

Overview of Tardive Dyskinesia

Differential Diagnosis





Table of Contents

[Introduction to DRBA-Induced Movement Disorders](#) 

[Acute Dystonia](#) 

[Akathisia](#) 

[Drug-Induced Parkinsonism](#) 

[Tardive Dyskinesia](#) 



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 disorders⁵
 - Requires specific management⁵

“Extrapyramidal symptoms” (EPS) is an **obsolete umbrella term** that has been used to describe a collection of DRBA-induced movement disorders³

- 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}

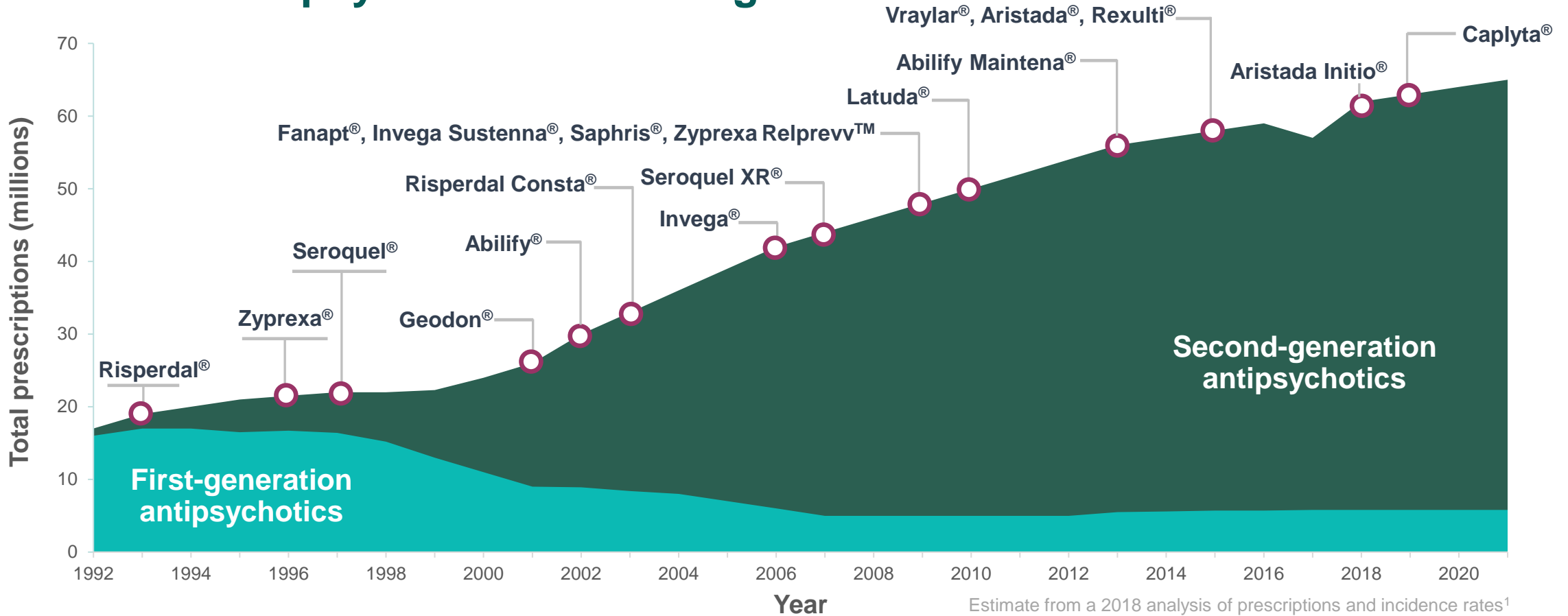
Onset:	Hours	Days	Weeks	Months	Years
Acute dystonia	Acute presentation		Prolonged use		
Acute akathisia	Prolonged use	Acute presentation		Prolonged use	
Drug-induced parkinsonism (DIP)	Prolonged use	Acute presentation			Prolonged use
Tardive Dyskinesia (TD)	Prolonged use			Acute presentation	

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



- > 4-fold increase in antipsychotic use over 25 years¹
- Use of second-generation antipsychotics (SGAs) in new conditions and client populations has grown over the past ~2.5 decades²

