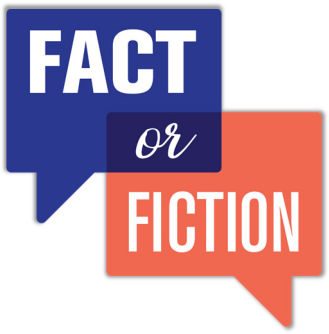

Fact or Fiction? Test Your Knowledge on Assessment and Management Strategies in Tardive Dyskinesia

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Definition

Tardive Dyskinesia

"Late" or "Delayed" | **"Abnormal Movement"**

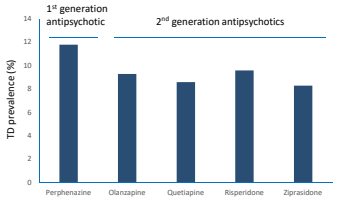
Introduction

- **Tardive dyskinesia** (TD) is characterized by involuntary movements of the body
- The face, lips, jaws, and tongue are most often affected.[1] However, movements of the upper extremities, lower extremities, and trunk can also occur
- TD differs from other movement-related extrapyramidal symptoms (EPS), such as drug-induced parkinsonism
- Patients with TD present with arrhythmic movements of the body parts listed above, whereas patients with parkinsonism presents with rhythmic tremors, rigidity, and a shuffling gait[2]
- TD can have a devastating impact on patients' lives, interfering with their ability to carry out daily tasks, reducing their quality of life, and increasing social withdrawal[3]

1. Waln O, Jankovic J. *Tremor Other Hyperkinet Mov (N Y).* 2013;3:tre-03-161-4138-1. 2. Ward KM, Citrome L. *Neurol Ther.* 2018;7(2):233-248. 3. McEvoy J, et al. *Neurology*. 2018;90(S15):P4.077.

Overview

- TD can be observed with long-term treatment with ***dopamine receptor blocking agents*** such as antipsychotic agents[1,2]
- First described in 1957 by Schonecker, about 5 years after the commencement of neuroleptic treatment in psychiatry[1,3]
- Lower TD risk for second-generation antipsychotics (SGA) than for first-generation antipsychotics (FGA), but ***rates are not zero***[4]



Prevalence of TD in CATIE Schizophrenia trial. TD was diagnosed if modified Schooler-Kane TD criteria were met on at least 1 post-baseline AIMS assessment. Data from Miller DD, et al. *Br J Psychiatry*. 2008;193(4):279-288.

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; AIMS = Abnormal Involuntary Movement Scale.

1. Jankelowitz SK. *Neuropsychiatr Dis Treat*. 2013;9:1371-1380. 2. Citrome L. *J Neurol Sci*. 2017;383:199-204. 3. Schonecker M. *Nervenarzt*.1957;28(12):550-553. 4. Miller DD, et al. *Br J Psychiatry*. 2008;193(4):279-288.

Overview (cont'd)

- TD can be associated with significant and often irreversible functional impairment and can also be socially stigmatizing - TD remains a ***significant treatment issue***
- ***New treatment approaches*** to persistent TD—the VMAT2 inhibitors—are available, as approved by the US FDA for this purpose

VMAT2 = vesicular monoamine transporter type 2; FDA = Food and Drug Administration.
Citrome L. *J Neurol Sci.* 2017;383:199-204.

What is a "Vesicular Monoamine Transporter Type 2"?

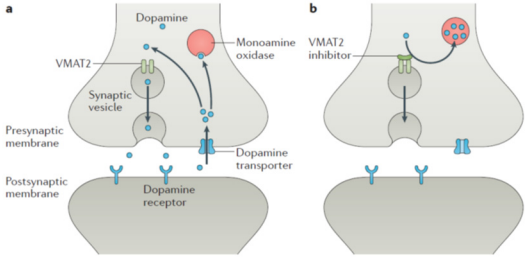


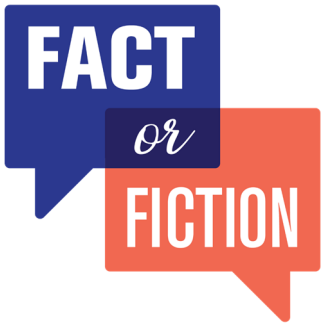
Figure 1 | **Mechanism of action of VMAT2 inhibitors. a** | Normally, vesicular membrane transport type 2 (VMAT2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase. **b** | VMAT2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase.

Jankovic J. Nat Rev Neurol. 2017;13(2):76-78.

