Neuroscience Education Institute

# IT MATTERS TO ME: IMPROVING THE MONITORING, DIAGNOSIS, AND TREATMENT OF TARDIVE DYSKINESIA

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# Learning Objectives

1. Recognize the potential impact of TD on medical, psychological, and psychosocial factors important for patient outcomes and quality of life
2. Collaborate with patients, caregivers, and the care team to improve the early detection of TD in order to increase treatment adherence and improve patient outcomes
3. Collaborate with patients and members of the care team to implement treatments for TD based on the individual needs of the patient

# Diagnosis of TD

# What Is Tardive Dyskinesia?

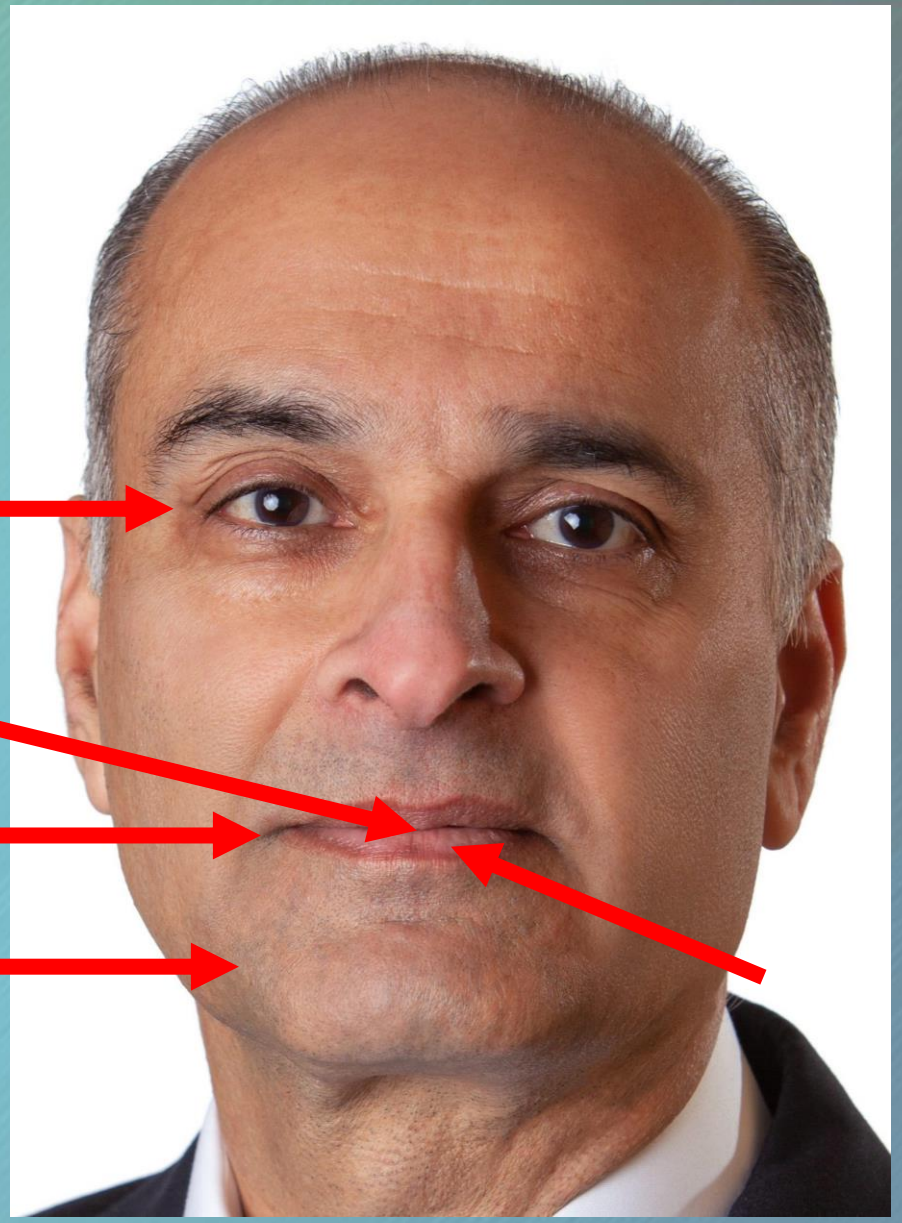
- Involuntary **choreoathetoid** movements usually associated with lower facial and distal extremity musculature (truncal movements also possible)
  - **Chorea**: Quick, irregular, non-stereotyped movements
  - **Athetosis**: Slow, writhing, serpentine movements
- Not associated with direct sensory problems
- Of considerable clinical, medical, and legal concern because of potential persistence despite drug discontinuation

# 1. Which Parts of the Body?

- Majority are on the **face**: perioral, bucco-lingual
- But **let's not miss other parts** of the body!

# The Face

- **Eyes**: Squeezing
- **Mouth**: Pulling back of the corners of the mouth
- **Lips**: pouting, puckering, smacking
- **Tongue**: Twisting, protruding in and out, “bon-bon” sign
- **Jaw**: Lateral movement, chewing movement



# 2. What Type of Movements?

Tip: Compare all of this with a hand tremor

Type of movements

**Variable** (“Polymorphic”)

Speed and pattern

**Irregular** = NOT repetitive and rhythmic

**Relatively slow** (often); often, about one per second

# 3. Patients' Experience of the Movements

**No pain** (unlike acute dystonia)

**No awareness (often)** — until pointed out or become severe

Hauser RA et al. CNS Spectr 2022;27(2):208-17; Emsley R et al. Eur Psychiatry 2011;26(5):293-6; Arango C et al. Am J Psychiatry 1999;156(7):1097-9; Macpherson R, Collis R. Br J Psychiatry 1992;160:110-2.

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# 4. Over What Time Frame Do They Develop?

- **After at least a few months** on a D2 antagonist
- May develop after a **shorter period in older persons**
- (Actually, **no minimum duration**)
- **Evolves SLOWLY** (over weeks or months)
- Contrast with acute dyskinesia and “withdrawal-emergent” dyskinesia

Hauser RA et al. CNS Spectr 2022;27(2):208-17; American Psychiatric Association. Diagnosis and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013.

