Tardive Dyskinesia: A Review

NEUROCRINE® BIOSCIENCES

MED-MSL-TD-US-0136_v6

Tardive Dyskinesia (TD) is Associated with Prolonged Exposure to Dopamine Receptor Blocking Agents (DRBAs)

Tardive Dyskinesia

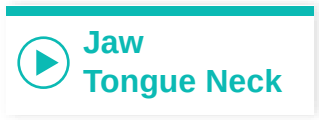
Defined as abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with medications that block post-synaptic dopamine receptors

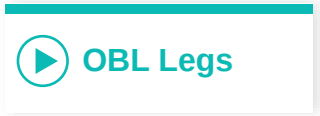
TD movements may be:*

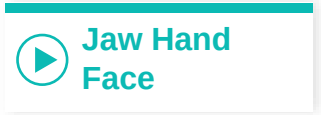
Choreiform	Rapid, jerky, nonrepetitive
Athetoid	Slow, sinuous, continual
Semirhythmic	E.g., stereotypies

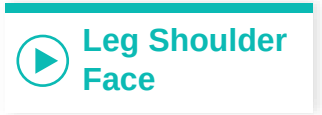
DRBAs can include:

- First-generation antipsychotics
- Second-generation antipsychotics
- Gastrointestinal medications, such as metoclopramide







