CME CAST EPISODE 2

Making the Right Moves for the Long-Term Management of Antipsychotic-Induced TD: Evidence-Based Strategies to Improve Quality of Life and Patient-Centered Outcomes

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CME OUTFITTERS

Learning Objective

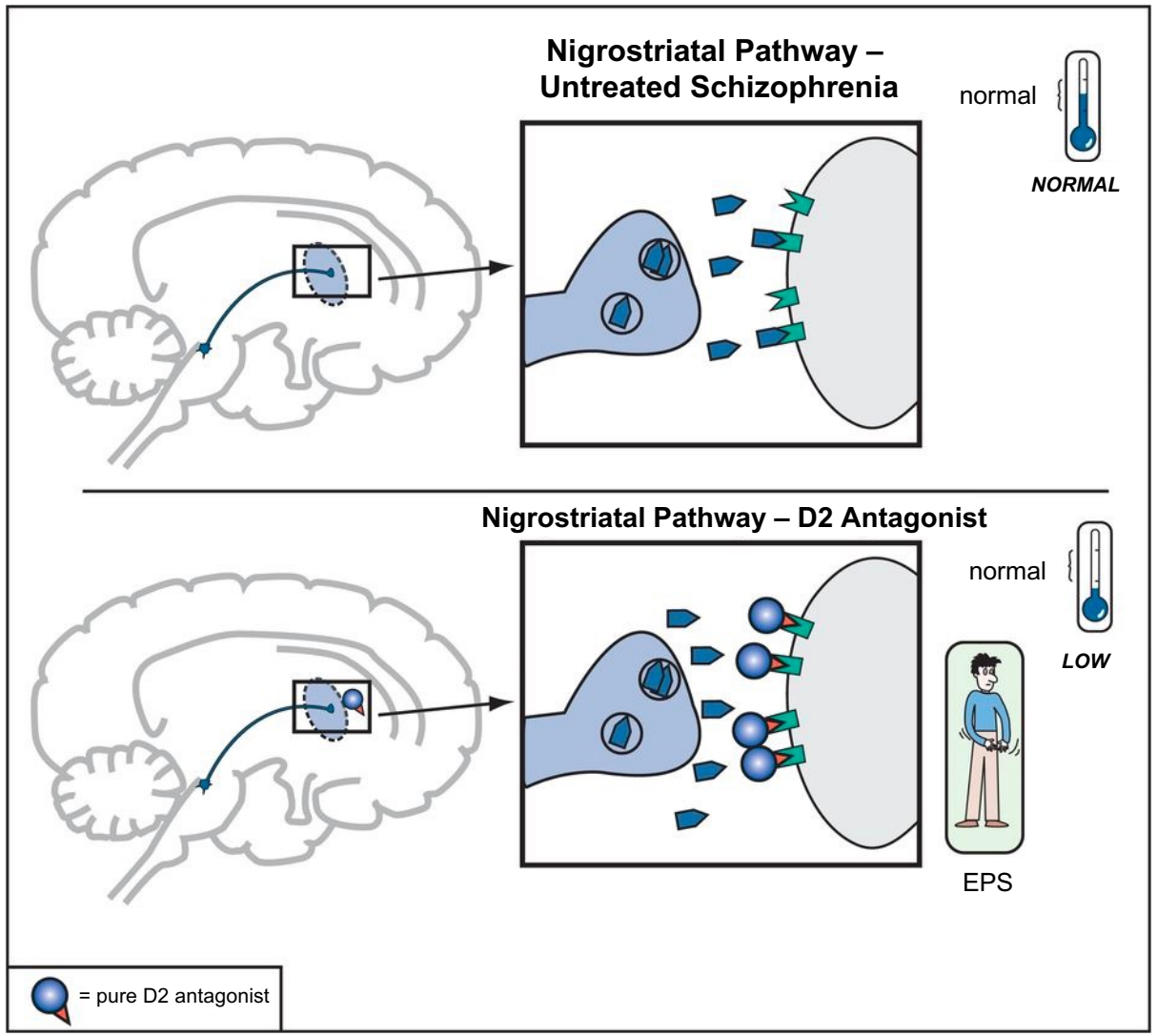
Incorporate evidence-based, expert guidance on the use of VMAT2 inhibitors to minimize the burden and improve QoL in patients with TD

TD Prevalence: A Meta-Analysis

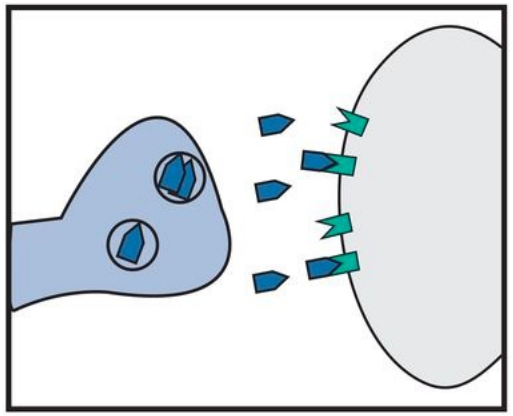
Year	No. of Patients	Percentage Naïve / Currently Taking Antipsychotics
2000-2015	5,103	SGAs: 20.7%
2000-2015	5,062	FGAs: 30%
2000-2015	346	FGA naïve: 7.2%
2000-2015	11,493	Pooled prevalence: 25.3%
Global Mean TD prevalence: 25.3%		
≥ 2 Antipsychotic Classes/Combinations		
SGAs vs. FGAs		Risk ratio = 0.80, p = 0.011
SGA+FGA vs. FGA		Risk ratio = 0.80, p < 0.001

