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AIMing to Optimize Tardive Dyskinesia Care

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Disclosures

Christoph U. Correll, MD: *consultant/advisor/speaker:* AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/Johnson & Johnson, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Viatris; *researcher:* Janssen, Takeda; *stock/stock options:* Cardio Diagnostics, LB Pharma, Mindpax, Quantic.

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Learning Objectives

- Identify relative prevalence and risk of TD across various disease states
- Interpret screening tools for the identification of TD, including patient and caregiver reports
- Construct an individualized treatment plan for patients with TD with age-related or other special characteristics

Overview

- What Is TD?
 - Definition, Risk Factors, Patient Insight
- How Often Does TD Occur?
- How Do We Screen for and Diagnose TD?
- How Can We Prevent and Treat TD?

What Is TD?

Definition, Risk Factors, Patient Insight



What Is Tardive Dyskinesia?

- Involuntary repetitive, but irregular, movements
 - **Choreiform** movements (ie, rapid, jerky, nonrepetitive), **athetoid** movements (ie, slow, sinuous, continual), **(semi)rhythmic** movements (ie, stereotypies)
 - Mostly in the oral, lingual, and buccal regions; less often, movements are present in hands, legs, feet, and torso
 - eg, tongue protruding, puckering, chewing, and grimacing
- Tardive dyskinesia can be severe and persistent and have medical and psychosocial consequences
- Most associated with the use of dopamine receptor–blocking agents—namely, antipsychotics—but can also be because of other agents, including metoclopramide

Impact of TD on Everyday Life: Medical/Physical

- Motor system impairments—*topography matters*
- Orolingual TD
 - Speech (eg, dysarthria; issues with respiration, phonation, articulation), verbal communication
 - Dentition (eg, attrition, abfraction)
 - Temporomandibular joint pain/myalgia
 - Swallowing difficulties
- Upper extremity TD
 - Fine motor skills, instrumental activity of daily living, written communication
- Truncal, lower extremity TD
 - Gait, posture, and postural stability
 - Strength, power flexibility, physical capacity, exercise

Strassnig et al. CNS Spectr. 2018;23:370.

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Impact of TD on Everyday Life: Psychological/Cognitive

- Awareness (depends on topography, impairment, feedback, and insight)
- Cognition (associative studies), related to awareness
- Anxiety, worsened paranoia, isolation, stigma, social, and/or educational/vocational impairment
- Depression, suicidality

Strassnig et al. CNS Spectr. 2018;23:370.

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Impact-TD Scale

- Healthcare professional-rated scale
- Measure **interference**, **frequency**, and **distress** of functional impact of TD on a patient's life
 - 4 domains: Psychological/Psychiatric, Physical, Vocational/Educational/Recreational, Social Interactions
 - Each domain is rated 0 (no impact) to 3 (severe impact)*
**When rating overall impact of functional domain, consider degree of interference, distress, and frequency.*
 - Highest domain score = Global Impact-TD Score
- May use in addition to AIMS to monitor disease progress and response to treatment

Jackson et al. J Clin Psychiatry. 2022;84:22cs14563.

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Impact-TD Scale and Its Components

“For each of the 4 domains . . . consider information derived from the patient, caregiver, and your observations, then estimate the level of impact associated with [TD movements].”

Functional Domains and Consequences of TD

Psychological/Psychiatric	Vocational/Educational/Recreational
▪ Sadness, depression ▪ Anxiety, worry, concern ▪ Low self-esteem ▪ Hopelessness, loss of sense of purpose ▪ Poor concentration, attention, memory	▪ Problems gaining/maintaining job ▪ Problems with performance ▪ Challenges getting to school/work/activities ▪ Difficulty with colleague/classmate/customer interactions ▪ Difficulty performing tasks independently
Physical	Social Interactions
▪ Problems breathing ▪ Pain because of TD ▪ Difficulty sitting still/falling asleep ▪ Difficulty using utensils, writing, typing, dressing; speaking, chewing, swallowing; walking, maintaining balance	▪ Difficulty participating in social events ▪ Self-consciousness, embarrassment ▪ Avoid interacting with others ▪ Reduced quality of interpersonal communication

Jackson et al. J Clin Psychiatry. 2022;84:22cs14563.

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Tardive Dyskinesia: Risk Factors

Unmodifiable	Modifiable
<u>Patient Related</u>	<u>Comorbidity Related</u>
Older age (≥45 yr)	Diabetes
Female sex	Smoking
White and Black races	Alcohol/substance abuse
<u>Illness Related</u>	Baseline EPS
Longer illness duration	<u>Treatment Related</u>
Intellectual disability and brain damage	Dopamine receptor blocker
Negative symptoms in schizophrenia	Higher cumulative and current antipsychotic dose or plasma levels
Mood disorders	Early parkinsonian adverse effects
Cognitive symptoms in mood disorders	Treatment-emergent akathisia
Gene polymorphisms involving antipsychotic metabolism and dopamine functioning	Anticholinergic cotreatment
	Use of FGAs

Carbon et al. J Clin Psychiatry. 2017;78:e264. Solmi et al. J Neurol Sci. 2018;389:21.

Slide credit: clinicaloptions.com



Patient Awareness of Tardive Dyskinesia Varies

- Patients may not be aware of their TD symptoms
 - Not believed to be linked to sociodemographic or clinical profiles
 - Lack of awareness ≠ lack of impact on quality of life
- Studies over the years have consistently demonstrated this low awareness
 - 1999: among 43 patients with SCZ and TD, 46.5% had at least moderate unawareness of their TD; awareness did not improved over the study period of 2 yr
 - 2001: among 242 patients with SCZ who met criteria for TD, 67.4% were not aware of the presence of their TD symptoms
 - 2011: among 130 patients with SCZ and TD, 51% had no or low awareness of their TD
 - Although 94 (72%) of these patients had at least mild impairment of insight into their mental illness, this was not significantly correlated with low awareness of TD

Patients with low/no awareness of their symptoms will likely not seek care and treatment; thus, caregiver input and routine screening are important to monitor for TD and initiate early management

Chong et al. J Clin Psychopharmacol. 2001;21:235. Emsley et al. Eur Psychiatry. 2011;26:293. Arango et al. Am J Psychiatry. 1999;156:1097.

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How Often Does TD Occur?



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Tardive Dyskinesia Prevalence Meta-analysis: Overview

41 studies: N = 11,493, mean age: 42.8 yr, male: 66.4%, schizophrenia-spectrum disorders: 77.1%

The global mean TD prevalence was 25.3% (95% CI: 22.7-28.1)

Rates were lower with current SGA treatment (20.7%; 95% CI: 16.6-25.4, N = 5103) vs current FGA treatment (30.0%; 95% CI: 26.4-33.8, N = 5062; $P = .002$)

Lower TD prevalence of SGA relative to FGA was also confirmed in the subgroup of studies assessing and directly comparing ≥ 2 antipsychotic classes/combinations:

- SGAs vs FGAs (risk ratio: 0.80; 95% CI: 0.67-0.95; $P = .011$)
- SGA + FGA vs FGA (risk ratio: 0.80, 95% CI: 0.71-0.90; $P < .001$)

TD prevalence with SGAs was especially low in the 4 studies reporting on patients without prior FGA treatment: 7.2%

Carbon et al. J Clin Psychiatry. 2017;78:e264.

