Tardive Dyskinesia: A Review

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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

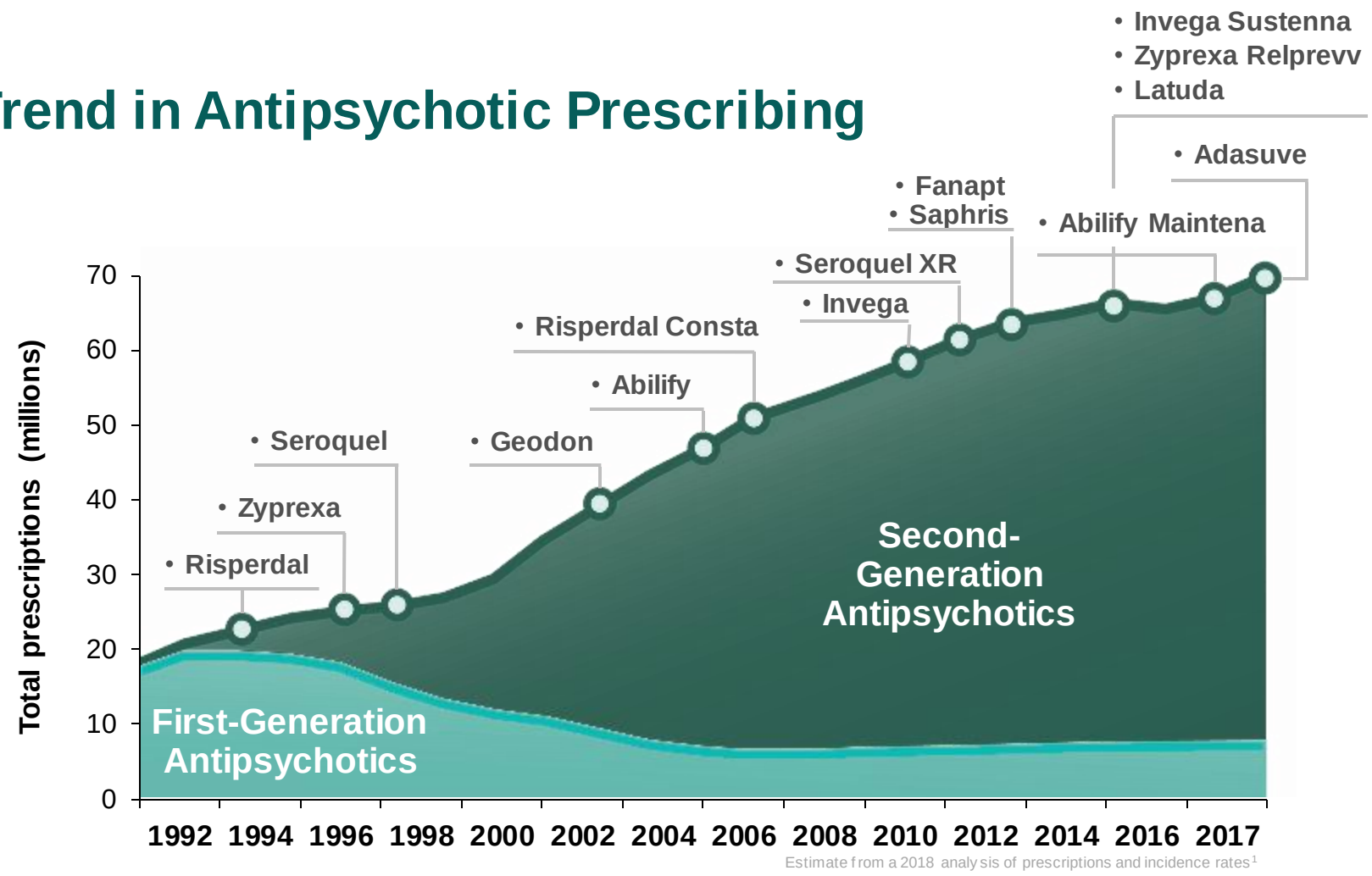
Leg Shoulder Face

*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

Trend in Antipsychotic Prescribing



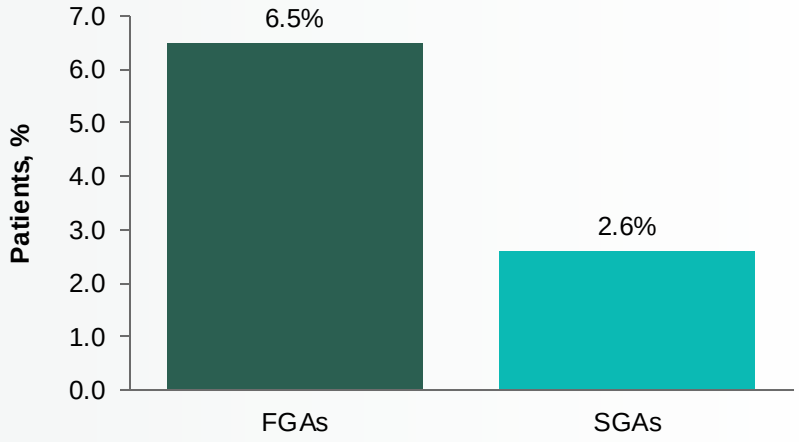
- **> 4-fold increase in antipsychotic use over 25 years[1]**
- **Use of second-generation antipsychotics (SGAs) in new conditions and client populations has grown over the past ~2.5 decades[2]**

