MED-MSL-TD-US-0155_v6

Use of Anticholinergics in DRBA-Induced Movement Disorders

NEUROCRINE® BIOSCIENCES

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.

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

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.

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

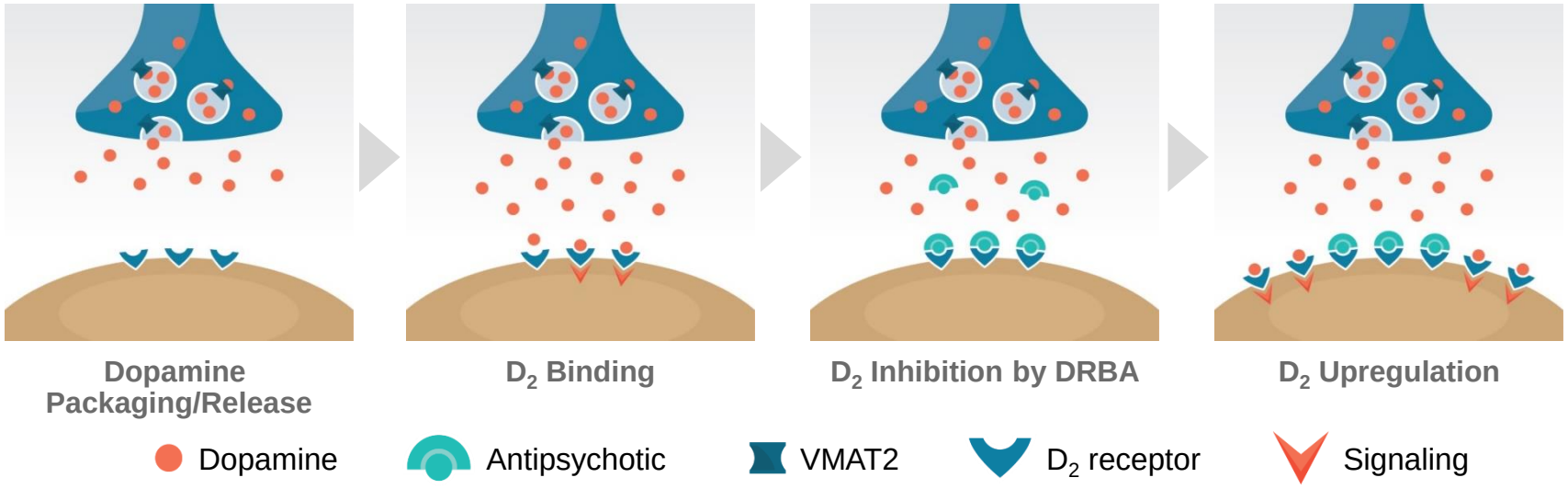
Use of **multiple treatment options** may be necessary in patients with multiple DRBA-induced movement disorders

DRBA, dopamine receptor–blocking agent.

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

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 gamma-aminobutyric acid (GABA) and/or serotonin pathways[3,4]



VMAT2, vesicular monoamine transporter 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.

