Neurocrine Biosciences: Overview of Valbenazine and Related Disease States

NEUROCRINE® BIOSCIENCES

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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

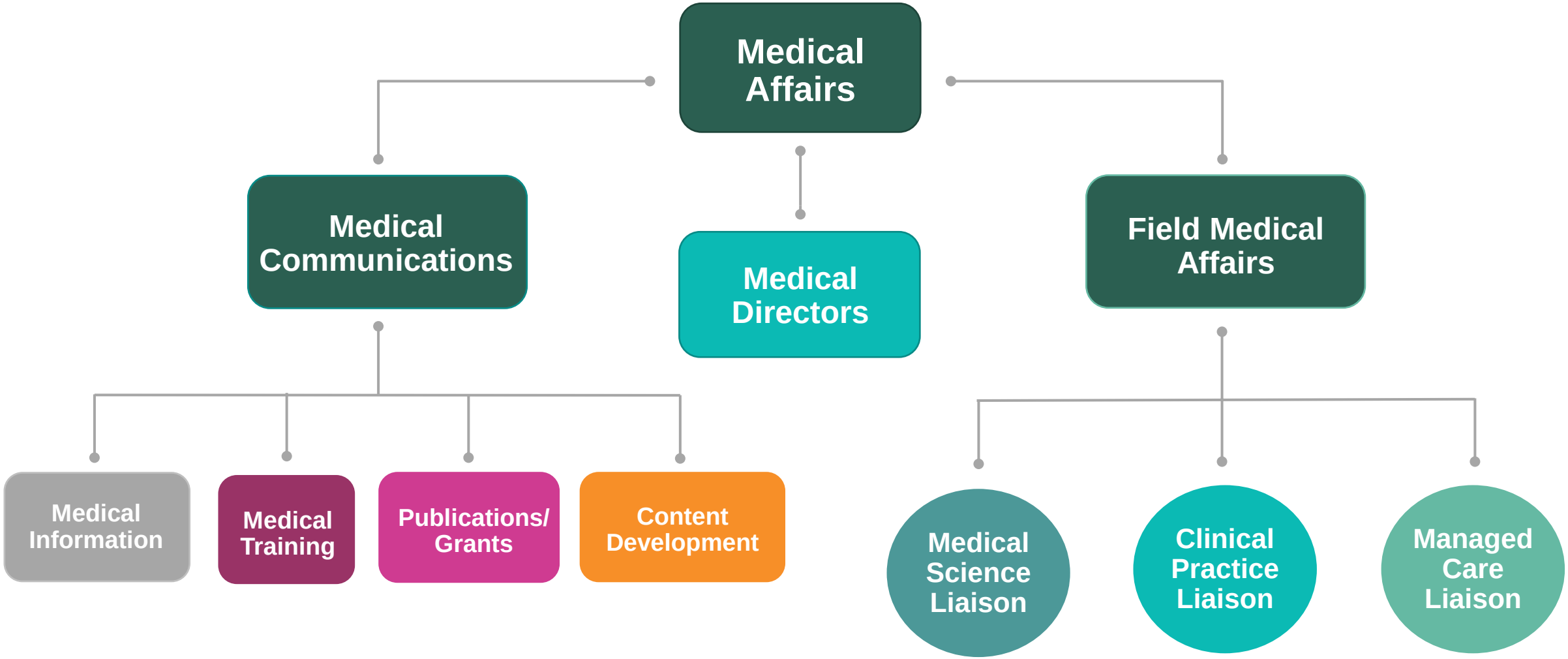
To relieve suffering for people with great needs, but few options

