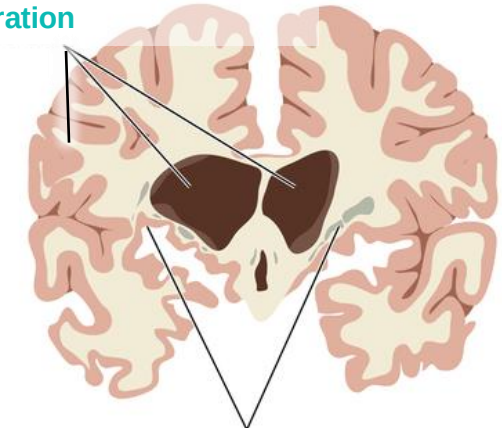
HD, Huntington's disease. OBL, Oral-Buccal-Lingual.

1. Yohrling G, et al. *Neurology.* 2020;94(15 Supplement). 2. Huntington's Disease Society of America. Accessed March 27, 2023. https://hdsa.org/what-is-hd/overview-of-huntingtons-disease. 3. Nance M, et al. *A Physician's Guide to the Management of Huntington's Disease 3rd Edition.* Huntington's Disease Society of America; 2011. 4. Frank S. *Neurotherapeutics*. 2014;11(1):153-160. 3 5. Cubo E, et al. Accessed July 7, 2021. https://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Chorea--Huntingtons-Disease.htm.

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

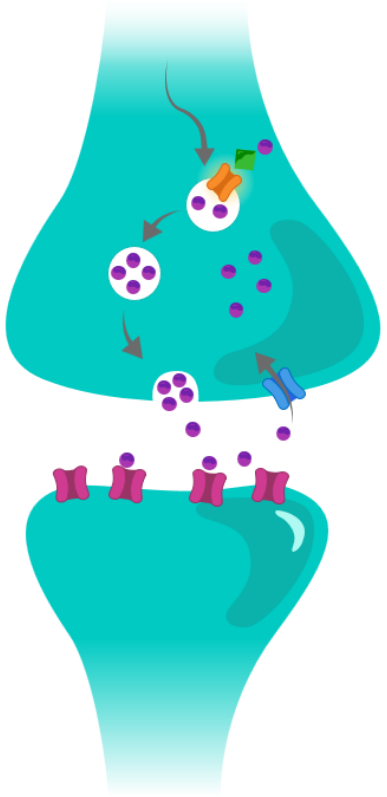
↓

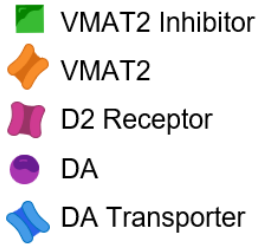
Overstimulation of **DA receptors**

↓

Choreiform movement

HD DA synapse





HD Chorea Mechanism of Disease Video

Valbenazine MOA in HD Chorea

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

Impact of Chorea on Patients With HD

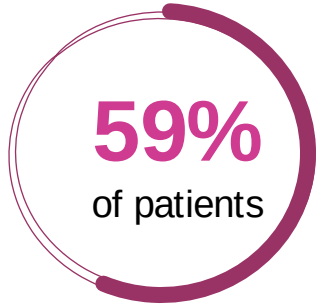
Physical/Functional Impact[1-3]

- 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]***



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 (HRQoL); Survey was a 4-point Likert scale; question "How important is it to you to control of manage your chorea?"[1]
^In the same survey assessing impact of chorea on overall functioning and HRQoL; based on respondents who reported managing chorea was at least "slightly important": asked as an open-ended question why it was important to mange chorea. Overall themes listed.[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.

Appendix

Screen All Patients Taking Antipsychotics at Each Visit

Due to the serious and persistent nature of TD, accurate diagnosis is critical[1]

- Accurate diagnosis may be challenging due to the subtle and often fluctuating symptoms, especially in an older population with various comorbidities
- Misdiagnosis and inappropriate treatment selection can worsen TD[2]
- TD assessments should include regular clinical assessments and periodic assessments using a structured instrument (e.g., AIMS)[1,2]

Clinical Assessments[1,2]

All patients

Baseline → **Every clinical encounter[3]**

Structured Assessments[1]

All patients	Higher risk for TD	Lower risk for TD
Baseline	Every 6 months	Every 12 months

If new onset or exacerbation of movements is detected at any visit

CMS, Centers for Medicare & Medicaid Services; TD, tardive dyskinesia; AIMS, Abnormal Involuntary Movement Scale.

1. American Psychiatric Association. Clinical practice guidelines for treatment of patients with schizophrenia. Accessed on March 8, 2023. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841.
2. Caroff SN, et al. *J Clin Psychiatry.* 2020;81(2):19cs12983. 3. CMS. State operations manual. Appendix PP – guidance to surveyors for long term care facilities. Revised February 3, 2023. Accessed March 31, 2023. https://www.cms.gov/medicare/provider-enrollment-and-certification/guidanceforlawsandregulations/downloads/appendix-pp-state-operations-manual.pdf.

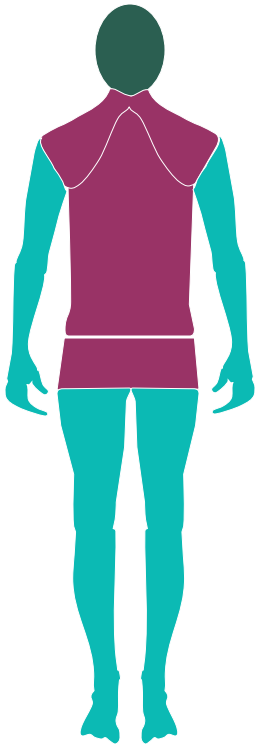
Scoring Abnormal Involuntary Movement Scale

AIMS is a 12-item, clinician-rated scale used to assess TD severity

	Facial and Oral Movements	None	Minimal	Mild	Moderate	Severe
1.	Muscles of facial expression	0	1	2	3	4
2.	Lips and perioral area	0	1	2	3	4
3.	Jaw	0	1	2	3	4
4.	Tongue	0	1	2	3	4
	Extremity Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
5.	Upper (arms, wrists, hands, fingers)	0	1	2	3	4
6.	Lower (legs, knees, ankles, toes)	0	1	2	3	4
	Trunk Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
7.	Neck, shoulders, hips	0	1	2	3	4

AIMS Total Dyskinesia Score=Sum of Items 1–7

8. Global severity of abnormal movements
9. Incapacitation
10. Awareness
11–12. Dental status



Screening Guidelines

AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.
0=no dyskinesia; 1=low amplitude, present during some, but not most of, the exam; 2=low amplitude and present during most of the exam (or moderate amplitude and present during some of the exam); 3=moderate amplitude and present during most of exam; or 4=maximal amplitude and present during most of exam.

Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Revised 1976. (DHEW publication number ADM 76-338). National Institute of Mental Health, Psychopharmacology Research Branch; 1976:534-537.

www.neurocrinemedical.com

Neurocrine Medical Affairs

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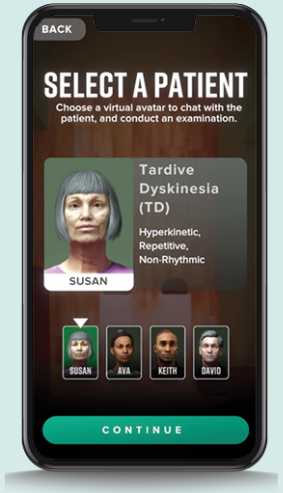
FREE EDUCATIONAL RESOURCES on Tardive Dyskinesia and Other Drug-Induced Movement Disorders

These educational resources were sponsored and developed by Neurocrine Biosciences, Inc.

