REAL PSYCHIATRY

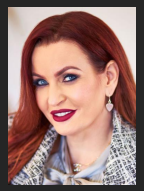
An Educational Experience Designed for and by
APPs on the Frontline of Modern Practice

EXTRAPYRAMIDAL SYMPTOMS*

WHEN ARE THEY TARDIVE DYSKINESIA?

— JANUARY 13, 2024 —

**AKA DRUG-INDUCED MOVEMENT DISORDERS (DIMDS)*

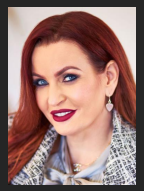


Program Overview

- **Tardive dyskinesia (TD)** is relatively common among those treated with antipsychotic medications. However, its spectrum of clinical presentations and overlap with other DIMDs make it challenging to identify.
- **Anticholinergics,** while helpful in treating various forms of DIMDs like drug-induced Parkinsonism and dystonia, are not beneficial for TD or akathisias and may even worsen TD symptoms.
- **Vesicular monoamine transporter-2 (VMAT2) inhibitors** are FDA-approved for treatment of TD and can be added to most treatment regimens.

- **OBJECTIVE:** To guide clinicians through the most up-to-date tools and strategies to differentiate TD from other DIMDs and effectively manage it.
  - This activity will utilize expert-led case-based discussion to highlight key decision-points and corresponding approaches in the accurate identification and optimal treatment of TD

DIMDs = drug-induced movement disorders



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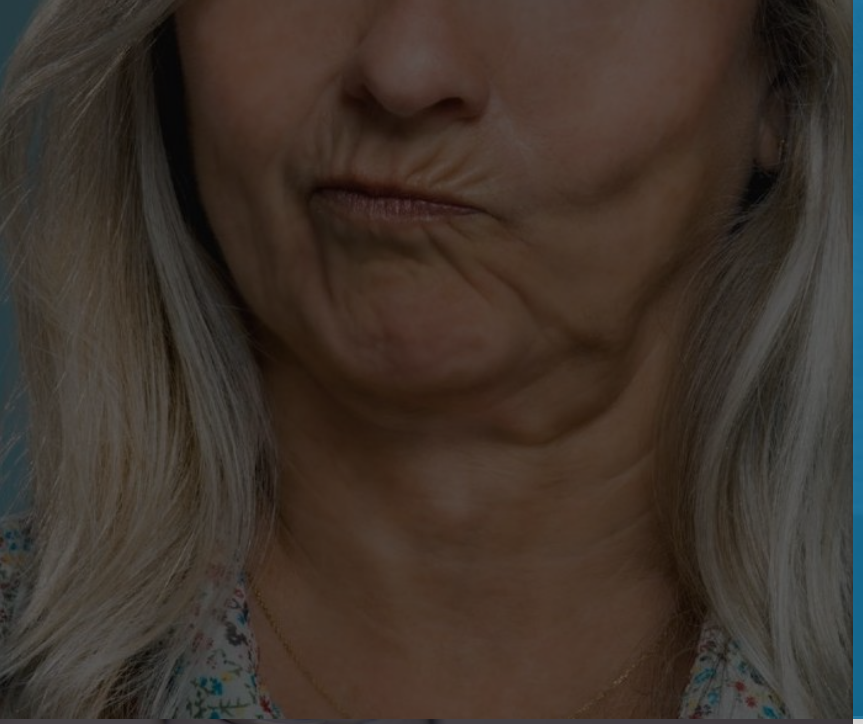

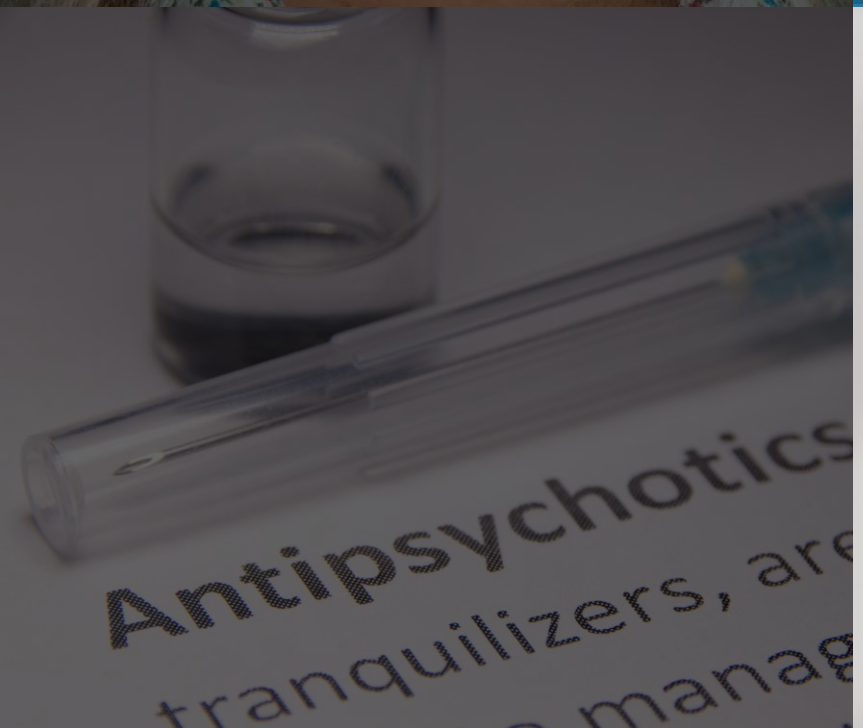

MODULE
— 1 —

MAKE A CALL: DIFFERENTIATING DRUG-INDUCED MOVEMENT DISORDERS AND THEIR IMPACT

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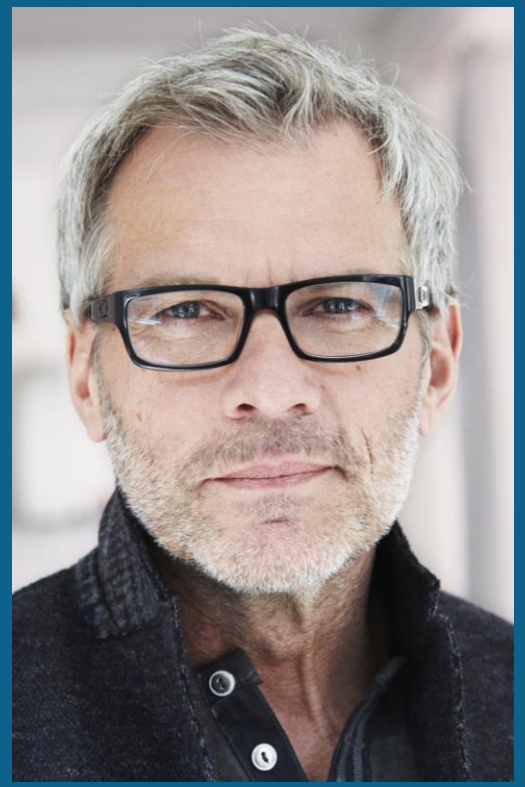
CASE 1*

INTRODUCTION

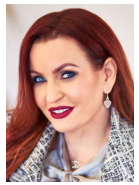
Ryan, a 53-year-old male with a history of bipolar depression, presents to your office. He notes he has had multiple hospital admissions for severe depression and suicidal ideation. During his last admission 4 months ago, he was started on quetiapine 400 mg, venlafaxine 75 mg, and trazodone 150 mg.

Upon exam, Ryan demonstrated ***involuntary movements of his chin, hands, and hips when at rest.*** *He notes that these movements are* ***"embarrassing"*** *and interfere with daily life.*

What is this patient exhibiting?



*Fictionalized representation based on a real medical case.



DRUG-INDUCED MOVEMENT DISORDERS

PATHOPHYSIOLOGY

DEFINITION: Drug-induced involuntary or uncontrollable movement
GENERAL MECHANISM: ***Alteration of dopamine signaling*** in the dorsal striatum

CULPRITS[1]

Not only dopamine antagonists

- **Typical antipsychotics**
- **Atypical antipsychotics**
- **SSRIs**
- **TCAs**
- **Others**

Includes ***antiemetics***
(e.g., metoclopramide, droperidol, prochlorperazine)

#1 CAUSE
*(**Typical** > atypical)*
*(**FGA** > SGA)*

Many classes of medications can contribute!

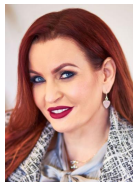
1. D'Souza RS et al. Extrapyramidal Symptoms. In: *StatPearls*. NCBI Bookshelf. StatPearls Publishing; Updated January 9, 2024. Accessed January 9, 2024. https://www.ncbi.nlm.nih.gov/books/NBK534115/

FGA: first-generation antipsychotic
SGA: second-generation antipsychotic

AUDIENCE POLL

How comfortable are you in identifying tardive dyskinesia (TD)?

a) Very comfortable
b) Somewhat comfortable
c) Neutral
d) Somewhat uncomfortable
e) Very uncomfortable



DRUG-INDUCED MOVEMENT DISORDERS

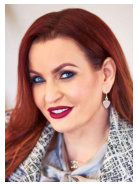
CLINICAL PRESENTATION

How do you differentiate DIMDs clinically?

	AKATHISIA	DYSTONIA	DIP	TD
Onset	**Acute**[1] Hours or days	**Acute**[2] Hours or days	**Acute or subacute**[3] Hours, days, or weeks	***Delayed***[3] Weeks, months, years
Symptoms	**Restlessness** Often misattributed to other causes (e.g., anxiety, withdrawal)	**Sustained or intermittent muscle contractions** Generalized or restricted (e.g., torticollis, writer's cramp)	**Parkinsonism** Tremor (rhythmic), rigidity, shuffling gait, bradykinesia	**Arrhythmic involuntary athetoid or choreiform movements** (e.g., lip smacking, tongue protrusion)
Reversible?	**Usually, yes**			***Often, no***

DIMDs: drug-induced movement disorders; **DIP:** drug-induced parkinsonism; **TD**: tardive dyskinesia

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. **3.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.



