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New Approaches to the Clinical Challenges of Tardive Dyskinesia

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Disclosures

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Learning Objective 1

Identify the signs and symptoms of tardive dyskinesia (TD).

Learning Objective 2

Integrate assessment scales to accurately identify and assess the severity of TD in at least 80% of patients on antipsychotics throughout the course of treatment.

Learning Objective 3

Individualize treatment selection for patients with TD based on evidence-based data.

Tardive Dyskinesia: Description

- Mouth and tongue movements such as puckering, lip smacking, sucking, grimacing
- Choreoathetoid-like movements of the limbs, fingers and toes, slow writhing movements of the trunk
- Tend to increase with arousal and decrease with relaxation
- Severe forms may include tardive dystonias and tardive akathisias

Vijayakumar D, et al. *Drugs*. 2016;76:779-787.

Tardive Dyskinesia: Scope of the Problem

- May affect 20%-30% of people chronically exposed to antipsychotic medications[1]
- An estimated 573,000 people are affected in the US[2]
- All dopamine receptor antagonists – including first and second generation antipsychotics and anti-emetics such as metoclopramide – are implicated
- Since antipsychotics are being prescribed for more indications, the number of individuals at risk is growing

1. Waln O, et al. *Tremor Other Hyperkinet Mov (N Y).* 2013;3. 2. A. Dhir, et al. *Mov Disord.* 2017; 32 (suppl 2). http://www.mdsabstracts.org/abstract/estimation-of-tardive-dyskinesia-incidence-and-prevalence-in-the-united-states/. Accessed October 24, 2017.

Recent Meta-Analysis by Carbon et al, 2017

- Reviewed studies published since 2000
- Overall prevalence of TD was 25.3% in patients exposed to antipsychotics
- Prevalence on first generation antipsychotics 30.0%
- Prevalence on second generation antipsychotics 20.7%

Carbon M, et al. *J Clin Psychiatry*. 2017;78:e264-e274.

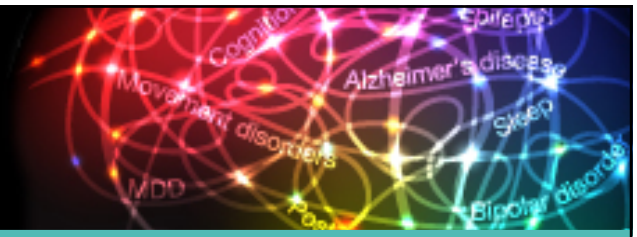
Tardive Dyskinesia: Risk Factors

- Increasing age
- Mood disorders
- History of EPS
- Organic mental illness
- Other possible risk factors are high dose treatment and the duration of drug treatment.

EPS = extrapyramidal symptoms.

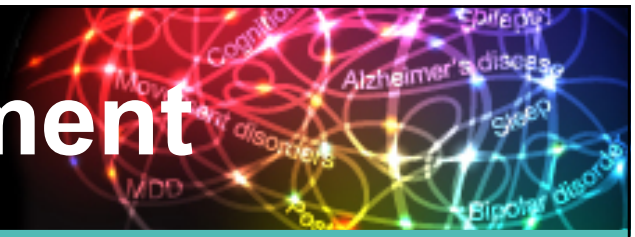
Mehta SH, et al. *Neurol Clin*. 2015;33:153-174.

Burden of TD



- May affect walking, use of upper and lower extremities
- May affect oral health
- May affect swallowing and may make speech unintelligible
- Even mild forms may be stigmatizing

TD Screening and Assessment



- Patients receiving dopamine blocking drugs should be assessed on a regular basis for both acute extrapyramidal side effects and TD
- The optimal instrument for screening should be relatively brief but sufficiently sensitive to detect mild abnormalities, eg, Brief Clinical Assessment
- The best instrument for following patients with TD and for evaluating treatment effects should be sensitive to meaningful change. The AIMS scale meets these criteria.

