



Psych Congress

MasterClass

# Moving Mountains with Molecules in Tardive Dyskinesia:

## Optimizing Strategies for Challenging Cases

Supported by independent educational grants from Neurocrine Biosciences, Inc. and Teva Pharmaceuticals, USA, Inc.



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# Faculty Disclosures

- **Kristian Dambrino, DNP, PMHNP-BC:** Advisory Board – Johnson & Johnson (J&J); Consultant – Axsome Therapeutics, Neurocrine Biosciences, Johnson & Johnson (J&J); Speaker’s Bureau – Axsome Therapeutics, Alkermes, Bristol Myers Squibb, Intra-Cellular Therapies, Neurocrine Biosciences
- **Christoph Correll, MD:** Advisory Board – AbbVie, Alkermes, Allergan, Angelini, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Compass, Gedeon Richter, Janssen/J&J, Karuna, LB Pharmaceuticals, Lundbeck, Medincell, Merck, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Rovi, Sage, Seqirus, SK Life Science, Sunovion, Supernus, Teva, Vertex, Viatrix; Consultant – AbbVie, Alkermes, Allergan, Angelini, Autobahn, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Compass, Denovo, Eli Lilly, Gedeon Richter, GH, Intra-Cellular Therapies, Janssen/J&J, Karuna, Kuleon Bioscience, LB Pharmaceuticals, Lundbeck, Medincell, Medlink, Merck, Mindpax, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sunovion, Supernus, Teva, Vertex, Viatrix; Grant/Research Support – Boehringer Ingelheim, Janssen, Takeda

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# Learning Objectives

1. Apply strategies to improve TD screening, assessment, and monitoring, including the use of validated rating scales and telemedicine visits
2. Identify the diagnostic criteria for TD and potential clinical features of the disorder that differentiate it from other conditions with similar presentations
3. Evaluate the MOA and latest clinical data associated with available VMAT2 inhibitors for TD
4. Assess the pharmacologic differences between available VMAT2 inhibitors to inform treatment selection and adjustments for patients with TD

# Symptoms and Course of TD

Frequency and Risk Factors



# Basics of Tardive Dyskinesia

Tardive = tending to or characterized by lateness, especially in development...

Dyskinesia = impairment of voluntary movements...

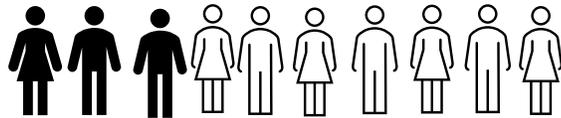


Symptoms vary in severity over time

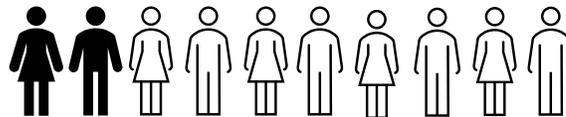
Movements range from mild to severe and can be disabling

Generally chronic and irreversible

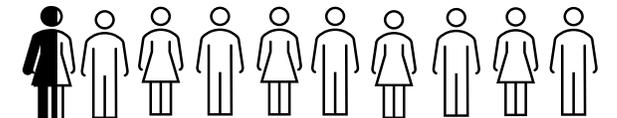
30% of patients taking typical antipsychotics



20% of patients taking atypical antipsychotics with history of typical antipsychotic treatment



7% taking atypical antipsychotics with no known history of typical antipsychotic use



DRBA = dopamine receptor blocking agent.

Carbon M, et al. *J Clin Psychiatry*. 2017;78(3):e264-e278. Lerner PP, et al. *Psychiatry Clin Neurosci*. 2015;69(6):321-334. Merriam-Webster Medical Dictionary. Accessed September 2025. <https://www.merriam-webster.com/medical>. O'Brian A. *Int J Geriatr Psychiatry*. 2016;31(7):683-693.

# Tardive Dyskinesia Incidence (New Cases): Meta-Analysis

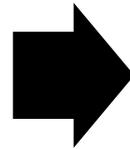
- TD risk and annualized TD rates were lower with SGAs vs FGAs
  - Risk ratio (observed risk): 0.47 (95% CI: 0.39-0.57;  $P < .0001$ ) → Risk reduction by 53%
  - Rate ratio (corrected by observation time): 0.35 (95% CI: 0.28-0.45;  $P < .0001$ ; NNT=20) → Risk reduction by 65%
- FGA-SGA TD rate ratios differed by SGA ( $P = .003$ )
- Aripiprazole and olanzapine had lower TD risk than FGAs
- Lower TD risk with aripiprazole vs all other SGAs
- Lower TD risk with olanzapine vs risperidone and quetiapine
- Risperidone was not worse than non-olanzapine SGAs

SGAs = second-generation antipsychotics; FGAs = first-generation antipsychotics; NNT = number needed to treat.

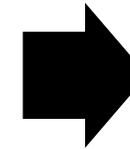
Carbon M, et al. *World Psychiatry*. 2018;17(3):330-340.

# Tardive Dyskinesia Prevalence and Risk Factors in Bipolar Disorder

Among patients with bipolar disorder (N=1132), TD prevalence was 5.1%



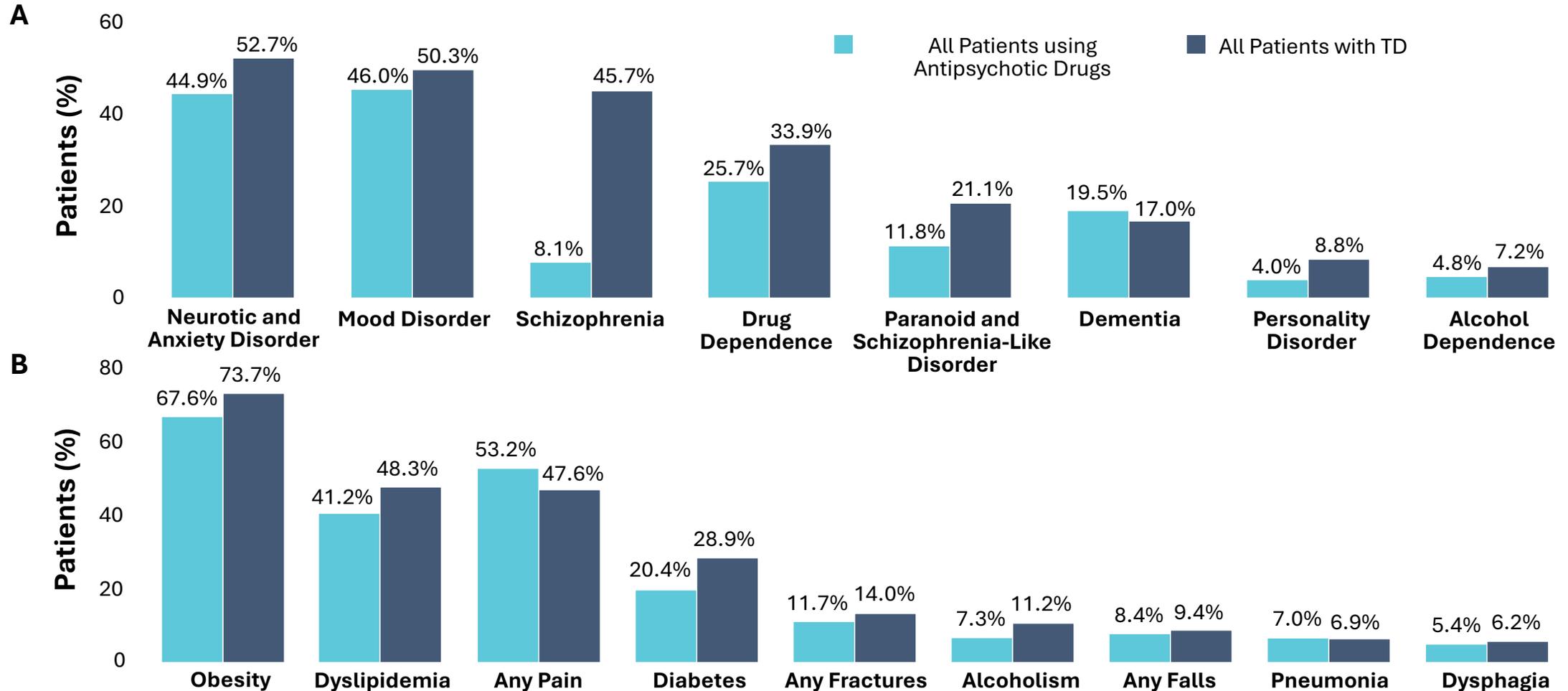
60% of the TD+ group were on antipsychotics (78% SGAs) at an average dose of  $5.9 \pm 3.5$  mg haloperidol equivalents and a mean cumulative exposure to antipsychotics of  $18.2 \pm 15.6$  yrs



## TD risk factors included

- Older age
- Female sex
- Type I bipolar illness

# Psychiatric and Physical Diagnoses in Patients with/without TD



# Tardive Dyskinesia: Risk Factors

## Unmodifiable

### Patient-Related

Older age

Female sex

White and African descent

### Illness-Related

Longer illness duration

Intellectual disability and brain damage

Negative symptoms in schizophrenia

Mood disorders

Cognitive symptoms in mood disorders

Gene polymorphisms involving antipsychotic metabolism and dopamine functioning

## Modifiable

### Comorbidity-Related

Diabetes

Smoking

Alcohol/substance abuse

### Treatment-Related

Dopamine receptor blocker

Higher cumulative and current antipsychotic dose or plasma levels

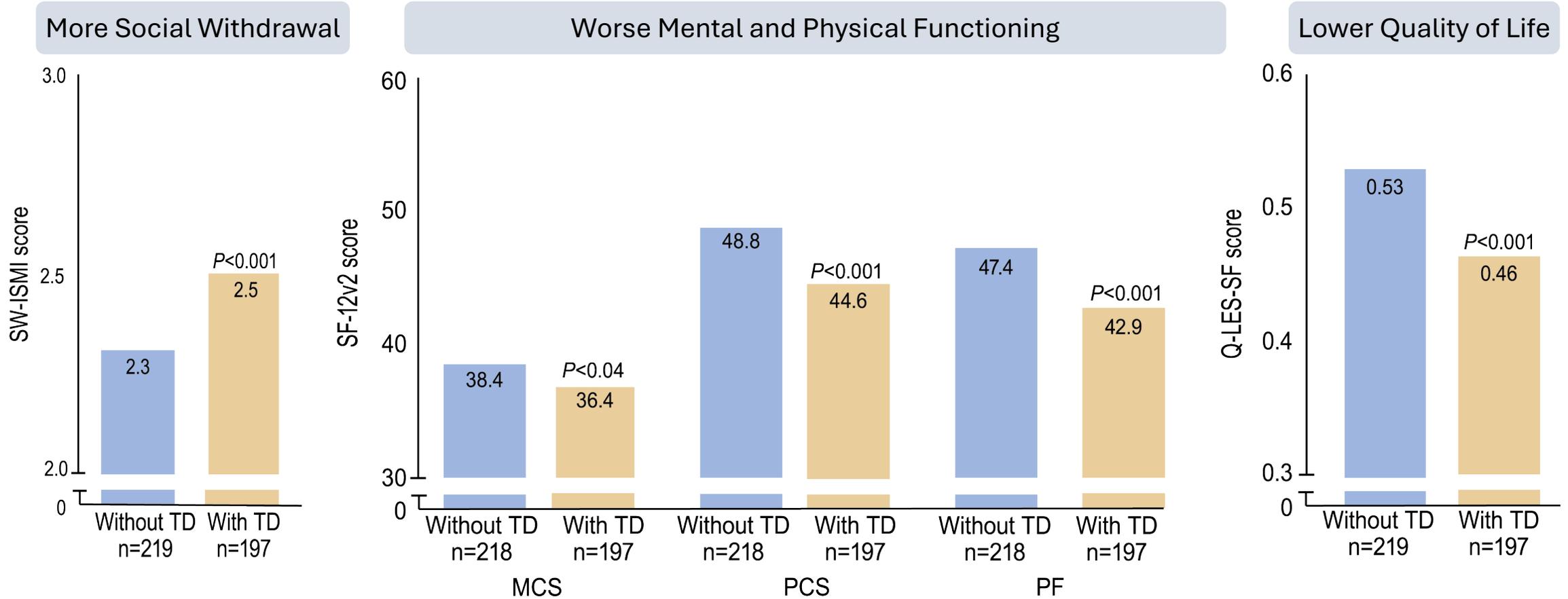
Early parkinsonian adverse events

Treatment-emergent akathisia

Anticholinergic cotreatment

# The Burden of TD

Survey of patients with clinician-confirmed diagnosis of BPD, MDD, or SCZ with vs without TD shows those with TD have significantly:



**BPD = bipolar disorder; MDD = major depressive disorder; SCZ = schizophrenia; SW-ISMI = Social Withdrawal subscale of the Internalized Stigma of Mental Illness scale; MCS = Mental Component Summary of the SF-12; PCS = Physical Component Summary of the SF-12; PF = physical functioning of the SF-36v2; Q-LES-Q SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; SF-12 = SF-12v2 Health Survey.**