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# “Withdrawal-Emergent Dyskinesia”

- Can occur after an **antipsychotic is suddenly stopped**
- Mainly in **children**
- Instead of oro-bucco-lingual, mainly in the **neck, trunk, limbs**

Savitt D, Jankovic J. J Neurol Sci 2018;389:35-42.

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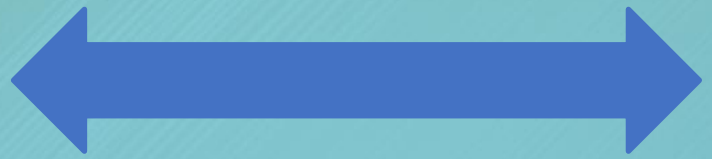
# Risk Factors for TD

# Key Risk Factors



The person

The treatment

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# Key Risk Factors of TD: The Person

1. Age: Older than 55 yrs. old; 5X risk of TD
2. Biological Sex: Female—small increase in risk of TD
3. Duration of Illness: Longer duration of illness increases risk of TD
4. Prominent negative symptoms

Hauser RA et al. CNS Spectr 2022;27(2):208-17; Liddle PF et al. Br J Psychiatry 1993;163:776-80; Solmi M et al. J Neurol Sci 2018;389:21-7; Yassa R, Jeste DV. Schizophr Bull 1992;18(4):701-15.

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# Key Risk Factors of TD: The Person

5. Co-morbidities:
   Psychiatric—mood disorder, substance use disorders (includes smoking)

   Neurological / Brain Related—central nervous system injury, intellectual disability

   Other Medical—diabetes

Solmi M et al. J Neurol Sci 2018;389:21-7.

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# Key Risk Factors: Treatment Related

1. First-generation (“typical”) antipsychotics
2. High-potency D2 receptor antagonists
3. Higher cumulative exposure—dose and duration
4. Previous side effects from antipsychotic treatments:
   - Dystonia
   - Parkinsonism
   - Akathisia

American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, 3rd ed. Washington, DC: American Psychiatric Association; 2020; Solmi M et al. J Neurol Sci 2018;389:21-7; Carbon M et al. World Psychiatry 2018;17(3):330-40; O‘Brien A. Int J Geriatr Psychiatry 2016;31(7):683-93; Correll CU et al. Am J Psychiatry 2004;161(3):414-25; Dolder CR, Jeste DV. Biol Psychiatry 2003;53(12):1142-5.

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# What Risk Assessment Could Do

## Influence our choice of medication

- Avoid antipsychotics (e.g., mood disorders)
- Avoid first-generation antipsychotics
- Avoid strong D2-blocking antipsychotics
- Minimizing dose/duration of treatment

## Influence documentation & monitoring:

- Documentation of informed consent—e.g., that TD is a potentially *irreversible* side effect of treatment
- More frequent screening for TD

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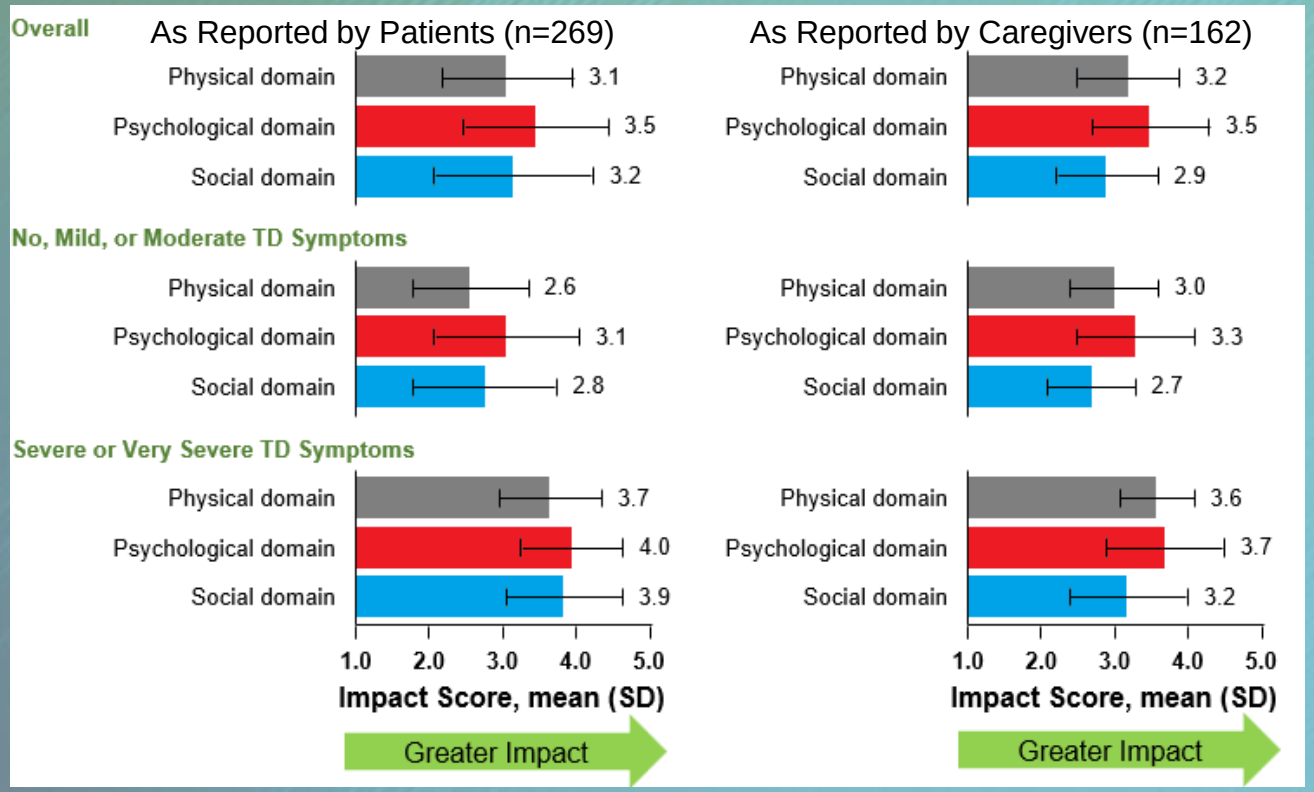
# Impact of TD

# Impact of TD on Physical, Social, and Psychological Factors




- Even mild TD imposes burden on patient's well-being and psychosocial function, along with their physical functioning
- TD also affects how patients manage their underlying condition and medication adherence
- Large impact of TD on older patients who live in assisted living facilities and nursing homes

Jain R et al. J Patient Rep Outcomes 2023;7(1):122.

