MED-MSL-TD-US-0095 v8

Approaches to Tardive Dyskinesia (TD) Treatment

2020 American Psychiatric Association (APA) Guideline

2013 American Academy of Neurology (AAN) Guideline

2018 Systematic Review

NEUROCRINE® BIOSCIENCES

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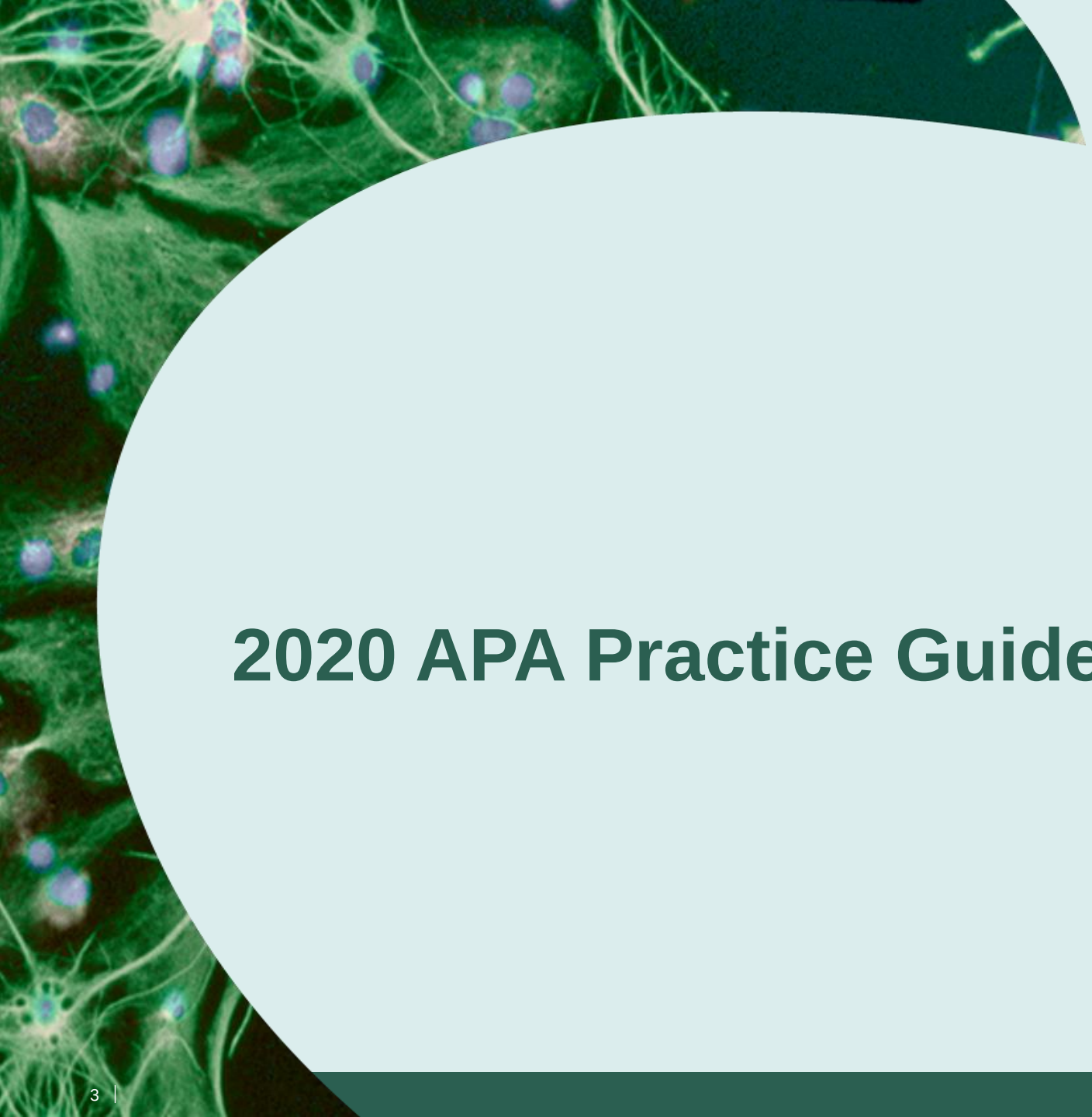