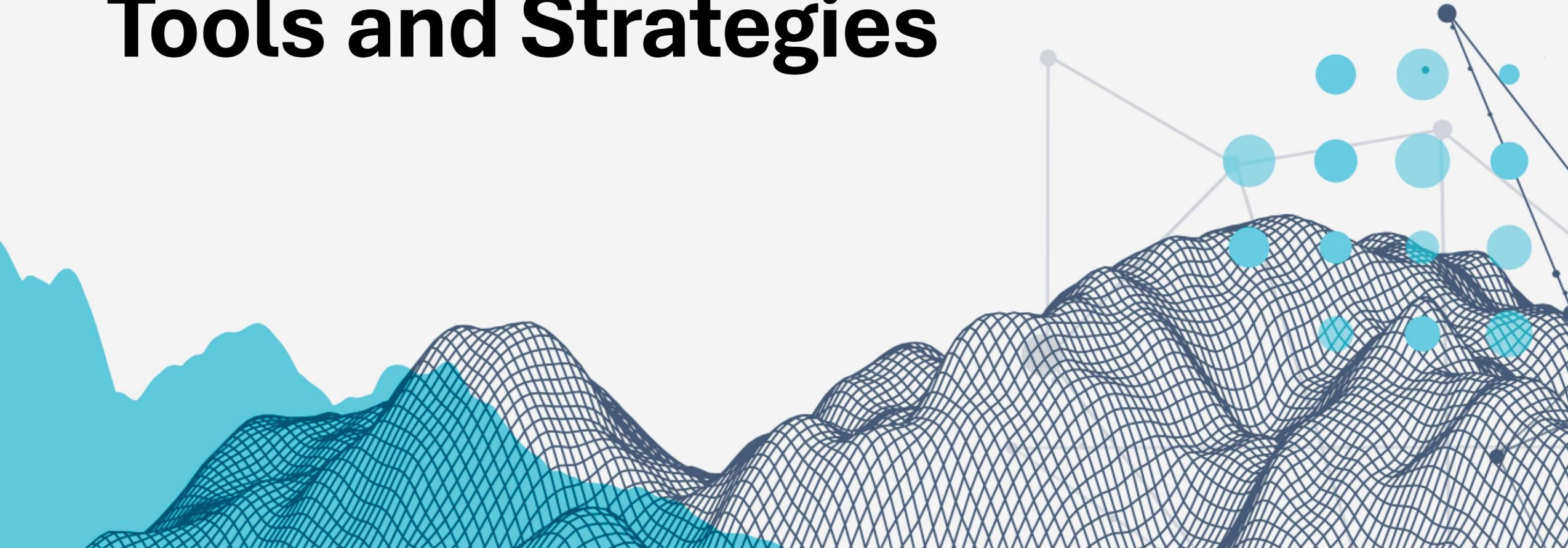
**McEvoy J, et al. *Qual Life Res.* 2019;28:3303-3312.**

# Key Learning Points



- ✓ **TD** can present **within 3 months of starting DRBAs**, but **usually begins much later** and **can occur after discontinuation** of a DRBA
- ✓ **The most important risk factors** for TD are **age** and **cumulative exposure** to DRBAs
- ✓ **TD usually persists** even after the antipsychotic is discontinued

# Assessing TD with Recommended Tools and Strategies



# Symptoms of TD and DSM Criteria for Diagnosis

## Involuntary choreiform, athetoid, or dystonic movements



- **Most often, orofacial**

- Lip smacking
- Tongue thrusting
- Grimacing
- Eye blinking



- **Limbs may be affected**

- Dance-like arm movements
- “Piano-playing” movements of fingers and toes



- **Torso may also be affected**

- Shoulder shrugging
- Respiratory involvement may occur

- Develop at least a few months after exposure to a DRBA (may be earlier in older adults)
- Withdrawal-emergent dyskinesia usually time-limited (4-8 weeks)
- Persistence of symptoms beyond 4-8 weeks is considered TD
- Cause distress or functional impairment
- Symptoms NOT explained by other neurologic or medical condition

**Early detection is crucial to prevent worsening symptoms**

# Tardive Dyskinesia: Symptom-Based Differential Diagnosis

**Mannerisms**  
(semipurposeful  
movements)

**Stereotypies**  
(repetitive complex  
movements)

**Tics**  
(quick, repetitive  
movements)

**Myoclonus**  
(quick, may be  
irregular)

**Dystonias**  
(sustained or  
repetitive muscle  
contraction)

**Tremor**  
(rhythmic, regular)

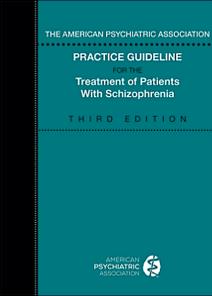
**Akathisia**  
(restlessness,  
shifting of position)

**Parkinsonism**  
(akinesia, rigidity,  
tremor)

# How Frequently Should We Be Screening?

And What Is an Accurate Assessment?

# Structured Screening Is Standard of Care



**11%**  
of patients on antipsychotics receive regular TD screenings, according to one study

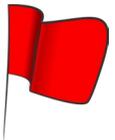


- Risk Factors**
- 3-5x risk if >50 years old
  - History of akathisia, dystonia, or parkinsonism (“EPS”)
  - Dosage, duration, and potency of DRBA
  - Substance use disorder
  - Mood disorder > psychotic disorder diagnosis

AP = antipsychotic.  
Keller WR, et al. *J Nerv Ment Dis.* 2014;202(1):6-12. Caroff SN, et al. *J Clin Psychiatry.* 2020;81(2):19cs12983. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia.* 3rd ed. APA Publishing; 2021. Aquino CC, Lang AE. *Parkinsonism Relat Disord.* 2014;20(Suppl 1):S113-117. Jankelowitz SK. *Neuropsychiatr Dis Treat.* 2013;9:1371-1380. D’Abreu A, et al. *J Neurol Sci.* 2018;389:17-20.

# Semi-Structured Exam: Identify Opportunities to Observe Patients

- **Involve the entire treatment team in noticing involuntary movements**
  - Unobtrusively so patients will not mask movements
  - When the patient is in the waiting room
  - When the patient is walking to the exam room
- **Semi-structured assessments are quick and should be utilized when AIMS is not performed, and include**
  - Patient or caregiver recognition of abnormal movements when reviewing APD side effects
  - Visual observation of abnormal movements on examination
    - Examine face and tongue at rest, with speech, and with physical activation
- **If the semi-structured assessment reveals abnormal movements, a full AIMS should be performed**

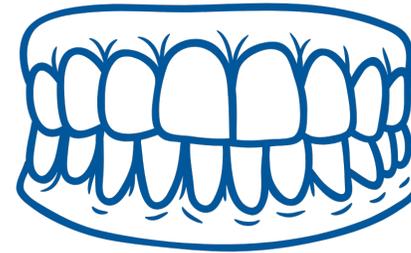


AIMS = Abnormal Involuntary Movement Scale; APD = antipsychotic drug.

American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia*. 3rd ed. APA Publishing; 2021.

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

# Abnormal Involuntary Movement Scale (AIMS): Preliminaries



The **chair** to be used in the examination should be a hard, firm one without arms

Ask the patient whether there is **anything in his or her mouth** (such as gum or candy) and, if so, to remove it

Ask about the current condition of the patient's **teeth** and if they wear dentures

Ask **whether the patient notices any movements** in his or her mouth, face, hands, or feet

# AIMS Rating Scale Is Used to Assess Severity of TD Symptoms

Movement Ratings		Score				
Facial & Oral Movements	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	5. Upper (arms, wrists, hands, fingers)	0	1	2	3	4
	6. Lower (legs, knees, ankles, toes)	0	1	2	3	4
Trunk Movements	7. Neck, shoulders, hips	0	1	2	3	4
Global Judgments	8. Severity of abnormal movements overall	0	1	2	3	4
	9. Incapacitation due to abnormal movements	0	1	2	3	4
	10. Patient awareness of abnormal movements	0	1	2	3	4
Dental Status	11. Current problems with teeth/dentures?	No	Yes			
	12. Are dentures usually worn?	No	Yes			

- AIMS is a clinician-rated scale
  - Items 1-4 assess orofacial movements
  - Items 5-7 assess extremity and truncal movements
  - Item 8 assesses the overall severity of movements
- Scoring
  - Total score is calculated using items 1-7 for a total (max) score of 28
  - Item 8 score is based on the highest single score in any of the items 1-7

0=None, 1=Minimal, 2=Mild, 3=Moderate, 4=Severe

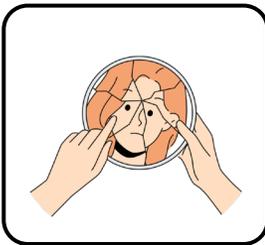
# Patients with TD Express Negative Sentiments

In a social media listening study, patients with TD expressed:



## ANGER

- Frustrated or spiteful
- Extreme tardive dyskinesia symptoms affecting life
- Recovering but terrible experience
- Suffering because of tardive dyskinesia



## INSECURITY

- Feel ugly, weird, or insecure
- Feel unaccepted by society and uncomfortable in own skin
- Rather be dead
- Fear of people judging or asking questions



## SYMPTOMS

- Encourage open discussion of symptoms
- Struggles dealing with symptoms and treatment
- Details of symptoms with descriptions like “raw” or “jerky”

A 2020 study found

**75% of patients were aware**

Mood disorder: 81%

Psychotic disorder: 71%

**3 out of 4 patients**

with TD reported feeling ***self-conscious***  
or ***embarrassed*** about it

# Is TD a Matter of Life or Death?

- In some meta-analyses and cohort studies, patients with TD have been linked to higher risk of death compared to those without TD
- Odds ratios for all-cause mortality range from 1.4 to 2.2
- Ultimately, the link between mortality and tardive dyskinesia remains unclear
- In one 6-year cohort of patients with schizophrenia
  - Hazard ratio for mortality in those with TD was 2.62 and was dependent on age
  - After adjusting for age, adverse effect of TD on survival rate remained
- In a 2019 long-term study using the US National Death Index
  - The association between TD and increase in mortality was significant ( $P < .001$ )
  - This relationship was not significant when including drug course and age

It may not always be life or death, but early detection is key, and age is a risk factor for developing TD

# Assessing the Impact of TD

**Mild score  
on AIMS  
may not =  
mild impact**

Impact TD Scale	
Domain	Problems may include
Social	<ul style="list-style-type: none"> <li>• Difficulty participating in events with family and others (eg, holiday gatherings, religious services)</li> <li>• Self-consciousness/embarrassment about movements or being seen/asked about them by others (eg, stigma, rejection)</li> <li>• Avoidance of interaction with others (eg, declines invitations, avoids leaving home, isolation)</li> <li>• Reduced quality of interpersonal communication (eg, distraction from conversation, problems interpreting body language)</li> </ul>
Psychological/ Psychiatric	<ul style="list-style-type: none"> <li>• Feelings of sadness, depression</li> <li>• Feelings of anxiety, worry, concern</li> <li>• Feelings of low self-esteem</li> <li>• Feelings of hopelessness, loss of sense of purpose</li> <li>• Poor concentration, attention, memory</li> <li>• Worsening or recurrence of previous symptoms/disorder (eg, depressed mood, anxiety, psychosis)</li> <li>• Difficulty with appropriate treatment of mental disorder (eg, reduced adherence with medication regimens, discontinuation of treatment)</li> <li>• Unhealthy coping strategies (eg, substance use/abuse)</li> </ul>
Physical	<ul style="list-style-type: none"> <li>• Difficulty using utensils, writing, typing, dressing</li> <li>• Difficulty speaking, chewing, or swallowing</li> <li>• Difficulty walking or maintaining balance (eg, stumbling, need for assistive device)</li> <li>• Problems breathing (eg, shortness of breath, gasping for air)</li> <li>• Pain due to TD (eg, biting inside of mouth, jaw clenching)</li> <li>• Difficulty sitting still, falling asleep</li> </ul>
Vocational/ Educational/ Recreational	<ul style="list-style-type: none"> <li>• Problems gaining or maintaining employment</li> <li>• Problems with recreational or vocational/educational performance (eg, poor concentration, trouble communicating, physical limitations)</li> <li>• Challenges getting to work/school or other activities</li> <li>• Difficulty with colleague/classmate/customer interactions</li> <li>• Difficulty performing tasks independently</li> </ul>

Zutshi D, et al. *Tremor Other Hyperkinet Mov (NY)*. 2014;4:266. Jackson R, et al. *Neuropsychiatr Dis Treat*. 2021;17:1589-1597. Jackson R, et al. *J Clin Psychiatry*. 2022;84(1):22cs14563.

# Tardive Dyskinesia Impact Scale (TDIS)

**TDIS is a validated 11-item questionnaire to assess how TD affects daily function over the previous 7 days**

- Designed to fill gap, as there is no validated patient-reported outcome measure specific to TD
- 11-item questionnaire captures physical and socio-emotional effects of TD
- TDIS shown to be responsive to change in treatment (eg, decrease in TD movements, decrease in AIMS score)

Domain	TDIS Item	Corresponding TDRS Item
<b>Mouth/throat function</b>	1. Speech	Item 2. Speech
	2. Mouth noises	Not applicable
	3. Swallowing	Item 3. Chewing and swallowing
<b>Dexterity</b>	4. Gripping	Item 4. Eating tasks Item 5. Dressing Item 6. Hygiene Item 8. Hobbies
	5. Writing	Item 7. Handwriting
<b>Mobility</b>	6. Walking	Item 9. Walking and balance
	7. Balance	
<b>Pain</b>	8. Leg pain	Item 12. Dyskinesia pain
<b>Social</b>	9. Unwanted attention	Item 10. Public and social settings
<b>Emotional</b>	10. Embarrassed	Not applicable
	11. Self-conscious	

# Key Learning Points



- ✓ The **AIMS** assessment of TD severity should be performed **every 3 to 12** months depending on the patient's risk factors and whether they are taking a **first- or second-generation AP**
- ✓ A **semi-structured evaluation** can be done every time you see a patient (**just by observing and activating!**)
- ✓ TD is more than a movement disorder; **ask** about and **measure the impact of TD** with rating scales such as **TDIS** or **Impact TD**

# Treating Patients with TD



# Minimizing the Risk of Tardive Dyskinesia through Patient and Caregiver Education

It is important to minimize the risk of TD by educating patients and caregivers about the risks of and alternatives to antipsychotic medication; it is also important to discuss the early signs of TD

## Preventive principles include

- Confirm and document the indication for dopamine antagonist antipsychotic medications
- Use conservative maintenance doses
- Consider the use of SGAs, especially in those at high risk for EPS
- Avoid anticholinergic medications
- Inform patients and caregivers of the risk for TD
- Assess for incipient signs of TD regularly using the AIMS

EPS = extrapyramidal side effects.

Caroff SN, et al. *Curr Psychiatry*. 2011;10(10):23-32.