Carbon M, et al. *J Clin Psychiatry.* 2017;78(3):e264-e278

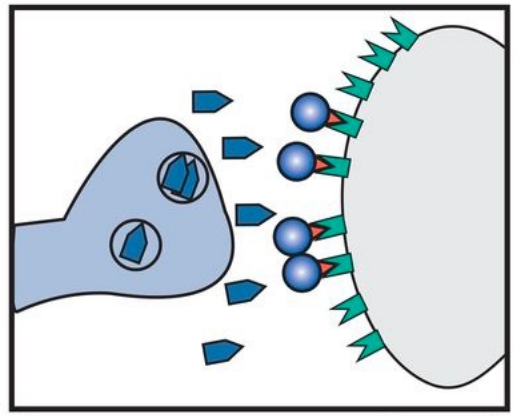
Pathogenesis of Tardive Dyskinesis (TD)



Blockade of D2 receptors in the Nigrostriatal dopamine pathway Causes them to upregulate



This upregulation may lead to tardive dyskinesia



Adapted from Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. 2013:129-236.

Goals of Treatment in TD

Maintain psychiatric stability

Generally, do not attempt to eliminate all TD due to risk of adverse effects with overtreatment

- VMAT2 inhibitors: parkinsonism and sedation

Reduce severity of TD so that it is no longer impacting quality of life significantly:

- Interfering with activities of daily living (ADLs)
- Causing physical problems (such as dental damage)
- Affecting social function including embarrassment
- Adversely affecting mood or psychiatric symptoms

Bhidayasiri R, et al. *J Neurol Sci*. 2018;389:67-75.; Keepers GA, et al. *The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia*. 3rd edition. Available at psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841.

American Academy of Neurology:
Updated Recommendations for Treatment of Tardive Syndromes

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***
• New generation VMAT2 inhibitors (deutetrabenazine and valbenazine)	• Benzodiazepine* • Ginkgo biloba	• Antiparkinsonian agents • Early-approved VMAT2 inhibitor (tetrabenazine*) • Pallidal deep brain stimulation (intractable TD)	• Withdrawing causative agents • Switching from typical to atypical antipsychotic

*Benzodiazepine and tetrabenazine are not FDA-approved for the treatment of tardive syndromes.
VMAT = vesicular monoamine transporter type 2
Adapted from: Bhidayasiri R, et al. *J Neurol Sci*. 2018;389:67-75.

American Psychiatric Association: VMAT2 Medications for Tardive Dyskinesia

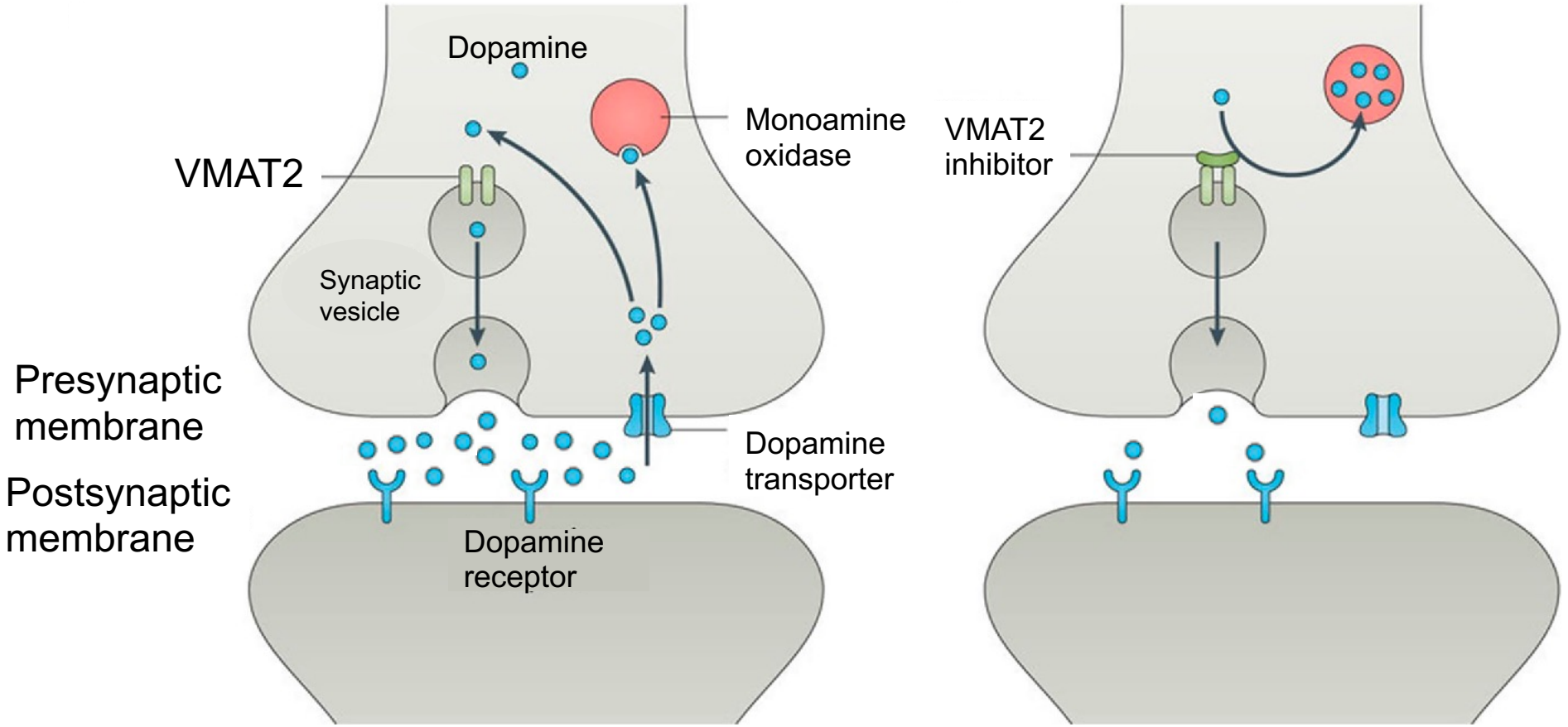
APA *recommends* (1B) that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).[1]