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Tardive Dyskinesia in Older Patients: FGAs

- Cumulative rates of TD after cumulative antipsychotic treatment in neuroleptic-naïve patients aged ≥ 55 yr were (n = 261):
 - After 1 yr: 25%
 - After 2 yr: 34%
 - After 3 yr: 53%
- Greater risk associated with history of ECT, higher mean daily and cumulative antipsychotic doses, presence of EPS early in treatment
- Despite lower doses, TD rates for patients beginning treatment with conventional antipsychotics aged ≥ 50 yr were 3-5 times that of younger patients

Woerner et al. Am J Psychiatry. 1998;155:1521.

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Tardive Dyskinesia in Older Patients: SGAs

Cumulative TD With Risperidone and Olanzapine

- Prospective nonrandomized inception cohort study of 207 antipsychotic-naïve inpatients and outpatients aged ≥ 55 yr identified at the time of antipsychotic treatment initiation with risperidone or olanzapine

- Mean age: 79.8 yr
- Female: 70.0%
- White: 86.5%
- Predominant diagnosis

- Dementia: 58.9%
- Major mood disorder: 30.9%
- Although principal treatment target was psychosis (78.7%), in 59.4% with agitation

TD risk was higher in females, Black patients, and patients without past antidepressant treatment or with FGA cotreatment

Group	n	1 Yr		2 Yr	
		Rate, %	95% CI	Rate, %	95% CI
Total	207	5.7	1.5-10.0	8.2	2.9-13.4
All risperidone	159	5.3	0.7-9.9	7.2	1.4-12.9
All olanzapine	48	6.7	0-15.6	11.1	0-23
"Pure" risperidone	159	4.7	0-9.5	7.1	0.6-13.7
"Pure" olanzapine	48	4.0	0-11.8	10.4	0-25

Woerner et al. Neuropsychopharmacology. 2011;36:1738.

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TD in Older Patients: Why the Increased Risk?

- Aging is associated with:
 - A decrease in dopaminergic neurons
 - Greater sensitivity to developing parkinsonism and akathisia
 - Less buffer against oxidative stress
 - Less cellular regeneration and resilience
 - Longer cumulative exposure to DRBAs

Citrome et al. Neuropsychiatr Dis Treat. 2021;17:3127. Estevez-Fraga et al. Drugs Aging. 2018;35:959.
Ukrainitseva et al. Mech Ageing Dev. 2021;194:111418.

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Tardive Dyskinesia Incidence Meta-analysis: Relative TD Risk (SGA vs FGA and SGA vs SGA)

- TD risk and annualized TD rates were lower with SGAs vs FGAs:
 - Risk ratio: 0.47 (95% CI: 0.39-0.57; $P < .0001$)
 - Rate ratio: 0.35 (95% CI: 0.28-0.45; $P < .0001$; NNT = 20)
- No FGA dose effect on FGA/SGA comparisons ($Z = -1.03$; $P = .30$)
- FGA-SGA TD rate ratios differed by SGA ($P = .003$), with a significant advantage of aripiprazole and olanzapine vs FGAs
- SGA-SGA comparisons confirmed the olanzapine advantage vs non-clozapine SGAs:
 - Rate ratio: 0.66 (95% CI: 0.49-0.88; $P = .006$; NNT = 100)
- Risperidone was not worse than non-olanzapine SGAs (rate ratio: 0.94; 95% CI: 0.65-1.35; $P = .72$)

Carbon et al. World Psychiatry. 2018;17:330.

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How Do We Screen for and Diagnose TD?



Abnormal Involuntary Movement Scale: The Standard of Care

Movement Ratings		Score				
Facial and 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			

- Observer-rated, 12-item anchored scale; takes 5-10 min to complete

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

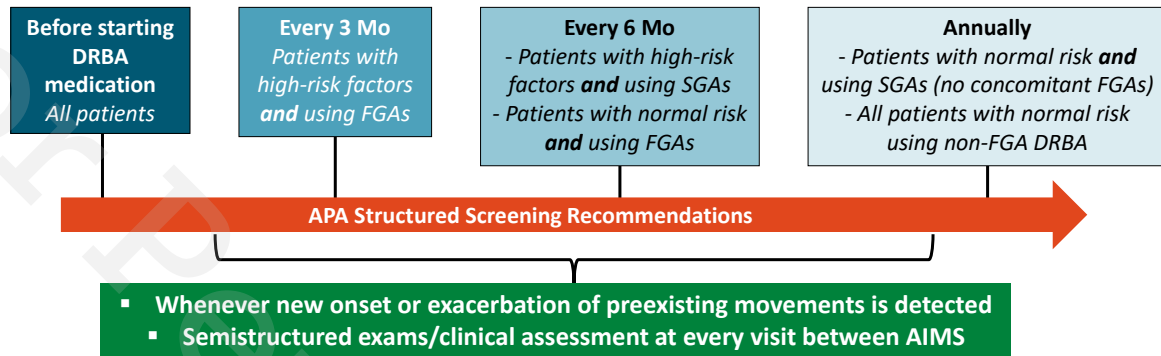
- Scoring
 - Total calculated using items 1-7 for a total (max) score of 28
 - Item 8 (severity) based on highest single score in any of items 1-7

Gharabawi et al. Schizophr Res. 2005;77:119. Guy. ECDEU Assessment Manual for Psychopharmacology. 1976:534. STABLE National Coordinating Council Resource Toolkit Workgroup. provider.medmutual.com/pdf/STABLE_toolkit.pdf. OHSU. www.ohsu.edu/sites/default/files/2019-10/%28AIMS%29%20Abnormal%20Involuntary%20Movement%20Scale.pdf.

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APA Screening Recommendations



High-risk factors (incomplete list): older age; history of dystonic reactions, akathisia, clinically significant parkinsonism; substance use, mood disorders

Jankelowitz. Neuropsychiatr Dis Treat. 2013;9:1371. emedicine.medscape.com/article/1151826.
APA. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, 3rd ed. 2020.

