MED-MSL-TD-US-0099_v9

Distinguishing Tardive Dyskinesia (TD) from Other Dopamine Receptor Blocking Agent (DRBA)-Induced Movement Disorders

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Introduction to DRBA-Induced Movement Disorders

DRBA, dopamine receptor blocking agent

DRBA-Induced Movement Disorders

- Dopamine Receptor Blocking Agent (DRBA)-induced movement disorders are associated with medications commonly used to manage psychiatric disorders, such as antipsychotics[1,2]
- Extrapyramidal Symptoms (EPS) is an obsolete umbrella term that has been used to describe a collection of DRBA-induced movement disorders despite each having a distinct presentation, pathophysiology, and treatment[3]
- Tardive dyskinesia (TD) is an often persistent, clinically distinct DRBA-induced movement disorder[2,4]
    - Can coexist with other DRBA-induced movement disorders[4]
    - Requires specific management[4]

1. Fahn S. Principles and Practice of Movement Disorders. 2nd ed. *Elsevier Health Sciences*; 2011. 2. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. American Psychiatric Association: Washington, DC; 2013. 3. Dilks S, et al. *Nurs Clin North Am*. 2019 Dec;54(4):595-608. 4. Van Harten PN, et al. *Schizophr Res*. 1997;26:235-242.

Clinical Characteristics of DRBA-Induced Movement Disorders

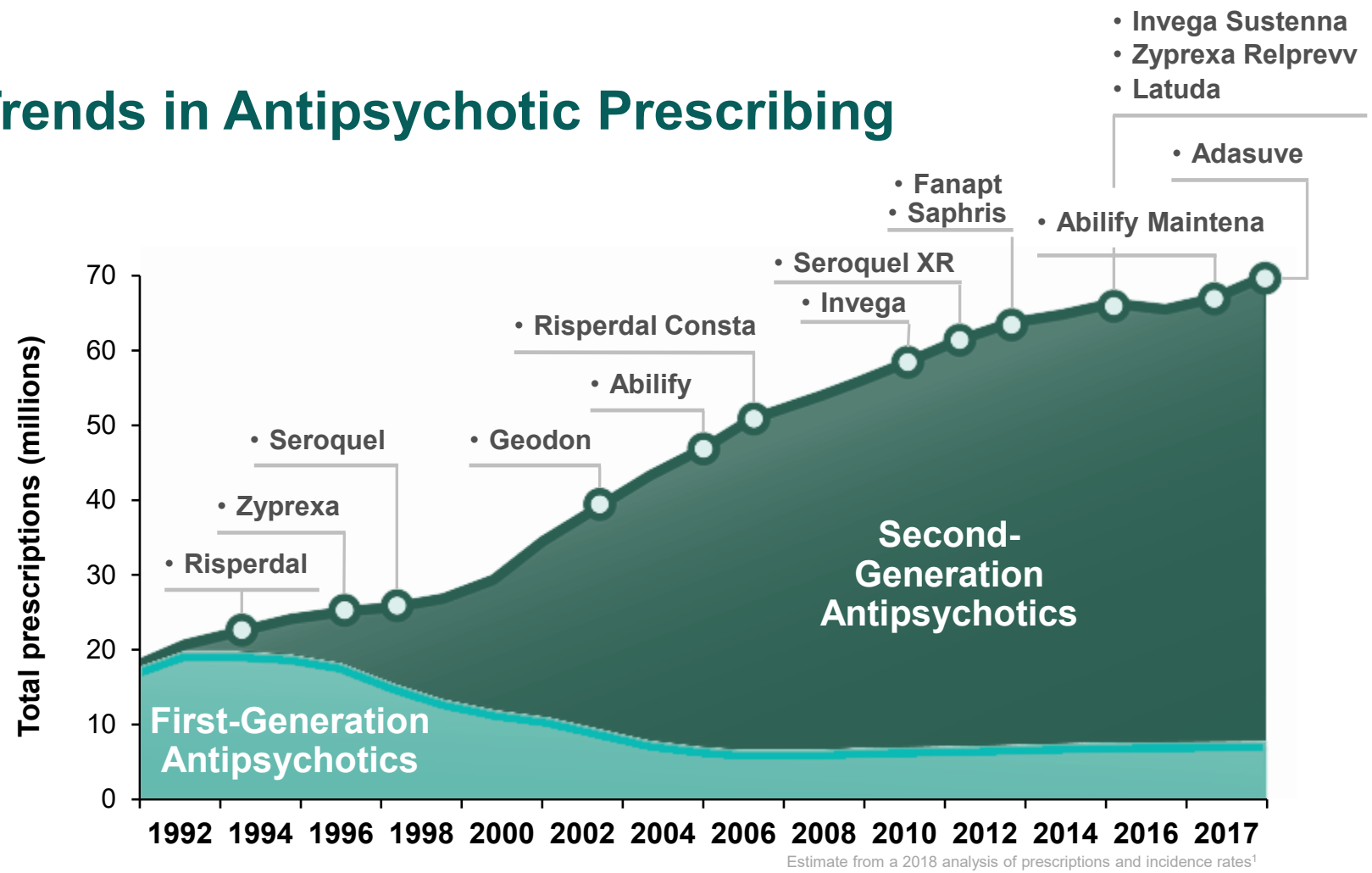
- DRBA-induced movement disorders can include acute presentations or may present after prolonged use of DRBAs (i.e., tardive)[1]