Based on information from a good-quality systematic review[2] on deutetrabenazine and valbenazine treatment and less robust clinical trials on tetrabenazine*

*Tetrabenazine is not FDA-approved for tardive dyskinesia.

1. Keepers GA, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd edition. Available at psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841.; 2. Solmi M, et al. *Drug Des Devel Ther*.; 2018;12:1215-1238.

How Do VMAT2 Inhibitors Reduce TD?



Niemann N, et al. *Drugs*. 2018;78(5):525-541.

Key Features of Deutetrabenazine and Valbenazine

	Deutetrabenazine	Valbenazine
Frequency of Administration	Twice daily	Once daily
Titration	Dose to efficacy/tolerability	Titrate to target dose of 80 mg/d
Food Requirement	Yes	No
Drug Interactions	CYP2D6 modulators	CYP2D6 and CYP3A4 modulators
Contraindications	Hepatic impairment, taking reserpine, monoamine oxidase inhibitors, or tetrabenazine, suicidal or untreated/inadequately treated depression	Known hypersensitivity to valbenazine or any components of the product
Warnings	Neither deutetrabenazine nor valbenazine have black box warnings for depression or suicidality	

Correll CU, et al. *J Clin Psychiatry*. 2021;82(6):NU20016AX1C.; Drugs@FDA.gov.;
Schneider F, et al. *Clin Pharmacol Drug Dev*. 2021;10(6):647-659.; Khorassani F, et al. *Am J Health-Syst Pharm*. 2020; 77:167-174.

Adverse Effects (≥ 4%) of Deutetrabenazine and Valbenazine

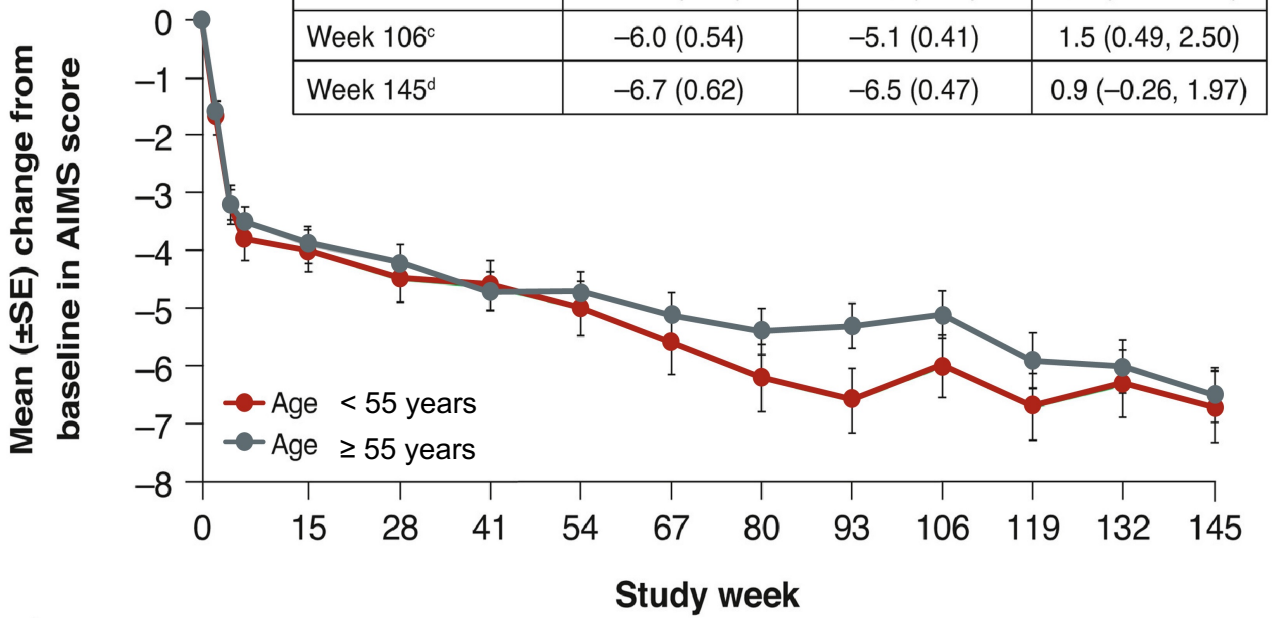
	Deutetrabenazine	Valbenazine
Somnolence	X	X
Diarrhea	X	
Dry mouth	X	X
Fatigue	X	X
Urinary tract infection	X	
Insomnia	X	
Anxiety	X	
Constipation	X	X
Contusion	X	
Balance disorders (falls, gait disturbance, dizziness)		X
Disturbance in attention		X
Blurred vision		X
Urinary retention		X
Sedation		X

