MED-MSL-TD-US-0178_v8

Overview of Tardive Dyskinesia Differential Diagnosis

NEUROCRINE® BIOSCIENCES

Table of Contents

DRBA, dopamine receptor blocking agent

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]
- **Tardive dyskinesia (TD)** is an often persistent, clinically distinct DRBA-induced movement disorder[1,5]
  - Can coexist with other DRBA-induced movement disorders[5]
  - Requires specific management[5]

"Extrapyramidal symptoms" (EPS) is an **obsolete umbrella term** that has been used to describe a collection of DRBA-induced movement disorders[3]

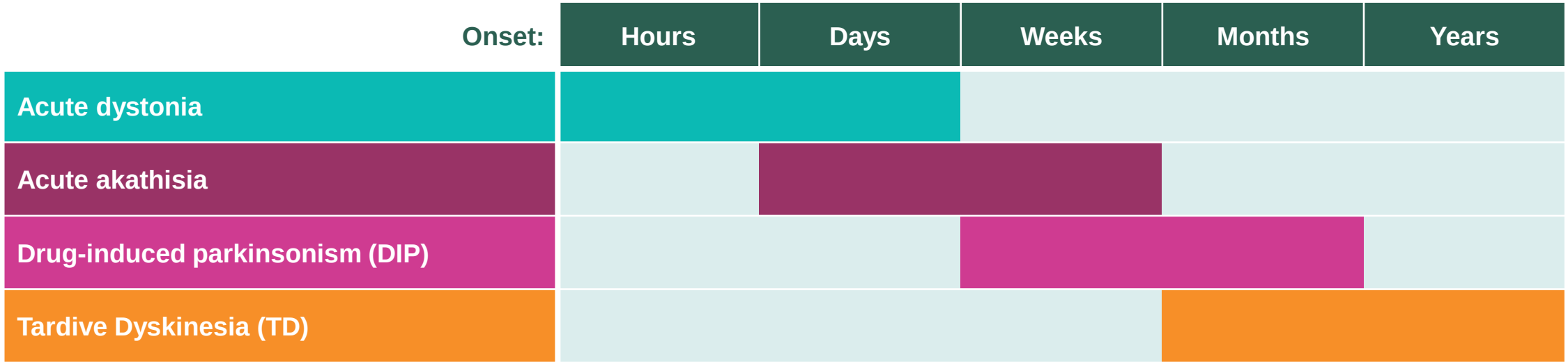
- Classification of these under EPS may be problematic as **each syndrome has its own pathophysiology, presentation, and treatment**[4]

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. 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. 4. Caroff SN, Campbell EC. *Psychiatr Clin North Am*. 2016;39(3):391-411. 5. Van Harten PN, et al. *Schizophr Res.* 1997;26:235-242.

DRBA-induced Movement Disorders Can Occur With FGA or SGA Use

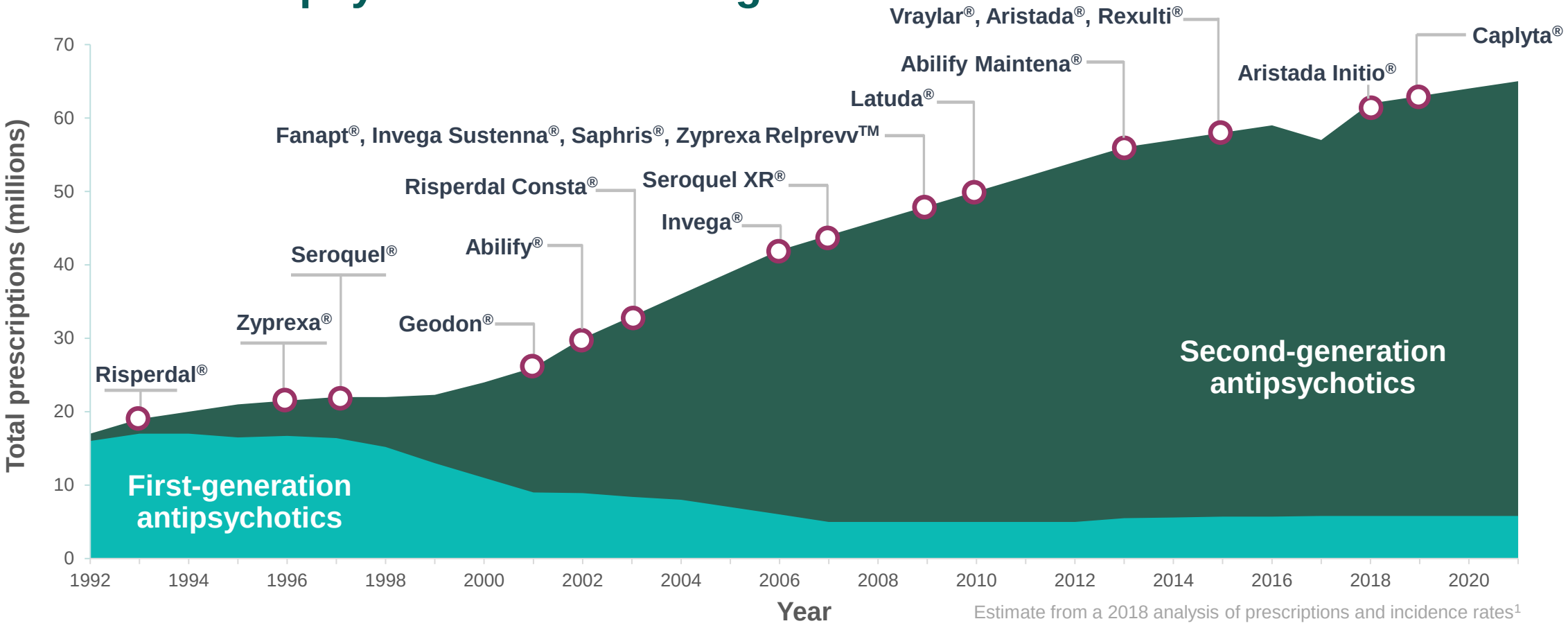
- DRBA-induced movement disorders can include acute presentations or may present after prolonged use of DRBAs (i.e., tardive)[1,2,3]



DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

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.