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

The Case of Monique

- Monique is a 27-year-old woman with bipolar disorder
- At a visit to her psychiatrist, she reports that her supervisor recently took her aside at work and complained that the "expressions" she has been making during department meetings are distracting
- Monique says she had been unaware that she was making unusual expressions, but since then she has also noticed that her legs are moving on their own when she sits at her desk
- She is currently taking a combination of risperidone and valproate daily for maintenance of her bipolar disorder, which included severe depressive episodes before she began treatment
- She has been taking this combination for a little over a year; she has never tried another treatment regimen, as this one has been controlling her bipolar symptoms well



"Patients like Monique are rare. Tardive dyskinesia has gone away with the use of second-generation antipsychotics. I just don't see it anymore!"

FICTION

Although TD is less prevalent with second-generation antipsychotics than with first-generation antipsychotics, it remains common. The use of antipsychotics is increasing, such as in the case of patients with bipolar disorder or major depressive disorder, and TD will continue to be seen.

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Incidence of TD: CATIE Schizophrenia Trial

Observed TD Events for People with No TD at Baseline[a]

	OLANZ	PERP	QUET	RISP	ZIPR
All eligible patients, n	228	229	234	241	134
Schooler-Kane TD[b]	1.1%	3.3%	4.5%	2.2%	3.3%
Modified S-K TD[c]	9.3%	11.8%	8.6%	9.6%	8.3%
Discontinued for TD	0%	1%	<1%	0%	0%
Added medications for TD	<1%	0%	<1%	1%	0%

[a] Patients with no TD at baseline met none of the criteria for Modified Schooler-Kane TD or borderline TD.
[b] Schooler-Kane TD criteria required on at least 2 consecutive post-baseline AIMS assessments.
[c] modified Schooler-Kane (S-K) TD criteria required on only 1 post-baseline AIMS assessment.

OLANZ = olanzapine; PERP = perphenazine; QUET = quetiapine; RISP = risperidone; ZIPR = ziprasidone.

Source: Miller DD, et al. *Br J Psychiatry.* 2008;193(4):279-288.

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FACT or FICTION

"I can diagnose tardive dyskinesia just by spending a few minutes with Monique. The Abnormal Involuntary Movement Scale (AIMS) examination is irrelevant."

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FICTION

While clinical examination is relevant and can reveal much in the recognition of TD, the AIMS takes only 5-10 minutes and is widely used for the routine, yet comprehensive, assessment of involuntary movements.

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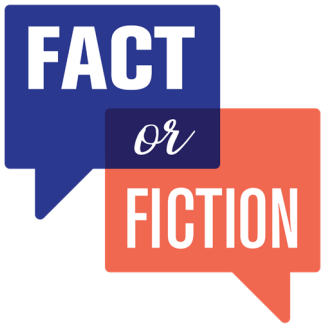

"When I see abnormal movements, like Monique's, I'll use benztropine. That will work for all kinds of extrapyramidal symptoms."

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Benztropine can increase risk for or worsen TD.

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Benztropine

- Increases risk of TD[1]
- Can make TD worse[1]
- Impairs cognition[1]
- If patient needs it for more than a few weeks, then think of another antipsychotic that won't require use of benztropine
- TD and drug-induced parkinsonism are sometimes mistaken for one another, but they respond very differently to treatment, including benztropine[1]
- It is important to be able to distinguish between the two conditions, which can sometimes coexist within the same patient

1. Citrome L. *J Neurol Sci.* 2017;383:199-204.

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Is it Tardive Dyskinesia or Drug-Induced Parkinsonism?

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, deutetrabenazine), amantadine	Anticholinergics (eg, benztropine), amantadine

Source: Ward KM, Citrome L. *Neurol Ther.* 2018;7(2):233-248.

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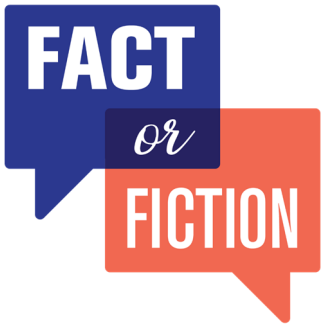

"Monique's tardive dyskinesia is likely to go away if I decrease the dose of the antipsychotic."

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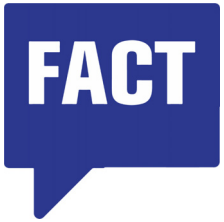

Decreasing the dose of antipsychotics may ultimately reduce symptoms of TD; however, there may be worsening at first. In many cases the TD persists.

