Clinical Management of Tardive Dyskinesia: *Five Steps to Success*

Leslie Citrome, MD, MPH
New York Medical College, Valhalla, NY

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Disclosures

- In the past 12 months, consultant: Acadia, Alkermes, Allergan, Impel, Indivior, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, Vanda
- In the past 12 months, speaker: Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva
- Stocks (small number of shares of common stock): Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased > 10 years ago
- Royalties: Wiley (Editor-in-Chief, International Journal of Clinical Practice), UpToDate (reviewer), Springer Healthcare (book)

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Outline

- Definitions and Overview: Why Care?
- Step 1: Recognition
- Step 2: Assessment
- Step 3: Harm reduction
- Step 4: Interventions
- Step 5: Follow-up
- Summary

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- **Definitions and Overview: Why Care?**
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Tardive Dyskinesia

"Late" or "Delayed"

"Abnormal movement"

Overview

- **Tardive dyskinesia** (TD) can be observed with long-term treatment with ***dopamine receptor blocking agents*** such as antipsychotic agents
- First described in 1957 by Schonecker, about five years after the commencement of neuroleptic treatment in psychiatry
- Lower TD risk for second-generation antipsychotics (SGA) than for first-generation antipsychotics (FGA), but ***rates are not zero***
- Can be associated with significant functional impairment and can be socially stigmatizing - TD remains a ***significant treatment issue***
- ***New treatment approaches*** to persistent TD are available, as approved by the US FDA for this purpose

Jankelowitz SK. *Neuropsychiatric Disease and Treatment*. 2013;9:1371-80; Schonecker M. *Nervenarzt.*1957;28:550–3; Citrome L. *J Neurol Sci. 2017*;383:199-204.

Tardive Dyskinesia (ICD-10 Code G24.0)

- TD consists of *involuntary* movements of the tongue, lips, face, trunk, and extremities that occur in patients treated long-term with dopamine antagonist medications
  - Can see grimacing, tongue movements, lip smacking, lip puckering, pursing of the lips, excessive eye blinking
  - Rapid, involuntary movements of the limbs, torso, and fingers ("piano-playing") may also occur
  - Respiratory system (diaphragmatic) involvement can sometimes occur
- Variants of TD include tardive dystonia and tardive akathisia
- 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

Citrome L et al. *American Journal of Managed Care*. 2007;13(Suppl):1-12.
Lerner V, Miodownik C. *Curr Psychiatry Rep*. 2011;13(4):295-304.
Brasic JR. *Medscape*. Aug 8, 2015. http://emedicine.medscape.com/article/1151826.
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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

promethazine and antiemetic medications such as metoclopramide used for gastroesophageal reflux and for diabetic gastroparesis

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Tardive Dyskinesia: Awareness

- Six hundred seven 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

Chong SA et al. *J Clin Psychopharmacol*. 2001 Apr;21(2):235-7.

Tardive Dyskinesia: Continued Concern

- Thousands of patients are left with TD as a legacy of past treatment
- TD, once established, can be irreversible
- The “indications” for dopamine antagonist antipsychotic medications have expanded, and large numbers of persons are receiving these medications

Caroff SN et al. *Current Psychiatry*. 2011;10(10): 23-32.

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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

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

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Tardive Dyskinesia: What We Can Expect

- In a prospective study of 352 initially TD-free outpatients, compared with subjects treated with FGAs alone since the previous visit, the adjusted TD incidence rate-ratio for subjects treated with SGAs alone was 0.68 (95% CI, 0.29–1.64, hence not statistically significantly different)
  - **The incidence and prevalence TD was similar to previous findings at this site in the 1980s**
  - **TD rating scale scores were only slightly lower among incident cases of TD appearing after recent SGA exposure vs. recent FGA exposure**

Woods SW et al. *J Clin Psychiatry*. 2010;71:463-74.

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Of note, staff involved in this study were well trained to identify TD, and systematically looked for it. **What would the yield be in your practice if you were to screen your own patients for TD on a regular basis?**

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Tardive Dyskinesia: Differential Diagnosis

Conditions That May Resemble TD
Spontaneous dyskinesias occurring in the elderly[19,37] and in schizophrenia[10,34,40]*
Oral movements from ill-fitting dentures and other dental problems[10,25]
Drug-induced dyskinesias from antiparkinsonian drugs or stimulants[10,11,16]
Autism[16]
Chronic motor tic disorder[37]
Huntington's disease[11,16,37]
Meige's syndrome[37]
Restless legs syndrome[16]
Rett's syndrome[16]
Senile chorea[37]
Sydenham's chorea[37]
Tourette syndrome[37]
Wilson's disease[11,37]

TD indicates tardive dyskinesia.
*If documented to have begun after initiation of antipsychotic treatment, spontaneous dyskinesias are more likely TD.[13]

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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[11,37]

Caveat: People with TD and dentures often have denture problems

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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 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 (e.g., benztropine)	Can worsen	Improves
Pharmacotherapeutic treatment options	VMAT2 inhibitors (tetrabenazine, valbenazine, deutetrabenazine), Ginkgo biloba, clonazepam, amantadine	Anticholinergics (for example, benztropine), amantadine

Ward L, Citrome L. *Neurol Ther.* 2018.

My Opinion About Benztropine (Cogentin)

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

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

- Observer-rated 12-item anchored scale that takes 5-10 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 (e.g., 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 (ed): *ECDEU Assessment Manual for Psychopharmacology*, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. *J Neurol Sci*. 2017;383:199-204.

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

Items 1 to 7: Four items dedicated to the face, lips, jaws, tongue. Only one 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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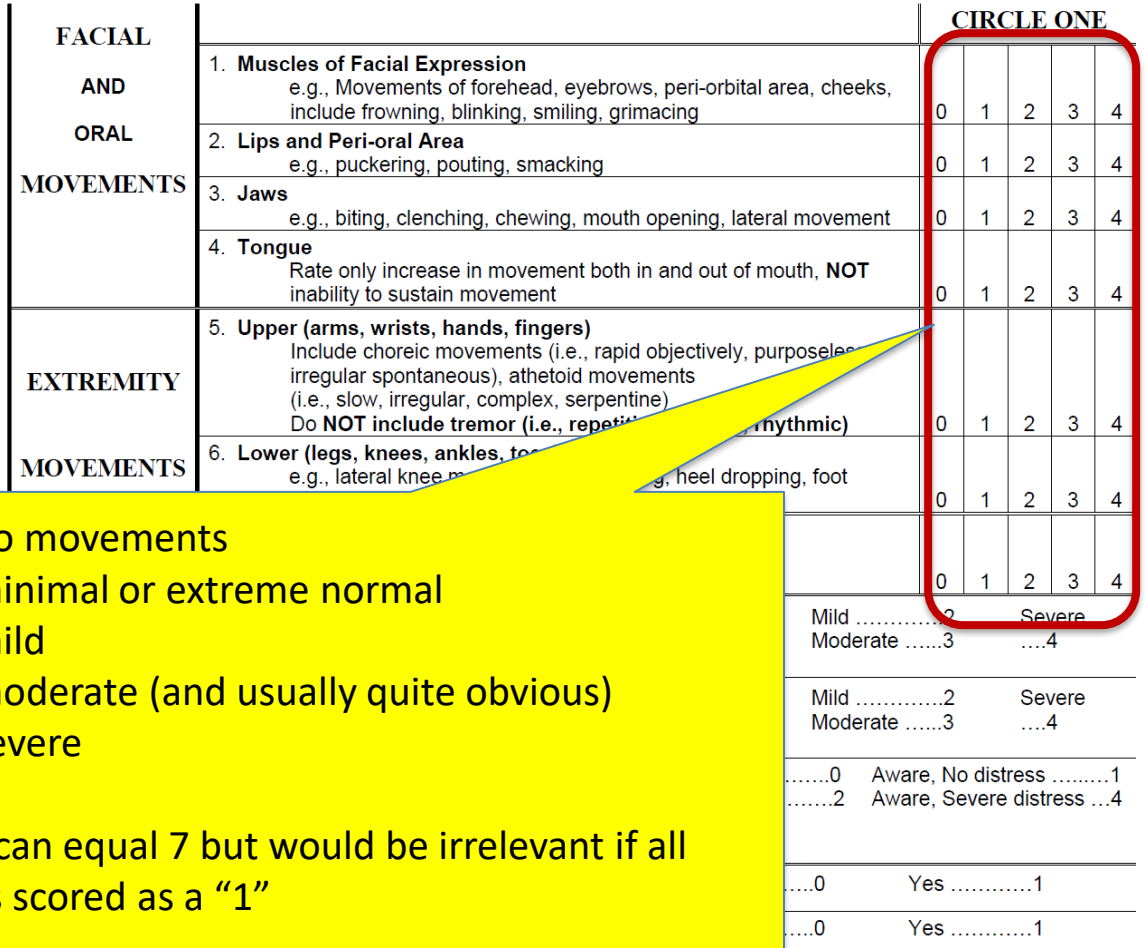

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	6. **Lower (legs, knees, ankles, toe…** e.g., lateral knee m… …g, heel dropping, foot	0	1	2	3	4
		0	1	2	3	4

Mild ……2 Severe
Moderate ……3 ….4

Mild ……2 Severe
Moderate ……3 ….4

……0 Aware, No distress ……1
……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 one 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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...REMITY ...EMENTS	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 ...OVEMENTS	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 (ed): *ECDEU Assessment Manual for Psychopharmacology*, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. *J Neurol Sci*. 2017;383:199-204.

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

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 persons with schizophrenia to have little insight into their dyskinetic movements; however, patients with mood disorders may be better able to articulate their distress

- dystonic reactions, aka 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				
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	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
GLOBAL JUDG TS	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 (ed): *ECDEU Assessment Manual for Psychopharmacology*, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; 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 5-10 minutes
- Adopted by many agencies for routine clinical use
- With FGAs, examine for TD at least every 6 months
- With SGAs and no concomitant FG
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  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
	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 (ed): *ECDEU Assessment Manual for Psychopharmacology*, revised ed. DHEW Publ No ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976; Citrome L. *J Neurol Sci*. 2017;383:199-204.

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

- Observe the patient unobtrusively at rest (e.g. 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 **two 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.

Guy W. *ECDEU Assessment Manual for Psychopharmacology*, 1976 Revised: NIMH

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 her/his knees, legs slightly apart & feet flat on the floor
   - Look at entire body for movements while in this position

Guy W. *ECDEU Assessment Manual for Psychopharmacology*, 1976 Revised: NIMH

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 her/his mouth
   - Observe tongue at rest within mouth
   - Do this twice
7. Ask the patient to protrude her/his tongue
   - Observe abnormalities of tongue in movement
   - Do this twice
8. Ask the patient to tap her/his thumb, with each finger, as rapidly as possible for 10-15 seconds; separately with right hand, then with left hand
   - Observe facial and leg movements

Guy W. *ECDEU Assessment Manual for Psychopharmacology*, 1976 Revised: NIMH

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, 1976 Revised: NIMH

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*, 1976 Revised: NIMH; 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 one 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 one ≥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	

DSM = *Diagnostic and Statistical Manual of Mental Disorders*; Dx = diagnosis; APA = American Psychiatric Association.

Schooler NR, Kane JM. *Arch Gen Psychiatry.* 1982;39:486-487. Glazer WM et al. *J Clin Psychiatry.* 1993;54:133-139. APA. DSM-IV. Washington DC: APA; 1994. APA. DSM-V. Washington DC: APA; 2013.