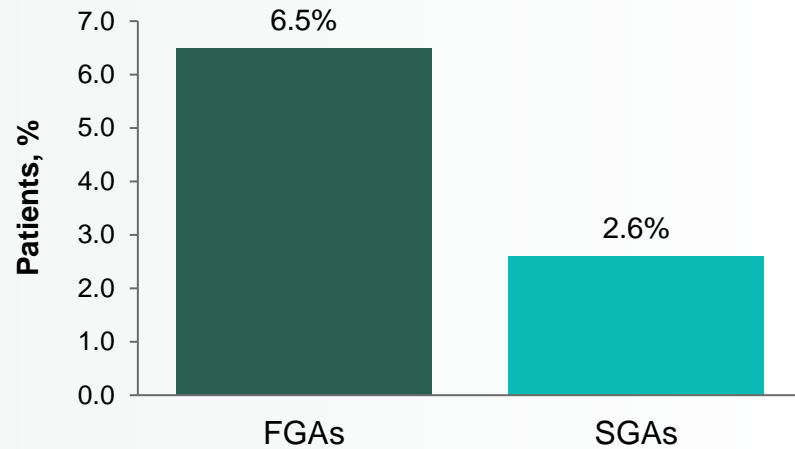
FGAs: first-generation antipsychotics; SGAs: second-generation antipsychotics

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

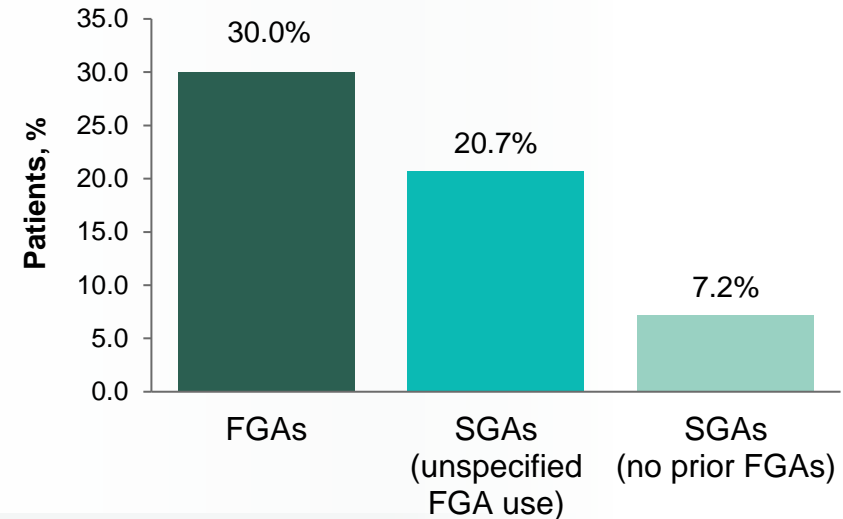


TD Is Associated With Prolonged DRBA Treatment

TD Annual Incidence^{1*}



TD Prevalence^{2†}



~5 million patients in the US are treated with antipsychotics³
≥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-hospitalization³

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



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



Treatment Approaches for Acute Dystonia

2020 APA Schizophrenia Practice Guidelines: ¹	Category
<ul style="list-style-type: none">- Anticholinergics<ul style="list-style-type: none">- Benztropine & Artane (trihexyphenidyl)	1C
<ul style="list-style-type: none">- Antihistamines<ul style="list-style-type: none">- Benadryl (diphenhydramine)	N/A ^a

Additional Medication Options ^{*2}
<ul style="list-style-type: none">- Benzodiazepines

*Botulinum Toxin Type A and B have also been used to treat certain forms of dystonia.^{3,4}

^aGRADE ratings were only assigned for primary guideline statements

APA, American Psychiatric Association

1. American Psychiatric Association. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia. American Psychiatric Association; 2021 2. Stroup, et al. *World Psychiatry*. 2018;17(3):341-356.