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Tardive Dyskinesia and Decisions About Antipsychotic Treatment

- Evidence indicates that decreasing the dose of antipsychotics, or discontinuing them entirely, ameliorates TD symptoms for many patients—but it may take time[1,2]
- Dyskinesias can first appear *after* antipsychotic cessation and may disappear several weeks later; these symptoms, called ***withdrawal dyskinesia***, reflect the action of antipsychotics to suppress or mask dyskinesia.[3] If withdrawal dyskinesia persists, we call it TD
- Research shows that tapering off and discontinuing antipsychotics results in
  - Initial worsening of TD in 33–53% of patients[1]
  - Long-term improvement in 36–55%[1]
- However, we have limited randomized controlled trial-based evidence on this topic, so our understanding of the rate and timing of complete remission is uncertain
- It is difficult to justify continuing antipsychotic treatment in non-psychotic patients with TD. However, because the risk of psychotic relapse is significant among psychotic patients with TD,[3] tapering or discontinuing antipsychotic treatment is often not an acceptable choice

1. Egan MF, et al. *Schizophr Bull*. 1997;23(4):583-609. 2. Glazer WM, et al. *Br J Psychiatry*. 1990;157:585-592. 3. Gilbert PL, et al. *Arch Gen Psychiatry*. 1995;52(3):173-188.

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Now let's move on…

to another case that requires important TD diagnostic and management decisions.

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The Case of Harold

- Harold is a 53-year-old man with a history of schizophrenia
- Upon examination, Harold has puckering of the lips and sometimes sticks out his tongue
- When asked, Harold is unaware that he is making these movements
- Harold's sister provides the history that these movements have been going on for several years and that everyone tends to stare at him when he is in public, and she feels embarrassed to be with him because of this
- Harold acknowledges that not many people talk to him and that at his visits to the clinic, no one sits next to him
- Harold's hallucinations and delusions are under good control with his current medication regimen and he does not want to stop his medications; Harold's sister provides additional history that Harold has become violent when medication changes were attempted

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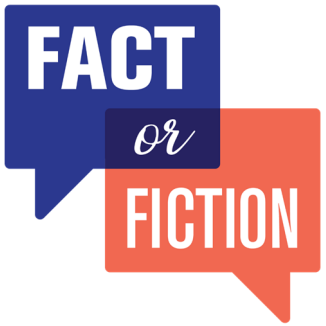

"When considering Harold's case, it's important to consider that the most important risk factors for developing tardive dyskinesia are older age and cumulative exposure to antipsychotics."

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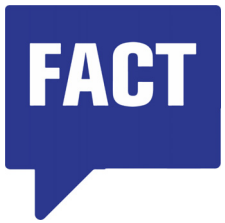

Age and cumulative exposure are important risk factors for development of TD in patients receiving an antipsychotic.

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Tardive Dyskinesia: Risk Factors

Major risk factors for TD include

- **Age.** Older individuals are at 4-5 times increased risk for TD (5% vs 20% per year)
- **Cumulative exposure to dopamine receptor blocking agents, including commonly used agents such as metoclopramide, as well as antipsychotics**. In the CATIE Schizophrenia Trial, the average number of years since first antipsychotic was 21.5 years for patients with TD vs 12.8 years for patients without TD (P<0.0001)[1]

Minor risk factors for TD: female sex; race; preexisting mood, movement, or cognitive disorder; alcohol use; diabetes; human immunodeficiency virus (HIV) positivity[2]

- The ***occurrence of acute extrapyramidal symptoms (ie, drug-induced parkinsonism)*** on initial exposure to dopamine antagonist medications is associated with increased risk of developing TD in the future; reducing the dose of the dopamine antagonist medication greatly reduces risk for both drug-induced parkinsonism and TD. **Masking drug-induced parkinsonism with anticholinergic medications, such as benztropine, does not reduce the risk of developing TD in the future**

1. Miller DD, et al. *Schizophr Res.* 2005;80(1):33-43. 2. Jankelowitz SK. *Neuropsychiatr Dis Treat*. 2013;9:1371-1380.

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Correlates and Risk Factors for TD

CATIE Schizophrenia Trial baseline data			
	TD (n = 212)	Non-TD (n = 1098)	*P* value
Age, mean years (SE)	47.2 (0.6)	38.9 (0.3)	<0.0001
Gender, male	78%	74%	0.2248
Years since first antipsychotic (SE)	21.5 (0.7)	12.8 (0.3)	<0.0001
AIMS (total)	7.6 (0.3)	0.3 (0.02)	<0.0001
Current antipsychotic			0.051
None	26%	27%	
SGA only	47%	60%	
FGA only	28%	14%	
Current anticholinergic use	28%	14%	<0.0001
Diabetes	13%	9%	0.6825
Hypertension	41%	33%	0.4056
Substance abuse	42%	37%	0.0032

212 meeting modified Schooler-Kane criteria for TD vs 1098 with no item on AIMS rated higher than 1 and no history of TD.

Source: Miller DD, et al. *Schizophr Res.* 2005;80(1):33-43.