Brief Clinical Assessment of Movement Disorders for Patients on Antipsychotic Medications

Side Effect and Examination Procedure
Akathisia
• Observe for restless movements • Inquire about difficulty sitting still, restless feelings, and pacing
Rigidity and tremor
• Observe for spontaneous movements and tremor • Examine for cogwheeling • Observe arm swing and gait while patient is walking
Tardive movements
• Observe abnormal face and extremity movements while patient is sitting still with feet flat and again while patient is distracted with alternating thumb and finger tapping • Observe truncal, pelvic, and arm/hand movements while patient is walking

Bratti IM, et al. *AM J Psychiatry*. 2007;164(11):1648-1654.

Abnormal Involuntary Movement Scale (AIMS)

- Includes an examination procedure
- Developed by NIMH and in the public domain
- The exam can usually be done in 10 minutes or less

NIMH = National Institute of Mental Health.

Abnormal Involuntary Movement Scale (AIMS)

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

NAME:_____
DATE: _____
Prescribing Practitioner: _____

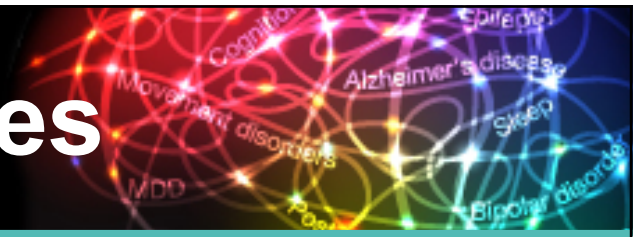
CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 - Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.) before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date	RATER Date	RATER Date	RATER Date
Facial and Oral Movements	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows periorbital area, cheeks, including frowning blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	O 1 2 3 4
Extremity Movements	**5. Upper (arms, wrists,, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures**	No Yes	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes	No Yes
	13. Edentia?	No Yes	No Yes	No Yes	No Yes
	14. Do movements disappear in sleep?	No Yes	No Yes	No Yes	No Yes

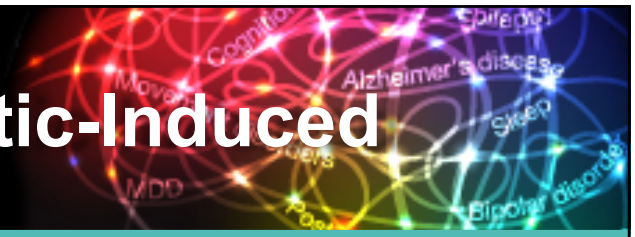
This scale is available in the public domain and has not been modified. Final 9/2000.

TD Management Approaches



- Discontinue antipsychotics
- Reduce the dose
- Change to an antipsychotic with reduced D_2 affinity

Systemic Review of Interventions for Treatment or Preventing Antipsychotic-Induced Tardive Dyskinesia



- Very limited and poor quality studies
- Dosage reduction or change to placebo: No clear clinically meaningful effect
- Change antipsychotics: Small and low quality data suggesting some improvement with change to risperidone or quetiapine
- No clear effect of benzodiazepines or vitamin E.
- One small study from China found an effect of buspirone on TD

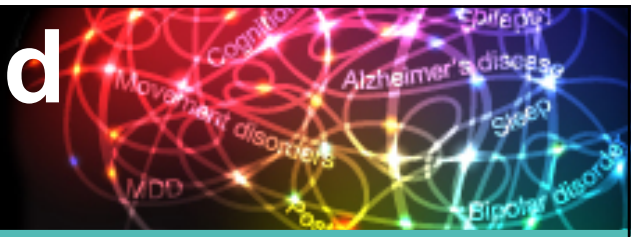
Bergman H, et al. *Health Technol Assess*. 2017;21(143):1-218.

New Treatments for Tardive Dyskinesia

- Drugs related to tetrabenazine* – inhibitors of vesicular monoamine transporter 2 (VMAT2)
- VMAT 2 is responsible for the storage and release of dopamine from synaptic vesicles in brain
- Inhibitors including tetrabenazine, deutetrabenazine, and valbenazine reduce dopamine transmission

*Not FDA approved for TD.