2020 APA Practice Guideline

2020 APA Guideline: TD Recommendations

Reversible VMAT2 inhibitors are recommended in patients with moderate to severe or disabling TD

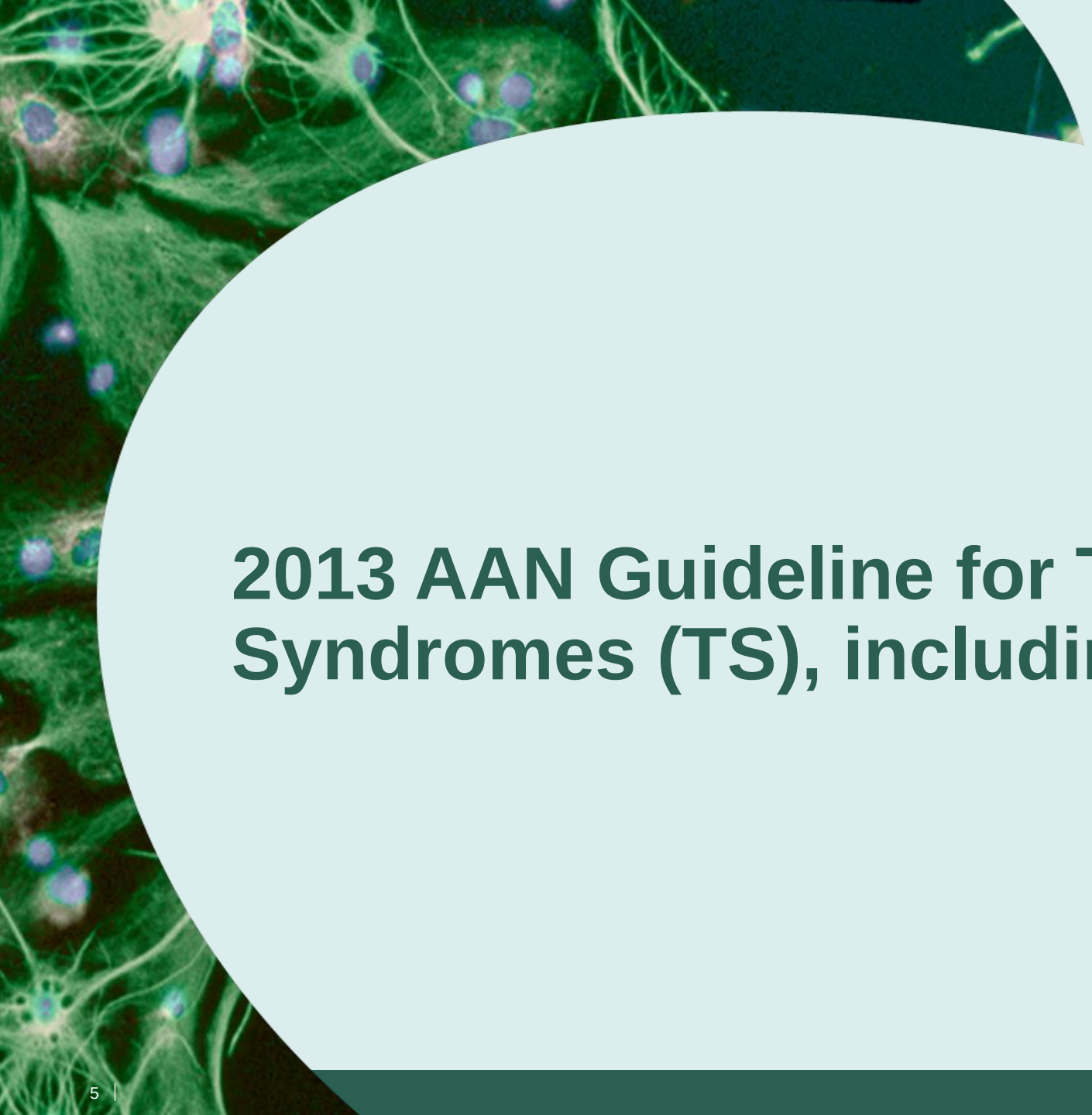
VMAT2 inhibitors can also be considered for patients with mild TD

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.



