Psych Congress Network

TARDIVE DYSKINESIA 360

Practical Strategies for Patient Follow-Up and Long-Term VMAT2 Inhibitor Treatment

This activity is supported by independent educational grants from Neurocrine Biosciences and Teva Pharmaceuticals.

Faculty

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San Antonio, Texas

Faculty Disclosure

- **Dr. Citrome**: Consultant—Acadia, Alkermes, Allergan, Indivior, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda; Speakers Bureau—Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva; Stocks—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer; Royalties—Wiley (Editor-in-Chief, *International Journal of Clinical Practice*), *UpToDate* (reviewer), Springer Healthcare (book).
- **Dr. Saklad**: Consultant—Alkermes, Otsuka, NCS Pearson, Texas Health and Human Services Commission, San Antonio State Hospital, Pharmacy Department; Grant/Research Support—Alkermes; Speakers Bureau—Alkermes, Neurocrine.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
    - The off-label use of amantadine, clonazepam, ginkgo biloba, tetrabenazine, and other agents for the treatment of TD will be discussed.
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Evaluate the available clinical trial data surrounding the long-term efficacy and tolerability of vesicular monoamine transporter type 2 (VMAT2) inhibitors for the treatment of tardive dyskinesia (TD)
- Outline the discrete dosing schedules and patient population-specific treatment considerations of available VMAT2 inhibitors for the treatment of TD
- Engage in available patient support programs and communication practices that facilitate VMAT2 inhibitor access through the specialty pharmacy and subsequent treatment continuation

Outline

- Definitions and Overview
- Differential Diagnosis
- AIMS
- Harm Reduction
- Interventions
- Follow-up
- Summary

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Definition of Tardive Dyskinesia

Tardive dyskinesia:

A type of dyskinesia that typically emerges after long-term use of antipsychotic drugs (DRBAs)

Tardive

Appearing or tending to appear late

Dyskinesia

Distortion or impairment of voluntary movement

Socially stigmatizing, functionally impairing, and probably irreversible medical condition

***DSM* Dx of Tardive Dyskinesia** (highlights)**:**

- Involuntary movements of the tongue, jaw, trunk, or extremities have developed in association with the use of neuroleptic medication
- The involuntary movements are present over a period of at least 4 weeks and occurring in any of the following patterns: (1) choreiform movements (ie, rapid, jerky, nonrepetitive); (2) athetoid movements (ie, slow, sinuous, continual); (3) rhythmic movements (ie, stereotypies)

- Symptoms develop during exposure to a neuroleptic medication or within 4 weeks of withdrawal from an oral (or within 8 weeks of withdrawal from a depot) neuroleptic medication
- There has been exposure to neuroleptic medication for at least 3 months (1 month if age ≥ 60 years)

DRBA = dopamine receptor blocking agent.

Lerner PP, et al. *Psychiatry Clin Neurosci*. 2015;69(6):321-334. Dorland's Online Medical Dictionary. www.dorlands.com.

Tardive Dyskinesia: *Fast Facts*

- First described in 1957 by Schonecker, about 5 years after the commencement of neuroleptic treatment in psychiatry
- Lower TD risk for SGAs than for FGAs, but ***rates are not zero***
- Can also be seen after use of antitussive agents, such as promethazine, and antiemetic medications, such as ***metoclopramide*** used for gastroesophageal reflux and for diabetic gastroparesis
- TD, once established, has proved to be ***irreversible*** in most cases
- Can be associated with significant functional impairment and can be socially stigmatizing—TD remains a ***significant treatment issue***
- The ***indications for antipsychotic medications have expanded***, and large numbers of people are receiving these medications, increasing the number of people who can get TD
- ***New treatment approaches*** to persistent TD are available, as approved by the US FDA for this purpose

FGA = first-generation antipsychotic; SGA = second-generation antipsychotic.

Jankelowitz SK. *Neuropsychiatr Dis Treat*. 2013;9:1371-1380. Schonecker M. *Nervenarzt*. 1957;28(12):550-553. Citrome L. *J Neurol Sci*. 2017;383:199-204. Caroff SN, et al. *Current Psychiatry*. 2011;10(10):23-32.

Tardive Dyskinesia: *Prevalence Rates*

- Meta-analysis of 41 studies
- N=11,493, mean age = 42.8 years, male = 66.4%, schizophrenia spectrum = 77.1%

Findings

- Overall TD prevalence = 25.3%
- Prevalence with current SGAs = 20.7%
- Prevalence with current FGAs = 30.0%
- TD prevalence with SGAs was especially low in the 4 studies reporting on patients without prior FGA treatment: **7.2%**
- Risk factors: **Older age**, longer illness duration, early EPS, African American ethnicity

EPS = extrapyramidal symptoms.

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

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Tardive Dyskinesia: *Prevalence and Clinical Factors*

Parameter	Number of Studies Included	R^2	*P*
Mean Age	39	0.173	.0037
Psychiatric Illness Duration (Mean 18.7 years)	21	0.154	.034

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

What is Withdrawal Dyskinesia?

- Of note, 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
- If the withdrawal dyskinesia persists, we call it TD

Tardive Dyskinesia: *Awareness*

- 607 patients in a state mental hospital in Singapore were assessed using the Abnormal Involuntary Movement Scale (AIMS)
- Of the 607 patients, 242 (39.9%) met criteria for TD
- 163 of those 242 patients with TD (67.4%) were **not aware** of the presence of TD
- The majority of patients with SMI who have TD will not seek treatment themselves – relatives will ask for help with them, or clinicians will intervene
- **Caveat**: The patients studied may have been quite different from people with TD who have been exposed to antipsychotics for treatment of MDD or bipolar disorder, or metoclopramide for GI disorders, and who have substantial insight regarding their abnormal movements

GI = gastrointestinal; MDD = major depressive disorder; SMI = serious mental illness.

Chong SA, et al. *J Clin Psychopharmacol*. 2001;21(2):235-237.

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- Definitions and Overview
- **Differential Diagnosis**
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Tardive Dyskinesia: *Differential Diagnosis*

Conditions That May Resemble TD
Spontaneous dyskinesias occurring in the elderly and in schizophrenia*
Oral movements from ill-fitting dentures and other dental problems
Drug-induced dyskinesias from antiparkinsonian drugs or stimulants
Autism
Chronic motor tic disorder
Huntington's disease
Meige's syndrome
Restless legs syndrome
Rett's syndrome
Senile chorea
Sydenham's chorea
Tourette syndrome
Wilson's disease

***If documented to have begun after initiation of antipsychotic treatment, spontaneous dyskinesias are more likely TD.**

Citrome L, et al. *Am J Manage Care*. 2007;13(Suppl):1-12.

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Kraepelin, 1907—
"…convulsive movement, involving the muscles of the eye and speech which is both *characteristic and of frequent occurrence* in dementia praecox…smacking of the lips, clucking of the tongue, sudden grunting, sniffing and coughing… More often there exists a peculiar choreiform movement of the mouth"

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Wilson's disease

Caveat: People with TD and dentures often have denture problems

***If documented to have begun after initiation of antipsychotic treatment, spontaneous dyskinesias are more likely TD.**

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Tardive Dyskinesia: *Diagnosis Caveats*

Volitional or psychotic mannerisms, tics, and **drug-induced parkinsonism** must be distinguished from TD and can coexist with TD in the same patients

- Drug-induced parkinsonism worsens with increased antipsychotic dose, but TD can be "masked" and appears improved
- Drug-induced parkinsonism can improve with reduced antipsychotic dose, but TD may appear worse
- Anticholinergics such as benztropine used to treat drug-induced parkinsonism does not treat the TD and can make it worse
- Moreover, anticholinergic medication has a deleterious effect on cognition and can further disadvantage a person with schizophrenia who already is struggling with cognitive impairment

The nature and severity of abnormal movements may vary considerably over time

- TD can worsen with emotional stress or made more active during movement of other parts of the body, such as during walking; TD disappears entirely during sleep

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

Is it TD 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 choreoathetoid) 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), ginkgo biloba, clonazepam, amantadine	Anticholinergics (for example, benztropine), amantadine

Ward KM, et al. *Neurol Ther*. 2018;7(2):233-248.

By the Way, Our Opinion about Benztropine

- Increases risk for TD
- Can make TD worse
- Impairs cognition
- Causes constipation
- If patient needs it for more than few weeks, then think of another antipsychotic that won't require use of benztropine
- Use amantadine instead

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Abnormal Involuntary Movement Scale (AIMS): *The Standard of Care*

- Observer-rated 12-item anchored scale that takes 5 to 10 minutes
- Adopted by many agencies for routine clinical use
- With FGAs, examine for TD at least every 6 months
- With SGAs and no concomitant FGAs, examine for TD annually
- With patients at high risk for EPS (eg, older age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the *primary outcome measure* in research of drugs for TD

		CIRCLE ONE				
FACIAL AND ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0	1	2	3	4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0	1	2	3	4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0	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
	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
TRUNK MOVEMENTS	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
GLOBAL JUDGMENTS	8. Severity of abnormal movements	None, Normal ...0 Minimal 1		Mild .....2 Moderate 3		Severe 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal 1		Mild .....2 Moderate 3		Severe 4
	10. Patient's awareness of abnormal movements ***RATE ONLY PATIENT'S REPORT***	No Awareness .....0 Aware, Mild distress 2			Aware, No distress .....1 Aware, Severe distress ...4	
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0		Yes 1		
	12. Does patient usually wear dentures?	No.....0		Yes 1		

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537. Citrome L. *J Neurol Sci.* 2017;383:199-204.

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Items 1 to 7: 4 items dedicated to the face, lips, jaws, tongue. Only 1 item each for the upper extremities, lower extremities, and trunk. The sum of the score of these 7 items is the **dyskinesia score**, and is used as the *primary outcome measure* for TD studies.

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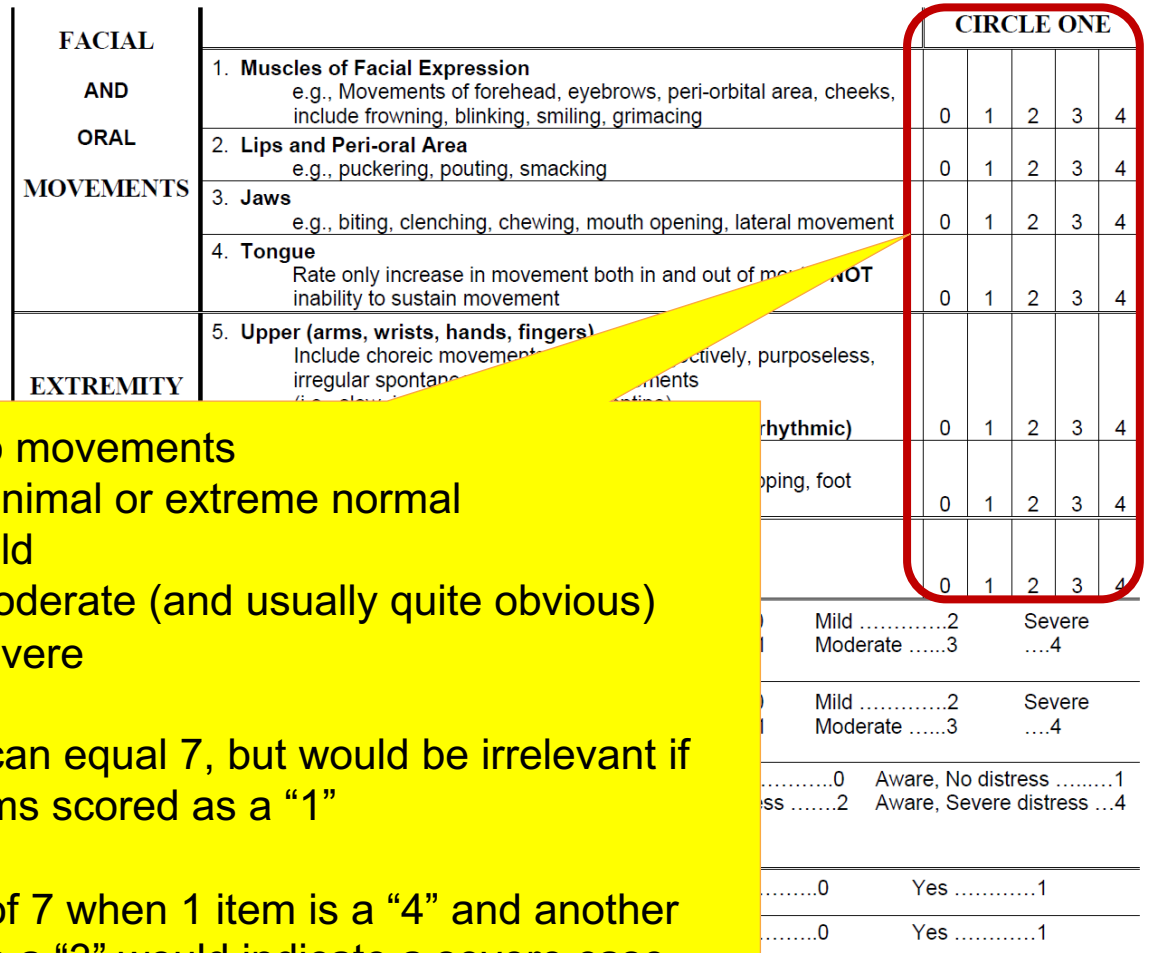

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…Mild ……2 Severe ….4
Moderate ……3

…Mild ……2 Severe ….4
Moderate ……3

……0 Aware, No distress ……1
…ss ……2 Aware, Severe distress …4

……0 Yes ……1

……0 Yes ……1

0 = no movements
1 = minimal or extreme normal
2 = mild
3 = moderate (and usually quite obvious)
4 = severe

Sum can equal 7, but would be irrelevant if all items scored as a "1"

Sum of 7 when 1 item is a "4" and another item is a "3" would indicate a severe case

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	2. Does patient usually wear dentures?	No.....0		Yes 1		

Global severity: Based on the highest single score in the first 7 items

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Degree of incapacitation due to abnormal movements – the patient will need to be asked to what extent any movements interfere with activities such as eating, drinking, speaking, breathing, dressing oneself, writing, working, leisure activities, being with others, etc.