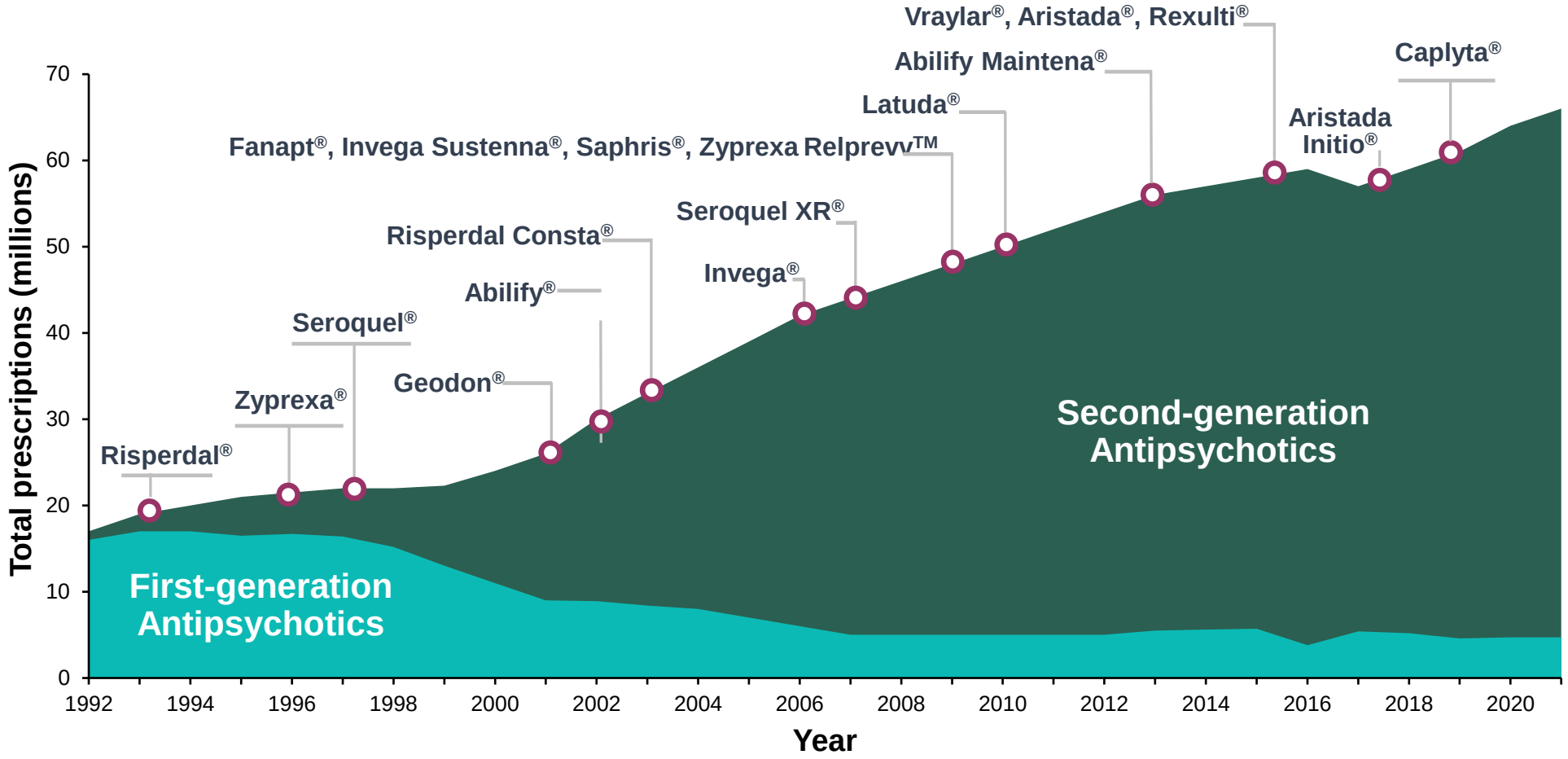


*Movements are distinctly different from the rhythmic tremors (3-6 Hz) commonly seen in drug-induced parkinsonism[1]

DRBA, dopamine receptor–blocking agent; TD, tardive dyskinesia; OBL, oral-buccal-lingual.

American Psychiatric Association: *Diagnostic and Stat Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition – Text Revision. American Psychiatric Association: Washington, DC; 2022

Trend in Antipsychotic Prescribing



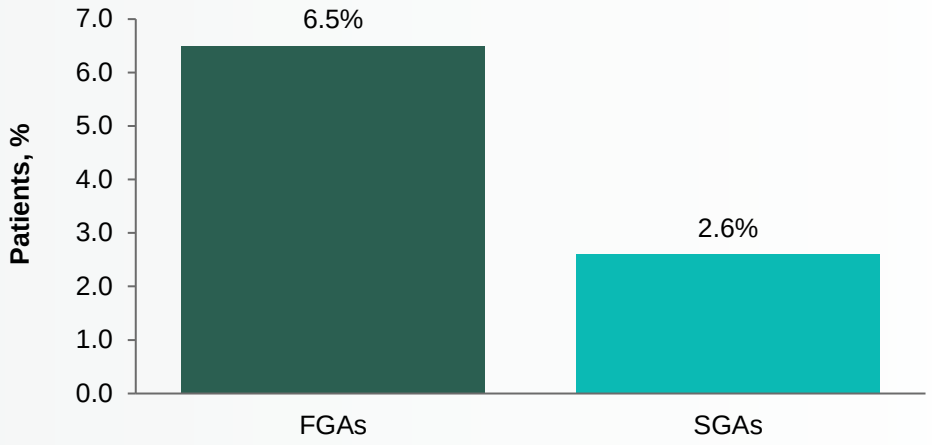
- > 4-fold increase in antipsychotic use over 25 years[1]
- Use of second-generation antipsychotics (SGAs) in new conditions and client populations has grown over the past 3 decades[1,2]