# The Anticholinergic Controversy

Used **extensively**, and often *prophylactically*, upon the initiation of antipsychotic medication to manage DIP

However, anticholinergics can **increase the risk of developing TD**, can **worsen comorbid TD**, and *negatively impact cognition*

**Avoid in the elderly due to an increased risk of delirium**

**Peripheral side effects** such as blurred vision, dry mouth, constipation, and urinary retention can also be encountered

If prescribed, a typical duration of anticholinergic use is 3 months, and they should be **periodically stopped to assess the need for continued use**

Consider **amantadine as an alternative to anticholinergic medication** to manage DIP

# Withdrawing DRBA Is Unlikely to Result in Remission

## TD is more than a side effect

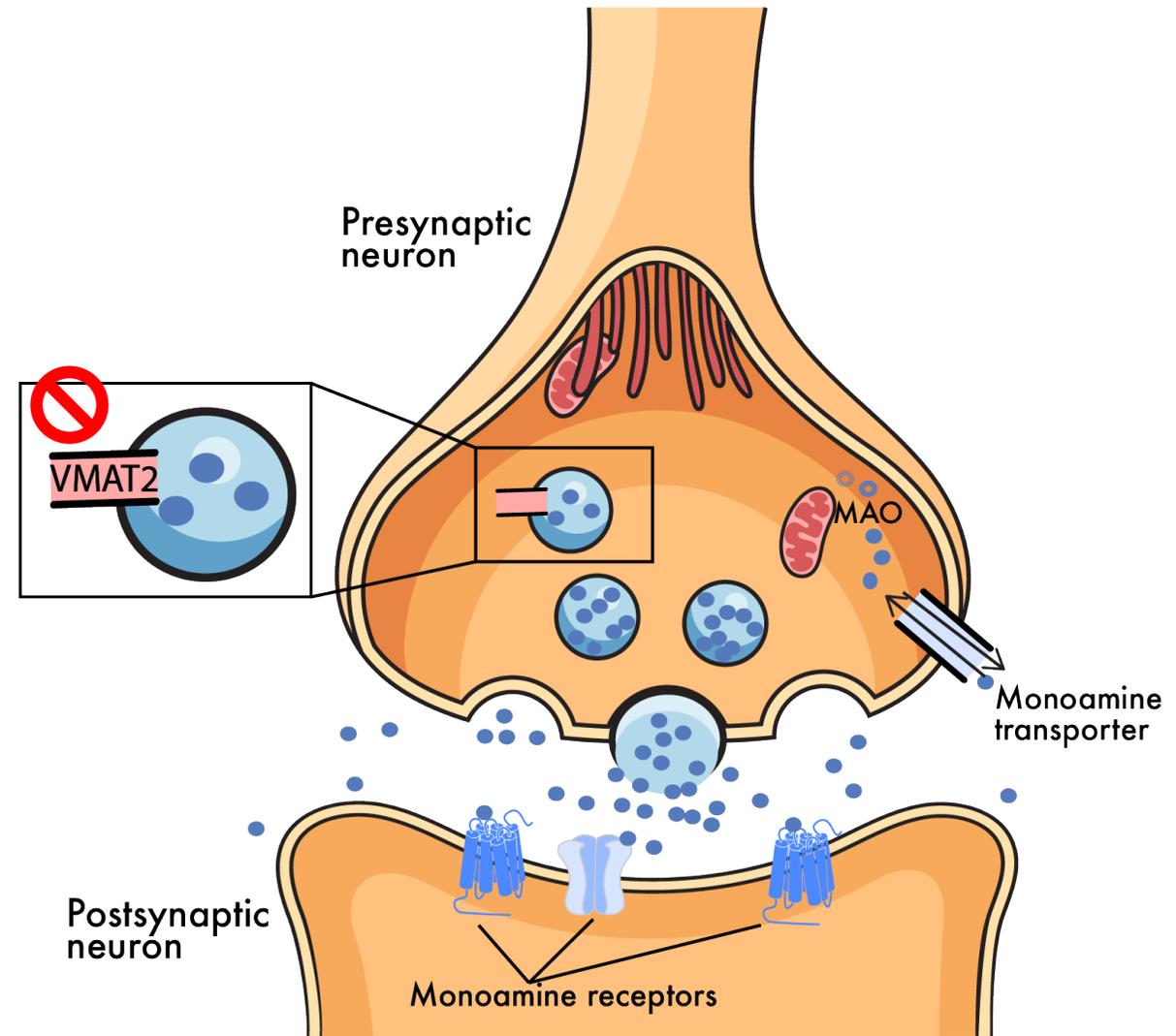
- Withdrawing the “offending agent”—the DRBA—may make TD worse
- Estimates of reversibility (eg, remission) and resolution (eg, symptom improvement) vary widely
  - **Populations** and **treatment conditions** studied **also varied** widely among studies
  - 3 studies evaluated the course of TD in patients who discontinued DRBAs\*

Outcome after Withdrawal of DRBA	Glazer, et al (1990) N=49	Kiriakakis, et al (1998) N=107	Zutshi, et al (2014) N=108
Stable or worse	80%	47%	60%
Improvement	20%	39%	27%
Remission rate with TD treatment	0%	14%	13%
Remission rate without TD treatment	N/A	N/A	2%
Mean time to remission	N/A	5.2 years	3.2 years
Mean follow-up	40 weeks	8.3±6.2 years	3.1±3.4 years
Study design*	Prospective	Retrospective	Retrospective

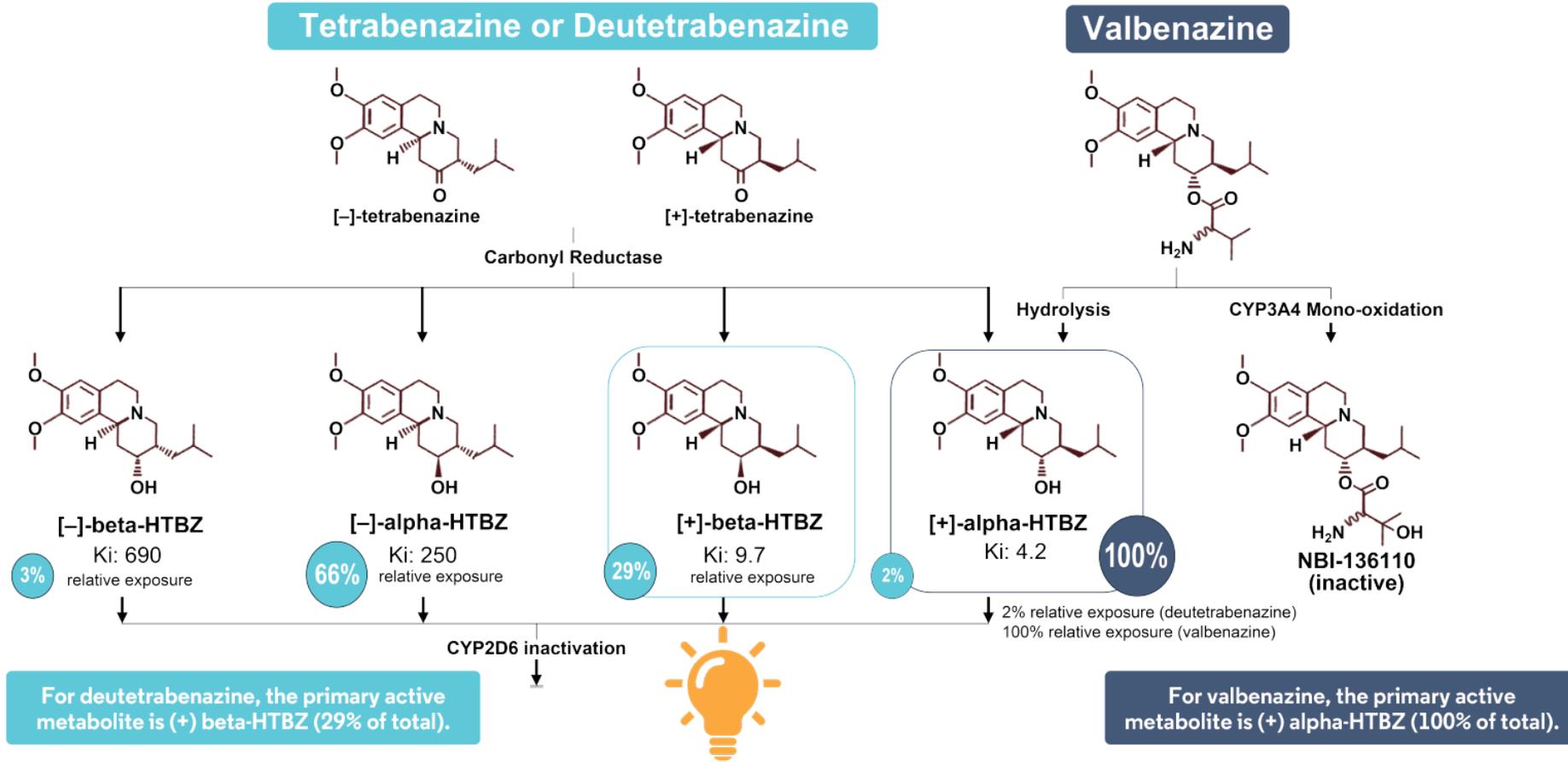
\*Limitations: All studies were observational with no comparator, and each was from a single movement disorder center where cases seen may be more likely to be severe/refractory; retrospective studies are subject to confirmation bias

# What Are VMAT2 Inhibitors?

- VMAT2 packages and transports monoamine neurotransmitters into synaptic vesicles
  - Serotonin
  - Dopamine
  - Histamine
  - Norepinephrine
- Inhibiting VMAT2 decreases amount of neurotransmitter released when neuron fires
- VMAT2 inhibitors
  - Reduce dopamine release in dorsal striatum
  - Reducing dyskinetic movements resulting from the **hyper**dopaminergic state of TD



# Differences in Metabolism of Valbenazine and Tetrabenazine/Deutetabenazine

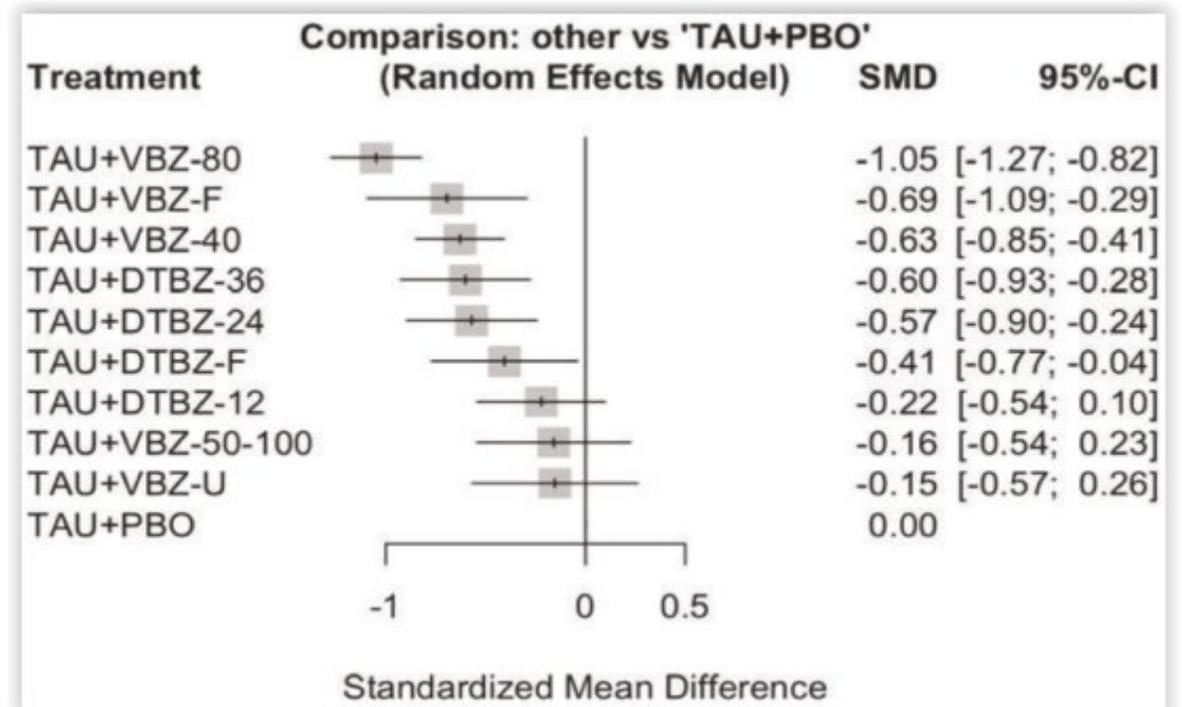
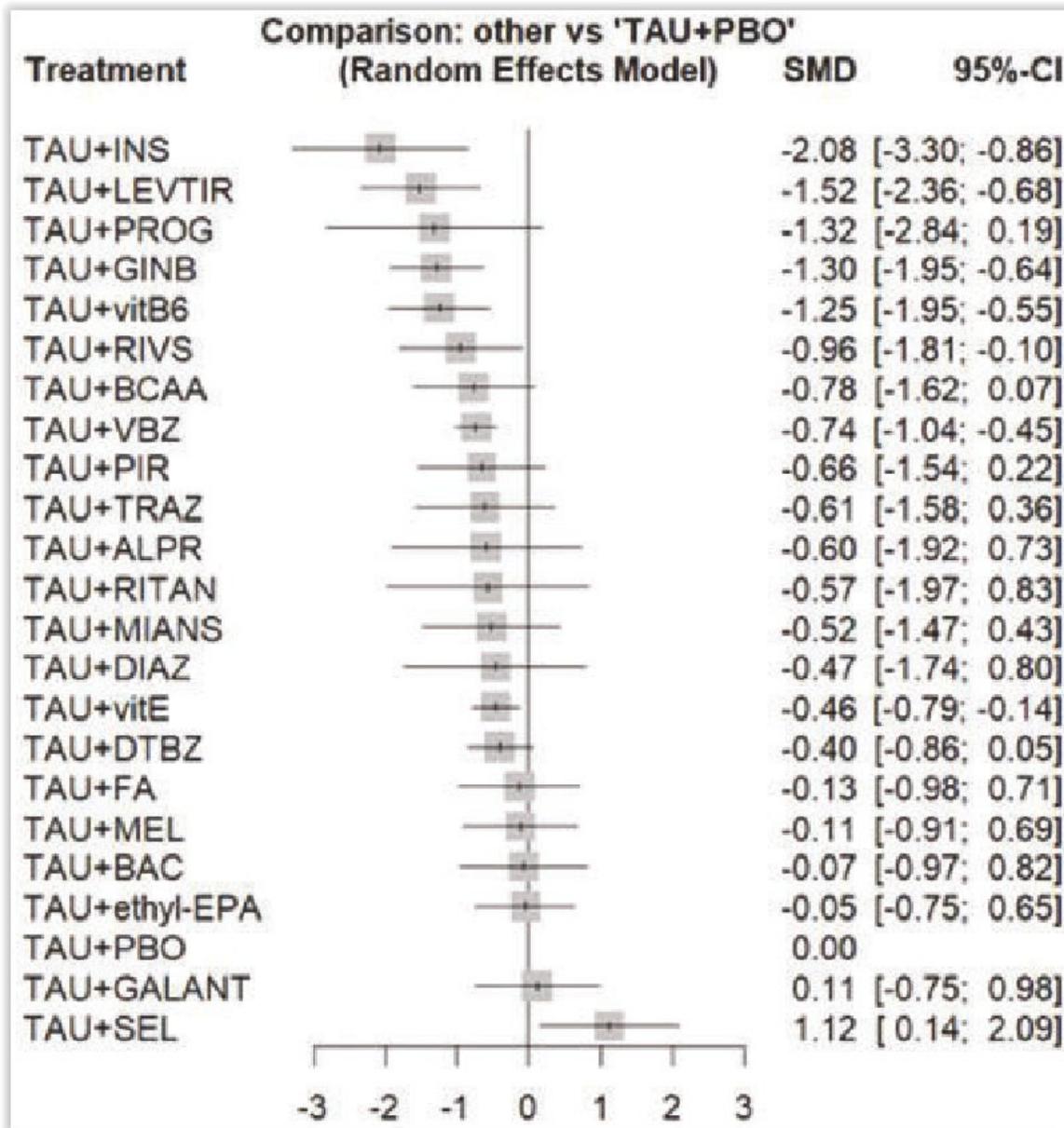


Affinity and selectivity for VMAT2 varies between each metabolite. The + alpha and + beta metabolites have been found to have very high affinity for VMAT2.