DRUG-INDUCED MOVEMENT DISORDERS

CLINICAL COURSE / EVALUATION

	AKATHISIA[1]	DYSTONIA	DIP	TD
Onset	Acute Hours or d			*Delayed*[2] Weeks, months, years
Symptoms	Restlessn Often misattrib other causes (e.g withdraw			**Arrhythmic involuntary athetoid or choreiform movements** (e.g., lip smacking, tongue protrusion)
Reversible?				*Generally, no*

CLINICAL TRANSLATION[1,2]

Athetoid = slow, continuous, writhing, involuntary

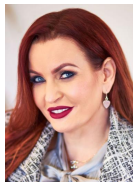
Choreiform = brief, irregular, jerky, dance-like

Commonly involve ***muscles of the lower face/jaw*** *(but can involve the trunk and upper/lower extremities)*

Persist for more than 2 months even ***after stopping offending agent***

DIP: drug-induced parkinsonism; **TD:** tardive dyskinesia

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.



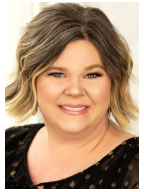
DRUG-INDUCED MOVEMENT DISORDERS

CLINICAL COURSE / EVALUATION

CLINICAL TRANSLATION[1,2]	DIP	TD
	Acute or subacute[2] Hours, days, or weeks	***Delayed[2]*** Weeks, months, years
TIMELINE: DIP develops earlier than TD, which can take years to present	**Parkinsonism** Tremor (rhythmic), rigidity, shuffling gait, bradykinesia	**Arrhythmic involuntary athetoid or choreiform movements** (e.g., lip smacking, tongue protrusion)
MOVEMENT CHARACTERISTICS: The parkinsonian tremor seen in DIP is rhythmic (3-6 Hz) vs arrhythmic involuntary choreoathetoid movements of TD		

DIP: drug-induced parkinsonism; **TD:** tardive dyskinesia

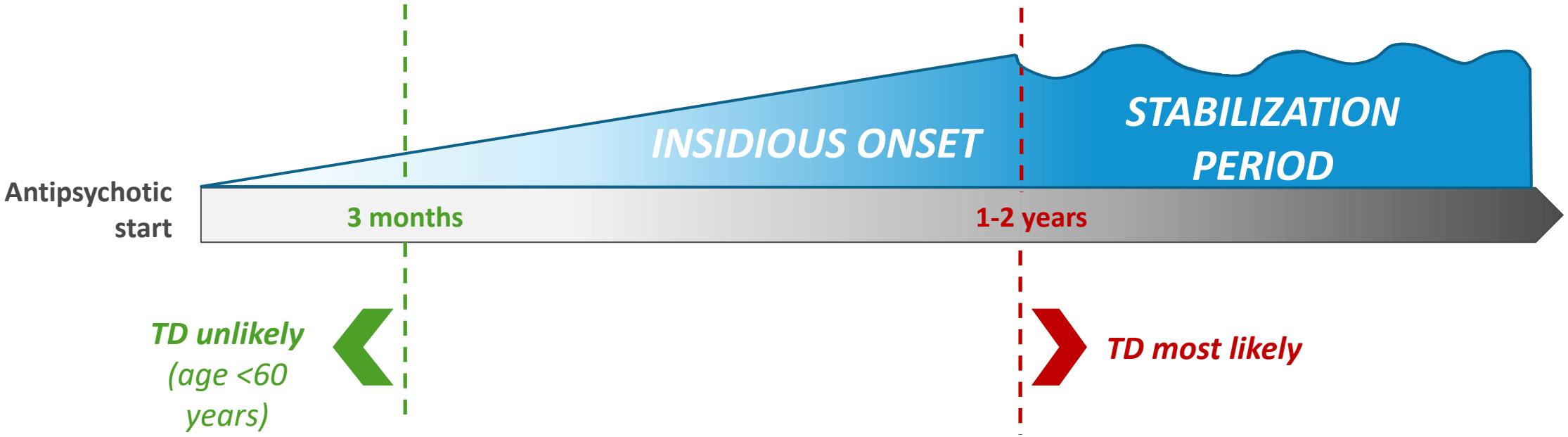
1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.



TARDIVE DYSKINESIA

RELATIVE TIMELINE[1,2]

- Typically requires ***continuous/chronic exposure*** to antipsychotics
- Chronically waxes and wanes



1. Cornett EM et al. Medication-induced tardive dyskinesia: a review and update. *Ochsner J*. 2017;17(2):162-174. **2.** Waln O et al. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-161-4138-1.

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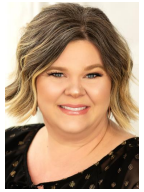
TARDIVE DYSKINESIA

RISK FACTORS



NON-MODIFIABLE

- **AGE**[1-4] → *Increased risk in older adults*
- **FEMALE SEX**[1-3] → *Increased prevalence* | *Increased severity?* | *Postmenopausal?*[5]
- **SCHIZOPHRENIA**[1,3,4] → *Illness-related (not only secondary to antipsychotic use)*
- **MOOD DISORDERS**[1,4] → *Potentially increased risk with bipolar type 1*

MODIFIABLE

- **ANTIPSYCHOTIC USE**[1-5] → *Duration (exposure)* | *Higher doses?* | *Typical vs atypical*
- **HISTORY OF ACUTE DIP, DYSTONIA, AKATHISIA**[1,4] → *Acute = emergent within the first 31 days of starting treatment*
- **SUBSTANCE DEPENDENCE/ADDICTION**[1,2,4] → *Alcohol* | *Cocaine*

1. Solmi M et al. Clinical risk factors for the development of tardive dyskinesia. *J Neurol Sci*. 2018;389:21-27. **2.** Debrey SM et al. Tardive dyskinesia: spotlight on current approaches to treatment. *Focus (Am Psychiatr Publ)*. 2021;19(1):14-23. **3.** Jain R et al. Tardive dyskinesia: recognition, patient assessment, and differential diagnosis. *J Clin Psychiatry*. 2018;79(2):nu17034ah1c. **4.** Vardar MK et al. Assessment of risk factors for tardive dyskinesia. *Psychopharmacol Bull*. 2020;50(3):36-46. **5.** Waln O et al. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-161-4138-1.

DIP: drug-induced parkinsonism

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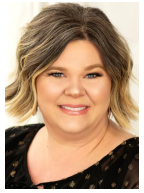
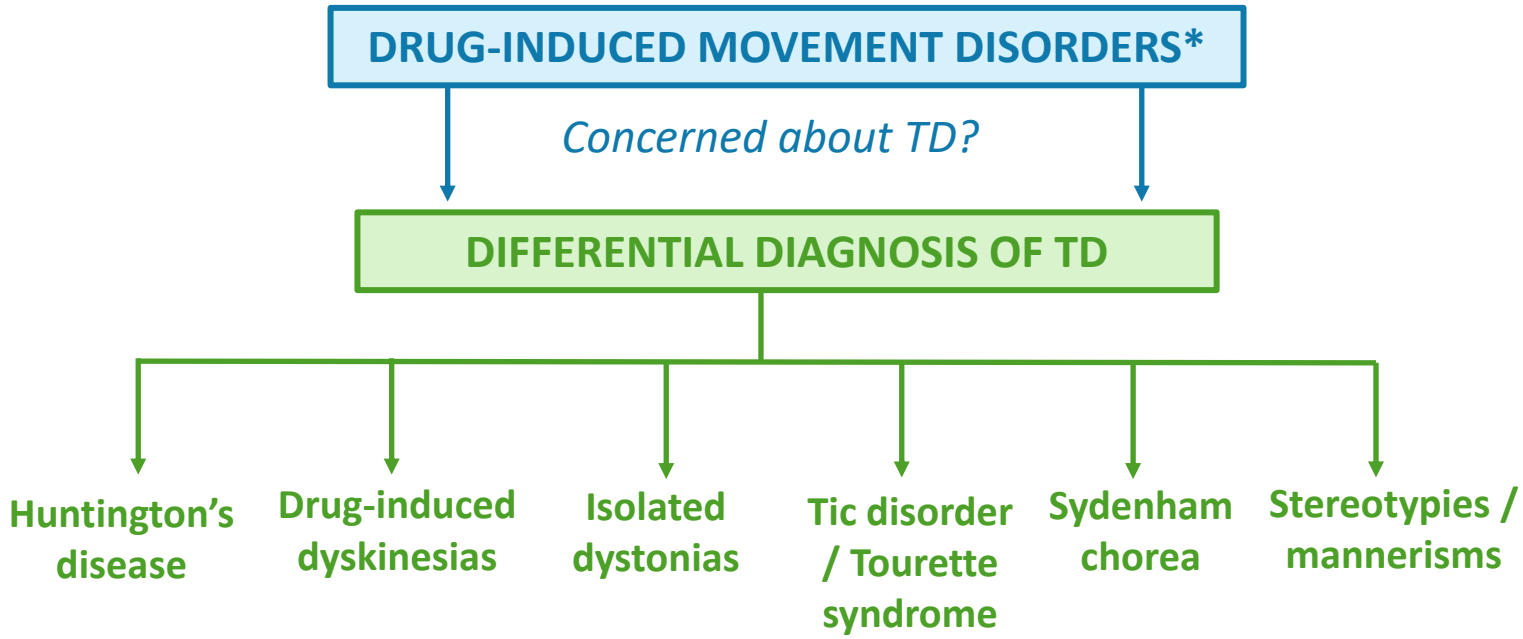


TARDIVE DYSKINESIA
DIFFERENTIAL DIAGNOSIS

- Rule out other movement disorders and medical conditions prior to diagnosing TD[1]
  - ***If known, the timeline of antipsychotic initiation and symptom onset*** helps to differentiate other drug-induced dyskinesias
- Always ask about a ***family history of Huntington's disease***
  - Prompts early neurology consultation[2]



**This illustration is not an exhaustive list for the differential diagnosis of TD*

1. Hauser RA et al. Differentiating tardive dyskinesia: a video-based review of antipsychotic-induced movement disorders in clinical practice. *CNS Spectr*. 2022;27(2):208-217.
2. Caroff SN et al. A modified Delphi consensus study of the screening, diagnosis, and treatment of tardive dyskinesia. *J Clin Psychiatry*. 2020;81(2):19cs12983.