3. BOTOX [package Insert]. Madison, NJ: Allergan, Inc.; 2019. 4. 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



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



Treatment Approaches for Akathisia

2020 APA Schizophrenia Practice Guidelines: ¹	Category
- Lower the dosage of the antipsychotic medication	
- Switch to another antipsychotic medication	
- Beta-adrenergic blockers - Inderal (propranolol)	
- Benzodiazepines - Klonopin (clonazepam) & Ativan (lorazepam)	
- Serotonergic treatments - Remeron (mirtazapine)	N/A ^a

^aGRADE ratings were only assigned for primary guideline statements

APA, American Psychiatric Association

1. American Psychiatric Association. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia. American Psychiatric Association; 2021



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




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

DIP, drug-induced parkinsonism

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



Treatment Approaches for Drug-Induced Parkinsonism (DIP)

2020 APA Schizophrenia Practice Guidelines: ¹	Category
- Lower the dosage of the antipsychotic medication	
- Switch to another antipsychotic medication	
- Anticholinergics - Benztropine and Artane (trihexyphenidyl)	
- Antihistamines - Benadryl (diphenhydramine)	N/A ^a
- Symmetrel (amantadine)	N/A ^a

^aGRADE ratings were only assigned primary guideline statements.

APA, American Psychiatric Association; DIP, drug-induced parkinsonism

1. American Psychiatric Association. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia. American Psychiatric Association; 2021



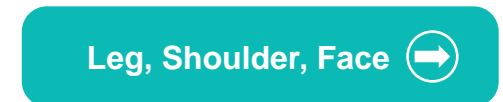
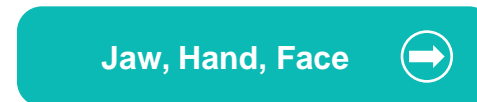
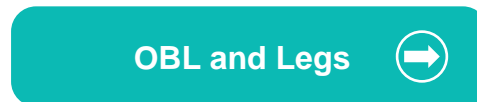
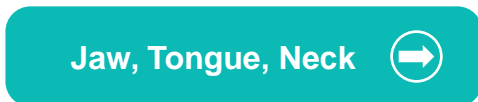
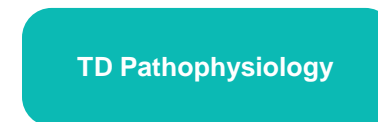
Tardive Dyskinesia (TD) is a Clinically Distinct, Delayed DRBA-induced Movement Disorder

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



*Movements are distinctly different from the rhythmic tremors (3-6 Hz) commonly seen in drug-induced parkinsonism¹
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:



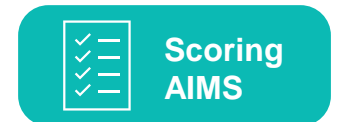
During exposure to DRBA



Within 4 weeks of withdrawal from an oral DRBA*



Within 8 weeks of withdrawal from LAI DRBA*



*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			2020 APA Guideline Recommendations ²		
Intervention	Category	Conclusion	Intervention	Category	Conclusion
VBZ	LEVEL A	Recommended as first-line treatment	Reversible VMAT2 inhibitor for treatment of TD	1B	Recommended in moderate to severe, or disabling TD
Deutetrabenazine	LEVEL A	Recommended as first-line treatment		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. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia. American Psychiatric Association; 2021.



Anticholinergics: Not Recommended for use in TD

American Academy of Neurology (AAN)	American Psychiatric Association (APA)
<ul style="list-style-type: none">• 2013 AAN Evidence-Based Guidelines¹:<ul style="list-style-type: none">• 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 (<u>Level U</u>)	<ul style="list-style-type: none">• 2020 APA Schizophrenia Practice Guidelines – TD Recommendations²:<ul style="list-style-type: none">• 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 worse³⁻⁷
- Anticholinergics are associated with risk of dementia⁸
 - 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



1. Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469. 2. American Psychiatric Association. The American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia. American Psychiatric Association; 2021. 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 disorder¹

*When treating DRBA-induced
movement disorders*

One Size Doesn't Fit All



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

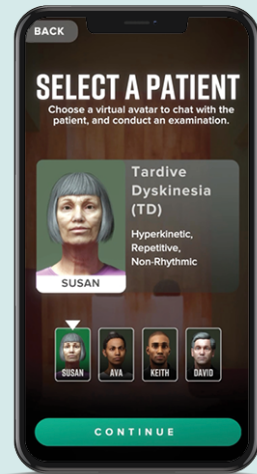
Use of **multiple treatment
options** may be necessary in
patients with multiple DRBA-
induced movement disorders

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



^aFor educational purposes only. Should not be interpreted as medical advice for any particular patient. Individual results may vary.