Outline

- Definitions and Overview: Why Care?
- Step 1: Recognition
- Step 2: Assessment
- **Step 3: Harm reduction**
- Step 4: Interventions
- Step 5: 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 care-givers 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 dopamine receptor blocking agents, and also to lesser degrees, female sex, race, pre-existing mood, movement or cognitive disorder, alcohol use, diabetes, and human immunodeficiency virus (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 4-5 times increased risk for TD (5% versus 20% per year)
- Remember, ***prolonged use*** of dopamine antagonist medications increases risk

Jankelowitz SK. *Neuropsychiatric Disease and Treatment*. 2013;9:1371-80.
Brasic JR. *Medscape*. Aug 8, 2015. http://emedicine.medscape.com/article/1151826.

Treatment of TD: Antipsychotics
Treatment Decisions on Antipsychotic Treatment

Tapering off and discontinuing antipsychotics?

- Initial worsening of TD in 33–53% of patients
- Long-term improvement in 36–55%
- 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;52:173-188. Egan MF et al. *Schizophr Bull.* 1997;23:583-609. Gardos G, Cole JO. The treatment of tardive dyskinesias. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: the Fourth Generation of Progress*. NY, NY: Raven Press;1995. Casey DE, Gardos G. *Tardive Dyskinesia and Neuroleptics: From Dogma to Reason*. American Psychiatric Publications;1986. Glazer WM et al. *Br J Psychiatry.* 1990;157:585-592.

Treatment of TD

Methodologic Problems in Evaluating Treatments

- Distinguishing between suppression (masking) vs recovery
- Controlling for the natural course of TD
  - Persistent and fluctuating course of TD requires repeated examinations
  - In most cases, TD is non-progressive, and even with continued antipsychotic treatment, there may be improvement over time, especially if the lowest effective doses can be employed
  - “Improvement” in 14–36% even with continuation of first-generation antipsychotics
  - Some may develop more severe forms

Egan MF et al. *Schizophr Bull.* 1997;23:583-609. Gardos G, Cole JO. The treatment of tardive dyskinesias. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: the Fourth Generation of Progress*. NY, NY: Raven Press;1995

Outline

- Definitions and Overview: Why Care?
- Step 1: Recognition
- Step 2: Assessment
- Step 3: Harm reduction
- **Step 4: Interventions**
- Step 5: Follow-up
- Summary

Tardive Dyskinesia: Pathophysiology May Drive Therapy I

- Chronic high levels of dopamine antagonist may starve, and subsequently **up-regulate dopamine receptor number and responsiveness**; randomly available dopamine molecules may initiate abnormal involuntary movements in a hyper-sensitive system
  - This is the rationale for treatment with **VMAT2 inhibitors** which decrease dopamine release and also explains why "masking" of TD can occur by increasing antipsychotic dose or switching to an antipsychotic with higher affinity to D2 receptors
  - Also contributory are possible abnormalities of striatal **GABA** neurons and degeneration of striatal **cholinergic** interneurons; hence the rationale for treatment with **clonazepam,** and the observation that **benztropine** can make TD worse
  - SGAs may cause less TD because they have less impact on the basal ganglia and are less likely to cause postsynaptic dopamine hypersensitivity

Brasic JR. *Medscape*. Aug 8, 2015. http://emedicine.medscape.com/article/1151826; Margolese HC et al. *Can J Psychiatry*. 2005;50:541-7.

Tardive Dyskinesia: Pathophysiology May Drive Therapy II

- **Oxidative stress** created from chronic antipsychotic use; hence the rationale for treatment with ginkgo biloba or Vitamin E
- **Amino acid metabolism**; hence the rationale for treatment with branched-chain amino acids
- **NMDA receptor** excitotoxicity; hence the rationale for treatment with amantadine
- **Genetic vulnerability** may also be a factor
  - TD has been associated with several different polymorphisms of dopamine receptor genes, the dopamine transporter gene, and the manganese superoxide dismutase gene

Brasic JR. *Medscape*. Aug 8, 2015. http://emedicine.medscape.com/article/1151826; Margolese HC et al. *Can J Psychiatry*. 2005;50:541-7.

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 - One high-quality study or several studies with some limitations
Level C – Low - One or more studies with severe limitations

Bhidayasiri R et al. *Neurology.* 2013;81:463-9.

What "Works" - American Academy of Neurology Evidence-Based Guideline

Medication	Evidence Level	Recommendation
Clonazepam	Moderate	Probably effective for decreasing TD symptoms short term (~3 months); may be considered for short-term treatment
Ginkgo Biloba	Moderate	Probably useful in TD treatment, but data are limited to patients with schizophrenia
Amantadine	Weak	Amantadine with neuroleptics may be considered to treat TD for short-term use
Tetrabenazine	Weak	Possibly reduces TD symptoms; may be considered in treating TD

Previous reviews/meta-analyses and guidelines are limited in clinical application.

- Treatments studied have limited evidence, based on small trials that are often underpowered, uncontrolled, unblinded, from single sites, or unreplicated
- Focus is on design and statistical validity but less so on tolerability, reliability, and availability of products
- Antipsychotics and antimuscarinics are analyzed equally with specific antidyskinetics, apart from psychiatric necessity
- **Recent RCTs of novel VMAT-2 inhibitors are not included and far exceed previous levels of evidence**

Bhidayasiri R. et al. *Neurology.* 2013;81:463-469.

Branched-Chain Amino Acids (BCAA)

- BCAA have been approved by the FDA as a **medical food** for the dietary management of TD in males
  - Made from the branched-chain amino acids L-Leucine, L-Valine, and L-Isoleucine,
  - Dose 15 grams TID
- Evidence has suggested an association between TD and impaired clearance of **phenylalanine**
  - Ingesting BCAA decreases availability of phenylalanine to the brain and thus BCAAs might improve TD by decreasing amine neurotransmitter synthesis
  - In one study of high-dose BCAA vs. placebo in men with TD, TD movements decreased 36.5% in the BCAA group but increased 3.4% in the placebo group
- Although this product, “Tarvil,” is no longer being manufactured, compounding pharmacies can make it using the same ratio of ingredients that was tested in the clinical trial
- Problematic was the presence of sugar for palatability, 52 calories in each 15 gram packet
  - 3 packets a day equates to 156 extra calories per day

Richardson MA et al. *Am J Psychiatry*. 2003;160:1117-24.
Roth LS. *Federal Practitioner*. 2004: 21(11): 48, 53, 56, 62.

Clonazepam

- 12-week, double-blind, placebo-controlled, crossover study of clonazepam, with an open-label 9-month extension
- 19 chronically ill patients with tardive dyskinesia being treated with neuroleptics
- Initial week of placebo was followed by a 4-week treatment period (placebo or clonazepam), followed by 2 weeks of placebo, and then the second 4-week clonazepam or placebo treatment period; dose was initiated at 2 capsules of clonazepam 0.5 mg or placebo per day, and increased by two capsules every 3-4 days, with a maximum dose of 9 capsules per day, as tolerated
- 11 subjects received 4.0-4.5 mg of clonazepam, six subjects received 3 mg/d, and two subjects received 2 mg/d
- The primary efficacy endpoint was the change in dyskinesia score using the Maryland Psychiatric Research Center Movement Disorder Scale as assessed by blinded video raters
- Clonazepam treatment reduced dyskinesia scores by 37.1% in the patient group overall, an effect that was reversed during placebo administration, *however **tolerance** developed in the 5 patients receiving clonazepam in the long-term extension after 5-8 months of use*

Thaker GK, et al. *Am J Psychiatry.* 1990;147:445-451.

Ginkgo Biloba

- Extract of Ginkgo biloba (EGb) is a potent antioxidant possessing free radical-scavenging activities; EGb-761 is a standardized extract given in capsule form
- 12-week, double-blind, placebo-controlled, parallel-group study of 157 inpatients with schizophrenia conducted in China; after the treatment period the Egb-761 group was followed up for 6 months
- Subjects were randomized to receive EGb-761 240 mg/d (N=78) or placebo (N=79); study completion rates was 97%
- Primary outcome measures were (1) change from baseline in the AIMS score and (2) proportion of patients with a ≥ 30% reduction in their AIMS total score at week 12
- EGb-761 treatment significantly decreased the AIMS total score in patients with TD compared to those who were given a placebo (2.13 vs -0.10; $P < .0001$), with 40 (51.3%) and 4 (5.1%) patients achieving response in the EGb-761 and placebo treatment groups, respectively; therapeutic effect was maintained after stopping treatment

Zhang WF, et al. *J Clin Psychiatry*. 2011; 72: 615-621.

Amantadine

- Two double-blind, placebo-controlled, cross-over studies
- In Pappa et al., 22 subjects were treated with amantadine 400 mg/d or placebo, together with their antipsychotic medication
  - Subjects were randomly assigned to receive either amantadine or placebo for 2 weeks followed by a washout period of 4 days, followed by the second treatment period
  - The primary efficacy end point was changes in AIMS score
  - After amantadine treatment, patients exhibited a reduced average score of total AIMS (from 13.5 before treatment to 10.5 after treatment, P = 0.000); with amantadine, the average total AIMS reduction was 22% compared to no reduction with placebo
- In Angus et al., 16 subjects were treated with amantadine 300 mg/d or placebo, together with their antipsychotic medication
  - A 2-week baseline period preceded the administration of amantadine; subjects were then randomly assigned to two groups, and amantadine or an identical placebo capsule was given over a 7-week period.
  - The primary efficacy end point was changes in AIMS score
  - On amantadine, four patients increased their AIMS score, but overall there is a 15% reduction; the difference between amantadine and placebo is significant at the 0.05 level.

Pappa S, et al. *Clin Neuropharmacol*. 2010; 33:271-275;
Angus S, et al. *J Clin Psychopharmacol.* 1997; 17: 88-91

Tetrabenazine, the 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 US as an **orphan drug** for the treatment of choreiform movements associated with Huntington's Disease
- Tetrabenazine used "off-label" in the US 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;11:166-176; Bernstein AI et al. *Neurochemistry International*. 2014;73:89-97; Leung JG & Breden EL. *Annals of Pharmacotherapy*. 2011;45:525-531; Kazamatsuri H, et al. *Arch Gen Psychiatry*. 1972; 27: 95–99.