CASE 1*

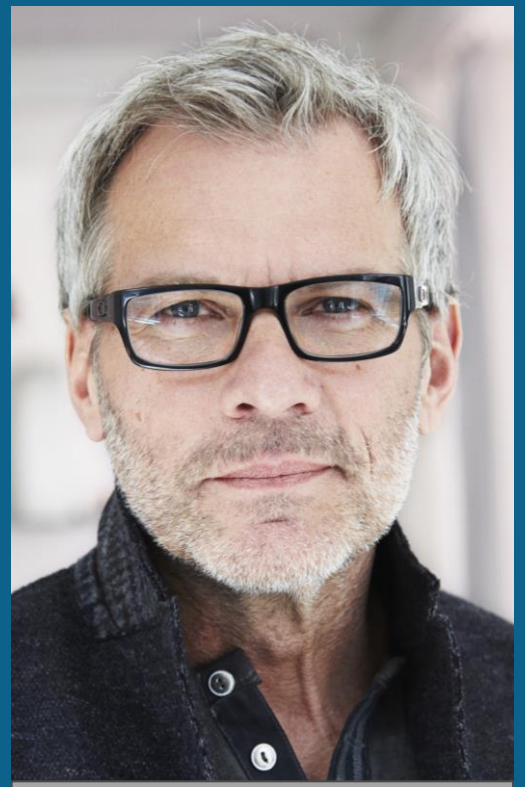
DIAGNOSTIC TESTING

CASE RECAP:

- 53-year-old male with bipolar depression
- History of inpatient admission and suicidal ideation
- Currently taking quetiapine, venlafaxine, and trazodone
- Developed movement-related abnormalities in the lower face/jaw (lip puckering), hands, and hips

You conclude his symptoms are suspicious for TD.

Which assessments would you use to evaluate this patient's symptoms?



RYAN

*Fictionalized representation based on a real medical case.

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AUDIENCE POLL

In addition to history and physical exam, which of the following, if any, would you prioritize to assess this patient who has developed abnormal orofacial and extremity movements after starting an antipsychotic?

a) History and physical exam only
b) Barnes Akathisia Scale
c) Abnormal Involuntary Movement Scale
d) Tardive Dyskinesia Rating Scale
e) Extrapyramidal Symptom Rating Scale
f) Dyskinesia Identification System: Condensed User Scale

AUDIENCE POLL

In addition to history and physical exam, which of the following, if any, would you prioritize to assess this patient who has developed abnormal orofacial and extremity movements after starting an antipsychotic?

a) History and physical exam only

b) Barnes Akathisia Scale

c) Abnormal Involuntary Movement Scale **FACULTY RECOMMENED**

d) Tardive Dyskinesia Rating Scale

e) Extrapyramidal Symptom Rating Scale

f) Dyskinesia Identification System: Condensed User Scale

STRUCTURED TD SCREENING
STANDARD OF CARE

- Historically, HCPs ***do not regularly monitor for TD*** (only 11% adherence to structured TD screenings)[1,2]
- Consensus recommendations strongly support both structured/formal and ***semi-structure evaluations***[3,4]

SEMI-STRUCTURED EVALUATIONS[3,4]

- Patient /caregiver reports of abnormal movements
- Visual inspection for motor abnormalities

Perform at every visit!

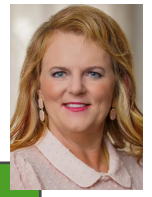
STRUCTURED EVALUATIONS[2,3]

- Recommend Abnormal Involuntary Movement Scale (AIMS)
- Time-consuming compared with semi-structured evaluations

Perform every 3 to 6 months

HCP: healthcare practitioner

1. Keller WR et al. Community adherence to schizophrenia treatment and safety monitoring guidelines. *J Nerv Ment Dis*. 2014;202(1):6-12. **2.** Caroff SN et al. A modified Delphi consensus study of the screening, diagnosis, and treatment of tardive dyskinesia. *J Clin Psychiatry*. 2020;81(2):19cs12983. **3.** Butala N et al. Impact of a pharmacist-driven tardive dyskinesia screening service. *Ment Health Clin*. 2021;11(4):248-253. **4.** Keepers GA et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry*. 2020;177(9):868-872.



ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

- May be used both as a ***screening tool*** and to ***monitor TD severity*** over time[1,2]
- Pay particular attention to **orofacial dyskinesias** (upwards of 72% of tardive syndromes have been found to have orofacial involvement)[3]
- Validated via **telemedicine/videoconferencing;** however, further research is required to formalize this method[4]

How do you conduct, score, and interpret AIMS?

ABNORMAL INVOLUNTARY MOVEMENT SCALE	
FACIAL AND ORAL MOVEMENTS	1. Muscles of facial expression
	2. Lips and perioral area
	3. Jaw
	4. Tongue
EXTREMITY MOVEMENTS	5. Upper (arms, wrists, hands, fingers)
	6. Lower (legs, knees, ankles, toes)
TRUNK MOVEMENTS	7. Neck, shoulders, hips
GLOBAL JUDGMENTS	8. Severity
	9. Incapacitation
	10. Patient awareness
DENTAL STATUS	11. Problems with teeth/dentures? 12. Usually wear dentures

Adapted from Guy W. ECDEU Assessment Manual for Psychopharmacolog. U.S. Department Of Health, Education, And Welfare; 1976

1. Kane JM et al. Revisiting the Abnormal Involuntary Movement Scale: proceedings from the Tardive Dyskinesia Assessment workshop. *J Clin Psychiatry*. 2018;79(3):17cs11959.
2. Munetz MR et al. How to examine patients using the Abnormal Involuntary Movement Scale. *Hosp Community Psychiatry*. 1988;39(11):1172-1177. **3.** Waln O et al. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)*. 2013;3:tre-03-161-4138-1. **4.** Ben-Pazi H et al. The promise of telemedicine for movement disorders: an interdisciplinary approach. *Curr Neurol Neurosci Rep*. 2018;18(5):26.

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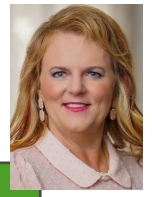

AIMS SCORING

RESEARCH CRITERIA FOR TD[1,2]
Score = 2 in at least two movement categories OR Score = ≥ 3 in a single movement category

Scoring guidance[3]:
Severity: Rate highest severity observed
Activation: Rate movements that occur upon activation one less than those observed spontaneously

ABNORMAL INVOLUNTARY MOVEMENT SCALE	
0 = none 1 = minimal 2 = mild 3 = moderate 4 = severe	1. Muscles of facial expression
	2. Lips and perioral area
	3. Jaw
	4. Tongue
	5. Upper (arms, wrists, hands, fingers)
	6. Lower (legs, knees, ankles, toes)
	7. Neck, shoulders, hips

Offers information on global symptom severity/impact and patient awareness (not included in AIMS score)

The sum scores of items 1 to 7 is called the AIMS Total Dyskinesia Score or AIMS Total Score

Adapted from Guy W. *ECDEU Assessment Manual for Psychopharmacolog.* U.S. Department Of Health, Education, And Welfare; 1976

1. Gharabawi GM et al. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. *Schizophr Res.* 2005;77(2-3):119-128. **2.** Stacy M et al. Abnormal Involuntary Movement Scale in tardive dyskinesia: minimal clinically important difference. *Mov Disord*. 2019;34(8):1203-1209. **3.** Guy W. *ECDEU Assessment Manual for Psychopharmacology.* U.S. Department Of Health, Education, and Welfare; 1976.

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AIMS
PHYSICAL EVALUATION

Don't perseverate… ACTIVATE!

Activation mimics activities that bring out TD

TD is <u>more prominent</u> when other muscles are activated voluntarily

PHYSICAL ACTIVATION MANEUVERS[1]

Ask patient to:

1. ***Open their mouth***
2. ***Stick out their tongue***
3. *Tap using **alternating fingers***
4. ***Walk***
5. *Stand with **arms extended***

Record the greatest severity observed during any of these maneuvers.

EXPERT TIP: When the patient is standing with arms extended in front of them, *use **mental activation maneuvers** (e.g., reciting the name of the months backwards, counting backwards from 100)*

1. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. U.S. Department Of Health, Education, and Welfare; 1976.

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CASE 1
AIMS SCORE

THIS PATIENT:

AIMS total score = 11

☑ ≥3 score in one category

☑ More than 2 categories with score ≥2

Patient is diagnosed with TD

Score indicates moderate disease severity/impact with patient awareness

What is the utility in calculating the AIMS total score?

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)	
2 out of 4	1. Muscles of facial expression
1 out of 4	2. Lips and perioral area
3 out of 4	3. Jaw
1 out of 4	4. Tongue
2 out of 4	5. Upper (arms, wrists, hands, fingers)
2 out of 4	6. Lower (legs, knees, ankles, toes)
0 out of 4	7. Neck, shoulders, hips
3 out of 4	8. Severity
1 out of 4	9. Incapacitation
2 out of 4	10. Patient awareness

Item 8 is generally scored by the highest individual score observed in items 1 through 7.