Discover TD®



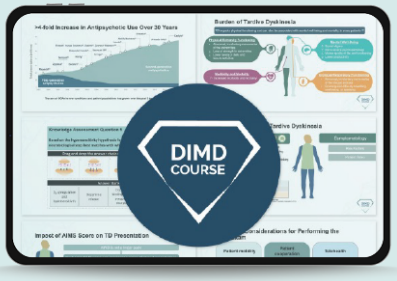
Discover TD® is an interactive experience designed to inform health care providers about tardive dyskinesia and other drug-induced movement disorders. By interacting with hypothetical virtual patients, you can diagnose and determine an appropriate management plan.[a]

[a]For educational purposes only. Should not be interpreted as medical advice for any particular patient. Individual results may vary.

Experience Discover TD®

mind-td.com/discover-td

DIMD Course



The **DIMD Course** is a free, virtual learning resource for health care providers that delves into various clinical aspects of the most common DRBA-induced movement disorders.

Join the DIMD Course

dimdcourse.getlearnworlds.com

Neurocrine Medical Website

The **Neurocrine Medical Website** houses a variety of resources, such as educational podcasts and videos, to assist healthcare providers in the recognition and appropriate differentiation of DRBA-induced movement disorders.

Visit the Neurocrine Medical Website

neurocrinemedical.com

DIMD, drug-induced movement disorder; DRBA, dopamine receptor-blocking agent; TD, tardive dyskinesia.

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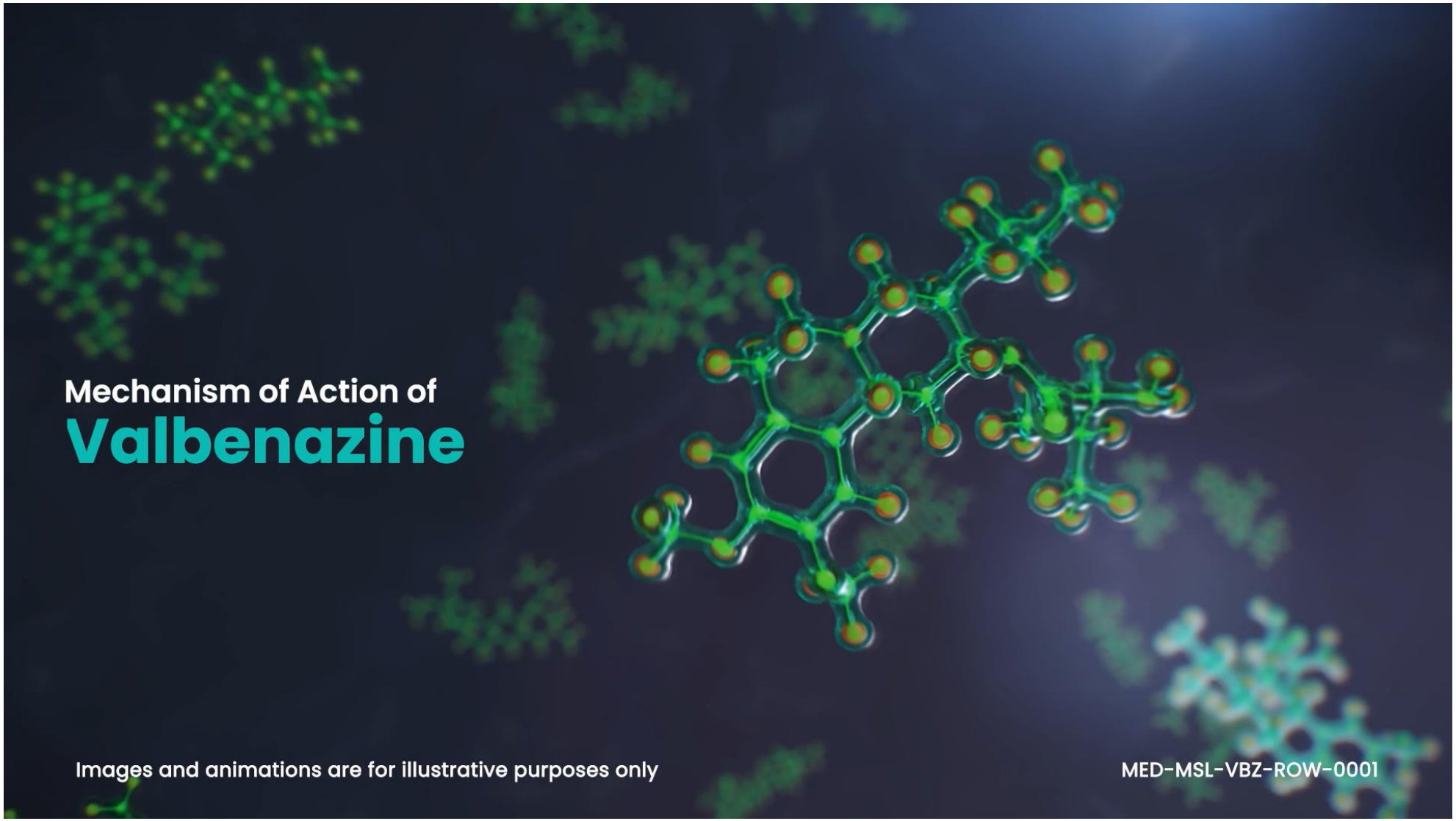
NEUROCRINE® BIOSCIENCES

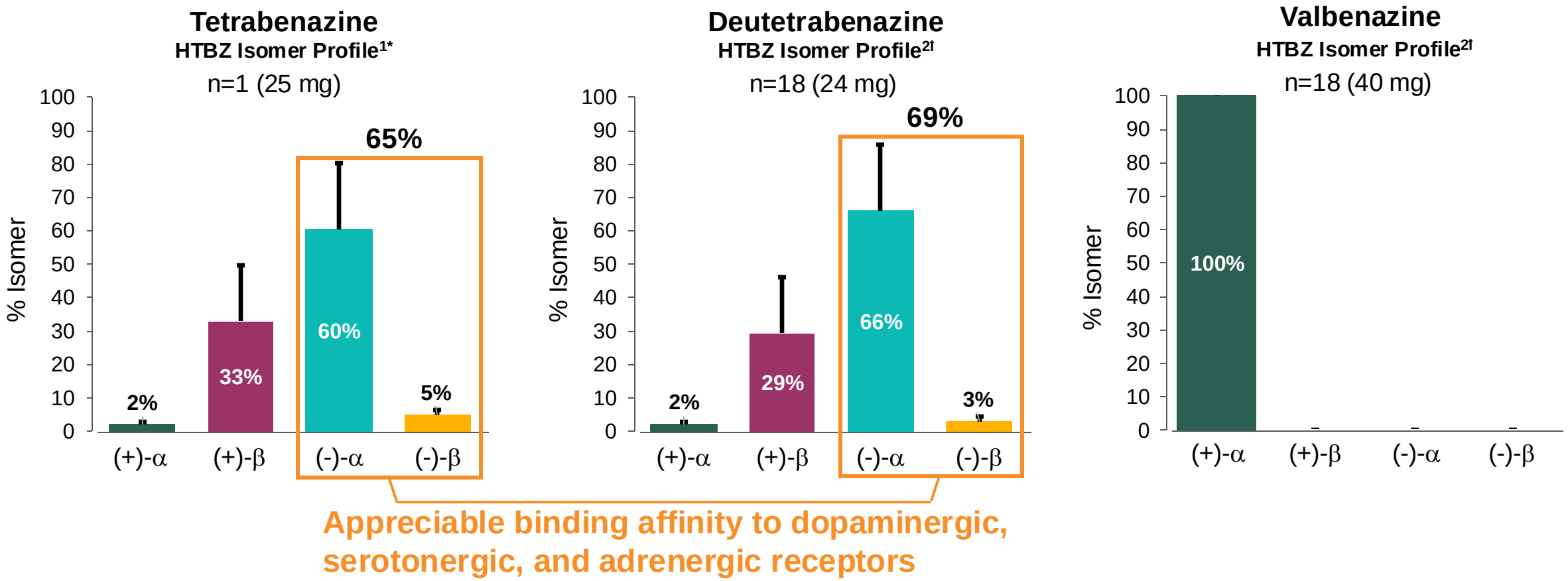
Back-Up

Valbenazine Mechanism of Action Video



Relative Concentration of HTBZ Stereoisomers of Deutetrabenazine and Valbenazine: (-) Isomer Activity