# NMA of Pharmacological Interventions for TD

(Green Highlight: Agents with  $\geq 2$  Studies with  $\geq 20$  Patients)

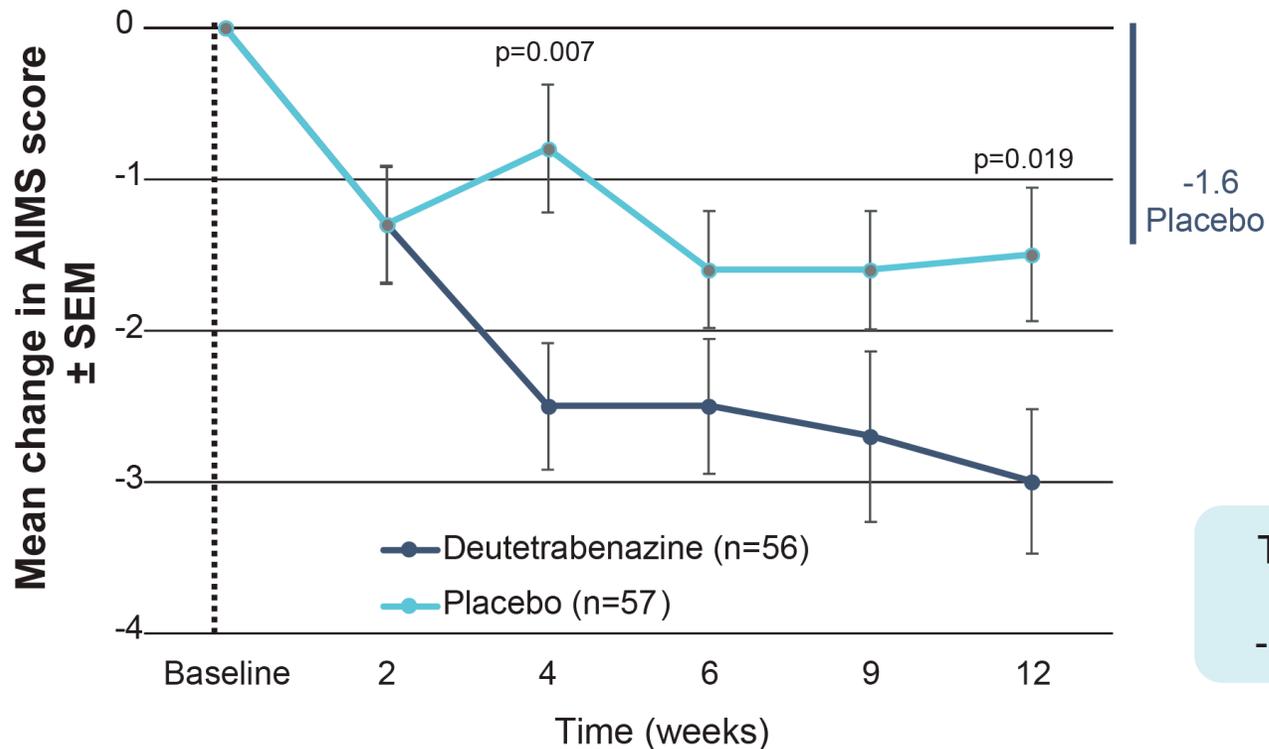
## Dose-Response NMA



# Clinical Data Overview of Deutetrabenazine

# Flexible-Dose Study of Deutetrabenazine (ARM-TD)

Change in Abnormal Involuntary Movement Scale (AIMS)  
from Baseline to Week 12



Deutetrabenazine significantly reduced AIMS total score by Week 12 compared with placebo (p=0.019)

Treatment effect of -1.4 points

Mean dose at the end of titration was 38.8 mg/day

SEM = standard error of the mean.

Fernandez HH, et al. *Neurology*. 2017;88(21):2003-2010.

# Deutetrabenazine Safety and Tolerability in Short-Term Studies

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%

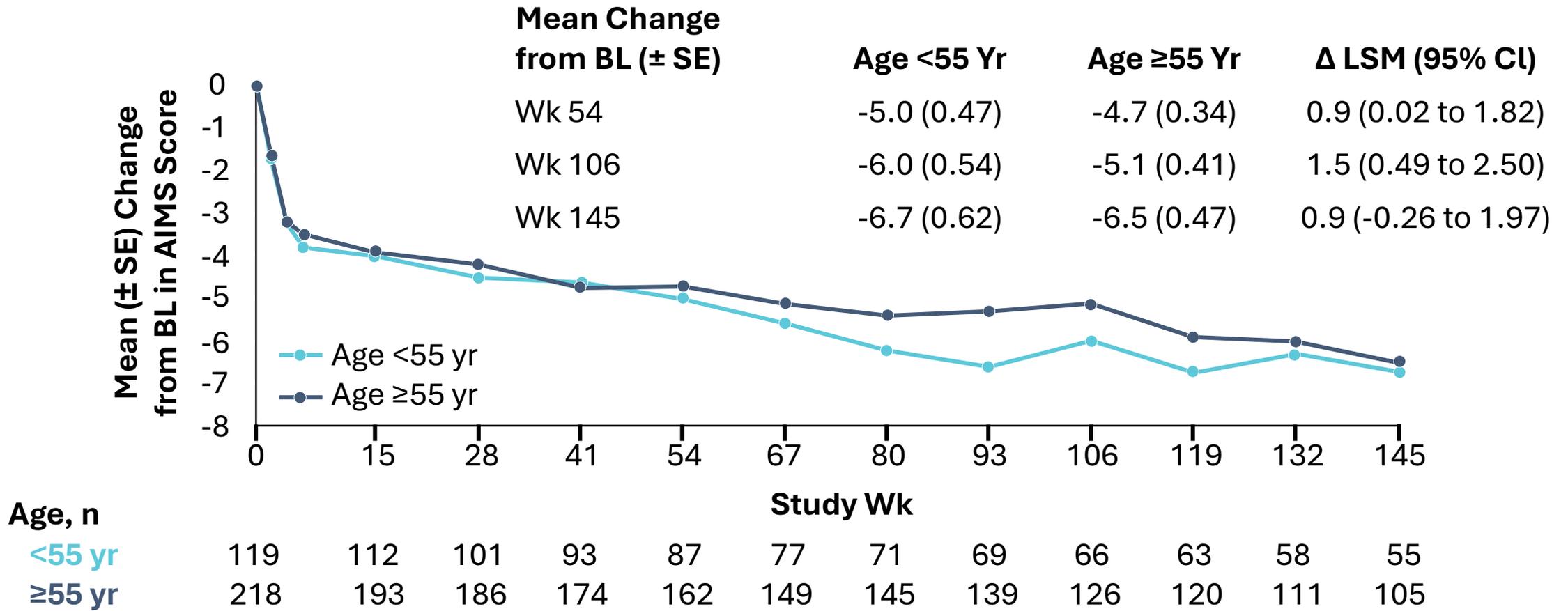
\* AEs occurring at a greater rate in patients taking deutetrabenazine than in patients taking placebo

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

AEs = adverse events.

Anderson KE, et al. *Lancet Psychiatry*. 2017;4(8):595-604. Fernandez HH, et al. *J Neurol Neurosurg Psychiatry*. 2019;90(12):1317-1323.

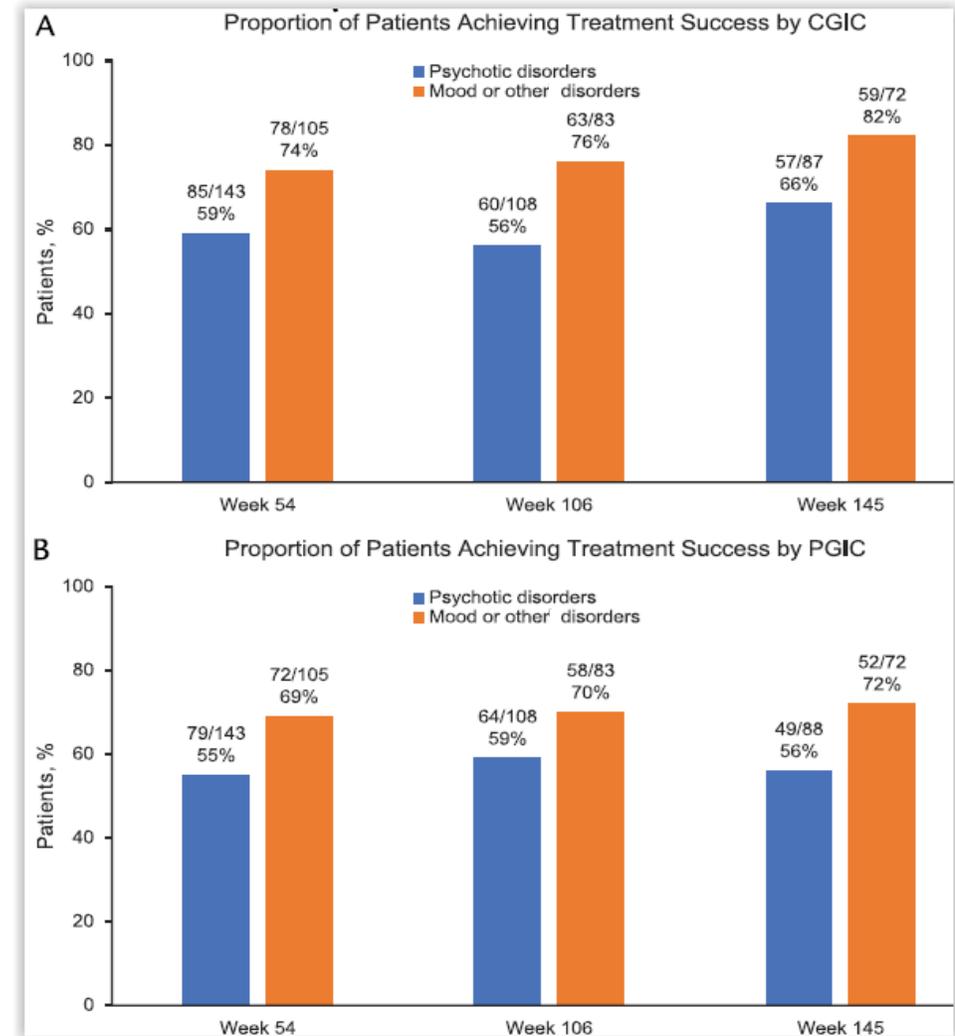
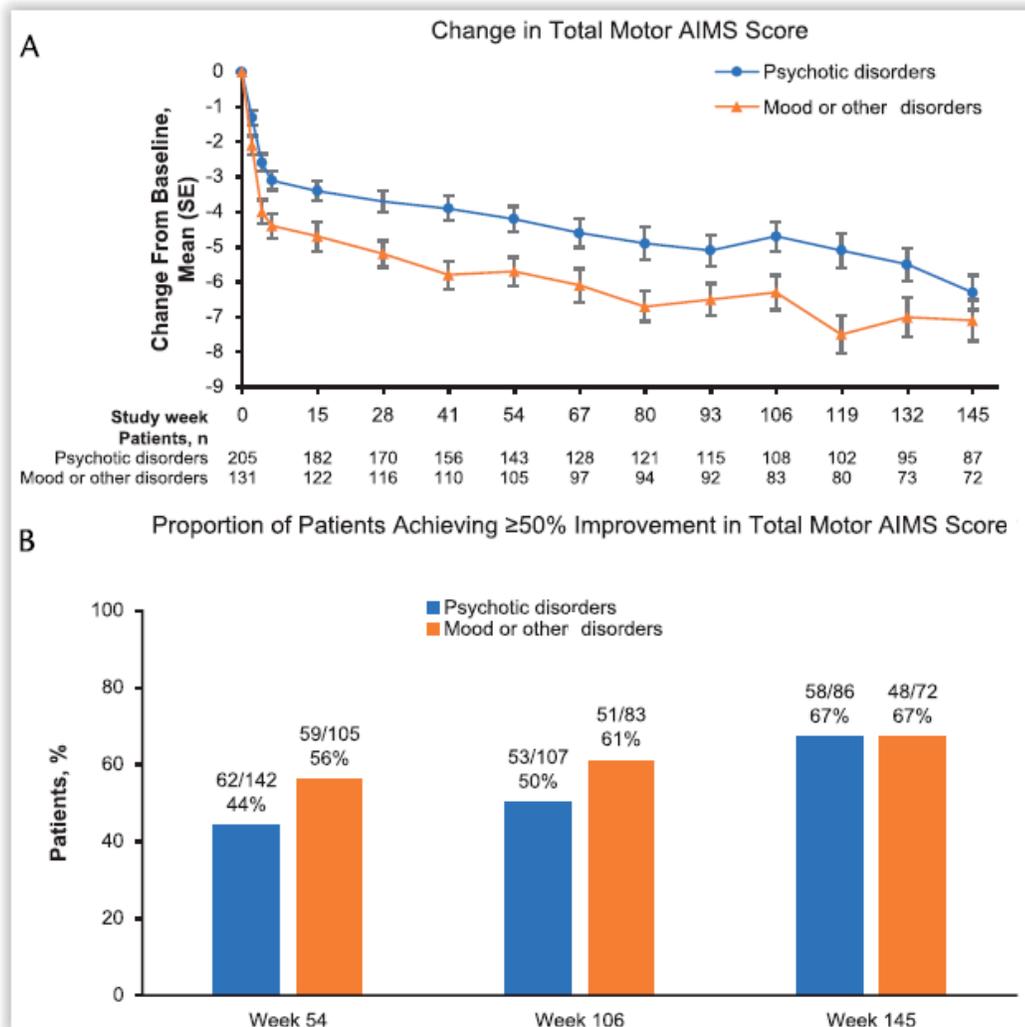
# Deutetrabenazine Improves TD over Time Both in Younger and Older Patients with TD