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

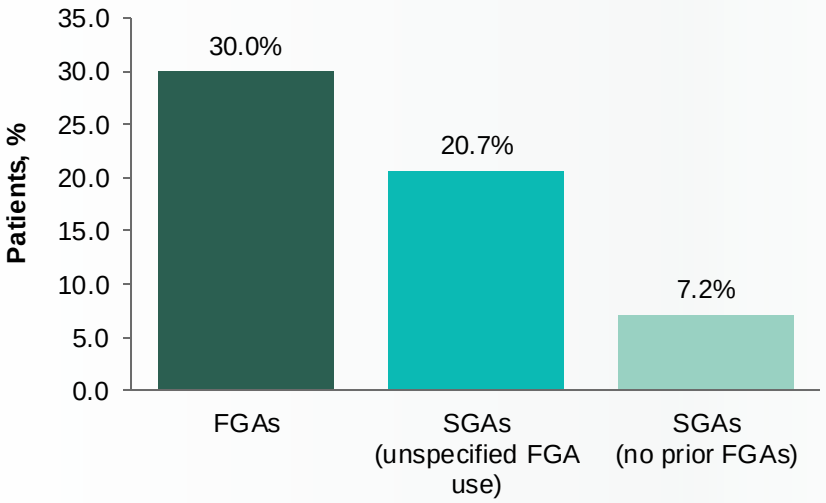
1. Data on file. Neurocrine Biosciences. 2. Alexander GC, et al. *Pharmacoepidemiol Drug Saf*. 2011;20(2)177-184.

TD Is Associated With Prolonged DRBA Treatment

TD Annual Incidence[1]*



TD Prevalence[2]†



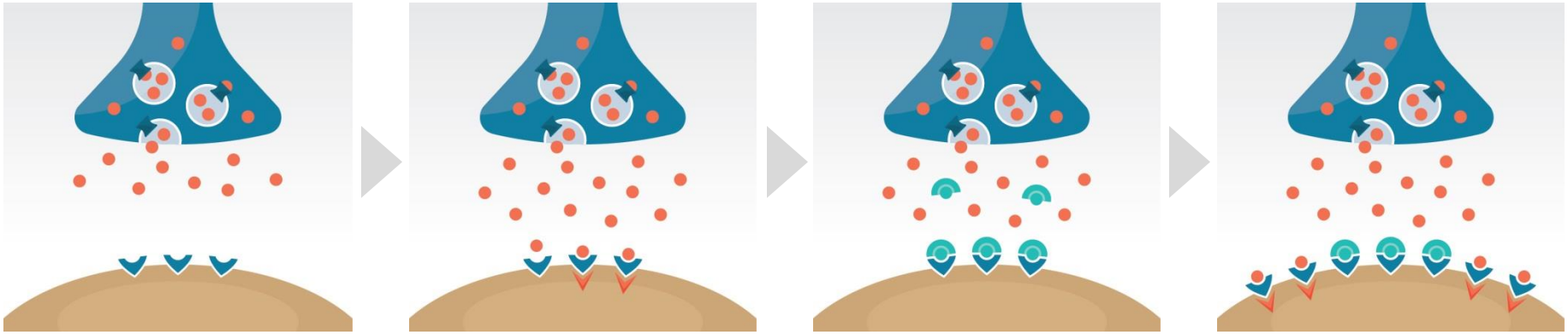
~5 million patients in the US are treated with antipsychotics[3]
≥600,000 patients may have TD[3,4‡]

*2018 meta-analysis of 57 randomized controlled trials (FGA-SGA studies, N=10,706; SGA-SGA studies, N=9153). †2017 meta-analysis of 41 studies (N=11,493).
‡Estimate from a 2014 analysis of prescriptions and incidence rates.
DRBA, dopamine receptor–blocking agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; TD, tardive dyskinesia.

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

TD Pathophysiology

- The mechanism underlying TD is complex and the exact cause has not been fully elucidated[1–4]
- A leading theory is the upregulation and subsequent hypersensitivity of brain dopamine D_2 receptors following prolonged exposure to DRBAs[1]
- Additional hypotheses include DRBA-induced:
  - Oxidative stress from free radical formation[2]
  - Dysfunction of GABA and/or serotonin pathways[3,4]



TD Mechanism of Disease Video

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

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 symptoms (EPS)[1]	Diagnosis of mood disorder[3,4]
Potency of DRBA[2]	Postmenopausal women[5]
Neuroleptic withdrawal-emergent dyskinesia[6]	

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

1. Miller DD, et al. *Schizophr Res*. 2005;80:33-43. 2. Divac N. *Biomed Res Int*. 2014;[Epub]. 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.