VMAT2 Inhibitors: Proposed Mechanism of Action



- Long-term blockade of dopamine leads to an upregulation of post-synaptic dopamine receptors.
- TD results from the heightened sensitivity of these receptors to dopamine.
- VMAT regulates the transporting and packaging of dopamine and other monoamines from the cytoplasm into neuronal vesicles for storage and ultimate release into the synapse.
- VMAT2 inhibitors decrease the amount of dopamine released into synapses

Tetrabenazine*

- A VMAT2 inhibitor
- Approved for chorea in HD
  - Boxed warning for suicidality and associated with depression
- Several case reports suggest effectiveness for TD

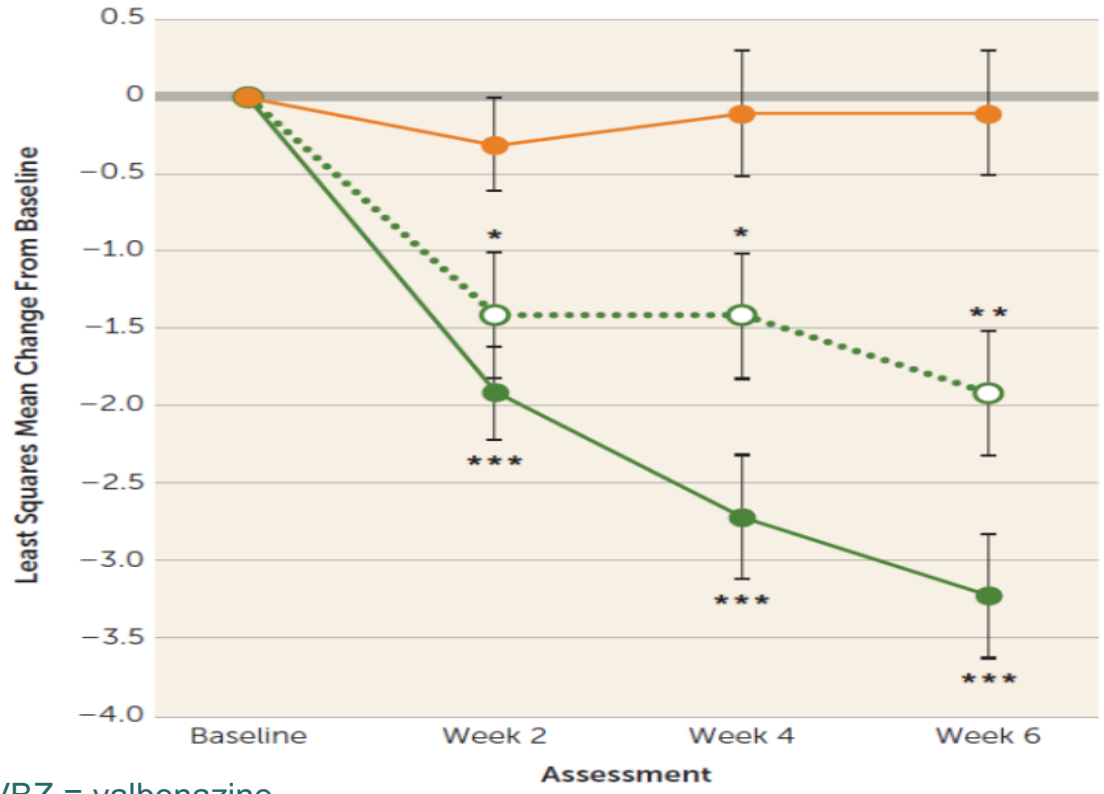
HD = Huntington's disease.
*Not FDA approved for tardive dyskinesia.