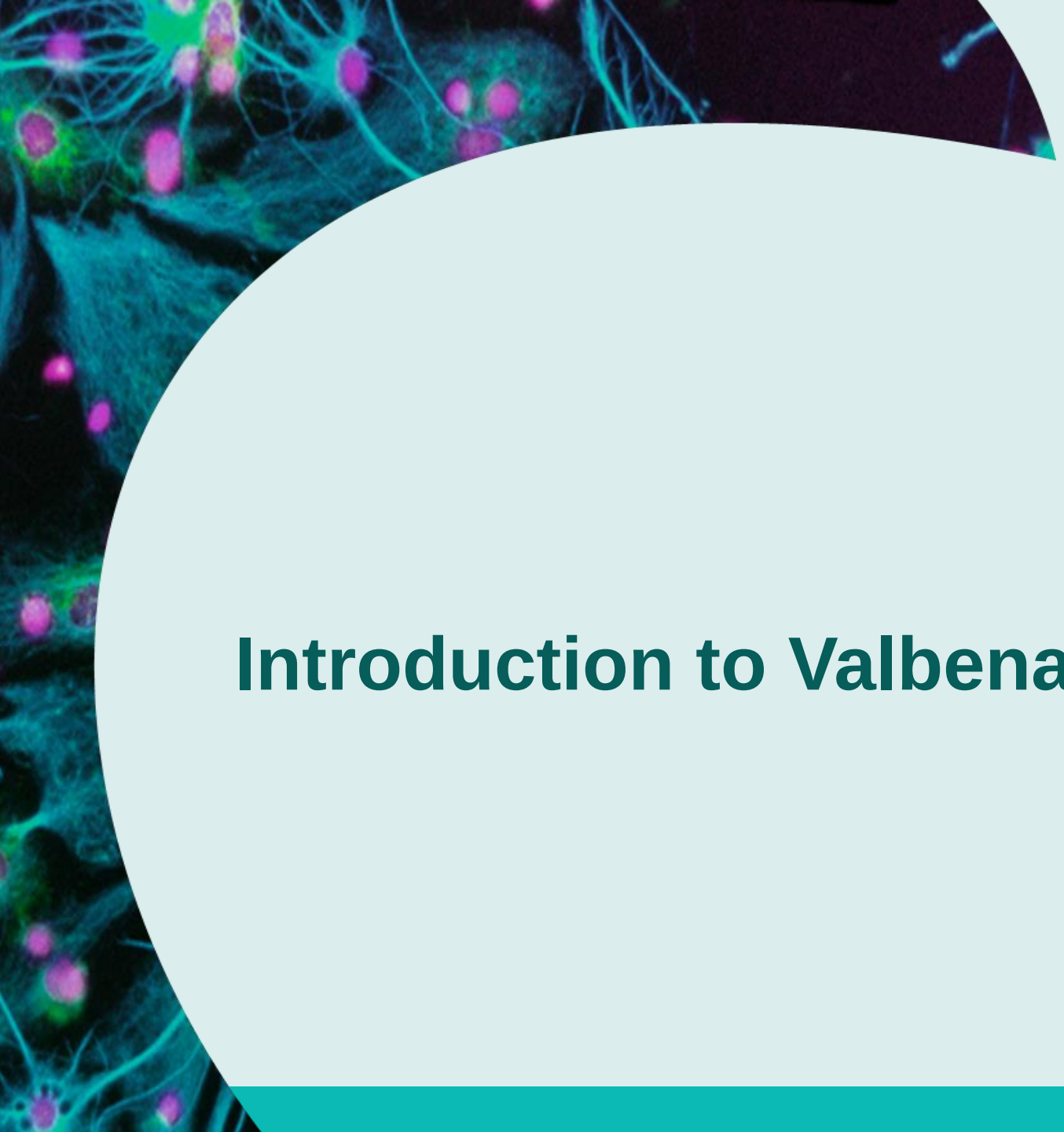
Our Values

Passion
Integrity
Collaboration
Innovation
Tenacity

Neurocrine Biosciences is dedicated to advancing science through research and development