Trends in Antipsychotic Prescribing



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

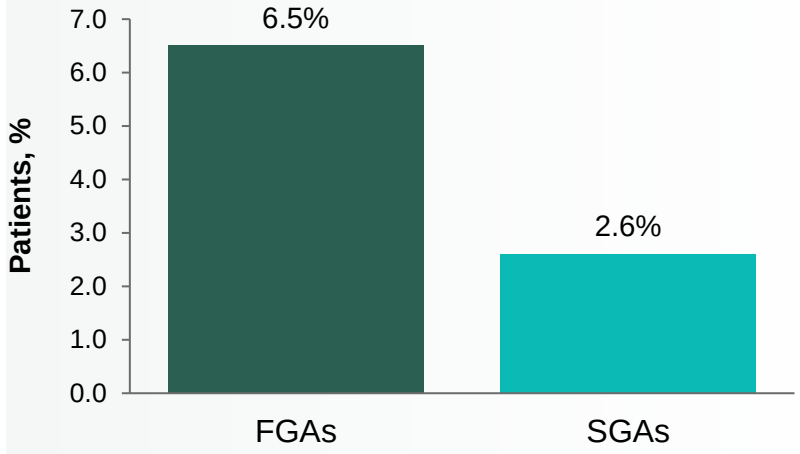
- **> 4-fold increase in antipsychotic use over 25 years[1]**
- **Use of second-generation antipsychotics (SGAs) in new conditions and client populations has grown over the past ~2.5 decades[2]**

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

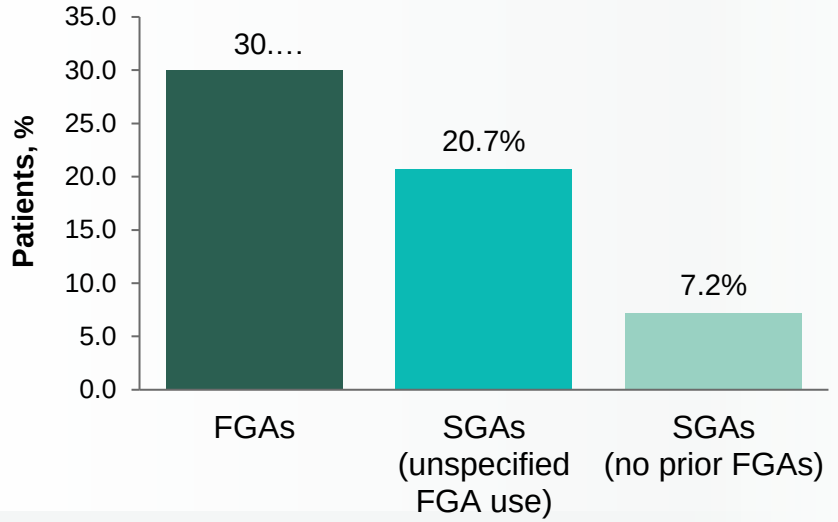
1. Data on file. Neurocrine Biosciences. 2. Alexander GC, et al. *Pharmacoepidemiol Drug Saf*. 2011;20(2)177-184.

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.

Stigma Associated with DRBA-Induced Movement Disorders

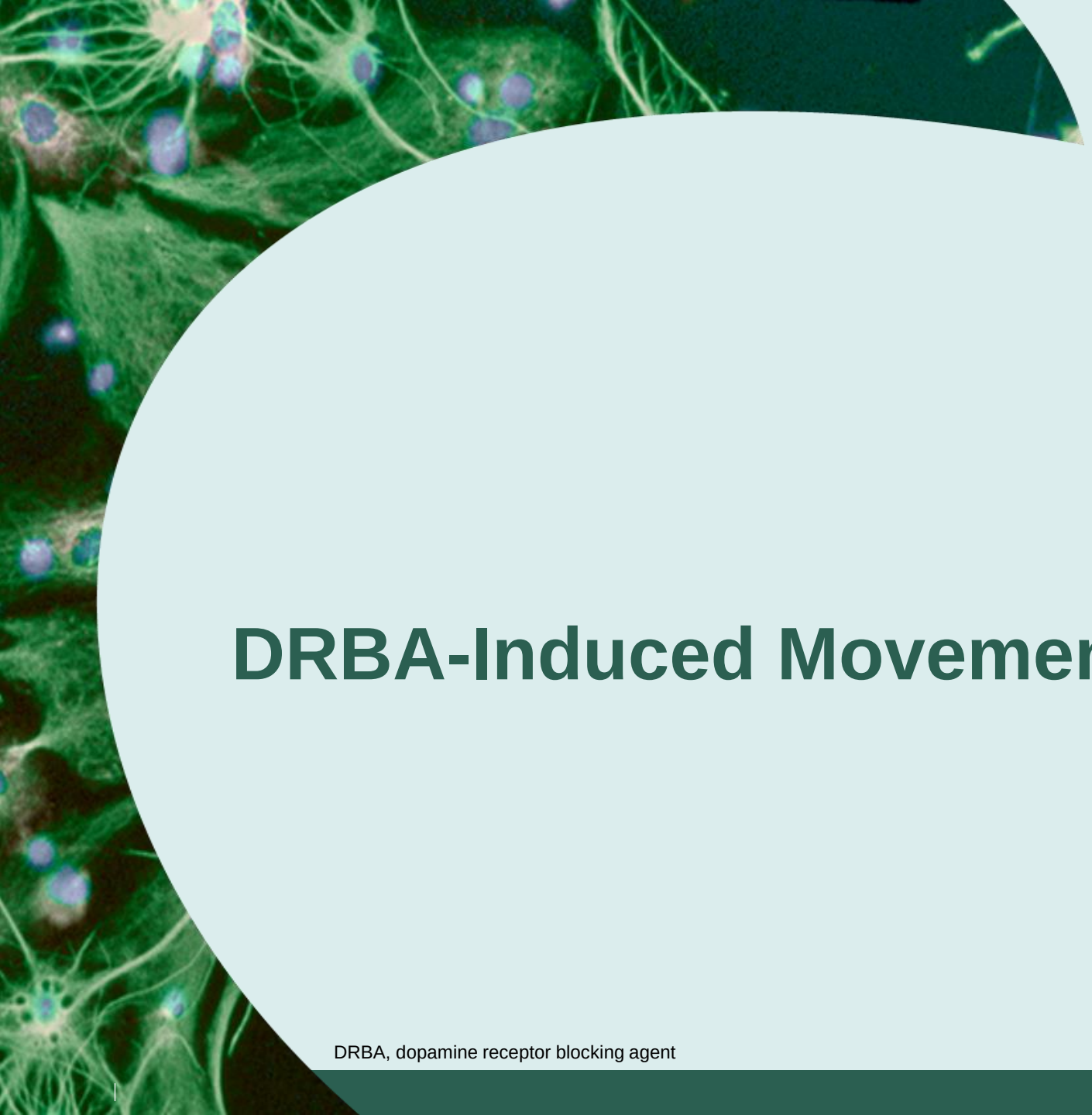
- DRBA-induced movement disorders visually stigmatize patients: psychiatric symptoms are internal, but movement disorders are obvious to all[1,2]
- DRBA-induced movement disorders can be stigmatizing and may influence compliance, relapse, and re-hospitalization[3]

In some patients, TD is associated with[2,4,5]:

- More severe psychopathology
- Worse quality of life and functioning
- Lower levels of daily and leisure activities
- Lower productivity
- Social stigma
- Increased morbidity and mortality

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

1. Gerlach J, et al. *Acta Psychiatr Scand*.1988;77(4):369-78. 2. Boumans CE, et al. *Schizophr Bull*.1994;20(2):339-44.2. 3. Caroff S, et al. *Psychiatric Clinics of North America*. 2016;39(3):391-411. 4. Ascher-Svanum H, et al. *J Clin Psych*. 2008;69(10):1580-1588. *5.* Ballesteros J, et al. *J Clin Psychopharmacol*. 2000;20:188-194.