Adapted from Guy W. *ECDEU Assessment Manual for Psychopharmacolog.* U.S. Department Of Health, Education, And Welfare; 1976

1. Kane JM et al. Revisiting the Abnormal Involuntary Movement Scale: proceedings from the Tardive Dyskinesia Assessment workshop. *J Clin Psychiatry*. 2018;79(3):17cs11959.

AIMS TOTAL SCORE
MONITORING

*Trending the AIMS total score enables clinicians to **monitor disease progression and therapeutic responses***

Interval: 3-6 months → **Interval: 3-6 months** → **Interval: 3-6 months** → **Interval: 3-6 months**

- *Baseline AIMS*
  Calculate AIMS total score
- *Repeat AIMS*
  Compare delta AIMS total score
- *Repeat AIMS*
  Compare delta AIMS total score
- *Repeat AIMS*
  Compare delta AIMS total score

≥ 2-point decrease is considered clinically meaningful

BUT: even a 1-point decrease may be important if it means the tongue remains in the oral cavity!

1. Stacy M et al. Abnormal Involuntary Movement Scale in tardive dyskinesia: minimal clinically important difference. *Mov Disord*. 2019;34(8):1203-1209.

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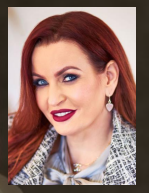

MODULE
— 2 —

MAKE A LINK: PHARMACOTHERAPY ASSOCIATIONS WITH EMERGENT DIMDS

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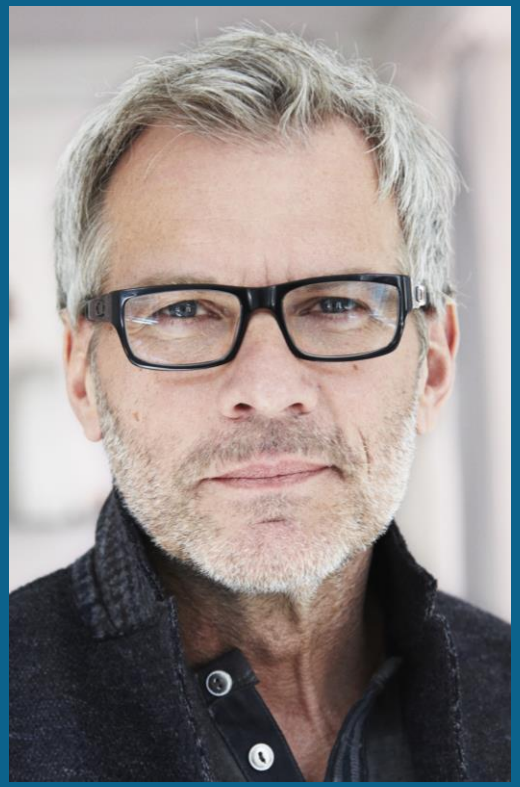
CASE 1*
CONTINUED

CASE RECAP:

Ryan, a 53-year-old male with bipolar depression, presents with current medications of quetiapine, venlafaxine, and trazodone.

Diagnosed with TD

Which agent is the most likely offending agent?



*Fictionalized representation based on a real medical case.

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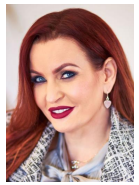


TARDIVE DYSKINESIA

PREVALENCE BY ANTIPSYCHOTIC CLASS

STUDY DESIGN

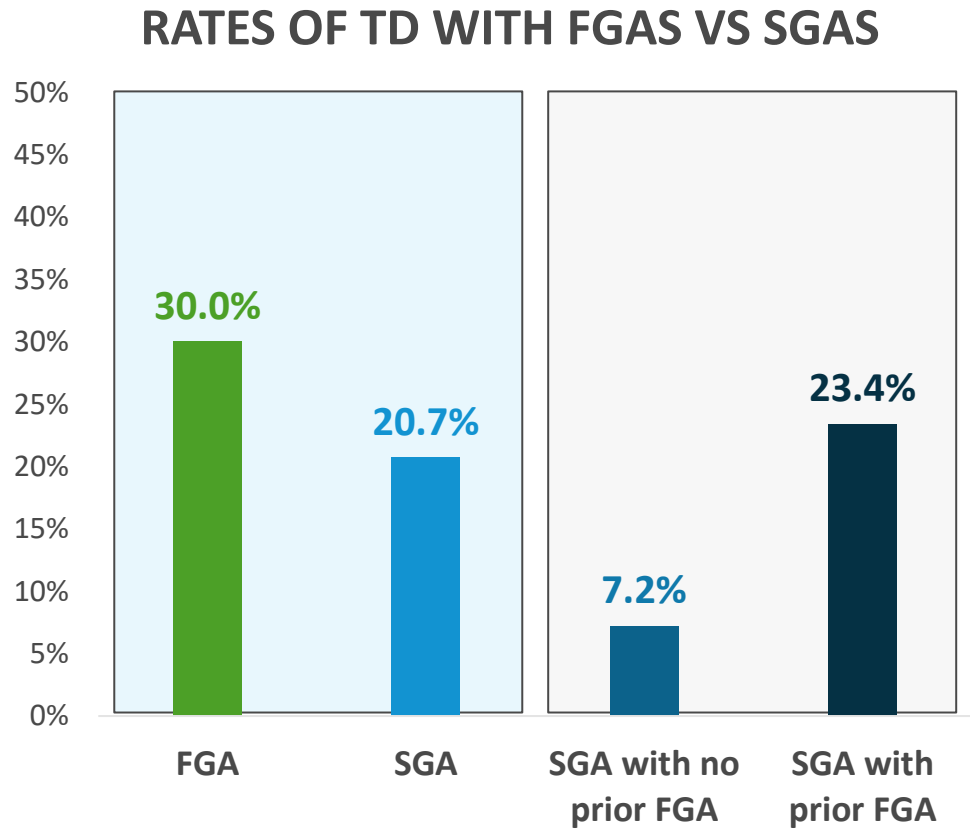
- Meta-analysis (41 studies included)

RESULTS

- Mean TD prevalence = 25.3%
- ***SGA:*** Lower TD rates compared with FGAs (*P*=0.002)
- ***FGA exposure***: When treating with an SGA, rates of TD dramatically increase if patient has been exposed to prior FGA (*P*<0.001)

CONCLUSION:

- SGAs less likely to lead to the development of TD



TD may be less likely with SGAs, but it still happens!
How do you warn patients about the possibility of TD when initiating antipsychotic therapy?

FGA: first-generation antipsychotic; **SGA:** second-generation antipsychotic

1. Carbon M et al. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry*. 2017;78(3):e264-e278.

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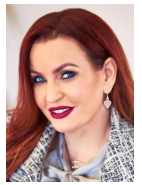
DRUG-INDUCED MOVEMENT DISORDERS

ANTIPSYCHOTIC GENERATIONS



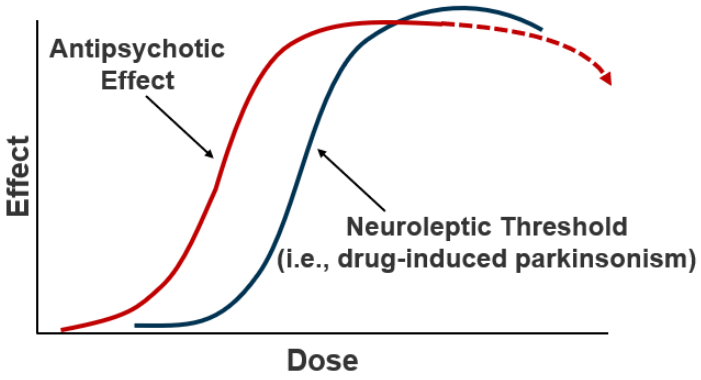
Both generations of antipsychotics block postsynaptic D_2 receptors in the dorsal striatum[1,2]

Subsequent upregulation of D_2 receptors in dorsal striatum leads to DIMDs

SGAs can have lower D_2 receptor affinity and a ***wider therapeutic window*** compared with FGAs[2]

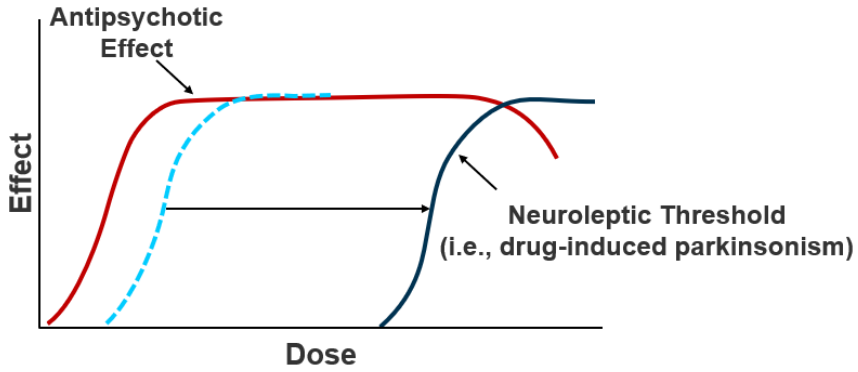
May result in better tolerability / adherence as they lead to fewer DIMDs at effective antipsychotic doses

FGA Dose-Responsive Curve



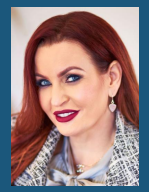
Narrow therapeutic window

SGA Dose-Responsive Curve



Wider therapeutic window

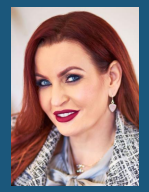
1. Stahl SM. Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectr*. 2018;23(3):187-191. 2. Sykes DA et al. Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D_2 receptors. *Nat Commun*. 2017;8(1):763.



AUDIENCE POLL

Recent data suggests that which of the following VMAT2 inhibitors is associated with fewer drug-drug interactions?

a) Valbenazine
b) Deutetrabenazine
c) I do not know/ I am unsure.