- (-) isomers have a **lower affinity for VMAT2** with **varying affinity for off-target receptors**[1,2]



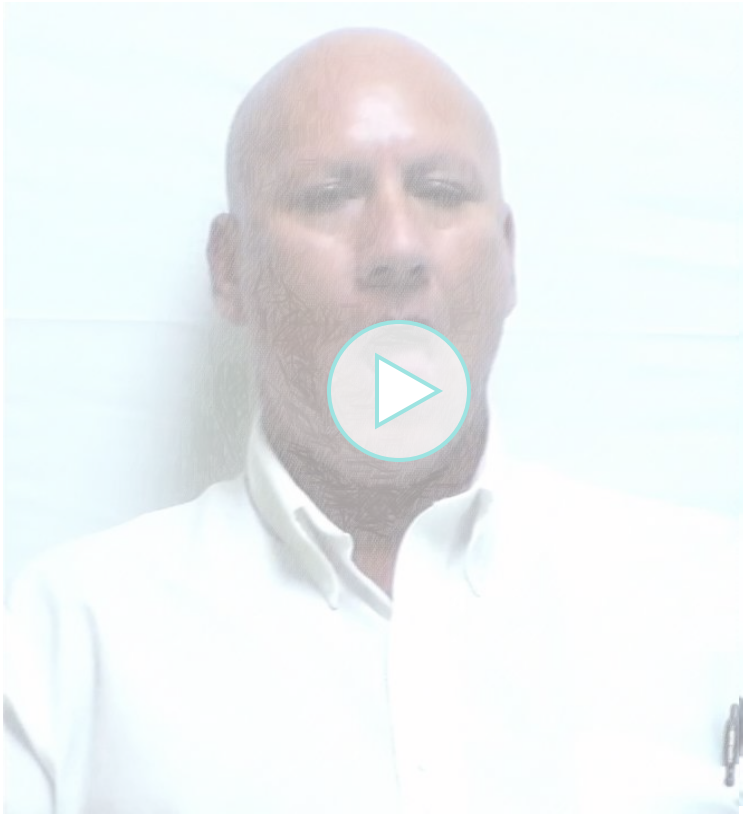
Appreciable binding affinity to dopaminergic, serotonergic, and adrenergic receptors

*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 assessedin 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 type 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.

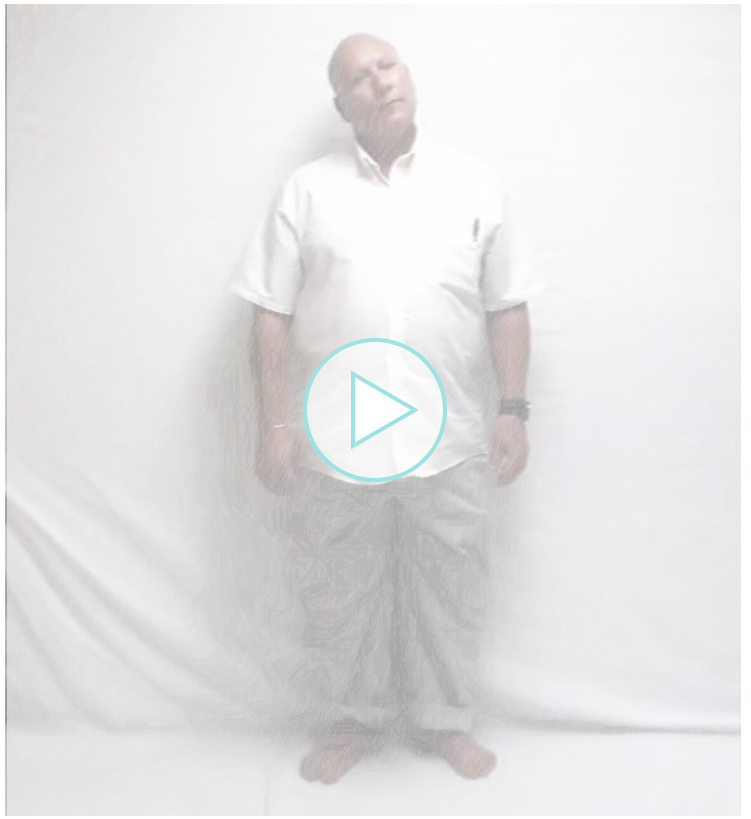
These data do not imply superiority of any compound. Head-to-head trials comparing tetrabenazine, deutetrabenazine, or valbenazine have not been conducted.

Moderate Cervical & Jaw

Open Mouth & Tongue

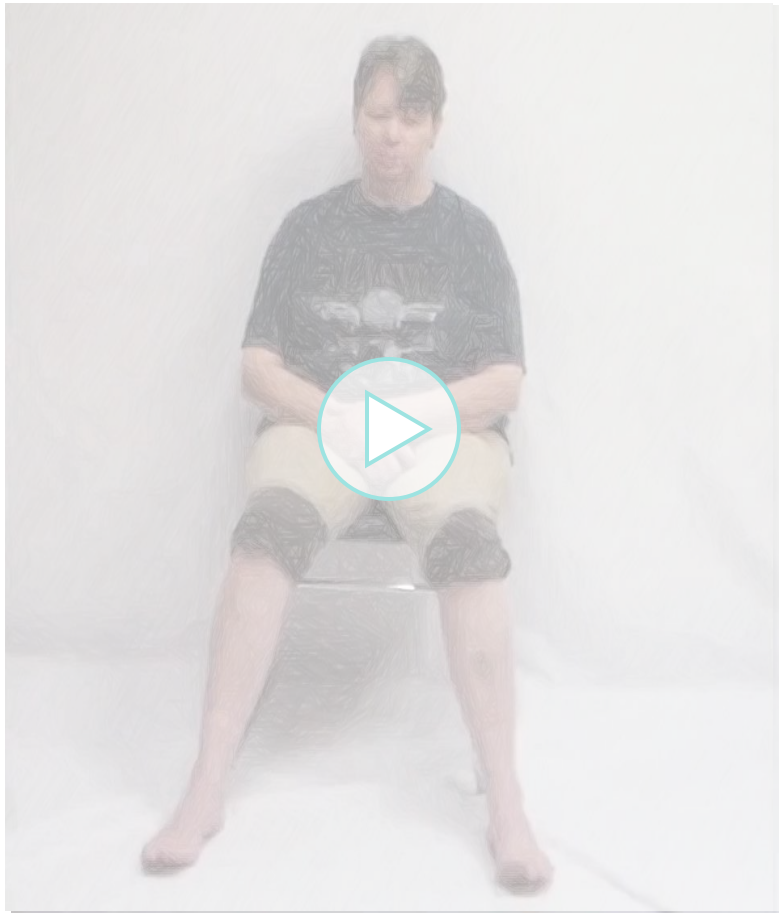


Neck, Shoulder, Hands (Standing and Walking)