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	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal 1		Mild .....2 Moderate 3		Severe 4
	10. Patient's awareness of abnormal movements ***RATE ONLY PATIENT'S REPORT***	No Awareness .....0 Aware, Mild distress 2		Aware, No distress .....1 Aware, Severe distress ...4		
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0		Yes 1		
	12. Does patient usually wear dentures?	No.....0		Yes 1		

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537. Citrome L. *J Neurol Sci.* 2017;383:199-204.

Abnormal Involuntary Movement Scale (AIMS): *The Standard of Care*

- Observer-rated 12-
  that takes 5 to 10 m
- Adopted by many a
  clinical use
- With FGAs, examin
  6 months
- With SGAs and no
  examine for TD ann
- With patients at hig
  older age, history of dystonic reactions, akathisia, clinically significant parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the *primary outcome measure* in research of drugs for TD

Patient's awareness (and distress level) of the abnormal movements (0–4, with 0 noting no awareness, 1 noting being aware with no distress, and 2–4 noting awareness and distress rating from mild to moderate to severe)

It is not unusual for individuals with schizophrenia to have little insight into their dyskinetic movements; however, patients with mood disorders may be better able to articulate their distress

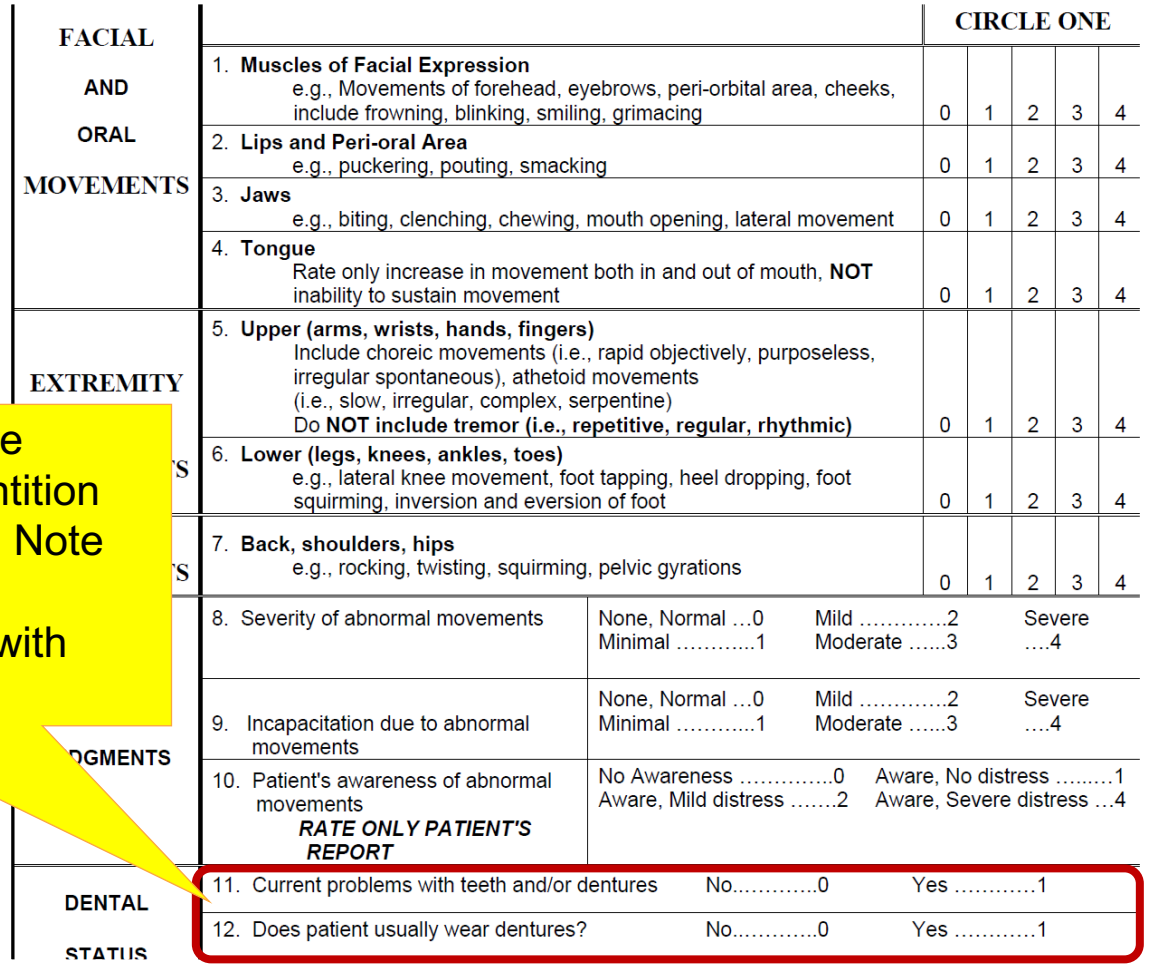
		CIRCLE ONE
CIAL ND RAL MENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0 1 2 3 4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0 1 2 3 4
EMITY MENTS	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
	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
UNK MENTS	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
LOBAL JUDGME	8. Severity of abnormal movements	None, Normal ...0 Mild .....2 Severe Minimal .....1 Moderate 3 4
	9. Incapacitation due to abnormal movements	None, Normal ...0 Mild .....2 Severe Minimal .....1 Moderate 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, Severe distress ...4
DENTAL STATUS	11. Current problems with teeth and/or dentures	No.....0 Yes 1
	12. Does patient usually wear dentures?	No.....0 Yes 1

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537. Citrome L. *J Neurol Sci.* 2017;383:199-204.

Abnormal Involuntary Movement Scale (AIMS): *The Standard of Care*

- Observer-rated 12-item anchored scale that takes 5 to 10 minutes
- Adopted by many agencies for routine clinical use
- With FGAs, examine for TD at least every 6 months
- With SGAs and no cor
  examine for TD annua
- With patients at high r
  older age, history of dy
  akathisia, clinically sig
  parkinsonism), examine every 3 months with FGAs or 6 months with SGAs
- Is the *primary outcome measure* in research of drugs for TD

The last 2 items of the AIMS are yes/no questions regarding dentition status and the use of dentures. Note that people with TD who wear dentures often have problems with them.



		CIRCLE ONE				
FACIAL AND ORAL MOVEMENTS	1. **Muscles of Facial Expression** e.g., Movements of forehead, eyebrows, peri-orbital area, cheeks, include frowning, blinking, smiling, grimacing	0	1	2	3	4
	2. **Lips and Peri-oral Area** e.g., puckering, pouting, smacking	0	1	2	3	4
	3. **Jaws** e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
	4. **Tongue** Rate only increase in movement both in and out of mouth, **NOT** inability to sustain movement	0	1	2	3	4
EXTREMITY	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
S	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
S	7. **Back, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4
	8. Severity of abnormal movements	None, Normal ...0 Minimal 1		Mild .....2 Moderate 3		Severe 4
OGMENTS	9. Incapacitation due to abnormal movements	None, Normal ...0 Minimal 1		Mild .....2 Moderate 3		Severe 4
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Abnormal Involuntary Movement Scale (AIMS): *Instructions for Performing the Exam*

Observe the patient unobtrusively at rest (eg, in waiting room) either before or after completing the examination

Use a hard, firm chair without arms for the exam

- It is ideal to have **2 identical hard, firm chairs with no arms** placed facing each other – one for the patient and one for the examiner. In this manner the clinician can easily model what is being asked of the patient.

Recommend asking the patient to remove shoes and socks prior to the exam

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537.

Abnormal Involuntary Movement Scale (AIMS): *Instructions for Performing the Exam*

1. Ask the patient whether there is anything in his/her mouth (gum, candy, etc.) and if there is, ask to remove it
2. Ask patient about the current condition of his/her teeth
   - Ask the patient if he/she wears dentures
   - Do teeth or dentures bother patient now?
3. Ask the patient whether he/she notices any movements in mouth, face, hands, or feet
   - If yes, ask to describe and to what extent they currently bother patient or interfere with his/her activities
4. Have the patient sit in a hard chair with hands on his/her knees, legs slightly apart and feet flat on the floor
   - Look at entire body for movements while in this position

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537.

Abnormal Involuntary Movement Scale (AIMS): *Instructions for Performing the Exam*

5. Ask the patient to sit with hands hanging unsupported
   - If male, between his legs
   - If female and wearing a dress, hanging over knees
   - Observe hands and other body areas
6. Ask the patient to open his/her mouth
   - Observe tongue at rest within mouth
   - Do this twice
7. Ask the patient to protrude his/her tongue
   - Observe abnormalities of tongue in movement
   - Do this twice
8. Ask the patient to tap his/her thumb, with each finger, as rapidly as possible for 10 to 15 seconds; separately with right hand, then with left hand
   - Observe facial and leg movements

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537.

Abnormal Involuntary Movement Scale (AIMS): *Instructions for Performing the Exam*

9. Flex and extend the patient's left and right arms
   - One at a time
   - Note any rigidity and rate on separate scale if applicable
10. Ask the patient to stand up
    - Observe in profile
    - Observe all body areas again, hips included
11. Ask the patient to extend both arms outstretched in front with palms down
    - Observe trunk, legs, and mouth
12. Have the patient walk a few paces, turn, and walk back to chair
    - Observe hands and gait
    - Do this twice

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537.

AIMS Scoring

- The thumb-finger tapping, arm extension, and walking are “activation” maneuvers used to elicit abnormal movements in other body areas
  - Score ***activated movements*** the same way; do not lower those numbers as was proposed at one time
  - An additional activation maneuver that can be used is a cognitive task such as asking the patient to count backwards from 100 or to recite the months of the year in reverse order
- Score the ***highest amplitude or frequency*** in a movement on the 0–4 scale, not the average
- The instructions for the AIMS also include an assessment of upper extremity **rigidity** by flexing and extending the patient’s left and right arms, as well as observation of **gait**, but these are not rated
  - Nevertheless, findings from these actions may be helpful when determining if the patient has drug-induced parkinsonian side effects

Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised 1976*. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:534-537. Citrome L. *J Neurol Sci.* 2017;383:199-204.

Diagnostic Criteria for TD

Source	Exposure	Severity Threshold	Duration	Miscellaneous
Schooler-Kane (1982)	≥ 3 months	AIMS items: ≥ 3 in 1 area or ≥ 2 in 2 areas	Persistent ≥ 3 months	Dx of exclusion
Glazer et al. (1993)	≥ 3 months	AIMS items: ≥ 3 total with at least 1 ≥ 2 in 1 area	Persistent ≥ 2 exams	Dx of exclusion
DSM-IV (1994) 333.82	≥ 3 months ≥ 1 month if ≥ 60 years	Involuntary movements	≥ 4 weeks	Dx of exclusion
DSM-5 (2013) 333.85 (G24.01)	At least few months	Involuntary movements	≥ 8 weeks	

Schooler NR, et al. *Arch Gen Psychiatry*. 1982;39(4):486-487. Glazer WM, et al. *J Clin Psychiatry*. 1993;54(4):133-139.

Outline

- Definitions and Overview
- Differential Diagnosis
- AIMS
- **Harm Reduction**
- Interventions
- Follow-up
- Summary

Prevention of Tardive Dyskinesia

It is important to minimize the risk 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 SN, et al. *Current Psychiatry*. 2011;10(10):23-32.

Tardive Dyskinesia: *Risk Factors*

- ***Risk factors*** for TD primarily include **age** and **cumulative exposure** to DRBAs, and also to lesser degrees, female sex, race, pre-existing mood, movement or cognitive disorder, alcohol use, diabetes, and HIV positivity
- The ***occurrence of acute EPS*** on initial exposure to dopamine antagonist medications is associated with increased risk; reducing the dose of the dopamine antagonist medication greatly reduces risk
  - **Masking acute EPS with anticholinergic medications does not reduce risk**
- Remember, ***older individuals*** are more susceptible to acute EPS at equivalent doses of dopamine antagonist medications *and* at 4 to 5 × increased risk for TD (5% vs 20% per year)
- Remember, ***prolonged use*** of dopamine antagonist medications increases risk

Jankelowitz SK. *Neuropsychiatr Dis Treat*. 2013;9:1371-1380. Brasic JR. *Medscape*. Aug 8, 2015.
https://emedicine.medscape.com/article/1151826-overview

Treatment of TD: Antipsychotics Treatment Decisions on Antipsychotic Treatment

Tapering off and discontinuing antipsychotics?

- Initial worsening of TD in 33% to 53% of patients
- Long-term improvement in 36% to 55%
- Limited RCT-based evidence
- Rate and timing of complete remission uncertain
- Non-psychotic patients: Continuation difficult to justify
- Psychotic patients: Risk of psychotic relapse significant

RCT = randomized controlled trial.

Gilbert PL, et al. *Arch Gen Psychiatry*. 1995;52(3):173-188. Egan MF, et al. *Schizophr Bull*. 1997;23(4):583-609. Gardos G, et al. The treatment of tardive dyskinesias. In: Bloom FE, et al. (Eds.). *Psychopharmacology: the Fourth Generation of Progress*. New York, NY: Raven Press;1995. Casey DE, et al. *Tardive Dyskinesia and Neuroleptics: From Dogma to Reason*. American Psychiatric Publications;1986. Glazer WM, et al. *Br J Psychiatry*. 1990;157:585-592.

Outline

- Definitions and Overview
- Differential Diagnosis
- AIMS
- Harm Reduction
- **Interventions**
- Follow-up
- Summary

Before FDA Approved Treatments for TD:
American Academy of Neurology Evidence-Based Guideline

Evidence-based options	Clonazepam (Level B, short-term only), ginkgo biloba (Level B), amantadine (Level C), and tetrabenazine (Level C)
Not recommended	Diltiazem (Level B), galantamine (Level C), eicosapentaenoic acid (Level C)
Insufficient data to support (or refute) their use	Acetazolamide, bromocriptine, thiamine, baclofen, vitamin E, vitamin B6, selegiline, melatonin, nifedipine, levetiracetam, buspirone, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, alpha-methyldopa, reserpine, and pallidal deep brain stimulation

Level B: *Moderate* – 1 high-quality study or several studies with some limitations
Level C: *Low* – ≥ 1 studies with severe limitations

Bhidayasiri R, et al.; American Academy of Neurology. *Neurology*. 2013;81(5):463-469.