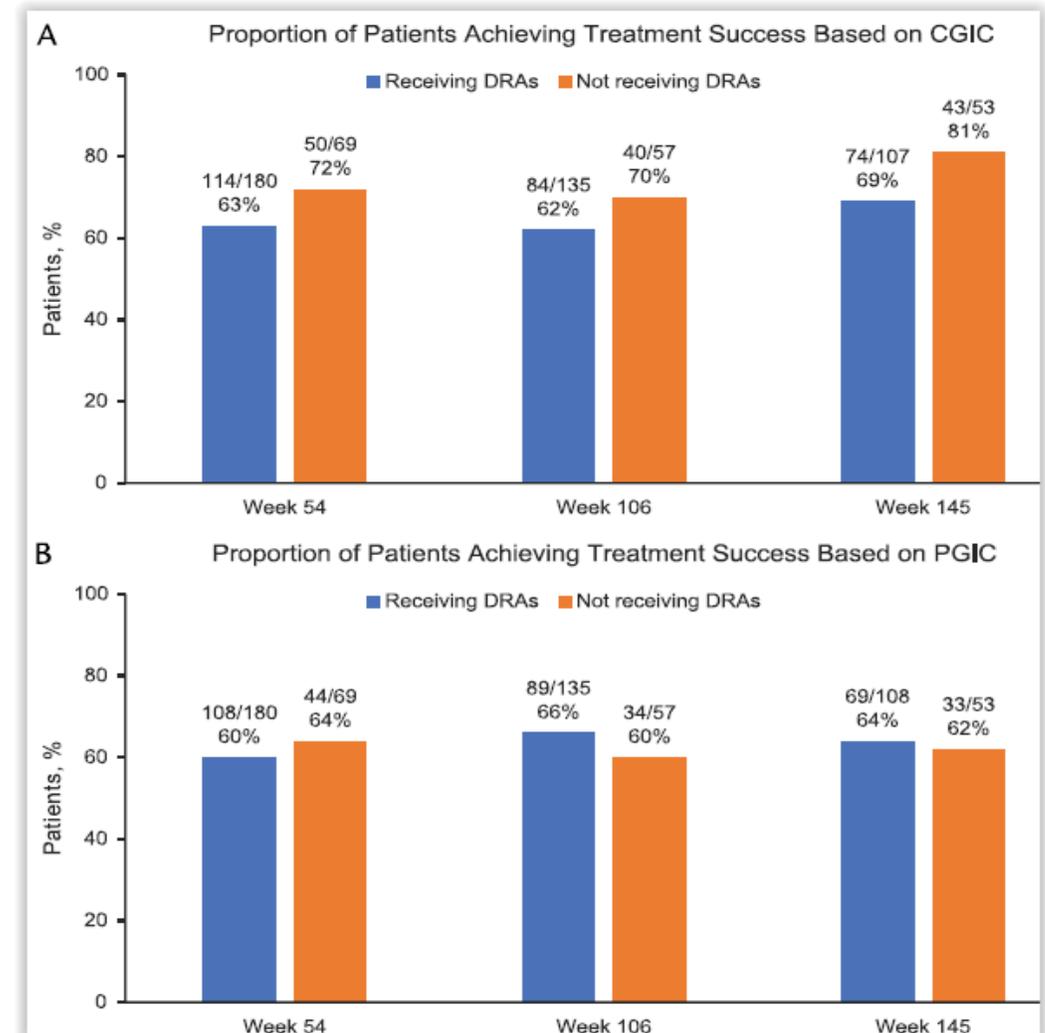
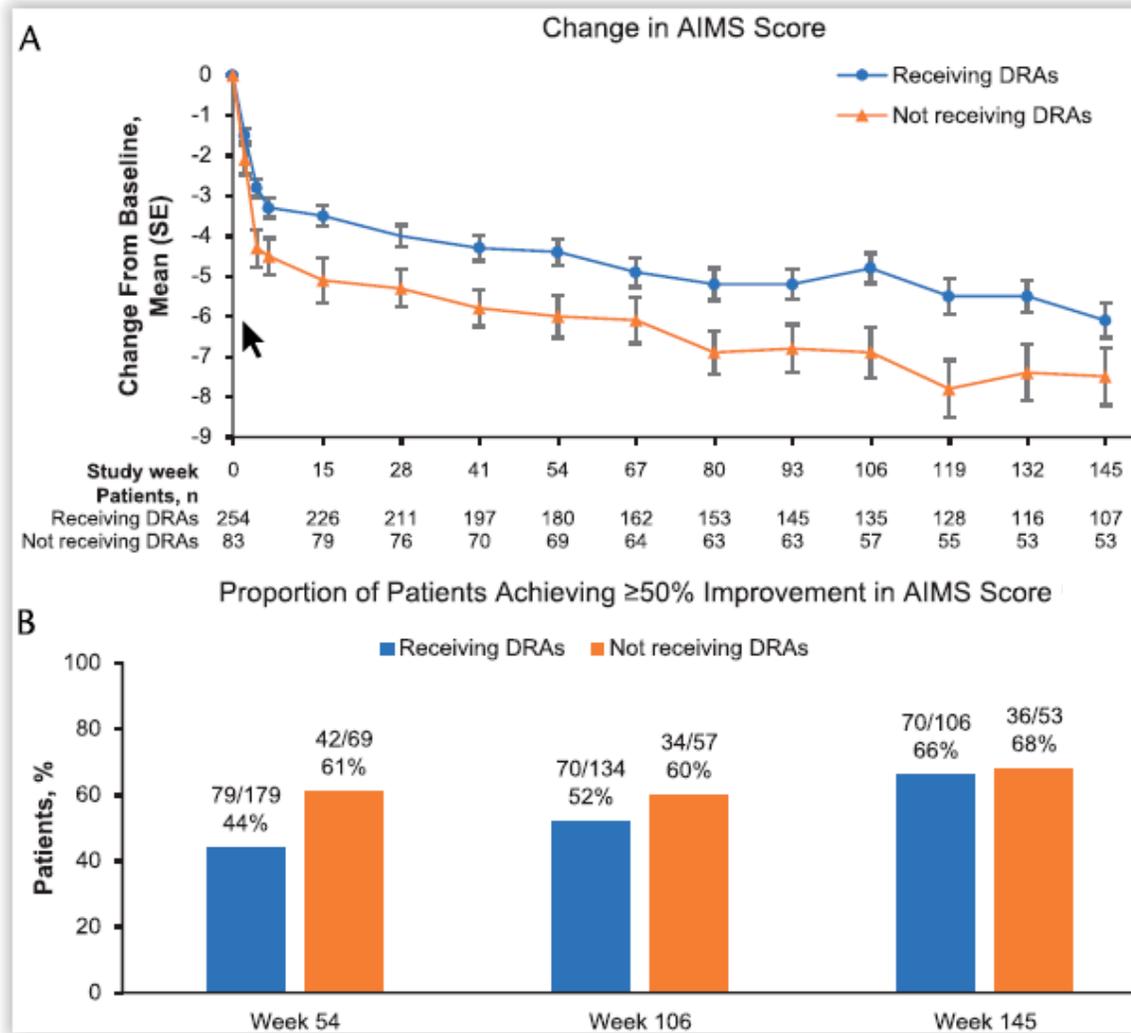
BL = baseline; CI = confidence interval.

Sajatovic M, et al. *Am J Geriatr Psychiatry*. 2022;30(3):360-371.

# Deutetrabenazine Improves TD over 3 Years, Independent of Diagnosis



# Deutetrabenazine Improves TD over 3 Years, Independent of Dopamine Receptor Blocking Agents (DRBAs) Rx

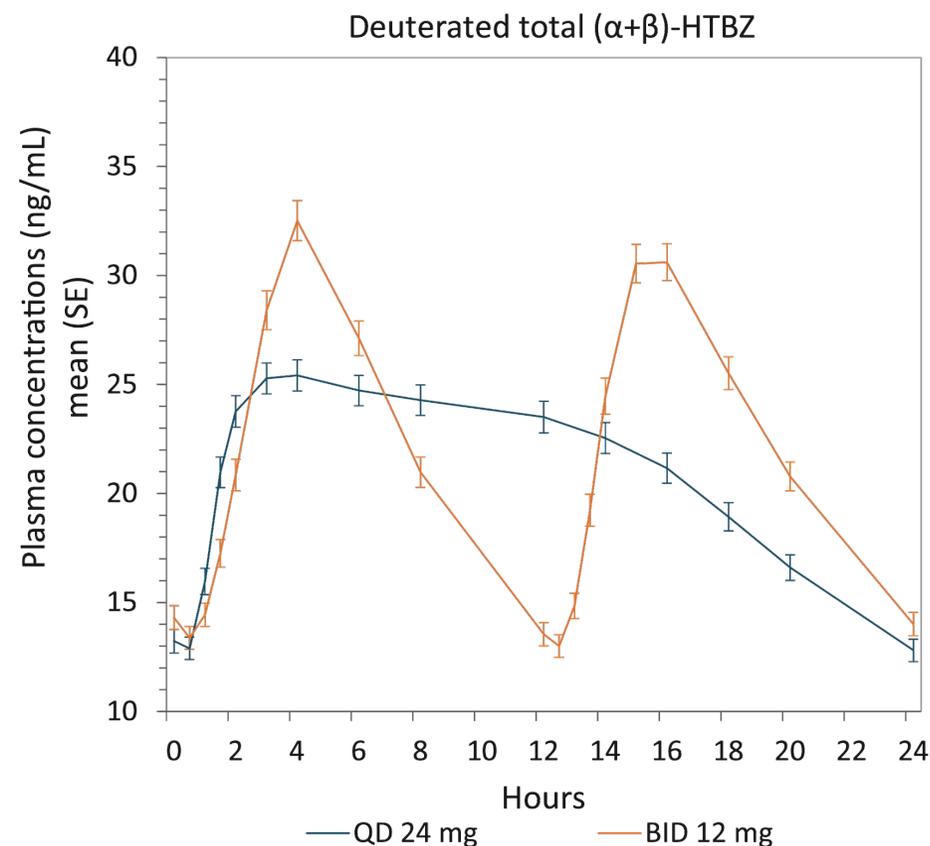




# Pharmacology and Formulations of Deutetrabenazine

	Deutetrabenazine XR
<b>Dosage forms</b>	Tablets: 6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg
<b>Dosing</b>	Start 12 mg qD once daily with or w/o food, increase by 6 mg weekly to a at least 24 mg qD
<b>Active metabolites</b>	(+)deuterated $\beta$ -HTBZ (primary), (+)deuterated $\alpha$ -HTBZ
<b>CYP Interactions</b>	Max dose 36 mg with strong 2D6 inhibitors Not studied in 2D6 PM, but expected to be comparable to strong 2D6 inhibition
<b>Contraindications</b>	Use with MAOIs or other VMAT inhibitors Suicidal or inadequately treated depression in Huntington's, hepatic impairment

## Deutetrabenazine XR Once Daily is Bioequivalent to Deutetrabenazine BID



MAOIs = monoamine oxidase inhibitors.

Deutetrabenazine PI. US Food and Drug Administration. Drugs@FDA: FDA Approved Drugs. Accessed September 2025.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/208082s016s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208082s016s017lbl.pdf). Sunzel EM, et al. *Clin Pharmacol Drug Dev.* 2024;13(3):224-232.