Slide credit: clinicaloptions.com



Classifying TD: Schooler-Kane and Glazer Morgenstern Criteria

- By itself, the AIMS examination does not diagnose TD
- In 1982, Schooler and Kane developed 3 diagnostic criteria for TD
 - Alternative: Glazer-Morgenstern-Doucette criteria

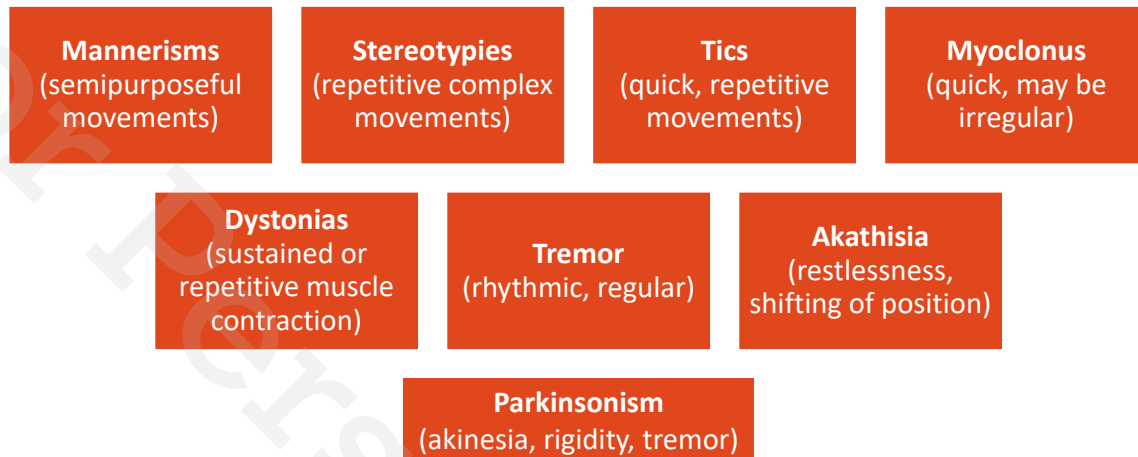
Source	DRBA Exposure	Severity Threshold	Symptom Duration
Schooler-Kane criteria	≥3 mo cumulative	AIMS score ≥3 in ≥1 area <i>or</i> ≥2 in ≥2 areas	≥3 mo (persistent) Absence of other conditions that might produce involuntary movements
Glazer-Morgenstern-Doucette criteria	≥3 mo	AIMS score ≥3 total score <i>and</i> ≥2 in ≥1 area	2 consecutive assessments

Schooler, Kane. Arch Gen Psychiatry. 1982;39:486. Morgenstern, Glazer. Arch Gen Psychiatry. 1993;50:723.

Slide credit: clinicaloptions.com



Tardive Dyskinesia: Symptom-Based Differential Diagnosis



Hauser et al. CNS Spectr. 2020;27:208. Jain, Correll. J Clin Psychiatry. 2018;79:nu17034ah1c. Frei et al. J Neurol Sci. 2018;389:10.

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Chorea: Differential Diagnosis

Differential	Considerations
Huntington's disease	Genetic; age of onset: 25-50 yr; begins with psychiatric symptoms (eg, depression, suicidality, impulsivity)
Benign familial chorea	Genetic, associated with chromosome 14; often early-onset; no overt psychiatric/cognitive symptoms
Metabolic conditions	Electrolyte (Na, Ca, Mg) imbalances; hyper/hypoparathyroidism; vitamin B ₁₂ deficiency, uremia
Sydenham's chorea	Youth onset, post-streptococcal infection (<6 mo); may present with concomitant OCD, impulsivity, ADHD, depression; often self-resolves within a few months
Systemic lupus erythematosus	Often sudden onset, accompanied with psychiatric symptoms
Inflammatory	Herpes simplex virus, varicella, mumps measles, rubella
Substance induced	May be associated with antipsychotics, anticholinergics, antiepileptics, psychostimulants (eg, amphetamine, methcathinone, methylphenidate), methadone, steroids, manganese, toluene, aluminum

Davico et al. Front Neurol. 2018;9:164. Bhidayasiri, Truong. BMJ. 2004;80. Punukollu, et al. DMCN. 2015;58:16. Walker. Curr Neurol Neurosci Rep. 2011;11:385. Hermann, Walker. Curr Neurol Neurosci Rep. 2015;15:1.

Slide credit: clinicaloptions.com



TD vs DIP

TARDIVE DYSKINESIA		DRUG-INDUCED PARKINSONISM
Increased blinking Raised eyebrows Chewing, grimacing Mouth puckering, pursing Tongue protrusion Lateral jaw movement	FACE	No facial expression Reduced blinking Rhythmic tremor in jaw or tongue Mouth open
Arching backward Head nodding Irregular respiration, grunting Cervical dystonia	NECK / TRUNK	Stooped posture Slow gait Overall slowness
Piano-playing Dancing feet Dystonic postures	EXTREMITIES	Rhythmic, resting tremor Cogwheel rigidity on exam Slowed repetitive movements

Hauser et al. CNS Spectr. 2022;27:208.

Slide credit: clinicaloptions.com



Age-Related Differential Diagnosis

- Remove ill-fitting dentures prior to AIMS exam to differentiate voluntary denture relocating tongue movements from true involuntary dyskinesia
- Take careful medication history from patients, informants, and/or medical specialist to differentiate spontaneous dyskinesia from TD related to dopamine receptor-blocking agents (including metoclopramide)
- In patients in a wheelchair
 - Have them rest their forearms on the armrest instead of their knees, letting the wrist extend a few inches to hang freely with gravity to observe fingers at rest
 - Remove shoes and socks to inspect toes at rest
 - Prop up the leg from underneath the hollow of the knee to let the foot hang freely, not touching the ground, to inspect toes further

Menzies, Farrell. J Am Psychiatr Nurses Assoc. 2002;8:51.
 Guy. ECDEU Assessment Manual for Psychopharmacology. 1976. p. 534.

Slide credit: clinicaloptions.com



Diagnosis in Patients With Low Awareness of TD

- Spend extra time on psychoeducation
- Ask the patient concrete, descriptive questions about comments and reactions by others
- Involve a care partner or significant other to describe the TD symptoms and interference with daily living/functioning
- Ask care partner or significant other to point out the TD symptoms and interference with daily living/functioning to the patient in between visits
- Present the patient with a mirror
- Provide hope TD movements are treatable and can improve

Warren et al. Issues in Mental Health Nursing. 2022;43:22. Caroff. Neuropsychiatr Dis Treat. 2019;15:785.

Slide credit: clinicaloptions.com



How Can We Prevent and Treat 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 and 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
- Inform patients and caregivers of the risk
- Assess for incipient signs of TD regularly using the AIMS

Caroff et al. Current Psychiatry. 2011;10:23.

Slide credit: clinicaloptions.com



Treatment Options (Varying Degrees of Evidence)

- Branched-chain amino acids
- Amantadine
- Tetrabenazine
- Deutetrabenazine*
- Valbenazine*
- Antioxidants/radical scavenger (eg, vitamin E, vitamin B₆, ginkgo biloba, eicosapentaenoic acid [fish oil])
- Melatonin
- Clonazepam
- Donepezil

ANTICHOLINERGICS CAN MAKE TD WORSE

*Deutetrabenazine and valbenazine are the only FDA-approved treatment options for TD.
Ricciardi et al. Can J Psychiatry. 2019;64:388. American Psychiatric Association. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. Third edition. 2021. Bhidayasiri et al. J Neurol Sci. 2018;389:67. Caroff et al. J Clin Psychiatry. 2020;81:19cs12983.