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Correlates and Risk Factors for TD (cont'd)

TD and Neurocognitive Tests, EPS, and Akathisia			
	TD (n = 212) Mean (SE)	Non-TD (n = 1098) Mean (SE)	*P* value
Neurocognitive composite (Z-score)	–0.19 (0.05)	0.02 (0.02)	0.7725
PANSS			
Total	78.2 (1.2)	75.1	0.0019
Positive	19.4 (0.4)	18.3	0.0584
Negative	20.2 (0.4)	20.1	0.0137
General psychopathology	38.6 (0.7)	36.7	0.0035
Simpson-Angus EPS	0.40 (0.03)	0.16 (0.01)	<0.0001
Barnes akathisia	2.06 (0.14)	0.78 (0.04)	<0.0001

PANSS = Positive and Negative Symptom Scale.

Source: Miller DD, et al. *Schizophr Res.* 2005;80(1):33-43.

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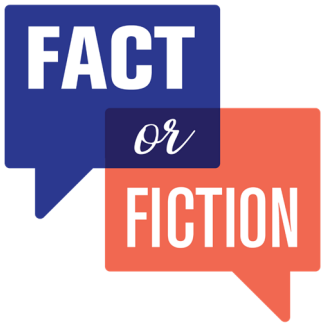

"Harold isn't complaining about his tardive dyskinesia, so there is no need to treat it."

27

Many patients with TD are not aware they have it and will not seek treatment for it. However, TD is potentially stigmatizing and can impair social and behavioral functioning. Because TD can become irreversible, it is important to recognize and address it early.

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FACT or FICTION

"Harold's tardive dyskinesia will likely improve with the use of VMAT2 inhibitors."

29

FACT

Treatment with newly approved VMAT2 inhibitors has been shown to improve TD symptoms in randomized clinical trials.

30

Treatment of TD with the New VMAT2 Inhibitors Approved by the FDA: Randomized, Double-Blind, Placebo-Controlled Trials

To date, randomized, double-blind, placebo-controlled trials have shown that treatment with valbenazine or deutetrabenazine improves TD symptoms.

RCT	VMAT2	N	Daily Dose	Duration	Results
KINECT-2	Valbenazine	102	Flexible dose 25-75 mg (76% on 75 mg)	6 weeks	LS mean change from baseline, −2.6 vs −0.2; *P*=0.0005
KINECT-3	Valbenazine	234	40 mg, 80 mg	6 weeks	LS mean change from baseline (80 mg), −3.2 vs −0.1; *P*<0.0001
ARM-TD	Deutetrabenazine	117	Flexible dose 12-48 mg (mean 39 mg)	12 weeks	LS mean change from baseline, −3.0 vs −1.6; *P*=0.019
AIM-TD	Deutetrabenazine	298	12 mg, 24 mg, 36 mg	12 weeks	LS mean change from baseline (24 mg) −3.2, *P*=0.003; (36 mg) −3.3, *P*=0.001; placebo −1.4

LS = least squares.
Sources: 1. Citrome L. *Int J Clin Pract*. 2017;71(11):e13030. 2. Citrome L. *Int J Clin Pract*. 2017;71(7):e12964.

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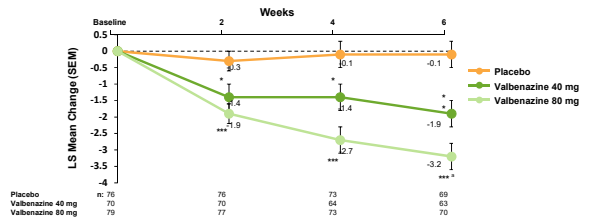
Valbenazine (KINECT 3): AIMS Change from Baseline by Study Visit (Fixed-Dose Study Design)



In the 6-week KINECT 3 trial, patients who received 80 mg valbenazine achieved significantly greater reductions in TD symptoms than patients who received placebo.

Intent-to-treat population: Included all randomized participants who had at least one post-randomization AIMS value.
*P<0.05; **P<0.01; ***P≤0.001 for valbenazine vs placebo. [a]Dose that was statistically significantly different from placebo after adjusting for multiplicity.

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

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Adverse Reactions in 3 Placebo-Controlled Studies of Valbenazine 6-Week Treatment Duration Reported at ≥ 2% and > Placebo

Adverse Reaction[a]	Valbenazine[b] (n=262) (%)	Placebo (n=183) (%)
General Disorders		
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Nervous System Disorders		
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 Disorders		
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Musculoskeletal Disorders		
Arthralgia	2.3%	0.5%

Collectively, these data indicate that the most common adverse effect is somnolence. Very few patients discontinued the trials because of adverse events (3% for valbenazine vs 2% for placebo).