DRBA-Induced Movement Disorders

DRBA, dopamine receptor blocking agent

Clinical Characteristics of Dystonia

Typical Time to Onset[a]

- **Acute – Hours to Days**
- **Tardive – Weeks to Years**

Movement Phenomenology

- Pulling, twisting, sustained, & repetitive movements or postures that are usually focal, involving:
  - Head
  - Neck
  - Eyes
  - Mouth
  - Jaw
  - Tongue
  - Face
- Torticollis, trismus, jaw opening, grimacing, blepharospasm or oculogyric crisis, tongue protrusion, biting, or twisting

Other Clinical Features:

- Muscle pain or cramps
- Distress
- Anxiety
- Dysarthria
- Dysphagia
- Respiratory stridor

Risk Factors for Acute Dystonia

Acute Dystonia Patient Video #1

Acute Dystonia Patient Video #2

[a]Following DRBA initiation or change in dose. Onset may occur earlier or later than the typical time frames listed (see manuscript text for further information).

Hauser RA, et al. *CNS Spectrums*. 2020:1-10.

Treatment Approaches for Acute Dystonia

- 2020 APA Schizophrenia Practice Guidelines recommend treatment with an anticholinergic medication for acute dystonia[4]

Medication Options*[1,2,3,4]
- Anticholinergics   - Benztropine & Artane (trihexyphenidyl)
- Antihistamines   - Benadryl (diphenhydramine)
- Benzodiazepines   - Klonopin (clonazepam) & Valium (diazepam)

*Botulinum Toxin Type A and B have also been used to treat certain forms of dystonia.[5,6]

1. Owens DG. A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs. *Cambridge University Press*. 2014. 2. Lehman, AF. *American Psychiatric Association.* 2010: p.32. 3. Stroup, et al. *World Psychiatry*. 2018;17(3):341-356. 4. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. 5. BOTOX [package Insert]. Madison, NJ: Allergan, Inc.; 2019. 6. MYOBLOC [package Insert]. Louisville, KY: Solstice Neurosciences, LLC.; 2019.

Clinical Characteristics of Akathisia

Typical Time to Onset[a]

- **Acute – Days to Months**
- **Tardive – Weeks to Years**

Movement Phenomenology

- Inner feeling of restlessness
- Urge to move
- Inability to stay seated
- May be associated with stereotypies:
  - Foot tapping
  - Shuffling
  - Shifting weight
  - Rocking

Risk Factors for Akathisia

Akathisia Patient Video

[a]Following DRBA initiation or change in dose. Onset may occur earlier or later than the typical time frames listed (see manuscript text for further information).

Hauser RA, et al. *CNS Spectrums*. 2020:1-10.

Treatment Approaches for Akathisia

- 2020 APA Schizophrenia Practice Guidelines suggests the following options for patients with akathisia[7]:
  - Lower the dosage of the antipsychotic medication
  - Switch to another antipsychotic medication
  - Add a benzodiazepine medication
  - Add a beta-adrenergic blocking agent

Medication Options
- Beta-adrenergic blockers[1,2,3]   - Inderal (propranolol hydrochloride)
- Benzodiazepines[1,3]   - Valium (diazepam), Klonopin (clonazepam) & Ativan (lorazepam)
- Anticholinergics[3,4]   - Benztropine
- Serotonergic treatments[1,3,5,6]   - Remeron (mirtazapine) & Zomig (zolmitriptan)
- Symmetrel (amantadine hydrochloride)[1]

1. Poyurovsky M. *Br J Psychiatry*. 2010;196(2):89–91. 2. Miller CH, et al. *Drug Saf*. 2000;22(1):73–81. 3. Stroup, et al. World Psychiatry. 2018;17(3):341-356. 4. Rathbone J, et al. *Cochrane Database Syst Rev*. 2006;(4):CD003727. 5. Avital A, et al. *Eur Neuropsychopharmacol*. 2009;19: 476-82. 6. Fischel T, et al. J Clin Psychopharmacol. 2001;21:612-5. 7. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

Clinical Characteristics of Drug-Induced Parkinsonism (DIP)

Typical Time to Onset[a]

- **Days or Weeks to Years**

Movement Phenomenology

- Tremor and/or bradykinesia
- Rigidity of neck, trunk, & extremities
- Hypomimia
- Reduced blink rate
- Reduced arm swing
- Flexed posture
- Shuffling or freezing gait
- Rabbit syndrome (a parkinsonian variant that includes jaw tremor)

Other Clinical Features:

- Soft speech
- Dysphagia
- Fatigue

Risk Factors for DIP

DIP Patient Video #1

DIP Patient Video #2

[a]Following DRBA initiation or change in dose. Onset may occur earlier or later than the typical time frames listed (see manuscript text for further information).

Hauser RA, et al. *CNS Spectrums*. 2020:1-10.

Treatment Approaches for Drug-Induced Parkinsonism

- 2020 APA Schizophrenia Practice Guidelines suggests the following options for patients who have DIP[6]:
  - Lower the dosage of the antipsychotic medication
  - Switch to another antipsychotic medication
  - Treat with an anticholinergic medication
- Other Management Strategies:
  - Switch to antipsychotic with lower risk (Quetiapine)[4,7]

Medication Options

- Anticholinergics[1-4]
  - Benztropine
  - Artane (trihexyphenidyl)

- Symmetrel (amantadine hydrochloride)[1-3,5]

DIP, drug-induced parkinsonism.

1. Lehman, AF. *American Psychiatric Association*. 2010: p.32. 2. Caroff S, et al. *Psychiatric Clinics of North America*. 2016;39(3):391-411. 3. Dayalu P, et al. *Pharmacother*. 2008;9(9):1451–62. 4. Stroup, et al. *World Psychiatry*. 2018;17(3):341-356. 5. Mamo DC, et al. *Drug Saf*.1999;20:269-75. 6. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. 7. Cortese L, et al. *J Clin Psychopharmacol*. 2008;28:69-73.

Tardive Dyskinesia (TD) is a Clinically Distinct, Delayed DRBA-induced Movement Disorder

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

Risk Factors for TD

TD Pathophysiology

Jaw, Tongue, Neck

OBL and Legs

Jaw, Hand, Face

Leg, Shoulder, Face

*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

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:

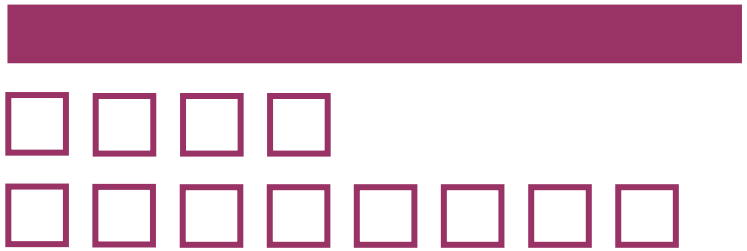
4 weeks

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*

Scoring AIMS

*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.