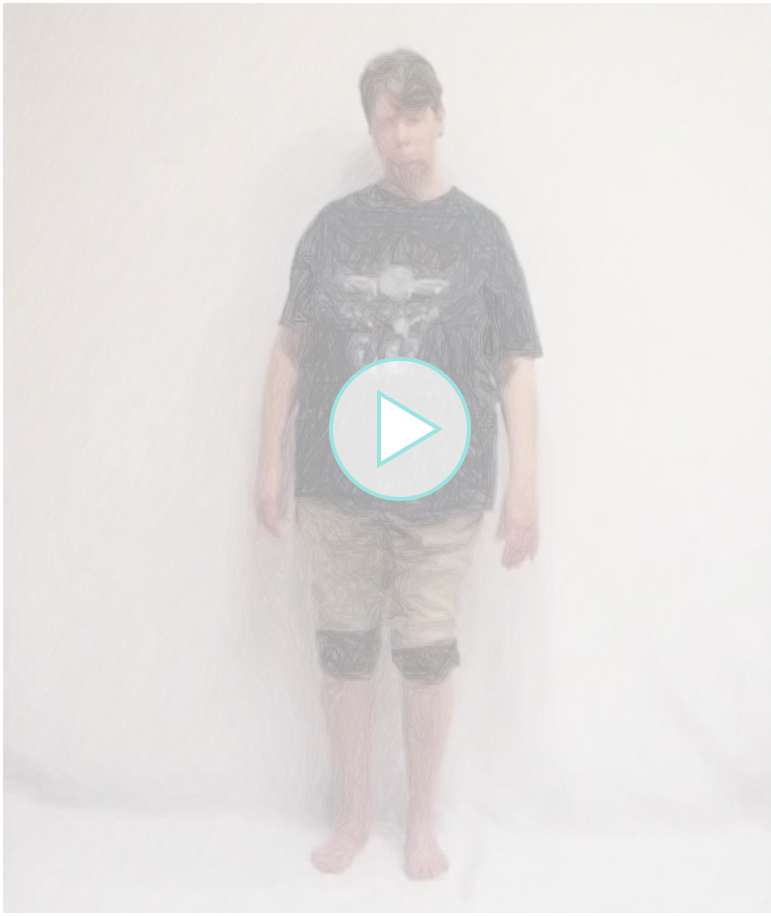


Oral-Buccal-Lingual, Legs

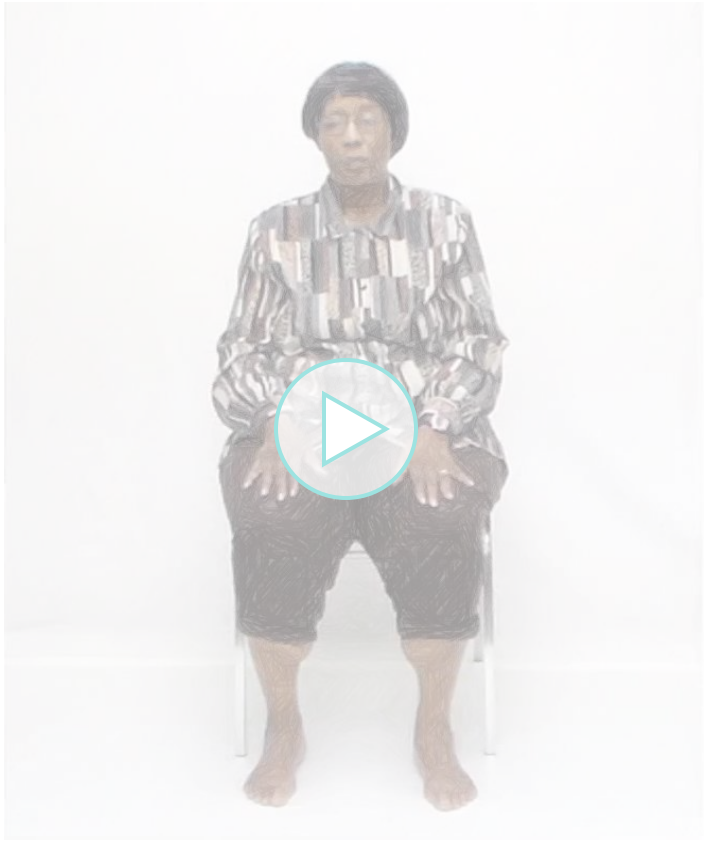
Sitting



Standing

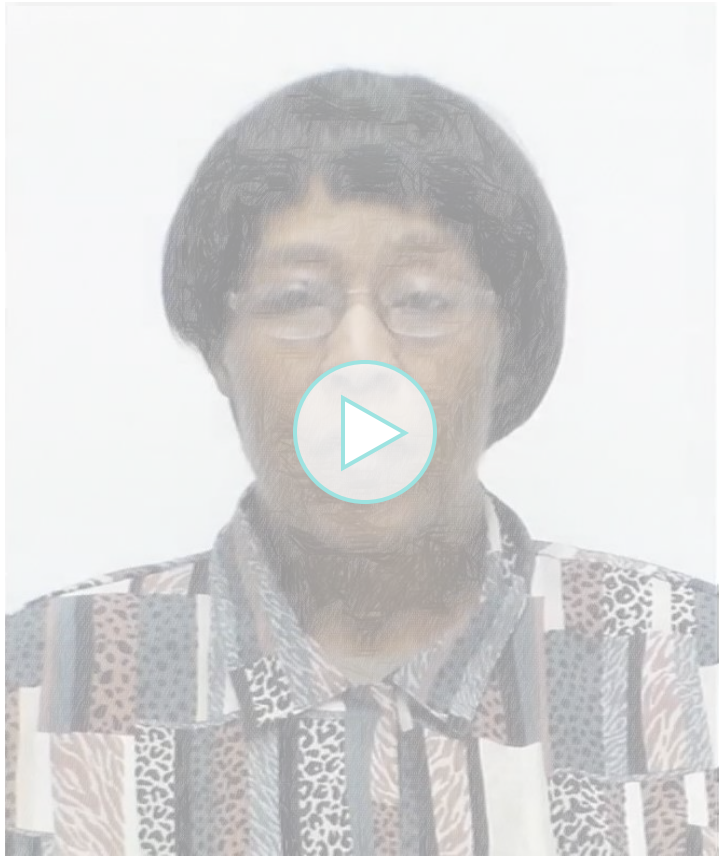


Mild Hand and Jaw



Activation with Hand Movement

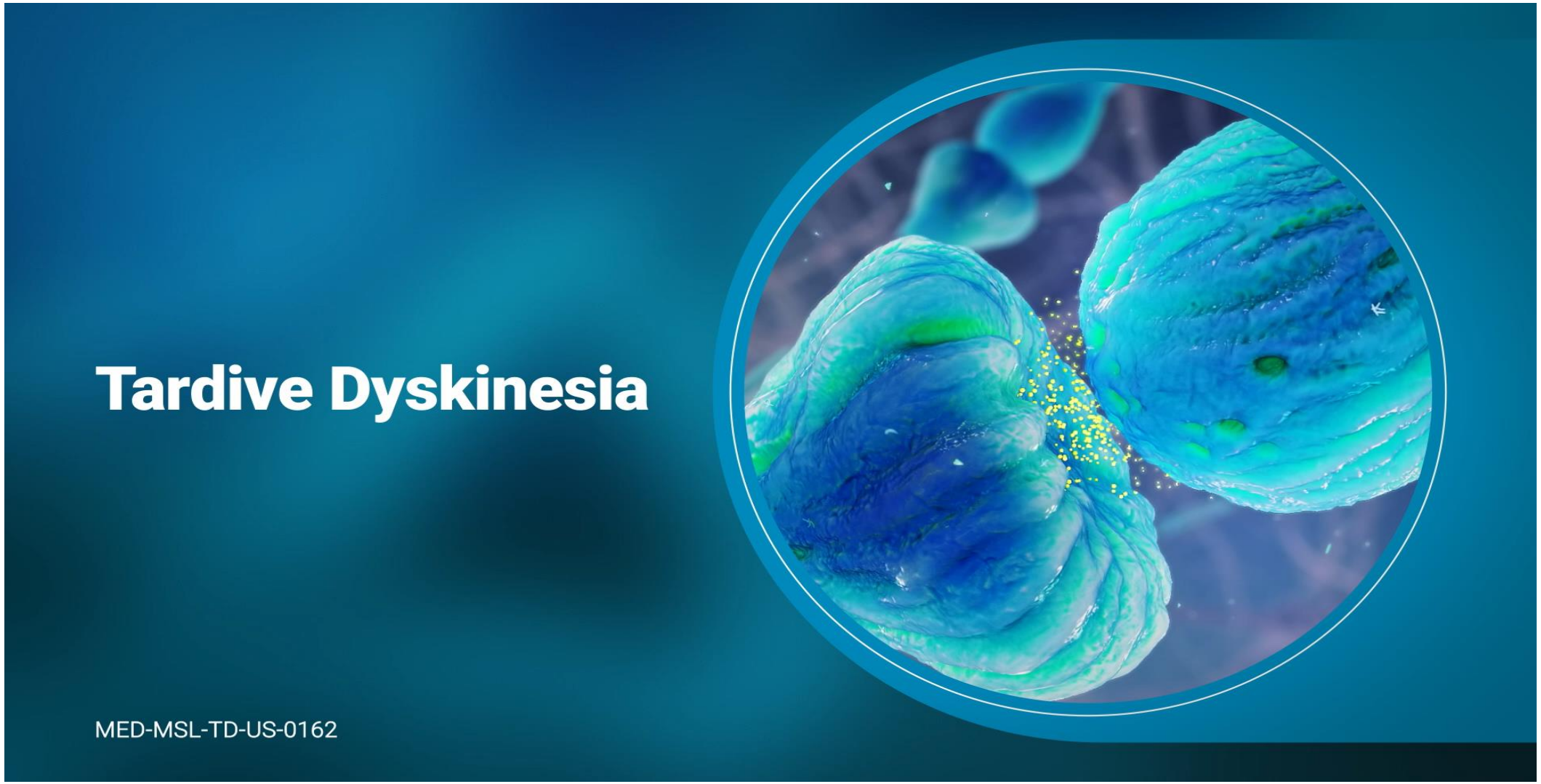
Increased Blinking and Jaw Activation



Leg and Shoulder Dyskinesia