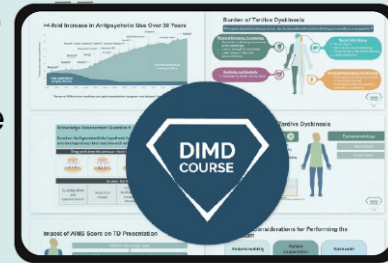
Experience
Discover TD®

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.

www.neurocrinemedical.com

Neurocrine Medical Affairs



1-877-641-3461





Appendix



Factors Associated With Increased Risk for Acute Dystonia

Risk Factors for Acute Dystonia

Younger age

Cocaine use

Male gender

Previous dystonic reactions

Family history of dystonia

Acute Dystonia

Retrocollis: repetitive, patterned, neck extension



Adapted from Marano M, et al. *Tremor Other Hyperkinet Mov (N Y)*. 2016 Dec 8;6:436. doi: 10.7916/D87P8ZS1. PMID: 28105387; PMCID: PMC5233782. under the Creative Commons CC BY license (<http://creativecommons.org/licenses/by/4.0/>)



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

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

Drug-induced Parkinsonism

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



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

Next Patient
Video



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	

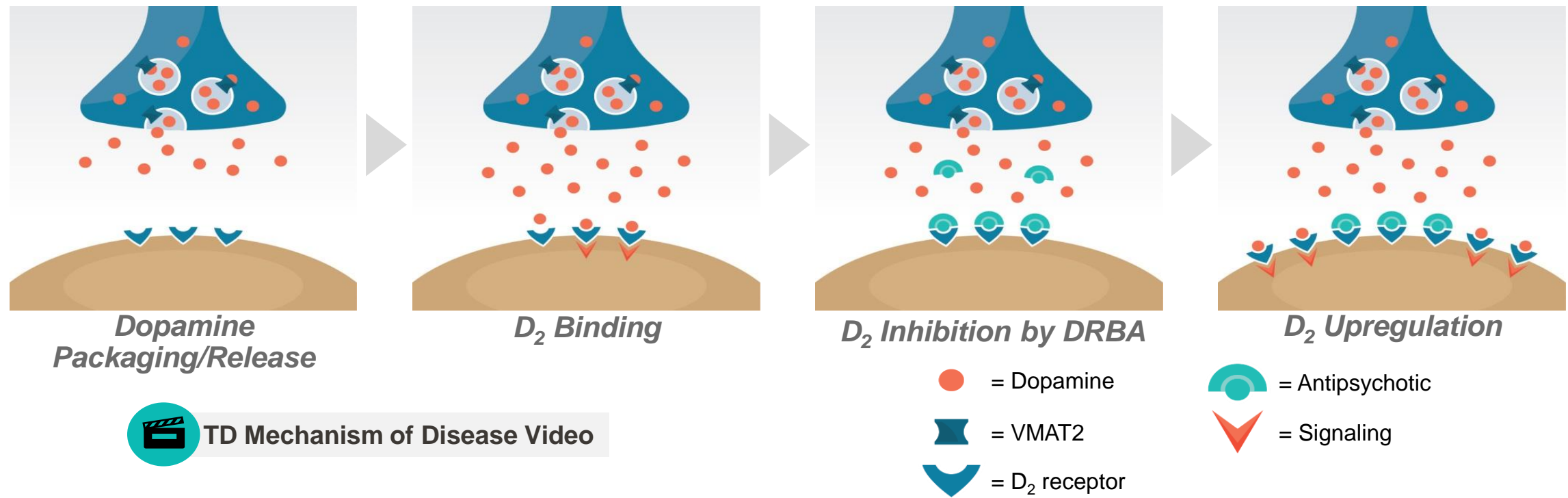
TD, Tardive Dyskinesia; DRBA, dopamine receptor blocking agent

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.* 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.