2013 AAN Guideline for Treatment of Tardive Syndromes (TS), including TD

2013 AAN Guideline: Background

- TS is an umbrella term for a group of delayed-onset, often persistent motor symptoms associated with the use of dopamine receptor blocking agents
- TD is associated with prolonged use of dopamine receptor blocking agents (DRBAs), such as antipsychotics
- TD is a persistent, uncontrolled hyperkinetic movement disorder
- At the time of the 2013 TD AAN Guideline development, there were no treatments indicated for adults with TD
- Off-label use of drugs for managing TD were given a recommendation of B or lower

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

2013 AAN Guideline: Overview

- 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 treatment strategies, 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 typical (first generation antipsychotic) to an atypical (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.

2013 AAN Guideline: Summary of Selected Agents for Off-Label Use for TD

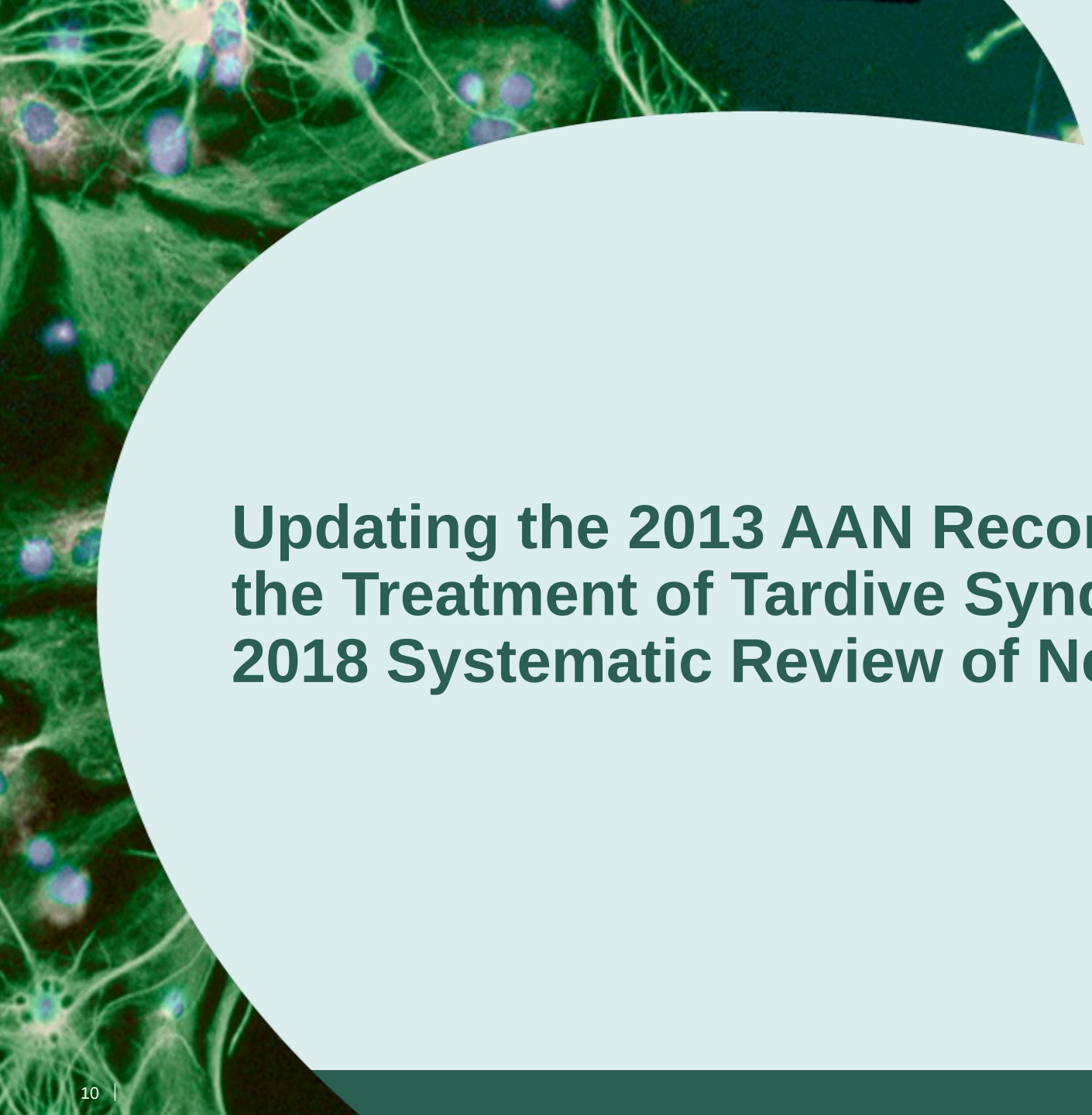
Benztropine	Amantadine	Clonazepam
• Level U recommendation • Insufficient data to determine its effectiveness • No Class I studies	• Level C recommendation • May be considered for short term use with neuroleptics • No Class I studies	• Level B recommendation • Should be considered for short term use (~ 3 months)