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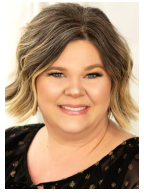


ATYPICAL ANTIPSYCHOTICS

IMPACT ON DRUG-INDUCED MOVEMENT DISORDERS

Relative rates of DIMDs are impacted by the degree of D_2 antagonism[1,2]

Antagonistic D_2 affinity	Atypical antipsychotic
Low	**CLOZAPINE** Quetiapine Iloperidone Lumateperone
Intermediate	Olanzapine Asenapine Paliperidone
High	Aripiprazole Brexpiprazole Cariprazine **RISPERIDONE**

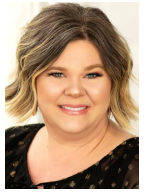
LOWEST RISK

Atypical antipsychotics have varying degrees of risk when looking at each DIMD individually (e.g., dystonia, DIP, TD)

HIGHEST RISK

Lower rates of DIMDs typically (but not always) come with the trade-off of more metabolic side effects[1,2]

1. Divac N et al. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int*. 2014;2014:656370. **2.** Shirzadi AA et al. Side effects of atypical antipsychotics: extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry*. 2006;14(3):152-164.



TARDIVE DYSKINESIA

ANTIPSYCHOTIC CONTROVERSY

ANTIPSYCHOTIC MANAGEMENT ARGUMENTS[1,2]

FOR REDUCING, SWITCHING, OR DISCONTINUING

- Goal is to ***remove the offending agent*** or switch to an atypical antipsychotic that causes less DIMDs

AGAINST REDUCING, SWITCHING, OR DISCONTINUING ANTIPSYCHOTIC

- Reducing, removing, or switching antipsychotic may lead to ***"withdrawal dyskinesia" or transient worsening of symptoms***
- American Academy of Neurology (AAN) states there is ***insufficient evidence*** to support withdrawing or switching antipsychotics

FOR INCREASING ANTIPSYCHOTIC DOSE

- May ***mask*** the symptoms of TD

What do TD experts recommend?

1. Bhidayasiri R et al. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci*. 2018;389:67-75. **2.** Ricciardi L et al. Treatment recommendations for tardive dyskinesia. *Can J Psychiatry*. 2019;64(6):388-399.

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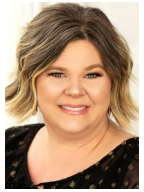

TARDIVE DYSKINESIA

ANTIPSYCHOTIC CONTROVERSY

ANTIPSYCHOTIC MANAGEMENT RECOMMENDATIONS[1,2]

REDUCE DOSE, SWITCH ANTIPSYCHOTICS, OR DISCONTINUE

NO CHANGE

CASE-BY-CASE EVALUATION[3]

Determine feasibility of reducing/switching antipsychotics by assessing:

Symptom/disease severity

Psychiatric stability on current antipsychotics

Risk of relapse

INCREASE DOSE

Not recommended[2]

- *Only transient masking*
- *Increased risk of drug-induced dyskinesia*

1. Bhidayasiri R et al. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci*. 2018;389:67-75. **2.** Ricciardi L et al. Treatment recommendations for tardive dyskinesia. *Can J Psychiatry*. 2019;64(6):388-399. **3.** Caroff SN et al. A modified Delphi consensus study of the screening, diagnosis, and treatment of tardive dyskinesia. *J Clin Psychiatry*. 2020;81(2):19cs12983.

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CASE 1*

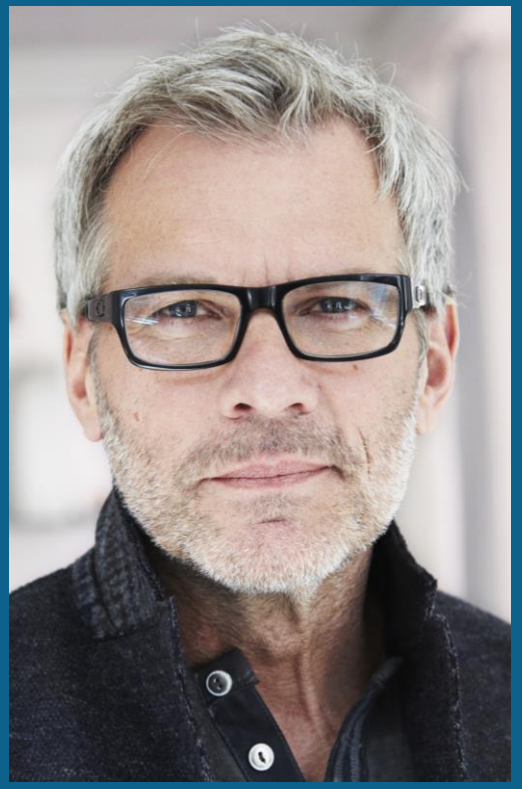
STEP 1

CASE RECAP:

Ryan is a 53-year-old male with bipolar depression with a history of multiple hospital admissions for his depression. He developed TD after starting quetiapine 4 months ago.

Since starting quetiapine, venlafaxine, and trazodone the patient notes significant improvement in his depressive symptoms.

Would you lower the patient's antipsychotic if feasible?



*Fictionalized representation based on a real medical case.

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CASE 1

ANTIPSYCHOTIC MANAGEMENT[1,2]

TD secondary to antipsychotic?

yes

Can antipsychotic be discontinued or lowered based on severity of mental illness?

yes

Discontinue or lower antipsychotic dose ***if feasible***

no

Is this patient currently on an atypical antipsychotic?

yes

Continue current antipsychotic dose

no

Switch to an atypical antipsychotic

no

Clarify diagnosis of the DIMD

1. Ricciardi L et al. Treatment recommendations for tardive dyskinesia. *Can J Psychiatry*. 2019;64(6):388-399. **2.** Bhidayasiri R et al. Updating the recommendations for treatment of tardive syndromes: a systematic review of new evidence and practical treatment algorithm. *J Neurol Sci*. 2018;389:67-75.

CASE 1*
STEP 1

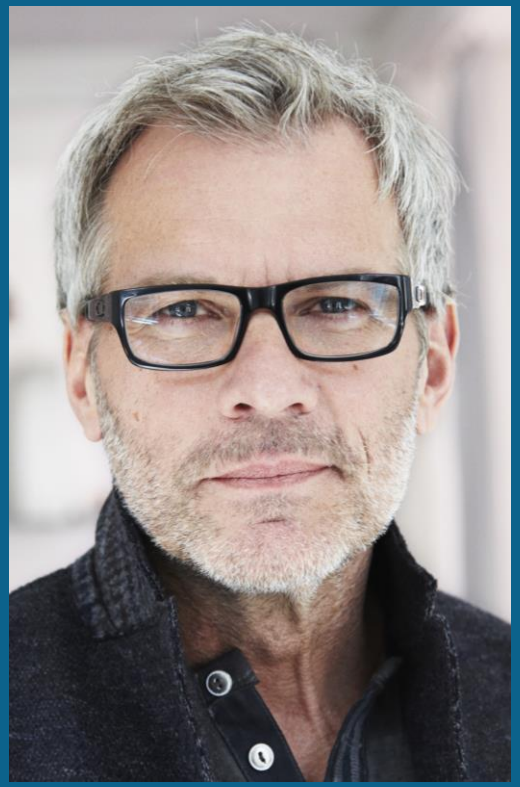
CASE RECAP:

Ryan, a 53-year-old male, was started on quetiapine for bipolar depression and developed TD.

Patient is continued on current quetiapine dose

DECISION BASED ON:

1. **Symptom severity:** History of multiple hospitalizations → severe depression and suicidal ideation
2. **Response to therapy:** Improvement in depressive symptoms since starting quetiapine and antidepressants → relapse concern



*Fictionalized representation based on a real medical case.

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MODULE
— 3 —

MAKE A MOVE: VMAT2 INHIBITORS FOR TD

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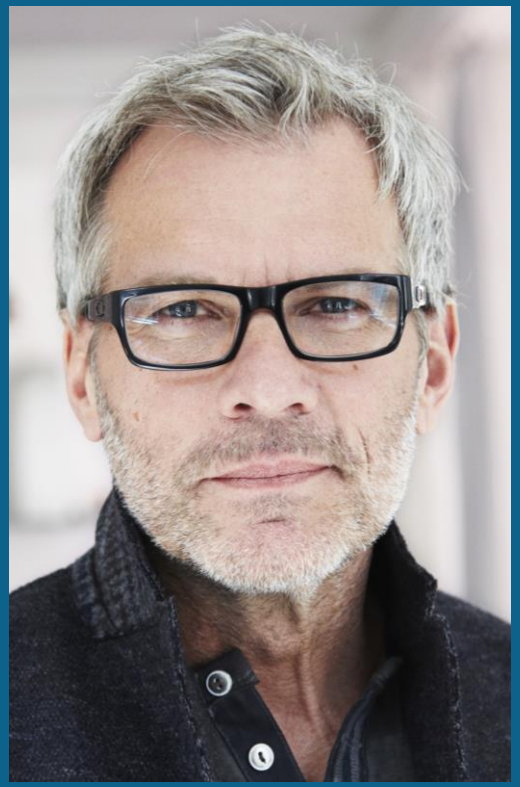
CASE 1*

STEP 1

CASE RECAP:

Ryan is a 53-year-old male who was started on quetiapine during an inpatient admission for bipolar depression who subsequently developed TD. Based on the severity of his depression and treatment response, the decision was made to continue his current dose of quetiapine.

What treatment options are available for tardive dyskinesia?



*Fictionalized representation based on a real medical case.