Slide credit: clinicaloptions.com



What About Modifying the Antipsychotic Dose?

- Antipsychotic discontinuation
 - Risk of worsening psychiatric condition/relapse
 - TD often continues
- Antipsychotic dose decrease
 - Evidence for this approach is minimal
 - Risk of worsening psychiatric condition/relapse
 - TD very often continues
- Antipsychotic dose increase
 - May mask dyskinesia temporarily
 - TD very often returns, leading to playing catchup
- Antipsychotic switch (ie, FGA to SGA; switch to olanzapine, quetiapine, clozapine, etc)
 - Risk of worsening psychiatric condition/relapse
 - TD often continues

Ricciardi et al. Can J Psychiatry. 2019;64:388. Caroff. Neuropsychiatr Dis Treat. 2019;15:785. psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841

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Guidelines for Treatment of TD

- Both APA and AAN state that VMAT2 inhibitors are first-line treatment choice for TD associated with antipsychotic therapy

2020 APA Practice Guideline for the Treatment of Patients With Schizophrenia

- “Patients who have moderate to severe or disabling TD associated with antipsychotic therapy be treated with a reversible VMAT2 inhibitor”
- “Treatment with a VMAT2 inhibitor can also be considered for patients with mild TD based on factors such as patient preference, associated impairment, or effect on psychosocial functioning”

2018 AAN Updated Treatment Guidelines for TD—Level of Evidence

- Level A: deutetrabenazine, valbenazine
- Level B: clonazepam, ginkgo biloba
- Level C: amantadine, tetrabenazine; DBS for medically refractory TD
- Level U: withdrawing causative agent or switching from typical to atypical antipsychotic agent

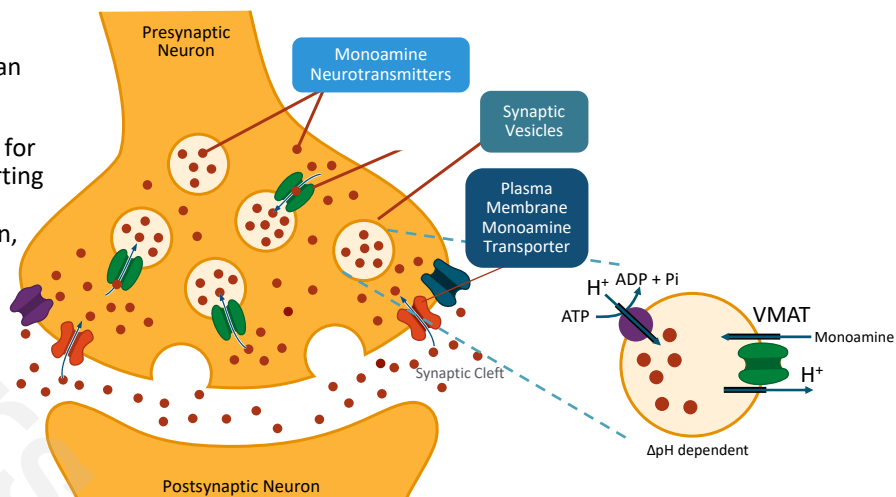
APA. Practice Guideline for the Treatment of Patients with Schizophrenia, 3rd ed. 2020. Bhidayasiri et al. J Neurol Sci. 2018;389:67.

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Vesicular Monoamine Transporter Type 2 (VMAT2)

- VMAT2 is a protein concentrated in the human brain
- It is primarily responsible for repackaging and transporting monoamines (dopamine, norepinephrine, serotonin, histamine) in presynaptic neurons



Meyer et al. J Neurochem. 2013;127:187. Bernstein et al. Neurochem Int. 2014;73:89.

Slide credit: clinicaloptions.com



Tetrabenazine

- FDA-approved VMAT2 inhibitor for chorea associated with HD
 - Used off label in the United States for TD
- 1:1 mixture of 2 enantiomers: α -tetrabenazine and β -tetrabenazine
 - Each metabolized to 2 isomers: (+) α and (-) α DHTBZ; (+) β and (-) β DHTBZ
- Half-life ~5-10 hr
 - Large peak-to-trough variations in plasma levels
 - C_{max} reached within 1-1.5 hr
 - Requires dosing up to 3 x/day

Caroff et al. JGER. 2018;7:135. Solmi et al. Drug Des Devel Ther. 2018;12:1215.

Slide credit: clinicaloptions.com



Deutetrabenazine

- Deuterated form of tetrabenazine
 - Incorporates deuterium (a stable, non-radioactive, non-toxic, and naturally occurring isotope of hydrogen) in place of hydrogen at the sites of primary metabolism, which results in metabolic clearance being slowed
- Compared to tetrabenazine:
 - Less frequent dosing (BID vs TID) and lower C_{max} values
 - XR formulation (approved 2023) only requires once-daily dosing
 - Comparable drug exposure with half the dose of tetrabenazine
 - Similar to tetrabenazine, there are α and β enantiomers and each gives rise to two isomers of a DHTBZ metabolite
- Also approved for use in chorea associated with Huntington's disease

Schneider et al. Clin Pharmacol Drug Dev. 2021;10:647. Deutetrabenazine PI.

Slide credit: clinicaloptions.com



AIM-TD: Baseline Characteristics

	Placebo Group (n = 72)	Deutetrabenazine Groups			Total (N = 293)
		12 mg/day (n = 74)	24 mg/day (n = 73)	36 mg/day (n = 74)	
Demographics					
Age, yr (mean [SD])	54.6 (12.1)	57.0 (10.0)	55.6 (11.3)	58.3 (11.6)	56.4 (11.3)
Sex, n (%)					
▪ Female	37 (51)	42 (57)	41 (56)	42 (57)	162 (55)
▪ Male	35 (49)	32 (43)	32 (44)	32 (43)	131 (45)
White race, n (%)	59 (82)	58 (78)	54 (74)	61 (82)	232 (79)
Clinical Characteristics					
TD duration, yr (mean, [SD])	6.0 (5.4)	5.5 (5.4)	5.0 (6.0)	5.9 (5.3)	5.6 (5.5)
Dopamine receptor agonist use, n (%)	56 (78)	56 (76)	57 (78)	53 (72)	222 (75)
▪ Typical antipsychotics	2 (3)	7 (10)	4 (6)	5 (7)	18 (6)
▪ Atypical antipsychotics	51 (71)	46 (62)	45 (62)	40 (54)	182 (62)
▪ Both	3 (4)	3 (4)	8 (11)	8 (11)	22 (8)
Primary Psychiatric Illness, n (%)					
Schizophrenia	31 (43)	32 (43)	42 (58)	40 (54)	145 (50)
▪ Schizoaffective disorder	11 (15)	8 (11)	7 (10)	4 (5)	30 (10)
Bipolar	17 (24)	15 (20)	7 (10)	12 (16)	51 (17)
Depression	11 (15)	17 (23)	11 (15)	16 (22)	55 (19)
Other	2 (3)	2 (3)	6 (8)	2 (3)	12 (4)