Valbenazine

- A VMAT2 inhibitor with a low NNT and a high NNH
- Patients should be started on 40 mg qd for a week and then increased to 80 mg qd
- Consider a lower dose for CYP2D6 poor metabolizers
- Indicated for tardive dyskinesia

NNT= number needed to treat, NNH = number needed to harm.
FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209241lbl.pdf

KINECT 3: Change From Baseline in AIMS Dyskinesia Score



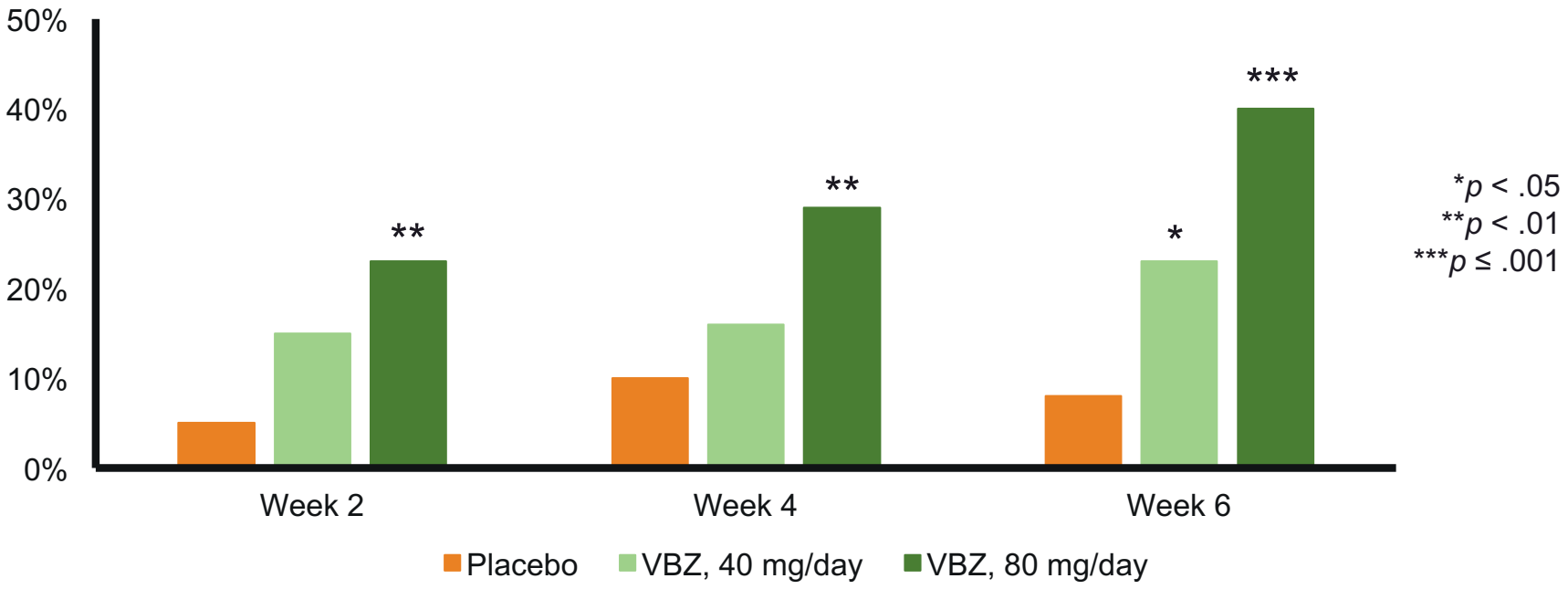
Placebo (n = 76)
VBZ, 40 mg/day (n = 70)
VBZ, 80 mg/day (n = 79)

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

VBZ = valbenazine.