DRBA-Induced Movement Disorders	Timing of Onset[1,2]	Common Distinguishing Features[1,2]
Acute dystonia	Hours to days	- Sustained muscle contractions
Akathisia	Days to months	- Inner restlessness with compulsion to move
Drug-induced parkinsonism (DIP)	Weeks to months	- Bradykinesia, rigidity, decreased arm swing, tremor, stooped posture
Tardive dyskinesia (TD)	Onset is generally later; months to years	- Repetitive movements: commonly grimacing, sticking out of tongue or smacking of lips - Movements can include limbs/trunk - May be rapid jerking movements or slow writhing movements

DRBA, Dopamine Receptor Blocking Agent.

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.

DRBA-Induced Movement Disorders: Epidemiology

- **~50% of patients** treated with high-potency FGAs develop acute DRBA-induced movement disorders within the first several days of treatment[1]
- CATIE study compared SGAs to an intermediate-potency FGA and found no difference in the rates of the below DRBA-induced movement disorders[2]

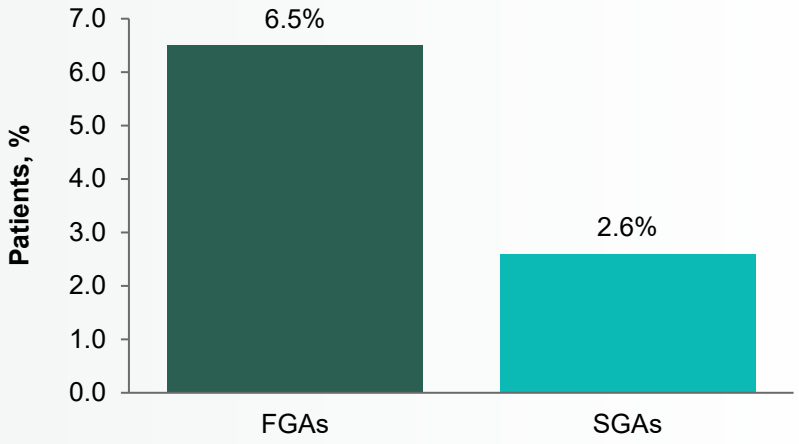
DRBA-Induced Movement Disorders	Epidemiology
Dystonia	• Incidence of 2 to 5% in patients receiving FGAs[3-5]
Akathisia	• Incidence varied from 21 to 75% across studies of FGAs[6-8]
Drug-induced Parkinsonism (DIP)	• Annual incidence rate of DIP found to be 3.3 per 100,000 person years, with FGAs being the most common cause[9]