Before FDA Approved Treatments for TD:
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Tetrabenazine is a VMAT2 inhibitor and inspired the development of the 2 FDA-approved medications for TD: valbenazine and deutetrabenazine

Level B: *Moderate* – 1 high-quality study or several studies with some limitations
Level C: *Low* – ≥ 1 studies with severe limitations

Bhidayasiri R, et al.; American Academy of Neurology. *Neurology*. 2013;81(5):463-469.

Tetrabenazine:
First Reversible and Specific VMAT2 Inhibitor

- The first systematic TD study with tetrabenazine was published in 1972; selected as an alternative to reserpine because of its lower risk for hypotension
- Tetrabenazine was approved in 2008 in the United States as an **orphan drug** for the treatment of choreiform movements associated with Huntington's Disease
- Tetrabenazine used "off-label" in the United States for moderate-to-severe forms of TD
- Use is limited due to significant side effects, short half-life, and drug-drug interactions

Cloud LJ, et al. *Neurotherapeutics*. 2014;11(1):166-176. Bernstein AI, et al. *Neurochem Int*. 2014;73:89-97. Leung JG, et al. *Ann Pharmacother*. 2011;45(4):525-531. Kazamatsuri H, et al. *Arch Gen Psychiatry*. 1972;27(1):95-99.

Tetrabenazine Historical Approvals

Country	Indication(s)	Year of Approval
Netherlands	Huntington's chorea	2007
Germany	Huntington's chorea and tardive dyskinesia	2007
Italy	Organic movement disorders and tardive dyskinesia	2007
France	Huntington's chorea and hemiballismus	2005
Israel	Organic movement disorders and tardive dyskinesia	2005
Portugal	Organic movement disorders and tardive dyskinesia	2003
Canada	Organic movement disorders and tardive dyskinesia	1995
Denmark	Hyperkinesias	1980
Australia	Organic movement disorders and tardive dyskinesia	1979
New Zealand	Organic movement disorders and tardive dyskinesia	1973
Ireland	Organic movement disorders (tardive refused)	1971
UK	Organic movement disorders and tardive dyskinesia	1971

http://wayback.archive-it.org/7993/20180126160441/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4328b1-02-Prestwick.pdf

What is a *Vesicular Monoamine Transporter Type 2*?

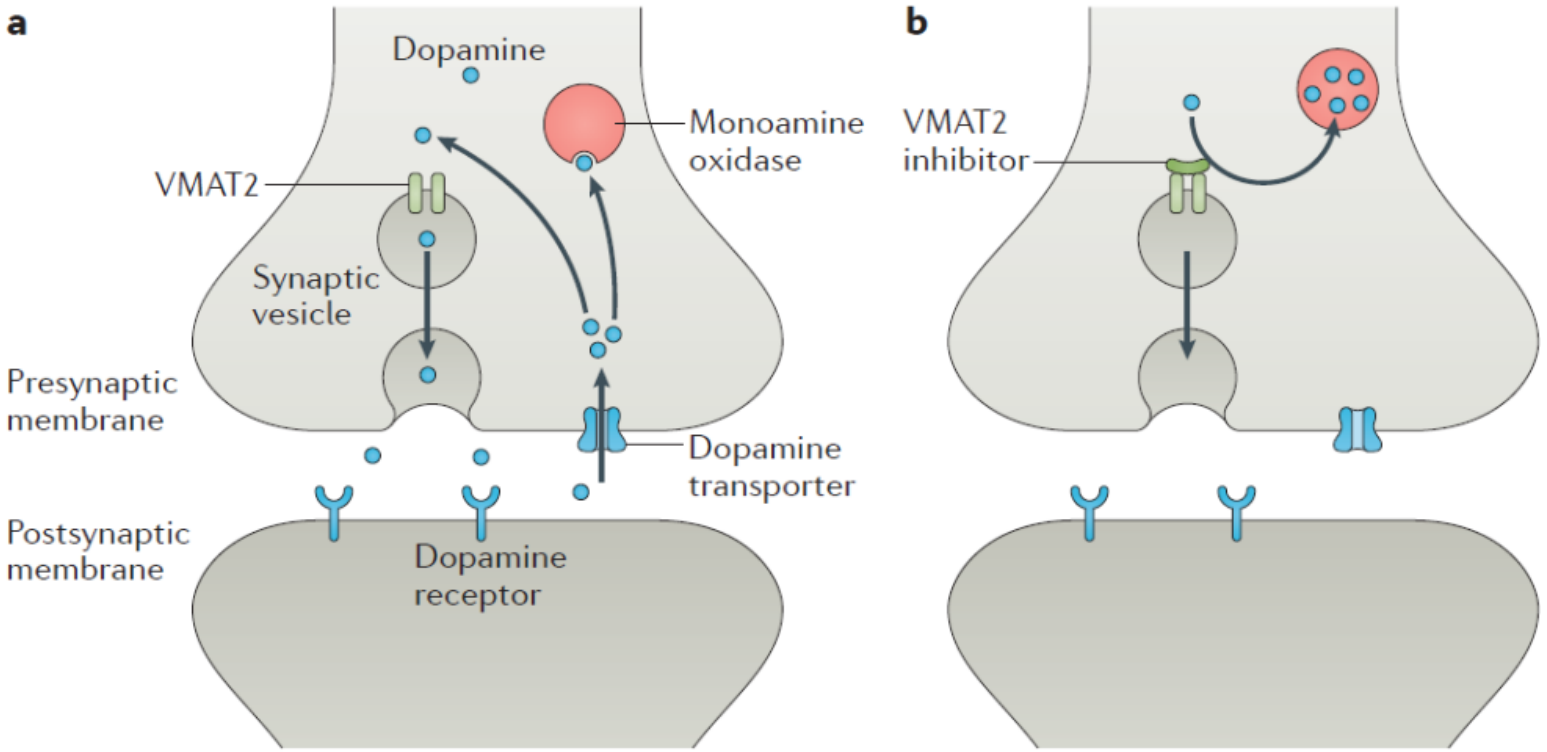


Figure 1 | **Mechanism of action of VMAT2 inhibitors. a** | Normally, vesicular membrane transport type 2 (VMAT2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase. **b** | VMAT2 inhibitors block transport of dopamine into synaptic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

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

Vesicular Monoamine Transporter Inhibitors

Medication	Reserpine	Tetrabenazine	Deutetrabenazine	Valbenazine
Mechanism of Action	• Irreversibly binds VMAT • Binds VMAT1 (PNS) and VMAT2 (CNS) • Binds cytoplasmic site	• Reversibly binds VMAT2 • Selectively binds VMAT2 (CNS) • Binds intravesicular site	• Reversibly binds VMAT2 • Selectively binds VMAT2 (CNS) • Binds intravesicular site	• Reversibly binds VMAT2 • Selectively binds VMAT2 (CNS) • Binds intravesicular site
Duration of Action	Several days	Short ($T_{1/2}$ 5.5 h)	Intermediate ($T_{1/2}$ 8.6 h)	Long ($T_{1/2}$ 20 h)
Peripheral Side Effects*	Frequent	Rare	Rare	Rare
Status	Discontinued	Approved HC	Approved HC and TD	Approved TD

***Orthostatic hypotension, stuffy nose, and GI side effects, such as nausea, vomiting, and diarrhea.**
CNS = central nervous system; HC = Huntington's chorea; PNS = peripheral nervous system; $T_{1/2}$ = half-life.
Jankovic J. *Expert Opin Pharmacother*. 2016;17(18):2461-2470.

Tetrabenazine: Does it Work in TD?

- One Class III study compared haloperidol use with tetrabenazine use in **13 participants** (100 mg/day for 14 weeks)
  - All neuroleptic and antiparkinsonian drugs were completely withdrawn and replaced by placebo for the first 4 weeks, and followed by either haloperidol 4 mg BID or tetrabenazine 50 mg BID
  - Tetrabenazine produced significant reduction in the frequency or oral dyskinesia with almost complete suppression in 2 patients
- Another Class III, **nonrandomized**, **single-blind** study compared tetrabenazine efficacy using a randomized videotape protocol pre- and posttreatment (**N=20**); participants discontinued neuroleptics and other TD treatments at least 30 days prestudy
  - One patient did not tolerate tetrabenazine owing to sedation; the remaining 19 were rated after a mean of 20.3 weeks at a mean tetrabenazine dose of 57.9 mg/day
  - Reductions in AIMS were seen posttreatment evaluated by the blinded videotape raters – mean score on the AIMS motor subset, improved 54.2%, from 17.9 to 8.2 ($P<.001$)
- These results are supported by Class IV, long-term, observational studies

Class I or II are RCTs, where Class I studies are of higher quality as per established criteria; **Class III:** All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in representative populations, where outcome is independently assessed, or independently derived by objective outcome measurement; **Class IV:** Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

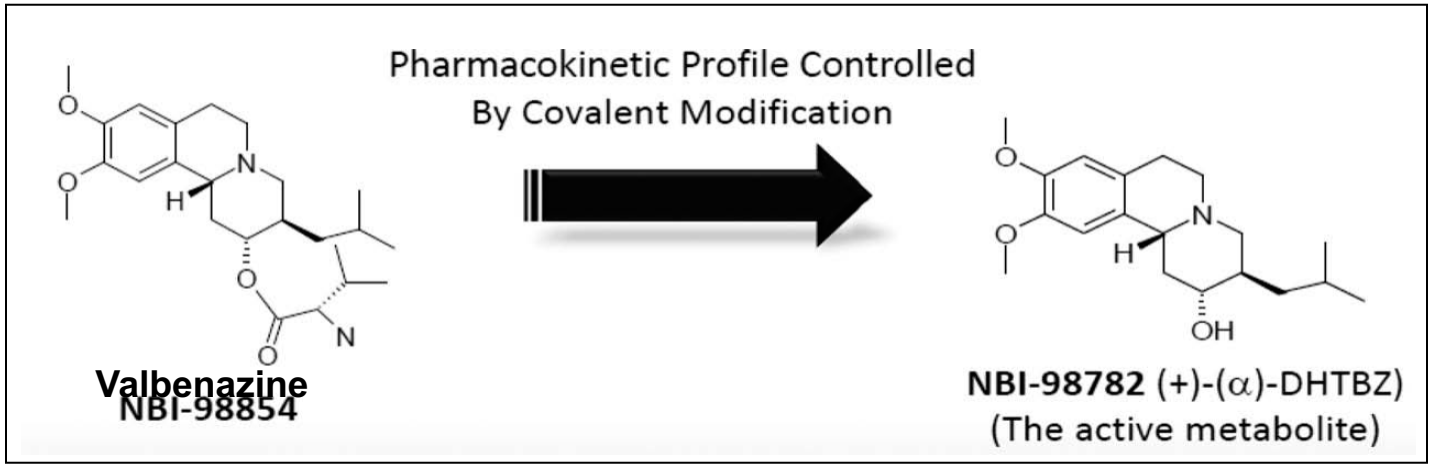
Bhidayasiri R, et al.; American Academy of Neurology. *Neurology*. 2013;81(5):463-469. Kazamatsuri H, et al. *Arch Gen Psychiatry*. 1972;27(1):95-99. Ondo WG, et al. *Am J Psychiatry*. 1999;156(8):1279-1281.

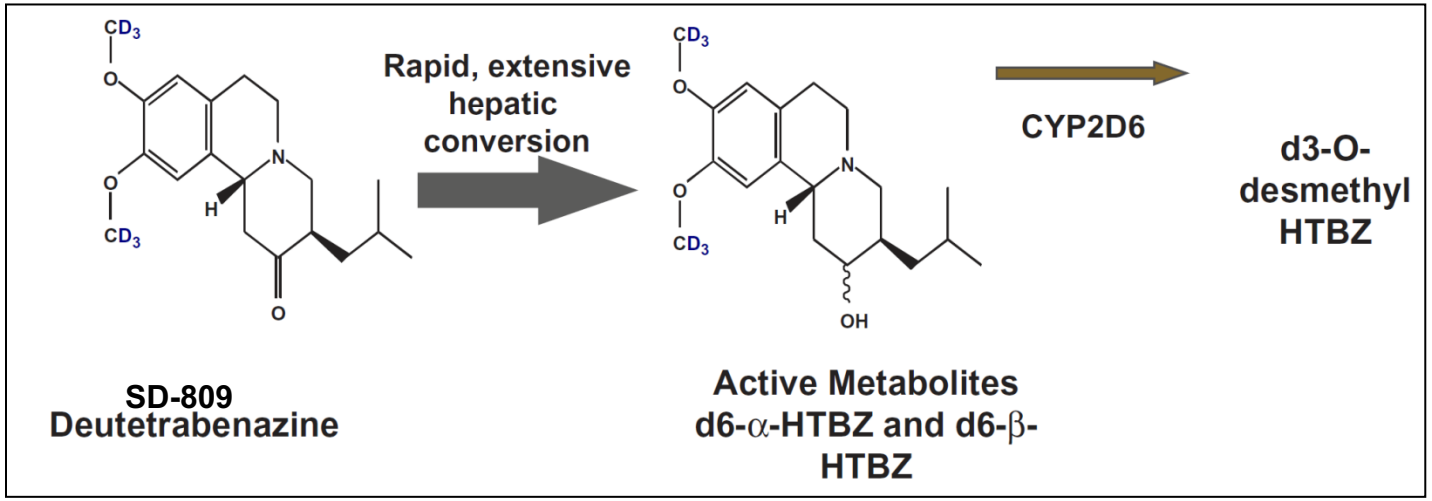
Tetrabenazine: Limitations Driven by *Pharmacokinetics* and *Pharmacodynamics*

- Use is limited due to **significant side effects** (somnolence, insomnia, depression, and akathisia), short half-life, and drug-drug interactions
  - The FDA label for tetrabenazine carries a boxed bolded warning for depression and suicide risk
- **Short half-life** leads to frequent dosing with high peaks (C_{max}) and valleys (C_{min})
- The drug itself is a one-to-one mixture of enantiomers
  - α and β enantiomers and each gives rise to 2 isomers of a dihydrotetrabenazine metabolite, for a total of 4 isomers
  - Those derived from **α-tetrabenazine** are active VMAT2 inhibitors and contribute to the therapeutic effects of the drug; these are metabolized via cytochrome P450 (CYP) 2D6 and 3A4
  - The 2 derivatives of β-tetrabenazine are antagonists at the dopamine D2 receptor and can induce sedation and parkinsonism; these are metabolized solely via CYP 2D6 thus side effects are more pronounced in the presence of CYP2D6 inhibitors
  - CYP 2D6 **genotyping** to screen for poor metabolizer status is required when exceeding 50 mg/day

Müller T. *Expert Opin Investig Drugs*. 2015;24(6):737-742. Shen V, et al. *Tremor Other Hyperkinet Mov*. 2013;3. pii: tre-03-191-4337-1. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Alternatives to Tetrabenazine: Valbenazine and Deutetrabenazine





Jankovic J. *Expert Opin Pharmacother*. 2016;17(18):2461-2470.