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# Consequences of Delayed TD Diagnosis

- TD impacts the whole body
  - TD can impact mental health
  - TD can impact TMJ pain, oral health, dysphagia, ADL independence
- Delay in diagnosis of TD has the following consequences:
  - Decline if underlying mental and physical issues
  - Misdiagnosis of TD as another medication-induced movement disorder
    - Possible iatrogenesis due to misdiagnosis

Jain R, Correll CU. J Clin Psychiatry 2018;79(2):20745; Hauser RA, Truong D. J Neurol Sci 2018;389:1-3; Kremens DE. J Clin Psychiatry 2019;81(1):27640.

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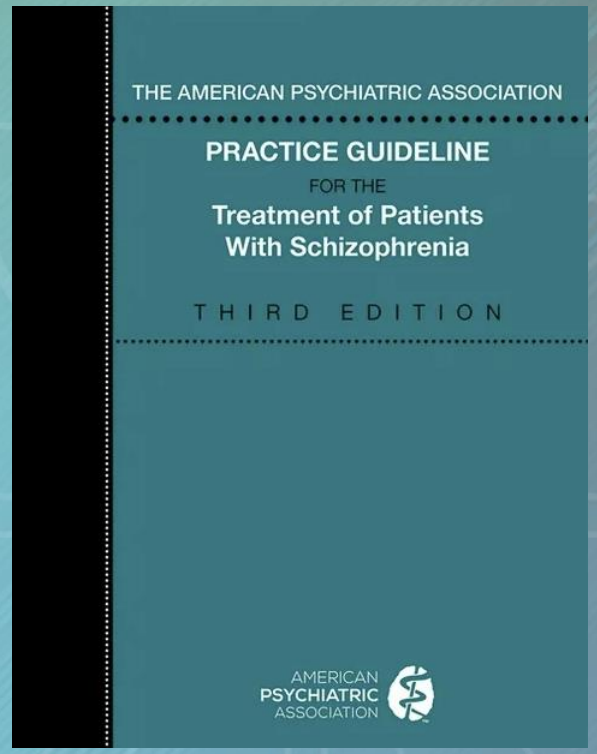
# Screening and Monitoring for Tardive Dyskinesia

# TD Screening Guidelines

The APA recommends for all patients treated with antipsychotics:

1. **Clinical assessment** of TD at baseline and every follow up visit
2. **Structured assessment** (e.g., AIMS, DISCUS) at least every 6 months in high-risk patients and every 12 months in other patients




Keepers GA et al. Am J Psychiatry 2020;177(9):868-72.

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# MONITOR: Regular Screening

1. **Informal** evaluation
2. **Semi-structured** evaluation
3. **Formal** evaluation (usually using the Abnormal Involuntary Movement Scale or AIMS)

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

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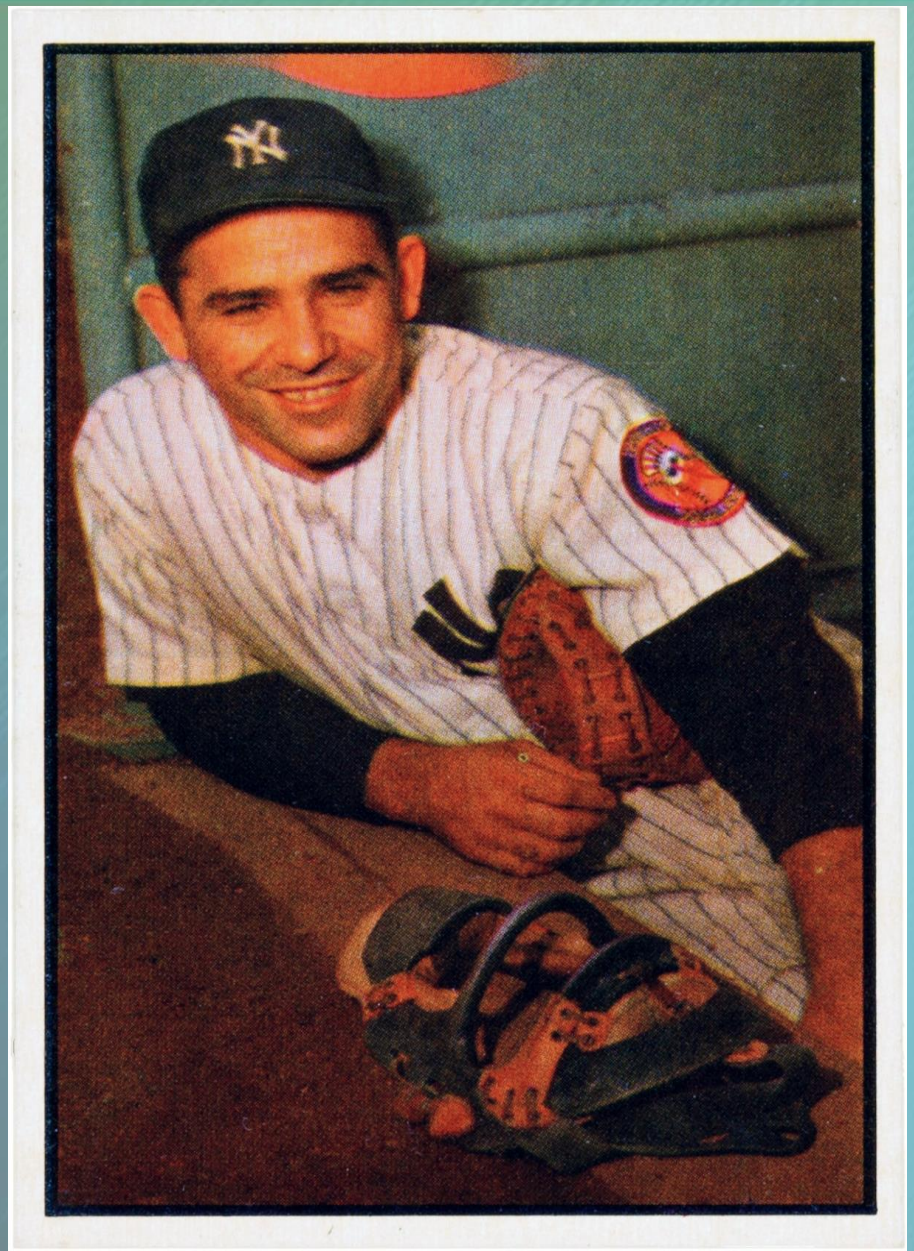
# Informal Evaluation