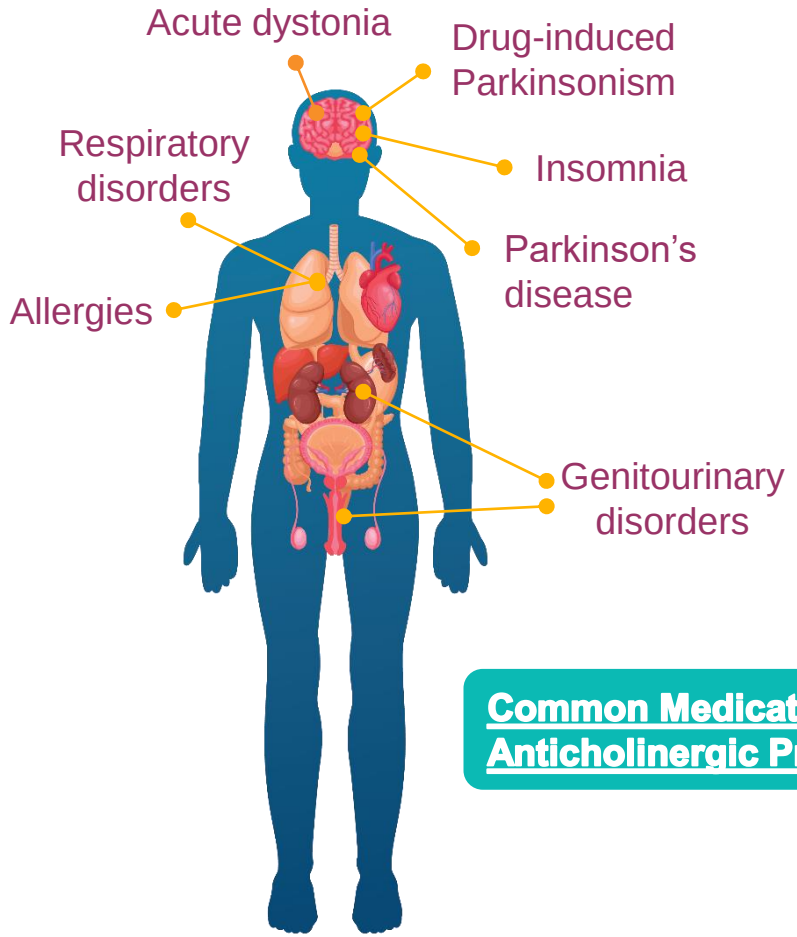
Anticholinergic Mechanism of Action

Anticholinergics **block acetylcholine receptors** in the central and autonomic nervous system, and are used to treat a variety of conditions[1,2a]

Antiparkinsonian Anticholinergics[1]

Benztropine

Trihexyphenidyl



Common Medications with Anticholinergic Properties

[a]Benztropine can also act as a dopamine reuptake inhibitor[3]

DIP, drug-induced parkinsonism

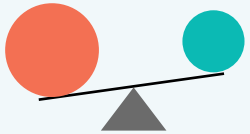
1. Desmarais JE, et al. *J Psychopharmacol.* 2012;26(9):1167-1174. 2. Ghossein N, et al. Anticholinergic Medications. StatPearls Publishing; 2020. 3. Kulkarni SS, et al. *Bioorg Med Chem*. 2006;14(11):3625-3634.

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

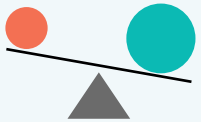
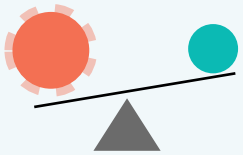
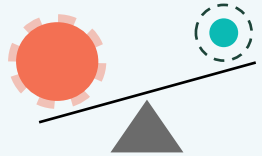
DA ↔ Ach	Pathophysiology
	None: Balanced System
	Parkinson's Disease: Loss of dopaminergic neurons of the basal ganglia
	Psychosis: Increased dopaminergic signaling

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

Dopamine | Increased Dopamine Signaling due to Dopamine Receptor Hypersensitivity | Acetylcholine | Anticholinergic Effects (i.e., reduced ACh activity)

Drug-Induced Parkinsonism	Drug-Induced Parkinsonism + Anticholinergic
When antipsychotics reduce DA signaling, ACh can become overly active[1] 	*Anticholinergics may reduce ACh activity, counterbalancing the reduced DA*[2] 
Tardive Dyskinesia	**Tardive Dyskinesia + Anticholinergic**
Through D2 hypersensitivity, TD may involve increased DA signaling[3,4] 	*By reducing ACh activity, anticholinergics could exacerbate the imbalance*[3] 

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.

Anticholinergics Should Not Be Used Routinely to Prevent Acute Dystonia[3]

Prophylactic use of anticholinergics is aimed at preventing potentially dangerous dystonic episodes[1]

Controversy exists surrounding the prophylactic of these agents, mainly due to a small number of evidence-based therapeutic options available and the variable response of patients

- Data suggest that the benefits from initial prophylaxis with anticholinergics vary depending on a variety of patient/treatment factors, such as:

Age

Potency and dose of antipsychotic

Phase of treatment

Prior history of DRBA-induced movement disorder

World Health Organization Recommendations (2012 Update)[3]

- Anticholinergics should not be used routinely for preventing EPS* in individuals with psychotic disorders (including schizophrenia) treated with antipsychotics

*Although EPS is used as an umbrella term here, evidence cited by this reference in support of this claim is specific to dystonia and parkinsonism

EPS, extrapyramidal symptoms; SGA, second-generation antipsychotic; FGA, first-generation antipsychotic

1. Burgyone K, et al. *Curr Pharm Des.* 2004;10(18):2239-2248. 2. Buchanan RW, et al. *Schizophr Bull*. 2010 Jan;36(1):71-93. 3. World Health Organization. 2012. https://www.who.int/teams/mental-health-and-substance-use/treatment-care/mental-health-gap-action-programme/evidence-centre/psychosis-and-bipolar-disorders/role-of-anticholinergic-medications-in-patients-requiring-long-term-antipsychotic-treatment-for-psychotic-disorders. Accessed May 22, 2024.