FGAs, first-generation antipsychotics; SGAs, second-generation antipsychotics; DRBA, dopamine receptor blocking agent

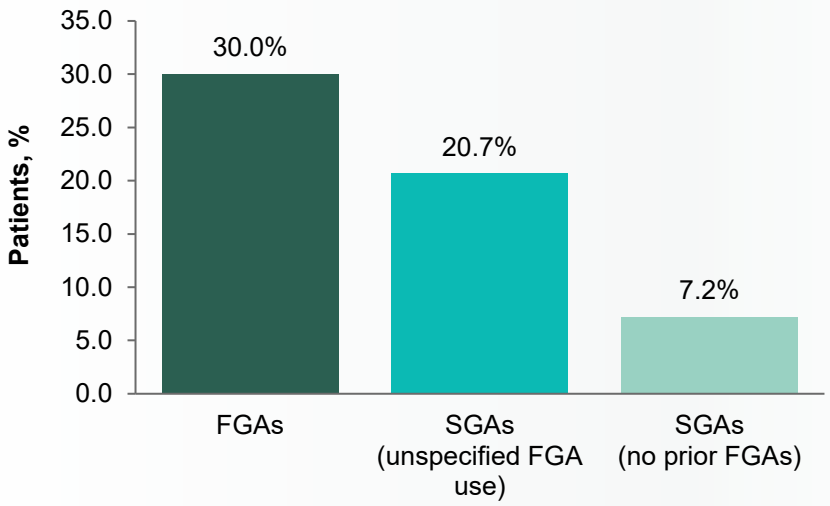
1. Divac N, et al. *Biomed Res Int*. 2014;1-6. 2. Miller DD, et al. *British Journal of Psychiatry*. 2008; 193(4), 279–288. 3.Tarsy D. *Clin Neuropharmacol*.1983;6 (Suppl1):S9–26. 4. van Harten PN, et al. *BMJ*.1999;319(7210):623–6. 5. Rupniak NM, et al. *Psychopharmacology (Berl)*.1986;88(4):403–19. 6. Kane JM, et al. *J Clin Psychiatry*. 2009;70(5): 627–43. 7. Owens DG. *Cambridge University Press*. 2014. 8.Sachdev P, et al. *Arch Gen Psychiatry*.1994;51(12):963–74. 9. Savica R, et al. *Mov Disord*. 2017; 32(2):227–34.

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.

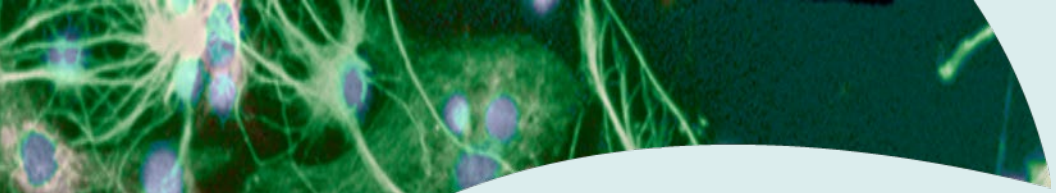
1. Carbon M, et al. *World Psychiatry*. 2018;17(3):330-340. 2. Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278. 3. Cloud LJ, et al. *Neurotherapeutics*. 2014;11:166-176.
4. Data on file. Neurocrine Biosciences.

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 disfiguring, 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 level of daily activity
  - Lower level of leisure activities
  - Lower productivity
  - Social stigma
  - Increased morbidity and mortality

DRBA, dopamine receptor blocking agent

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.



Clinical Presentation of 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

[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.

Factors Associated With Increased Risk for Acute Dystonia

Risk Factors for Acute Dystonia[1]	
Younger age	Family history of dystonia
Male gender	Cocaine use
Black race	Previous dystonic reactions

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

Dystonia
Retrocollis: repetitive, patterned, neck extension

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

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

[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.