# Clinical Data Overview of Valbenazine

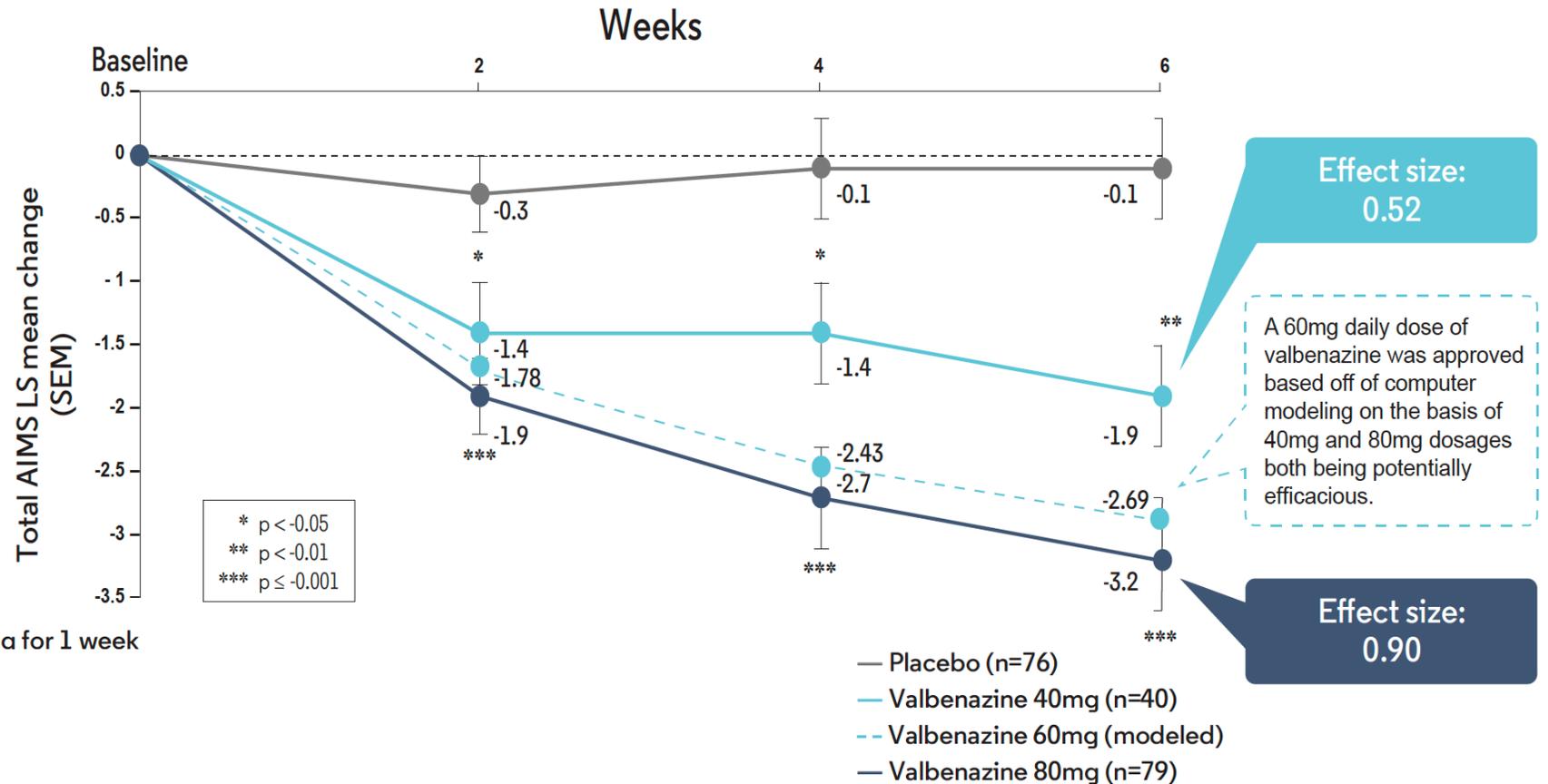
# 6-Week Placebo-Controlled, Fixed-Dose Study of Valbenazine (KINECT 3)

Mean baseline AIMS total score:  $10.0 \pm 4.0$

Placebo Subtracted Change from Baseline

VBZ 80 mg: -3.2 \*\*\*  
 VBZ 40 mg: -1.9 \*\*  
 Placebo: -0.1

All participants received valbenazine 40mg for 1 week



# Valbenazine Safety and Tolerability in Short-Term Studies

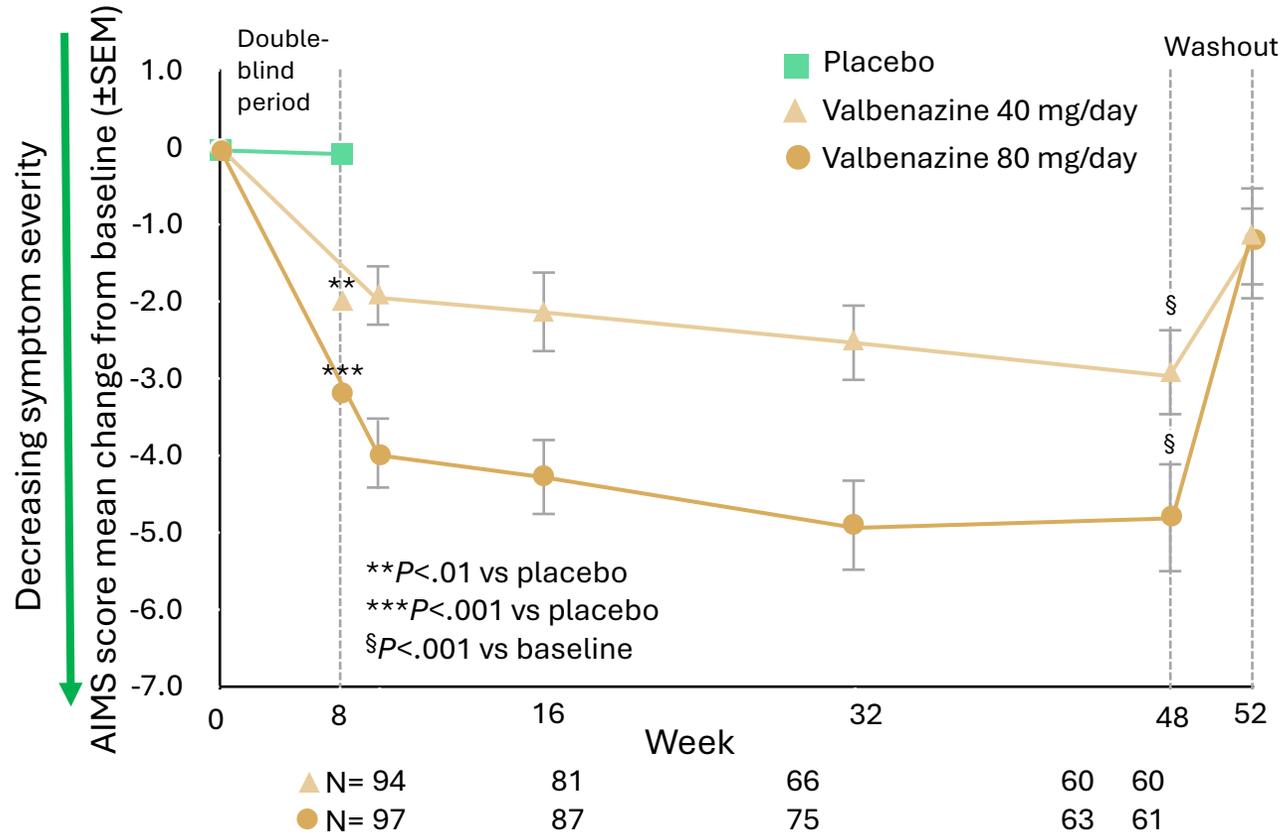
## Adverse Events in 6-Week Valbenazine DBPC Studies in North America Reported at $\geq 2\%$ and Greater Than Placebo

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

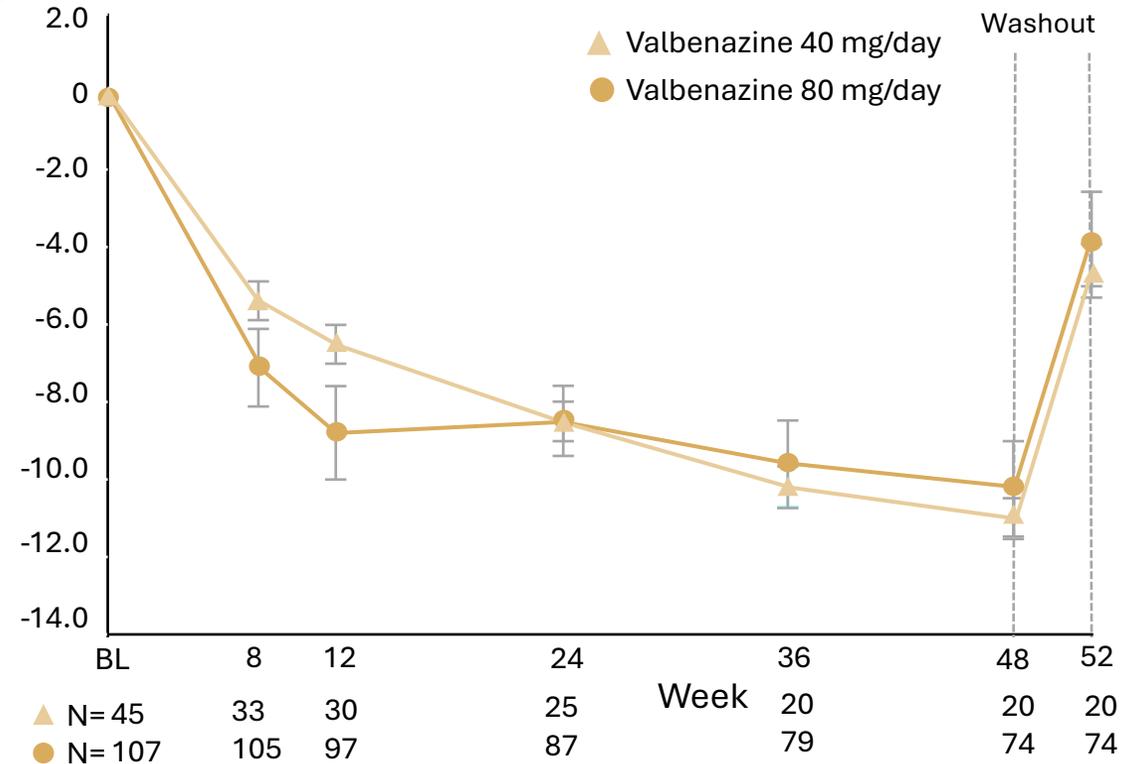
Discontinuation due to AEs occurred in 3% of patients  
taking valbenazine vs 2% of patients taking placebo