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.

Burden of Tardive Dyskinesia

- In some patients, TD is associated with[1-3]:
  - 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
- TD may persist for years or decades, even after discontinuing the causative drug[4]

1. Ascher-Svanum H, et al. *J Clin Psych*. 2008;69(10):1580-1588. *2.* Boumans CE, et al. *Schizo Bull.* 1994;20(2):339-344. 3. Ballesteros J, et al. *J Clin Psychopharmacol*. 2000;20:188-194. 4. Gardos G, et al. *Am J Psych.* 1994;151:836-841.

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.

Tardive Dyskinesia: Summary

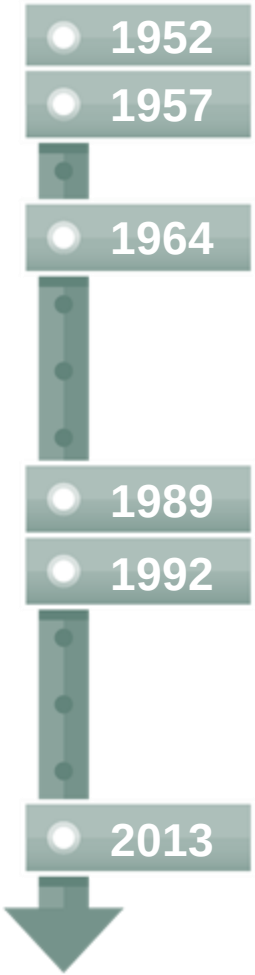
- TD is defined as abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with medications that block post-synaptic dopamine receptors[1]
- A leading theory of the mechanism of TD is the upregulation and subsequent hypersensitivity of brain dopamine D2 receptors following prolonged exposure to DRBAs[2]
- TD prevalence rates varied depending on exposure to DRBA[3]:
  - SGA use has increased substantially in the last 25 years
  - There is a 7-20% rate of TD in those taking SGAs, depending on prior history of FGA use
- The 2020 APA Schizophrenia Guidelines recommends reversible VMAT2 inhibitors in patients with moderate to severe or disabling TD[4]
  - VMAT2 inhibitors can also be considered for patients with mild TD

TD, tardive dyskinesia; DRBA, Dopamine Receptor Blocking Agent; FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; VMAT2, vesicular monoamine transporter 2; APA, American Psychiatric Association.

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. American Psychiatric Association: Washington, DC; 2013. 2. Klaw ans H, et al. *Acta Neurol Scand*. 1970;46:409-441. 3. Carbon M, et al. J Clin Psychiatry. 2017;78(3):e264-e278. 4. APA Practice Guideline for Treatment of Patients w ith Schizophrenia. Accessed on July 20, 2021. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