How are Tetrabenazine, Valbenazine, and Deutetrabenazine Related?

- Tetrabenazine and valbenazine share a common metabolite, **[+]-α-HTBZ**, which is a highly selective and potent VMAT2 inhibitor
- Deutetrabenazine is identical to tetrabenazine except for the substitution of **deuterium** for hydrogen at key locations in the molecule involved in metabolism; deuterium forms a stronger chemical bond to carbon than the C-H bond, thus the **pharmacokinetics** are altered in an advantageous way

HTBZ = dihydrotetrabenazine.

Jankovic J. *Expert Opin Pharmacother*. 2016;17(18):2461-2470.

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

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*=.0005
KINECT-3	Valbenazine	234	40 mg, 80 mg	6 weeks	LS mean change from baseline, (80 mg) –3.2 vs –0.1; *P*<.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*=.019
AIM-TD	Deutetrabenazine	298	12 mg, 24 mg, 36 mg	12 weeks	LS mean change from baseline, (24 mg) –3.2 *P*=.003, (36 mg) –3.3; *P*=.001, placebo –1.4

Systematic Reviews: Citrome L. *Int J Clin Pract*. 2017 Nov;71(11). Citrome L. *Int J Clin Pract*. 2017 Jul;71(7).

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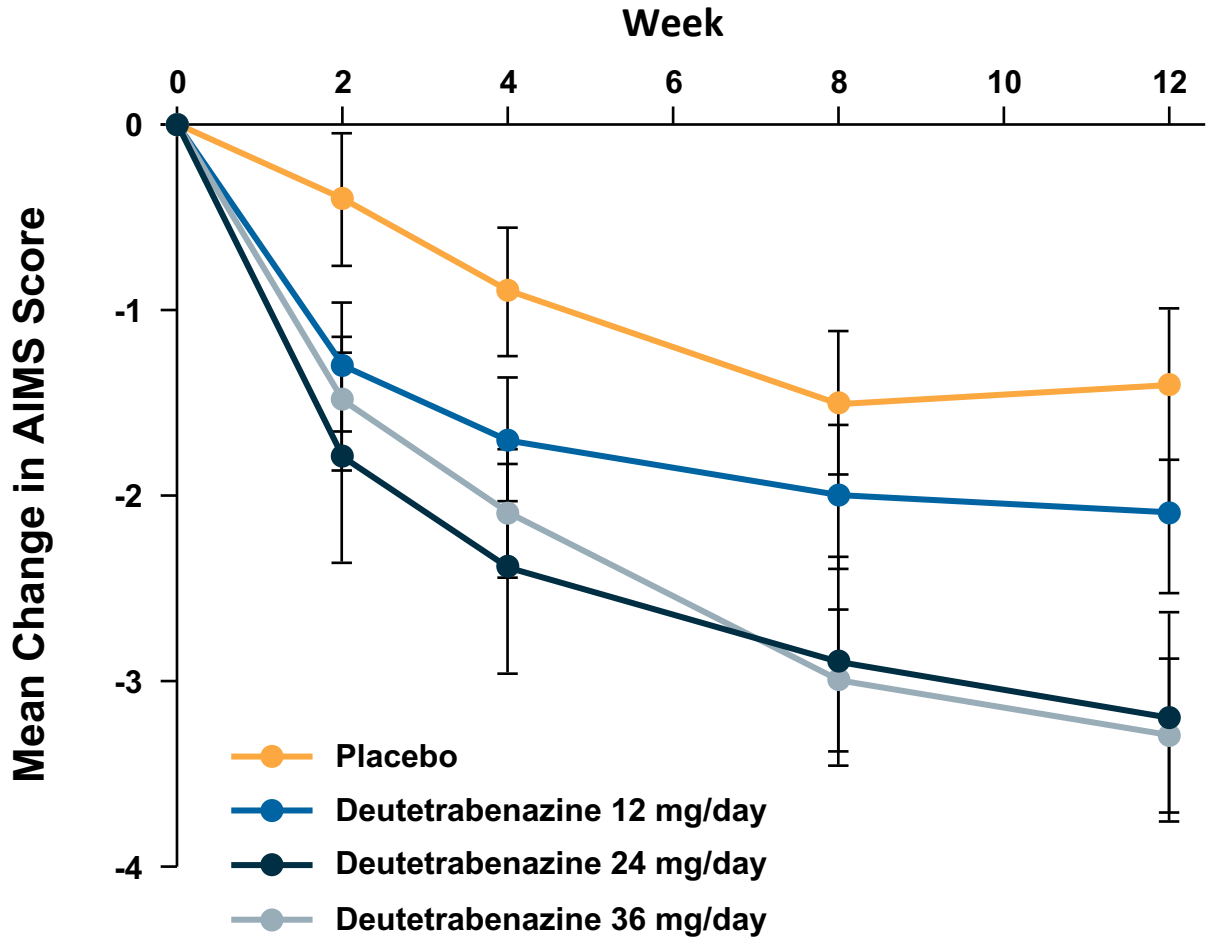
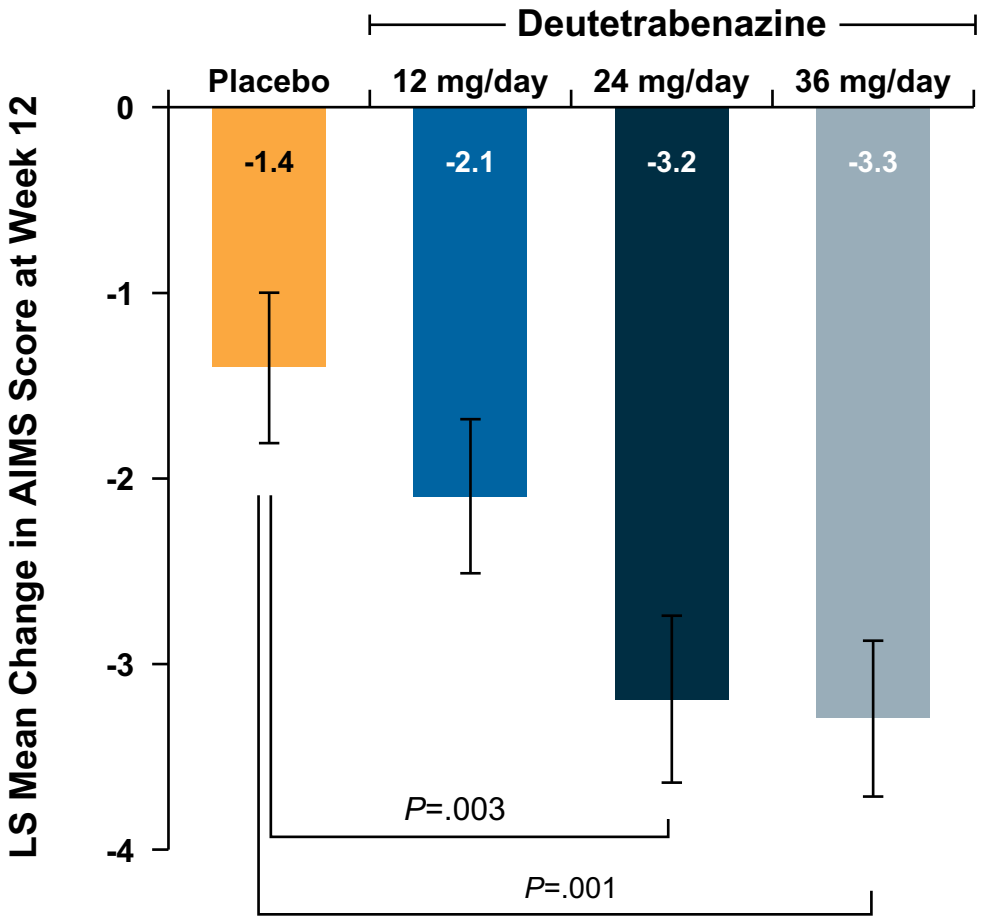
Systematic Reviews: Citrome L. *Int J Clin Pract*. 2017 Nov;71(11). Citrome L. *Int J Clin Pract*. 2017 Jul;71(7).

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





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

Deutetrabenazine Safety and Tolerability Profile in Placebo-Controlled TD Studies

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

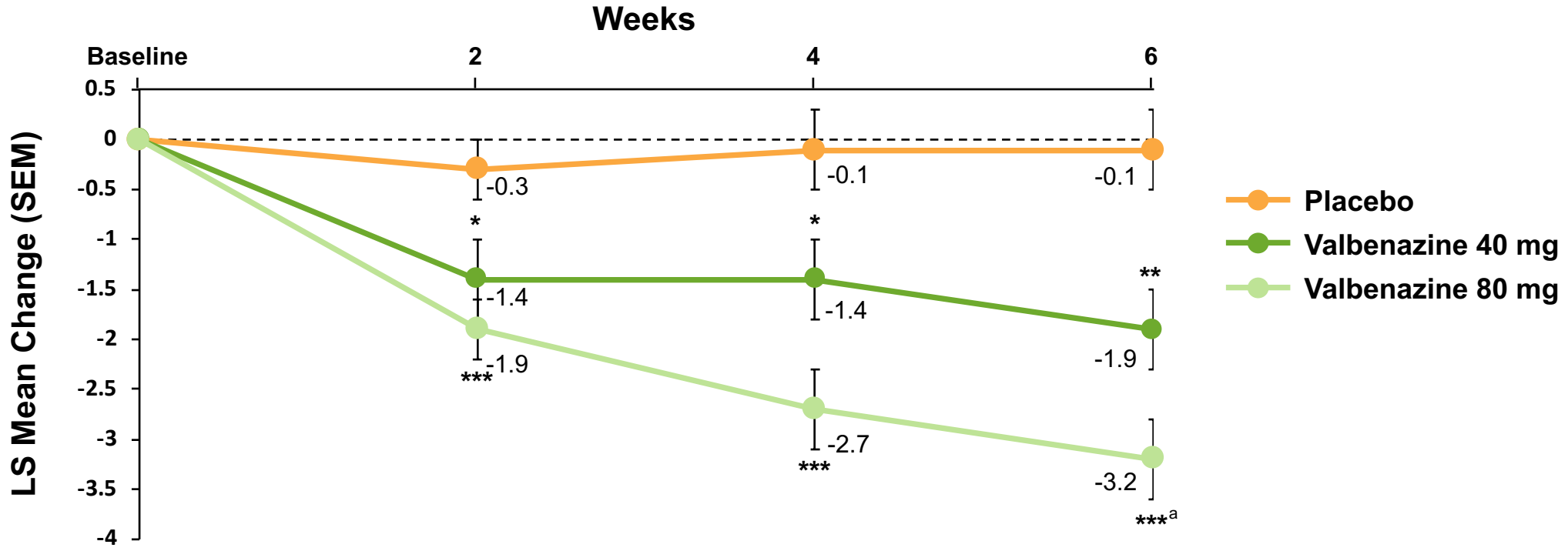
Adverse Reaction	Deutetrabenazine (n=279)	Placebo (n=131)
Headache	5%	8%
Somnolence	4%	7%
Diarrhea	4%	4%
Nasopharyngitis	4%	2%
Fatigue	4%	5%
Insomnia	4%	1%
Anxiety	4%	5%
Upper respiratory tract infection	3%	4%
Dry mouth	3%	5%
Nausea	2%	7%
Weight increased	2%	3%
Urinary tract infection	2%	2%
Depression/dysthymic disorder	2%	1%
Akathisia/Agitation/Restlessness	2%	1%

4% of patients required dose reduction of deutetrabenazine due to AEs vs 2% of patients taking placebo

AE = adverse effect.