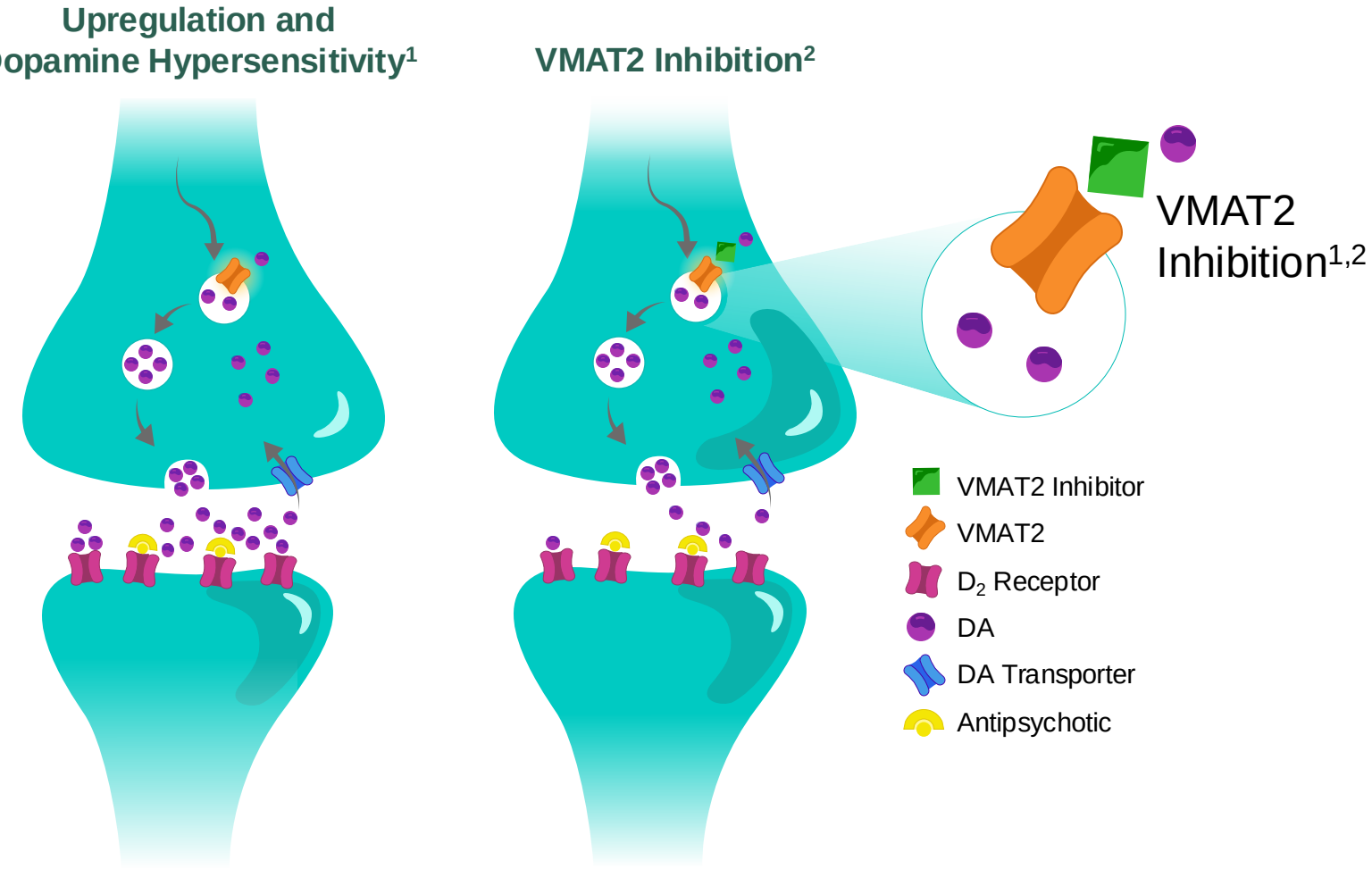
Facial Grimacing and Head Nodding

Valbenazine and TD Mechanism of Disease Video



Valbenazine Mechanism of Action

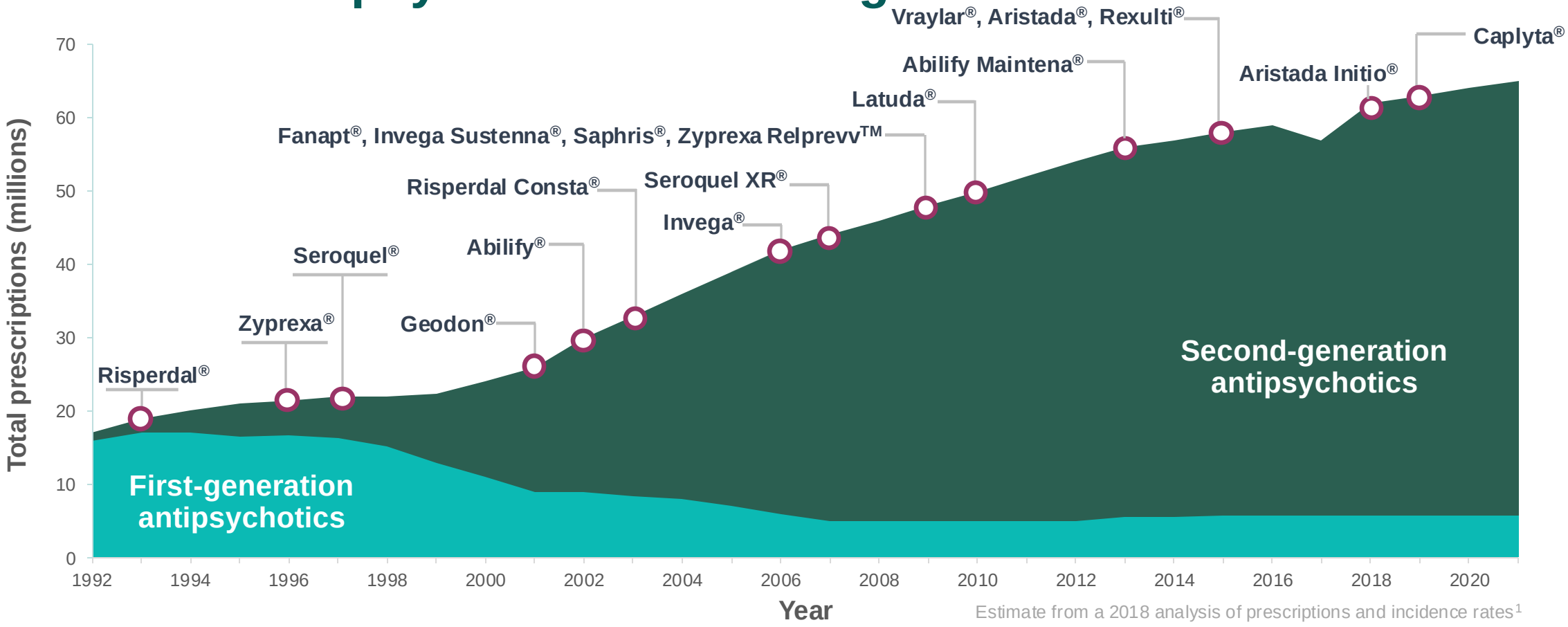
The mechanism of action of valbenazine for the treatment of TD is unclear, but is thought to be mediated through the reversible inhibition of VMAT2[2]



TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

1. Margolese HC, et al. *Can J Psychiatry*. 2005;50:541-547. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Trends in Antipsychotic Prescribing



Estimate from a 2018 analysis of prescriptions and incidence rates[1]

- **> 4-fold increase in antipsychotic use over 25 years[1]**
- **Use of second-generation antipsychotics (SGAs) in new conditions and client populations has grown over the past ~2.5 decades[2]**

FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics

1. Data on file. Neurocrine Biosciences. 2. Alexander GC, et al. *Pharmacoepidemiol Drug Saf*. 2011;20(2)177-184.

Scoring AIMS: Items 1-12

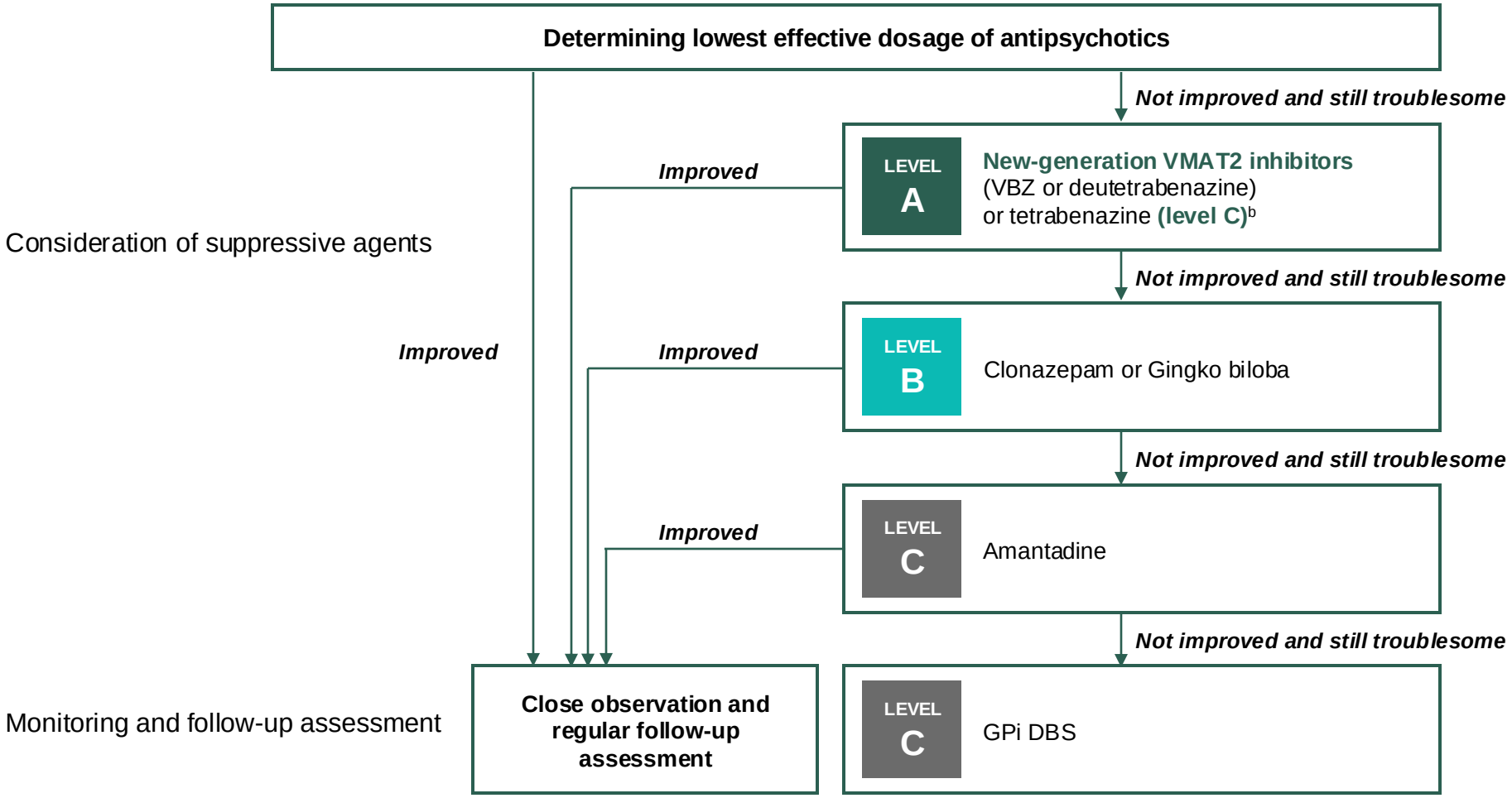
AIMS is a 12-item, clinician-rated scale used to assess TD severity

	Facial and Oral Movements	None	Minimal	Mild	Moderate	Severe
1.	Muscles of facial expression	0	1	2	3	4
2.	Lips and perioral area	0	1	2	3	4
3.	Jaw	0	1	2	3	4
4.	Tongue	0	1	2	3	4
	Extremity Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
5.	Upper (arms, wrists, hands, fingers)	0	1	2	3	4
6.	Lower (legs, knees, ankles, toes)	0	1	2	3	4
	Trunk Movements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
7.	Neck, shoulders, hips	0	1	2	3	4
	Global Judgements	**None**	**Minimal**	**Mild**	**Moderate**	**Severe**
8.	Overall severity	0	1	2	3	4
9.	Incapacitation	0	1	2	3	4
10.	Patient's awareness*	0	1	2	3	4
	Dental Status	**No**	**Yes**			
11.	Current problems with teeth/dentures?	0	1			
12.	Denture use?	0	1			

*0=no awareness; 1=aware, no distress; 2=aware, mild distress; 3=aware, moderate distress; or 4=aware, severe distress.
AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.

Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Revised (DHEW publication number ADM 76-338). National Institute of Mental Health, Psychopharmacology Research Branch; 1976:534-537.

2018 Systematic Review: Practical Treatment Algorithm[a]



GPi DBS, pallidus interna deep brain stimulation; TD, tardive dyskinesia; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.
[a]Adapted for the management of troublesome TD in patients receiving an approved antipsychotic treatment as indicated. Assessment of TD is necessary before treatment.
[b]Consider tetrabenazine if the new-generation VMAT2 inhibitors are unavailable.
Bhidayasiri R, et al. *J Neurol Sci.* 2018;389:67-75.