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

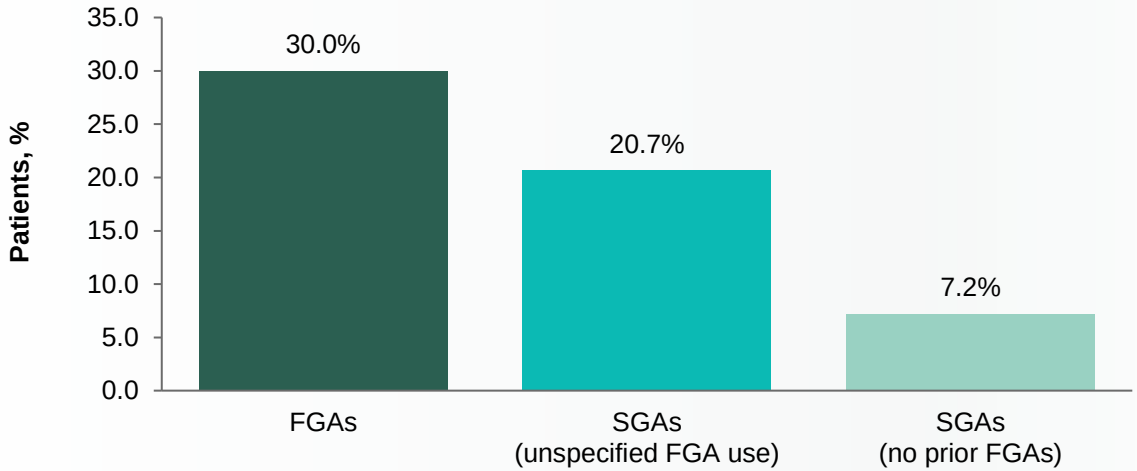
1. Data on file (VBZ-TD-0014). Neurocrine Biosciences, Inc. 2. Alexander GC, et al. *Pharmacoepidemiol Drug Saf*. 2011;20(2)177-184.

TD Is Associated With Prolonged DRBA Treatment

TD Annual Incidence[1]*



TD Prevalence[2]†



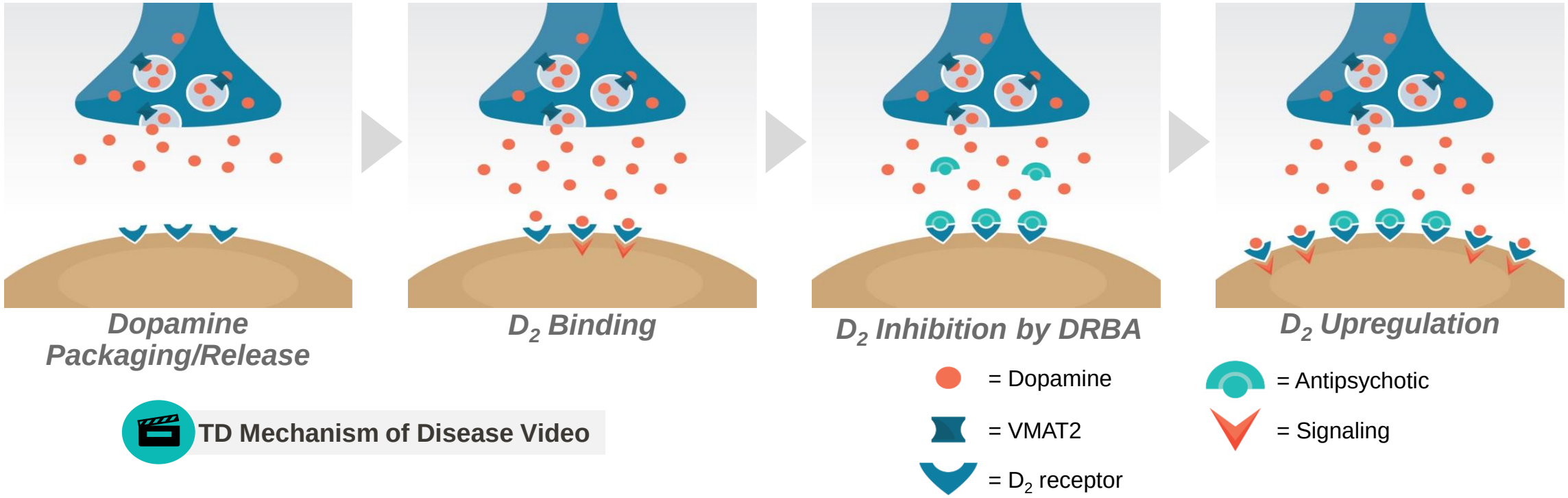
~5 million patients in the US are treated with antipsychotics[3]
≥600,000 patients may have TD[3,4]‡

*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 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

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

Factors Associated With Increased Risk for TD

Risk Factors for TD

Treatment Factors	Patient Factors
Cumulative exposure to antipsychotics[1]	Increased age[1]
Treatment with anticholinergics[1]	Substance abuse[1]
History of extrapyramidal symptoms (EPS)[1]	Diagnosis of mood disorder[3,4]
Potency of DRBA[2]	Postmenopausal women[5]
Neuroleptic withdrawal-emergent dyskinesia[6]	

DRBA, dopamine receptor–blocking agent; TD, tardive dyskinesia.