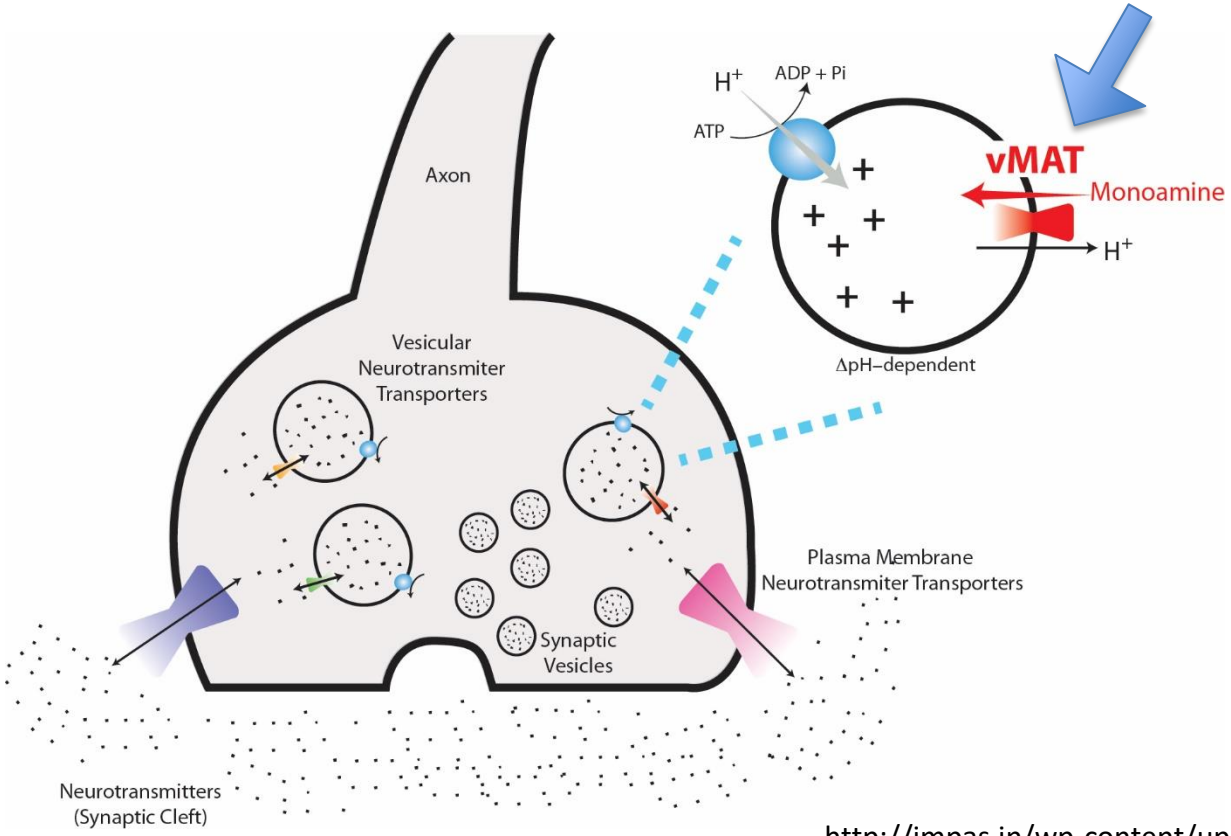
Tetrabenazine Historical Approvals

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

https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4328b1-02-Prestwick.pdf.

What is a "Vesicular Monoamine Transporter Type 2"?

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 pre-synaptic neurons



http://impas.in/wp-content/uploads/2017/04/vmat.jpeg

Vesicular Monoamine Transporter Inhibitors

Medication	Reserpine	Tetrabenazine	Deutetrabenazine	Valbenazine
Mechanism of action	• Irreversibly binds VMAT • Binds VMAT1 (PNS) & 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 ($T_{1/2}$ 5.5h)	Intermediate ($T_{1/2}$ 8.6h)	Long ($T_{1/2}$ 20h)
Peripheral side effects*	Frequent	Rare	Rare	Rare
Status	Discontinued	Approved HC	Approved HC, TD	Approved TD

*Orthostatic hypotension, stuffy nose, and gastrointestinal side effects, such as nausea, vomiting, and diarrhea

Updated from Jankovic J. *Expert Opinion on Pharmacotherapy*. 2016; 17: 2461-70.

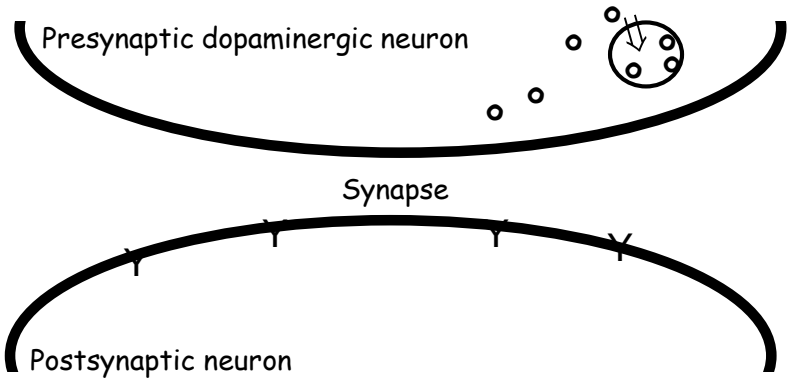
VMAT2 MOA Part I

How Vesicular Monoamine Transporter Type 2 (VMAT2) Inhibitors Work in Tardive Dyskinesia ①

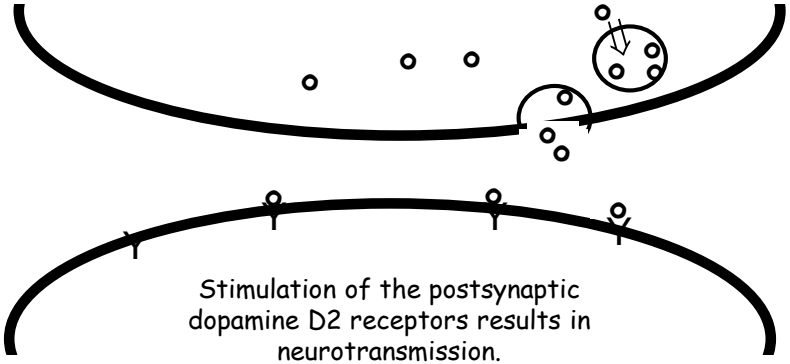
Dramatis Personae

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

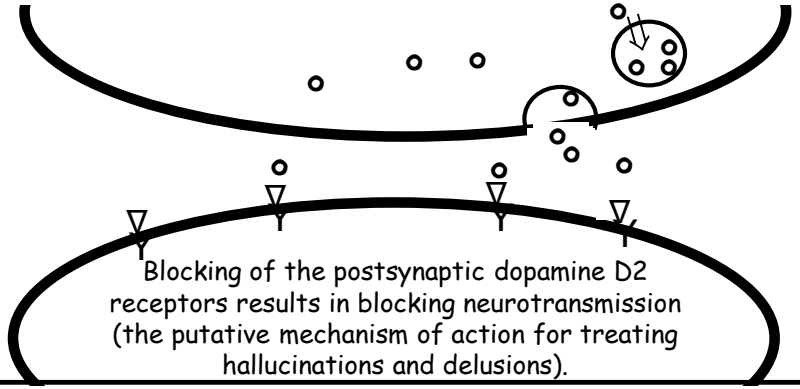
VMAT2 packages dopamine from the cytoplasm into vesicles in the presynaptic dopaminergic neuron. ②



When the dopaminergic neuron fires, dopamine is released from the vesicles (and *not* directly from the cytoplasm) and binds to dopamine D_2 receptors. ③



When dopamine receptor blocking agents are used, dopamine is prevented from binding to the dopamine D_2 receptor. ④



Citrome L. *Expert Review of Neurotherapeutics*. 2018 Apr;18(4):323-332.

VMAT2 MOA Part I

How Vesicular Monoamine Transporter Type 2 (VMAT2) Inhibitors Work in Tardive Dyskinesia ①

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

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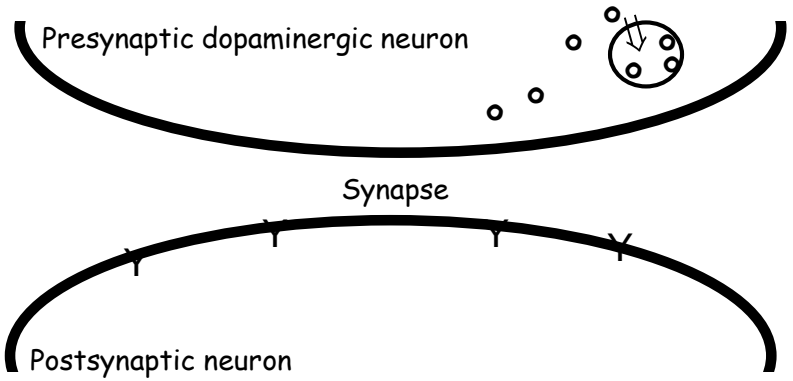

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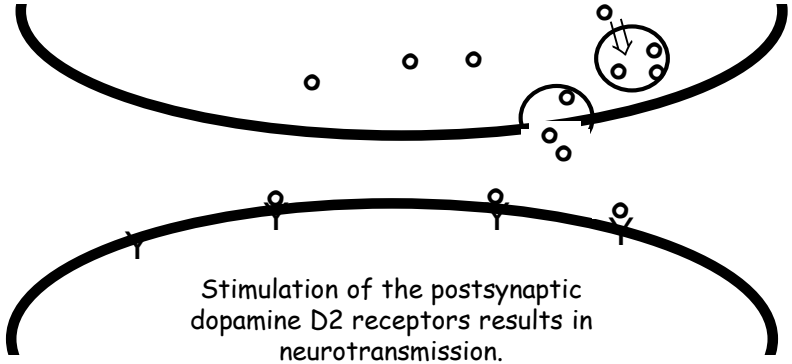

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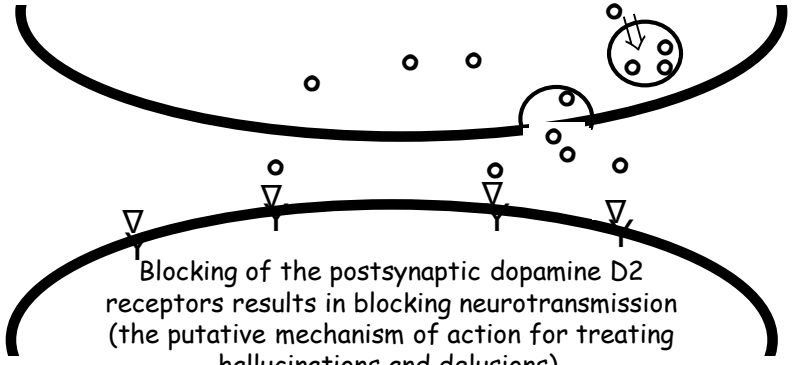

Citrome L. *Expert Review of Neurotherapeutics*. 2018 Apr;18(4):323-332.