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

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



	n:				
Placebo		76	76	73	69
Valbenazine 40 mg		70	70	64	63
Valbenazine 80 mg		79	77	73	70

Intent-to-Treat Population: Included all randomized participants who had at least one post-randomization AIMS value.
***P*<.05. ****P*<.01. *****P*≤.001 for valbenazine vs placebo. [a]Dose that was statistically significantly different from placebo after adjusting for multiplicity.**

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

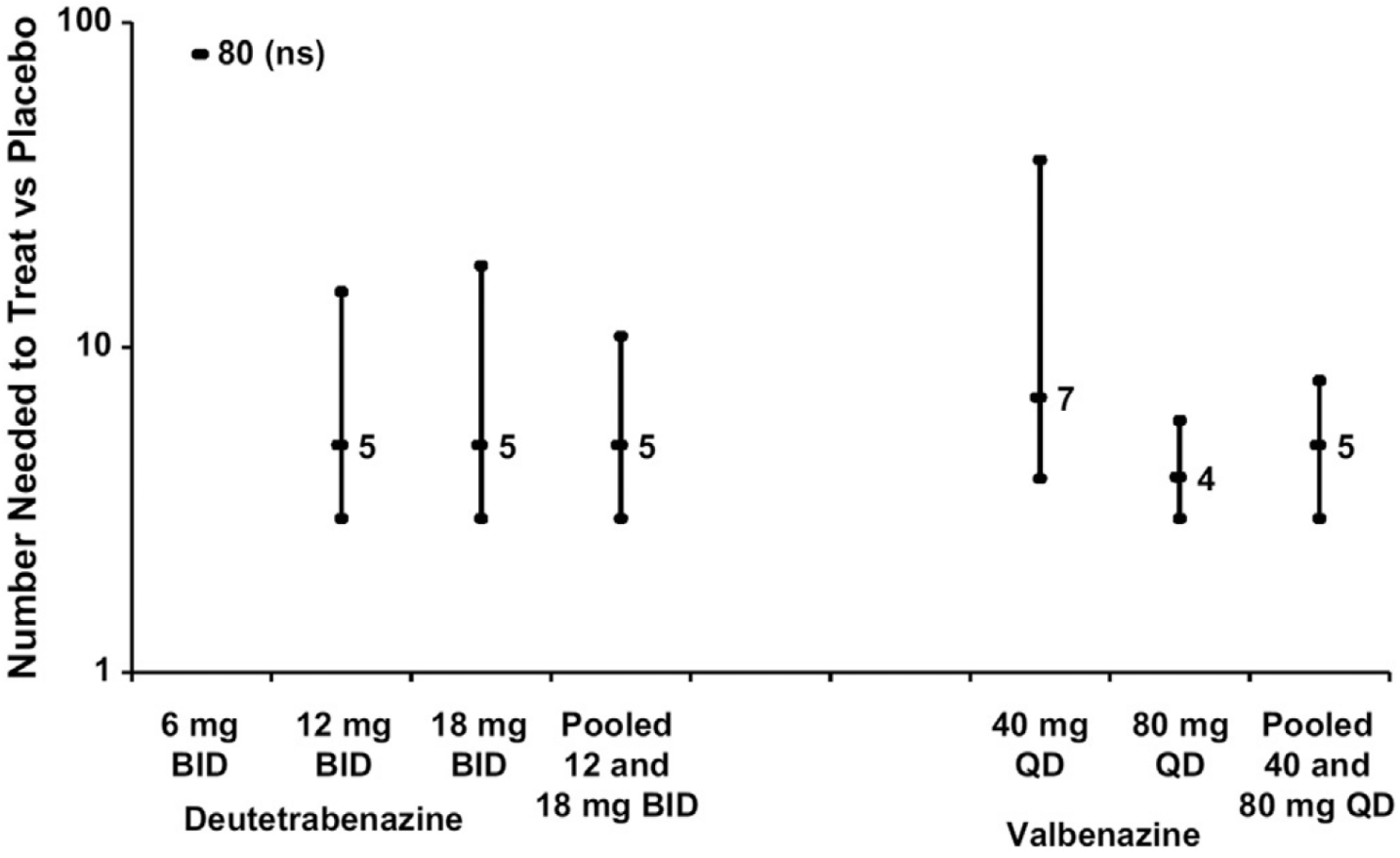
Adverse Reactions in 3 Placebo-Controlled Studies of Valbenazine 6-Week Treatment Duration Reported at ≥ 2% and > Placebo

Adverse Reaction[a]	Valbenazine (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%

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

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

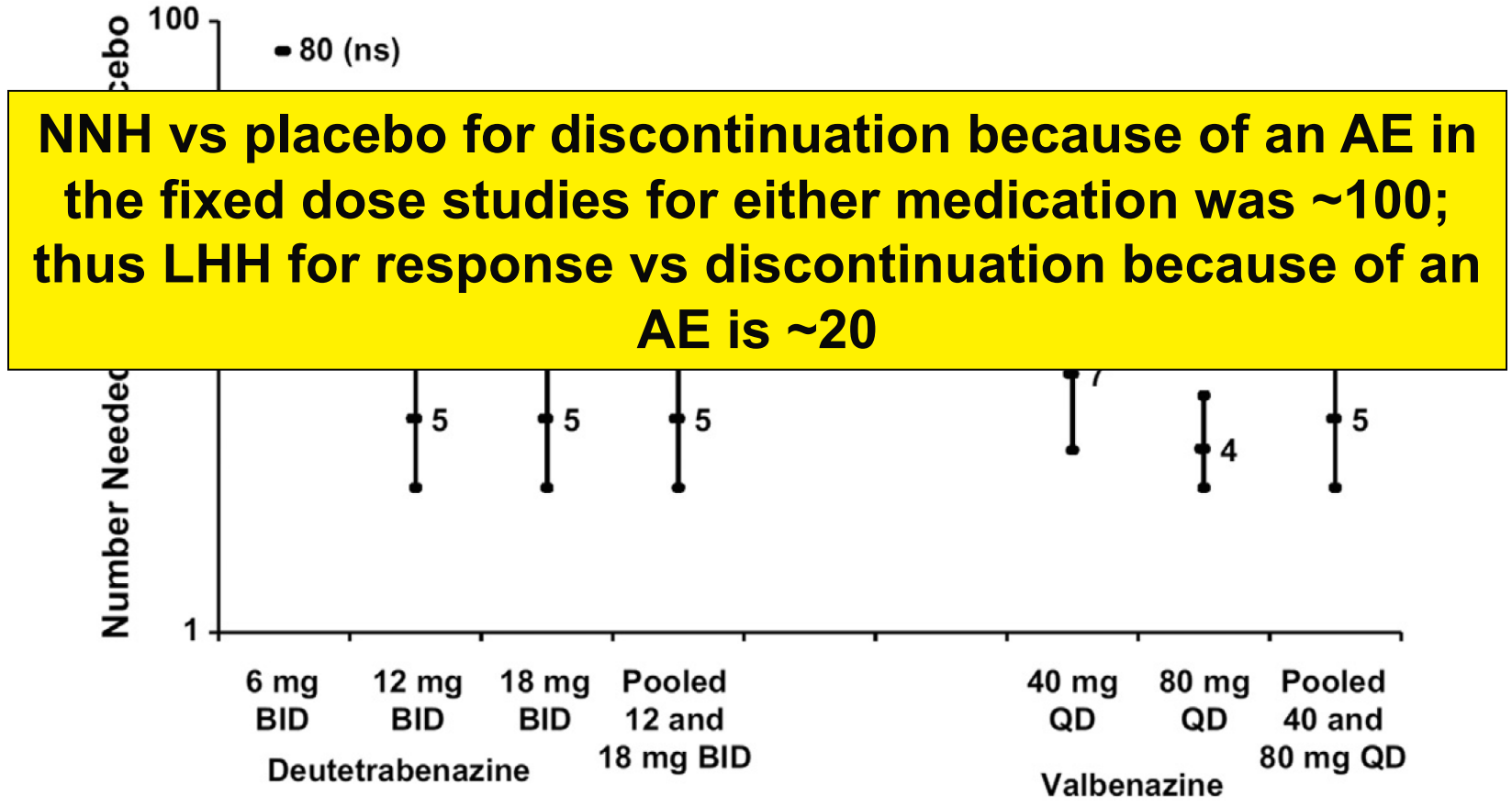
Deutetrabenazine vs Valbenazine: NNT in Fixed-Dose Trials



≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint, NNT vs placebo and 95% CIs, for the Phase III fixed-dose studies of deutetrabenazine (12 weeks) and valbenazine (6 weeks). NNT = number needed to treat.

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

Deutetrabenazine vs Valbenazine: NNT in Fixed-Dose Trials



NNH vs placebo for discontinuation because of an AE in the fixed dose studies for either medication was ~100; thus LHH for response vs discontinuation because of an AE is ~20

≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint, NNT vs placebo and 95% CIs, for the Phase III fixed-dose studies of deutetrabenazine (12 weeks) and valbenazine (6 weeks). LHH = likelihood of being helped or harmed; NNH = number needed to harm.

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

Deutetrabenazine vs Valbenazine: Mostly Similar with Some 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 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%
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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
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Citrome L. *J Neurol Sci*. 2017;383:199-204.

Additional Information: VMAT2 Inhibitors for TD

- Deutetrabenazine and valbenazine can reduce abnormal movements of TD that often cause substantial physical, social, and psychological impairment
  - Effective
  - Well-tolerated
- Patients can remain on antipsychotic therapy
  - Reduced risk of psychiatric decompensation
- Treatment goal = to reduce the severity and impact of TD
  - It is not necessary to eliminate all signs of TD
  - Attempting to completely suppress all TD will likely result in overtreatment and a greater potential for adverse effects

Margolius A, et al. *Parkinsonism Relat Disord*. 2018 Dec 19;[Epub ahead of print]. Citrome L. *J Neurol Sci*. 2018;389:61-66. Niemann N, et al. *Drugs*. 2018;78(5):525-541.

Additional Information: VMAT2 Inhibitors for TD (cont'd)

- There are no head-to-head studies of deutetrabenazine and valbenazine
- Customize therapy for patients in choosing drug
  - Consider adherence (valbenazine is once daily)
  - Consider need to fine-tune dosing regimen (greater dose flexibility with deutetrabenazine)
  - Consider side-effect profile

- Tolerability and efficacy between the 2 drugs may differ from patient to patient

Margolius A, et al. *Parkinsonism Relat Disord*. 2018 Dec 19:[Epub ahead of print]. Citrome L. *J Neurol Sci*. 2018;389:61-66. Niemann N, et al. *Drugs*. 2018;78(5):525-541.

Critical Issues to Remember with Both VMAT2 Therapies

- 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 irrespective of their diagnosis (schizophrenia or mood disorder)
- Neither VMAT2-based FDA approved medications destabilize depression, mania, psychosis, or induce suicidality

Margolius A, et al. *Parkinsonism Relat Disord*. 2018 Dec 19:[Epub ahead of print]. Citrome L. *J Neurol Sci*. 2018;389:61-66. Niemann N, et al. *Drugs*. 2018;78(5):525-541.

Cost / Access

- Both VMAT2 therapies are expensive
- It can be a threat to adherence
- It can lead to medication discontinuation

- Many, if not most, insurance carriers cover VMAT2 therapy around the nation
- Good documentation of need for VMAT2 therapy is critical
- Both VMAT2 therapies have robust access / patient assistance programs

Cost / Access (cont'd)

- Document need for VMAT2 therapy in the preauthorization paperwork well. Document the following:
  - The location and severity of abnormal movements
  - That the patient has a diagnosis of TD
  - Document the bio-psycho-social impairment caused by TD
  - Document why therapy with benztropine, clozapine, or clonazepam are inappropriate for this patient
  - Proactively document all 4 of the above. This reduces the chance of rejection of request for VMAT2 therapy

Patient Assistance Programs

- Valbenazine:

https://inbracesupportprogram.com/downloads/INGREZZA-ProviderOverview.pdf

- Deutetrabenazine:

www.austedo.com/hcp/shared-solutions-overview

Outline

- Definitions and Overview
- Differential Diagnosis
- AIMS
- Harm Reduction
- Interventions
- **Follow-up**
- Summary

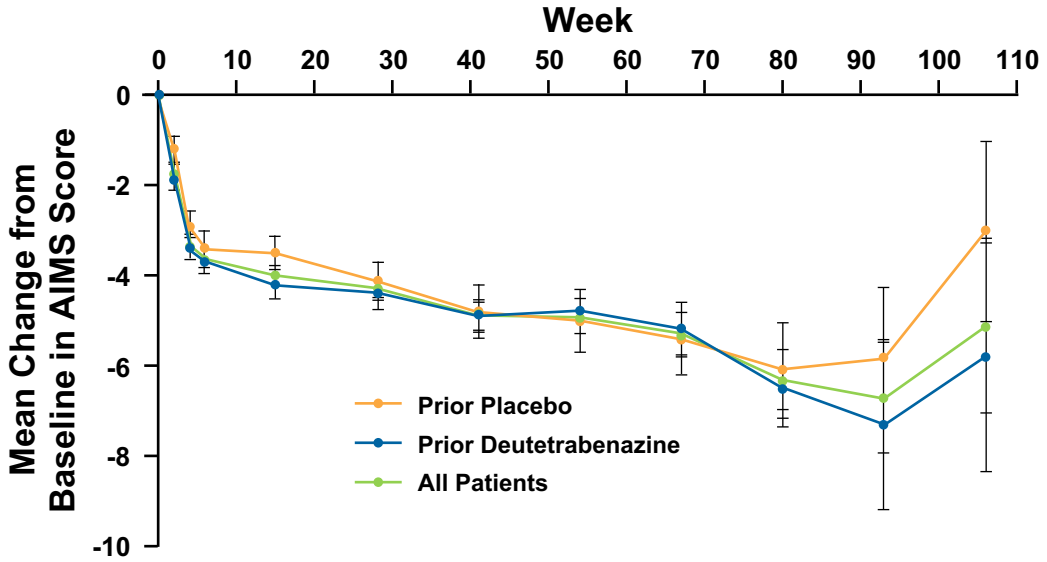
Tardive Dyskinesia: *Check Your Work*!