Drugs@FDA.gov

Deutetrabenazine: Sustained Efficacy in Younger (< 55) and Older (≥ 55) Patients with TD

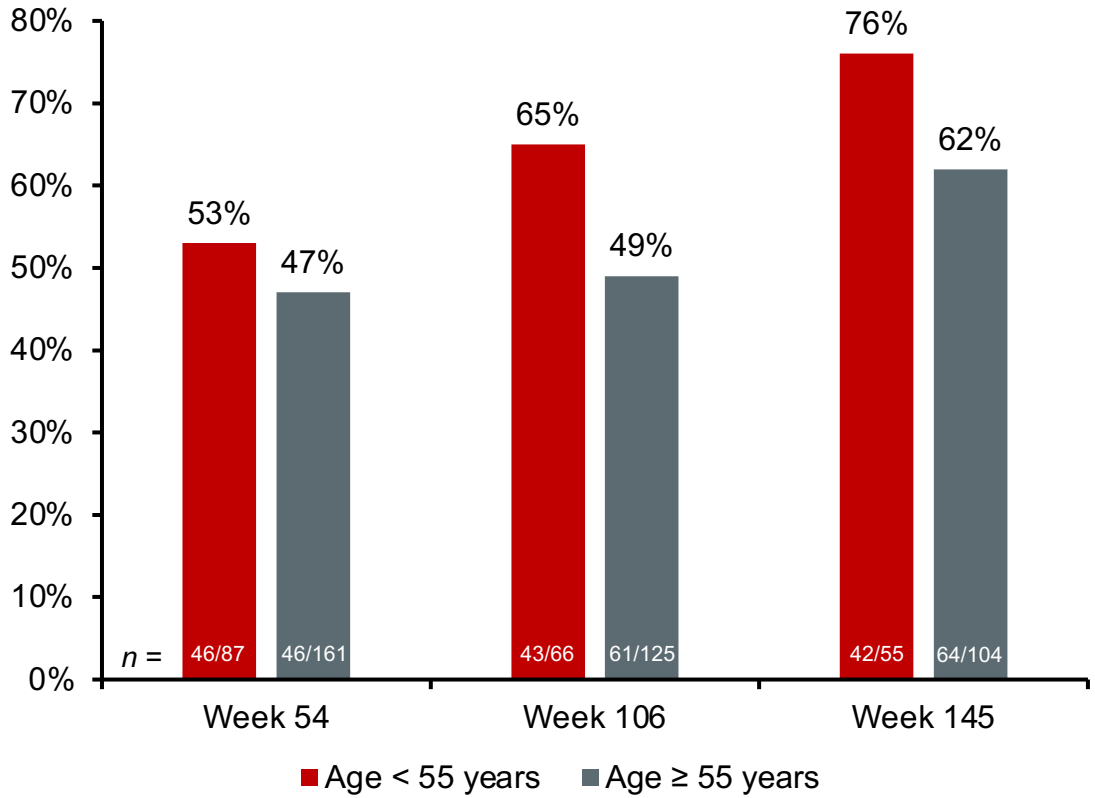
Change in AIMS by Age Group

Mean (±SE) change from baseline	Age <55 years	Age ≥55 years	ΔLSM (95% CI)
Week 54[b]	–5.0 (0.47)	–4.7 (0.34)	0.9 (0.02, 1.82)
Week 106[c]	–6.0 (0.54)	–5.1 (0.41)	1.5 (0.49, 2.50)
Week 145[d]	–6.7 (0.62)	–6.5 (0.47)	0.9 (–0.26, 1.97)



Age, n												
< 55 years	119	112	101	93	87	77	71	69	66	63	58	55
≥ 55 years	218	193	186	174	162	149	145	139	126	120	111	105