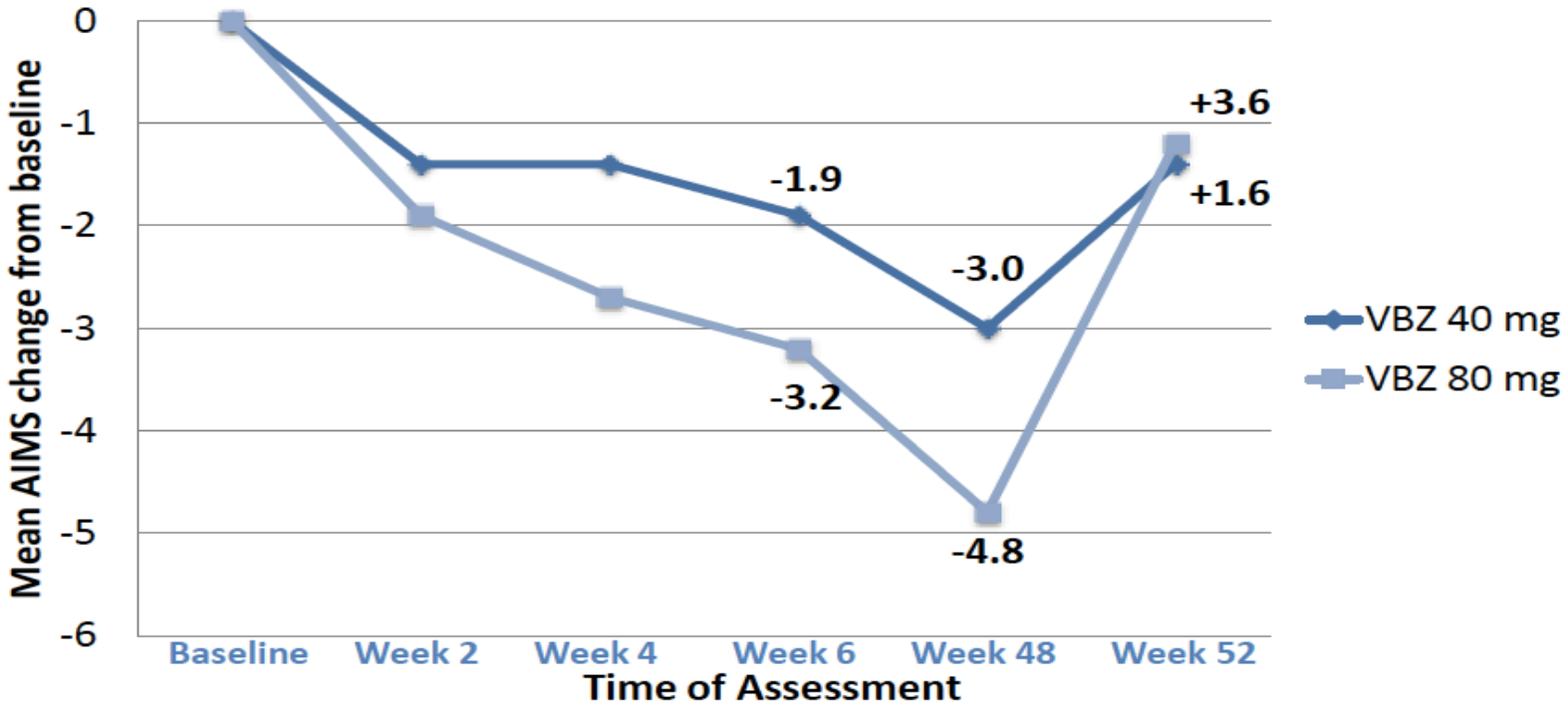
Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484.

KINECT 3: ≥ 50% Improvement in AIMS Dyskinesia Score



Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484.

KINECT 3-Extension Results



Factor SA, et al. *Neurology*. 2017;88(16):supplement S56.005.

Pooled Analysis of KINECT Studies

- Included patients in KINECT 2 and 3, KINECT 3-Extension, and KINECT 4
- Patients received VBZ 40 mg or 80 mg daily
- Common side effects included:
  - Somnolence
  - Urinary tract infection
  - Headache
- Serious adverse events occurred in 12.6%
- 6.1% required dose reduction
- 13.6% discontinued VBZ
- No significant differences in vital signs, ECG, or psychiatric status

Remmington G, et al. *Safety and Neurol*. 2017;88(16):P2.017; Lessig S, et al. *Mov Disord*. 2017;32(suppl 2). Abstract; Josiassen RC, et al. *Psychopharmacol Bull*. 2017;47(3):61-68.