"You can observe a lot by just watching."

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# Informal Evaluation: WHEN

1. **Baseline**

   At baseline before starting an antipsychotic
   - To document any pre-existing TD
   - Changes the discussion of risk

2. **Every visit**[1]

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

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# Informal Evaluation: HOW

- No extra time needed
- But very useful!

1. Sitting at rest
2. **Walking in/out** (fingers, hands, arms)

# Semi-Structured Evaluation

1. **Only SOME aspects of AIMS examination procedure**

   For example:

   - Open the mouth and hold it open for a few seconds while keeping the tongue in
   - Stick out their tongue and hold it out for a few seconds
   - Extend both arms out with palms down

2. **Ask!**

   - Ask **family members**
   - Ask the patient: **Has anyone commented?**

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# Systematic Examination for TD

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# The Aims of AIMS

**Abnormal Involuntary Movement Scale (AIMS)**

1. Use of its examination **method**
2. For quantifying the **severity**
3. For **documenting** the detailed assessment

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# Full AIMS Exam: How Often?

At higher risk (elderly, on first-generation antipsychotics)

- **At least every 6 months**

Not at higher risk:

- **At least every 12 months**

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

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# The 3s of AIMS

**3** things needed before starting

**3** positions in which to examine

**3** activation measures to use

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# THREE Things Are Needed for AIMS

**1. Appropriate Chair**

- Firm seat
- No armrests
- Hands hanging between legs

**2. Enough space** to walk back and forth

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# 3. Ask them to take shoes and socks off

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# THREE Positions in Which to Examine

## 1. Sitting

## 2. **Standing—<u>sideways</u>**

## 3. **Walking**

# THREE Activation Measures

- Very important!
- Often reveal involuntary movements that would otherwise be missed

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# Activation 1: Tap Thumb With Each Finger

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# THREE Possible Errors

**Correct method**

- **One hand at a time**
- Need a bit of time: about **10 to 15 seconds per finger**
- **Look at OTHER parts** (e.g., face, lower extremities), NOT at the hands

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# Activation 2: Extend Arms Out

- Extend both arms out with **palms down**
- **Look at OTHER parts** (e.g., mouth, trunk, legs), NOT at the hands

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# Activation 3: Walk

- **Very important** part of the examination
- Involuntary movements of fingers/hands/arms **<u>most commonly</u>** revealed with this
- But usually skipped ☹

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Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

# Activation 3: Walk

Find a place with enough space

*Instructions*

- "Walk a few steps, turn around, and walk back"
- "Just relax and walk normally"
- Look at the **gait** but ALSO **hands** and **arms**
- Repeat one more time

Munetz MR, Benjamin S. Hosp Community Psychiatry 1988;39(11):1172-7.

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# Practical Tools to Assist With Monitoring

## The MIND-TD Questionnaire

MIND·TD®

**The MIND-TD Questionnaire** is intended to facilitate a dialogue about abnormal movements with patients at risk for tardive dyskinesia. Diagnosis of tardive dyskinesia should be based on the patient's medical history, symptoms, and the clinician's best judgment.

**PART 1** This section may be administered by the treating clinician or by a medical staff member ahead of the visit. It can be administered in person or via video or audio-only telehealth.

**Use this questionnaire as part of a routine visit for a patient with any of the following:**

- ☐ Patients who are taking or have ever taken an antipsychotic medication (first or second generation)
- ☐ Patients who are taking anticholinergic medications, such as benztropine or trihexyphenidyl, in conjunction with current or past antipsychotic usage
- ☐ Patients who have a current diagnosis of tardive dyskinesia

| | | | |
|---|---|---|---|
| **M** | **Movement** Do you have extra or unwanted movements in your body? | ☐ yes | ☐ no |
| **I** | **Impact** Do you feel embarrassed or self-conscious about movements in your body? | ☐ yes | ☐ no |
| **N** | **Notice** Has someone else seen extra movements in your body? | ☐ yes | ☐ no |
| **D** | **Daily Activities** Do any movements cause problems during your daily routine? | ☐ yes | ☐ no |

**PART 2** This section should be administered by the treating clinician. The "Differentiate" section requires visual observation of the patient, either in person or via video telehealth.

**T** **Thorough Interview**

**Ask patient about:**

- ☐ Problems with eating, drinking, or swallowing
- ☐ Sores in the mouth, teeth grinding or dental issues, mouth noises (for example, lip smacking, tongue clicking)
- ☐ Problems speaking or involuntary grunting
- ☐ Difficulty gripping objects (for example, a zipper, buttons, silverware, cup, toothbrush)
- ☐ Change in handwriting or difficulty typing
- ☐ Foot tapping or fidgeting movement of the legs
- ☐ Difficulty walking or loss of balance
- ☐ Do they notice their big toe goes up in the air when they have their socks off?
- ☐ Do their legs move or twist, or do their knees knock when they sit?

**Instruct patient to say:**

- ☐ LaLaLaLaLaLaLaLaLaLa
- ☐ KaKaKaKaKaKaKaKaKaKa
- ☐ MaMaMaMaMaMaMaMaMa

***Listen for articulation problems.***

Lundt L et al. CNS Spectrums 2022;23(2):233-4.