- When treatment is initiated, a **baseline** assessment should be obtained and the AIMS examination is recommended for this purpose
- Advantages to using the AIMS include its ubiquity both in the clinic and in drug development
- **Follow-up** assessments should be done on a regular basis, and the AIMS in this case can facilitate communication among providers
- Lack of documented improvement can trigger additional enquiries regarding adherence or unidentified drug-drug interactions, as well as inform decisions on dose titration or changing the intervention
- Measuring the AIMS dyskinesia items alone is inadequate: Follow-up questions regarding **functional impairments** attributable to TD need to be asked (eg, interference with activities such as eating, drinking, speaking, breathing, dressing oneself, writing, working, leisure activities, being with others)
- Fortunately, the AIMS contains items that remind the clinician to evaluate impact on function and to determine the degree of associated distress

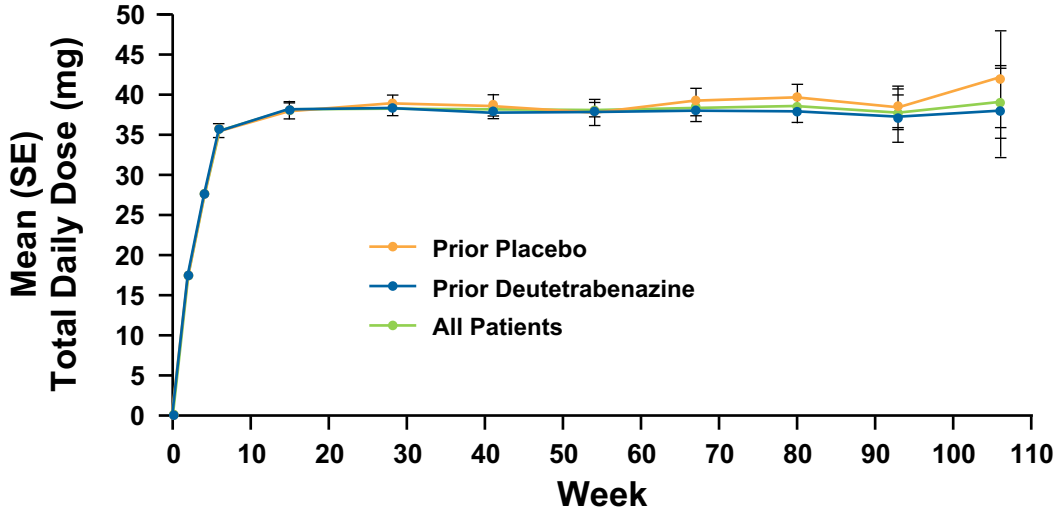
Citrome L. *J Neurol Sci.* 2017;383:199-204.

Deutetrabenazine: Long-Term Data is Reassuring

2-year (Week 106) open-label response rates are reported in this interim analysis. Of 343 patients enrolled in the extension study, 232 previously received deutetrabenazine and 111 previously received placebo.



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



Week	0	2	4	6	15	28	41	54	67	80	93	106
Prior Placebo (n)	111	111	108	104	95	78	62	47	32	27	10	2
Prior Deutetrabenazine (n)	232	228	226	220	204	160	132	94	67	39	13	6
All Patients (n)	343	339	334	324	299	238	194	141	99	66	23	8

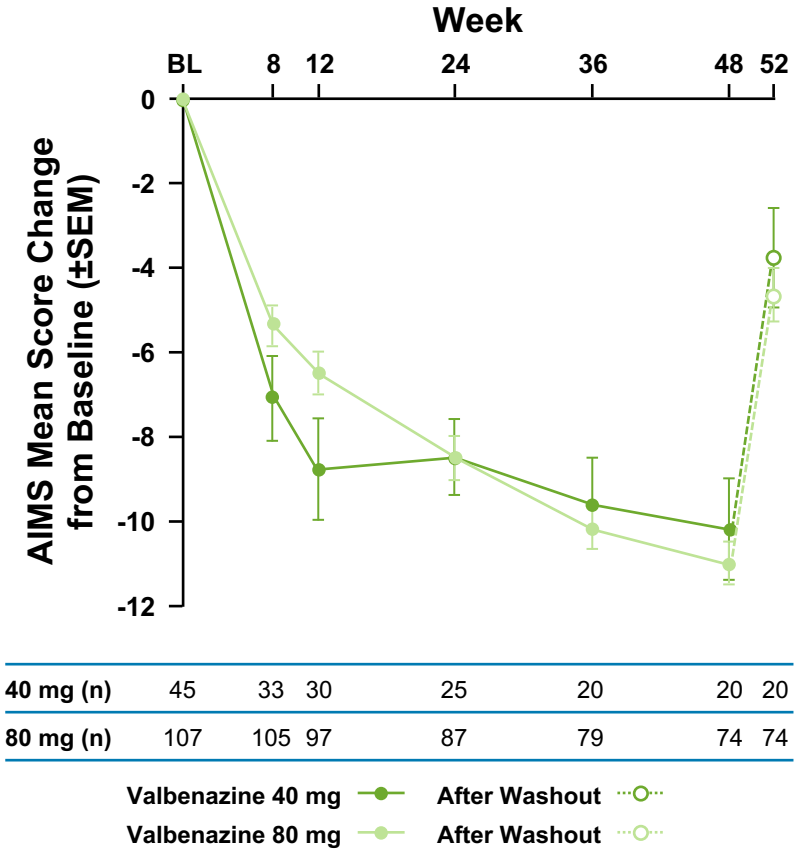
The mean total daily dose of deutetrabenazine at Week 80 was 38.6 (1.13) mg for all patients

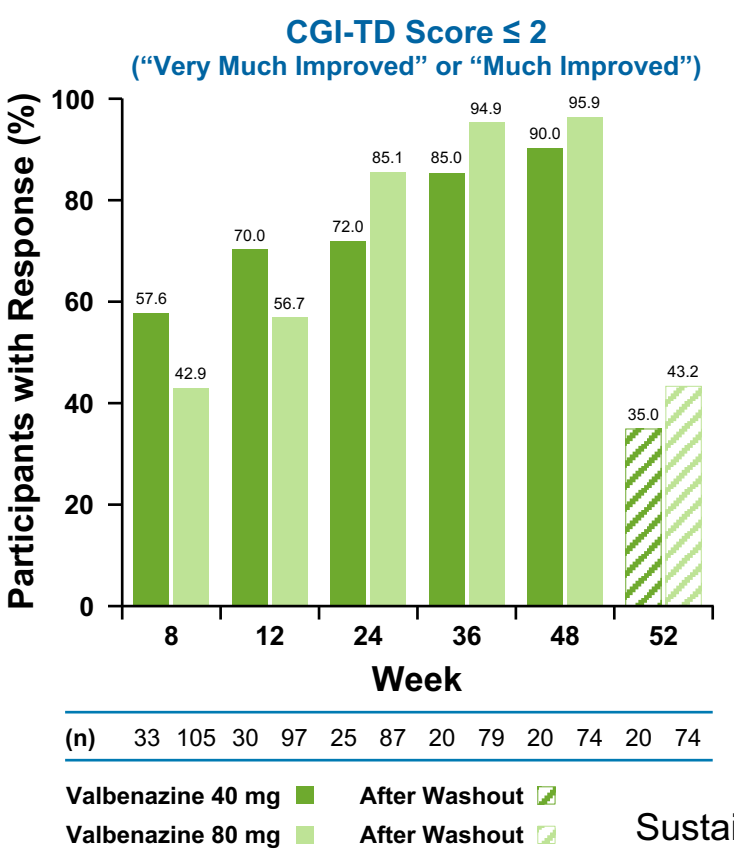
No new safety signals or concerns emerged in this long-term study

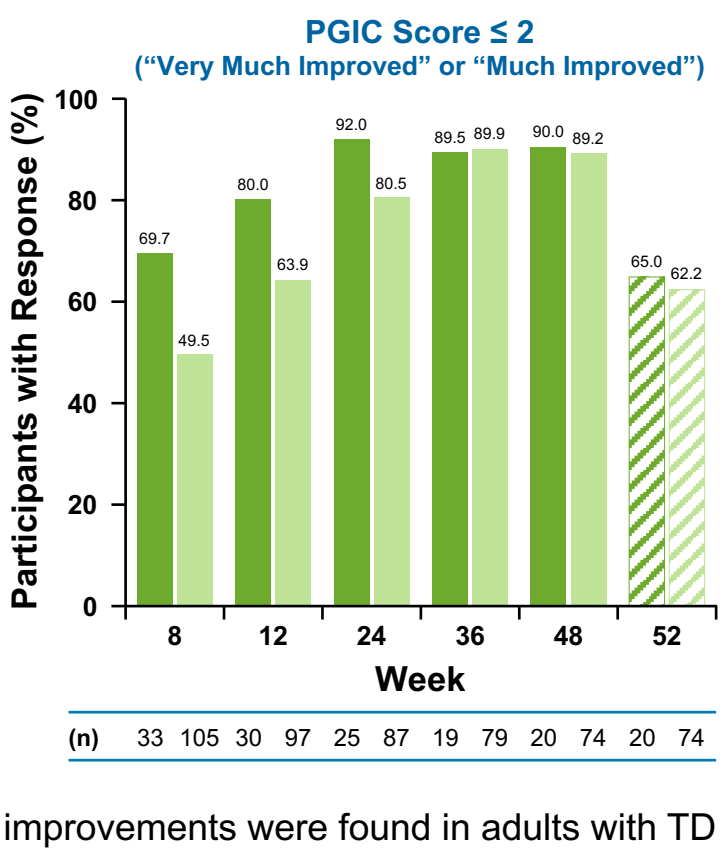
Hauser RA, et al. Long-Term Treatment With Deutetrabenazine Is Associated With Continued Improvement in Tardive Dyskinesia (TD): Results From an Open-Label Extension Study. Presented at: 70th Annual Meeting of the American Academy of Neurology; April 21–27, 2018; Los Angeles, CA.

Valbenazine: Long-Term Data is Reassuring

Of the 163 participants included in the analyses,149 completed the Week 8 visit and 103 completed Week 48







No new safety signals or concerns emerged in this long-term study

Sustained improvements were found in adults with TD who received once-daily valbenazine for up to 48 weeks, based on clinician- and patient-rated measures

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.

Long-Term Side Effects

- ✓ Good news. In long-term studies in TD with both the VMAT2 therapies (deutetrabenazine and valbenazine), no new or unexpected side effects emerged

- ✓ This is very reassuring. However, monitoring and vigilance for emergent side effects is prudent on part of every clinician

Fernandez HH, et al. Confirmed Safety of Deutetrabenazine for Tardive Dyskinesia in a 2-Year Open-Label Extension Study. Presented at: 31st Annual Psych Congress; October 25–28, 2018; Orlando, FL. Marder SR, et al. Long-Term Safety and Tolerability of Once-Daily Valbenazine in Patients with Tardive Dyskinesia. Presented at: 31st Annual Psych Congress; October 25–28, 2018; Orlando, FL.

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Tardive Dyskinesia: *Summary*

- **Assume** that TD exists in your practice
  - TD is still common, and will continue to be because of increasing use of antipsychotic medication
- **Prevent** if possible: Harm reduction
  - Minimize drug-induced parkinsonian symptoms by selecting agents with lower risk for this problem
  - Minimize use of anticholinergic medication
- **Screen** with scheduled AIMS exams, especially in the older population
- **Treat** as quickly as possible after it appears
  - Reliable, effective, and now well tolerated, treatments are available for persistent TD

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

Tardive Dyskinesia: *Summary* (cont'd)

- There are now 2 FDA-approved treatments for TD: **deutetrabenazine** and **valbenazine**
- Both are efficacious and tolerable
- They differ somewhat in terms of labeled instructions
  - Frequency of administration (twice daily for deutetrabenazine vs once daily for valbenazine)
  - Titration (dose to efficacy/tolerability for deutetrabenazine vs titrate to target dose of 80 mg/day for valbenazine)
  - Need for food (administer deutetrabenazine with food)
  - Drug-drug interactions (consider CYP 2D6 modulators for deutetrabenazine vs both CYP 2D6 and CYP 3A4 for valbenazine)
  - Contraindications (hepatic impairment for deutetrabenazine)
- **However, the clinical usefulness of these treatments is rendered moot if TD goes unrecognized**

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

Questions?

Supplemental Slides

VMAT2 Mechanism of Action: Part I

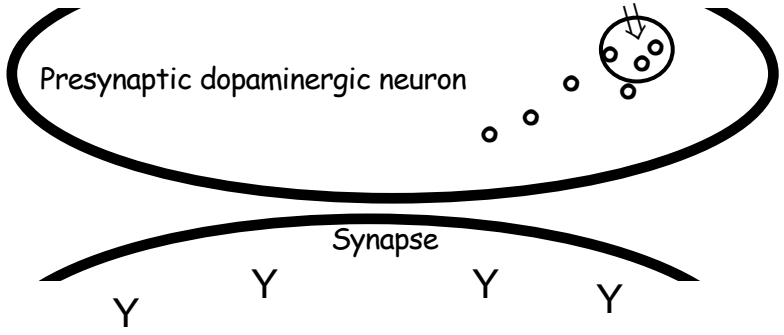
How Vesicular Monoamine Transporter Type 2 (VMAT2) Inhibitors Work in Tardive Dyskinesia

①

Dramatis Personae

- dopamine molecule
- dopamine D_2 receptor
- dopamine D_2 receptor blocking agent
- vesicle
- VMAT2
- VMAT2 inhibitor

② VMAT2 packages dopamine from the cytoplasm into vesicles in the presynaptic dopaminergic neuron.



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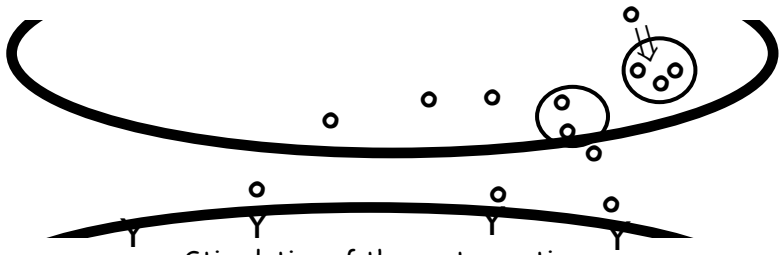

Stimulation of the postsynaptic dopamine D2 receptors results in neurotransmission.

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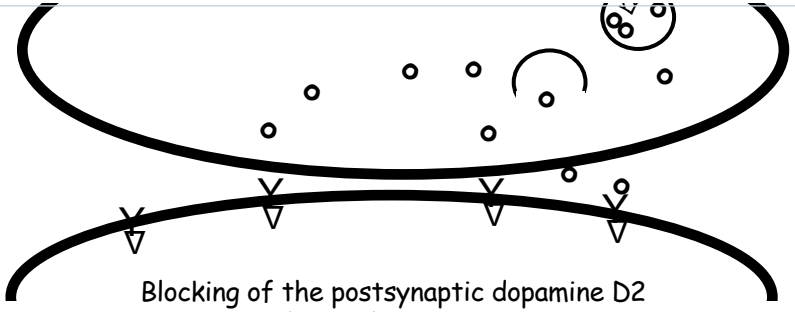

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Citrome L. *Expert Rev Neurother*. 2018;18(4):323-332.