AAN Guideline – Levels of Evidence

Category	Definition
Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks 1 criterion from A–E (next slide) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets B–E (next slide). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed or independently derived by objective outcome measurement.*
Class IV	Studies not meeting Class I, II or III criteria including consensus or expert opinion

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).
AAN, American Academy of Neurology.

Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

Class I Criteria for Levels of Evidence

A. Concealed allocation
B. No more than 2 primary outcomes specified
C. Exclusion/inclusion criteria clearly defined
D. Adequate accounting for dropouts (with ≥80% of enrolled participants completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
E. For noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs, the following are also required*:
   1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
   2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
   3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
   4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.
F. For crossover trials, both period and carry-over effect examined and statistical adjustments performed, if appropriate.

*Note that numbers 1–3 in Class IE are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

HD 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]

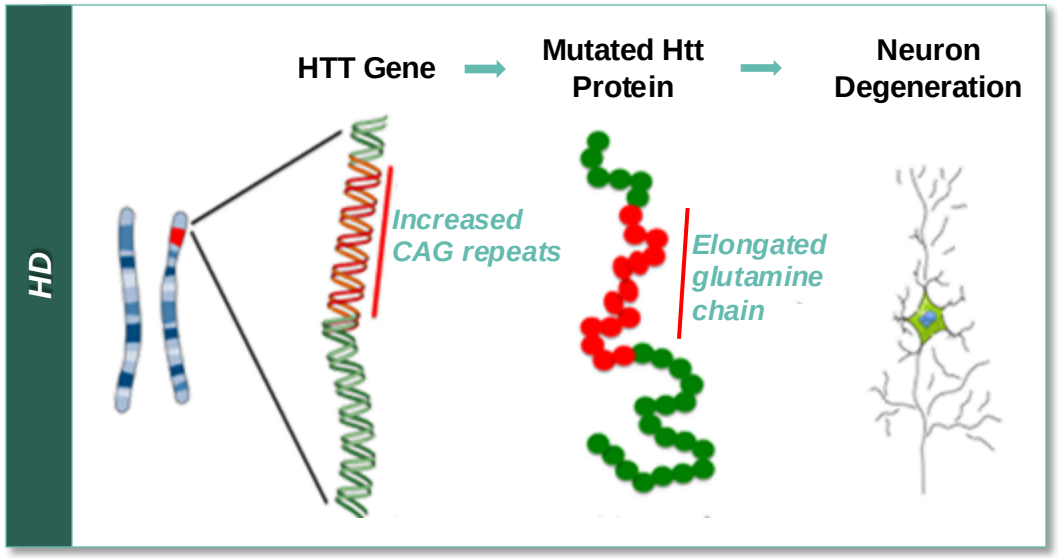


Image courtesy of Euro Stem Cell[2]

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.

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. EuroStemCell. Accessed July 7, 2021. https://www.eurostemcell.org/huntingtons-disease-how-could-stem-cells-help.