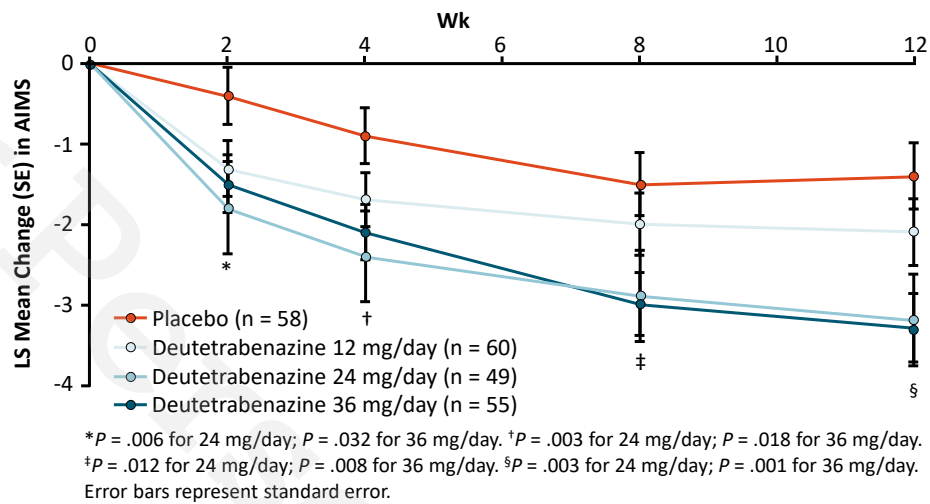
Anderson et al. Lancet Psychiatry. 2017;4:595.

Slide credit: clinicaloptions.com



Deutetrabenazine

AIM-TD: Change in AIMS Total Score From Baseline

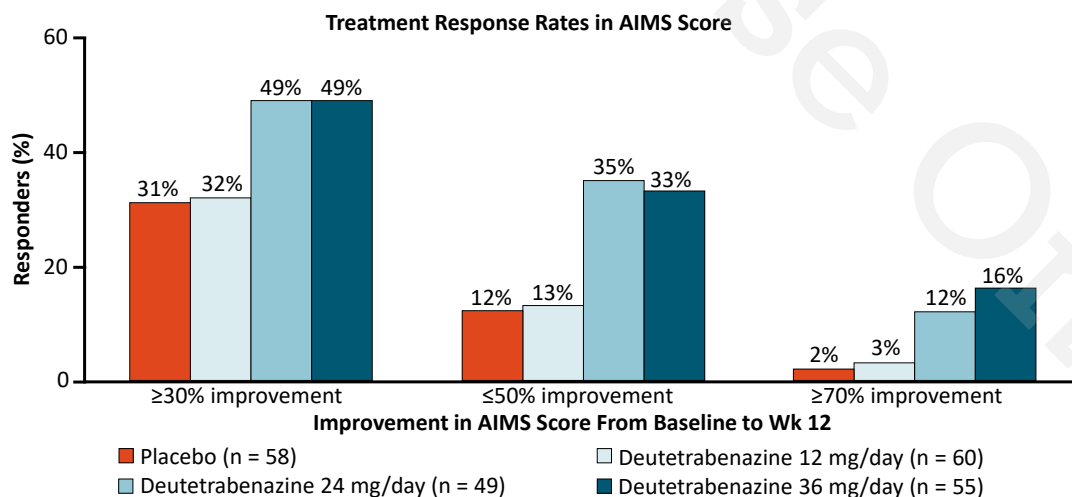


Anderson et al. Lancet Psychiatry. 2017;4:595.

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Response Rates With Deutetrabenazine vs Placebo Phase III Trial: AIM-TD



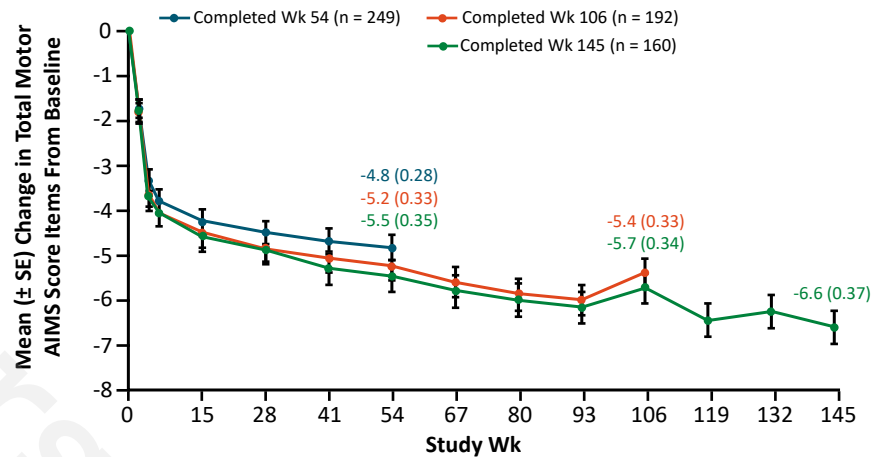
Anderson et al. Lancet Psychiatry. 2017;4:595.

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Long-term Efficacy With Deutetrabenazine: AIMS Score Change in 3-Yr OLE

- Study population consisted of patients with TD who were involved in AIM-TD or ARM-TD trials
- All patients underwent a 1-wk washout period and then 6-wk medication titration period
- Following titration, mean dose ranged from 38.3 mg/d – 39.4 mg/d



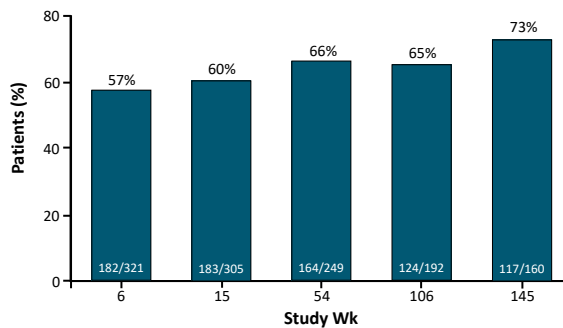
Hauser et al. Front Neurol. 2022;13:773999.