Anticholinergics are Used to Treat Acute Dystonia and DIP

Benztropine is FDA-approved as adjunct therapy for all forms of Parkinsonism and the control of extrapyramidal disorders (except tardive dyskinesia) due to neuroleptic drugs[1]

Acute Dystonia[2]

- Typically resolves within 10 – 20 minutes of administration of an anticholinergic or antihistamine

Drug-induced Parkinsonism (DIP)[3]

- Anticholinergics are a key component of the pharmacological management of DIP in younger patients

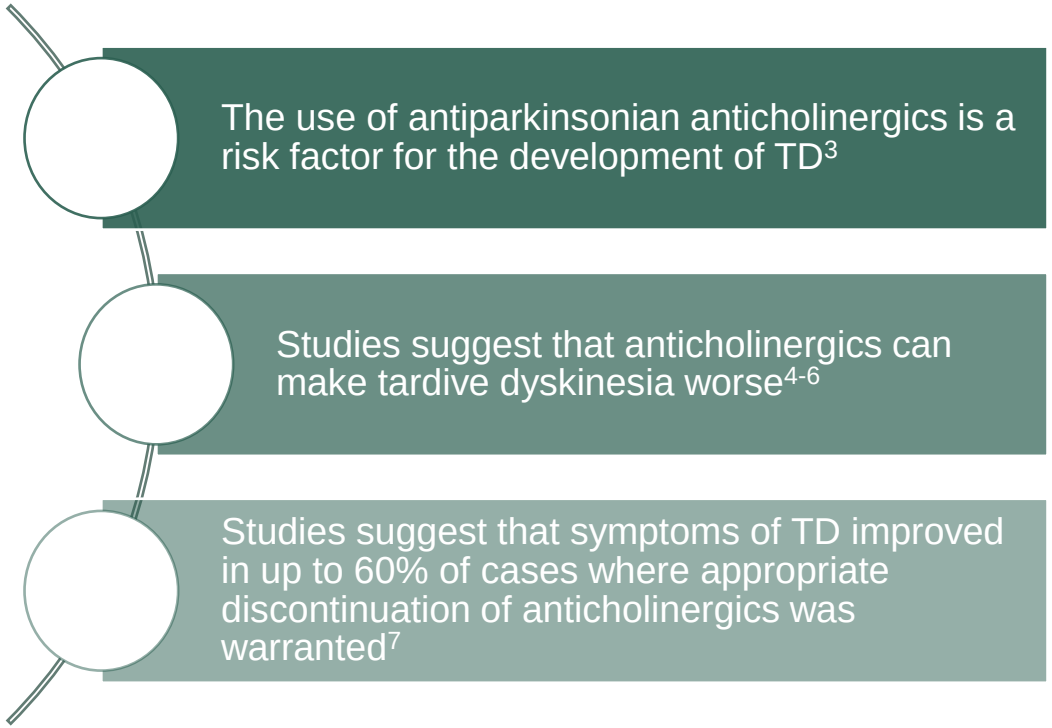
2020 APA Schizophrenia Treatment Guidelines[4]

- Recommends that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication
- Suggests multiple options for patients who have parkinsonism associated with antipsychotic therapy including treatment with an anticholinergic medication, lowering the dosage of antipsychotic medication, or switching to another antipsychotic medication

1.Benztropine mesylate [package insert]. Warren, NJ: Cipla USA, Inc.; 2020. 2.Caroff SN, et al. *Psychiatr Clin N Am*. 2016;39:391-411. 3.Ward KM, et al. *Neurol Ther*. 2018;7(2):233-248. 4. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

Anticholinergics Do Not Treat and in Some Cases May Worsen TD

Benztropine is FDA-approved as adjunct therapy for all forms of Parkinsonism and the control of extrapyramidal disorders **(except tardive dyskinesia)** due to neuroleptic drugs[1,2]



According to the Benztropine FDA Prescribing Information[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 or trihexyphenidyl.

ADS, anticholinergic drug scale; ARS, anticholinergic risk scale

1. Benztropine mesylate [package insert]. Warren, NJ: Cipla USA, Inc.; 2020. 2. Trihexyphenidyl hydrochloride [package insert]. Parsippany, NJ: Actavis Pharma, Inc.;2015. 3. Solmi M, et al. *J Neurol Sci*. 2018;389:21-27. 4. Klawans HL, et al. *J Neurol Neurosurg Psychiatry*. 1974;37(8):941-947. 5. Gerlach J, et al. *Int Pharmacopsychiatry*. 1976;11(1):1-7. 6. Waln O, et al. *Tremor Other Hyperkinet Mov (N Y)*. 2013 July 12;3. 7.Ward KM, et al. *Neurol Ther*. 2018;7(2):233-248.

Anticholinergics are Not Recommended for Use in TD

American Academy of Neurology (AAN)

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)

American Psychiatric Association (APA)

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

Modified Delphi Panel

2020 Modified Delphi Panel Consensus[5]:

- Review and consider modifying anticholinergic regimen in patients with TD (e.g., reduce dose, taper-off)

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. Caroff SN, et al. *J Clin Psychiatry*. 2020;81(2):19cs12983.