Back-up

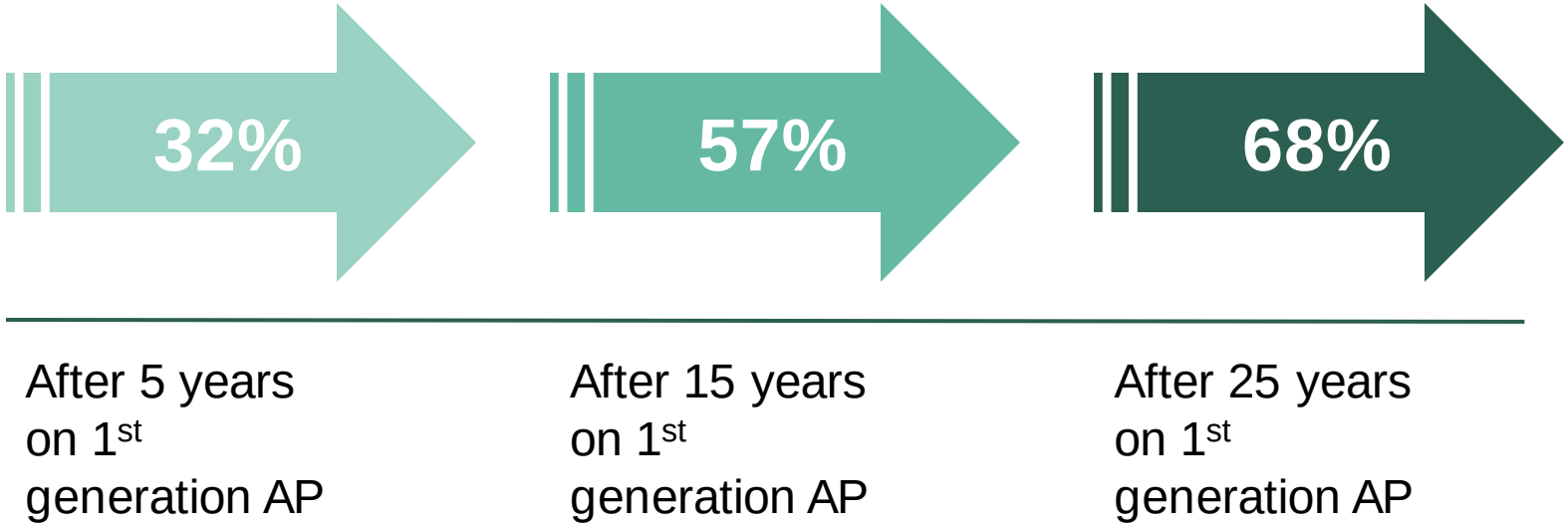
Brief History



- **1952**: The first antipsychotic drug (chlorpromazine) becomes commercially available[1]
- **1957**: Two women in Germany are reported as displaying lip-smacking dyskinetic movements, later recognized as the first reported cases of TD associated with antipsychotic use[2]
- **1964**: The term "Tardive Dyskinesia" is first used[3]
- **1989**: Clozaril (clozapine), the first second generation antipsychotic, is approved in the US[1]
- **1992**: APA Task Force publishes a report focused on TD[4]
- **2013**: AAN publishes guidelines for TD treatment[5]

1. Orange Book [FDA]. Retrieved June 6, 2016 from http://www.accessdata.fda.gov/scripts/cder/ob/. 2. Schonecker M. *Nervenarzt*. 1957;28:550-553. 3. Faurbye A, et al. Acta Psychiatr Scand. 1964;40:10-27. 4. American Psychiatric Association. Washington, DC 1992. 5. Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

Risk of TD Increases with Exposure to Antipsychotic Drug



**Estimated risk of TD is based on a long-term study of 362 outpatients who were free of TD at enrollment (1985-1986) and reexamined at least once during follow-up. The mean baseline age was 42 years (range 19-73 years of age), 53% were women, and 23% were African American. Previous neuroleptic use without TD and additional years of neuroleptic use were used to determine the time to TD occurrence*

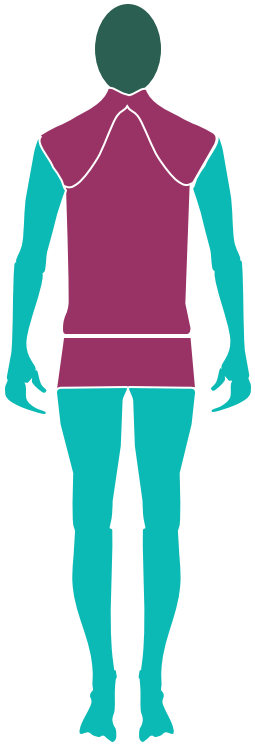
Glazer WM et al., *J Clin Psychiatry*. 1993; 54(4): 133-139.

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 **10.** Awareness
9. Incapacitation **11-12.** Dental Status

AIMS Items 1-12

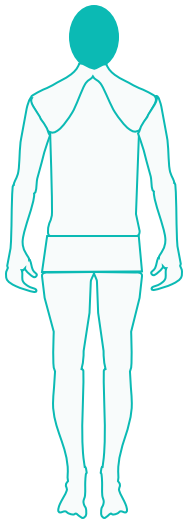
0=no dyskinesia; 1=low amplitude, present during some but not most of the exam; 2=low amplitude and present during most of the exam (or moderate amplitude and present during some of the exam); 3=moderate amplitude and present during most of exam; or 4=maximal amplitude and present during most of exam.
AIMS, Abnormal Involuntary Movement Scale; TD, tardive dyskinesia.

Guy W. *ECDEU Assessment Manual for Psychopharmacology*: Revised (DHEW publication number ADM 76-338). National Institute of Mental Health, Psychopharmacology Research Branch; 1976:534-537.

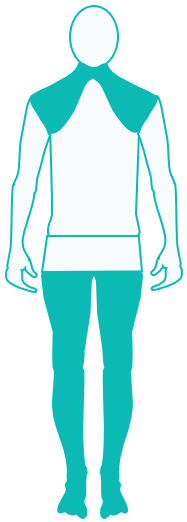
Impact of AIMS Score on TD Presentation

- AIMS is not a linear scale
- Each total AIMS score can represent a range of clinical presentations **with varying impact on each individual**

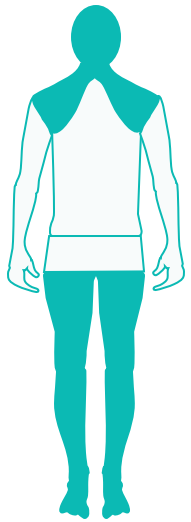
AIMS Score of 4



1 body region



2 body regions
(each score a 2)



4 body regions
(each score a 1)

Guy W. ECDEU Assessment Manual for Psychopharmacology: Revised (DHEW publication number ADM 76-338). Rockville, MD; National Institute for Mental Health, Psychopharmacology Research Branch, 1976: 534-537.