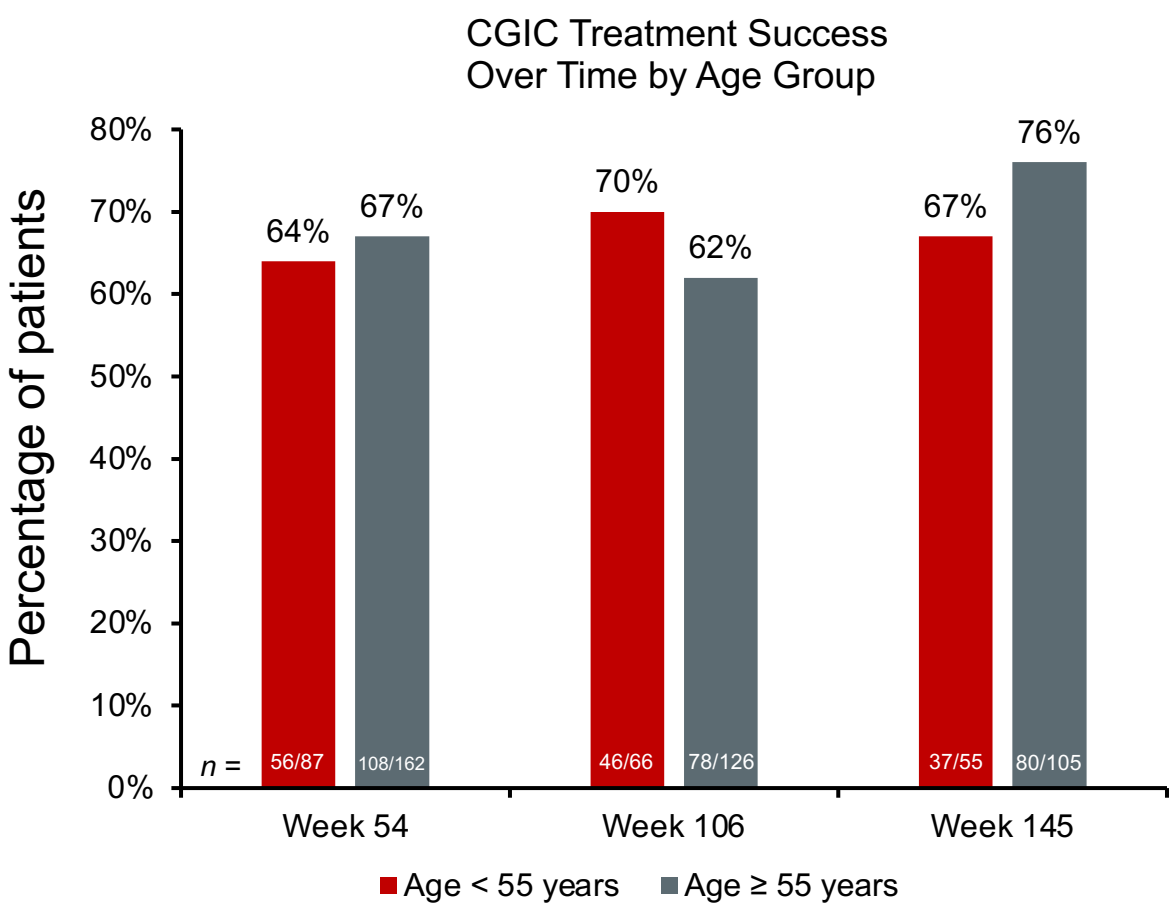
Percentage of Patients Achieving > 50% AIMS Improvement from Baseline