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

2013 AAN Guideline: Other Questions to Address

Questions	2013 AAN Guideline: Evidence[1]
Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TD treatment?	Data are insufficient to support or refute TD treatment of DRBA withdrawal (Level U)
Does switching from typical to atypical DRBAs reduce TD symptoms?	Data are insufficient to support or refute TD treatment by changing to atypical antipsychotics (Level U)
Do patients with TD benefit from chemodenervation with botulinum toxin (BoNT)?	Data are insufficient to support or refute BoNT use to treat TD symptoms (Level U)
Do patients with TD benefit from surgical therapy?	Data are insufficient to support or refute pallidal deep brain stimulation use in treating TD (Level U)

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



Updating the 2013 AAN Recommendations for the Treatment of Tardive Syndromes: 2018 Systematic Review of New Evidence

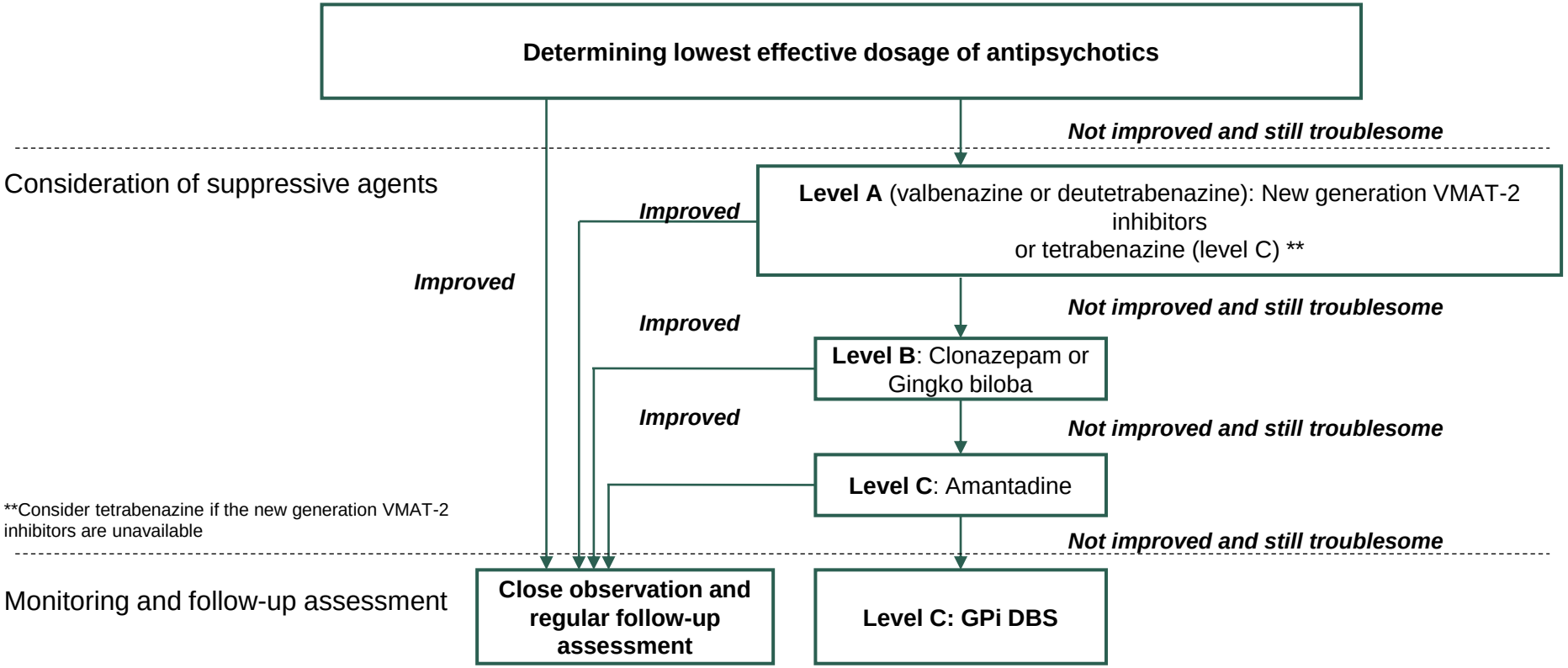
2018 Systematic Review: Background

- 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.

2018 Systematic Review: Summary of Selected Agents for Off-Label Use for TD

Benztropine[1,2]

- 2018 review: No changes
- 2013 Guideline:
  - Level U recommendation
  - Insufficient data to determine its effectiveness
  - No Class I study

Amantadine[1,2]

- 2018 review: No changes
- 2013 Guideline:
  - Level C recommendation
  - May be considered for short term use with neuroleptics
  - No Class I study

Clonazepam[1,2]

- 2018 review: No changes
- 2013 Guideline:
  - Level B recommendation