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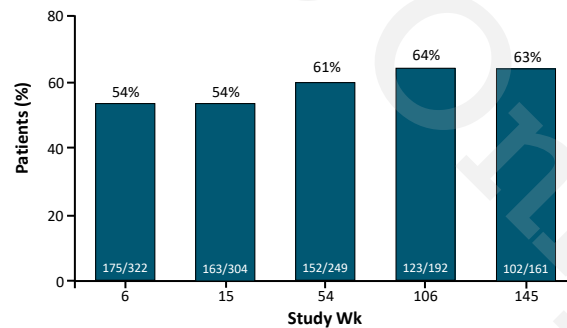


Long-term Efficacy With Deutetrabenazine: Clinician and Patient Global Impression of Change

Percent of Patients Meeting
Treatment of Success: CGIC



Percent of Patients Meeting
Treatment of Success: PGIC

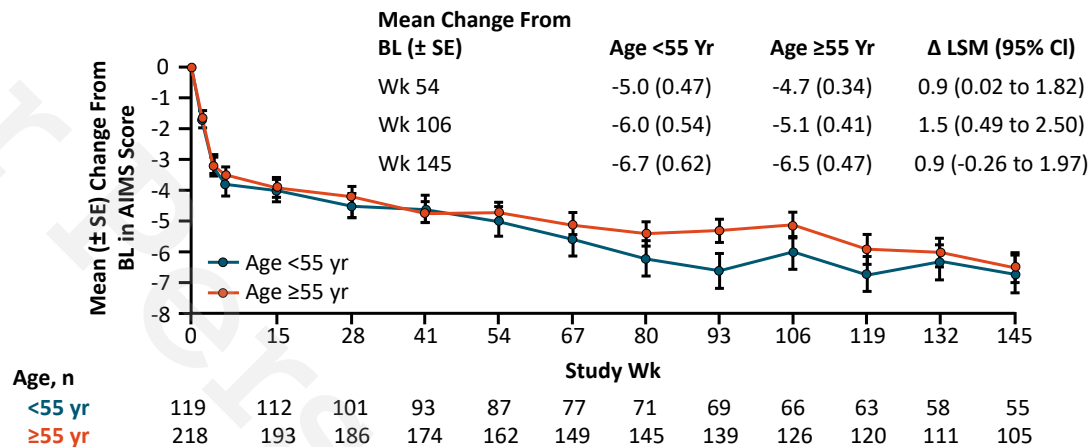


Treatment success = rating of "very much improved" or "much improved."
Hauser et al. Front Neurol. 2022;13:773999.

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Deutetrabenazine in Younger and Older Patients With TD: Change in AIMS Score Over Time by Age Group

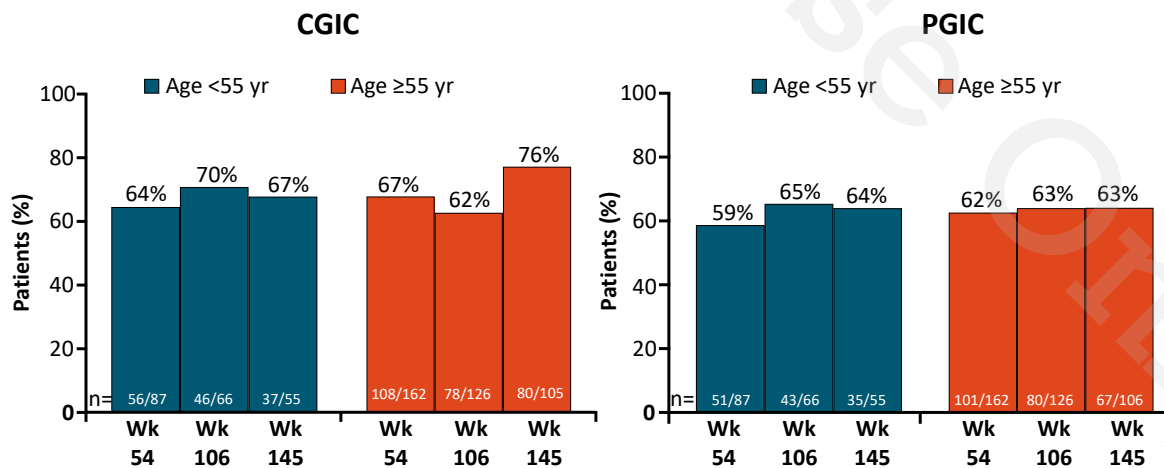


Sajatovic et al. Am J Geriatr Psychiatry. 2022;30:360.

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Treatment Success: CGIC and PGIC



Sajatovic et al. Am J Geriatr Psychiatry. 2022;30:360.

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Key Adverse Events Associated With Deutetrabenazine

**Placebo-Controlled TD Studies: AEs Reported
in $\geq 2\%$ of Patients Treated With Deutetrabenazine
and at Greater Rate Than Placebo**

AE, %	Deutetrabenazine (n = 279)	Placebo (n = 131)
Nasopharyngitis	4	2
Insomnia	4	1
Depression/dysthymic disorder	2	1
Akathisia/agitation/ restlessness	2	1

*Degree of QT prolongation is not clinically significant when deutetrabenazine is administered within the recommended dosage range.
Deutetrabenazine PI.

- Warnings for:
 - Parkinsonism
 - QTc prolongation*
 - Neuroleptic malignant syndrome
 - Akathisia, agitation, and restlessness
 - Sedation and somnolence
 - Hyperprolactinemia (seen with tetrabenazine)
 - Binding to melanin-containing tissues
- *In Huntington's disease*: depression and suicidality

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Valbenazine

- A novel, highly selective, VMAT2 inhibitor
- Orally active compound with 2 active metabolites, (+) α -DHTBZ and the oxidative metabolite of (+) α -DHTBZ; all 3 have VMAT2 binding
- Designed to deliver the active metabolites in a controlled fashion
- Designed to limit off-target receptor binding
- Half-life of 20 hr, allowing for once-daily dosing

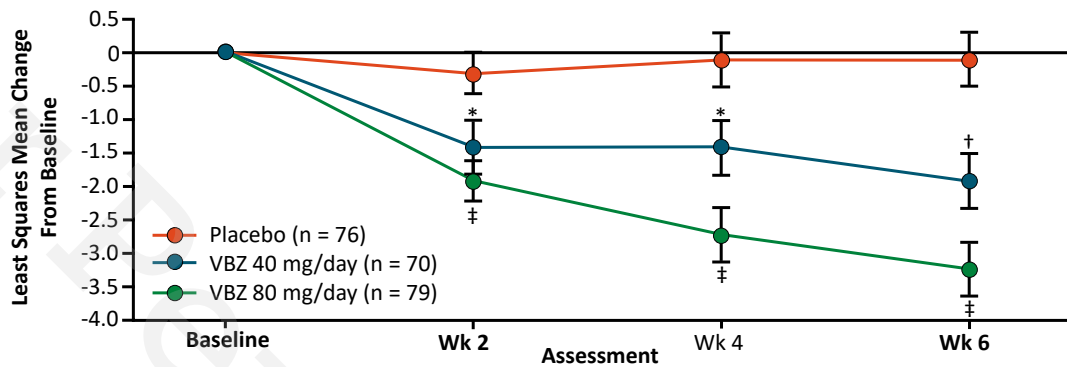
O'Brien et al. Mov Disord. 2015;30:1681.

Slide credit: clinicaloptions.com



Valbenazine

KINECT 3: Change in AIMS Total Score From Baseline



Mixed-effects model for repeated measures. Dyskinesia score is sum of AIMS items 1-7. Indicated significance levels refer to comparison with placebo. Error bars indicate standard error of the mean.