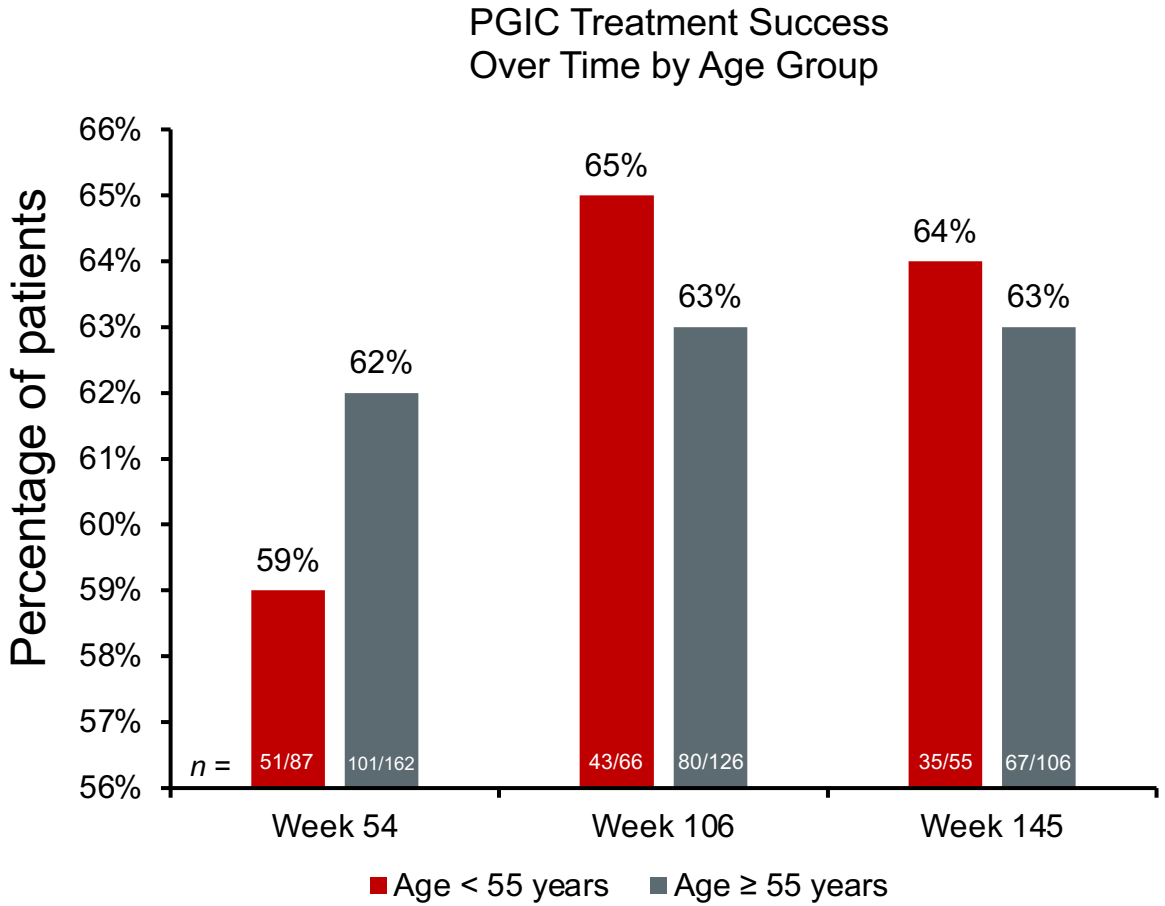


AIMS = Abnormal Involuntary Movement Scale; ΔLSM = least-squares mean difference; SE = standard error

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

Deutetrabenazine: Treatment Success Measured by CGIC and PGIC





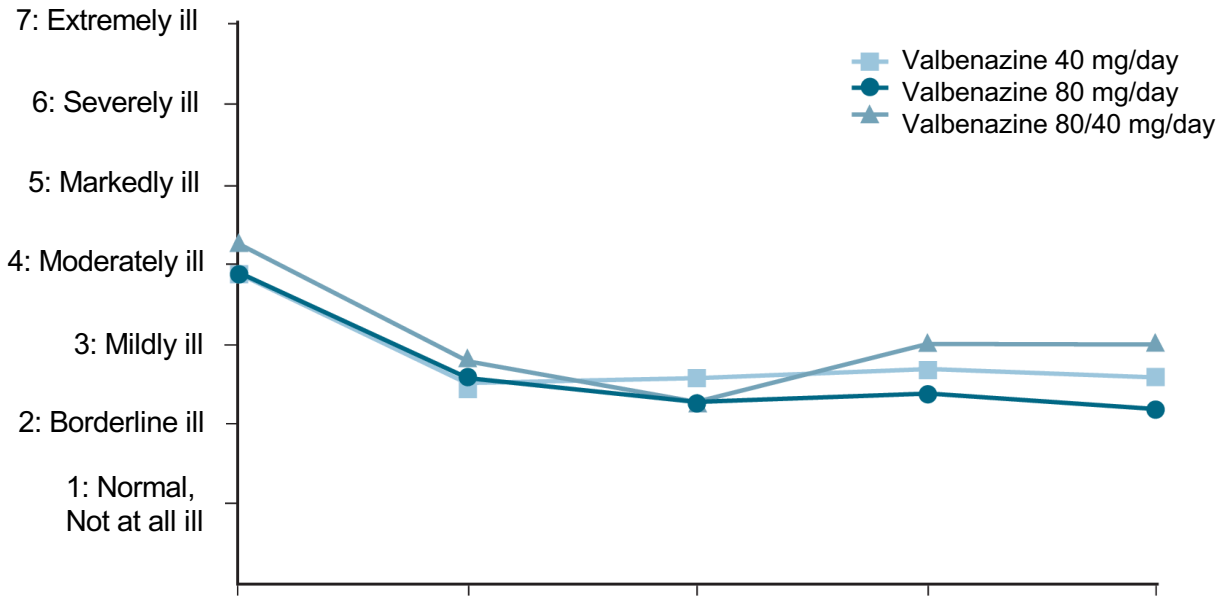
Younger and older patients also demonstrated improved quality of life from baseline to week 106 of treatment, particularly in terms of stigma, emotional, pain, activity of daily living, and social domains as measured by the modified Craniocervical Dystonia Questionnaire

CGIC = Clinical Global Impression of Change; PGIC = Patient Global Impression of Change
Treatment success was defined as “very much improved” or “much improved” on the CGIC/PGIC.