VMAT2 MOA 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

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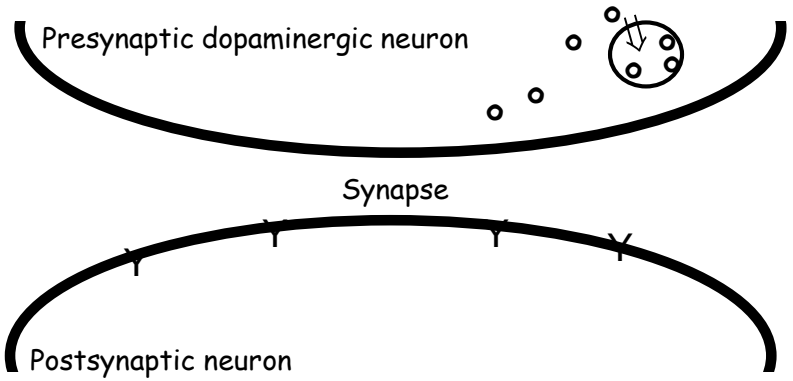

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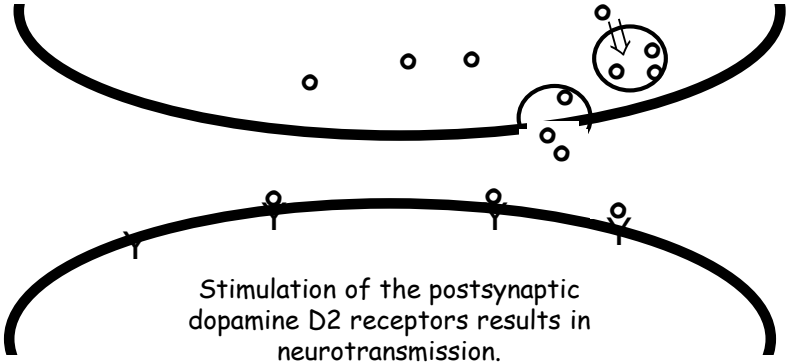

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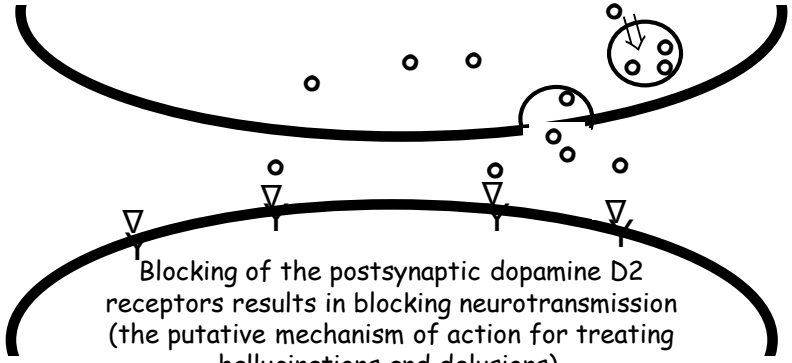

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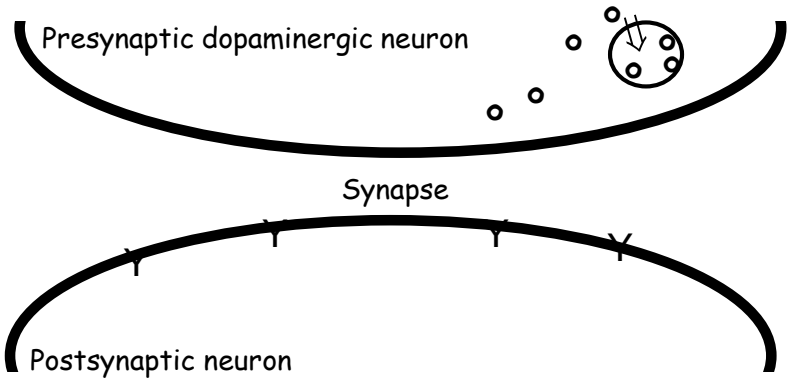

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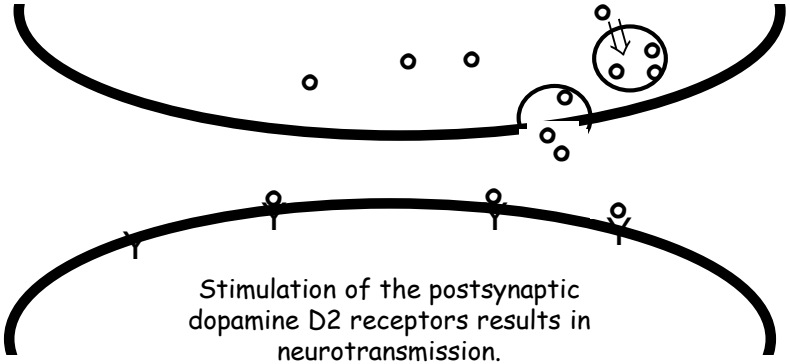

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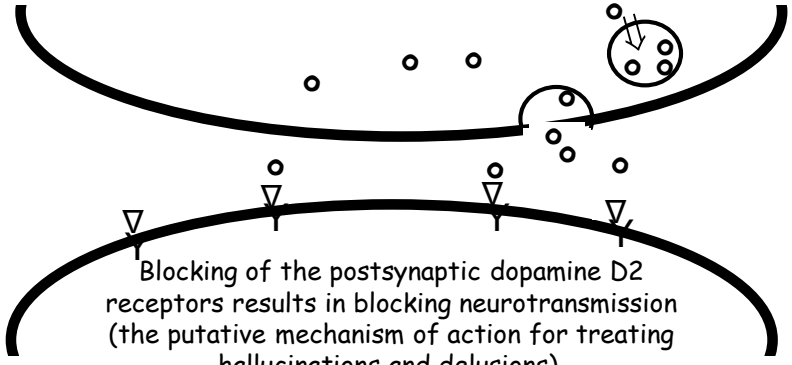

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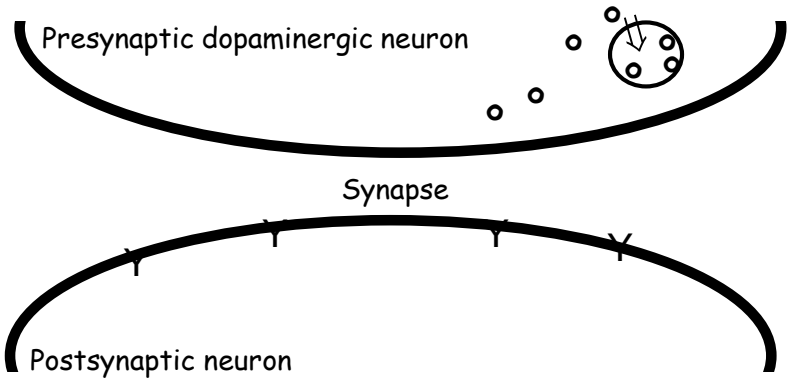

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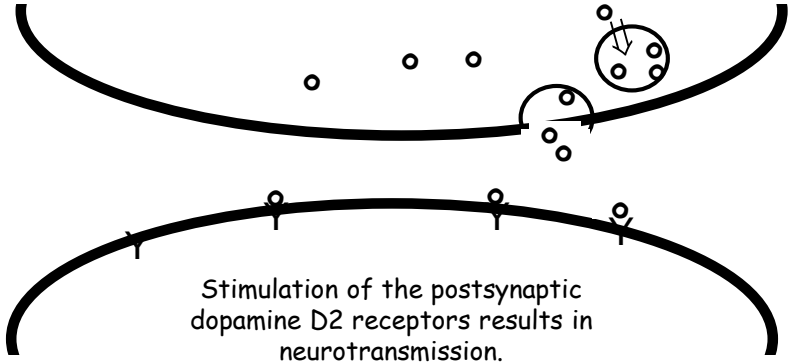

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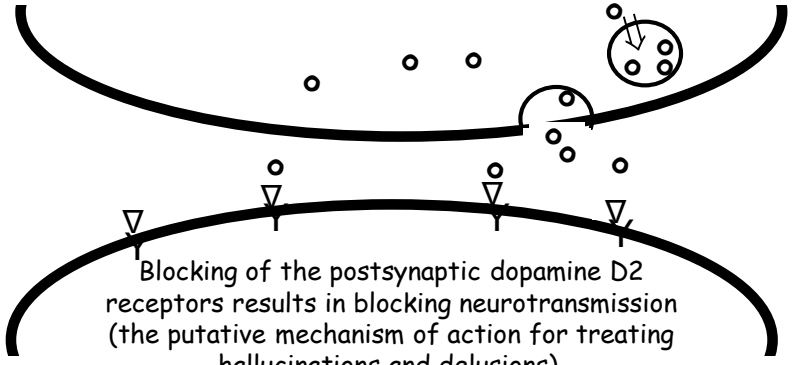

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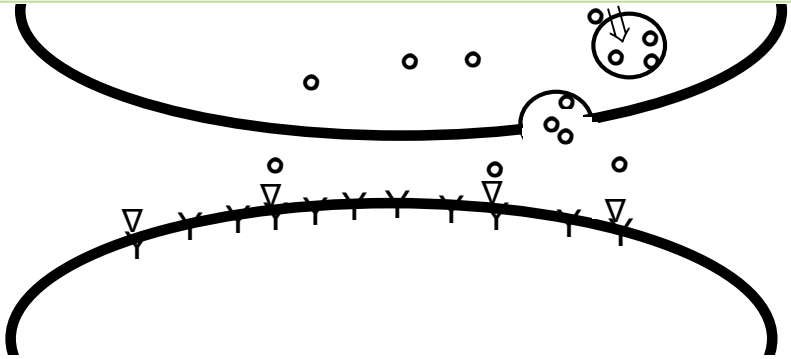

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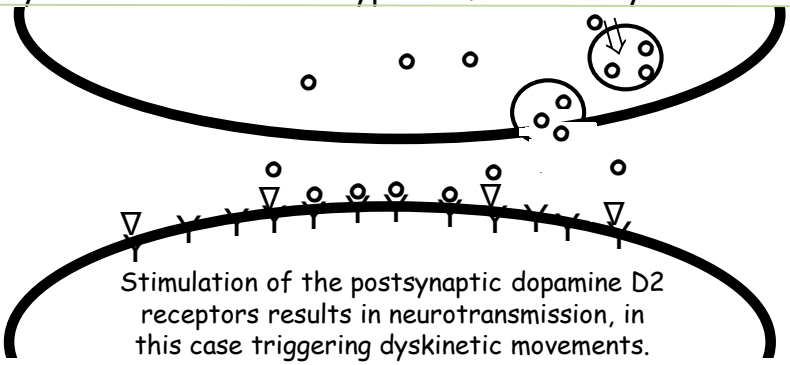

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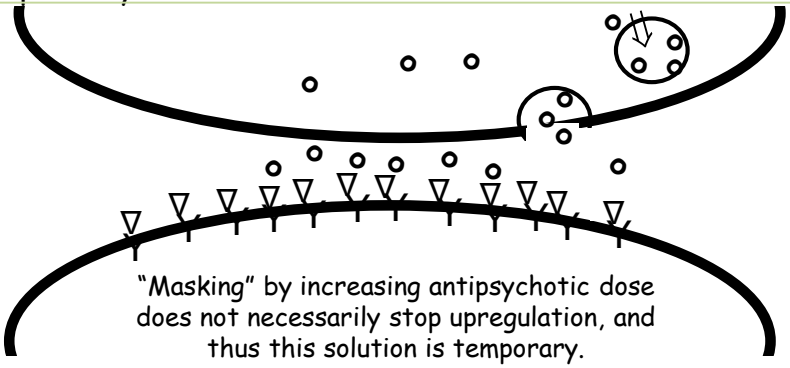

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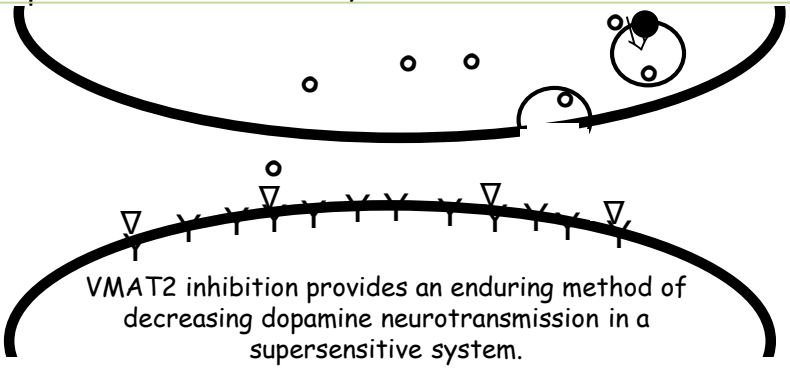