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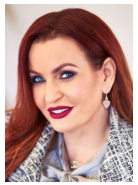
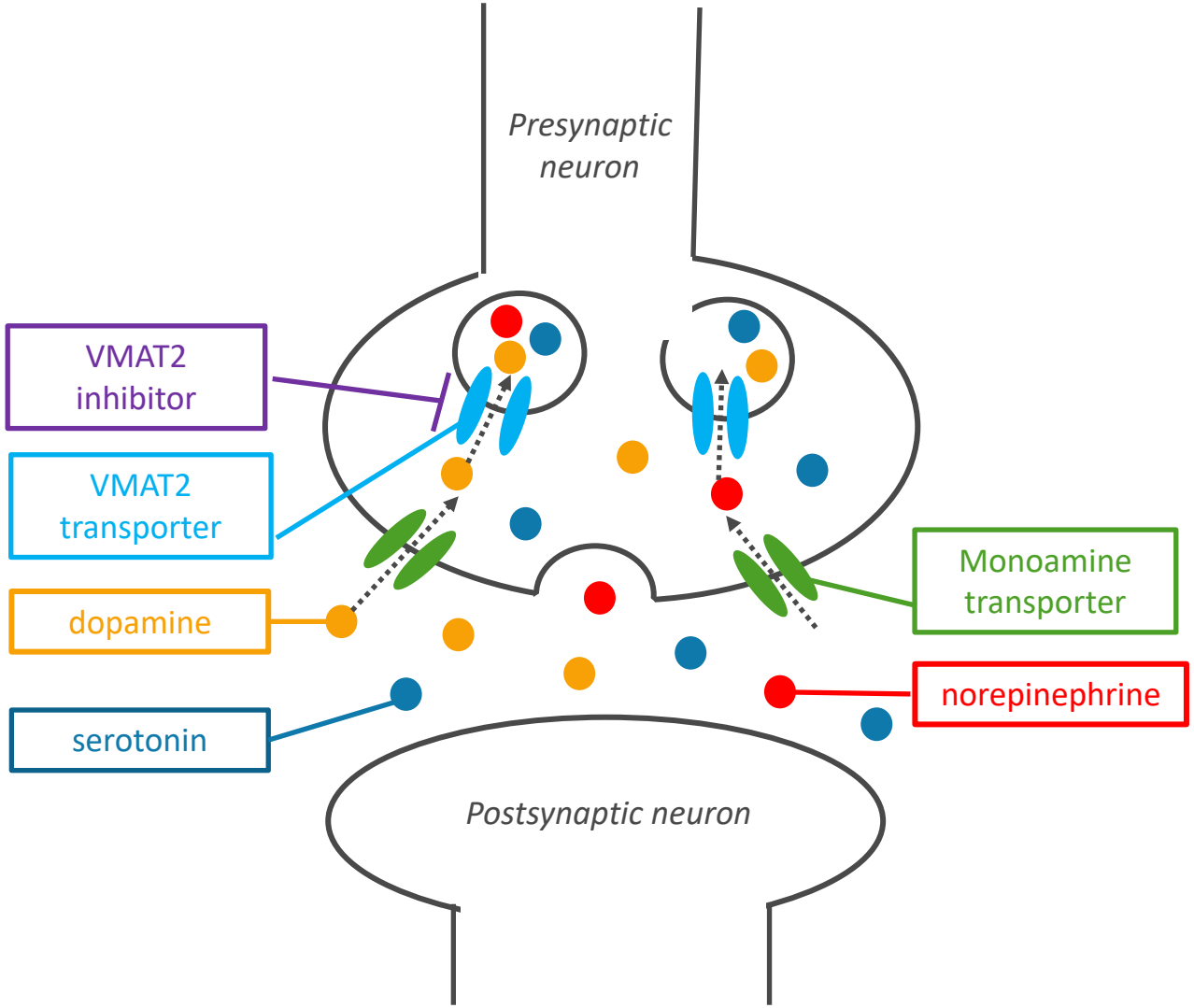
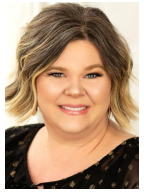


VMAT2 INHIBITORS
MECHANISM OF ACTION

- **Vesicular monoamine transporter type 2 (VMAT2):**
  - Responsible for monoamine (dopamine, serotonin, norepinephrine) transport into synaptic vesicles
- **VMAT2 inhibitors for TD:**
  - Block dopamine reuptake into vesicles, reducing the amount of dopamine ultimately released into the synapse when the dopaminergic neuron fires
    - **Valbenazine**
    - **Deutetrabenazine**



1. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert Rev Neurother*. 2018;18(4):323-332.



VMAT2 INHIBITORS

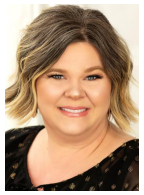
PHARMACOKINETICS/PHARMACODYNAMICS

Valbenazine (VBZ) and deutetrabenazine (DTBZ) are the only two FDA-approved VMAT2 inhibitors for TD[1]

- Both are ***reversible, selective VMAT2 inhibitors***

VMAT inhibitor	Half-life	Recommended target dose	T_{max}	CYP2D6 metabolism
VBZ[1]	20 hours	80 mg daily	4-10 hours	Max dose 40 mg daily for poor metabolizers; cannot be given with CYP3A4 inducers
DTBZ[1]	8.5 hours	18 mg BID with food	3-4 hours	Max dose DTBZ 18 mg BID for poor metabolizers
DTBZ - extended release *(Approved 2023[2-4])*		36 mg daily with or without food		

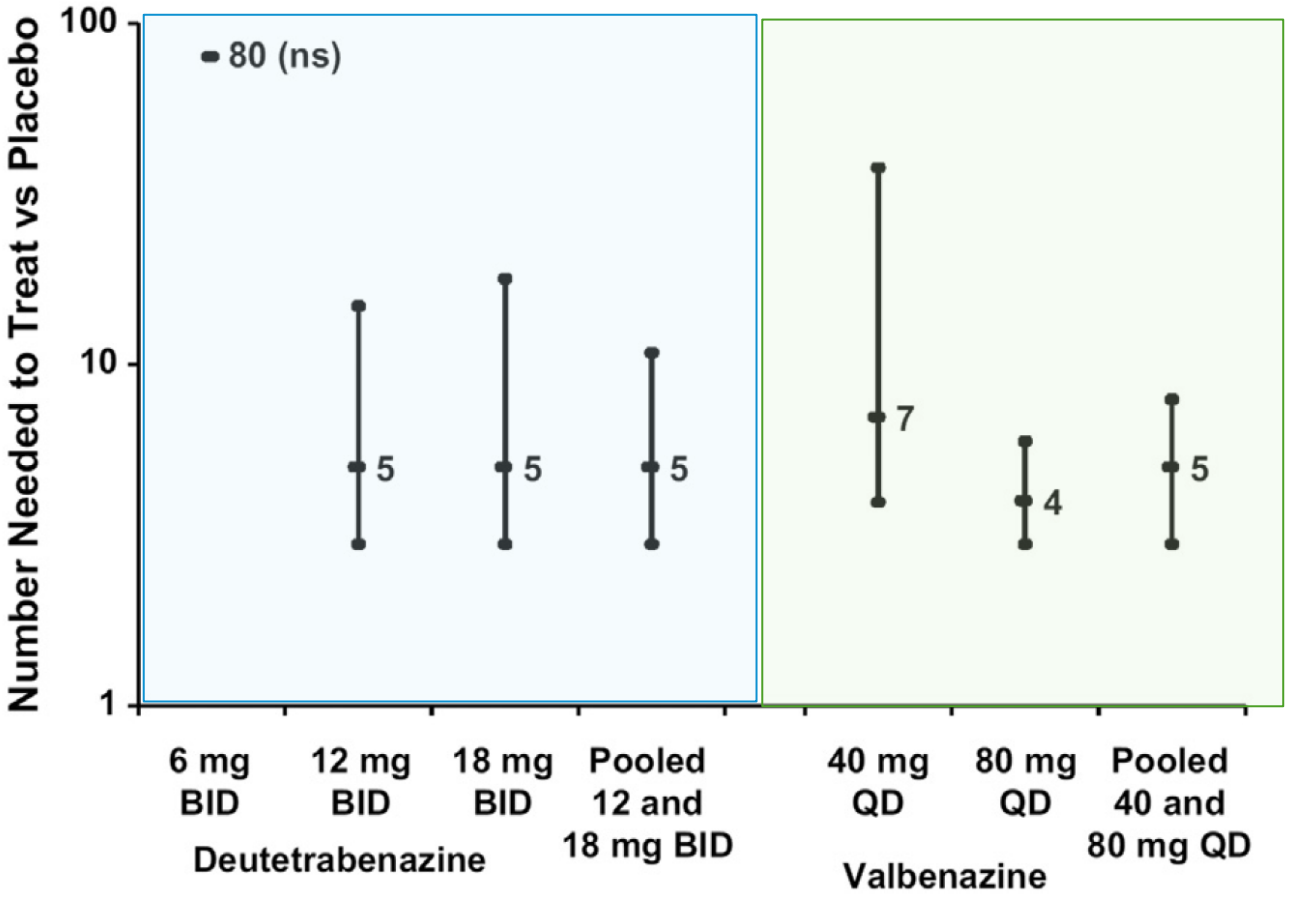
1. Caroff SN. Recent advances in the pharmacology of tardive dyskinesia. *Clin Psychopharmacol Neurosci*. 2020;18(4):493-506. **2.** AUSTEDO XR (deutetrabenazine) extended-release tablets and AUSTEDO (deutetrabenazine) tablets. Prescribing information.-Teva Neuroscience, Inc.; 2023. **3.** Sunzel EM et al. Assessment of dose proportionality of three dose strengths (6 mg, 12 mg and 24 mg) over the clinical dose range (6–48 mg) of the newly developed once-daily extended release tablet formulation of deutetrabenazine. Presented at: American Academy of Neurology 2023 Annual Meeting; Boston, MA; April 22-27, 2023. P2-11.0162023. **4.** Sunzel EM et al. A bioequivalence comparison at steady state between the newly developed once-daily extended release tablet formulation and the approved twice-daily tablet formulation of deutetrabenazine. Presented at: American Academy of Neurology 2023 Annual Meeting; Boston, MA; April 22-27, 2023. P2-11.015.