1. Miller DD, et al. *Schizophr Res*. 2005;80:33-43. 2. Divac N. *Biomed Res Int*. 2014;[Epub]. 3. Jeste DV, et al. *Schizophr Bull*. 1993;19:303-315. 4. Mukherjee S. *Arch Gen Psychiatry*. 1986;43:342-346. 5. Seeman et al. *Compr Psychiatry*. 1983;24(2):125-128. 6. Solmi M, et al. *J Neurol Sci*. 2018;389:21-27.

Diagnosis of TD

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

Movements must be present for at least:

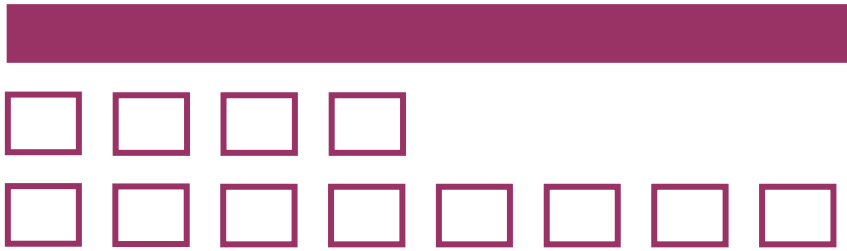
4 weeks

History of the offending agent for at least:

1 month in those 60 years and older

3 months in those younger than 60 years

Signs of TD may develop:



During exposure to DRBA

Within 4 weeks of withdrawal from an oral DRBA*

Within 8 weeks of withdrawal from LAI DRBA*

*Dyskinesia may remit with continued withdrawal. A diagnosis of TD may be warranted if the dyskinesia persists for at least 4 weeks.

DRBA, dopamine receptor–blocking agent; TD, tardive dyskinesia; LAI, long acting injectable.

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

Burden of Tardive Dyskinesia

- In some patients, TD is associated with[1-3]:
  - More severe psychopathology
  - Worse quality of life and functioning
  - Lower level of daily activity
  - Lower level of leisure activities
  - Lower productivity
  - Social stigma
  - Increased morbidity and mortality
- TD may persist for years or decades, even after discontinuing the causative drug[4]

1. Ascher-Svanum H, et al. *J Clin Psych*. 2008;69(10):1580-1588. *2.* Boumans CE, et al. *Schizo Bull.* 1994;20(2):339-344. 3. Ballesteros J, et al. *J Clin Psychopharmacol*. 2000;20:188-194. 4. Gardos G, et al. *Am J Psych.* 1994;151:836-841.

2020 APA Guideline: TD Recommendations

Reversible VMAT2 inhibitors are recommended in patients with moderate to severe or disabling TD

VMAT2 inhibitors can also be considered for patients with mild TD

There is insufficient evidence to support a guideline statement on the use of the following treatments in individuals with TD:

- Anticholinergics (e.g., benztropine)
- Benzodiazepines (e.g., clonazepam)
- Change in antipsychotic therapy to a lower-potency medication
- Ginkgo biloba
- Cessation or reduction of antipsychotic medication
- Amantadine
- Vitamin E

APA, American Psychiatric Association; TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter type 2.