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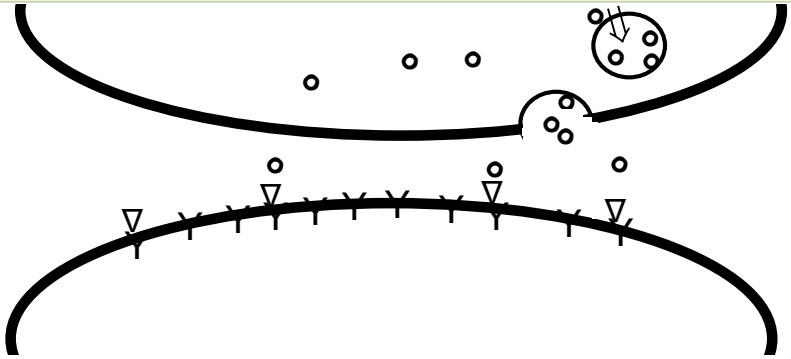

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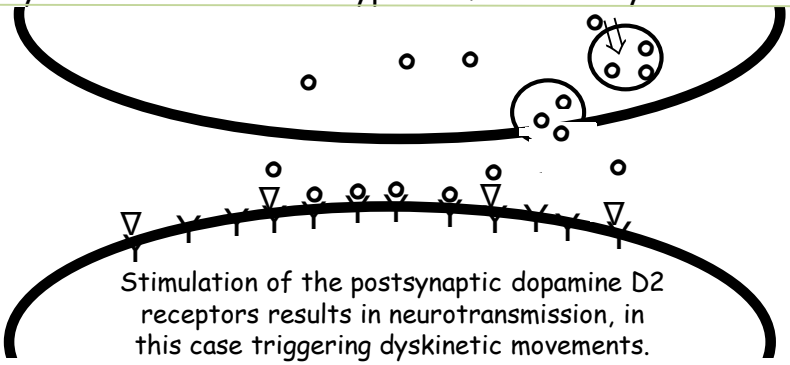

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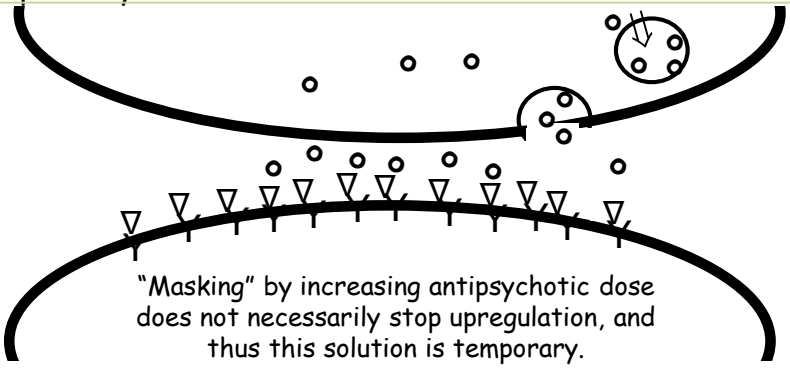

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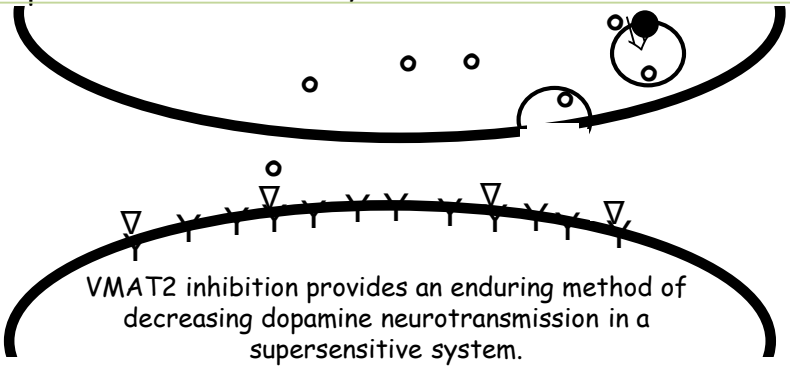

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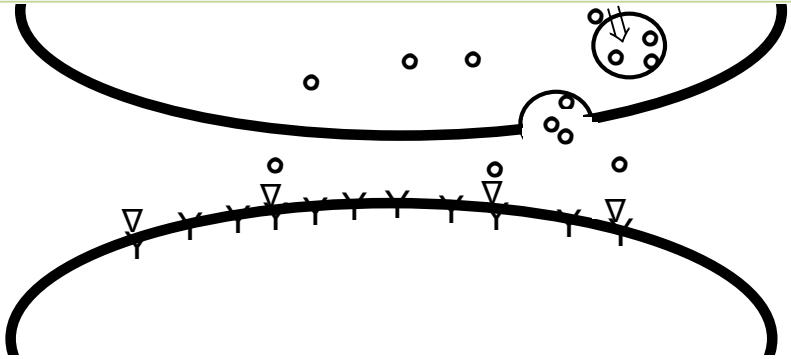

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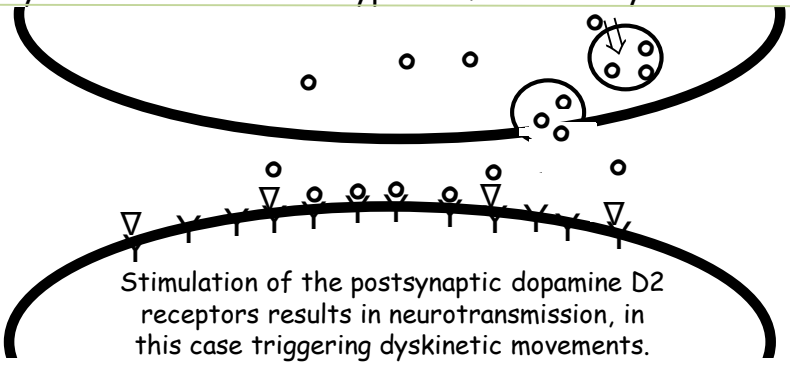

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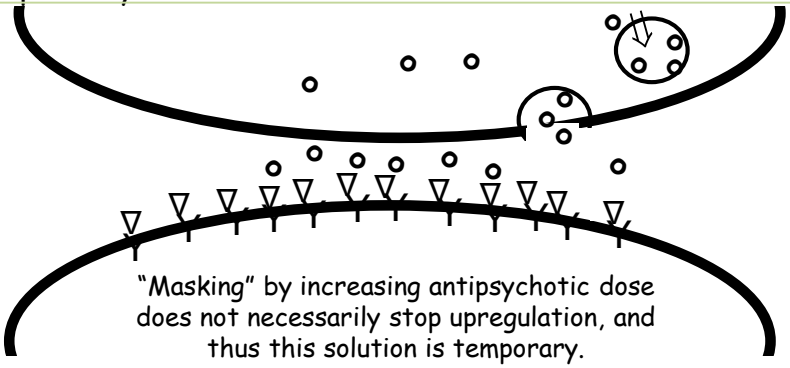

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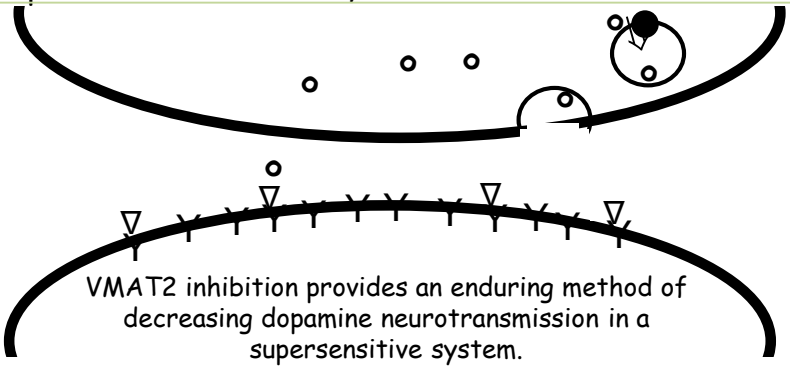

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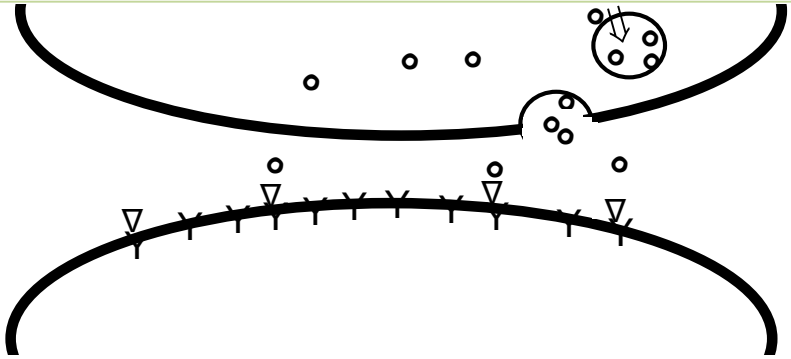

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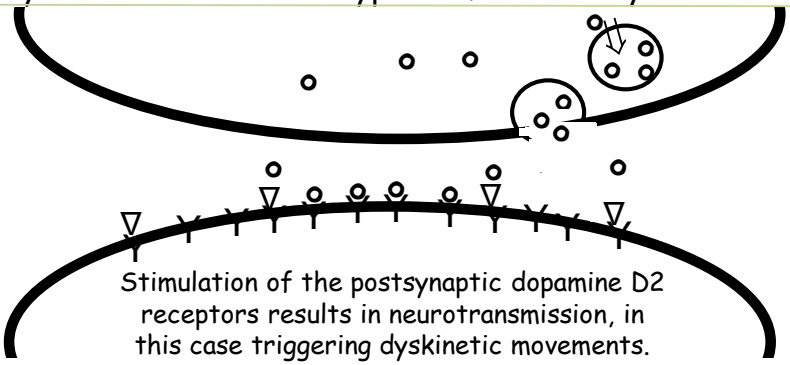

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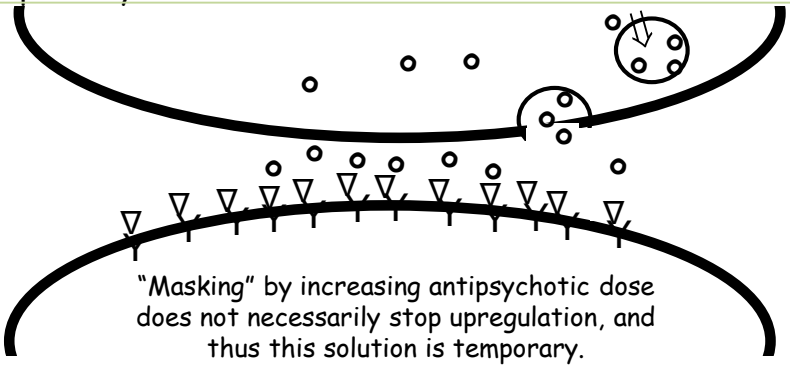