Factors Associated With Increased Risk for Akathisia

Risk Factors for Akathisia[1]	
Increasing age	Cognitive dysfunction
Female gender	Iron deficiency
Negative symptoms	Prior akathisia
Concomitant parkinsonism	Mood disorders

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

Akathisia

Data on File. Neurocrine Biosciences, Inc..

Clinical Characteristics of Drug-Induced Parkinsonism

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

[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.

Factors Associated With Increased Risk for Drug-Induced Parkinsonism

Risk Factors for Drug-Induced Parkinsonism[1]	
Advancing age	Family history of Parkinson's disease
Female gender	Preexisting extrapyramidal disease
Abnormalities of brain structure including dementia	Human Immunodeficiency Virus (HIV) infection

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

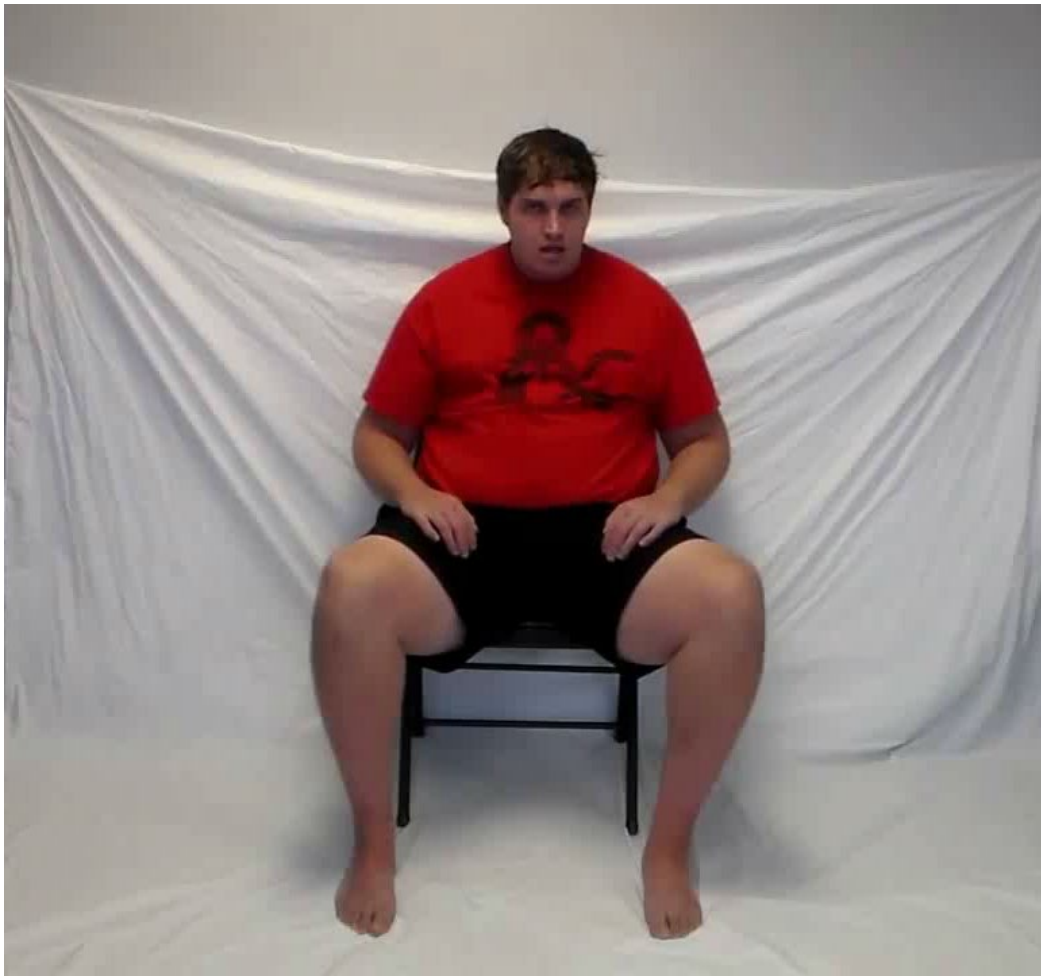
Drug-Induced Parkinsonism

Parkinsonian tremor: rhythmic, 3 to 4 Hz resting tremor

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

Drug-Induced Parkinsonism

Bradykinesia: slow speed and loss of amplitude in finger tapping and marked decrease in facial expression (masking)