VMAT2 INHIBITORS
CLINICAL EFFICACY

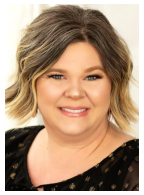
- No head-to-head comparisons of VBZ and DTBZ
- However, in phase 3 trials, both saw ≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint
- NNH vs placebo for either: ~100
  - **NNH/NNT = 20 times more likely to encounter robust response than discontinue due to an AE**

VBZ AND DTBZ: NNT IN FIXED-DOSE TRIALS



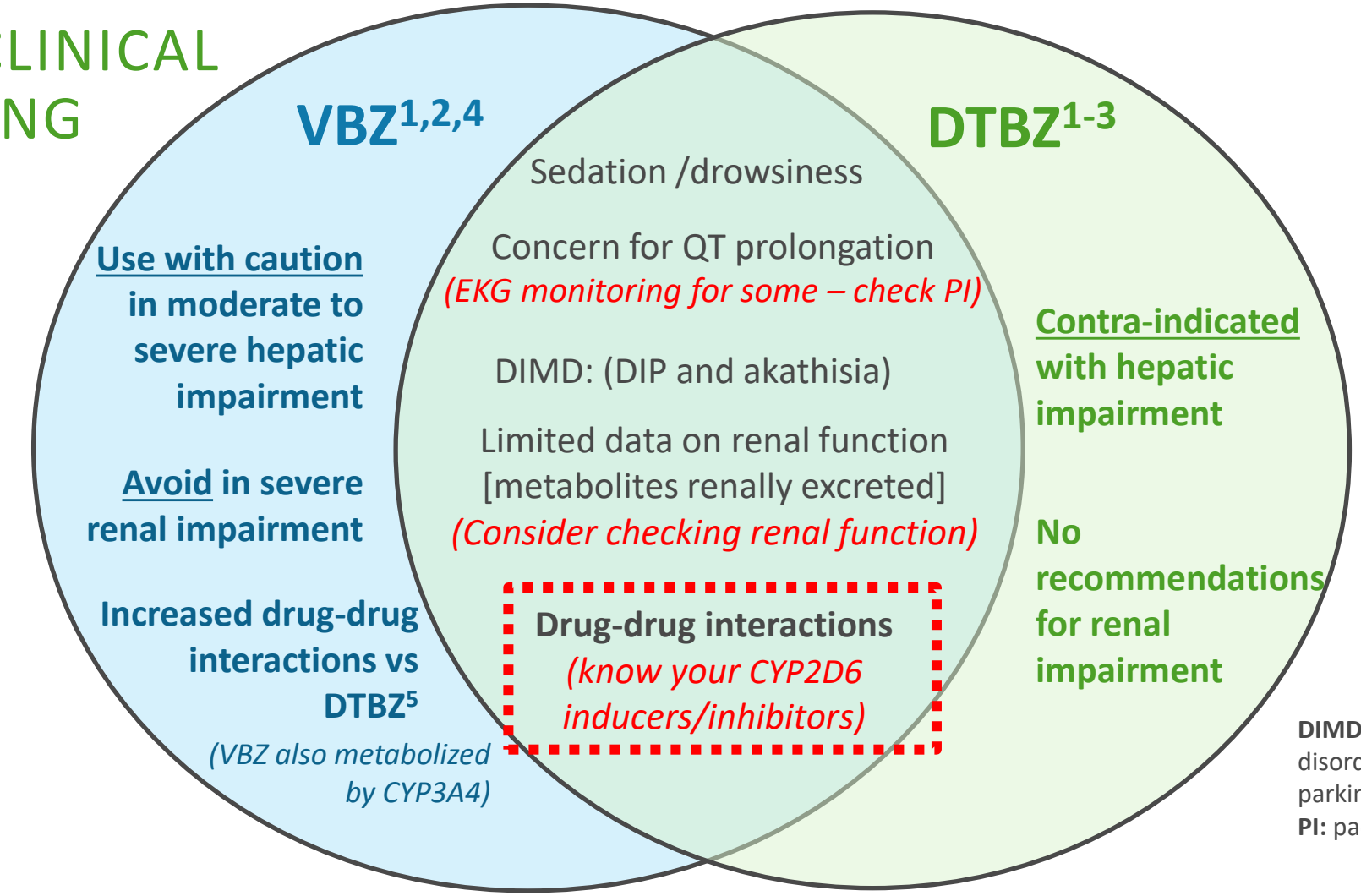
AIMS: abnormal involuntary movement scale; **DTBZ:** deutetrabenazine; **NNH:** number needed to harm; **NNT:** number needed to treat; **VBZ:** valbenazine

1. Citrome L. Clinical management of tardive dyskinesia: five steps to success. *J Neurol Sci*. 2017;383:199-204.



VMAT2 INHIBITORS

SAFETY / CLINICAL MONITORING



DIMD: drug-induced movement disorder; **DIP:** drug-induced parkinsonism; **DTBZ**: deutetrabenazine; **PI:** package insert; **VBZ**: valbenazine

1. Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248. **2.** Caroff SN. Recent advances in the pharmacology of tardive dyskinesia. *Clin Psychopharmacol Neurosci*. 2020;18(4):493-506. **3.** Austedo XR. Prescribing information. Teva Neuroscience Inc.; 2023. **4.** Ingrezza. Prescribing information. Neurocrine Biosciences, Inc.; 2019. **5.** Mychaskiw MA et al. Drug–drug interactions with vesicular monoamine transporter 2 inhibitors: population estimate of patients with tardive dyskinesia at risk in real-world clinical practice. Presented at: Psych Congress 2023; Nashville, TN; September 6-10, 2023.

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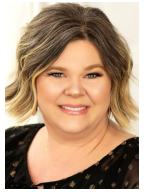
PHARMACIST QUICK TIP



TARDIVE DYSKINESIA

ADDITIONAL TREATMENT OPTIONS

TD MANAGEMENT[1,2]

- **Avoid anticholinergics (e.g., benztropine)**
- ***If feasible, consider reducing, switching, or discontinuing offending antipsychotic***

FIRST-LINE THERAPY
Typically for moderate to severe

VMAT2 inhibitors

SECOND-LINE THERAPY
Limited quality of evidence

Benzodiazepines / amantadine

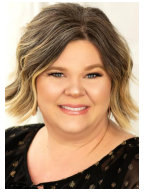
- Lack of anticholinergic activity of amantadine makes it an ideal choice if a patient requires ***both an antiparkinsonian and antidyskinetic agent***

THIRD-LINE THERAPY
Limited quality of evidence

Deep-brain stimulation

When do you consider and/or initiate amantadine in your TD management?

1. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert Rev Neurother*. 2018;18(4):323-332. **2.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.



TARDIVE DYSKINESIA

ADDITIONAL TREATMENT OPTIONS

TD management[1,2]

First-line therapy
Typically for moderate to severe

VMAT-2 inhibitors

Second-line therapy
Limited quality of evidence

Benzodiazepines / Amantadine

Third-line therapy
Limited quality of evidence

Deep-brain stimulation

- **Avoid anticholinergics (e.g., benztropine)**

- Lack of anticholinergic activity of amantadine makes it an ideal choice if a patient requires *both an antiparkinsonian and antidyskinetic agent*

When do you consider and/or initiate amantadine in your TD management?

1. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert Rev Neurother*. 2018;18(4):323-332. **2.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.

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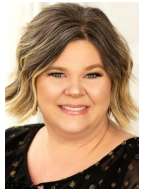


TARDIVE DYSKINESIA

ADDITIONAL TREATMENT OPTIONS

TD management[1,2]

First-line therapy
Typically for moderate to severe

VMAT-2 inhibitors

Second-line therapy
Limited quality of evidence

Benzodiazepines / Amantadine

Third-line therapy
Limited quality of evidence

Deep-brain stimulation

➢ **Avoid anticholinergics (e.g., benzotropine)**

May improve DIP but worsen symptoms of TD[1,2]

Always check your package insert

When do you consider and/or initiate amantadine in your TD management?

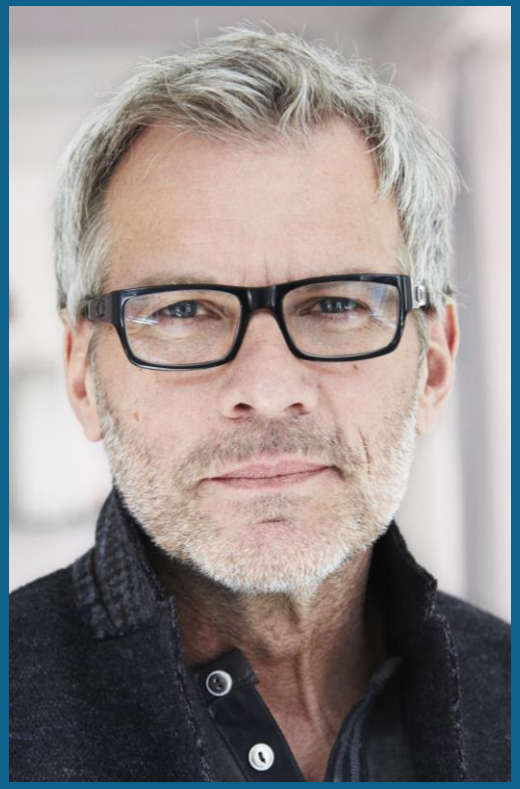
1. Citrome L. Tardive dyskinesia: placing vesicular monoamine transporter type 2 (VMAT2) inhibitors into clinical perspective. *Expert Rev Neurother*. 2018;18(4):323-332. **2.** Ward KM et al. Antipsychotic-related movement disorders: drug-induced parkinsonism vs. tardive dyskinesia-key differences in pathophysiology and clinical management. *Neurol Ther*. 2018;7(2):233-248.