KINECT Studies: Conclusions

Strengths	Limitations
• Blinded central reviewers • Analyzed effect based on diagnosis and concomitant medications • Rapid titration schedule to effective dose • Extended treatment with washout period • Robust criteria for % responders	• High percentage of patients on anticholinergic medications • No information on VBZ effect in different AIMS domains • No data on functional improvement • PGIC not included in later studies • Some patients had shorter treatment duration

Conclusion	• Once daily VBZ significantly reduced AIMS across diagnoses, antipsychotic use, and TD severity for up to 48 weeks • Minimally improved CGI-TD scores • No serious adverse events related to VBZ, including EPS • TD reappeared after medication was withdrawn

PGIC = patient global impression of change; CGI = clinical global impressions.

O'Brien CF, et al. Mov Disord. 2015;30(12):1681-1687; Factor SA, et al. *Neurology*. 2017;88(16):supplement S56.005; Hauser RA, et al. *Am J Psychiatry*. 2017;174(5):476-484.

Deutetrabenazine

- Indicated for HD and TD (with a black box warning for depression and suicidal behavior in HD)
- Patients with TD should be started on 6 mg bid with increased of 6 mg/day each week to a maximum of 24 mg bid. Should be taken with food; max 18 mg bid for poor CYP2D6 metabolizers
- Clinical studies show a low NNT of about 5 and a high NNH

FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208082s000lbl.pdf

ARM-TD Trial

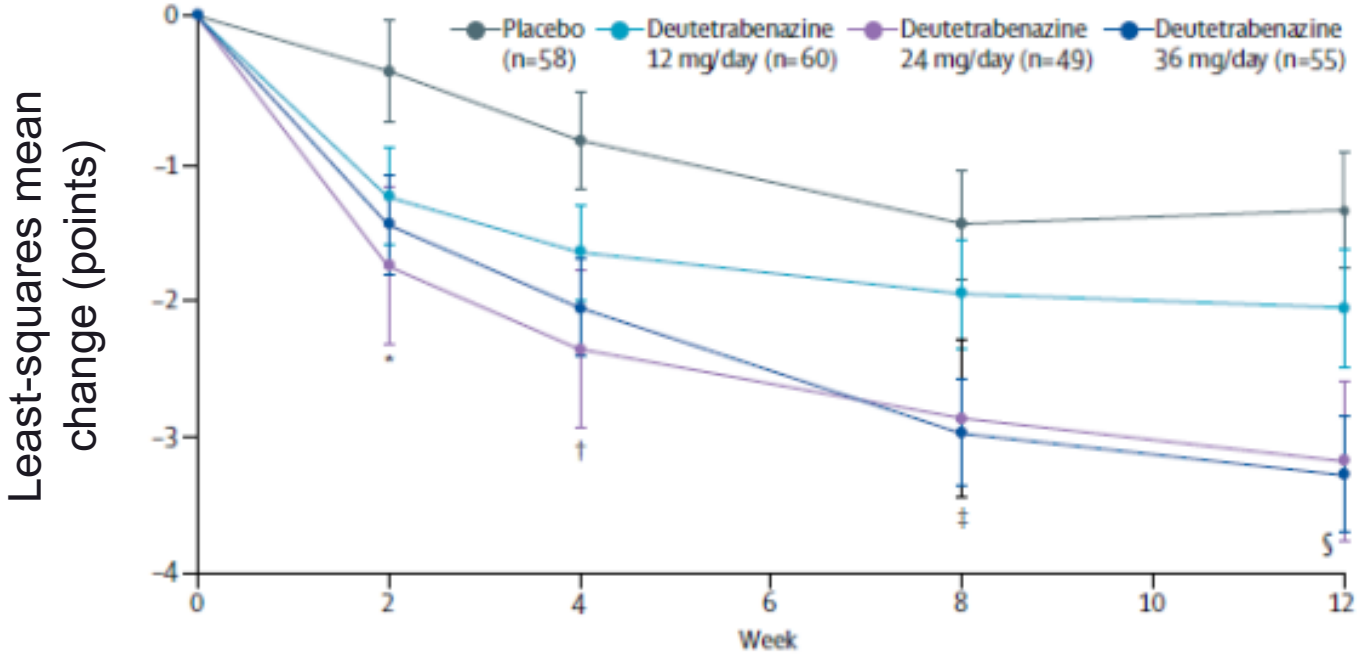
Outcome	DBZ	PBO	*p*-value (95% CI)
Primary (N = 113) AIMS change at 12 weeks (LS mean) Responders (%)	N = 56 -3.0 49	N = 57 -1.6 18	 .019 (-2.6, -0.2) <.002 (n/a)
Secondary (N = 113) Treatment success based on CGIC (%) Treatment success based on PGIC (%)	 48 43	 40 30	 NSD NSD
Safety (n = 117) Overall incidence of side effects (%)	N = 58 48	N = 59 36	 n/a