TD Guidelines:
2013 American Academy of Neurology (AAN)

- Some evidence to support the use of these medications to treat TD:
  - Clonazepam
  - Amantadine
  - Ginkgo biloba extract
  - Tetrabenazine
- Insufficient evidence to support or refute the use of other therapies, such as:
  - Unclear whether withdrawing antipsychotic treatment improves TD
    - Antipsychotics both produce and mask the symptoms of TD
    - Antipsychotic withdrawal may cause TD worsening
    - Patients may also risk psychotic relapse
  - Unclear whether switching from a first generation to a second generation antipsychotic can improve TD
  - Vitamins E and B6, melatonin
  - Anticholinergics (e.g., benztropine) or cholinergics (e.g., choline, donepezil)
  - GABA agonists (e.g., baclofen)
  - Electroconvulsive therapy (ECT) or deep brain stimulation (DBS)

Bhidayasiri R, et al. *Neurology.* 2013;81(5):463-469.

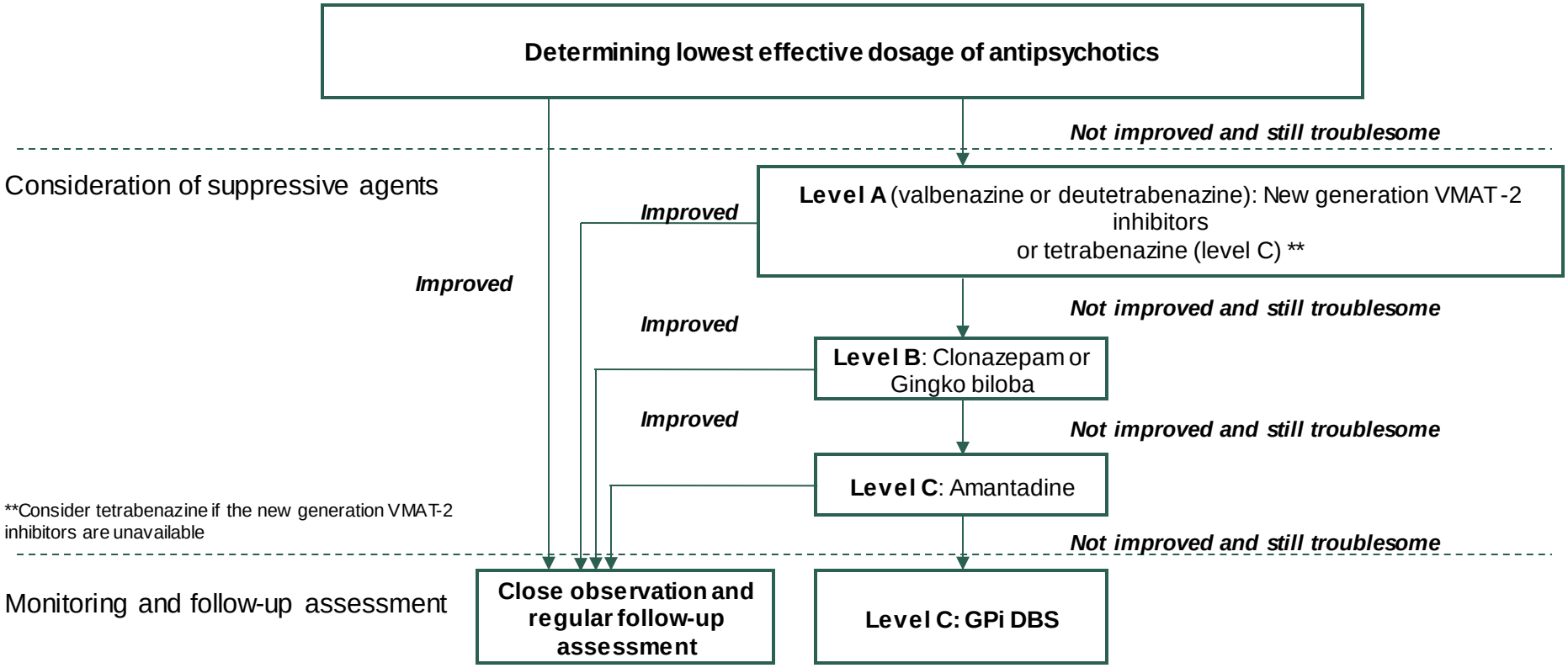
2018 Systematic Review: Updating the Recommendations for Treatment Guidelines

- Latest 2013 AAN guidelines were published before available treatments approved for adults with TD
  - This review aimed to update the evidence-based recommendations for the management of TD
- Valbenazine and deutetrabenazine approved for adults with TD were given a Level A classification and are recommended as first line treatment
- Included in the systematic review is a practical algorithm for treatment of TD

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

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.