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

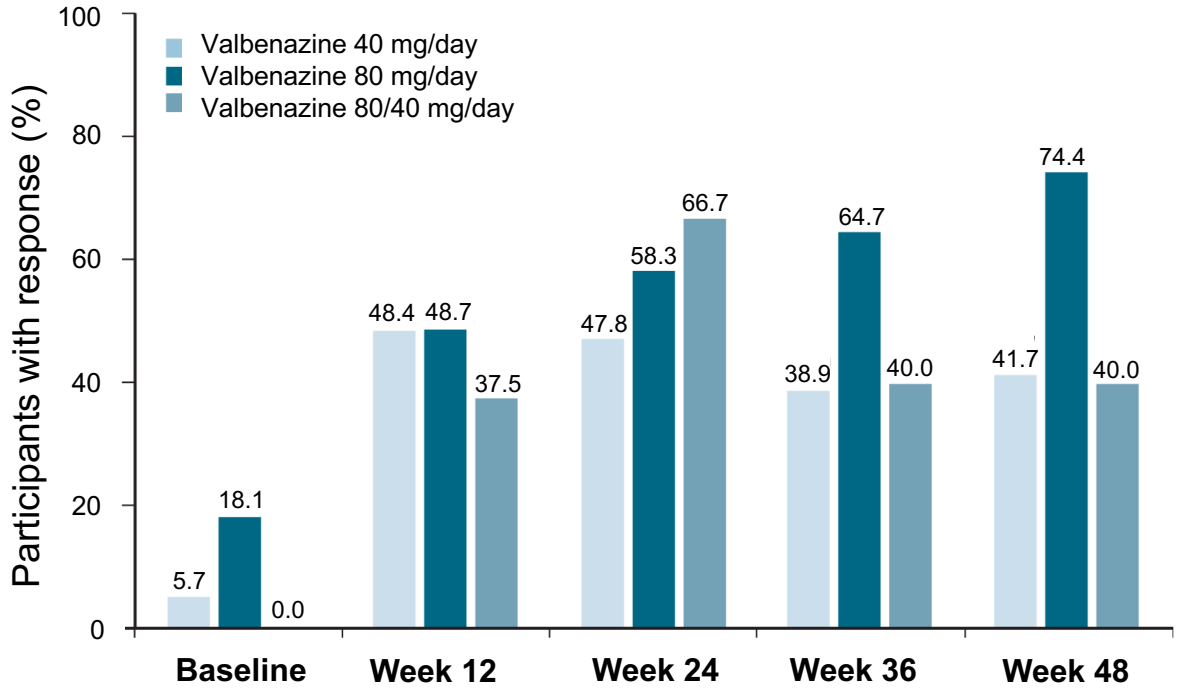
Valbenazine: Long-Term Efficacy in TD

CGIS-TD Means Scores by Visit and Dose



	Baseline	Week 12	Week 24	Week 36	Week 48
40 mg/day, N;	35	31	23	18	12
Mean (SD):	3.9 (1.1)	2.5 (0.9)	2.6 (1.2)	2.7 (0.9)	2.6 (0.8)
80 mg/day, N:	116	115	96	68	39
Mean (SD):	3.9 (1.3)	2.6 (1.0)	2.3 (1.0)	2.4 (1.1)	2.2 (1.1)
80/40 mg/day, N	8	8	6	5	5
Mean (SD):	4.3 (0.7)	2.8 (1.0)	2.3 (1.0)	3.0 (1.0)	3.0 (1.0)

Percentage of Patients with CGIS-TD score of 1 (“normal, not at all ill”) or 2 (“borderline ill”)



	Baseline	Week 12	Week 24	Week 36	Week 48
40 mg/day, N;	2/35	15/31	11/23	7/18	5/12
80 mg/day, N:	21/116	56/115	56/96	44/68	29/39
80/40 mg/day, N:	0/8	3/8	4/6	2/5	2/5

CGIS-TD = Clinical Global Impression of Severity-Tardive Dyskinesia

Lindenmayer J-P, et al. CNS Spectr. 2021;26(4):345-353.

Tardive Dyskinesia in Psychiatry Practices

Suggested Physical and Laboratory Assessments for Patients with Schizophrenia: Assessments related to other specific side effects of treatment

	Initial or Baseline Assessments	Follow-up Assessments
Antipsychotic-induced movement disorders	• Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia • Assessment with a structured instrument (e.g., AIMS, DISCUS) if such movements are present	• Clinical assessment of akathisia, dystonia, parkinsonism, and other abnormal involuntary movements, including tardive dyskinesia, at each visit • Assessment with a structured instrument (e.g., AIMS, DISCUS) at a minimum of every 6 months in patients at high risk of tardive dyskinesia and at least every 12 months in other patients, as well as, if a new onset or exacerbation of preexisting movements is detected at any visit • Use of telehealth

DISCUS = Dyskinesia Identification System: Condensed User Scale

Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-872.

Tardive Dyskinesia in Neurology Practices

Evaluation can be requested by patient, psychiatrist or other health care professional

Role of telehealth

Patients often are seeking knowledge, diagnosis and/or treatment

Psychiatrists/other health care professional may

- Refer for initial diagnosis or treatment
- Be seeking alternate treatment options for their patients
  - Due to lack of response to initial agent or management strategy
  - For management of persistent movement disorder