DBZ = deutetrabenazine; PBO = placebo; CGIC = clinician global impression of change; NSD = no significant difference.

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

Deutetrabenazine: AIM-TD Phase 3 Trial

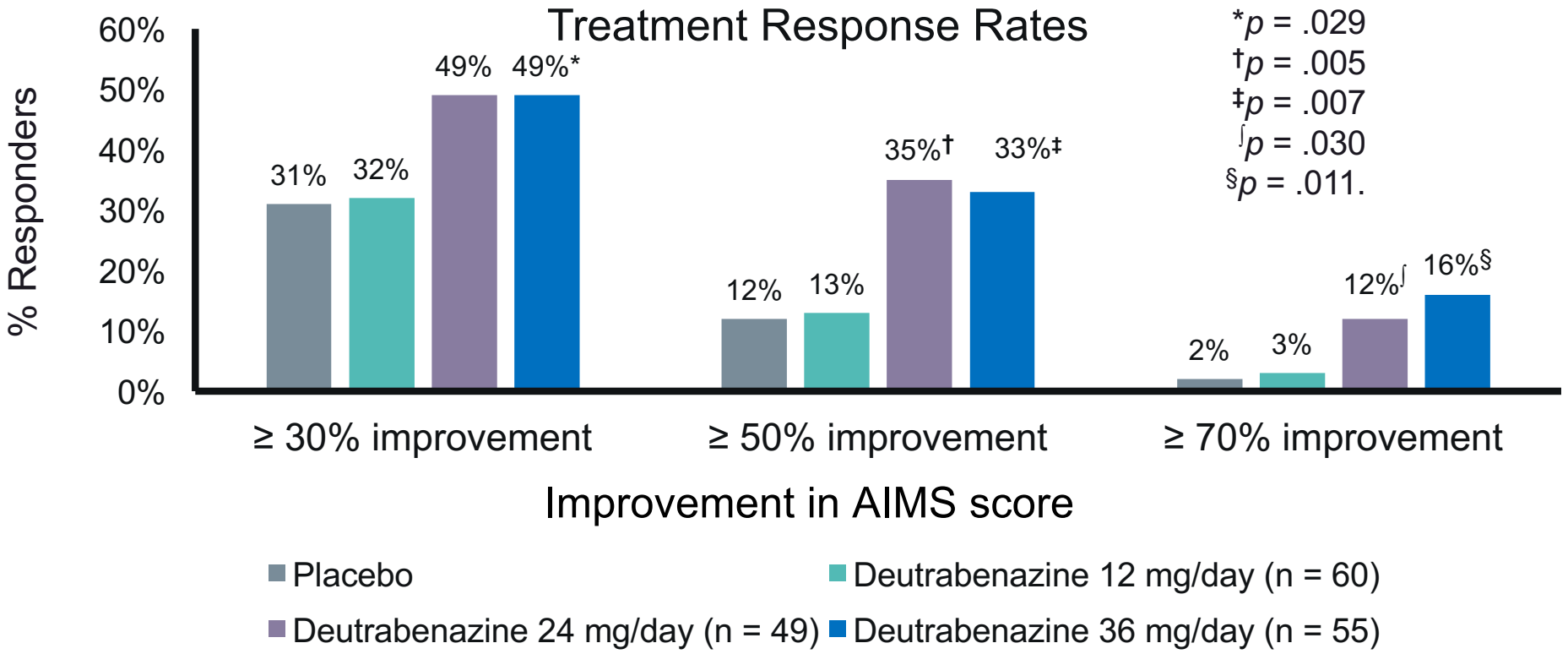
Mean Change Based on AIMS Score from Baseline to Week 12