[a]Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency. [b]All doses.

Source: US FDA. Drugs@FDA. www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

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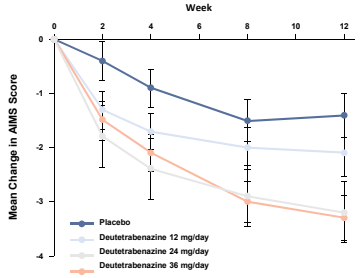
Deutetrabenazine (AIM-TD): Mean Change in AIMS Score (Fixed-Dose Study Design)



In the 12-week AIM-TD trial, patients who received 36 or 24 mg/d deutetrabenazine achieved significantly greater reductions in TD symptoms than patients who received placebo.

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

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Deutetrabenazine Safety and Tolerability Profile in Placebo-Controlled TD Studies

Placebo-Controlled TD Studies: Adverse Reactions Reported in ≥ 2% of Patients Treated with Deutetrabenazine

Adverse Reaction	Deutetrabenazine[a] (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%

A total of 4% of patients receiving deutetrabenazine required a dose reduction because of adverse reactions (vs 2% of patients taking placebo). Very few patients discontinued the trials because of adverse events (4% for deutetrabenazine vs 3% for placebo). [a]All doses.

Sources: 1. Anderson KE, et al. *Lancet Psychiatry*. 2017;4(8):595-604. 2. Fernandez HH, et al. *Neurology*. 2017;88(21):2003-2010.

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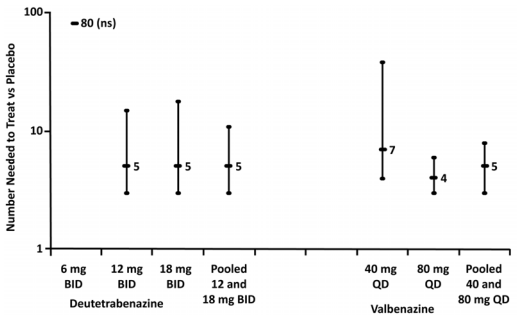
Deutetrabenazine vs Valbenazine: Number Needed to Treat in Fixed-Dose Trials

Number needed to harm vs placebo for discontinuation because of an adverse effect (AE) in the fixed-dose studies for either medication was ~100; thus likelihood to be helped or harmed for response vs discontinuation because of an AE is ~20.



Source: Citrome L. *J Neurol Sci*. 2017;383:199-204.

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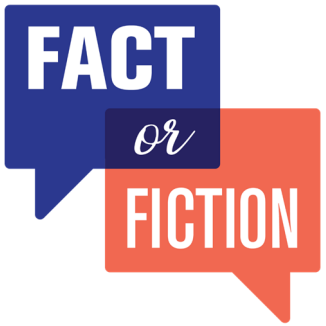

"It doesn't matter what VMAT2 inhibitor I prescribe for Harold.

The VMAT2 inhibitors are all essentially the same."

There are important differences between the VMAT2 inhibitors.

Deutetrabenazine vs Valbenazine: Similarities and Differences

	Deutetrabenazine	Valbenazine
Brand name	Austedo	Ingrezza
Date approved by US FDA for TD	August 2017	April 2017
Dose/formulation	Tablets: 6 mg, 9 mg, 12 mg	Capsules: 40 mg, 80 mg
Other indications	Chorea associated with Huntington's disease	None
Design rationale	Deuteration results in slower drug metabolism	Parent drug of [+]-α-HTBZ; no β-HTBZ
Metabolites	Active deuterated dihydro metabolites (HTBZ): α-HTBZ and β-HTBZ	Active metabolite: ([+]-α-HTBZ)
Half-life	Total (α + β)-HTBZ from deutetrabenazine: 9–10 h	Valbenazine and [+]-α-HTBZ: 15–22 h
Boxed bolded warnings relevant to TD	None	None
Contraindications relevant to TD	Hepatic impairment; taking reserpine, MAOIs, tetrabenazine, or valbenazine	None
Warnings and precaution contained in *Highlights of Prescribing Information*	QT prolongation; neuroleptic malignant syndrome; akathisia, agitation, restlessness, and parkinsonism (latter not applicable to TD); sedation/somnolence	Somnolence; QT prolongation
Dosing recommendations	Initial dose 12.5 mg/d, target dose 12–48 mg/d, administer BID with food; titrate at weekly intervals by 6 mg/d based on reduction of TD and tolerability	Initial dose 40 mg/d, target dose 80 mg, administer once daily with or without food; titrate to 80 mg/d after one week on 40 mg/d
CYP2D6 poor metabolizers	Maximum recommended dosage in poor CYP2D6 metabolizers is 36 mg/d	Consider dose reduction based on tolerability
Drug-drug interactions	Strong CYP2D6 inhibitors: maximum recommended dose is 36 mg/d; alcohol or other sedating drugs may have additive sedation and somnolence	MAOIs: avoid; strong CYP3A4 inducers: not recommended; strong CYP3A4 inhibitors: reduce dose to 40 mg; strong CYP2D6 inhibitors: consider dose reduction based on tolerability
Hepatic impairment	Contraindicated	Recommended dose for patients with moderate or severe hepatic impairment is 40 mg/d
Renal impairment	No clinical studies have been conducted to assess the effect of renal impairment	No dosage adjustment is necessary for patients with mild to moderate renal impairment; use is not recommended in patients with severe renal impairment
QT prolongation recommendations	For patients at risk for QT prolongation, assess the QT interval before and after increasing the total dosage above 24 mg/d	For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage
Most common AEs[a] and rate vs. placebo	Nasopharyngitis (4% vs. 2%), insomnia (4% vs. 1%)	Somnolence (10.9% vs. 4.2%)
Responder[b] rates, pooled	30.0% vs. 14.8%	36.5% vs. 12.4%
NNT (95% CI) vs. placebo	7 (4–18)	5 (3–7)
CGI responder[c] rates, pooled	46.9% vs. 33.0%	40.4% vs. 18.6%
NNT (95% CI) vs. placebo	8 (4–45)	5 (4–9)
Discontinuation rates due to an AE, pooled	3.6% vs. 3.1%	2.6% vs. 1.6%
NNH (95% CI) vs. placebo	189 (not significant)	76 (not significant)