TD Pathophysiology

- The mechanism underlying TD is complex and the exact cause has not been fully elucidated¹⁻⁴
- A leading theory is the upregulation and subsequent hypersensitivity of brain dopamine D₂ receptors following prolonged exposure to DRBAs¹
- Additional hypotheses include DRBA-induced:
 - Oxidative stress from free radical formation²
 - 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 

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

Open Mouth and Tongue



Jaw 

Tongue 

Neck 

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

Neck, Shoulder, Hands (Standing and Walking)



Jaw 

Tongue 


Neck 

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

Oral-Buccal-Lingual and Legs



Sitting 

Standing 

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

Oral-Buccal-Lingual and Legs



Sitting 

Standing 

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

Mild Jaw and Hand



- Jaw 
- Hand 
- Face 

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

Activation with Hand Movement



Jaw 

Hand 

Face 


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

Increased Blinking and Jaw Activation



Jaw 

Hand 

Face 

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

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



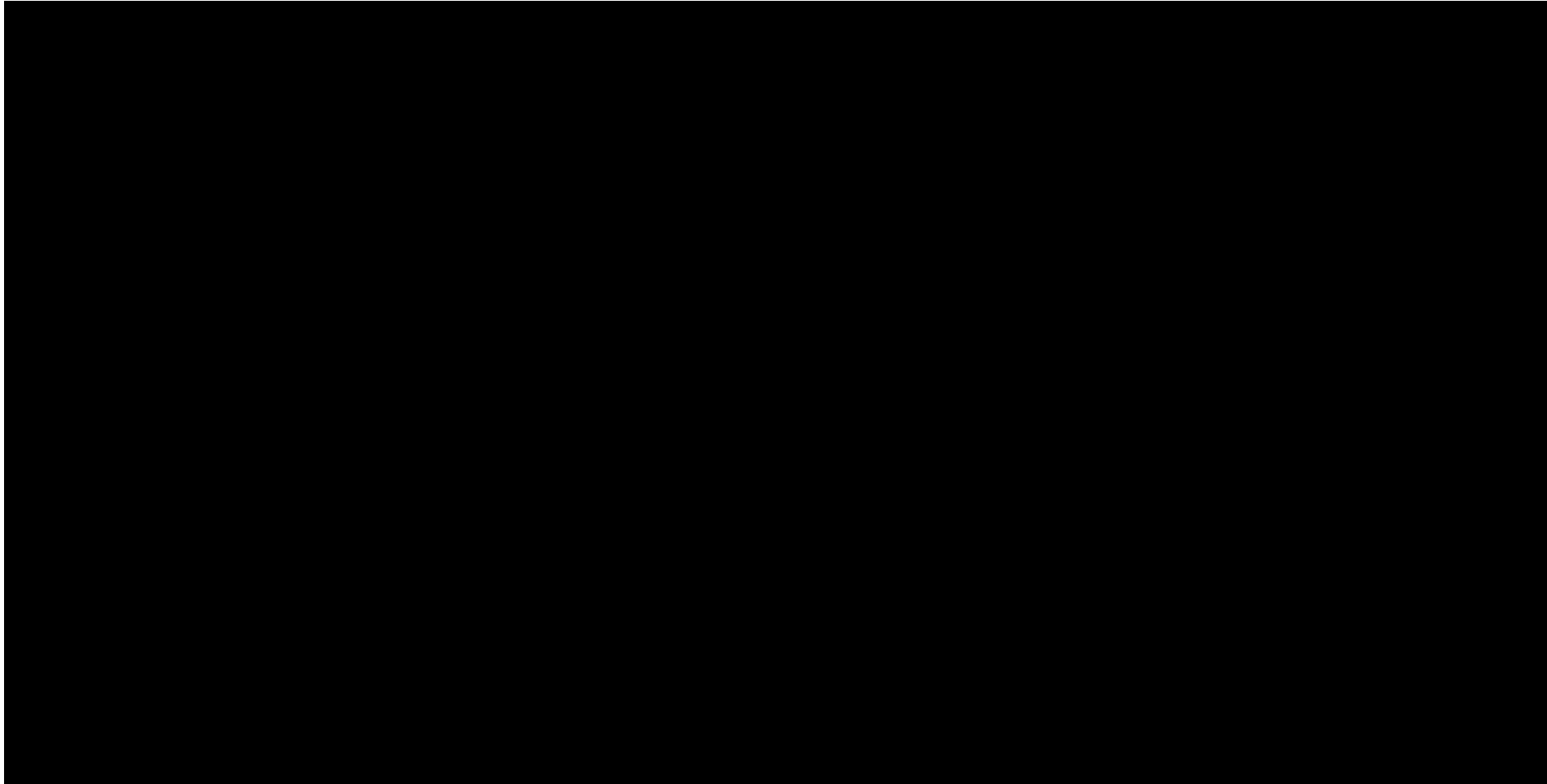
Leg and Shoulder 

Face 

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



Tardive Dyskinesia: Mechanism of Disease Video



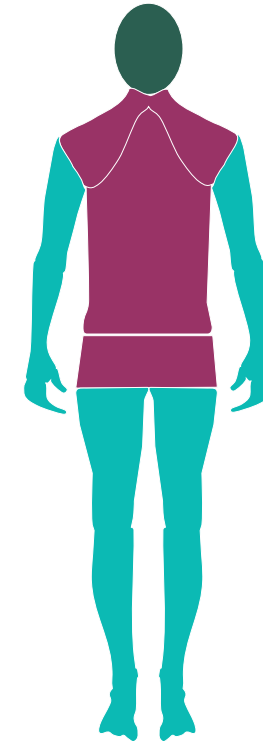
TD, tardive dyskinesia



Scoring AIMS

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

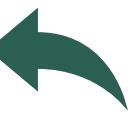
Facial and Oral Movements		None	Minimal	Mild	Moderate	Severe
1.	Muscles of facial expression	0	1	2	3	4
2.	Lips and perioral area	0	1	2	3	4
3.	Jaw	0	1	2	3	4
4.	Tongue	0	1	2	3	4
Extremity Movements		None	Minimal	Mild	Moderate	Severe
5.	Upper (arms, wrists, hands, fingers)	0	1	2	3	4
6.	Lower (legs, knees,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



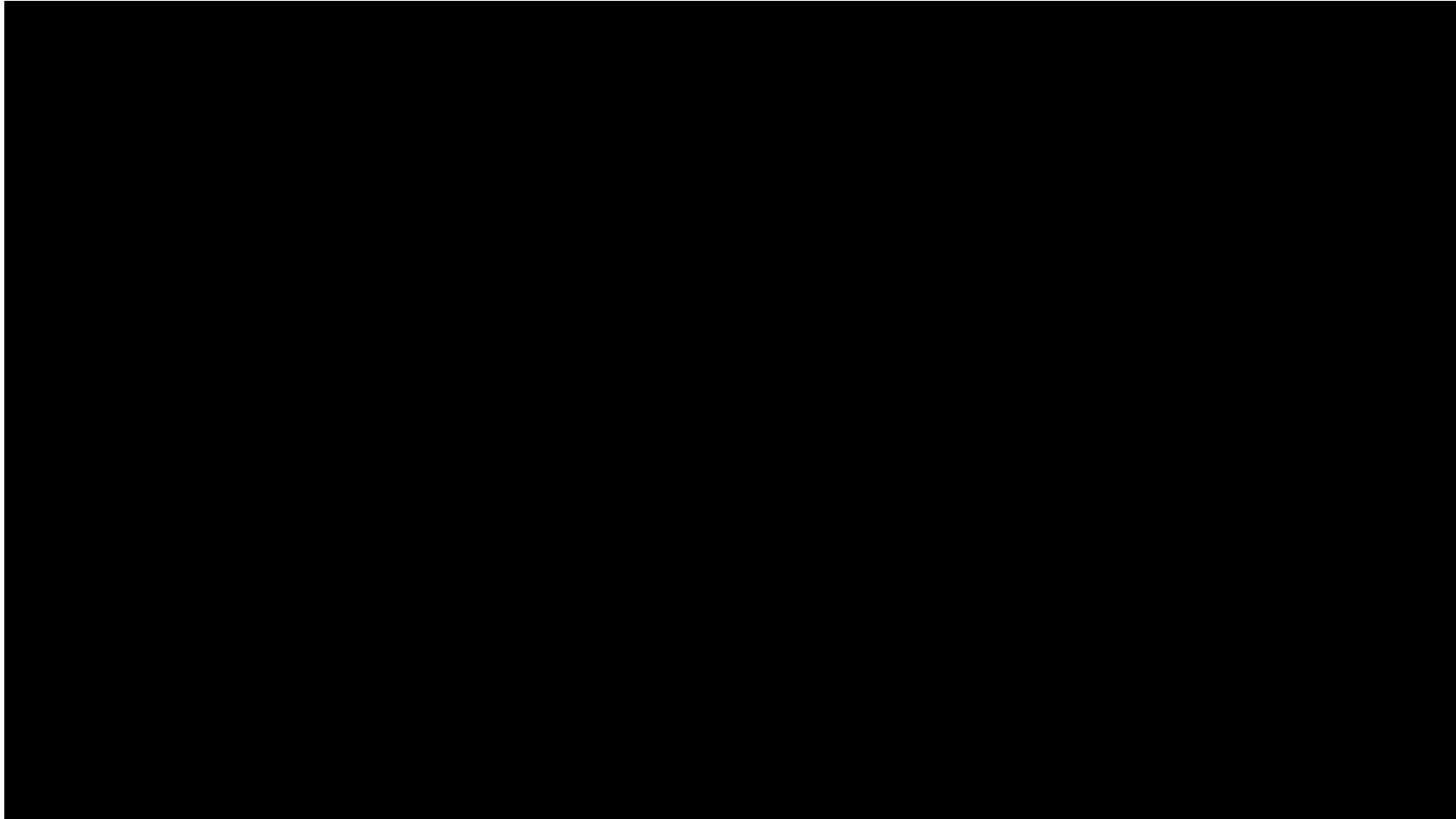
AIMS Total Dyskinesia Score=Sum of Items 1–7