AAN Guideline – Classification of Recommendations

Category	Definition
LEVEL A	Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires ≥2 consistent Class I studies.)*
LEVEL B	Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires ≥1 Class I study or 2 consistent Class II studies.)
LEVEL C	Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires ≥1 Class II study or 2 consistent Class III studies.)
LEVEL U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met, (2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

AAN, American Academy of Neurology.

Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

AAN Guideline – Levels of Evidence

Category	Definition
Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks 1 criterion from A–E (next slide) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets B–E (next slide). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed or independently derived by objective outcome measurement.*
Class IV	Studies not meeting Class I, II or III criteria including consensus or expert opinion

*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

AAN, American Academy of Neurology.

Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

Class I Criteria for Levels of Evidence

A. Concealed allocation
B. No more than 2 primary outcomes specified
C. Exclusion/inclusion criteria clearly defined
D. Adequate accounting for dropouts (with ≥80% of enrolled participants completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
E. For noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs, the following are also required*:
   1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
   2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
   3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
   4. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.
F. For crossover trials, both period and carry-over effect examined and statistical adjustments performed, if appropriate.

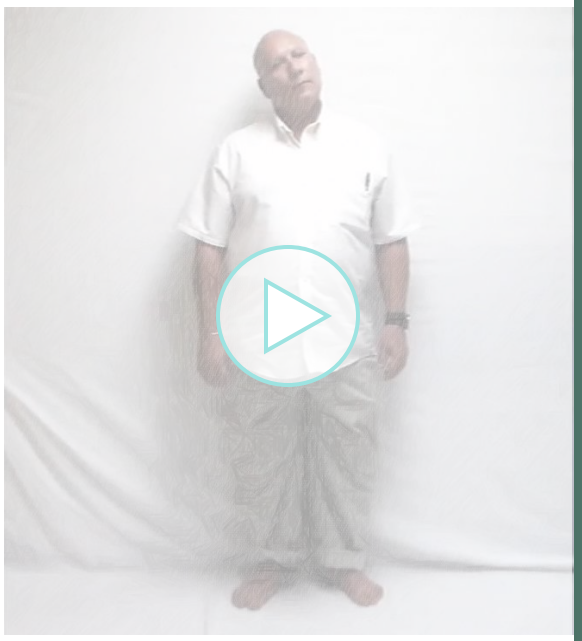
*Note that numbers 1–3 in Class IE are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Bhidayasiri R, et al. *Neurology*. 2013;81(5):463-469.

Moderate Cervical & Jaw

Open Mouth & Tongue

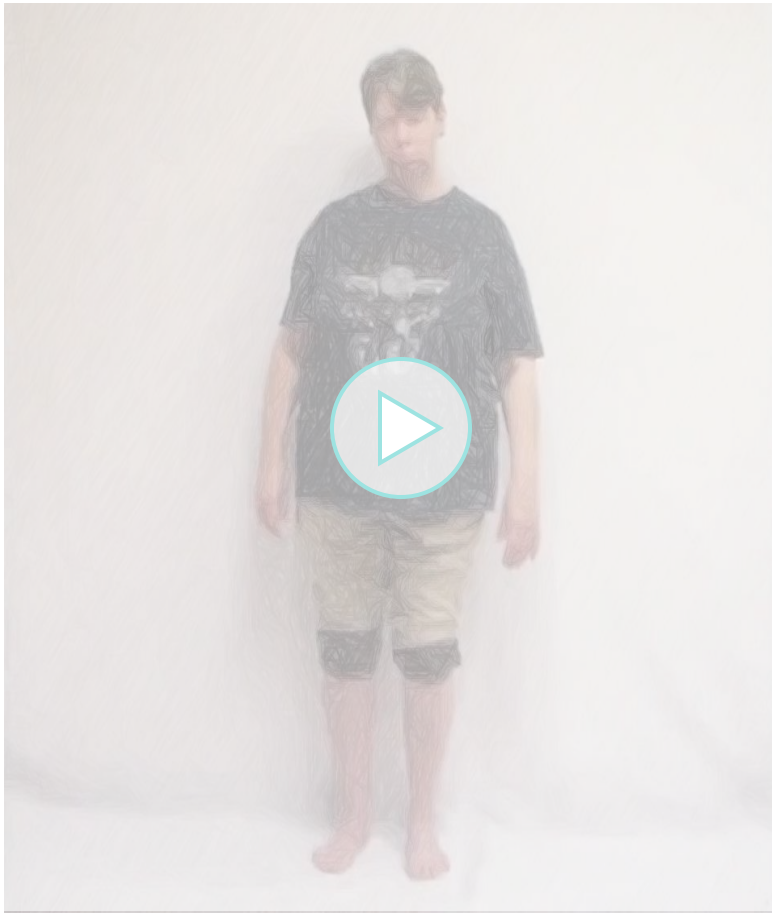
Neck, Shoulder, Hands (Standing and Walking)