Key Differences in Pharmacologic Effects of Anticholinergic Use on DRBA-induced Movement Disorders

DRBA-induced Movement Disorder	Add anticholinergic	Discontinue anticholinergic
Tardive Dyskinesia	May worsen	May improve
Acute Akathisia	Insufficient data	Insufficient data
Drug-induced Parkinsonism	Improves (approved for treatment of parkinsonism)[a]	May worsen
Acute Dystonia	May improve[a]	May worsen

[a]Benztropine is approved in the United States for all forms of parkinsonism and may be useful for acute DRBA-induced dystonia

DRBA, dopamine receptor blocking agent; TD, tardive dyskinesia.
Hauser RA, et al. *CNS Spectr*. 2020:1-10.

Summary

- TD should be distinguished from other DRBA-induced movement disorders as each have their own distinct pathophysiology, presentation, and treatment[1]
  - The use of EPS as an umbrella term is considered obsolete and clinically problematic[1]
- Anticholinergics are not recommended for use in TD (2013 AAN,[2] 2020 APA[3] & 2020 Delphi Panel Consensus[4])
- Benztropine is FDA-approved as adjunct therapy for all forms of Parkinsonism and the control of extrapyramidal disorders (except tardive dyskinesia) due to neuroleptic drugs[5]

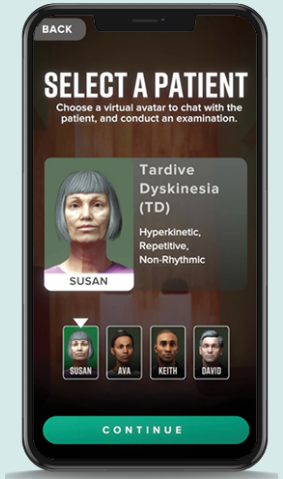
TD, tardive dyskinesia; DRBA, dopamine receptor blocking agent; EPS, extrapyramidal symptoms; AAN, American Academy of Neurology; APA, American Psychiatric Association; FDA, Food and Drug Association.

1. Greenbaum L, et al. *Front Neurol.* 2015;6:27. 2. Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469. 3. APA Practice Guideline for Treatment of Patients with Schizophrenia. Accessed on January 11 2020. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. 4. Caroff SN, et al. *J Clin Psychiatry*. 2020;81(2):19cs12983. 5. Benztropine mesylate [package insert]. Warren, NJ: Cipla USA, Inc.; 2020.

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]

[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

DIMD, drug-induced movement disorder; DRBA, dopamine receptor-blocking agent; TD, tardive dyskinesia.

MED-CON-TD-US-0101

NEUROCRINE® BIOSCIENCES

Neurocrine Medical Affairs

www.neurocrinemedical.com

1-877-641-3461

Appendix

Common Medications with Strong Anticholinergic Properties

Antihistamines

- Brompheniramine∗
- Carbinoxamine∗
- Chlorpheniramine∗†
- Clemastine∗
- Cyproheptadine†
- Dexbrompheniramine
- Dexchlorpheniramine
- Dimenhydrinate∗
- Diphenhydramine∗†
- Doxylamine
- Hydroxyzine∗†
- Meclizine∗
- Promethazine∗†
- Pyrilamine∗† (mepyramine)
- Triprolidine

Antiparkinson

- Benztropine∗†
- Trihexyphenidyl∗

Antiarrhythmic

- Disopyramide

Antimuscarinics

- Darifenacin∗
- Fesoterodine
- Flavoxate∗
- Oxybutynin∗†
- Solifenacin
- Tolterodine∗
- Trospium

Antidepressants

- Amitriptyline∗†
- Amoxapine
- Clomipramine∗
- Desipramine∗
- Doxepin∗
- Imipramine∗†
- Nortriptyline∗
- Paroxetine∗
- Protriptyline∗
- Trimipramine∗

Muscle Relaxants

- Cyclobenzaprine
- Orphenadrine∗

Antispasmodics

- Atropine∗†
- Belladonna alkaloids
- Clidinium-chlordiazepoxide
- Dicyclomine∗
- Homatropine†
- Hycoscyamine∗†
- Methscopolamine
- Propantheline∗
- Scopolamine∗

Antipsychotics

- Chlorpromazine∗†
- Clozapine∗
- Loxapine
- Olanzapine
- Perphenazine†
- Thioridazine∗†
- Trifluoperazine†

Antiemetics

- Prochlorperazine
- Promethazin∗†

Selected common medications with strong anticholinergic properties, based on American Geriatric Society Beers® criteria.[1] Medications that have a level 3 rating on the Anticholinergic Drug Scale (*) or a 3-point score on the Anticholinergic Risk Scale (†) are also noted[2,3]

1. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. J Am Geriatr Soc. 2023;2023(71):2052–81. 2. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. J Clin Pharmacol. 2006;46:1481–6. 3. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. Arch Intern Med. 2008;168:508–13.