Citrome L. *J Neurol Sci*. 2017;383:199-204.

Deutetrabenazine vs Valbenazine: Similarities and Differences (cont'd)

	Deutetrabenazine	Valbenazine
Brand name	Austedo	Ingrezza
Date approved by US FDA for TD	August 2017	April 2017
Dose/formulation	Tablets: 6 mg, 9 mg, 12 mg	Capsules: 40 mg, 80 mg
Other indications	Chorea associated with Huntington's disease	None
Design rationale	Deuteration results in slower drug metabolism	Parent drug of [+]-α-HTBZ; no β-HTBZ
Metabolites	Active deuterated dihydro metabolites (HTBZ): α-HTBZ and β-HTBZ	Active metabolite: ([+]-α-HTBZ)
Half-life	Total (α + β)-HTBZ from deutetrabenazine: 9–10 h	Valbenazine and [+]-α-HTBZ: 15–22 h
Boxed bolded warnings relevant to TD	None	None
Contraindications relevant to TD	Hepatic impairment; taking reserpine, MAOIs, tetrabenazine, or valbenazine	None
Warnings and precaution contained in *Highlights of Prescribing Information*	QT prolongation; neuroleptic malignant syndrome; akathisia, agitation, restlessness, and parkinsonism (latter not applicable to TD); sedation/somnolence	Somnolence; QT prolongation
Dosing recommendations	Initial dose 12.5 mg/d, target dose 12–48 mg/d, administer BID with food; titrate at weekly intervals by 6 mg/d based on reduction of TD and tolerability	Initial dose 40 mg/d, target dose 80 mg, administer once daily with or without food; titrate to 80 mg/d after one week on 40 mg/d
CYP2D6 poor metabolizers	Maximum recommended dosage in poor CYP2D6 metabolizers is 36 mg/d	Consider dose reduction based on tolerability
Drug-drug interactions	Strong CYP2D6 inhibitors: maximum recommended dose is 36 mg/d; alcohol or other sedating drugs may have additive sedation and somnolence	MAOIs: avoid; strong CYP3A4 inducers: not recommended; strong CYP3A4 inhibitors: reduce dose to 40 mg; strong CYP2D6 inhibitors: consider dose reduction based on tolerability
Hepatic impairment	Contraindicated	Recommended dose for patients with moderate or severe hepatic impairment is 40 mg/d
Renal impairment	No clinical studies have been conducted to assess the effect of renal impairment	No dosage adjustment is necessary for patients with mild to moderate renal impairment; use is not recommended in patients with severe renal impairment
QT prolongation recommendations	For patients at risk for QT prolongation, assess the QT interval before and after increasing the total dosage above 24 mg/d	For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage
Most common AEs[a] and rate vs. placebo	Nasopharyngitis (4% vs. 2%), insomnia (4% vs. 1%)	Somnolence (10.9% vs. 4.2%)
Responder[b] rates, pooled	30.0% vs. 14.8%	36.5% vs. 12.4%
NNT (95% CI) vs. placebo	7 (4–18)	5 (3–7)
CGI responder[c] rates, pooled	46.9% vs. 33.0%	40.4% vs. 18.6%
NNT (95% CI) vs. placebo	8 (4–45)	5 (4–9)
Discontinuation rates due to an AE, pooled	3.6% vs. 3.1%	2.6% vs. 1.6%
NNH (95% CI) vs. placebo	189 (not significant)	76 (not significant)

Citrome L. *J Neurol Sci*. 2017;383:199-204.