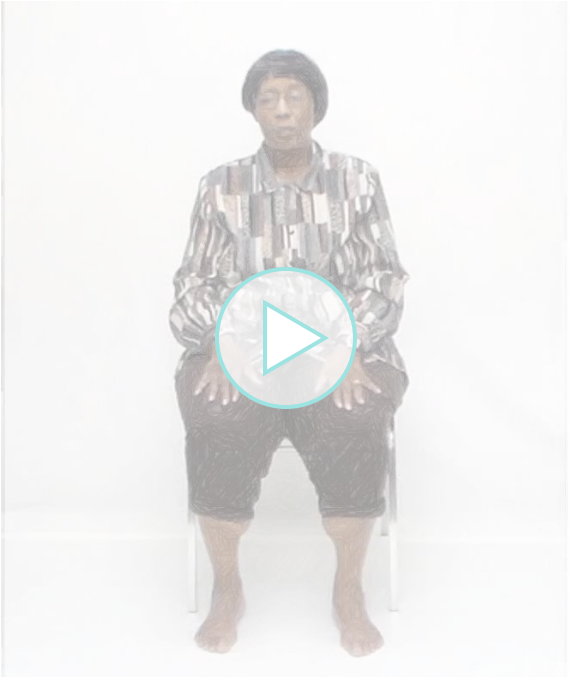
Oral-Buccal-Lingual and Legs

Sitting

Standing



Mild Jaw and Hand



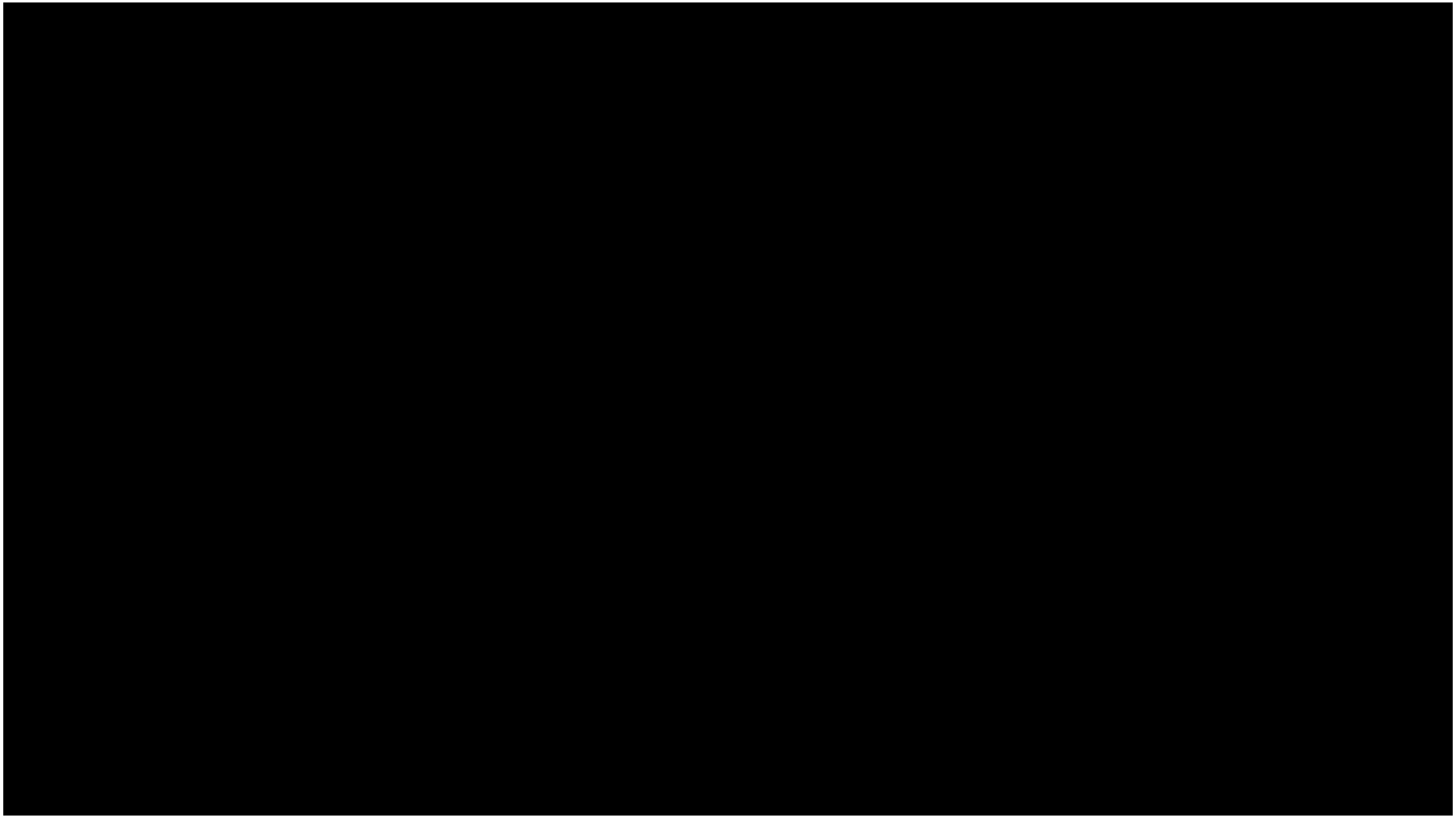
Activation With Hand Movement

Increased Blinking and Jaw Activation

Leg and Shoulder Dyskinesia

Facial Grimacing and Head Nodding

TD Mechanism of Disease Video



[Presenters' names (Field Medical personnel) and Contact Info]

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Introductory Questions

Introductory Question

How many years have you been in clinical practice?

- 1-5 years
- 6-10 years
- 11-15 years
- 16 or greater
- N/A

Introductory Question

What is your primary practice area?

- Primary care
- Psychiatry
- Pediatrics
- Geriatrics
- Neurology
- Academia
- Student/Resident
- Other (please specify)

Introductory Question

In your practice, approximately what percentage of patients are prescribed an antipsychotic medication?

- 0-25%
- 25-50%
- 50-75%
- 75-100%
- N/A

Introductory Question

How confident do you feel in differentiating abnormal movement secondary to dopamine-receptor blocking agents (DRBAs) (akathisia, dystonia, etc.), especially tardive dyskinesia?

- Very confident
- Somewhat confident
- Not confident
- Not sure

Introductory Question

The 2020 American Psychiatric Association practice guideline for the treatment of schizophrenia recommend the clinical assessment of involuntary abnormal movements:

- At baseline and every 6 months in patients taking FGA's and every 12 months in patients taking SGA's
- At baseline and every visit
- At baseline and every 3 months in patients taking FGA's and every 6 months in patients taking SGA's
- There are no guidelines

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic

Introductory Question

Who do you routinely screen for TD? (choose all that apply)

- All patients on antipsychotics
- Patients who have abnormal movements
- Patients who voice a concern about any abnormal movements
- Patients with high risk factors (history of DIMDs, older age, female gender, post-menopausal, substance abuse, etc.)
- Not screening

TD, tardive dyskinesia; DIMDs, drug-induced movement disorders.

Introductory Question

How often do you screen for TD? (choose all that apply)

- Annually
- Once every 6 months
- When symptoms are present
- Every clinical encounter
- Not screening

TD, tardive dyskinesia.

Introductory Question

To what degree has telepsychiatry impacted your ability to effectively screen for TD?

- None
- Somewhat
- Significantly