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# TD Treatment Guidelines and Practical Considerations

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# Role of Anticholinergics in the Setting of TD

- AAN Guidelines: There are **insufficient data to recommend anticholinergics** for the treatment of TD[2]

- Benztropine is indicated as an adjunct in the treatment of all forms of parkinsonism and is useful in the control of extrapyramidal disorders (except TD) due to neuroleptic drugs
- **Benztropine is not recommended for use in patients with TD**

- **Benztropine is not recommended for use in patients with TD**

- APA Schizophrenia Guideline: Anticholinergic medications **do not improve and may even worsen TD**[4]

- Delphi Panel Consensus 2020 As part of TD management, **providers should consider modifying anticholinergic agents** (e.g., reduce dose, taper off)[3]

**1.** Benztropine mesylate. Package insert. Akorn; 2017. **2.** Treatment of tardive syndromes. American Academy of Neurology. Published 2013. Accessed May 7, 2021. https://www.aan.com/Guidelines/Home/GetGuidelineContent/613 **3.** Caroff SN et al. J Clin Psychiatry 2020;81(2):19cs12983 **4.** Keepers GA et al. Am J Psychiatry 2020;177(9):868-72.

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# TD Treatment: APA Guidelines

1. APA recommends that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transport 2 (VMAT2)
2. Treatment with a VMAT2 inhibitor can also be considered for patients with mild TD based on patient preference, associated impairment, or effect on psychosocial functioning

**Disability is in the eye of the beholder.**
**Severity is defined by the impact of functional or quality-of-life impairment.**
**There is no minimum AIMS score required to diagnose and treat TD!**

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# American Academy of Neurology (AAN): Updated Recommendations for Treatment of Tardive Syndrome

| Level A | Level B | Level C | Level U |
|---|---|---|---|
| ***must*** *be recommended as treatment* | ***should*** *be considered as treatment* | ***might*** *be considered as treatment* | *insufficient evidence to support or refute* |
| • Deutetrabenazine<br>• Valbenazine | • Clonazepam<br>• Ginkgo biloba | • Amantadine<br>• Tetrabenazine<br>• Pallidal deep brain stimulation (intractable TD) | • Withdrawing causative agents<br>• Switching from typical to atypical dopamine receptor blocking agents (DRBA) |

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

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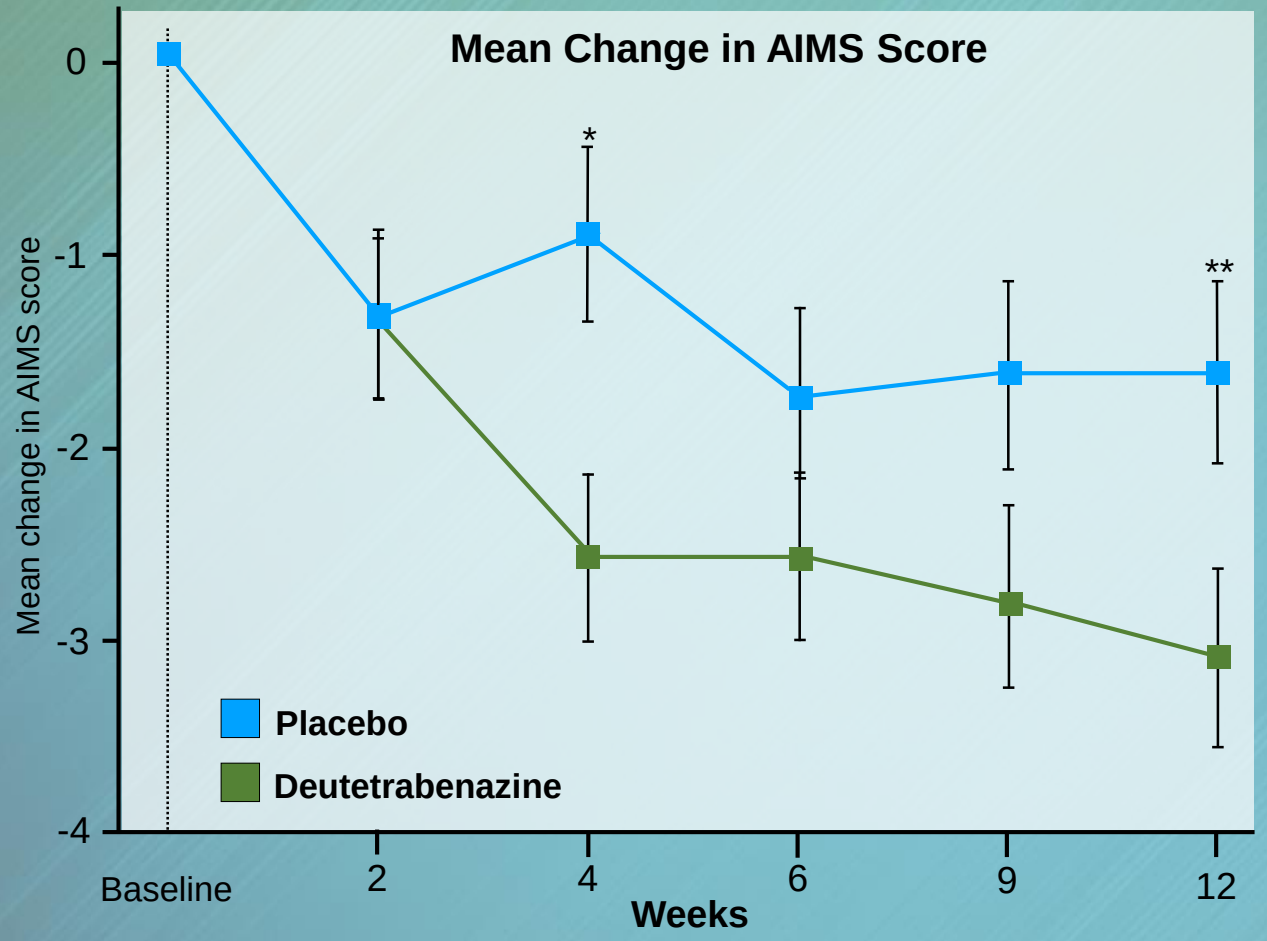
# Deutetrabenazine: Phase III
## Randomized ARM-TD Dose-Finding Trial

**Double-blind, placebo-controlled, parallel-group study**




AIMS: Abnormal Involuntary Movement Scale.