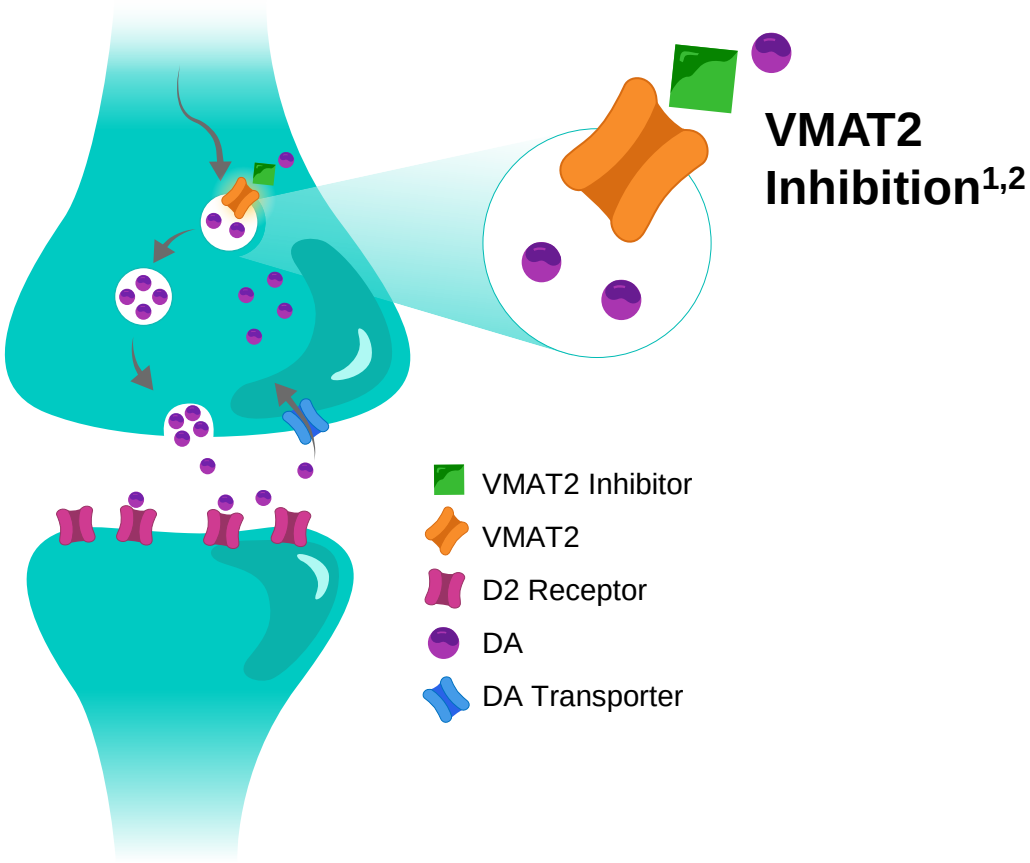
Groups Within Neurocrine Medical Affairs





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 in the treatment of TD and chorea in HD is unclear, but is thought to be mediated through the reversible inhibition of VMAT2[1]

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	40-80 mg, 1 capsule once daily
Dosage forms	Capsules: 40, 60, 80 mg
Active metabolites	[+]-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; MDD, major depressive disorder; VBZ, valbenazine; VMAT2, vesicular monoamine transporter type 2.

1. Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association; 2020. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 20, 2021. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Valbenazine Overview (cont'd)

Valbenazine[1]

Hepatic impairment	Maximum dose of 40 mg daily for moderate to severe impairment
Renal impairment	Dosage adjustment not necessary
Effect of food on bioavailability	Taken with or without food
Geriatric use	No dose adjustment required[2]

VBZ, valbenazine.

1. Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. Washington, DC: American Psychiatric Association; 2020. https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 20, 2021. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Valbenazine Important Safety Information

- **Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA, 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 is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA.

- **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.

VMAT2, vesicular monoamine transporter type 2.

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

Valbenazine Important Safety Information Cont.

- **Somnolence and Sedation:** INGREZZA 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

- **QT Prolongation:** INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA 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, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA is needed after recovery from NMS, patients should be monitored for signs of recurrence.