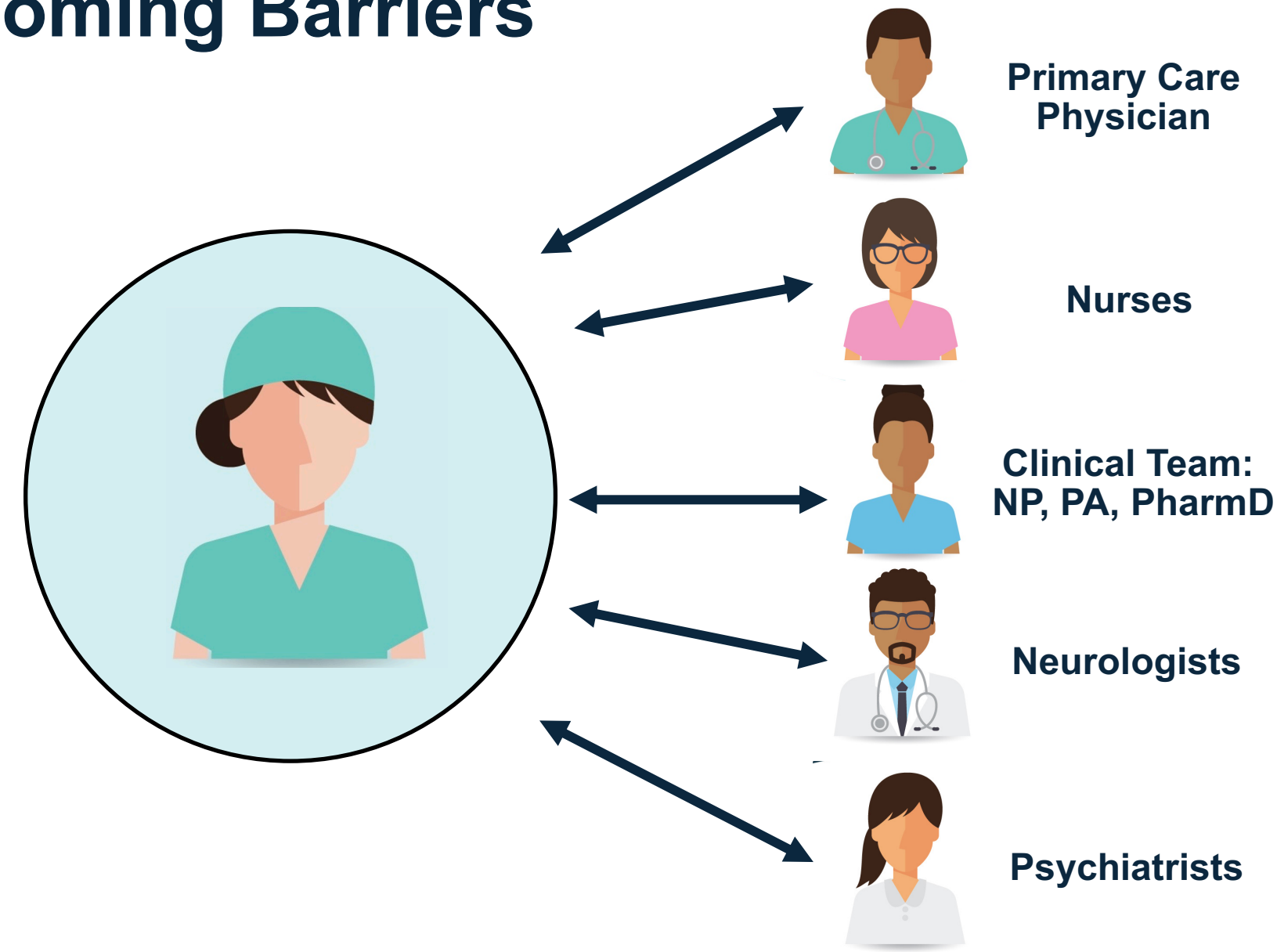
APD = Advanced Parkinson's Disease

Personalizing Care for TD

Perform	Perform regular and specific assessments for early tardive dyskinesia
Recognize and diagnose	Recognize and diagnose TD
Document	Document severity
Discuss	Discuss treatment options with patients and caregivers
Identify	Identify patients who can be safely: • Tapered off treatment if alternative therapies are available • Switched to another SGA • Reduced dosage
Individualize	Individualize use of VMAT2 inhibitors

Tarsy D, et al. *Handb Clin Neurol*. 2011;100:601-616; Caroff SN. *Neuropsychiatr Dis Treat*. 2019;15:785–794.

Success Requires the Whole Team: Identifying and Overcoming Barriers



Conclusions

- TD is a common, frequently permanent, and potentially disabling adverse effect of dopamine blocking medications (antipsychotics, metoclopramide)
- VMAT2 inhibitors are thought to decrease TD symptoms by depleting dopamine in presynaptic neurons
- Monitor patients at-risk for TD, and manage TD as quickly as possible after it appears
- FDA-approved VMAT2 inhibitors for persistent TD are:
  - Deutetrabenazine
  - Valbenazine

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider the pathogenesis of TD and the role of the FDA-approved VMAT2 inhibitors deutetrabenazine and valbenazine in reducing the burden of TD and improving QoL
- Routinely monitor at-risk patients (those taking first- and second-generation antipsychotics) for TD and effectiveness of treatment in those diagnosed with TD
- Individualize the management of TD using VMAT2 inhibitors

CME CAST EPISODE 1

Using Measurement-Based Care to Improve the Accurate, Early Detection of TD

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