- 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)

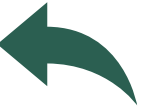
Change in antipsychotic therapy to a lower-potency medication

Ginkgo biloba

Cessation or reduction of antipsychotic medication

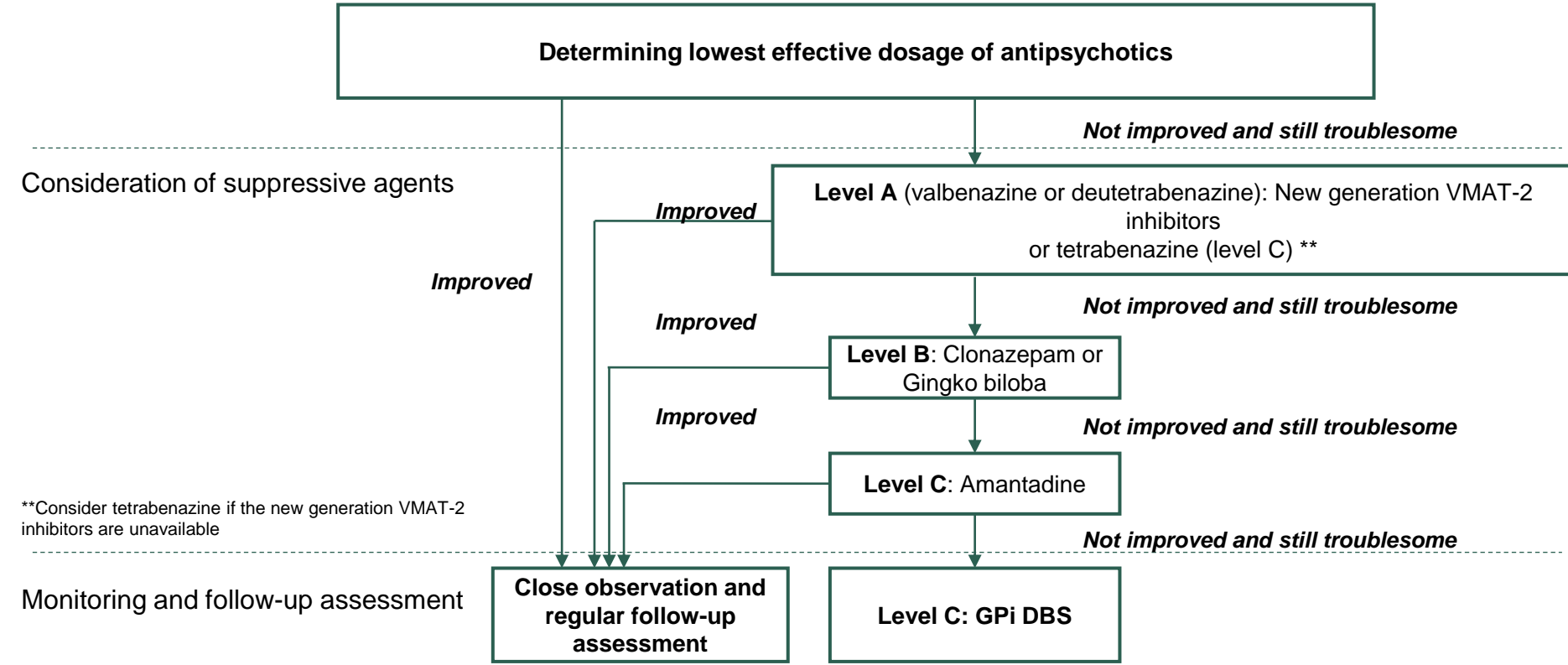
Amantadine

Vitamin E