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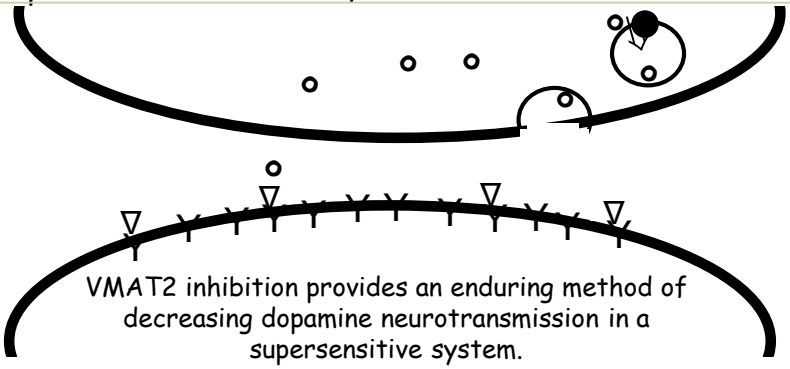

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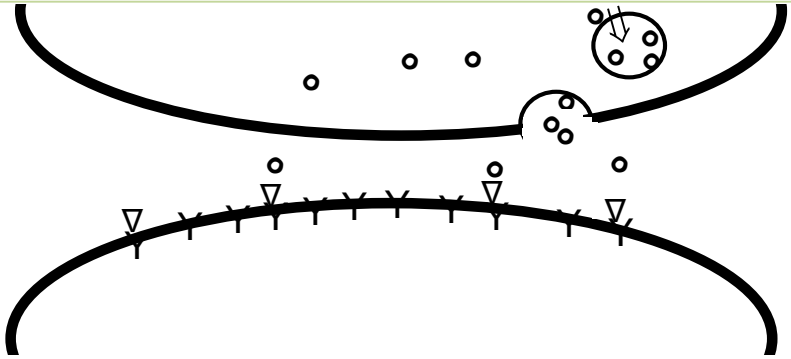

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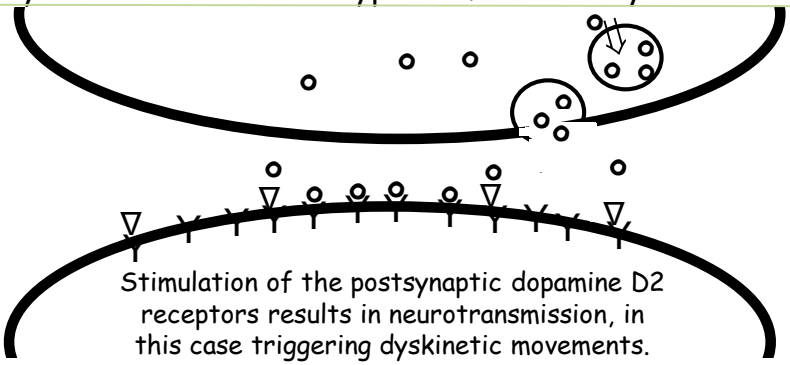

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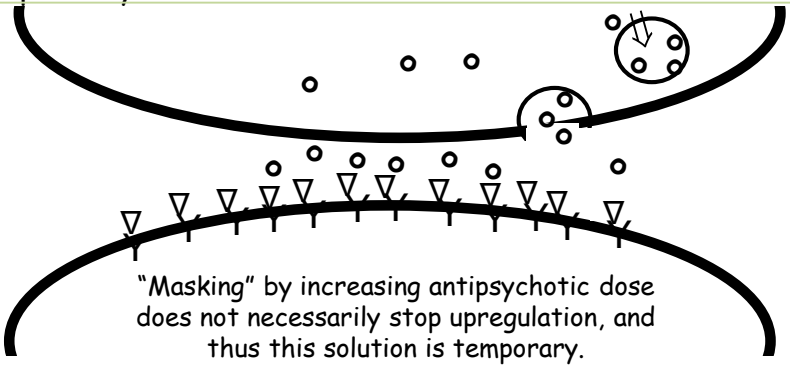

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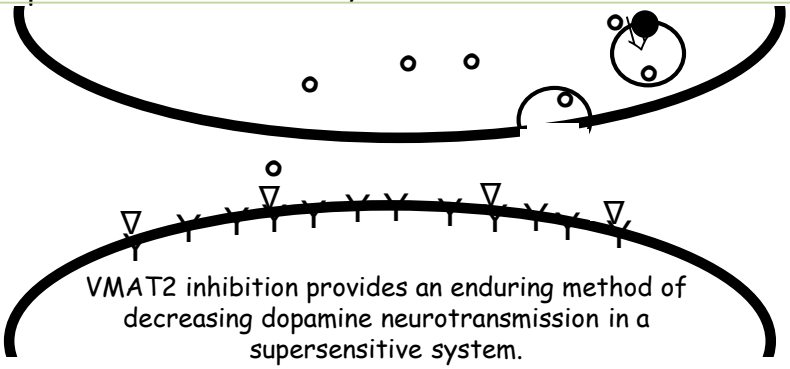

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Tetrabenazine – Does it Work in TD?

- One Class III study compared haloperidol use with tetrabenazine use in **13 subjects** (100 mg/d 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 two patients
- Another Class III, **nonrandomized, single-blind** study compared tetrabenazine efficacy using a randomized videotape protocol pre- and posttreatment (**N=20**); subjects 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 ($p < 0.001$)
- These results are supported by Class IV, long-term, observational studies

http://www.neurology.org/site/misc/TableClassificationScheme.pdf:
Class I or **II** are randomized controlled clinical trials, 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

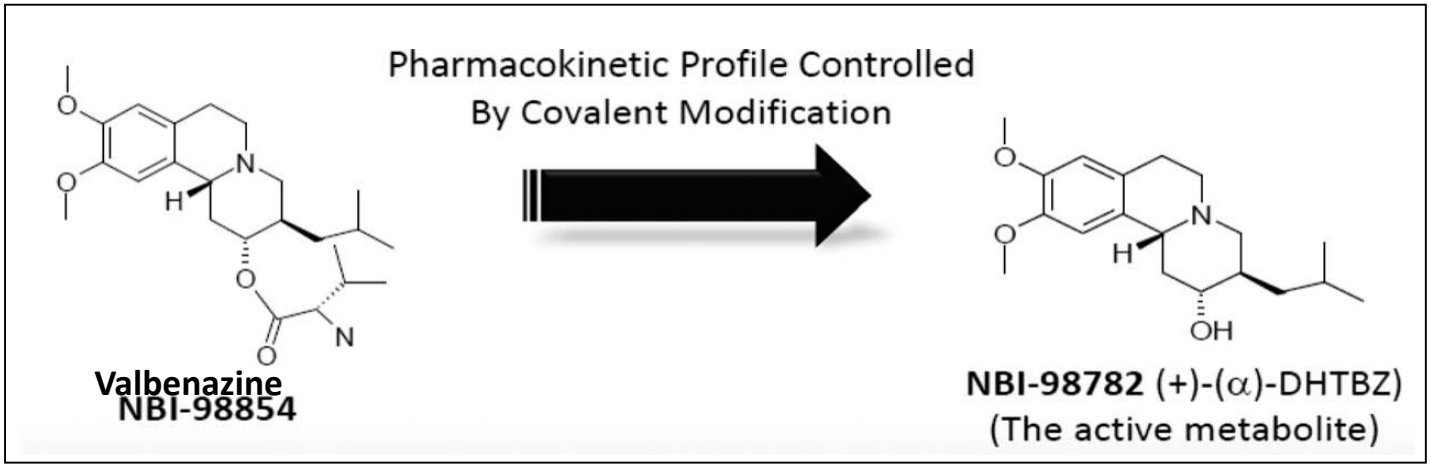
Bhidayasiri R et al. *Neurology*. 2013;81:463-9. Kazamatsuri H, et al. *Am J Psychiatry*.1973; 130: 479-483. Ondo WG, et al. *Am J Psychiatry*. 1999; 156: 1279-1281.

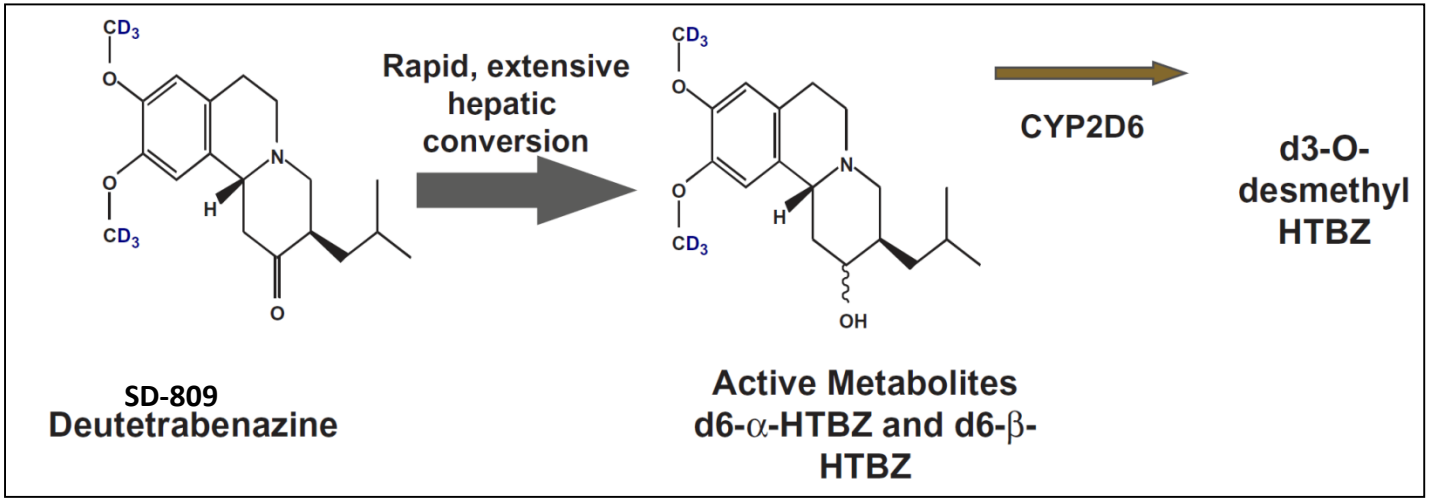
Tetrabenazine: Limitations Driven by PK and PD

- 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 two isomers of a dihydrotetrabenazine metabolite, for a total of four 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 two 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/d

Muller T. *Expert Opin Investig Drugs*. 2015;14:737-42; Shen V. *Tremor Other Hyperkinet Mov (N Y).* 2013 Oct 22;3. pii: tre-03-191-4337-1; Lundbeck. XENAZINE (tetrabenazine) tablets, for oral use. Prescribing information. June 2015. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf. Accessed April 16, 2017.

Alternatives to Tetrabenazine: Valbenazine and Deutetrabenazine





Jankovic J. *Expert Opinion on Pharmacotherapy*. 2016; 17: 2461-70.

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

Jankovic J. *Expert Opinion on Pharmacotherapy*. 2016; 17: 2461-70.

Treatment of TD with the New VMAT-2 Inhibitors Approved by the FDA: Randomized, Double-Blind, Placebo-Controlled trials

RCT	VMAT-2	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

Systematic reviews: Citrome L. *Int J Clin Pract*. 2017;71(11): e13030. Citrome L. *Int J Clin Pract.* 2017;71(7): e12964.

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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

Systematic reviews: Citrome L. *Int J Clin Pract*. 2017;71(11): e13030. Citrome L. *Int J Clin Pract.* 2017;71(7): e12964.