VMAT2 Inhibitors are Recommended as First-line Treatment for TD

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

VMAT2 inhibitor Mechanism of Action Video

2020 APA Guidelines: TD Recommendation

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.

Anticholinergics: Not Recommended for use in TD

American Academy of Neurology (AAN)	American Psychiatric Association (APA)

• **2013 AAN Evidence-Based Guidelines[1]:**
  • No controlled trials examining the efficacy of benztropine, biperiden, chlorprothixene, and trihexyphenidyl in treating TD
  • Insufficient data to determine the effectiveness of anticholinergics for the treatment of TD (Level U)
	• **2020 APA Schizophrenia Practice Guidelines – TD Recommendations[2]:**
	  • Anticholinergic medications do not improve and may even worsen tardive dyskinesia[3,4] in addition to producing significant side effects

- Anticholinergics can make tardive dyskinesia worse[3-7]
- Anticholinergics are associated with risk of dementia[8]
  - Study consisted of 58,769 patients with a diagnosis of dementia and 225,574 matched controls
  - Associations were also stronger in cases diagnosed with dementia before the age of 80 years

Anticholinergic Action in DIMDs

1. Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469. 2. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. 3. Benztropine mesylate [package insert]. Warren, NJ: Cipla USA, Inc.; 2020. 4. Bergman H, et al. *Cochrane Database of Systematic Reviews*. 2018;1:CD000204. 5. Waln O, et al. Tremor Other Hyperkinet Mov (NY). 2013 Jul 12;3. 6. Klawans HL. *The American Journal of Psychiatry*.1973;130(1):82-86. 7. Citrome L. *J Neurol Sci*. 2017;383:199-204. 8. Coupland CAC, et al. JAMA Intern Med. 2019 Jun 24.

Differential Diagnosis Is Necessary for Appropriate Treatment

As **each DRBA-induced movement disorder** has its own **presentation** and **pathophysiology**, treatment must be **distinct** to each movement disorder[1]

When treating DRBA-induced movement disorders

One Size Doesn't Fit All

Treatment options **recommended** for one DRBA-induced movement disorder may **worsen** others

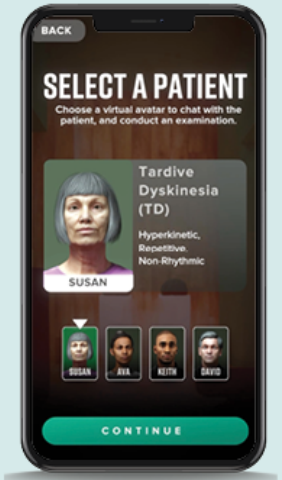
Use of **multiple treatment options** may be necessary in patients with multiple DRBA-induced movement disorders

DRBA, dopamine receptor–blocking agent.

1. Hauser RA, et al. *CNS Spectr*. 2020:1-10.

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

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Appendix

Factors Associated With Increased Risk for Acute Dystonia

Risk Factors for Acute Dystonia	
Younger age	Family history of dystonia
Male gender	Cocaine use
Black race	Previous dystonic reactions

Caroff S, et al. *Psychiatric Clinics of North America*. 2016;39(3):391-411.

Acute Dystonia

Retrocollis: repetitive, patterned, neck extension

Next Patient Video

Hauser RA, et al. *CNS Spectr*. 2020. Epub ahead of print.

Acute Dystonia

Retrocollis: repetitive, patterned, neck extension

Factors Associated With Increased Risk for Akathisia

Risk Factors for Akathisia	
Increasing age	Cognitive dysfunction
Female gender	Iron deficiency
Negative symptoms	Prior akathisia
Concomitant parkinsonism	Mood disorders

Caroff S, et al. *Psychiatric Clinics of North America*. 2016;39(3):391-411.

Akathisia

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

Factors Associated With Increased Risk for DIP

Risk Factors for DIP	
Advancing age	Family history of Parkinson's disease
Female gender	Preexisting extrapyramidal disease
Abnormalities of brain structure including dementia	Human Immunodeficiency Virus (HIV) infection

Caroff S, et al. *Psychiatric Clinics of North America*. 2016;39(3):391-411.

Drug-induced Parkinsonism

Parkinsonian Tremor: Rhythmic, 3 to 4 Hz Tremor in Lower Lip and Chin

Next Patient Video

Hauser RA, et al. *CNS Spectr*. 2020. Epub ahead of print.

Drug-Induced Parkinsonism

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

Factors Associated With Increased Risk for TD

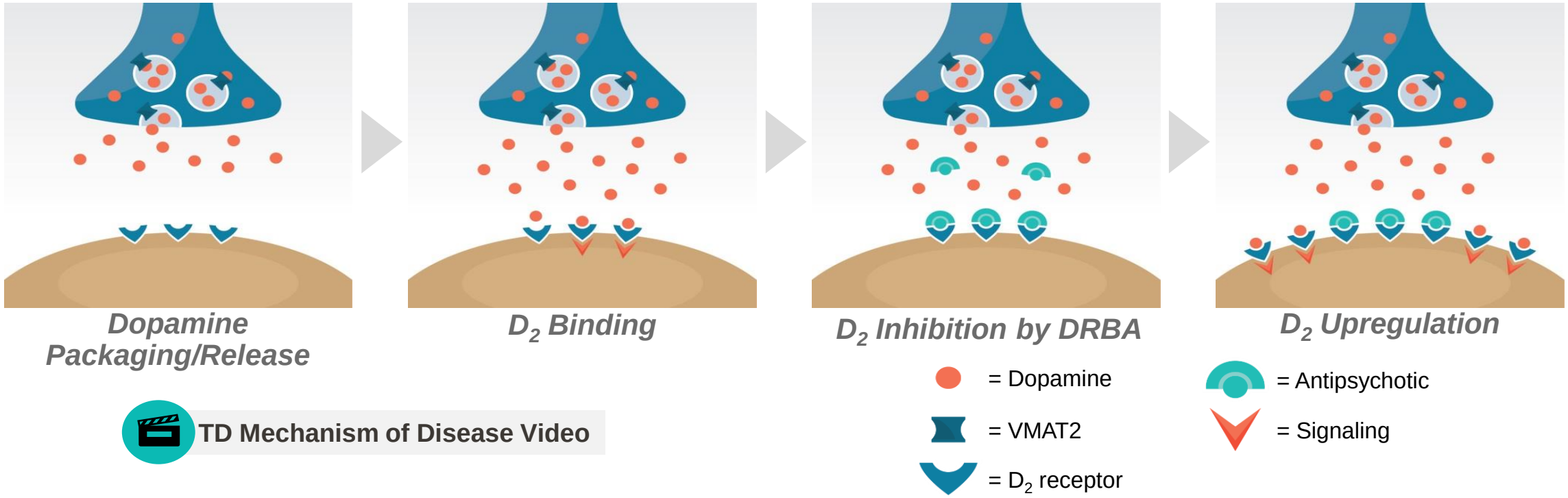
Risk Factors for TD	
Treatment Factors	**Patient Factors**
Cumulative exposure to antipsychotics[1]	Increased age[1]
Treatment with anticholinergics[1]	Substance abuse[1]
History of extrapyramidal side effects[1]	Diagnosis of mood disorder[3,4]
Potency of DRBA[2]	Postmenopausal women[5]
Neuroleptic withdrawal-emergent dyskinesia[6]	