Deutetrabenazine vs Valbenazine: Similarities and Differences (cont'd)

	Deutetrabenazine	Valbenazine
Brand name	Austedo	Ingrezza
Date approved by US FDA for TD	August 2017	April 2017
Dose/formulation	Tablets: 6 mg, 9 mg, 12 mg	Capsules: 40 mg, 80 mg
Other indications	Chorea associated with Huntington's disease	None
Design rationale	Deuteration results in slower drug metabolism	Parent drug of [+]-α-HTBZ; no β-HTBZ
Metabolites	Active deuterated dihydro metabolites (HTBZ): α-HTBZ and β-HTBZ	Active metabolite: ([+]-α-HTBZ)
Half-life	Total (α + β)-HTBZ from deutetrabenazine: 9–10 h	Valbenazine and [+]-α-HTBZ: 15–22 h
Boxed bolded warnings relevant to TD	None	None
Contraindications relevant to TD	Hepatic impairment; taking reserpine, MAOIs, tetrabenazine, or valbenazine	None
Warnings and precaution contained in *Highlights of Prescribing Information*	QT prolongation; neuroleptic malignant syndrome; akathisia, agitation, restlessness, and parkinsonism (latter not applicable to TD); sedation/somnolence	Somnolence; QT prolongation
Dosing recommendations	Initial dose 12 mg/d, target dose 12–48 mg/d, administer BID with food; titrate at weekly intervals by 6 mg/d based on reduction of TD and tolerability	Initial dose 40 mg/d, target dose 80 mg, administer once daily with or without food; titrate to 80 mg/d after one week on 40 mg/d
CYP2D6 poor metabolizers	Maximum recommended dosage in poor CYP2D6 metabolizers is 36 mg/d	Consider dose reduction based on tolerability
Drug-drug interactions	Strong CYP2D6 inhibitors: maximum recommended dose is 36 mg/d; alcohol or other sedating drugs may have additive sedation and somnolence	MAOIs: avoid; strong CYP3A4 inducers: not recommended; strong CYP3A4 inhibitors: reduce dose to 40 mg; strong CYP2D6 inhibitors: consider dose reduction based on tolerability
Hepatic impairment	Contraindicated	Recommended dose for patients with moderate or severe hepatic impairment is 40 mg/d
Renal impairment	No clinical studies have been conducted to assess the effect of renal impairment	No dosage adjustment is necessary for patients with mild to moderate renal impairment; use is not recommended in patients with severe renal impairment
QT prolongation recommendations	For patients at risk for QT prolongation, assess the QT interval before and after increasing the total dosage above 24 mg/d	For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage
Most common AEs[a] and rate vs. placebo	Nasopharyngitis (4% vs. 2%), insomnia (4% vs. 1%)	Somnolence (10.9% vs. 4.2%)
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Citrome L. *J Neurol Sci.* 2017;383:199-204.

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Deutetrabenazine and Valbenazine Also Have Some Important Similarities

- There is no need to discontinue or reduce or change antipsychotic therapy
- If patient is already on mood stabilizers and/or antidepressants – OK to continue therapy
- Both VMAT2 medications are effective in TD, regardless of the patient's diagnosis (schizophrenia or mood disorder)
- Neither of the VMAT2-based FDA-approved medications destabilizes depression, mania, or psychosis; or induces suicidality[1]

So which one should I use?

- There are no head-to-head studies of valbenazine and deutetrabenazine
- Customize therapy for patients in choosing medication
  - Consider adherence
  - Consider dosing regimen
  - Consider side-effect profile
- Tolerability and efficacy between the 2 medications may differ from patient to patient

1. Citrome L. *J Neurol Sci.* 2017;383:199-204.

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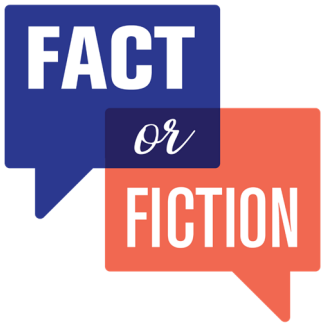

"It doesn't make sense to treat Harold with a VMAT2 inhibitor long term because we don't have long-term data."

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Long-term data with VMAT2 inhibitors demonstrate sustained improvements in TD.