# Long-Term Studies of Valbenazine

## KINECT 3 Open-Label Extension Study

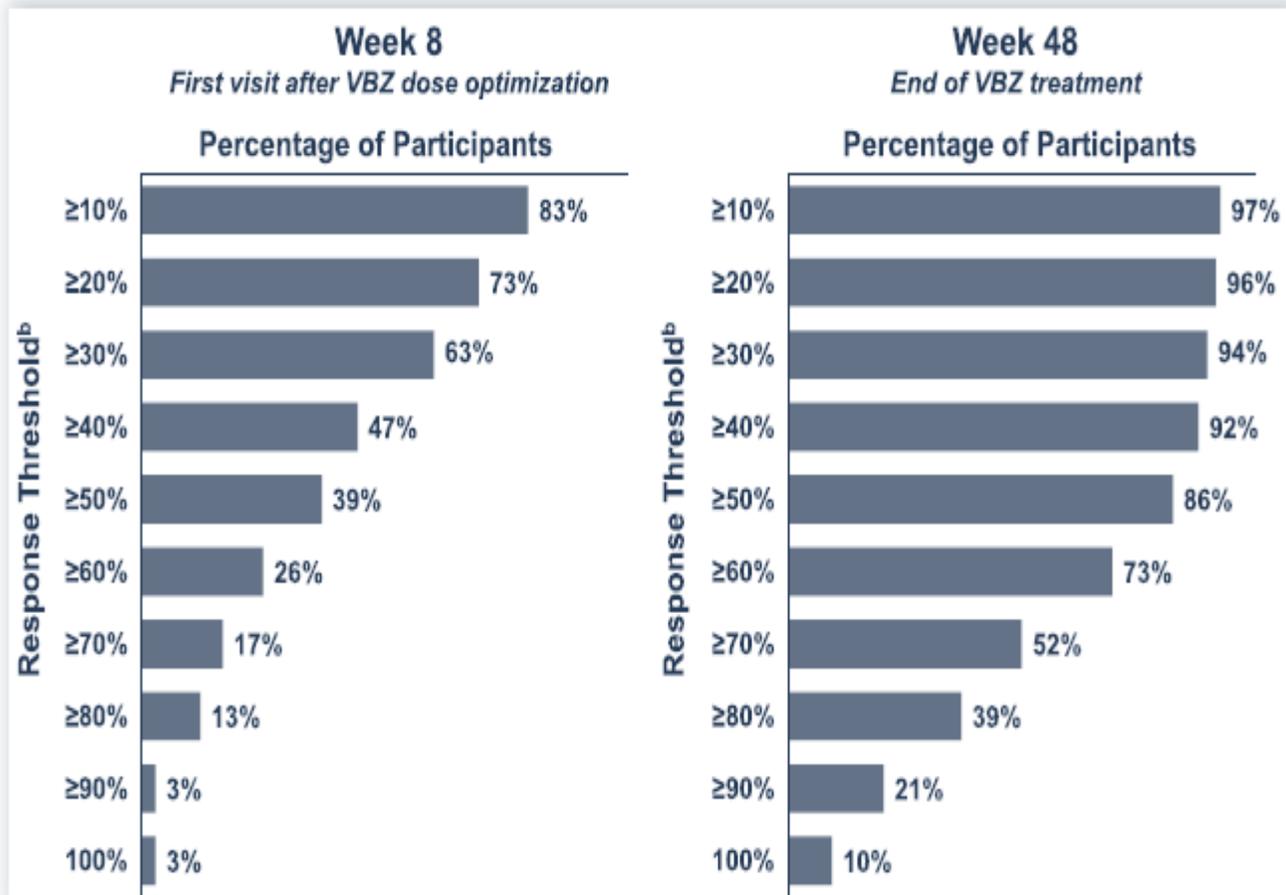


## KINECT 4 Study



No new safety signals or concerns emerged in either study

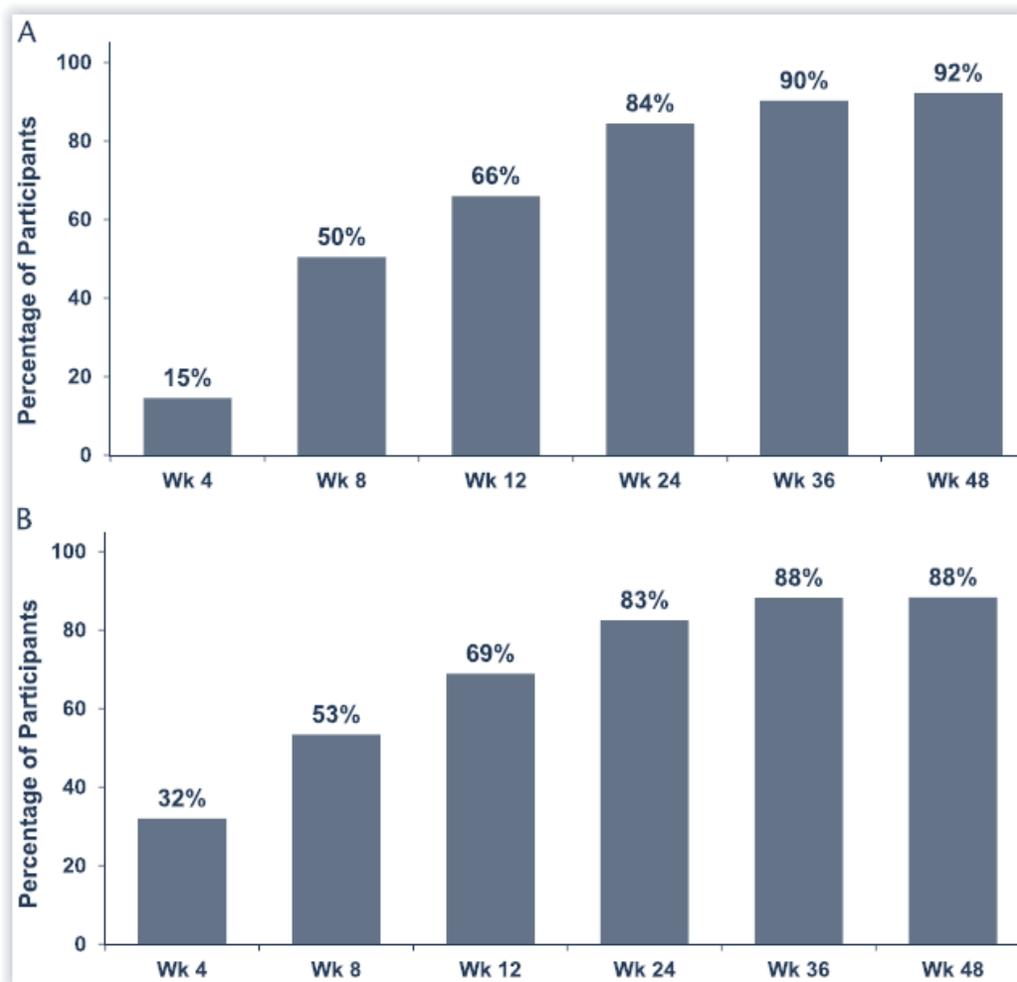
# Range of Total AIMS Score Response Thresholds at Week 8 and Week 48 with Valbenazine: KINECT 4 Study (N=103)



## Sustained Response with Valbenazine Treatment

≥50% AIMS improvement at Week 8 and at Week 48 (sustained response)	95% n/N = 38/40
<50% AIMS improvement at Week 8 but ≥50% AIMS improvement at Week 48	81% n/N = 51/63
≥50% AIMS improvement at Week 48	86% n/N = 89/103

# Much or Very Much Improved on Clinical Global Impression of Change (CGI-TD) and Patient Global Impression of Change (PGIC) AIMS Category Shifts at Week 48 with Valbenazine Treatment (N=103)



AIMS Item	Participants With AIMS Item Shifts (Score $\geq 3$ to $\leq 2$ <sup>†</sup> ), % (n/N)
1. Face	98 (40/41)
2. Lips	100 (63/63)
3. Jaw	98 (50/51)
4. Tongue	98 (58/59)
5. Upper extremities	100 (50/50)
6. Lower extremities	100 (29/29)
7. Trunk	89 (23/26)
8. Global (site-rater judgment) <sup>‡</sup>	96 (94/98)
8. Global (highest score from items 1–7) <sup>§</sup>	94 (93/99)

\* Total number of participants who completed 48 weeks of open-label, once-daily treatment with valbenazine (40 or 80 mg).

<sup>†</sup> Shift from “moderate” or “severe” to “mild” or better (based on AIMS scoring by site raters).

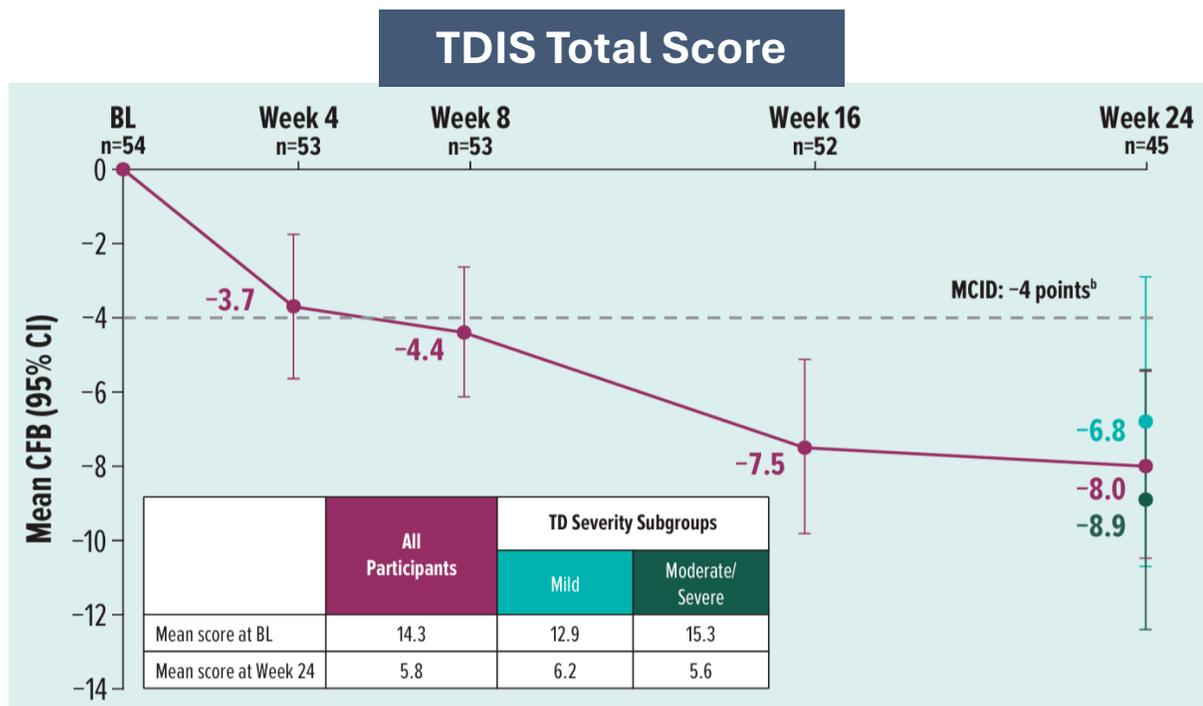
<sup>‡</sup> Based on investigators' ratings of item 8 (based on clinical judgment regarding the entire examination as a whole).

<sup>§</sup> Based on investigators' highest single score from items 1–7 (ie, determined algorithmically from the investigator's individual ratings).

N, number of participants with item score  $\geq 3$  at baseline; n, number of participants with item score  $\leq 2$  at Week 48.

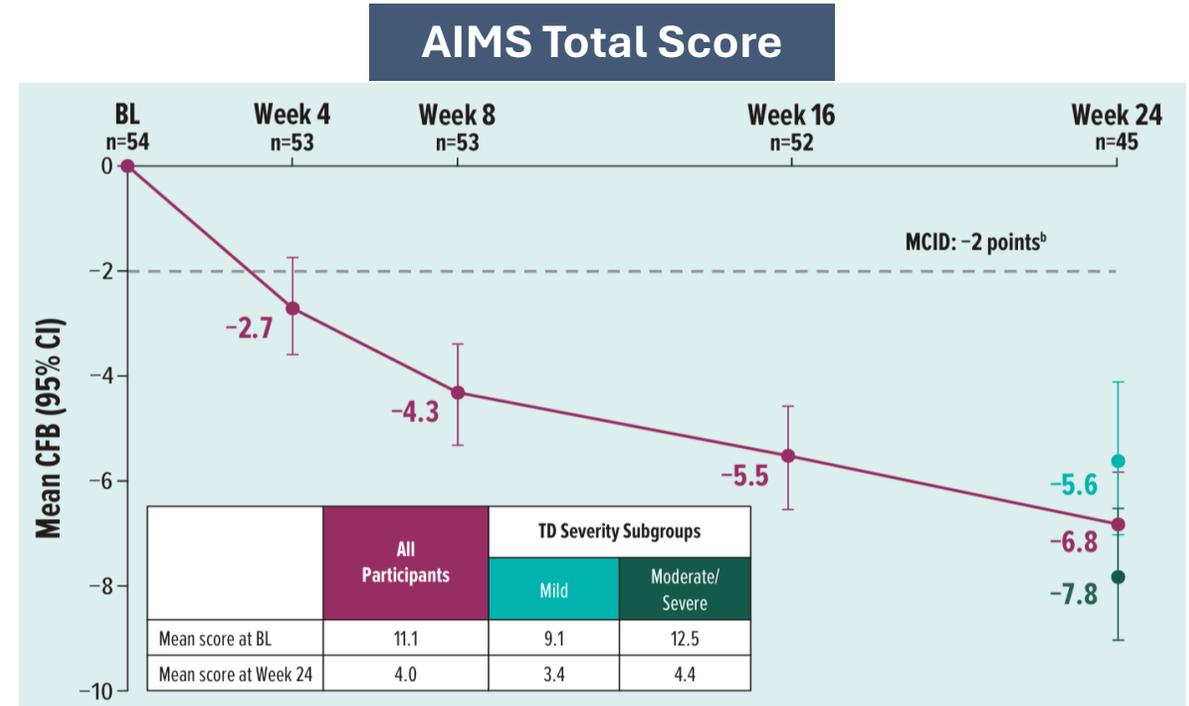
AIMS, Abnormal Involuntary Movement Scale.

# Valbenazine Improves the Impacts and Symptoms of TD: Topline Results of the Tardive Dyskinesia Impact Scale (TDIS) and AIMS Scale from the Phase 4 KINECT-PRO™ Study



<sup>a</sup> TDIS total score ranges from 0 to 44, with higher scores indicating worse impact. The total score is summed from the 11-item scores, each of which range from 0 (no impact) to 4 (extreme impact).

<sup>b</sup> From: Farber RH, et al. *Value in Health*. 2023;26(12):S462.



<sup>a</sup> AIMS total score ranges from 0 to 28, with higher scores indicating greater symptom severity. AIMS total score is comprised of the summed scores of AIMS items 1-7, each of which rate dyskinesia severity from 0 (no dyskinesia) to 4 (severe dyskinesia).

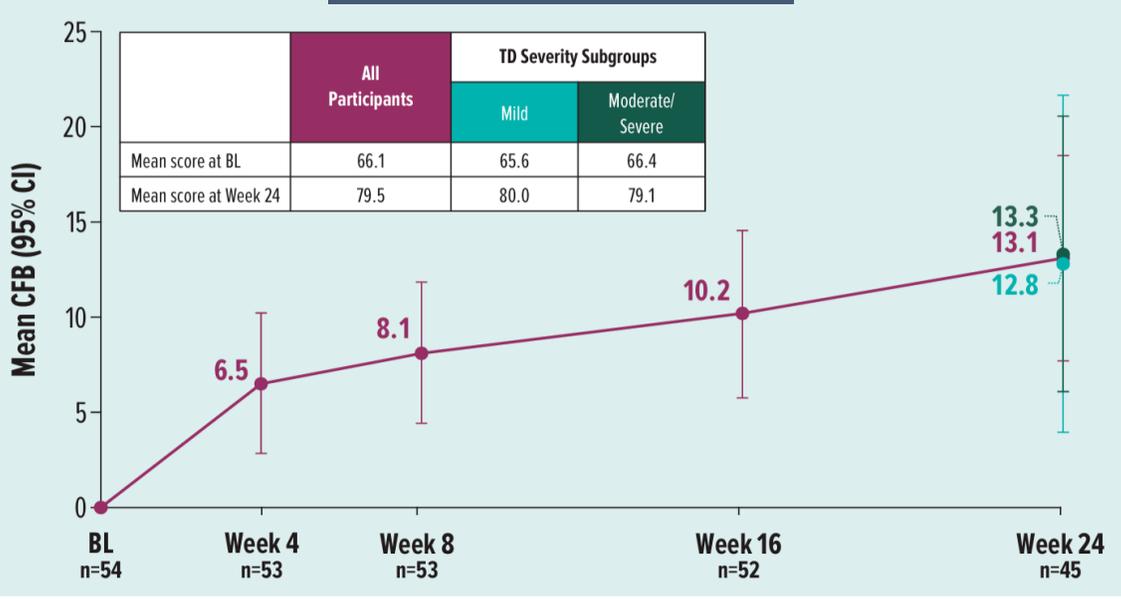
<sup>b</sup> From: Stacy M, et al. *Mov Disord*. 2019;34(8):1203-1209.

**CFB = change from baseline; MCID = minimum clinically important difference.**

**Dunayevich E, et al. Presented at: Psych Congress Elevate; May 28-31, 2025; Las Vegas, NV.**

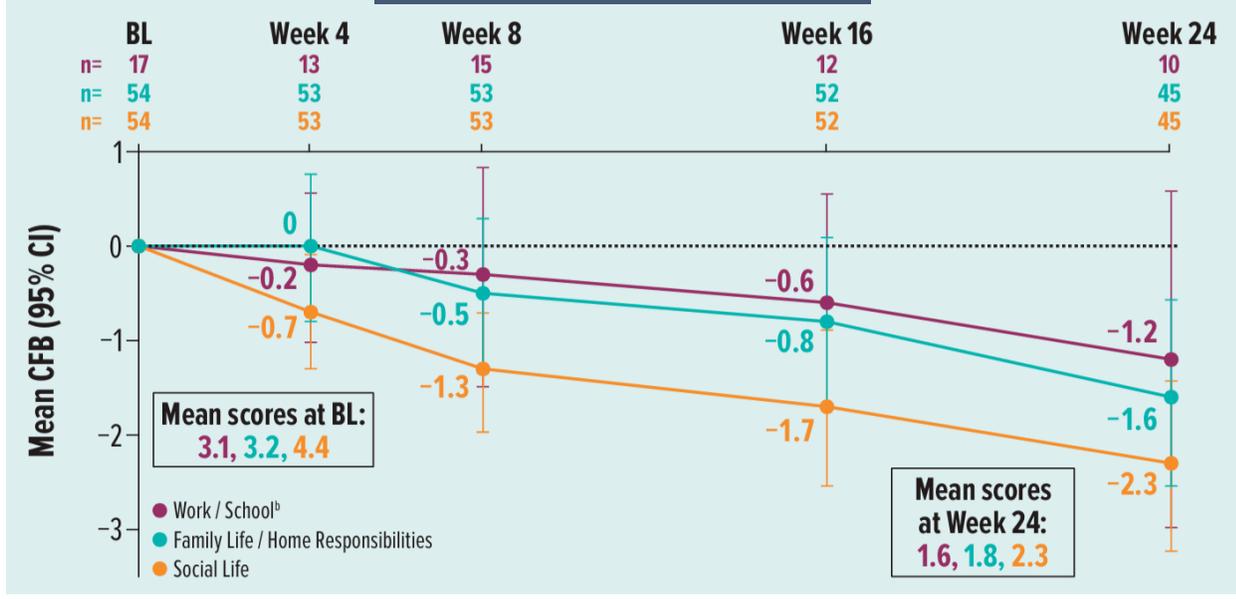
# Valbenazine Improves the Impacts and Symptoms of TD: Topline Results of the EuroQoL Visual Analogue Scale (EQ-VAS) and Sheehan Disability Scale (SDS) from the Phase 4 KINECT-PRO™ Study

## EQ-VAS Score



<sup>a</sup>EQ-VAS ranges from 0 (“worst health you can imagine”) to 100 (“best health you can imagine”).