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

Drug-Induced Parkinsonism

Parkinsonian tremor: rhythmic, 3 to 4 Hz tremor in lower lip and chin

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

Clinical Characteristics of Tardive Dyskinesia

Typical Time to Onset[a]

- **Weeks to Years[b]**

Movement Phenomenology

Movements:

- Choreoathetotic (irregular, dance-like)
- Athetotic (slow, writhing)
- Stereotypic (repetitive, purposeless)

Locations:

- Mouth, jaw, tongue & face
  - Mouth/jaw chewing
  - Tongue protrusion
  - Grimacing
  - Lip smacking or pursing
  - Blepharospasm
- Neck, trunk, & extremities
  - Piano-playing finger/hand movements
  - Foot tapping
  - Truncal rocking or thrusting

Other Clinical Features:

- Difficulty speaking, eating, or ambulating
- Embarrassment
- Social isolation

[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) [b]TD may be "masked" by DRBA treatment and first appear after DRBAs are withdrawn.

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

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

Jaw Tongue Neck

OBL 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*

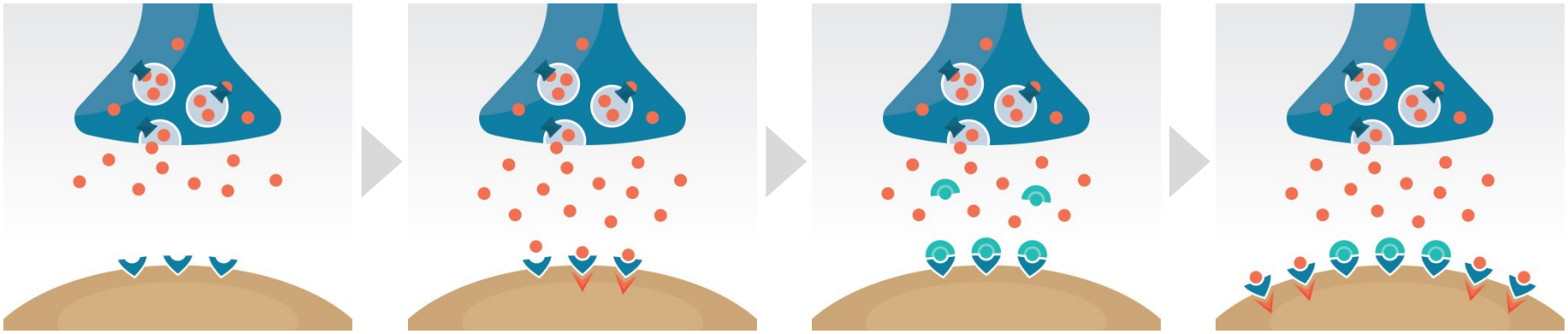
*Dyskinesia may remit with continued withdrawal. A diagnosis of TD may be warranted if the dyskinesia persists for at least 4 weeks.

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.

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]



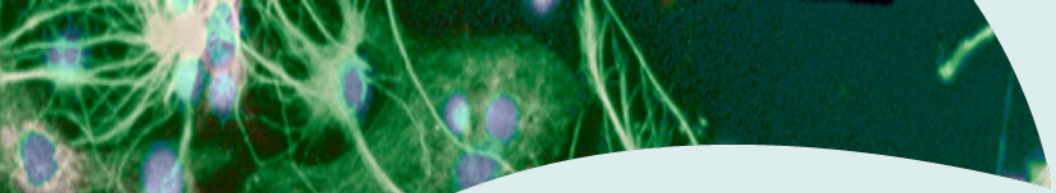
1. Klawans H, et al. *Acta Neurol Scand*. 1970;46:409-441.
2. Pai BN, et al. *Biol Psychiatry*. 1994;36:489-491.
3. Segman RH, et al. *Mol Psychiatry*. 2001;6(2):225-229.
4. Gittis AH, et al. *J Neurosci*. 2011;31(44):15727-15731.