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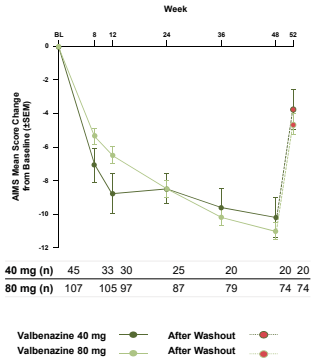
Valbenazine

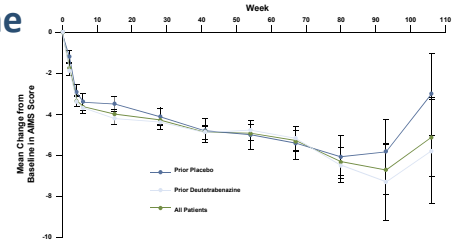
- Of the 163 participants in the KINECT 4 trial, 103 completed the long-term trial
- Sustained improvements were found in patients who received once-daily valbenazine, for both clinician- and patient-rated measures
- These improvements lasted until medication was discontinued at the end of the study
- No new safety signals or concerns emerged in this long-term study



Factor SA, et al. Effects of long-term valbenazine on tardive dyskinesia and patient-reported outcomes: results from the KINECT 4 Study. Presented at: 70th Annual Meeting of the American Academy of Neurology; April 21-27, 2018; Los Angeles, CA.

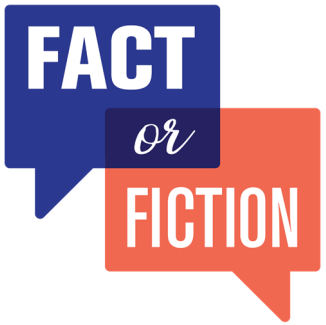
Deutetrabenazine

- Of 343 patients enrolled in the deutetrabenazine extension study, 232 had previously received deutetrabenazine and 111 had previously received placebo
- The mean total daily dose of deutetrabenazine in the long-term study was 38.6 (1.13) mg
- Sustained improvements were found, using clinician-rated measures, until the end of the study
- No new safety signals or concerns emerged

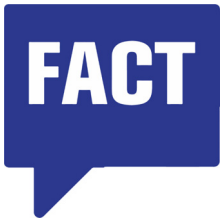


Week	0	2	4	6	15	28	41	54	67	80	93	106
Prior Placebo (n)	111	111	108	104	101	83	65	50	34	27	10	2
Prior Deutetrabenazine (n)	232	230	229	223	208	168	137	96	69	39	13	6
All Patients (n)	343	341	337	327	309	251	202	146	103	66	23	8

Hauser RA, et al. Long-term treatment with deutetrabenazine is associated with continued improvement in tardive dyskinesia (TD): results from an open-label extension study. Presented at: 70th Annual Meeting of the American Academy of Neurology; April 21-27, 2018; Los Angeles, CA.



"Making sure that patients like Harold can benefit from VMAT2 inhibitors will require overcoming access issues."



Clinicians can take steps to improve coverage of VMAT2 inhibitors, including thorough documentation in prior authorization requests.

Careful Documentation is a Must

- Many, if not most, US insurance carriers cover VMAT2 therapy
- However, good documentation of need for VMAT2 therapy is critical to obtain their approval. The following must be included in preauthorization paperwork:
  - The location and severity of abnormal movements
  - That the patient has a diagnosis of TD
  - The bio-psychosocial impairment caused by TD
  - Why therapy with benztropine is inappropriate for this patient

  Proactively document all 4 of the above. This reduces the chance of rejection of request for VMAT2 therapy.
- Both VMAT2 therapies have robust access/patient assistance programs

Summary

- **Assume** TD exists in your practice. It is still common and will continue to be because of increasing use of antipsychotic medications[1]
- **Screen** with scheduled AIMS exams, especially in the older population[1]
- **Treat** as quickly as possible after TD appears. Reliable, effective, and well-tolerated treatments are now available for persistent TD[1]
- There are 2 FDA-approved treatments for TD: **valbenazine** and **deutetrabenazine.** Both are efficacious and tolerable.[1] They differ in
  - Frequency of administration (once daily for valbenazine vs twice daily for deutetrabenazine)
  - Titration (titrate to target dose of 80 mg/d for valbenazine vs dose to efficacy/tolerability for deutetrabenazine)
  - Need for food (administer deutetrabenazine with food)
  - Drug-drug interactions (consider CYP2D6 modulators for deutetrabenazine vs both CYP2D6 and CYP3A4 for valbenazine)
  - Contraindications (hepatic impairment for deutetrabenazine)[1]
- **However, the clinical usefulness of these treatments is rendered moot if TD goes unrecognized**

1. Citrome L. *J Neurol Sci.* 2017;383:199-204.