TD, Tardive Dyskinesia; DRBA, dopamine receptor blocking agent

1. Miller DD, et al. *Schizophr Res*. 2005;80:33-43. 2. Divac N. *Biomed Res Int*. 2014;2014. 3. Jeste DV, et al. *Schizophr Bull*. 1993;19:303-315. 4. Mukherjee S. *Arch Gen Psychiatry. 1*986;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.

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.

Moderate Cervical and Jaw

Jaw

Tongue

Neck

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Open Mouth and Tongue

Jaw

Tongue

Neck

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Neck, Shoulder, Hands (Standing and Walking)

Jaw

Tongue

Neck

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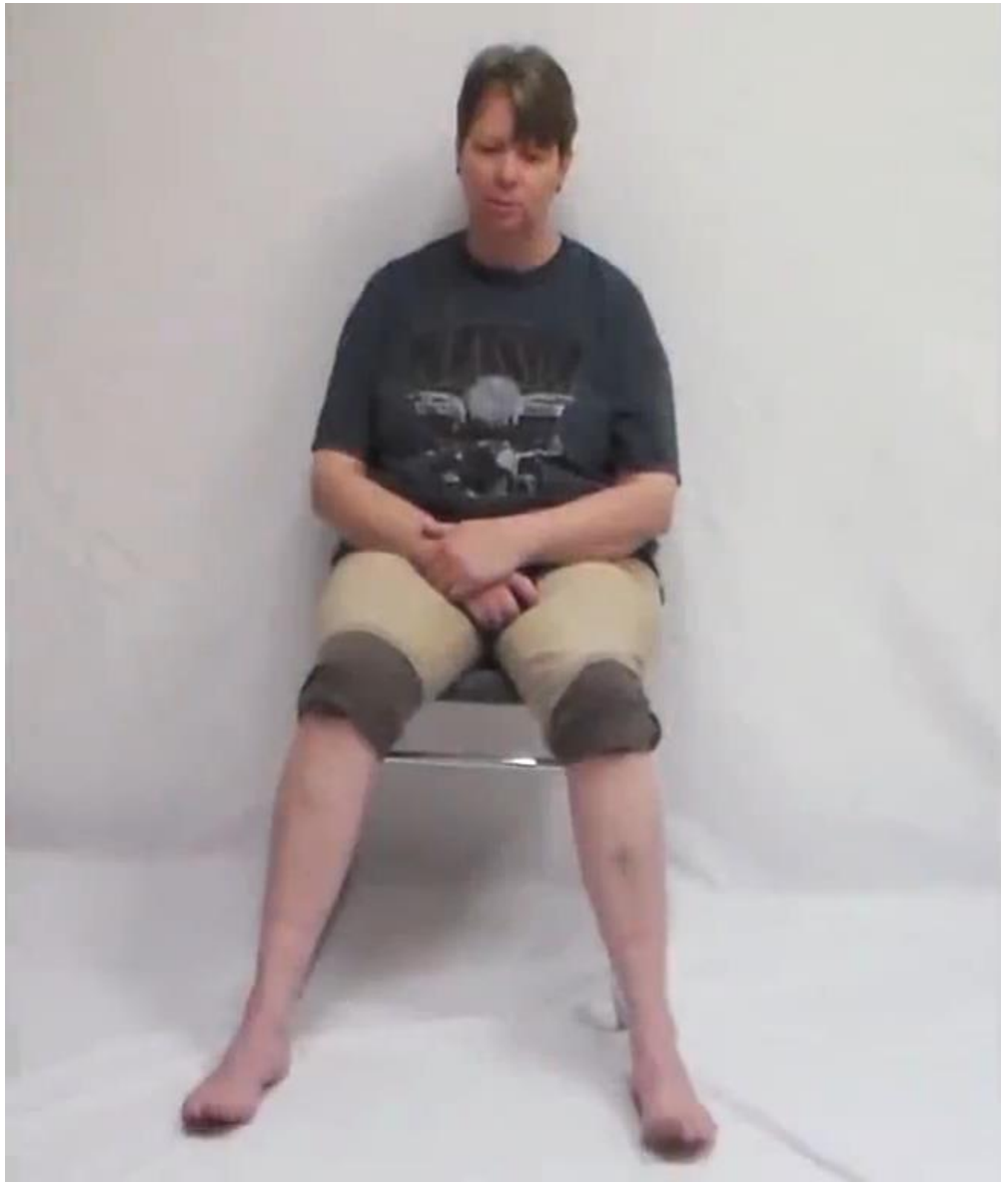
Oral-Buccal-Lingual and Legs



Sitting

Standing

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Oral-Buccal-Lingual and Legs

Sitting

Standing

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Mild Jaw and Hand

Jaw

Hand

Face

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Activation with Hand Movement

Jaw

Hand

Face

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Increased Blinking and Jaw Activation