**At Week 12**

**Placebo group**
(n=59)
Decrease in mean AIMS:
1.6 (SE=0.46)

**Deutetrabenazine group**
(n=58)
Decrease in mean AIMS:
3.0 (SE=0.45)

*p*=0.019

**AEs**: somnolence, headache

Fernandez HH et al. Neurology 2017;88(21):2003-10.

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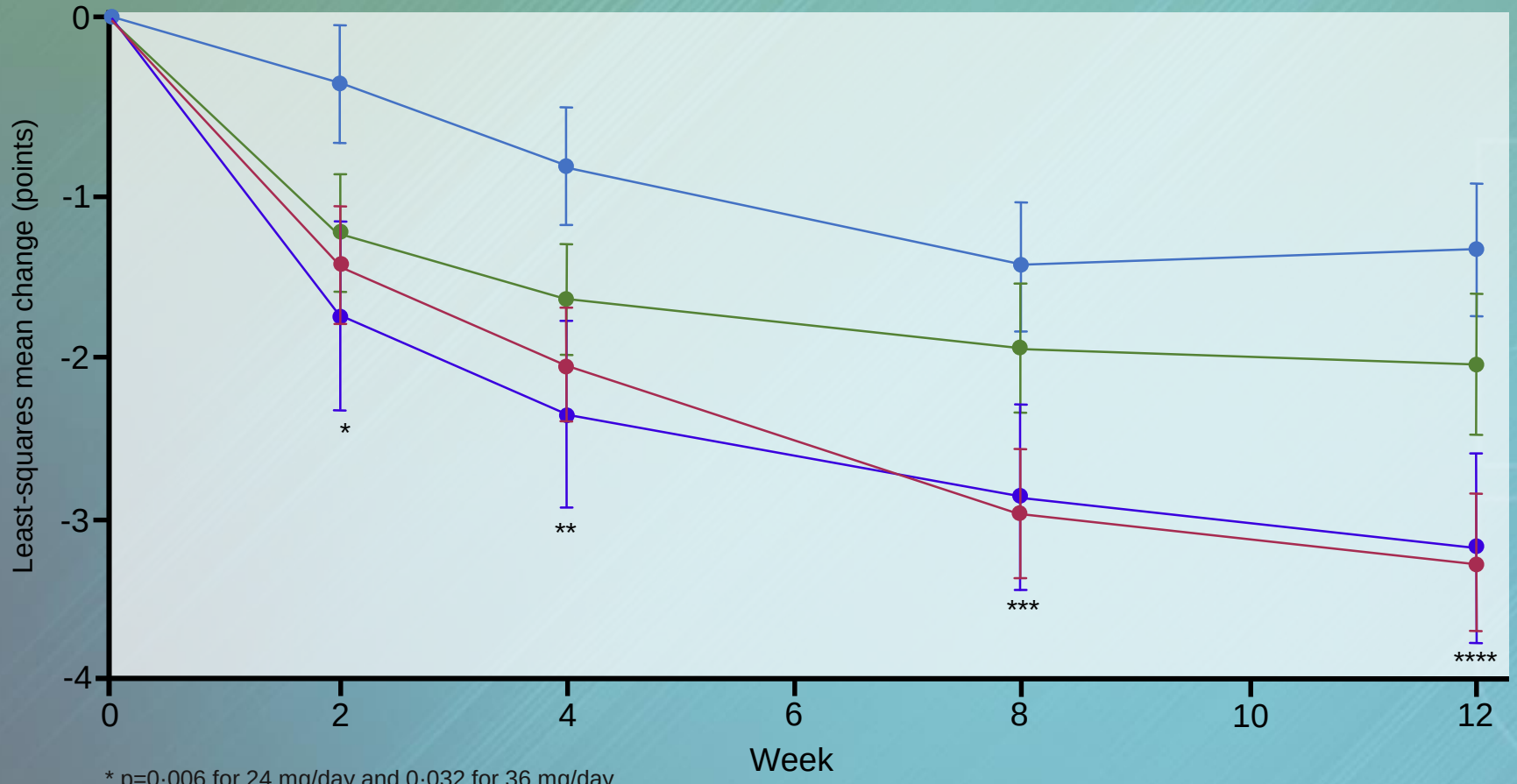
# Deutetrabenazine: Phase III
## Randomized AIM-TD Fixed-Dose Trial




* p=0·006 for 24 mg/day and 0·032 for 36 mg/day
** p=0·003 for 24 mg/day and 0·018 for 36 mg/day
*** p=0·012 for 24 mg/day and 0·008 for 36 mg/day
**** p=0·003 for 24 mg/day and 0·001 for 36 mg/day

AIMS: Abnormal Involuntary Movement Scale.

**At Week 12**

**Placebo group**
mean AIMS: -1.4 points (SE=0.41)

**Deutetrabenazine 12 mg/d**
mean AIMS: −2.1 points (SE 0.42)

**Deutetrabenazine 24 mg/d**
mean AIMS: −3.2 points (SE 0.45)

**Deutetrabenazine 36 mg/d**
mean AIMS: −3.3 points (SE 0.42)

Anderson KE et al. Lancet Psychiatry 2017;4(8):595-604.