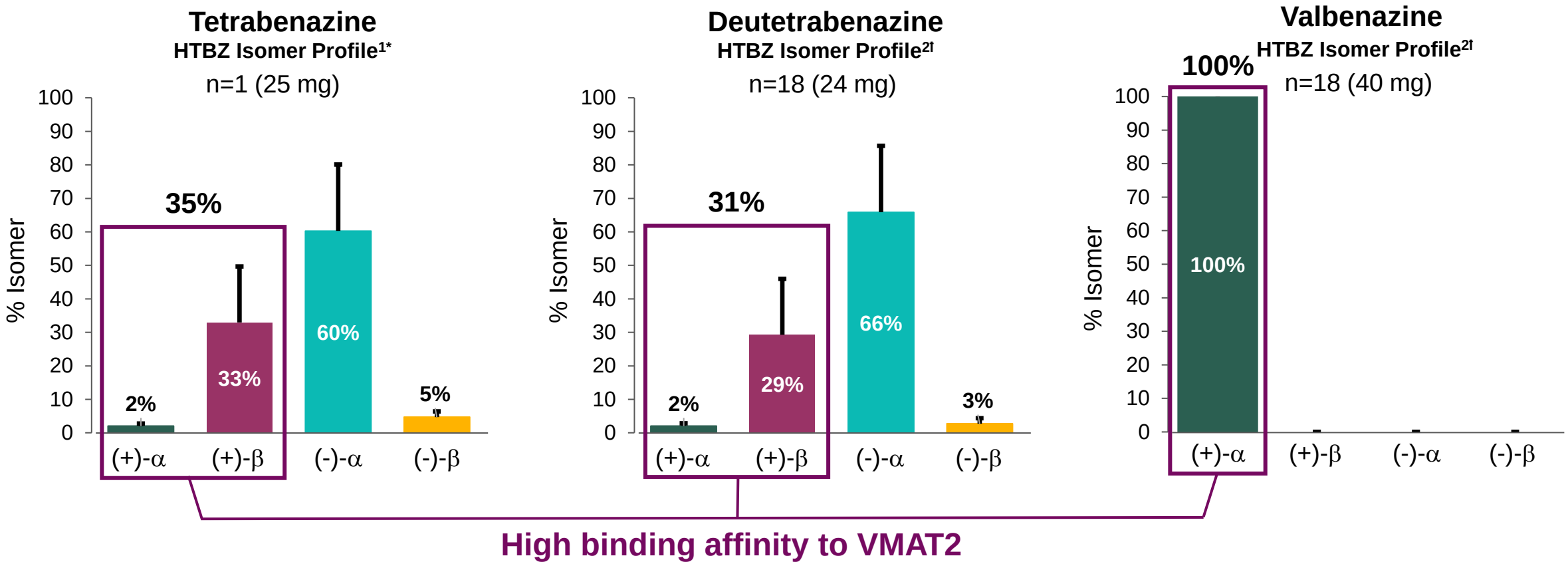
- **Parkinsonism:** INGREZZA may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

NMS, neuroleptic malignant syndrome;VMAT2, vesicular monoamine transporter type 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]



*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 type 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.