Jaw

Hand

Face

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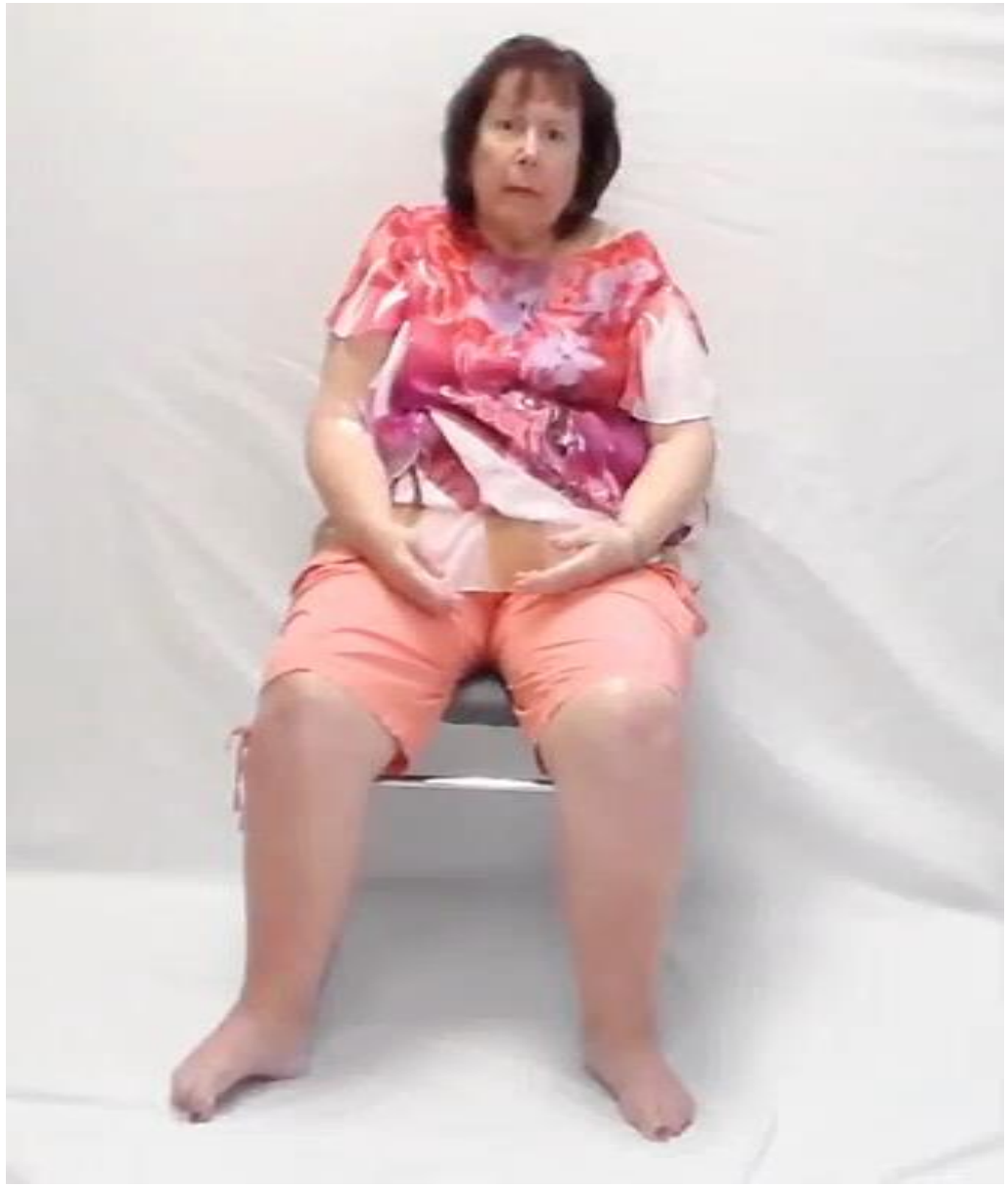
Leg and Shoulder Dyskinesia



Leg and Shoulder

Face

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

Facial Grimacing and Head Nodding

Leg and Shoulder

Face

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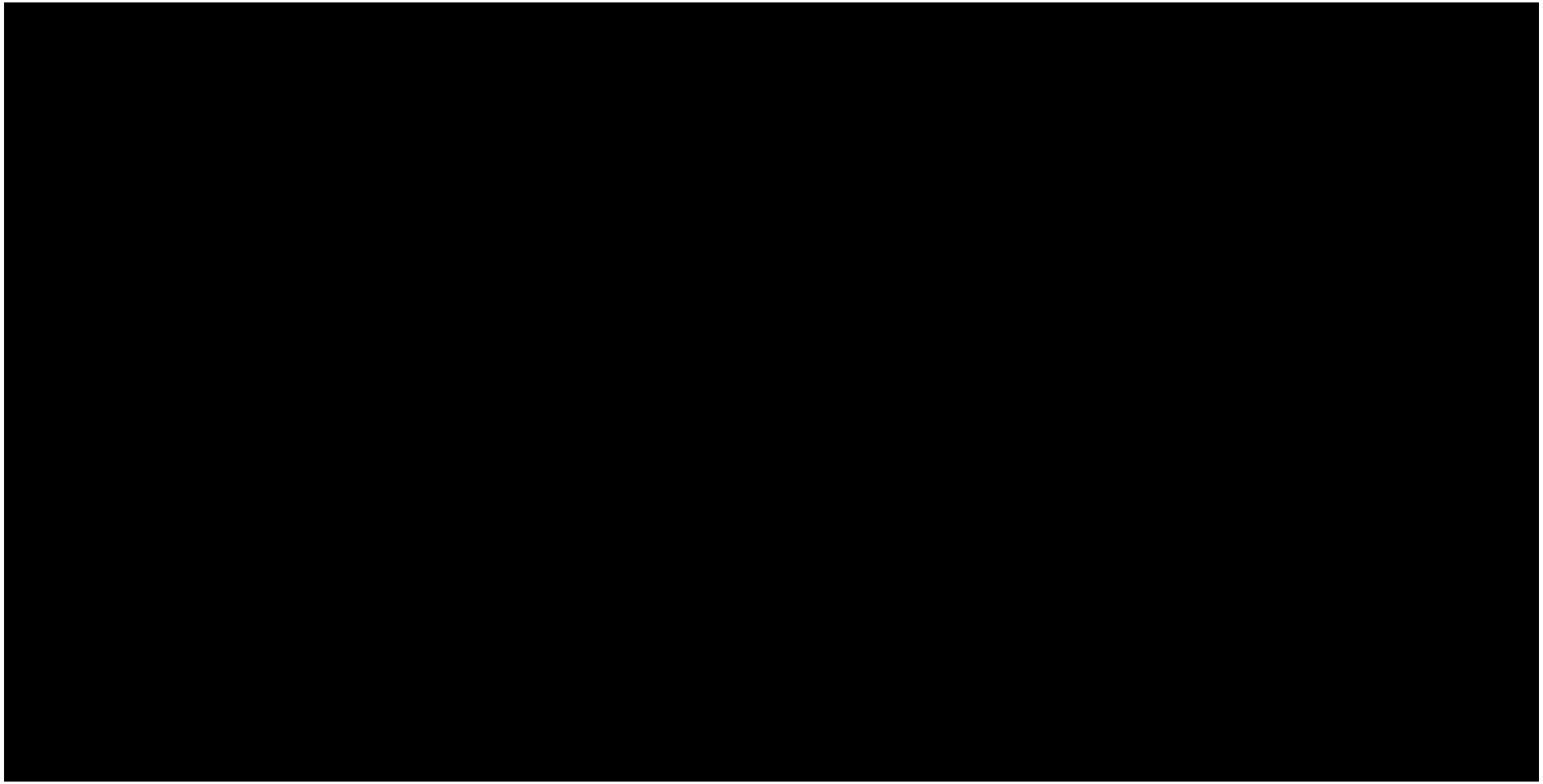
Tardive Dyskinesia: Mechanism of Disease Video



TD, tardive dyskinesia.