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

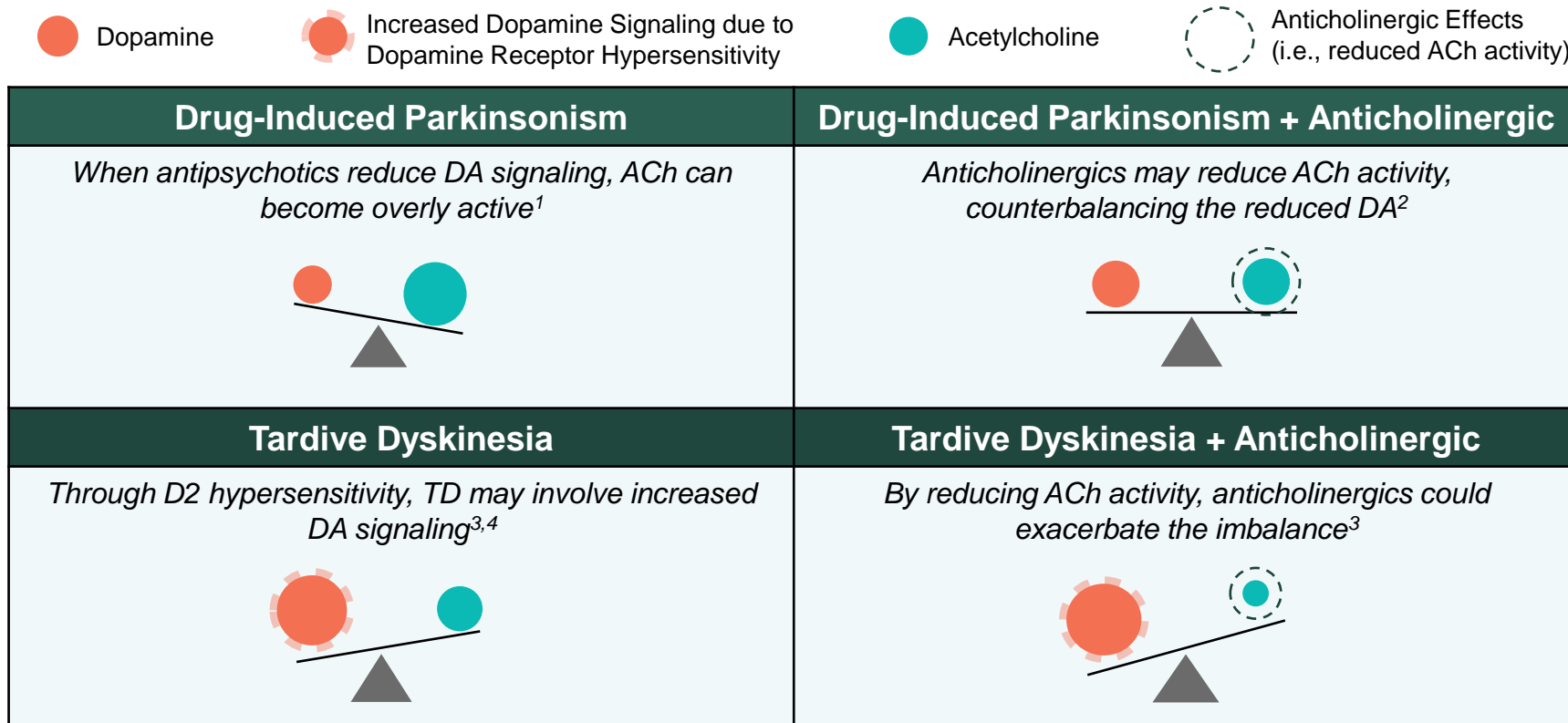


GPi DBS, globus pallidus interna deep brain stimulation; TD, tardive dyskinesia; VMAT-2, vesicular monoamine transporter type 2.
Bhidayasiri et al. *J Neurol Sci.* 2018;389:67-75.



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.