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 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.



Treatment Approaches for DRBA-Induced Movement Disorders

DRBA, dopamine receptor blocking agent

Key Differences in Pharmacologic Effects of Common Treatments on DRBA-Induced Movement Disorders

Action	TD	Acute Dystonia	Acute Akathisia	DIP
Add VMAT2 inhibitor	Improves (approved for treatment of TD)[a]	May worsen	Insufficient data	May worsen
Increase DRBA dose	May initially "mask" symptoms[b]	May trigger or worsen	May trigger or worsen	May trigger or worsen
Discontinue DRBA or reduce dose	Generally no effect, but may improve over time in some patients[c]	Improves	Improves	Improves

Abbreviations: TD, tardive dyskinesia; DIP, drug-induced parkinsonism; VMAT2, vesicular monoamine transporter type 2; DRBA, Dopamine Receptor Blocking Agent.

[a]Valbenazine and deutetrabenazine are approved in the US for the treatment of TD in adults and are recommended as first-line treatment for TD; [b]Increasing DRBA dose may diminish chances of recovery from TD; [c]DRBA discontinuation or reduction can initially trigger or exacerbate TD that had been "masked" by DRBA treatment; [d]Limited data available.

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

Key Differences in Pharmacologic Effects of Common Treatments on DRBA-Induced Movement Disorders

Action	TD	Acute Dystonia	Acute Akathisia	DIP
Add VMAT2 inhibitor	Improves (approved for treatment of TD)[a]	May worsen	Insufficient data	May worsen
Add anticholinergic	May worsen	May improve[b]	Insufficient data	Improves (approved for treatment of parkinsonism)[b]
Discontinue anticholinergic	May improve	May worsen	Insufficient data	May worsen

Abbreviations: TD, tardive dyskinesia; DIP, drug-induced parkinsonism; VMAT2, vesicular monoamine transporter type 2.

[a]Valbenazine and deutetrabenazine are approved in the US for the treatment of TD in adults and are recommended as first-line treatment for TD; [b]Benztropine is approved in the US for all forms of parkinsonism and may be useful for acute DRBA-induced dystonia. Anticholinergics can aggravate TD and should not be used for TD.

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

Benztropine: Not Recommended for the Treatment of TD

- Benztropine is indicated for the control of extrapyramidal disorders **except tardive dyskinesia** due to neuroleptic drugs[1]
- The Precautions section of the Benztropine FDA-approved full prescribing information states the following[1]:
  - Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines[a] and related agents, or may occur after therapy when these drugs have been discontinued
  - Antiparkinsonism agents[b] do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them
  - Benztropine **is not** recommended for use in patients with tardive dyskinesia

[a]Examples of phenothiazines include fluphenazine, chlorpromazine, and perphenazine (all first generation antipsychotics). [b]Refers to anticholinergics such at benztropine.