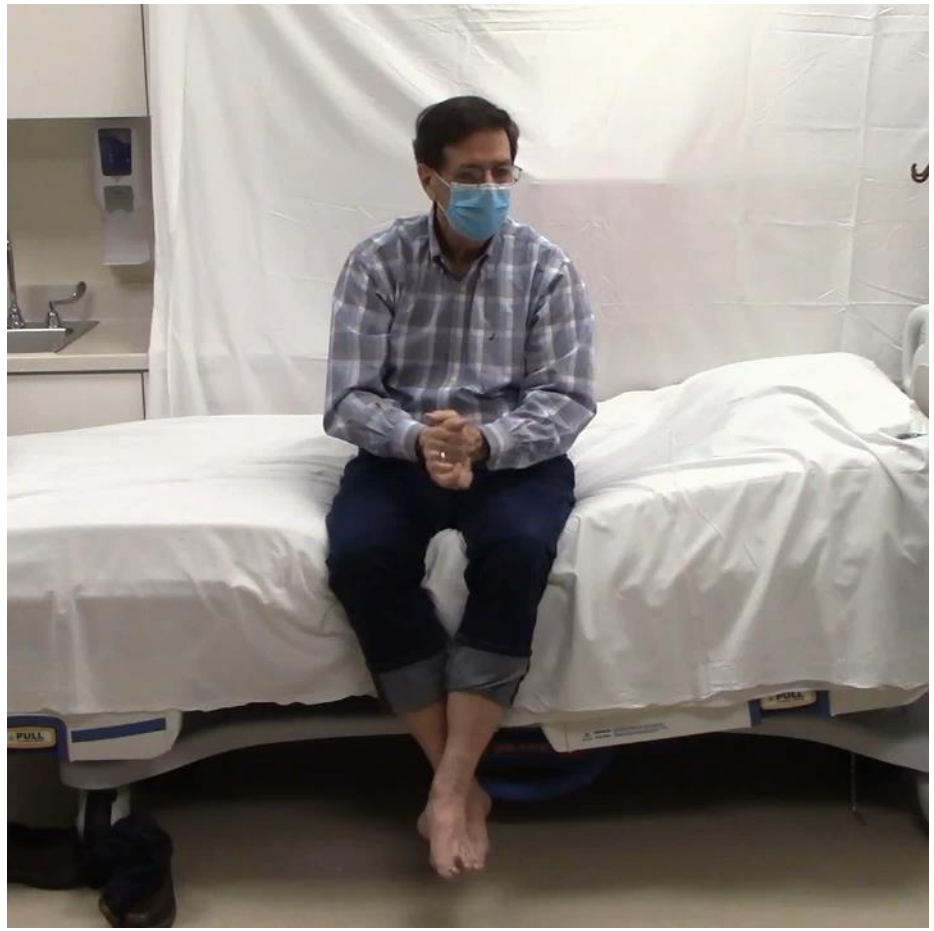
Face: Moderate

Buccal-Oral-Lingual: Severe

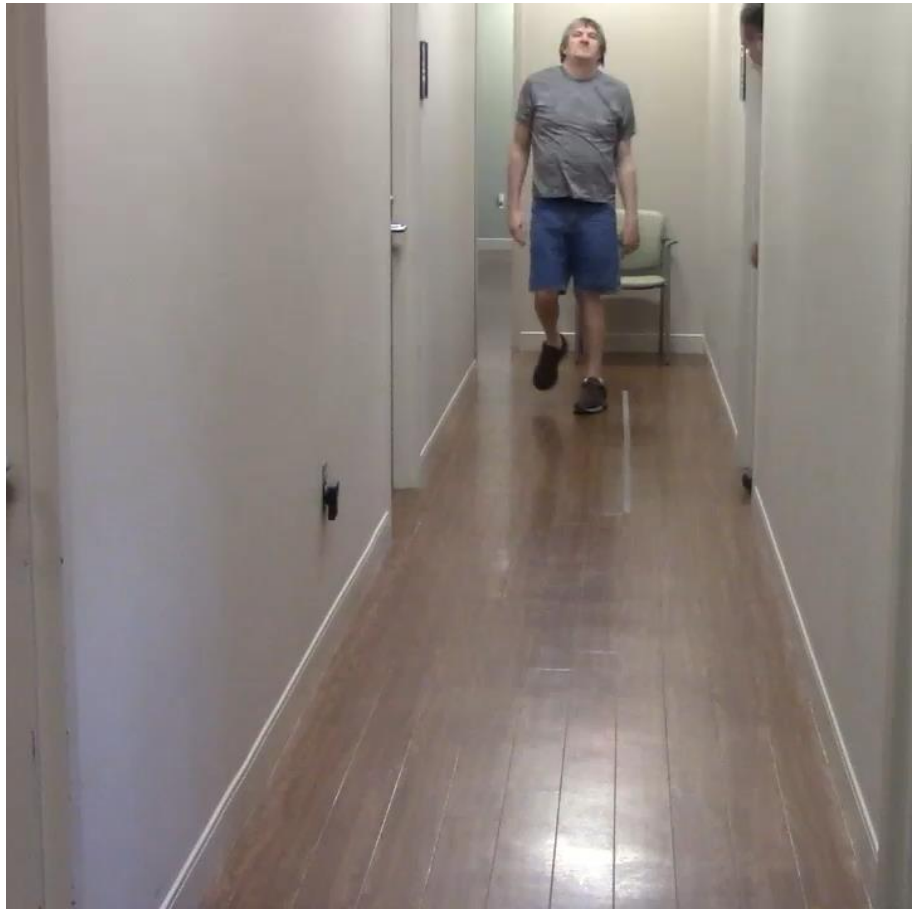
Trunk: Mild

Upper Extremities: Severe

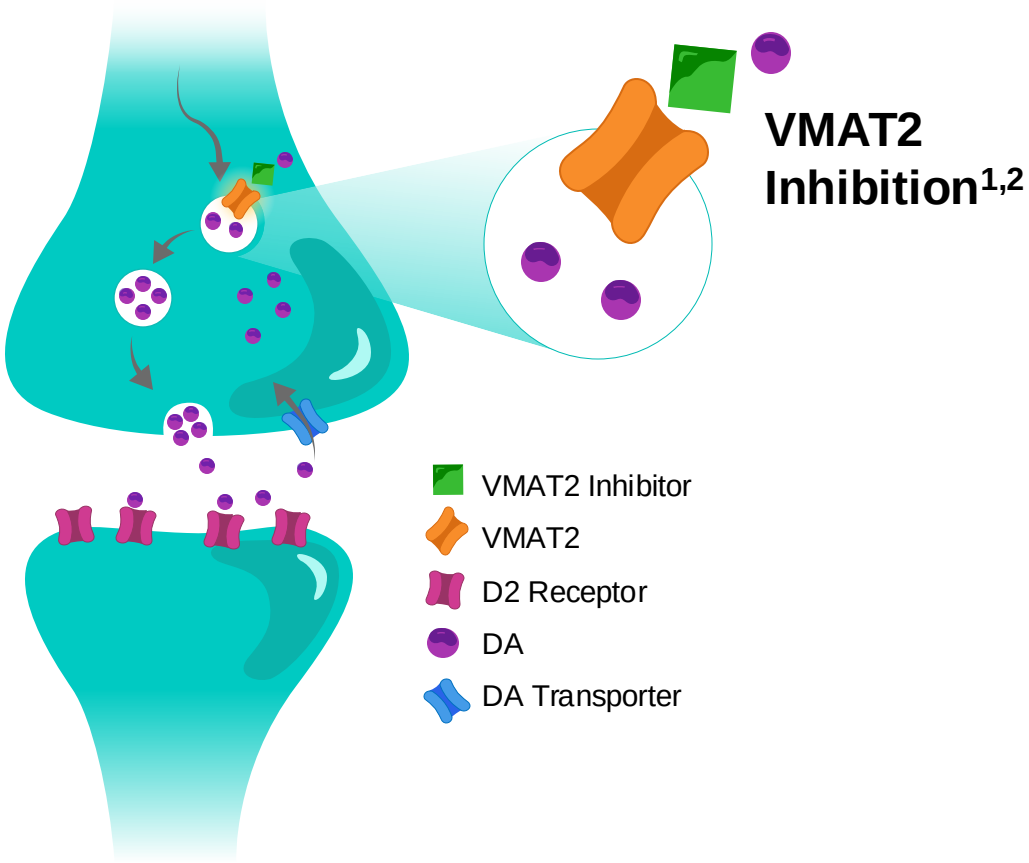
Lower Extremities: Moderate



Gait: Mild and Severe



Valbenazine Mechanism of Action



Valbenazine is FDA-approved for the treatment of adults with chorea associated with Huntington's disease (HD)

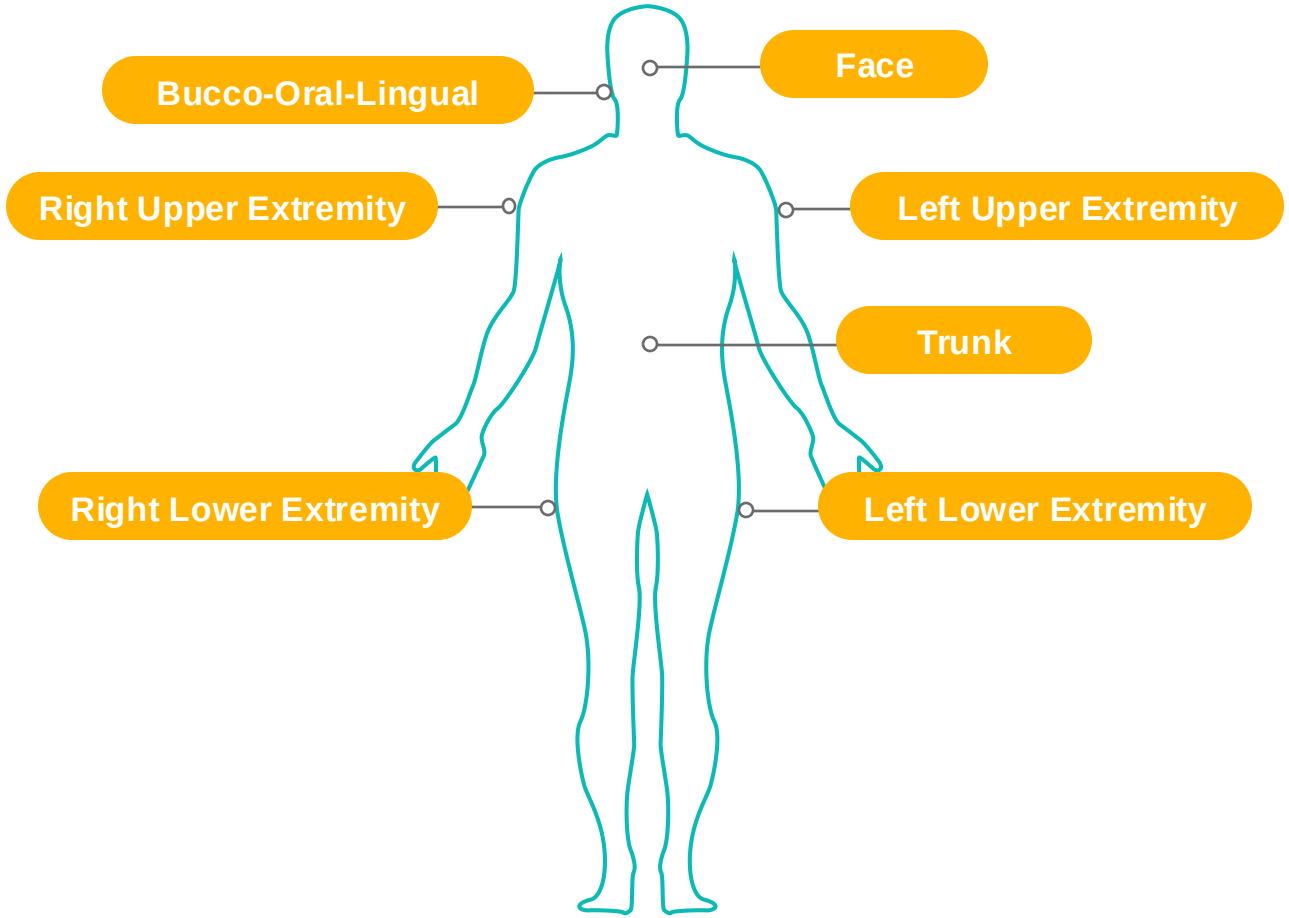
The mechanism of action of valbenazine for the treatment of chorea associated with HD is unclear, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for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

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

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

Valbenazine and HD Chorea Mechanism of Disease Video

Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) Score Rates Chorea in 7 Body Regions[1]



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.

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.