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# **Adverse Reactions in 12-Week Placebo-Controlled Studies of** Deutetrabenazine **Reported at ≥ 2% of Patients Treated With** Deutetrabenazine

| **Adverse Reaction** | Deutetrabenazine (n=279) | Placebo (n=131) |
|---|---|---|
| Headache | 5% | 8% |
| Somnolence | 4% | 7% |
| Diarrhea | 4% | 4% |
| Nasopharyngitis | 4% | 2% |
| Fatigue | 4% | 5% |
| Insomnia | 4% | 1% |
| Anxiety | 4% | 5% |
| Upper respiratory tract infection | 3% | 4% |
| Dry mouth | 3% | 5% |
| Nausea | 2% | 7% |
| Weight increased | 2% | 3% |
| Urinary tract infection | 2% | 2% |
| Depression/dysthymic disorder | 2% | 1% |
| Akathisia/agitation/restlessness | 2% | 1% |
| Arthralgia | 2% | 1% |

Only highlighted AEs occurred at a greater rate in patients taking deutetrabenazine than in patients taking placebo

Discontinuation due to AEs occurred in 4% of patients taking deutetrabenazine vs 3% of patients taking placebo

Austedo PI: www.austedo.com

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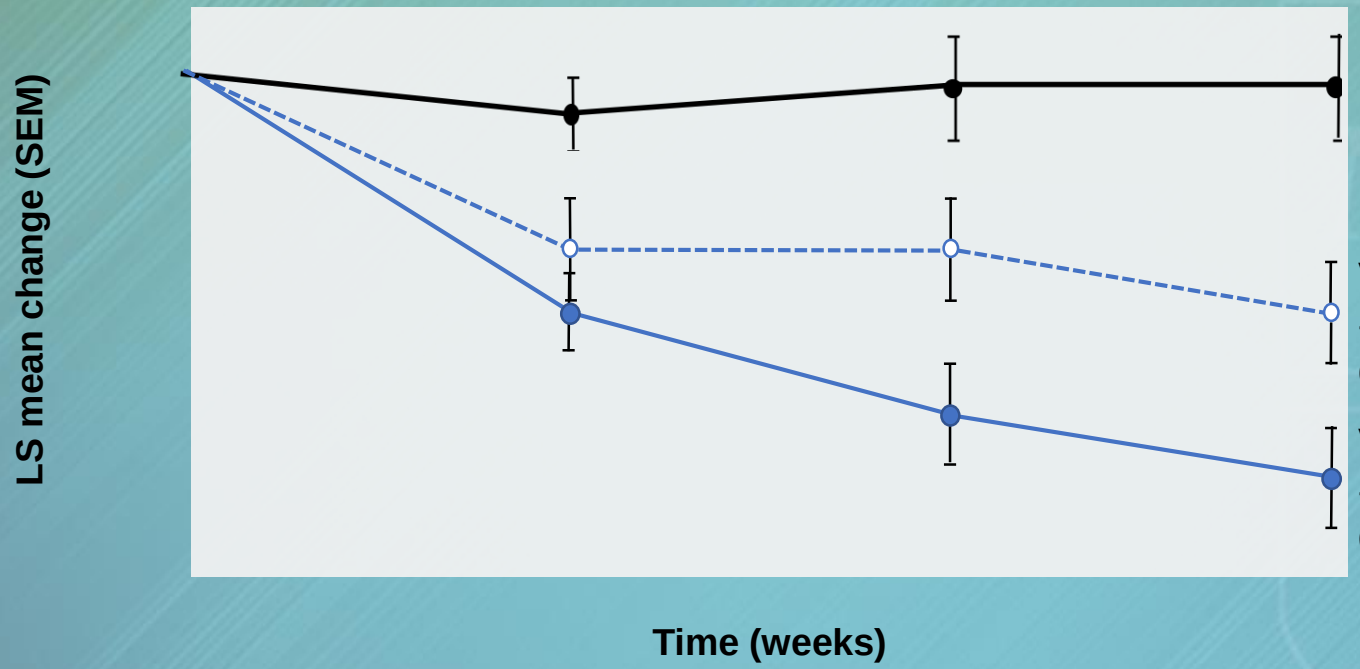
# Valbenazine Efficacy
## KINECT 3 AIMS Outcomes at Week 6

**Change from baseline in the severity of TD symptoms assessed by the Abnormal Involuntary Movement Scale (AIMS) through week 6**




**Placebo**

AIMS score (least squares [LS] mean change from baseline to week 6, MMRM):

**Valbenazine 40 mg**
-1.9 vs. -0.1 placebo; $p<0.05$; effect size, d=0.52

**Valbenazine 80 mg**
-3.2 vs. -0.1 placebo; $p<0.001$; effect size, d=0.90

**AIMS at week 6 for the valbenazine 80 mg dose was reduced 3.1 points more than placebo ($p<0.001$)**

Hauser RA et al. Am J Psychiatry 2017;174(5):476-84.

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# Valbenazine Safety and Tolerability in Short-Term Studies

**Adverse Events in 6-Week Valbenazine DBPC Studies in North America Reported at ≥ 2% and > Placebo**

| Adverse Event | Valbenazine (n=262) (%) | Placebo (n=183) (%) |
|---|---|---|
| **Somnolence** | 10.9% | 4.2% |
| **Anticholinergic effects** | 5.4% | 4.9% |
| **Balance disorders/fall** | 4.1% | 2.2% |
| **Headache** | 3.4% | 2.7% |
| **Akathisia (akathisia, restlessness)** | 2.7% | 0.5% |
| **Vomiting** | 2.6% | 0.6% |
| **Nausea** | 2.3% | 2.1% |
| **Arthralgia** | 2.3% | 0.5% |

Discontinuation due to AEs occurred in 3% of patients taking valbenazine vs 2% of patients taking placebo

AE = adverse events.

US Food and Drug Administration. Drugs@FDA: FDA-Approved Drug Products. Accessed January 19, 2023. www.accessdata.fda.gov/scripts/cder/daf/index.cfm; Horiguchi J et al. Psychiatry Clin Neurosci 2022;76(11):560-9.