*p = .006 for 24 mg/day and .032 for 36 mg/day, †p = .03 for 24 mg/day and .018 for 36 mg/day, ‡p = .012 for 24 mg/day and .008 for 36 mg/day, §p = .003 for 24 mg/day and .001 for 36 mg/day.

Anderson KE, et al. *Lancet Psychiatry*. 2017;4:595-604.

Deutetrabenazine: AIM-TD Phase 3 Trial



Anderson KE, et al. *Lancet Psychiatry*. 2017;4:595-604.

ARM-TD and AIM-TD Conclusions

Strengths	Limitations
Specified specific AIMS score at screening and baseline Stringent requirement for concomitant medication use (i.e., no strong anticholinergic medications	Placebo effect seen with AIMS score in both studies No long-term follow-up after study medication was stopped No comment on functional improvement Patients with AIMS <6 included

Conclusion	• Deutetrabenazine 24 mg and 36 mg daily provided a significant reduction in TD • Deutetrabenazine was safe and well tolerated • Long-term efficacy and safety is not established

Anderson KE, et al. *Lancet Psychiatry*. 2017;4:595-604.
Fernandez HH, et al. *Neurology*. 2017;88(21):2003-2010.

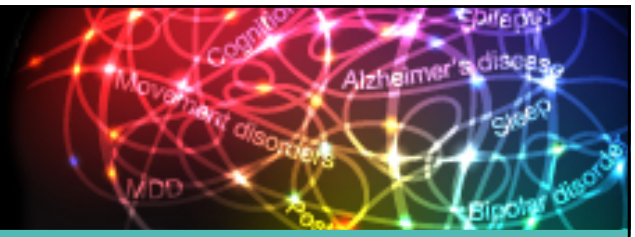
Comparison of VMAT-2 Inhibitors

	Valbenazine	Deutetrabenazine
Dosing	40-80 mg daily (with or without food)	6-48 mg daily (with food)
Formulation	Capsule	Tablet
Half-life	15-22 hours	9-10 hours
Metabolism	Carbonyl reductase CYP3A4 and CYPD6 inhibitors	Carbonyl reductase CYP3A4 and CYPD6 inhibitors
Dose adjustments	CrCL <30 mL/min, Hepatic impairment, CYP2D6 inhibitors	Hepatic impairment, CYP2D6 inhibitors
Warnings and Contraindications	Somnolence QTc prolongation	Depression/suicidal thoughts in patients with HD, Binding to melanin-containing tissues, Hepatic impairment, QTc prolongation, NMS

NMS = neuroleptic malignant syndrome.

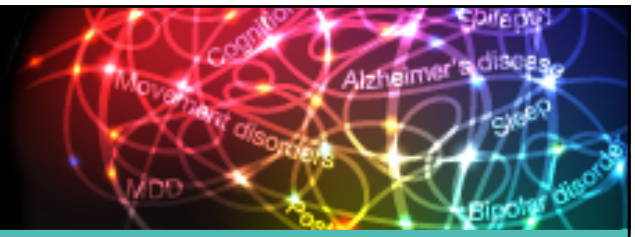
Valbenazine package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209241lbl.pdf; Deutetrabenazine package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208082s000lbl.pdf; Lexi-Drugs. http://online.lexi.com.

Summary



- Until recently, tardive dyskinesia was a potentially disabling condition without an evidence-based treatment approach.
- The introduction of two VMAT2 inhibitors – deutetrabenazine and valbenazine – provides new treatment options for patients with TD.

Call to Action



- Evaluate patients on antipsychotic medications for signs of TD and institute management strategies when appropriate.

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.