Deutetrabenazine vs. Valbenazine: NNT in Fixed-Dose Trials

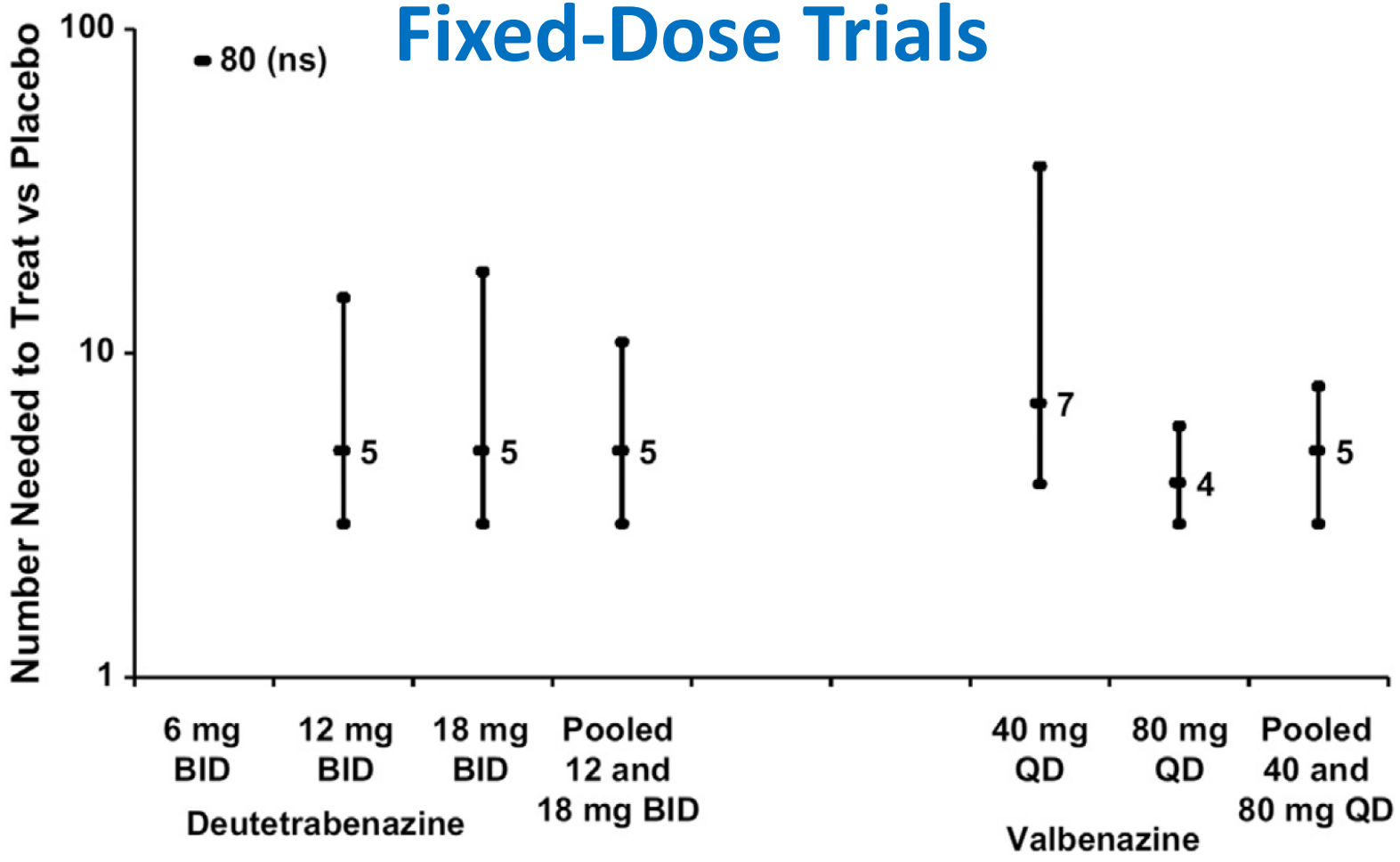
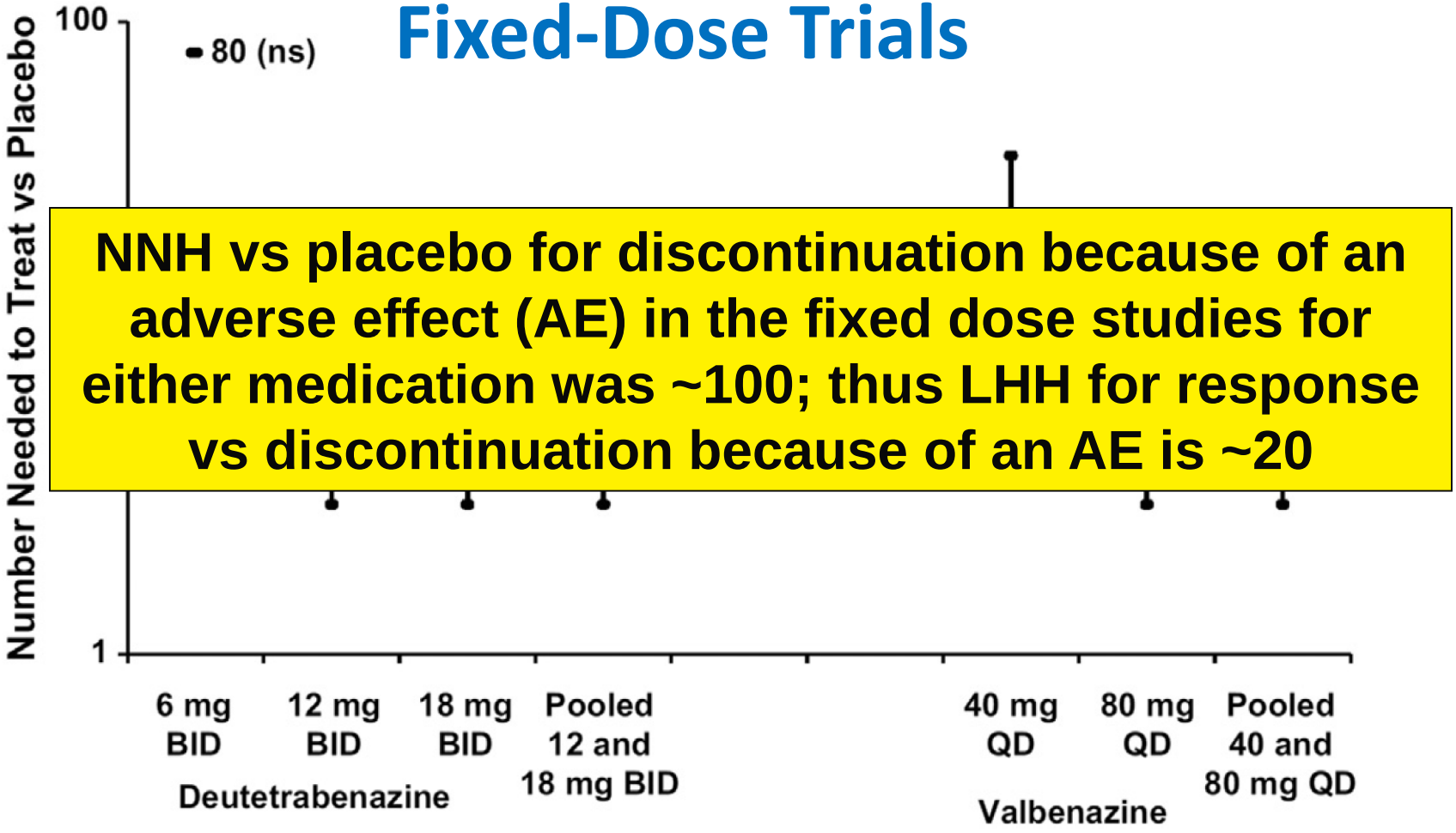


Fig. 1. ≥ 50% reduction in AIMS dyskinesia score from baseline to endpoint, NNT vs. placebo and 95% CIs, for the Phase III fixed-dose studies of deutetrabenazine (12 weeks) and valbenazine (6 weeks); reproduced with permission from [11].

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 adverse effect (AE) in the fixed dose studies for either medication was ~100; thus LHH for response vs discontinuation because of an AE is ~20

Fig. 1. ≥ 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); reproduced with permission from [11].

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%
NNH (95% CI) vs. placebo	189 (not significant)	76 (not significant)

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

Outline

- Definitions and Overview: Why Care?
- Step 1: Recognition
- Step 2: Assessment
- Step 3: Harm reduction
- Step 4: Interventions
- **Step 5: Follow-up**
- Summary

Tardive Dyskinesia: Check Your Work I

- 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

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

Tardive Dyskinesia: Check Your Work II

- Measuring the AIMS dyskinesia items alone is inadequate
- Follow up questions regarding **functional impairments** attributable to TD need to be asked (e.g., 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.

Outline

- Definitions and Overview: Why Care?
- Step 1: Recognition
- Step 2: Assessment
- Step 3: Harm reduction
- Step 4: Interventions
- Step 5: Follow-up
- **Summary**

Tardive Dyskinesia: Summary I

- **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 and effective FDA-approved treatments are available for persistent TD

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

Tardive Dyskinesia: Summary II

- 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/d 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?

citrome@cnsconsultant.com
or
nntman@gmail.com

Supplemental Slides

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 TD criteria required on only 1 post-baseline AIMS assessment.

Am J Psychiatry. 2008;193:279-288.

Treatment of TD: CATIE SGA Outcome Data

Among patients with TD at baseline treated with SGAs

- 55% met S-K criteria at two visits post-baseline
- 34% met S-K criteria at all subsequent visits
- 42% fluctuated between visits
- 24% did not meet criteria at any subsequent visit (suppressed)
- 32% showed a decrease of ≥50% in AIMS score
- Only 7% showed an increase of ≥50% in AIMS score

Caroff SN et al. *J Clin Psychiatry.* 2011;72:295-303

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	21.5 (0.7)	12.8 (0.3)	<0.0001
AIMS (total)	7.6 (0.3)	0.3 (0.02)	<0.0001
Current antipsychotic			.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

Miller DD et al. *Schizophr Res.* 2005;80:33-43.

Correlates and Risk Factors for TD

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)	078 (0.04)	<0.0001

Miller DD et al. *Schizophr Res.* 2005;80:33-43.