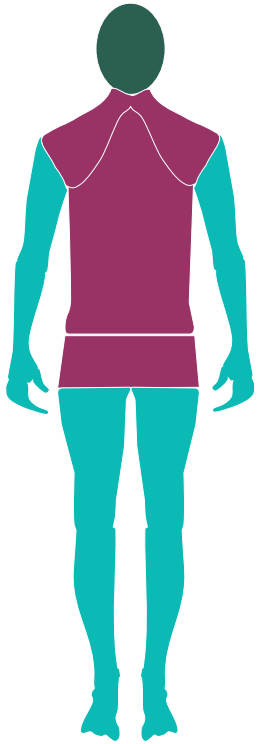
Scoring AIMS

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

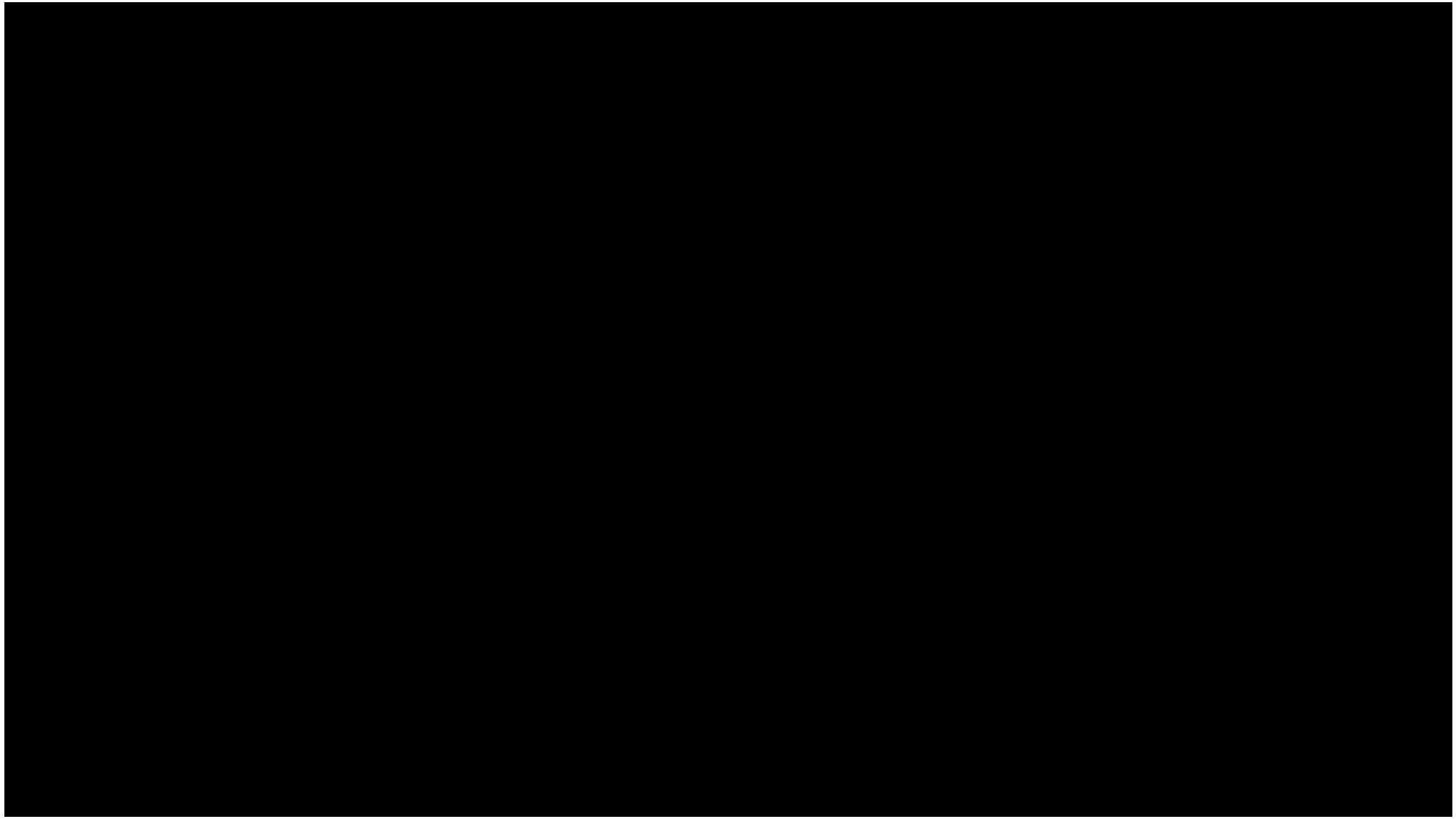
AIMS Total Dyskinesia Score=Sum of Items 1–7

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



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.

VMAT2 Inhibitor Mechanism of Action Video



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:

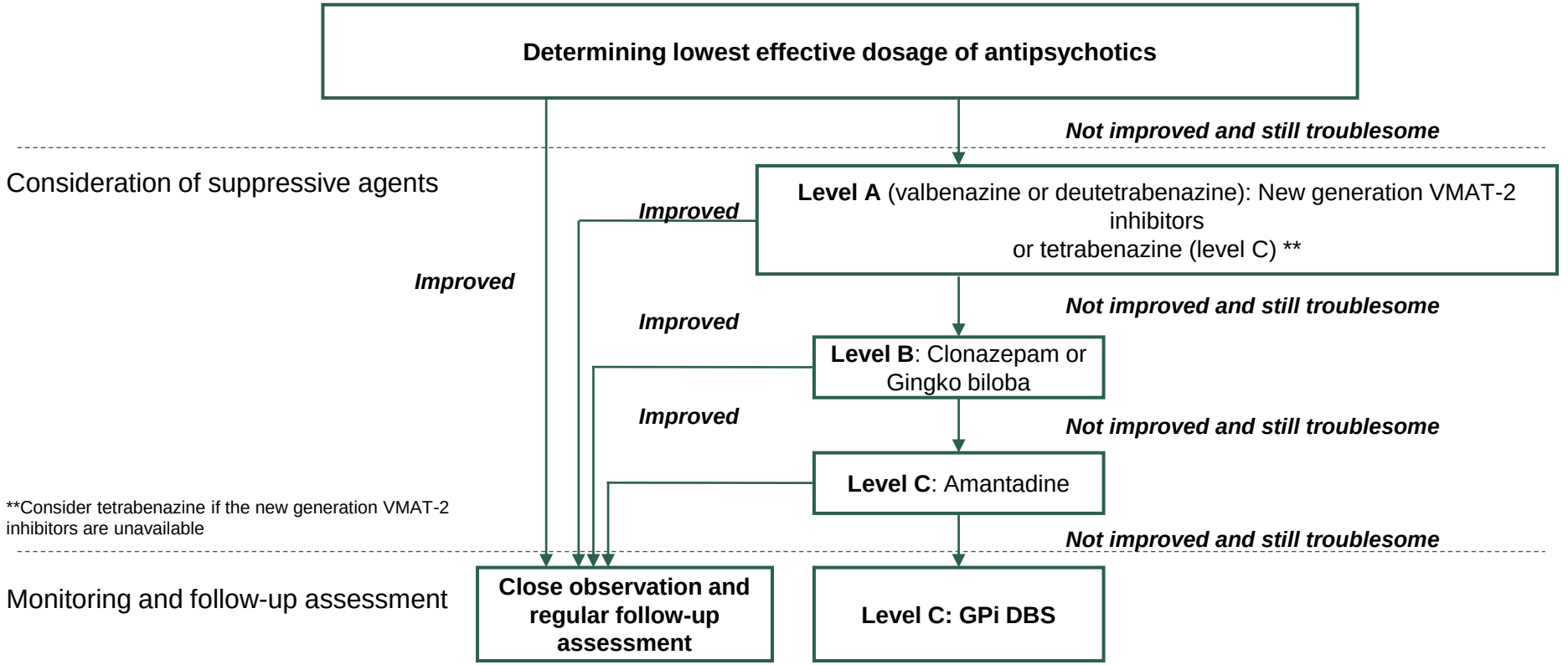
- Anticholinergics (e.g., benztropine)
- Benzodiazepines (e.g., clonazepam)
- Change in antipsychotic therapy to a lower-potency medication
- Ginkgo biloba
- Cessation or reduction of antipsychotic medication
- Amantadine
- Vitamin E