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

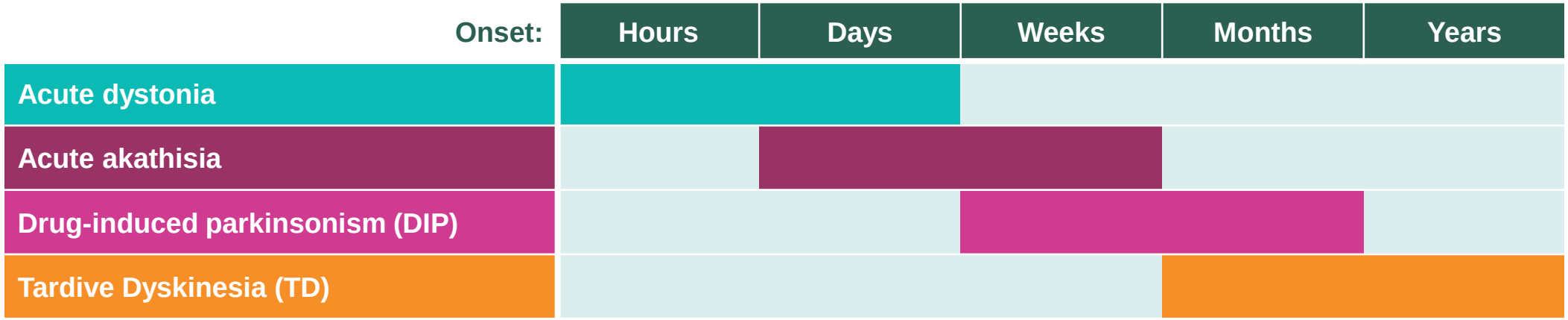
Tardive Dyskinesia and Valbenazine

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]

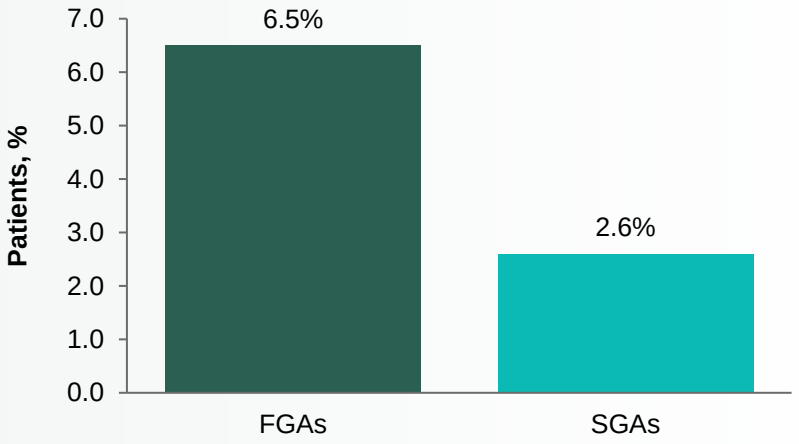


DRBA, dopamine receptor–blocking agent; EPS, extrapyramidal symptoms; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.

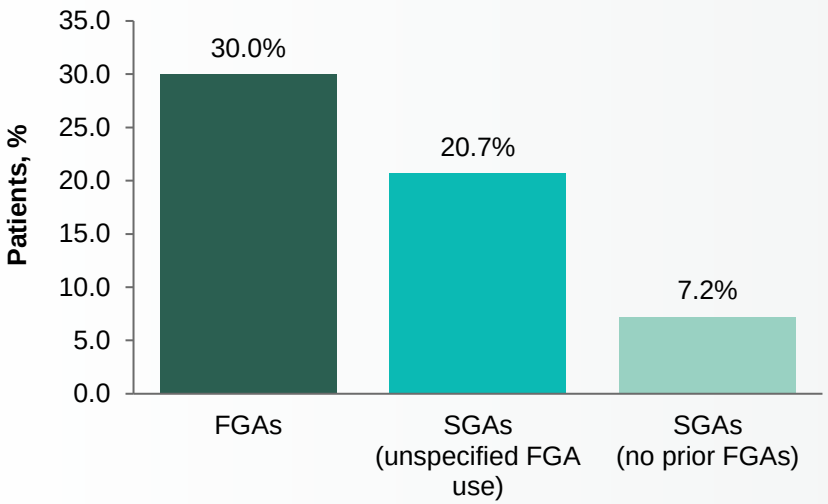
1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.* American Psychiatric Association; 2013. 2. Fahn S, et al. *Principles and Practice of Movement Disorders*. 2nd ed. Elsevier Inc.; 2011. 3. Hauser RA, et al. *CNS Spectrums*. 2020:1-10. 4. Mehta 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.