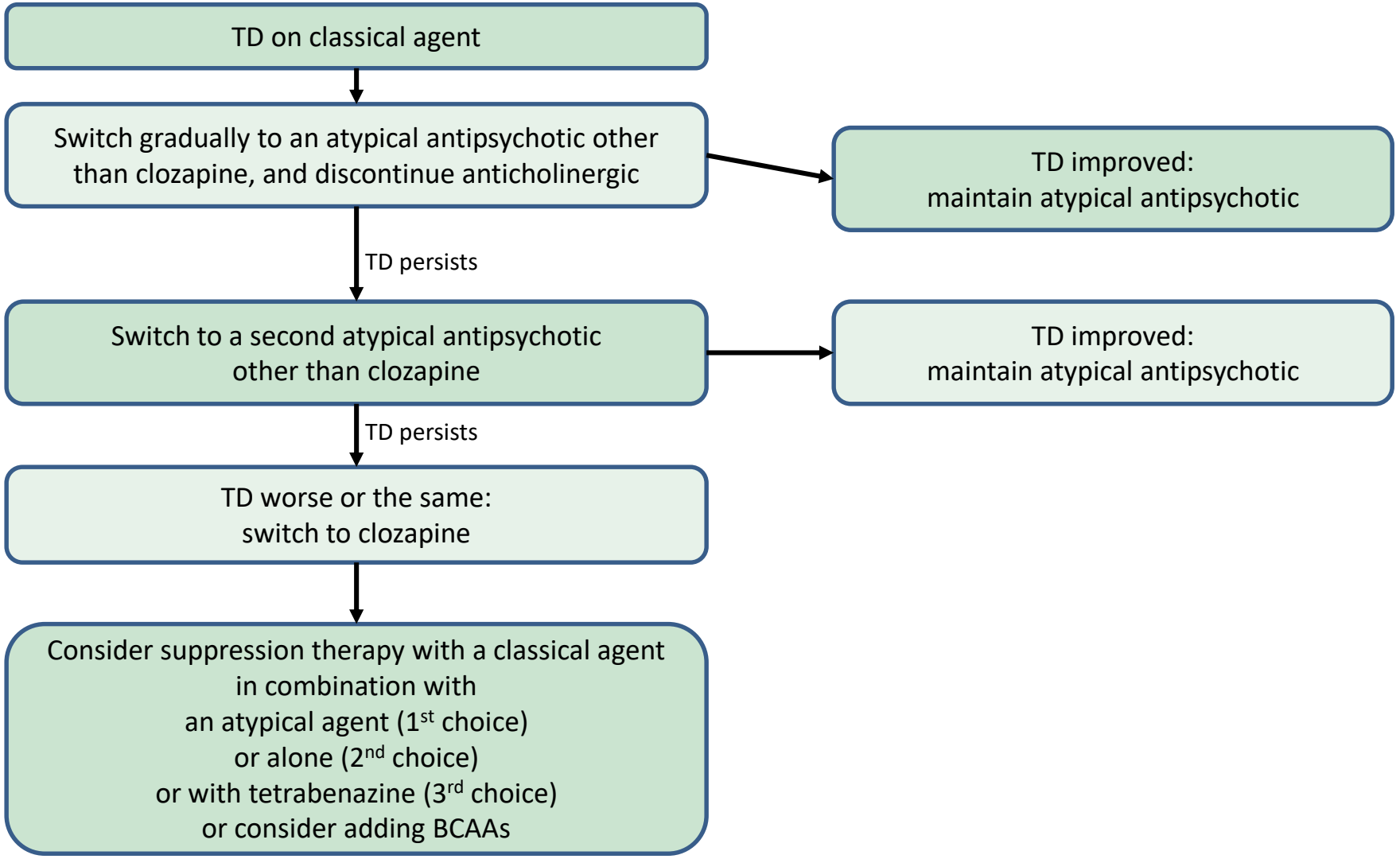
Genetics of TD

- **Receptors**
  - Dopamine: DRD2-4, SLC18A2 (VMAT-2)
  - Serotonin: 5-HT2A
  - GABAergic: SLC6A11
  - Cannabinoid: CNR1
- **Oxidative stress**
  - MnSOD, GSTM1, PIP5K2A, MTNR1A, IL10, TNFA
- **Drug metabolism**
  - CYP2D6, CYP2C19, CYP17A1
- **Miscellaneous**
  - Brain-derived neurotropic factor, adenosine A2A receptor, heparan sulfate proteoglycan 2, perlecan, dipeptidyl peptidase-like protein-6

VMAT = vesicular monoamine transporter; GABA = gamma aminobutyric acid.

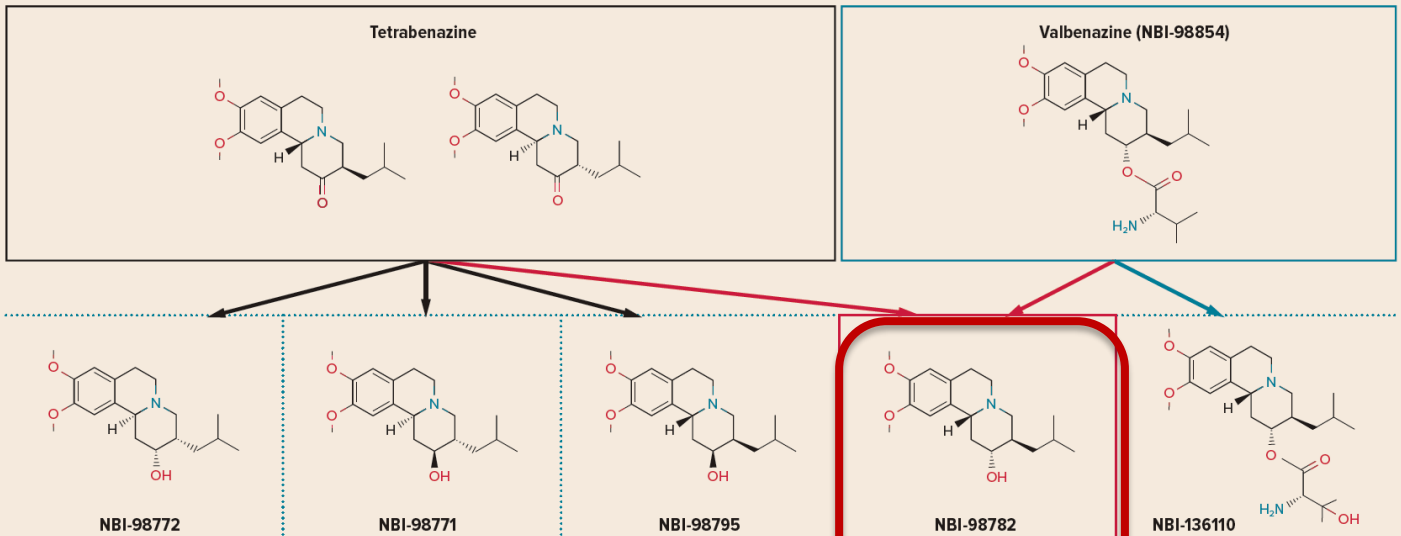
Lanning RK et al. *Pharmacogenomics.* 2016;17:1339-1351.

Tardive Dyskinesia: Management Circa 2007



Citrome L et al. *American Journal of Managed Care*. 2007;13(Suppl):1-12; Margolese HC et al. *Can J Psychiatry*. 2005;50:703-14.

Is It All About the Metabolites?

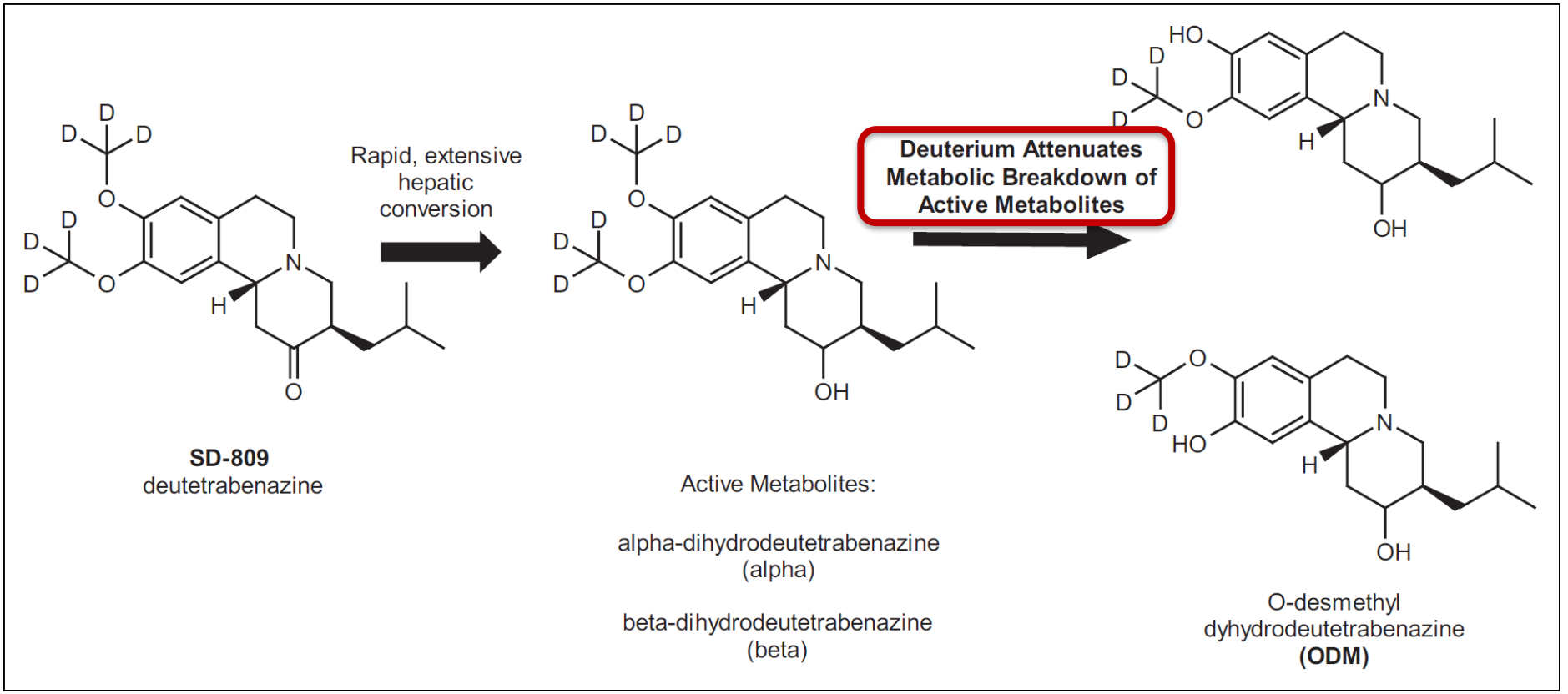


Receptor	(R,S,S)-(-)-β-DHTBZ	(S,S,S)-(-)-α-DHTBZ	(S,R,R)-(+)-β-DHTBZ	(R,R,R)-(+)-α-DHTBZ	NBI-136110
VMAT2	690 nM	250 nM	10 nM	4.2 nM	220 nM
Dopamine D_2	53 nM	180 nM	> 1000	> 1000	> 1000
Dopamine D_3	400 nM	230 nM	> 1000	> 1000	> 1000
Dopamine D_4	79 nM	> 1000	> 1000	> 1000	> 1000
Dopamine D_5	590 nM	> 1000	> 1000	> 1000	> 1000
Serotonin 5-HT_{1A}	> 1000	750 nM	> 1000	> 1000	> 1000
Serotonin 5-HT_{2B}	460 nM	600 nM	> 1000	> 1000	> 1000
Serotonin 5-HT_7	6 nM	71 nM	970 nM	> 1000	> 1000
Adrenergic α_{1A}	980 nM	> 1000	> 1000	> 1000	> 1000
Adrenergic α_{2A}	220 nM	> 1000	> 1000	> 1000	> 1000

Valbenazine itself has a K_i of 150 nM for VMAT2 with no activity at VMAT1 or other receptors, transporters or ion channels

Grigoriadis, DE, et al. *JPET*. Published April 12, 2017 as DOI: 10.1124/jpet.116.239160.

Is It All About the Pharmacokinetics?



Paton DM. *Drugs of Today.* 2017;53:89-102.