American Psychiatric Association. Clinical Practice Guidelines for Treatment of Patients with Schizophrenia. Accessed on November 8, 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

Tardive Dyskinesia: Summary

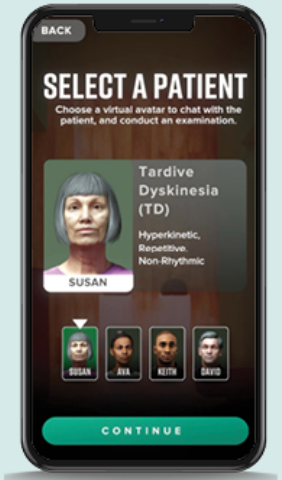
- TD is defined as abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with medications that block post-synaptic dopamine receptors[1]
- A leading theory of the mechanism of TD is the upregulation and subsequent hypersensitivity of brain dopamine D2 receptors following prolonged exposure to DRBAs[2]
- TD prevalence rates varied depending on exposure to DRBA[3]:
  - SGA use has increased substantially in the last 25 years
  - There is a 7-20% rate of TD in those taking SGAs, depending on prior history of FGA use
- The 2020 APA Schizophrenia Guidelines recommends reversible VMAT2 inhibitors in patients with moderate to severe or disabling TD[4]
  - VMAT2 inhibitors can also be considered for patients with mild TD

TD, tardive dyskinesia; DRBA, Dopamine Receptor Blocking Agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; VMAT2, vesicular monoamine transporter 2; APA, American Psychiatric Association.

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. American Psychiatric Association: Washington, DC; 2013. 2. Klawans H, et al. *Acta Neurol Scand*. 1970;46:409-441. 3. Carbon M, et al. J Clin Psychiatry. 2017;78(3):e264-e278. 4. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on July 20, 2021. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

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

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

This educational content was sponsored and developed by Neurocrine Biosciences, Inc.
DIMD, drug-induced movement disorder; DRBA, dopamine receptor-blocking agent; TD, tardive dyskinesia.

NEUROCRINE® BIOSCIENCES

Neurocrine Medical Affairs

www.neurocrinemedical.com

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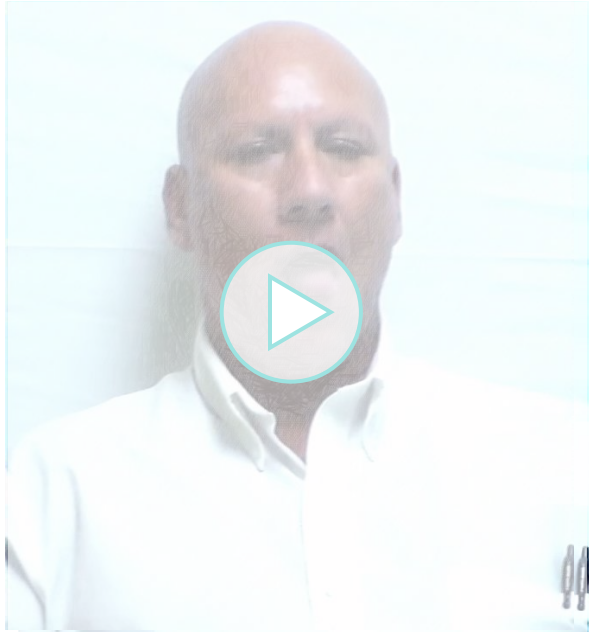
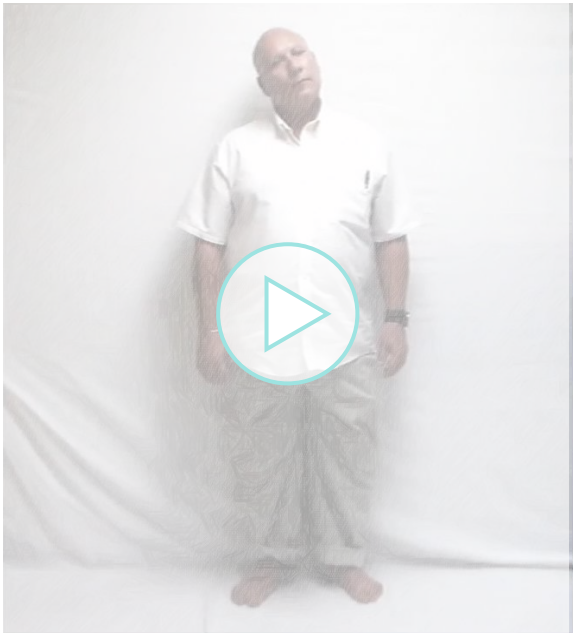
Appendix