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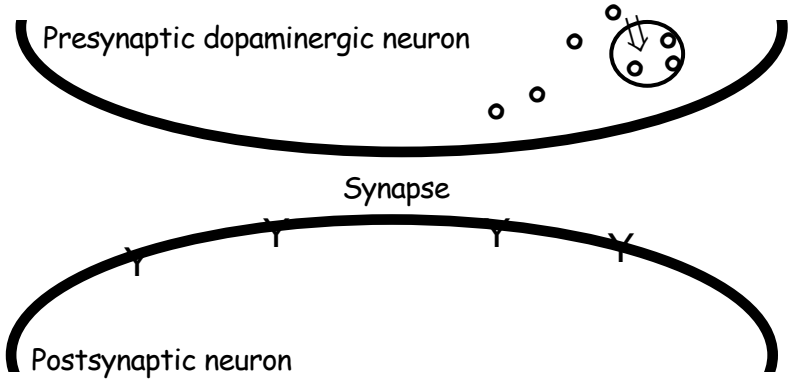

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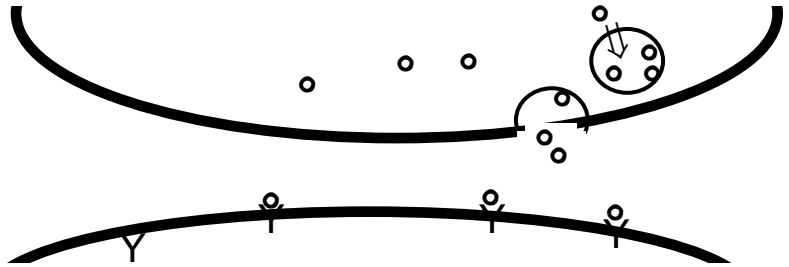

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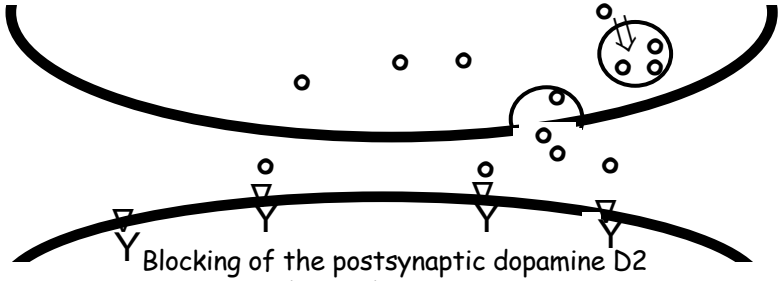

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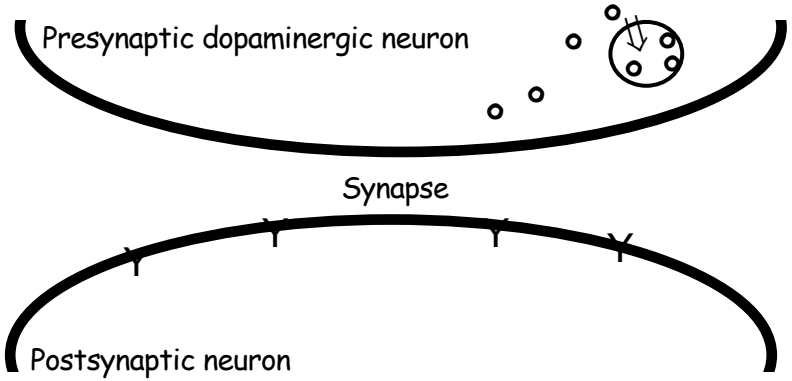

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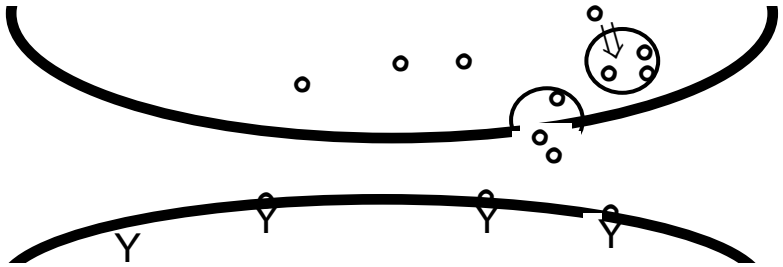

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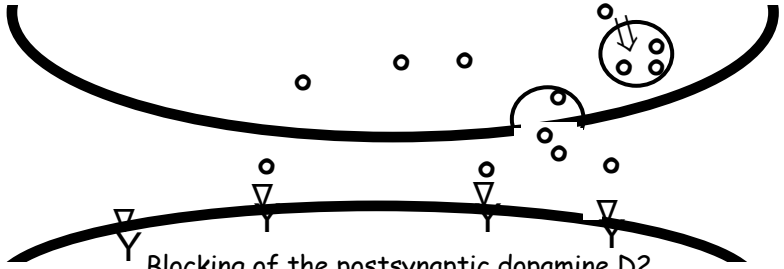

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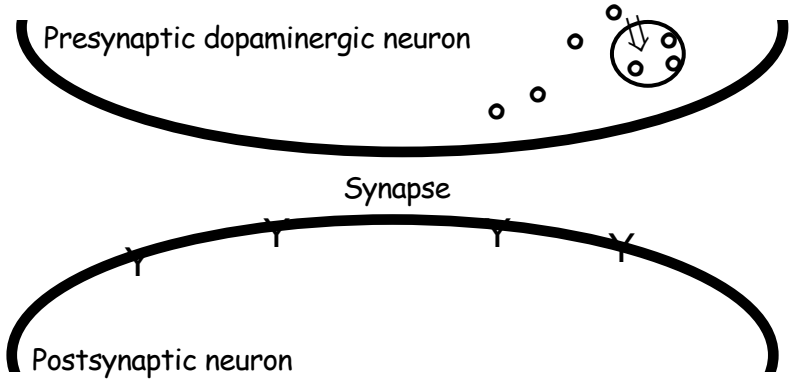

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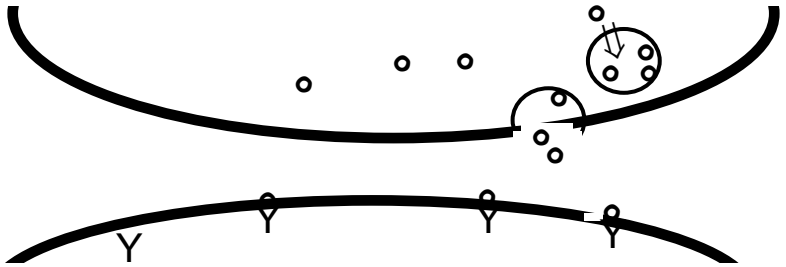

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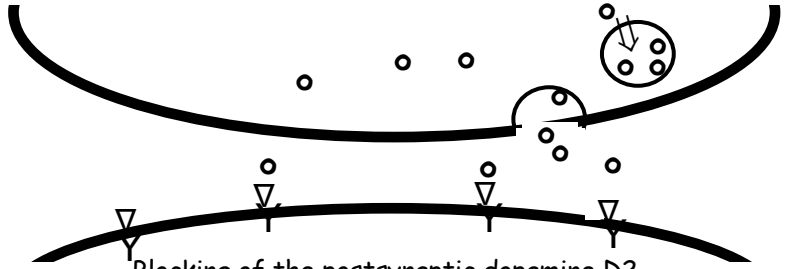

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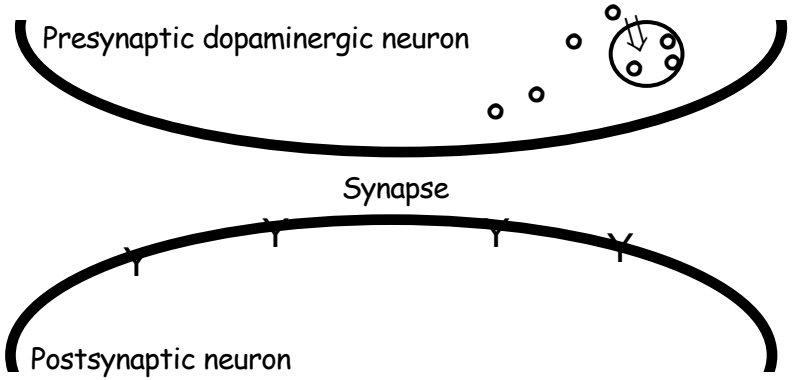

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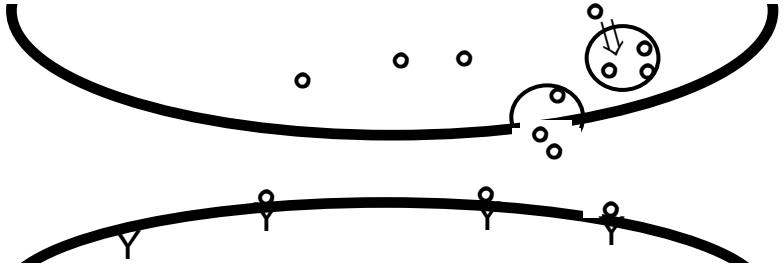

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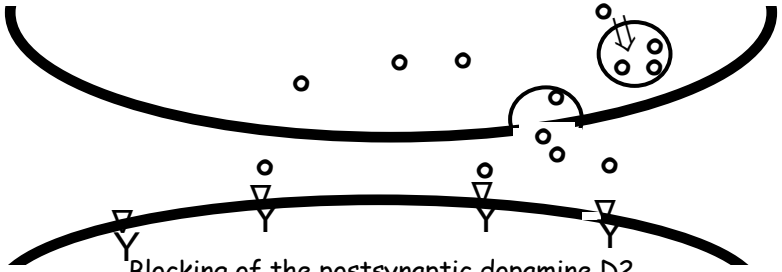

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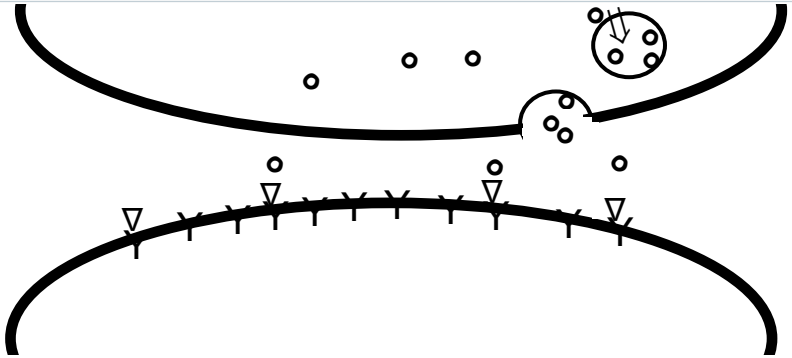
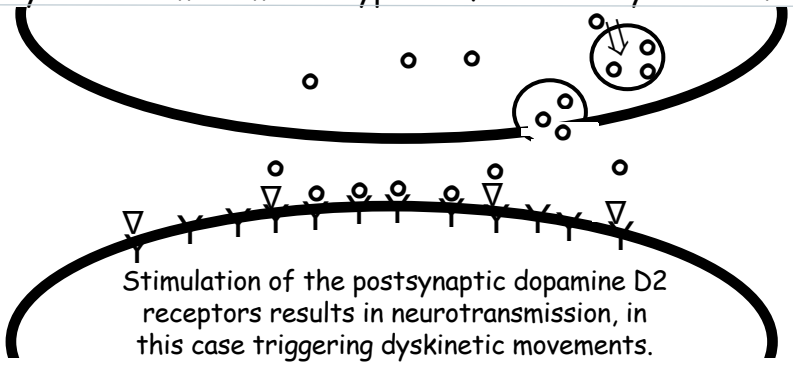
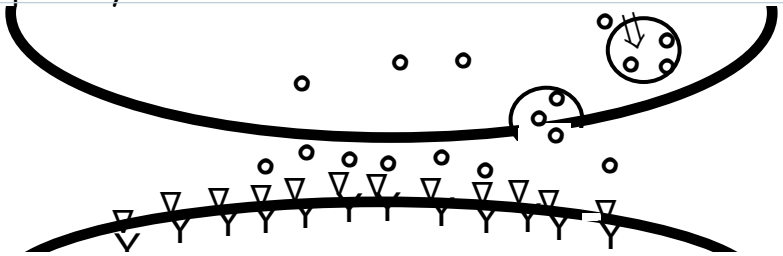


⑥ Upregulation of dopamine D2 receptors results in a "supersensitive" (or "hypersensitive") state, where if this phenomena occurs in the dorsal striatum, can lead to dyskinetic movements typical of tardive dyskinesia.



Stimulation of the postsynaptic dopamine D2 receptors results in neurotransmission, in this case triggering dyskinetic movements.

⑦ Increasing the dose of the dopamine receptor blocking agent may block more postsynaptic dopamine D_2 receptors, "masking" the dyskinetic movements temporarily.