  - Should be considered for short term use (~ 3 months)

1. Bhidayasiri R, et al. *Neurology.* 2013;81(5):463-469; 2. Bhidayasiri et al. *J Neurol Sci.* 2018;389:67-75.

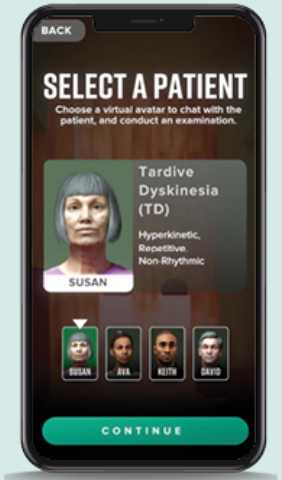
2018 Systematic Review: Other Questions to Address

Questions	2013 AAN Guideline: Evidence[1]	2018 Systematic Review[2]
Is withdrawal of dopamine receptor blocking agents (DRBAs) an effective TD treatment?	Data are insufficient to support or refute TD treatment of DRBA withdrawal (Level U)	No Changes
Does switching from typical to atypical DRBAs reduce TD symptoms?	Data are insufficient to support or refute TD treatment by changing to atypical antipsychotics (Level U)	No Changes
Do patients with TD benefit from chemodenervation with botulinum toxin (BoNT)?	Data are insufficient to support or refute BoNT use to treat TD symptoms (Level U)	No Changes
Do patients with TD benefit from surgical therapy?	Data are insufficient to support or refute pallidal deep brain stimulation use in treating TD (Level U)	Pallidal deep brain stimulation possibly improves TD and might be considered as a treatment for intractable TD (Level C)

1. Bhidayasiri R, et al. *Neurology.* 2013;81(5):463-469; 2. Bhidayasiri et al. *J Neurol Sci.* 2018;389:67-75.

FREE EDUCATIONAL RESOURCES on Tardive Dyskinesia and Other Drug-Induced Movement Disorders

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

This educational content was sponsored and developed by Neurocrine Biosciences, Inc.
DIMD, drug-induced movement disorder; DRBA, dopamine receptor-blocking agent; TD, tardive dyskinesia.

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