Moderate Cervical & Jaw

Open Mouth & Tongue



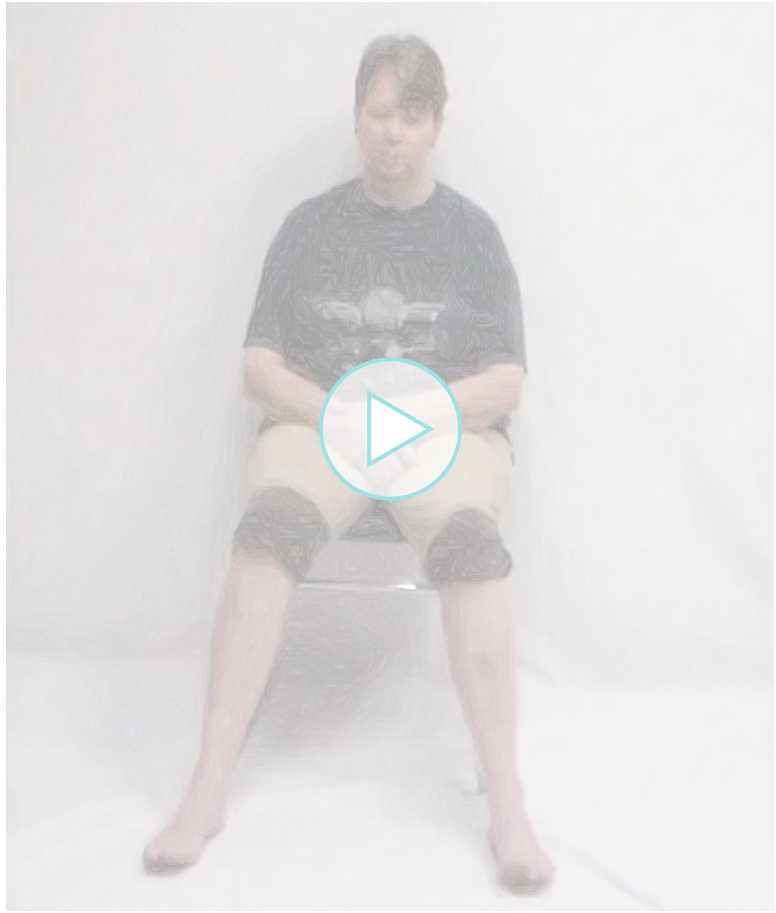
Neck, Shoulder, Hands (Standing and Walking)



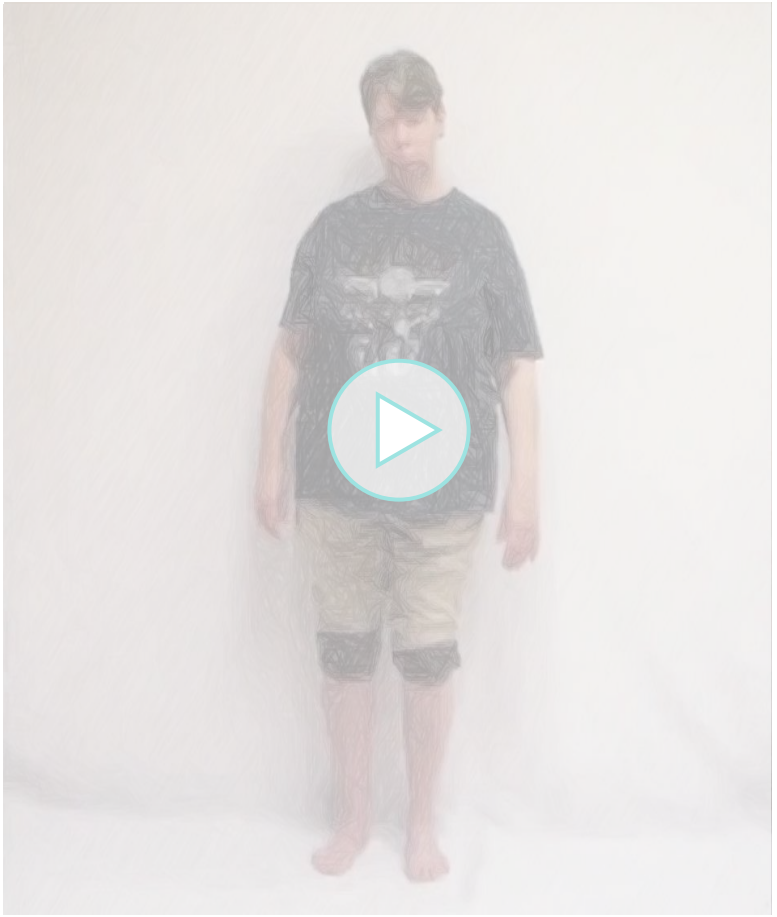
Patients have consented to Neurocrine's use of this video and their protected health information.