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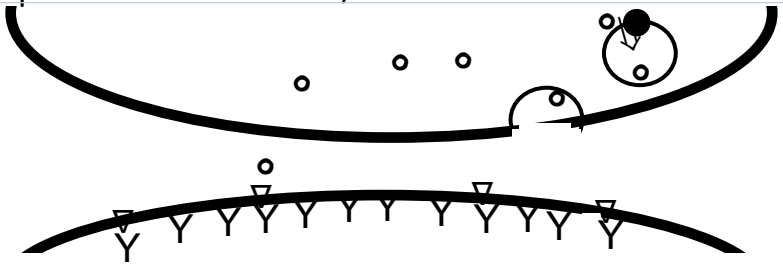

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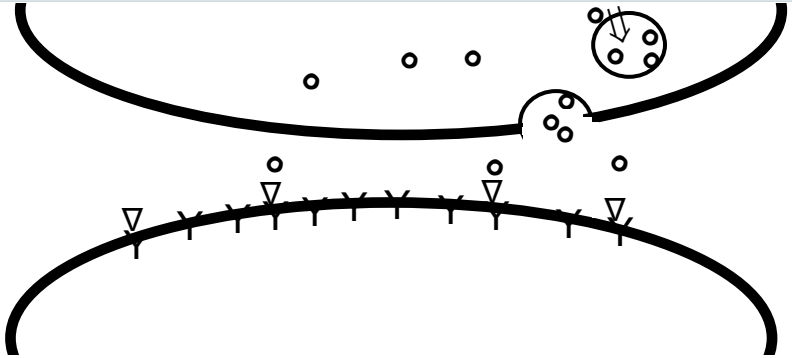

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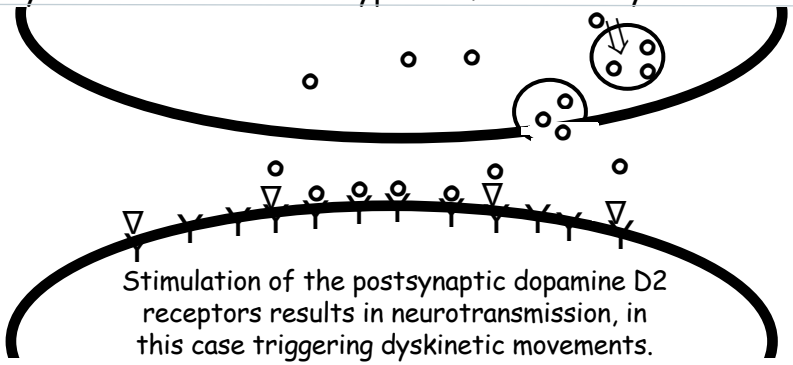

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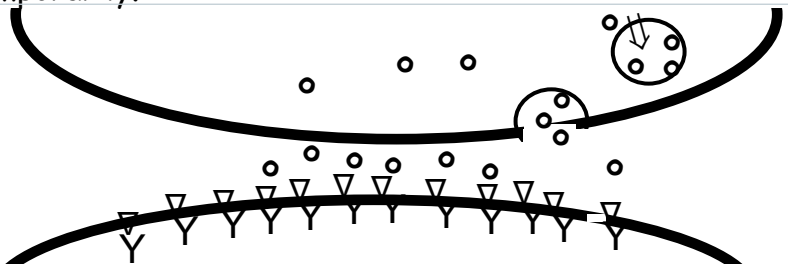

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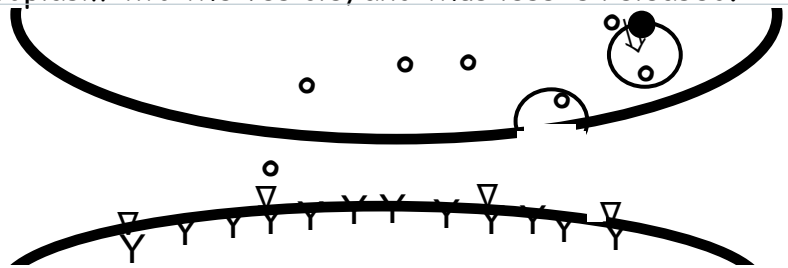

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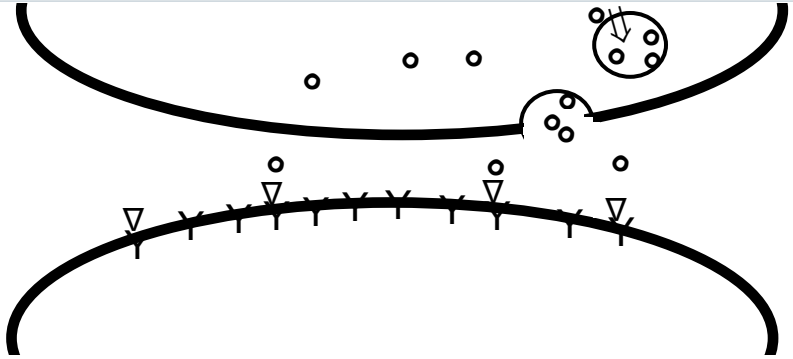

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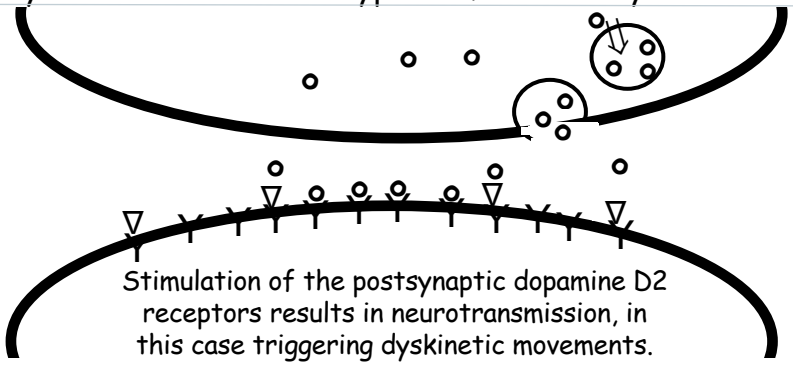

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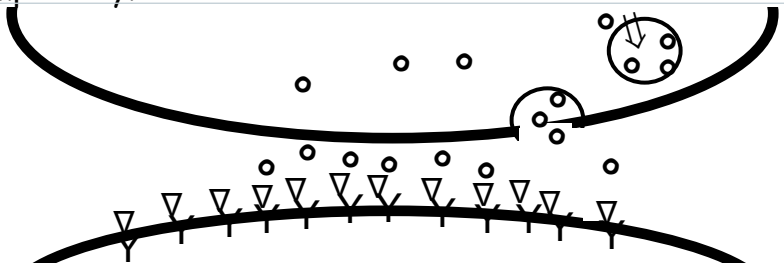

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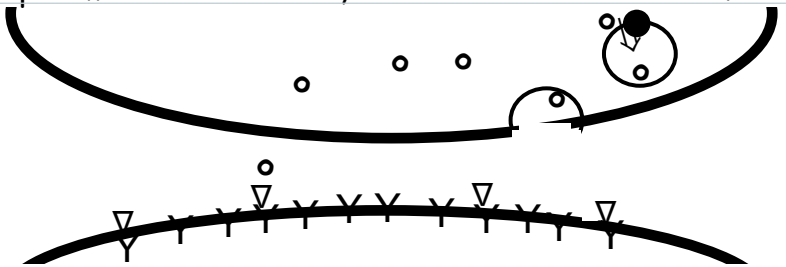

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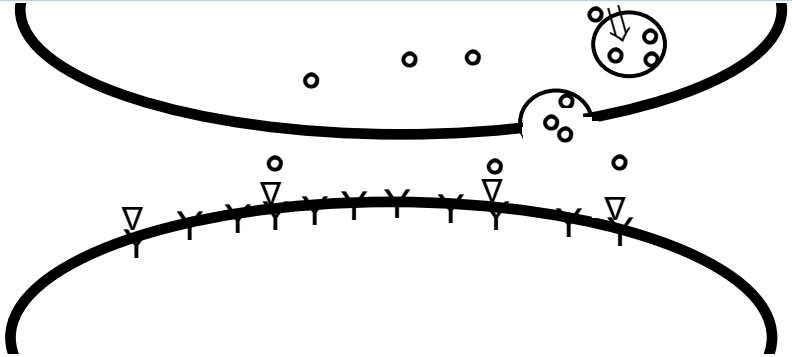

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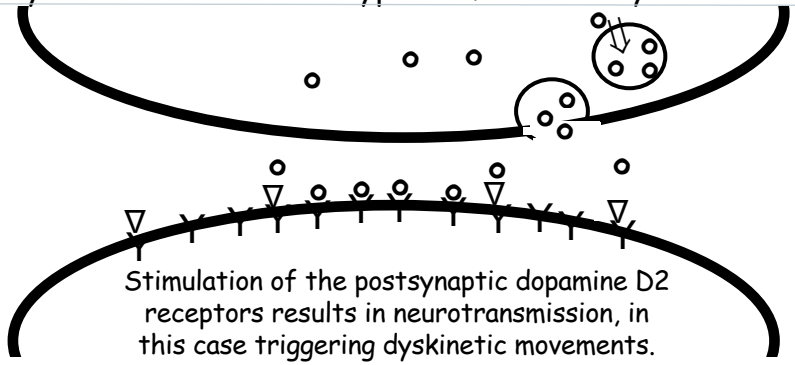

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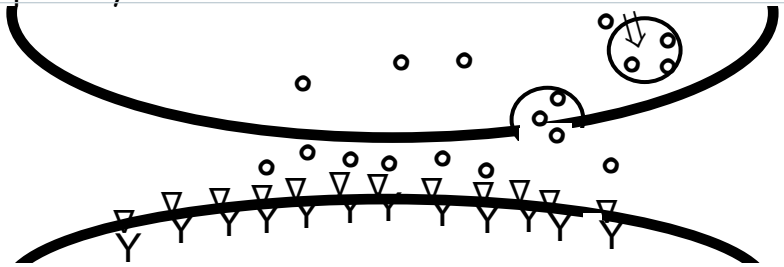

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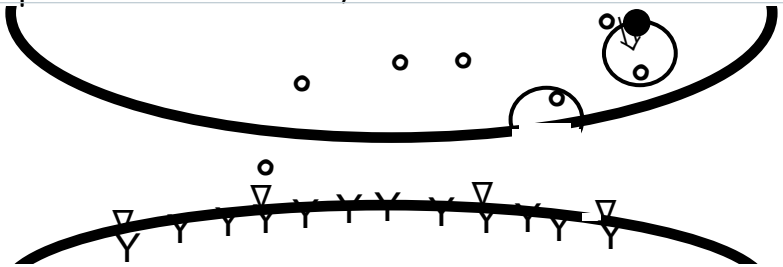

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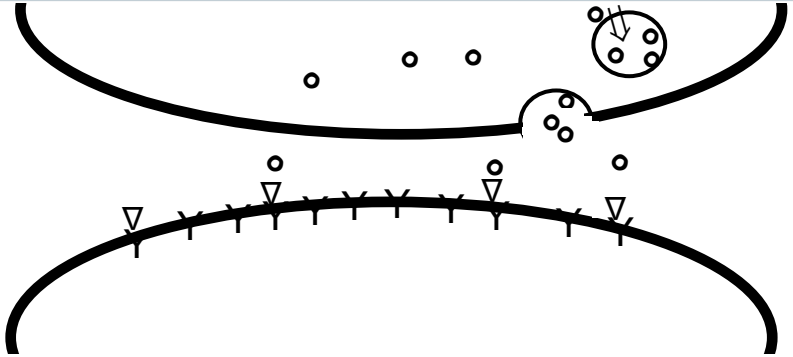

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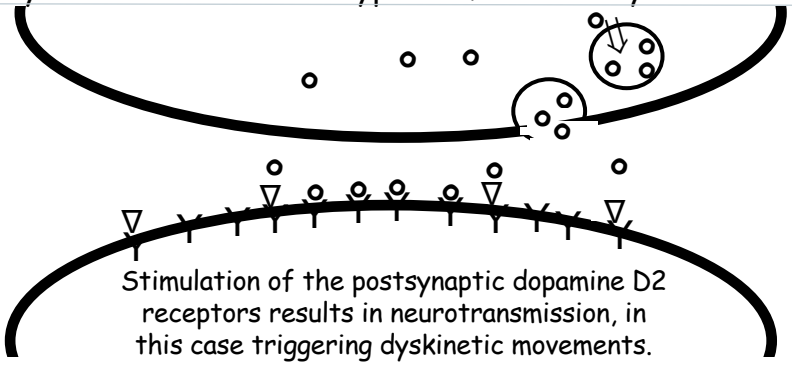

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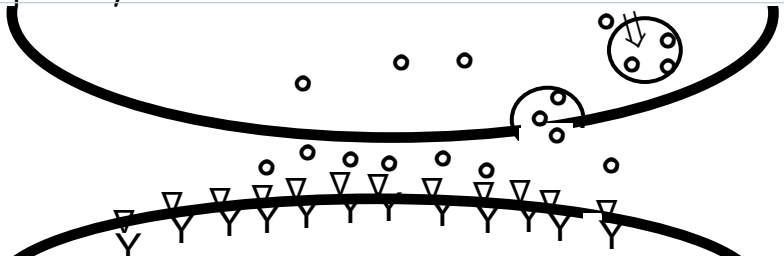

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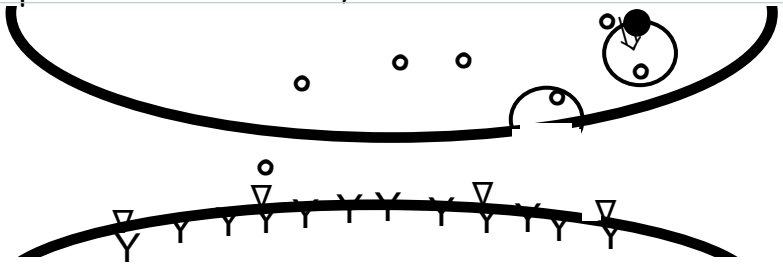

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How to Start a Patient

VMAT2 Inhibitor	Deutetrabenazine	Valbenazine
Patient Support Program Names and URLs to Initiate Prescription	Shared Solutions www.austedo.com/globalassets/austedo/tardive-dyskinesia-shared-solutions.pdf	INBRACE Support Program https://inbracesupportprogram.com
Patient Financial Assistance	• $0 copay (possibly) for commercial (nongovernment-funded) insurance • Assistance navigating Medicare D • Additional programs may exist	• $0 copay (possibly) for commercial (nongovernment-funded) insurance • Government-sponsored…provide information about independent organizations that can help you • No insurance and unable to pay…may be able to receive at no cost
Patient Support	Nurse Phone Support	
Patient Educational Resources	…help keep you informed, educated, and connected	
Free Trial		One month for new patients