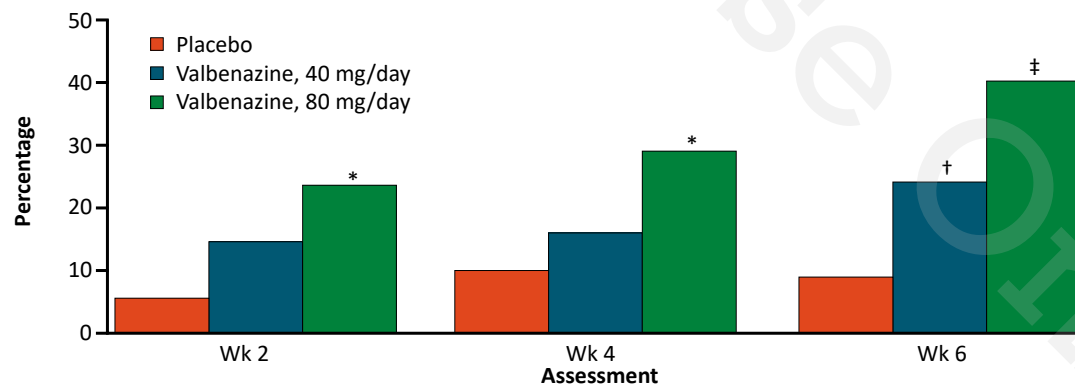
* $P < .05$. † $P < .01$. ‡ $P \leq .001$.

Hauser et al. Am J Psychiatry. 2017;174:476.

Slide credit: clinicaloptions.com



KINECT 3: Change in AIMS Total Score From Baseline



Treatment response was defined as a reduction of >50% from baseline in AIMS dyskinesia score. The indicated significance levels refer to comparison with placebo. Ns were as follows for Wk 2, 4 and 6, respectively: placebo group, 75, 72, 69; valbenazine 40 mg/day group, 70, 64, 63; valbenazine 80 mg/day group, 77, 73, 70.

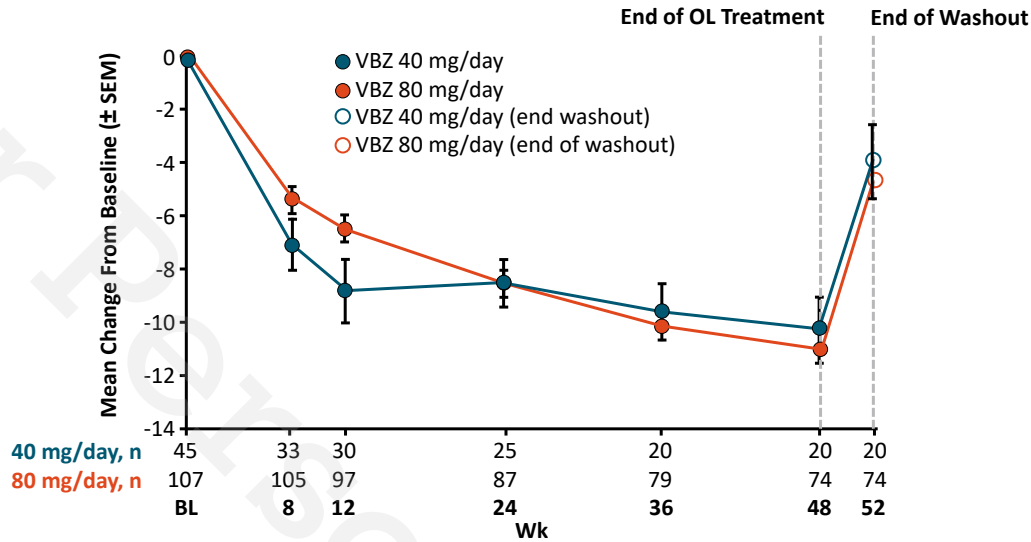
† $P < .05$; * $P < .01$; ‡ $P < .001$

Hauser et al. Am J Psychiatry. 2017;174:476.

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Valbenazine KINECT 4: AIMS Score

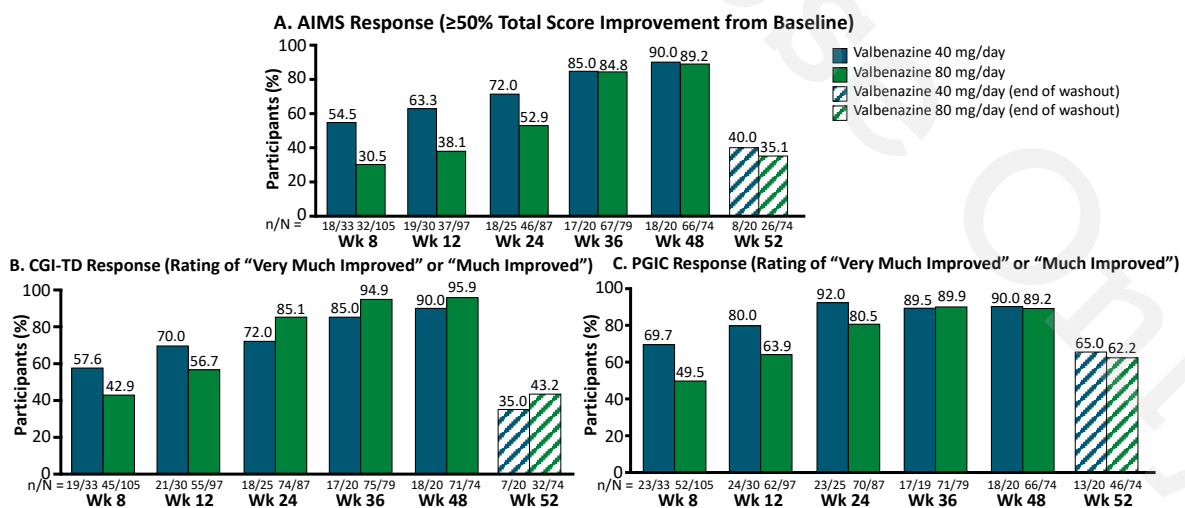


Marder et al. J Clin Psychopharm. 2019;39:620.

Slide credit: clinicaloptions.com



Valbenazine: Responses on AIMS, CGI-TD, and PGIC

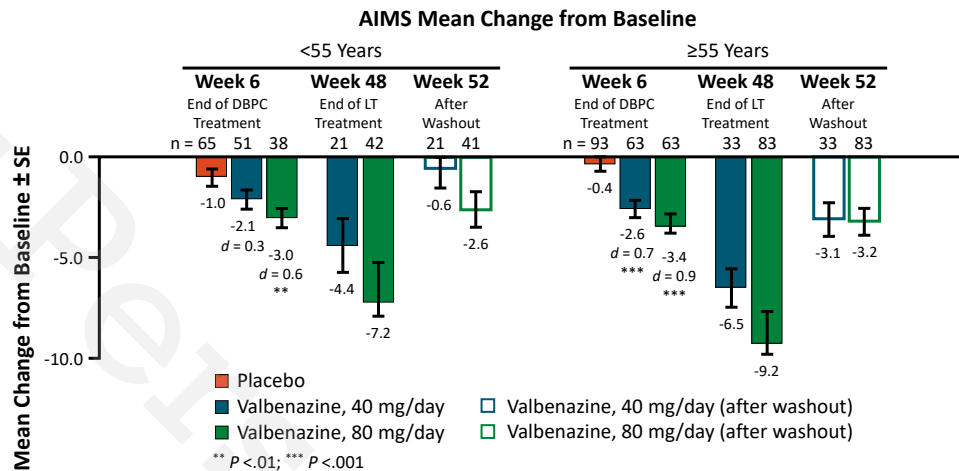


Marder et al. J Clin Psychopharm. 2019;39:620.