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

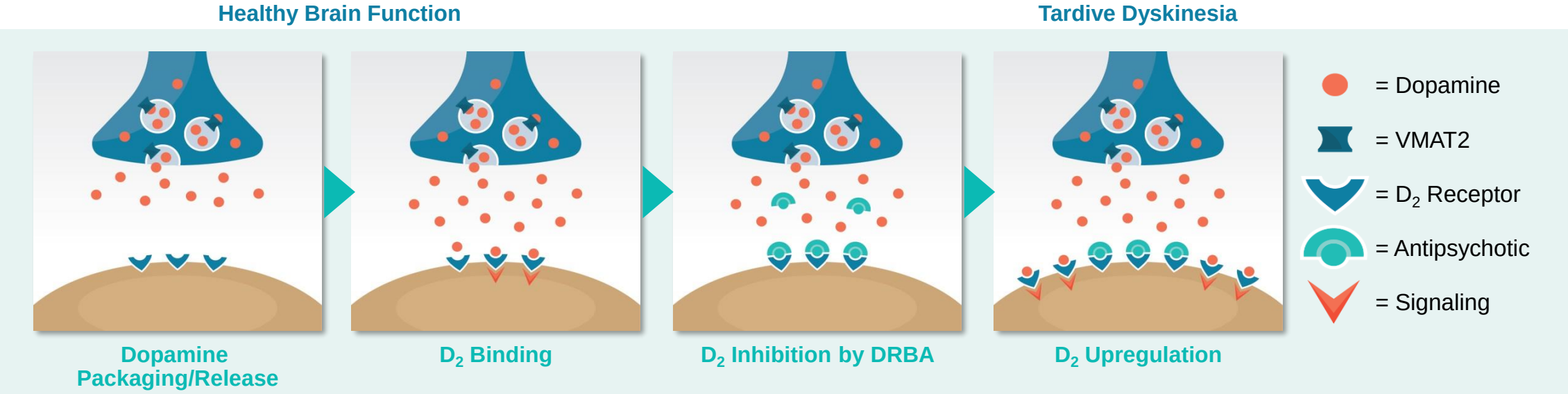
Jaw, Tongue, Neck → **OBL and Legs** → **Jaw, Hand, Face** → **Leg, Shoulder, Face**

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]

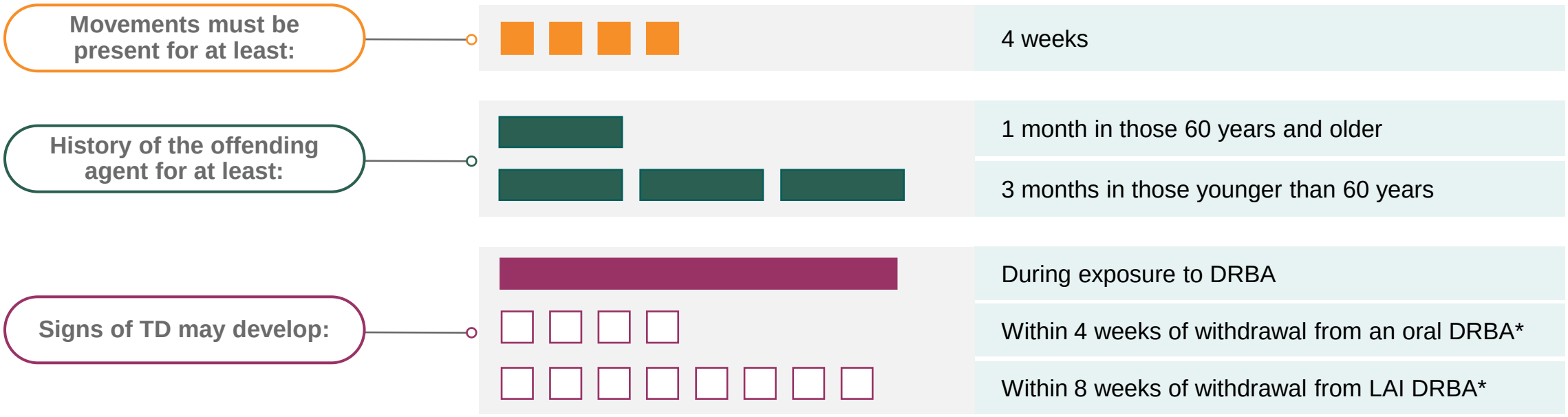


DRBA, dopamine receptor–blocking agent; GABA, gamma-aminobutyric acid; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2.