Oral-Buccal-Lingual and Legs

Sitting



Standing



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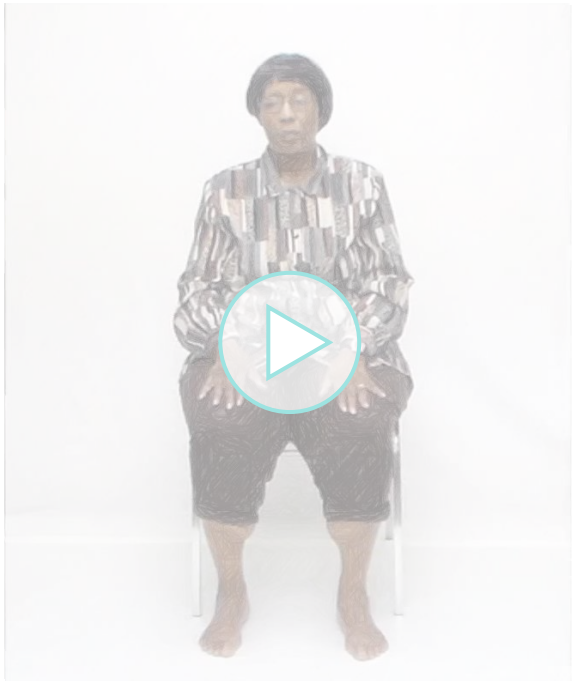
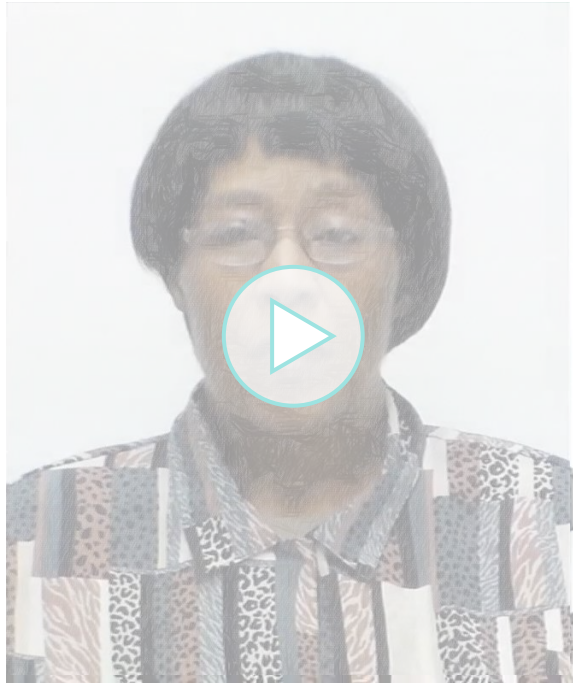
Mild Jaw and Hand



Activation With Hand Movement

Increased Blinking and Jaw Activation



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Leg and Shoulder Dyskinesia

Facial Grimacing and Head Nodding

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TD Mechanism of Disease Video