1. Benztropine mesylate [package insert]. Warren, NJ: Cipla USA, Inc.; 2020.

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

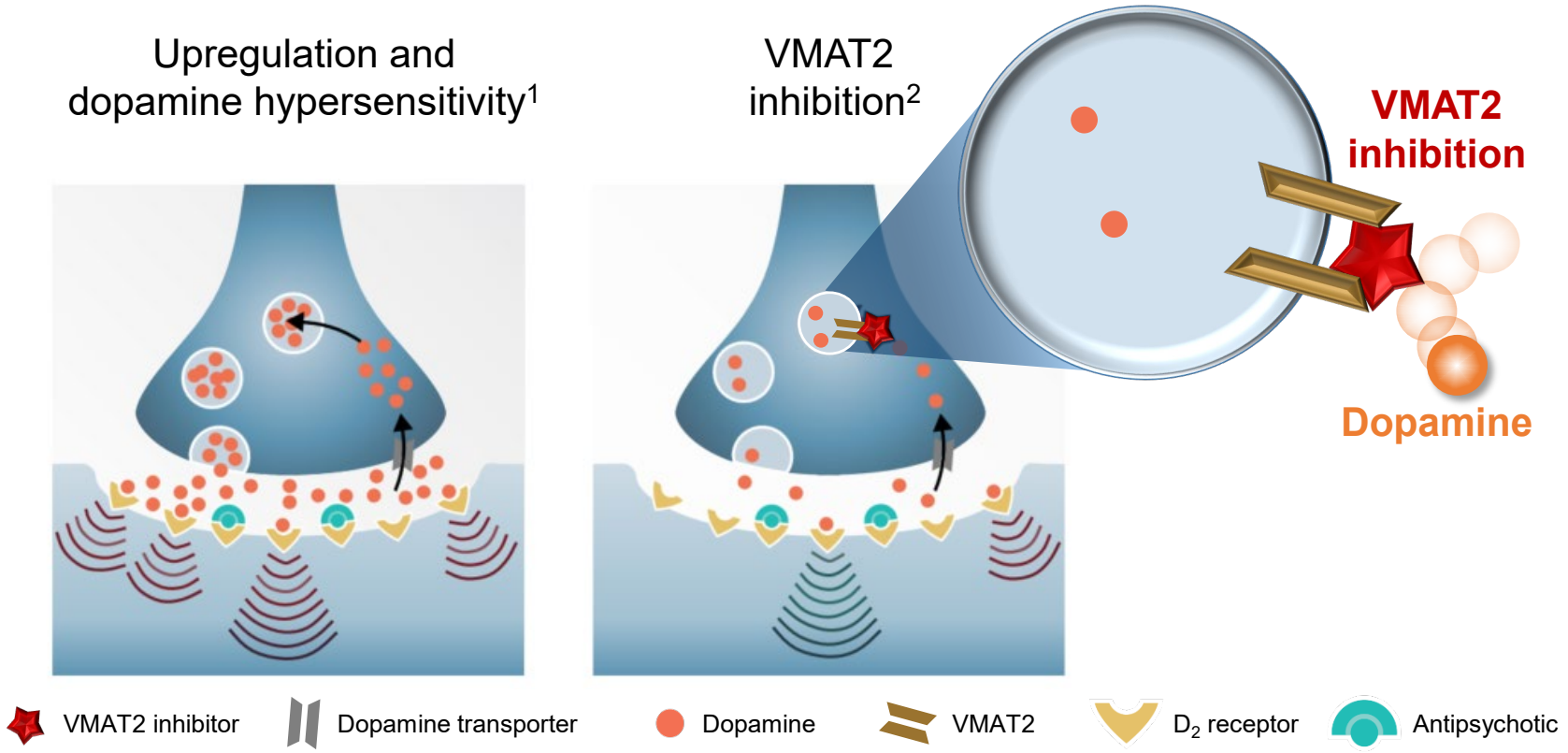
There is insufficient evidence to support a guideline statement on the use of the following treatments in individuals with TD:

- 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.

VMAT2 Inhibitor: Mechanism of Action



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

1. Margolese HC, et al. *Can J Psychiatry*. 2005;50:541-547. 2. Stahl SM. *CNS Spectr*. 2018;23(1):1-6.

Summary

- TD should be distinguished from other DRBA-induced movement disorders as each have their own distinct pathophysiology, presentation, and treatment
    - The use of EPS as an umbrella term is considered obsolete and clinically problematic
- Understanding the differences between TD and other DRBA-induced movement disorders will aid in finding the optimal treatment plan for patients

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