## SDS Domain Scores



<sup>a</sup>SDS domain scores each rate functional impairment from 0 (none at all) to 10 (extremely).

<sup>b</sup>Few study participants were working or attending school during the study (n=17 at BL). Therefore, interpretation of these results is limited.

# Formulations and Administration of Valbenazine

Valbenazine	
<b>Dosage forms</b>	<ul style="list-style-type: none"><li>• 40, 60, 80 mg capsules</li><li>• 40, 60, 80 mg sprinkle capsules</li></ul>
<b>Dosing</b>	<ul style="list-style-type: none"><li>• Start 40 mg once daily with or w/o food</li><li>• Increase to 60 or 80 mg/day after 1 week</li><li>• Sprinkle capsules are broken open and sprinkled on soft food</li></ul>
<b>Drug-drug interactions</b>	<ul style="list-style-type: none"><li>• MAOIs</li><li>• Strong CYP3A4 inducers</li><li>• Maximum dose 40 mg with strong CYP2D6 or strong CYP3A4</li></ul>
<b>Contra-indications</b>	<ul style="list-style-type: none"><li>• Known hypersensitivity to valbenazine or any components of capsule</li></ul>

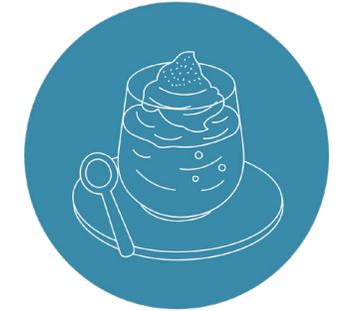
The valbenazine sprinkle capsule is bioequivalent to the original formulation, and may be sprinkled onto soft foods such as:



Apple sauce



Yogurt



Pudding

# Key Learning Points



- ✓ Both **deutetrabenazine** and **valbenazine** are **efficacious** and **well-tolerated** in treating TD, and **differ** in their **metabolism in the liver** to produce **metabolites with varying affinity and selectivity for VMAT2**
- ✓ **Discontinuation** or **change in antipsychotic or psychotropics** is **not needed** when initiating deutetrabenazine or valbenazine
- ✓ Deutetrabenazine and valbenazine **did not worsen psychiatric illness or increase suicidality** in TD trials, although both have warnings for DIP

# Panel Discussion: Difficult Cases



# Complexities and Challenges of Assessing TD

# Telepsychiatry and TD: Challenging, Yet Better than Nothing

## Current Challenges

- Telepsychiatry makes it harder to complete a full AIMS
- Video is a challenging medium to do a full body evaluation
- No specific guidelines currently exist for TD evaluation using telepsychiatry



## Potential Solutions

- A suboptimal AIMS is better than no AIMS
- Having a family member/support system present during telepsychiatry visit vastly improves quality of TD exam
- Most (though not all) of the TD exam can be conducted via telepsychiatry
- Consider asynchronous recording of movements

# Meet Camille

- Camille is a 68-year-old woman living at an adult residence and followed by the local ACT team for treatment of schizophrenia; she is seeing you as the locum provider via telehealth

## History

- Camille has been receiving fluphenazine decanoate 50 mg q2 weeks and benztropine 1 mg BID
- A new clinician on the team increases the dose of benztropine because of Camille's shuffling gait, and although her gait appeared better, jerky movements of her fingers became more prominent
- The benztropine dose was increased to 3 mg BID; Camille's finger movements worsened, and she appeared to be grimacing involuntarily

***What would be your next step?***

# Top Telemedicine AIMS Tips

## Assessing the Lower Body

- They can sit further back from the camera, or a helper can hold the device if present
- Angle camera downwards or place device on coffee table or on floor

## Asynchronous AIMS Is an Option

- Teach procedures (and give instruction sheets) so patients can record themselves
- Symptoms are variable and may wax and wane, so patients can catch “bad days”
- Saves time and can overcome low-speed connection issues

## Advantages to Remote AIMS

- Can stare directly at their face for 10-15 seconds without awkwardness
- No fear/embarrassment of smell when observing feet without socks and shoes

# Assessment Distinguishing between Tardive Dyskinesia and Drug-Induced Parkinsonism

## Drug-Induced Parkinsonism

- Occurs within a few weeks of DRBA initiation or dosage change
- Tremor is **rhythmic** and faster (3-6 cycles/sec) than TD movements (rarely >2 cycles/sec); jaw and hand tremors usually synchronous
- Associated with slowness (bradykinesia) and rigidity
- May coexist with TD
- Typically resolves with DRBA discontinuation, but may persist for months

Increased risk with advanced age and presence of other drug-induced movement disorders (eg, akathisia, dystonia)



# Is It Tardive Dyskinesia (TD) or Drug-Induced Parkinsonism (DIP)?

Characteristic	Tardive Dyskinesia	Drug-Induced Parkinsonism
Onset	Delayed (months-years) after initiation of an antipsychotic	Immediate (hours-days-weeks) after initiation of an antipsychotic or after dose is increased
Motor symptoms observed	Arrhythmic movements (generally choreo-athetoid) of the face, trunk, and extremities	Rhythmic tremor (3-6 Hz), rigidity, shuffling gait; akathisia may be present
Immediate (hours-days-weeks) effects of increasing antipsychotic dose	Improves	Worsens
Immediate (hours-days-weeks) effects of decreasing antipsychotic dose	Worsens	Improves
Effects of anticholinergic medications (eg, benztropine)	Can worsen	Improves
Pharmacotherapeutic treatment options	VMAT2 inhibitors (tetrabenazine, valbenazine, deutetabenazine), ginkgo biloba, clonazepam, amantadine	Anticholinergics (for example, benztropine), amantadine

# Several Opportunities Present Themselves

- Switch from fluphenazine decanoate to another LAI
- Deprescribe benztropine
- If the TD remains, consider a VMAT2 inhibitor
- If the DIP remains, consider amantadine

***What order should we follow?***

# Optimizing VMAT2 Selection and Dosing

# Meet Fred

- Fred is a 49-year-old man living with difficult-to-treat depression, and he is seeing you as the provider for outpatient follow-up

## History

- Fred is prescribed dextromethorphan HBr-bupropion HCl ER tabs 45 mg/105 mg BID and aripiprazole 2 mg qAM for MDD
- At follow-up, Fred exhibits increased blinking, jaw clenching, grimacing, and “piano-playing” finger movements, all of which are intermittent and non-rhythmic
- The previous provider noted “EPS” in the progress note from the last visit 8 weeks ago, decreasing aripiprazole from 5 mg qAM to 2 mg qAM, and Fred tells you, “my mood is not as good as it was”

***What would be your next step?***

# Overview of the VMAT2 Inhibitors FDA-Approved for TD

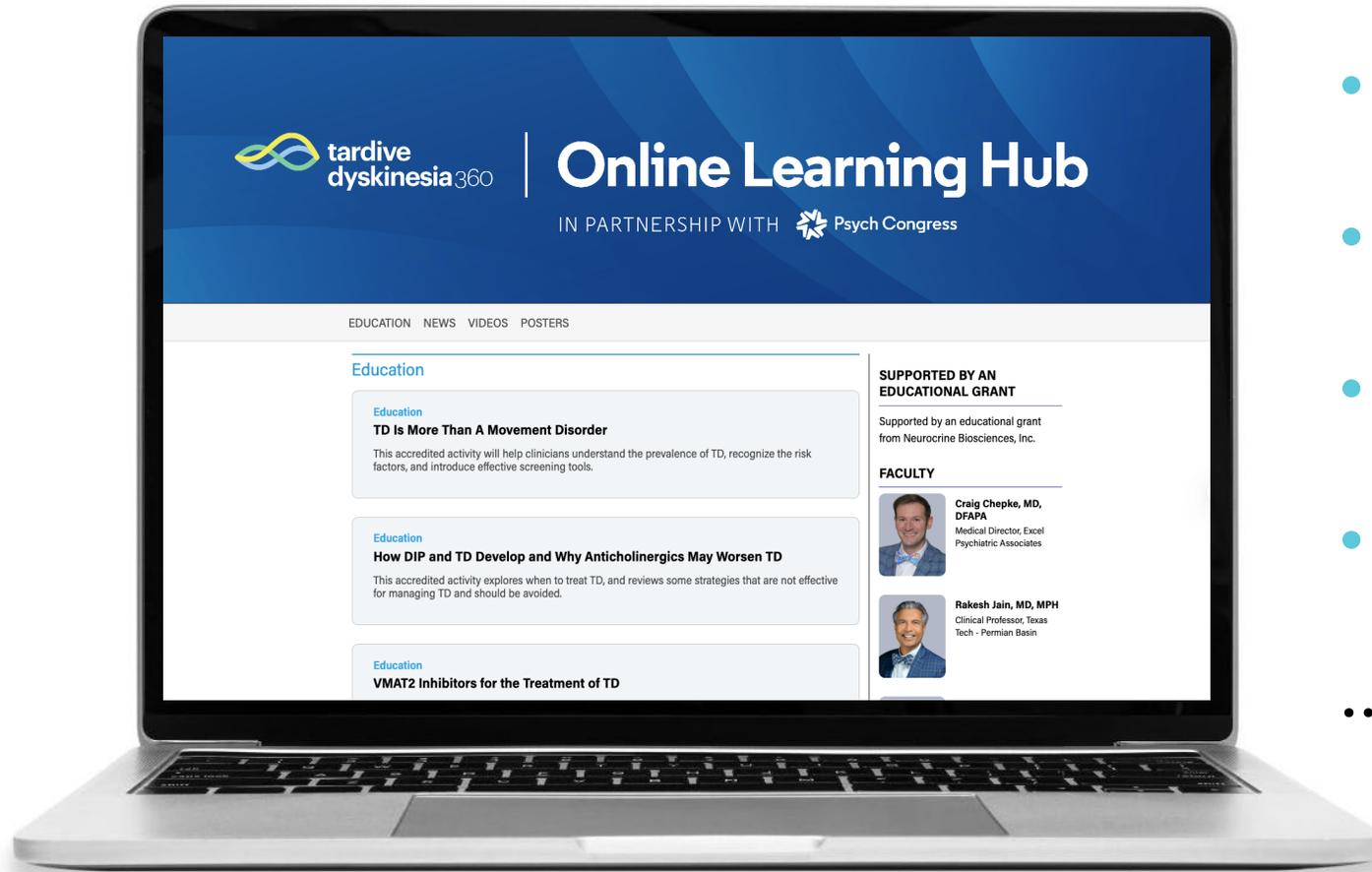
	Valbenazine	Deutetrabenazine XR
<b>Dosage forms</b>	Capsules and sprinkle capsules: 40 mg, 60 mg, and 80 mg	Tablets: 6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg
<b>Dosing</b>	Start 40 mg qD once daily with or w/o food x 1 week, increase to 60 or 80 mg qD	Start 12 mg qD once daily with or w/o food, increase by 6 mg weekly to at least 24 mg qD
<b>Active metabolites</b>	(+)α-HTBZ	(+)deuterated β-HTBZ (primary), (+)deuterated α-HTBZ
<b>CYP interactions</b>	Max dose 40 mg with strong 2D6 or 3A4 inhibitors or in 2D6 poor metabolizers; do not give with 3A4 inducers	Max dose 36 mg with strong 2D6 inhibitors Not studied in 2D6 PM, but expected to be comparable to strong 2D6 inhibition
<b>Contraindications</b>	Known hypersensitivity to valbenazine or any components of capsule	Use with MAOIs or other VMAT inhibitors Suicidal or inadequately treated depression in Huntington's, hepatic impairment

**Both deutetrabenazine and valbenazine are efficacious and well-tolerated in treating TD, regardless of psychiatric diagnosis**

**Neither requires discontinuation or change in antipsychotic or psychotropic**

**Neither was shown to worsen psychiatric illness or increase suicidality in TD trials; both have warnings about DIP**

# Visit the Resource Center



- Patient videos
- Expert insights
- Latest news
- Complimentary CME

...and more!

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QR code



# Practical Takeaways



**TD vs drug-induced parkinsonism (DIP):** TD and DIP are distinct disorders with different causes. TD has a delayed onset, and anticholinergic medications can worsen symptoms.



**Importance of regular monitoring:** A semi-structured assessment can be done at every patient visit through observation. Structured exams (eg, AIMS) should be conducted annually for individuals on second-generation antipsychotics, with increased monitoring for those on first-generation antipsychotics or at higher risk.



**Clinical impact vs AIMS score:** A low AIMS score does not always indicate a low impact on the patient's quality of life. Functional impairment should be assessed beyond the numeric score.



**Treatment considerations:** VMAT2 inhibitors (valbenazine and deutetrabenazine) are the recommended treatments for TD. These medications are effective, well-tolerated, and do not require adjustments to antipsychotic therapy. Anticholinergics should be avoided as they may worsen symptoms.

# Q&A