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# VMAT2 Inhibitors Characteristics

| | Deutetrabenazine | Valbenazine |
|---|---|---|
| **Indication** | Adults with TD, HD chorea | Adults with TD, HD chorea |
| **Dosing** | XR: 6mg/12mg/24mg doses available<br>Maximum dose: 48mg daily<br>Dosed once daily with or without food<br>BID dosing also available | 40mg/60mg/80mg<br>80mg/day recommended dose<br>Dosed once daily with or without food |
| **Adjustment recommendations based on CYP450 Pathway** | Max daily dose 36 mg with strong CYP2D6 inhibitors or poor metabolizers of CYP2D6 | Not recommended with strong CYP3A4 inducers; contraindicated for use with another VMAT2 inhibitor or MAOIs<br>Use 40 mg dose with CYP2D6 inhibitors, poor metabolizers of CYP2D6, and strong CYP3A4 inhibitors |
| **Contraindications** | Contraindicated with hepatic impairment, use of another VMAT2 inhibitor, reserpine, or MAOIs | Contraindicated for use with another VMAT2 inhibitor or MAOIs |
| **QTc prologation** | No clinically relevant QT prolongation with recommended dosing* | No clinically relevant QT prolongation with recommended dosing* |

Valbenazine PI. Deutetrabenazine PI.

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# Key Differences Between Valbenazine (VBZ) and Deutetrabenazine (DBZ)

- Differences in their profile, different metabolites and metabolism
- VBZ—once a day taken with or without food
  - Dose 40mg, 60mg, or 80mg
  - Hepatic metabolism CYP2D6 and CYP3A4

- DBZ—2x per day taken with food
  - Dose
  - Dose range 6mg / day – 48mg / day
  - Hepatic metabolism CYP2D6

- DBZ XR—**Once a day taken with or without food**
  - Doses 6mg, 12mg, and 24mg
  - Dose range 6mg – 48mg
  - If converting from DBZ, dose the total dose in XR form

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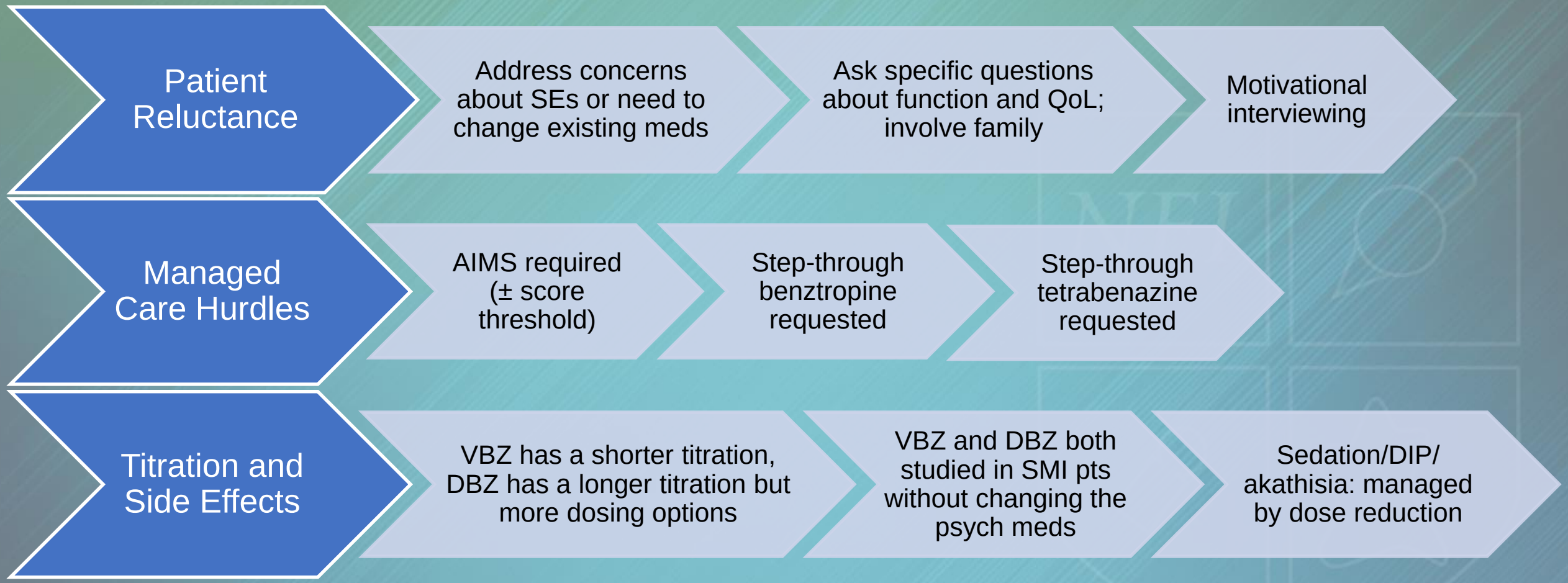
# VMAT2 Inhibitors: Practical Considerations




SE = side effect; SMI = severe mental illness.

Caroff SN. Neuropsychiatr Dis Treat 2019;15:785-94; Velligan DI et al. J Clin Psychiatry 2009;70(Suppl 4):1-46.

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# Summary

- Biggest risk factors for TD:
  1. **Older** adults
  2. **First-generation** antipsychotics
  3. Longer **duration of treatment**
- Most important when prescribing antipsychotics:
  1. Prefer **second-generation antipsychotics**
  2. **Document** informed consent
- Most important regarding diagnosis:
  1. **Early detection**: Informal examination; Semi-structured examination: Formal examination (AIMS--including **activation measures**)
  2. **Not everything that moves is TD** (but it could be)
- Most important regarding management:
  1. Slowly **taper off anticholinergic medication** if present (unless parkinsonism is also present)
  2. **Don't panic and stop the antipsychotic abruptly**
  3. **Consider adding a VMAT inhibitor**

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# Posttest Question 1 of 3

Anticholinergics can be beneficial in?

1. Tardive dyskinesia
2. Managing medication-induced parkinsonism
3. Akathisia
4. All of the Above
5. None of the above

# Posttest Question 2 of 3

What is the key difference between deutetrabenazine and valbenazine?

1. Hepatic vs renal metabolism
2. Mechanism of action
3. Potency
4. None of these is the key difference

# Posttest Question 3 or 3

Which of the following is not a risk factor for TD?

1. Prominent negative symptoms in the disease
2. Age—under 55 yrs old
3. History of drug-induced movement disorders
4. Biological female sex