- I do not screen for TD via telepsychiatry

TD, tardive dyskinesia.

Summary Questions

Summary Question

How confident do you feel in differentiating abnormal movement secondary to dopamine-receptor blocking agents (DRBAs) (akathisia, dystonia, etc.), especially tardive dyskinesia?

- Very confident
- Somewhat confident
- Not confident
- Not sure

Summary Question

The 2020 American Psychiatric Association practice guideline for the treatment of schizophrenia recommend the clinical assessment of involuntary abnormal movements:

- At baseline and every 6 months in patients taking FGA's and every 12 months in patients taking SGA's
- At baseline and every visit
- At baseline and every 3 months in patients taking FGA's and every 6 months in patients taking SGA's
- There are no guidelines

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic

Summary Question

Who will you routinely screen for TD? (choose all that apply)

- All patients on antipsychotics
- Patients who have abnormal movements
- Patients who voice a concern about any abnormal movements
- Patients with high risk factors (history of DIMDs, older age, female gender, post-menopausal, substance abuse, etc.)
- Not screening

TD, tardive dyskinesia; DIMDs, drug-induced movement disorders.

Summary Question

How often will you screen for TD? (choose all that apply)

- Annually
- Once every 6 months
- When symptoms are present
- Every clinical encounter
- Not screening

TD, tardive dyskinesia.

Program Feedback

Program Feedback

Which of the following do you find most helpful in helping you better differentiate TD from other DRBA-induced movements? (choose all that apply)

- Patient videos so I can see what the movements look like, and present them to patients and caregivers
- More training on conducting an AIMS examination and other assessment strategies so I know how to score the severity of TD
- More education on the pathophysiology of TD so I can understand the mechanism of the condition
- Better understanding of the characteristics and features of individual DRBA-induced movement disorders

TD, tardive dyskinesia.

Program Feedback

Were there any topics you wish had been covered in today's program (if so, please describe)?

- No
- Yes, _____

TD, tardive dyskinesia.

Program Feedback

As a result of your participation in this session, will you make a change in your practice?

- Yes
- Uncertain
- No

TD, tardive dyskinesia.

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