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



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.

Screening Guidelines

Scoring AIMS

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

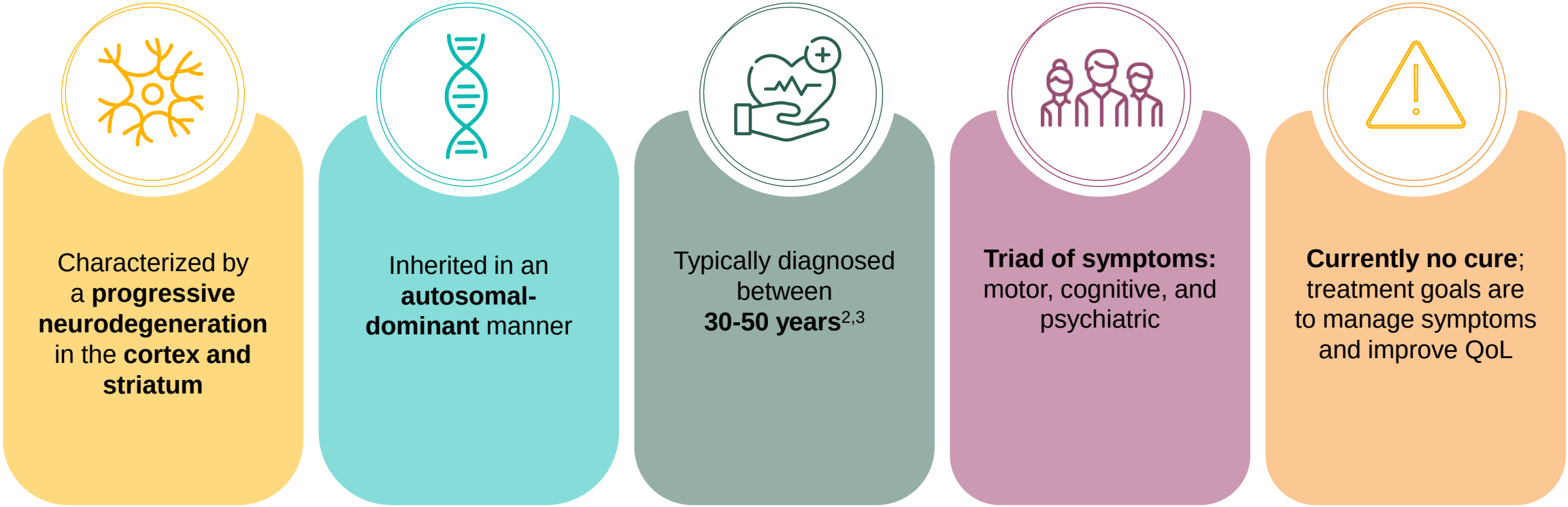
VMAT2 inhibitors are recommended and/or considered in the full severity spectrum of TD

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]

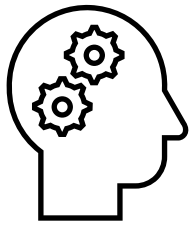


HD, Huntington's disease; QoL, quality of life.

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

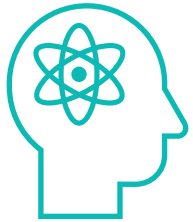
Involuntary movements (chorea) and impaired voluntary movements

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.

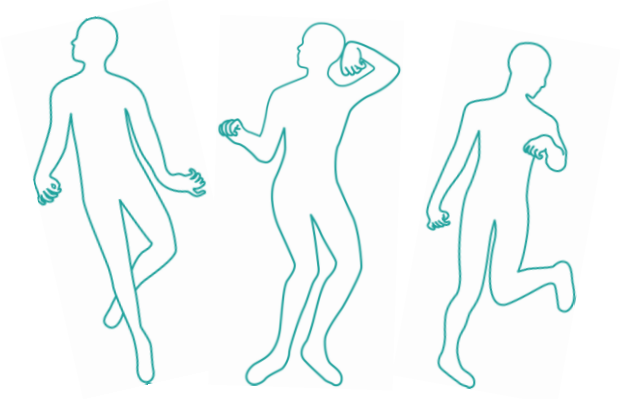
Chorea is a Hallmark Symptom of HD

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]