CASE 1*
RESOLUTION

CASE RECAP:
Ryan is a 53-year-old male who was started on quetiapine during an inpatient admission for bipolar depression and subsequently developed TD.

NEXT STEPS:
- First-line therapy: VMAT2 inhibitor

Which VMAT2 inhibitor would you initiate?



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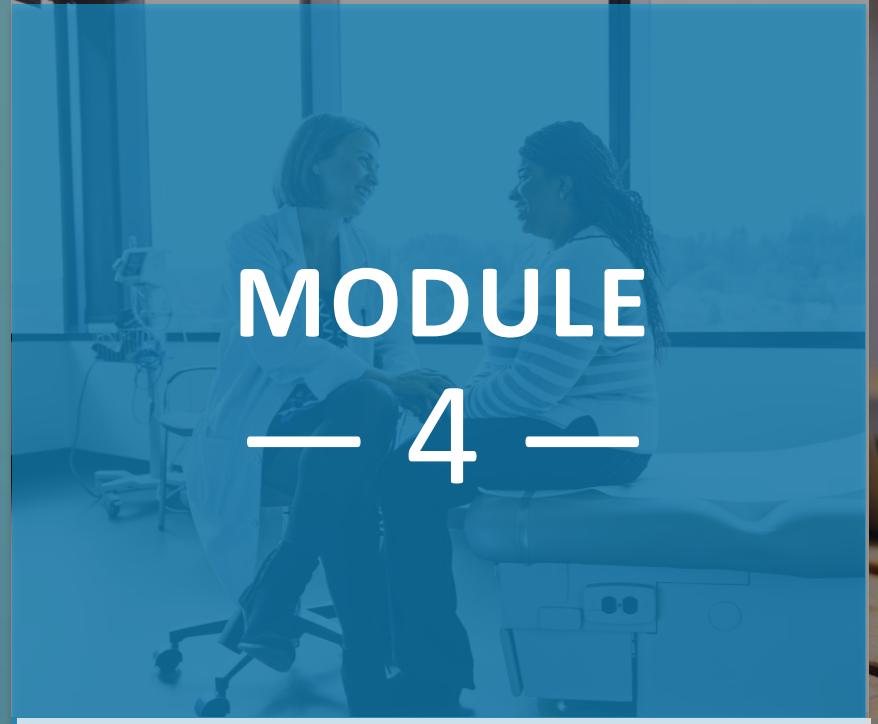

MODULE
— 4 —

MAKE A PLAN: THE IMPORTANCE OF DISTINCT MANAGEMENT APPROACHES BETWEEN DIMDS

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MINI-CASES ACROSS THE DMD SPECTRUM

Zoey, a 28-year-old female, was diagnosed with schizophrenia ***2 weeks ago***. She was seen by a psychiatrist and started on aripiprazole. One week after starting the new medication, Zoey began to experience ***restlessness.***

Upon exam, Zoey is ***pacing back and forth across the room***.

*Fictional case.

Where does this patient fall on the DIMDs spectrum and how should we treat her?

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DIMD SPECTRUM
MANAGEMENT

TREATMENT	Akathisia[1-3]
Taper/switch/discontinue antipsychotic	✓ *First-line*
Anticholinergics (e.g., benztropine)	✗
Benzodiazepines	✓ *Third-line*
Beta-blockers (e.g., propranolol)	✓ *Second-line*
Antihistamines (e.g., diphenhydramine)	✗
Muscle relaxants (e.g., baclofen)	✗
Botulinum toxin injections	✗
Amantadine	✗
Deep-brain stimulations	✗

ZOEY

ONSET: *one week*
SUBJECTIVE: *restlessness*
OBJECTIVE: **pacing back and forth across the room**

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Rummel-Kluge C et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bull*. 2012;38(1):167-177. **3.** Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. **4.** Sadnicka A et al. Dystonia. *BMJ*. 2022;377:e062659. **5.** Feldman M et al. Updated perspectives on the management of drug-induced parkinsonism (DIP): insights from the clinic. *Ther Clin Risk Manag*. 2022;18:1129-1142. **6.** Wisidagama S et al. Recognition and management of antipsychotic-induced parkinsonism in older adults: a narrative review. *Medicines (Basel)*. 2021;8(6):24.

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MINI-CASES*

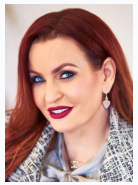
Where does this patient fall on the DIMDs spectrum and how should we treat him?

Paul, a 26-year-old male with a recent diagnosis of schizophrenia, was admitted to the hospital ***2 days ago*** due to acute psychosis. In the ED, the patient received ***2 doses of haloperidol***.

Today the patient reports ***neck pain and discomfort***. Upon exam, the patient is noted to have ***torticollis***.

*Fictional case.

*Fictional case.



DIMD SPECTRUM
MANAGEMENT

TREATMENT	Akathisia[1-3]	Dystonia[3,4]
Taper/switch/discontinue antipsychotic	✓ First-line	✓
Anticholinergics (e.g., benztropine)	✓ Third-line	✓ First-line
Benzodiazepines	✓ Third-line	✓ Third-line
Beta-blockers (e.g., propranolol)	✓ Second-line	✗
Antihistamines (e.g., diphenhydramine)	✗	✓ Second line
Muscle relaxants (e.g., baclofen)	✗	✓
Botulinum toxin injections	✗	✓
Amantadine	✗	✗
Deep-brain stimulations	✗	✗

PAUL

ONSET: *two days*
SUBJECTIVE: *neck pain*
OBJECTIVE: *torticollis*

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Rummel-Kluge C et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bull*. 2012;38(1):167-177. **3.** Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. **4.** Sadnicka A et al. Dystonia. *BMJ*. 2022;377:e062659. **5.** Feldman M et al. Updated perspectives on the management of drug-induced parkinsonism (DIP): insights from the clinic. *Ther Clin Risk Manag*. 2022;18:1129-1142. **6.** Wisidagama S et al. Recognition and management of antipsychotic-induced parkinsonism in older adults: a narrative review. *Medicines (Basel)*. 2021;8(6):24.

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MINI-CASES*

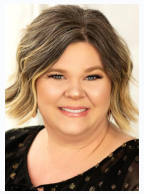
Where does this patient fall on the DIMDs spectrum and how should we treat her?

*Fictional case.

Leslie, a 55-year-old female with a history of bipolar disorder, was previously being treated with lithium monotherapy. ***One month ago***, Sandra had a manic episode. As a result, her psychiatrist augmented her therapy with ***quetiapine***.

Today, upon exam, Sandra has ***lower extremity stiffness, a shuffling gait, and reduced facial expression***

*Fictional case.



DIMD SPECTRUM
MANAGEMENT

TREATMENT	DIP[5,6]
Taper/switch/discontinue antipsychotic	✓ *First-line*
Anticholinergics (e.g., benztropine)	✓ *Second-line*
Benzodiazepines	✗
Beta-blockers (e.g., propranolol)	✗
Antihistamines (e.g., diphenhydramine)	✗
Muscle relaxants (e.g., baclofen)	✗
Botulinum toxin injections	✗
Amantadine	✓ *Second-line*
Deep-brain stimulations	✓ *Third-line*

LESLIE

ONSET: *one month*
OBJECTIVE: *shuffling gait, stiffness, hypomimia*

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. 2. Rummel-Kluge C et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bull*. 2012;38(1):167-177. 3. Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. 4. Sadnicka A et al. Dystonia. *BMJ*. 2022;377:e062659. 5. Feldman M et al. Updated perspectives on the management of drug-induced parkinsonism (DIP): insights from the clinic. *Ther Clin Risk Manag*. 2022;18:1129-1142. 6. Wisidagama S et al. Recognition and management of antipsychotic-induced parkinsonism in older adults: a narrative review. *Medicines (Basel)*. 2021;8(6):24.

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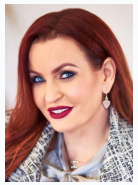

DIMD SPECTRUM
MANAGEMENT

TREATMENT	Akathisia[1-3]	Dystonia[3,4]	DIP[5,6]
Taper/switch/discontinue antipsychotic	✓ *First-line*	✓	✓ *First-line*
Anticholinergics (e.g., benztropine)	✗	✓ *First-line*	✓ *Second-line*
Benzodiazepines	✓ *Third-line*	✓ *Third-line*	✗
Beta-blockers (e.g., propranolol)	✓ *Second-line*	✗	✗
Antihistamines (e.g., diphenhydramine)	✗	✓ *Second line*	✗
Muscle relaxants (e.g., baclofen)	✗	✓	✗
Botulinum toxin injections	✗	✓	✗
Amantadine	✗	✗	✓ *Second-line*
Deep-brain stimulations	✗	✗	✓ *Third-line*

1. Pringsheim T et al. The assessment and treatment of antipsychotic-induced akathisia. *Can J Psychiatry*. 2018;63(11):719-729. **2.** Rummel-Kluge C et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia Bull*. 2012;38(1):167-177. **3.** Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. **4.** Sadnicka A et al. Dystonia. *BMJ*. 2022;377:e062659. **5.** Feldman M et al. Updated perspectives on the management of drug-induced parkinsonism (DIP): insights from the clinic. *Ther Clin Risk Manag*. 2022;18:1129-1142. **6.** Wisidagama S et al. Recognition and management of antipsychotic-induced parkinsonism in older adults: a narrative review. *Medicines (Basel)*. 2021;8(6):24.

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