Slide credit: clinicaloptions.com



Valbenazine in Younger and Older Patients With TD: Change in AIMS Score Over Time by Age Group

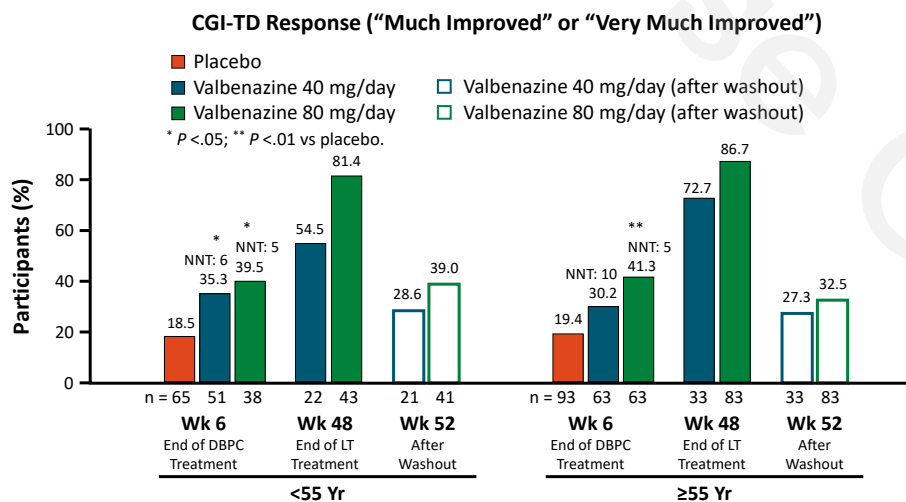


Sajatovic et al. Int J Geriatr Psychiatry. 2020;35:69.

Slide credit: clinicaloptions.com



Valbenazine in Younger and Older Patients With TD: CGI-TD Response by Age Group



Sajatovic et al. Int J Geriatr Psychiatry. 2020;35:69.

Slide credit: clinicaloptions.com



Key Adverse Events Associated With Valbenazine

AEs in 6-Wk Placebo-Controlled Studies of Valbenazine Reported at $\geq 2\%$ and $>$ Placebo

AE, %	Valbenazine (n = 262)	Placebo (n = 183)
General		
Somnolence (somnolence, fatigue, sedation)	10.9	4.2
Neurologic		
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4	4.9
Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)	4.1	2.2
Headache	3.4	2.7
Akathisia (akathisia, restlessness)	2.7	0.5
Gastrointestinal		
Vomiting	2.6	0.6
Nausea	2.3	2.1
Musculoskeletal		
Arthralgia	2.3	0.5

Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

Valbenazine PI.

Slide credit: clinicaloptions.com



Key Features of Deutetrabenazine and Valbenazine

Both can be given without modification of antipsychotic dose



Frequency of administration

Valbenazine: Once daily
Deutetrabenazine: Twice daily;
Once daily (XR)



Titration

Valbenazine: Titrate to target dose
of 80 mg/d
Deutetrabenazine: Dose to
efficacy/tolerability



Need for food

Valbenazine: No
Deutetrabenazine: Yes (XR: No)



Drug interactions

Valbenazine: CYP2D6 and CYP3A4
modulators
Deutetrabenazine: CYP2D6
modulators



Contraindications

Valbenazine: Known hypersensitivity to valbenazine or any
components of the product
Deutetrabenazine: Hepatic impairment; taking reserpine,
monoamine oxidase inhibitors, tetrabenazine, or valbenazine

Correll, Citrome. J Clin Psychiatry. 2021;82:NU20016AH2C. Deutetrabenazine PI. Valbenazine PI.

Slide credit: clinicaloptions.com



Considerations When Prescribing VMAT2 Inhibitors/ Treating TD in Special Populations

- In older patients
 - Slower titration may improve tolerability
 - Lower doses may be sufficient for efficacy/needed for tolerability
 - Polypharmacy is common; watch out for drug–drug interaction
- Patients on other medications
 - Cotreatment with strong cytochrome P450 pan-inducers (carbamazepine, phenytoin) may need to increase dose of deutetrabenazine and valbenazine
 - Cotreatment with strong cytochrome P450 2D6 inhibitors may need to reduce the dose of deutetrabenazine and valbenazine
 - Cotreatment with strong cytochrome P450 3A4 inhibitors may need to reduce the dose of valbenazine
- Patients with low insight into presence and impact of TD
 - Increase psychoeducation
 - Involve care partners/significant others

Ricciardi. Can J Psychiatry. 2019;64:388. Warren. Issues in Mental Health Nursing, 43;1:22. Deutetrabenazine PI. Valbenazine PI.

Slide credit: clinicaloptions.com



Clinical Pearls

- TD is a potential AE of all DRBAs (antipsychotics, metoclopramide)
- Prevention is the best strategy:
 - Confirm and document the indication for antipsychotic medication
 - Use conservative maintenance doses, avoid EPS
 - Consider the use of SGAs, especially in those at high risk for EPS
 - Inform patients and caregivers of the risk
- Monitor regularly for signs of TD with clinical observation, caregiver report, and the AIMS
- Manage TD as quickly as possible
 - Deutetrabenazine and valbenazine are FDA-approved treatments that are efficacious and safe for patients with persistent TD
 - Other options include antipsychotic dose adjustment, antipsychotic switch, vitamin E, benzodiazepines, BCAA, ginkgo biloba, tetrabenazine, etc, but insufficient evidence and not FDA approved for TD

Key Summary Points

- TD remains a risk with all dopamine receptor blockers
- Risk reduction and monitoring are key
- The FDA-approved VMAT2 inhibitors deutetrabenazine and valbenazine provide an evidence-based care option for the effective management of TD
- Deutetrabenazine requires titration over several wk and twice daily dosing (differs for XR formulation), whereas valbenazine can reach the maximum dose by the beginning of Wk 2 and is dosed once daily
- Deutetrabenazine should be taken with food (differs for XR formulation), but this is not needed for valbenazine
- Both VMAT2 inhibitors are generally well tolerated and have a positive benefit:risk ratio
- Both VMAT2 inhibitors are recommended by the APA guidelines as the preferred and only evidence-based treatment for TD

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