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.

2018 Systematic Review: Practical Treatment Algorithm

- Adapted for the management of troublesome TD in patients receiving an approved antipsychotic treatment as indicated.
- Assessment of TD is necessary prior to treatment



GPi DBS, globus pallidus interna deep brain stimulation; TD, tardive dyskinesia; VMAT-2, vesicular monoamine transporter type 2.

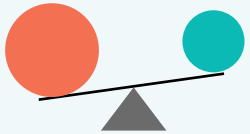
Bhidayasiri et al. *J Neurol Sci.* 2018;389:67-75.

The Balance of Dopamine and Acetylcholine[1,2]

- In a healthy brain, there is a balance between dopamine (DA) and acetylcholine (ACh) with complex feedback mechanisms and circuits
- DA and ACh have an indirect relationship: DA inhibits ACh release, while ACh increases DA release
- An imbalance between DA and ACh in the basal ganglia is thought to contribute to the motor symptoms experienced in neurological conditions, such as Parkinson's Disease

Dopamine Acetylcholine

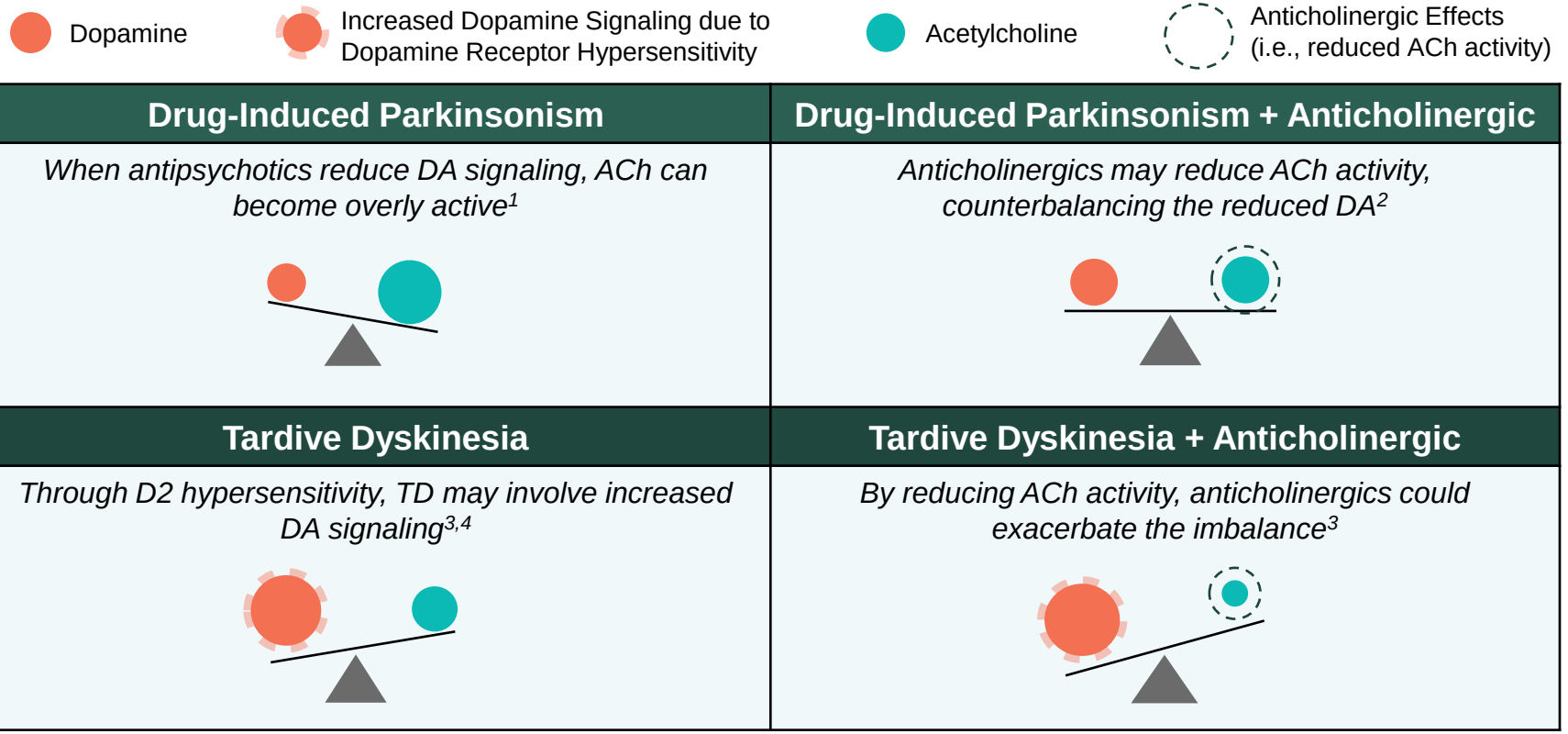
Overview of interaction in the CNS

DA ↔ Ach	Pathophysiology
	None: Balanced System
	Parkinson's Disease: Loss of dopaminergic neurons of the basal ganglia
	Psychosis: Increased dopaminergic signaling

1. Scarr E, et al. *Front in Cell Neurosci. 2*013;7:55. 2. Lester D, et al. *CNS Neurosci Ther*. 2010;16(3):137-162.

Anticholinergic Action in DRBA-Induced Movement Disorders

- Anticholinergic action in the basal ganglia can restore the dopamine-acetylcholine balance in certain disease states, while worsening it in others



DA, dopamine; ACh, acetylcholine

1. Stahl S. Antipsychotic agents. *Stahl's Essential Pharmacology*. 4th ed. Cambridge University Press; 2013:145-252. 2. Lester DB, et al. *CNS Neurosci Ther*. 2010;16(3):137-162. 3. Ward MW, Citrome L. *Neurol Ther*. 2018;7(2):233-248. 4. Stahl SM. *CNS Spectr*.2017;22(6):427-434.