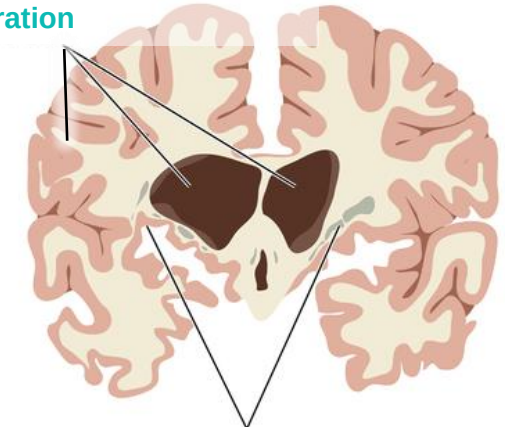
HD, Huntington's disease. OBL, Oral-Buccal-Lingual.

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

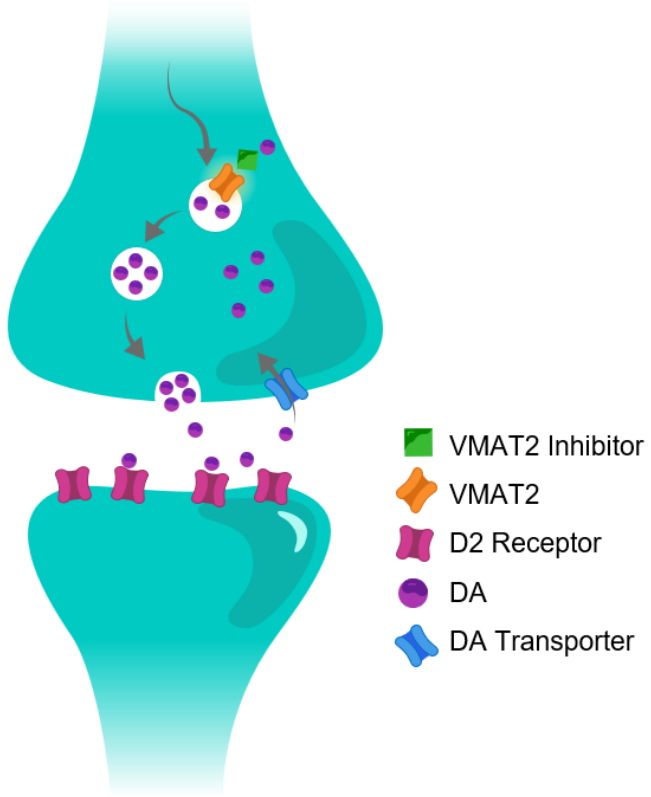


Image courtesy of The Huntington's Disease Association[3]

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

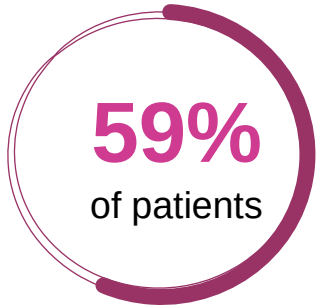
Physical/Functional Impact[1-3]

- 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.

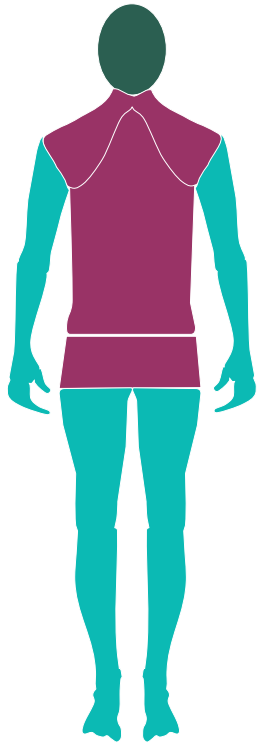
Scoring Abnormal Involuntary Movement Scale

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.