Tardive Dyskinesia (TD) Revisited: What's New?

Tardive Dyskinesia

"Late" or "Delayed"

"Abnormal movement"

Overview

- Tardive dyskinesia (TD) can be observed with long-term treatment with antipsychotic agents
- First described in 1957 by Schonecker, about five years after the commencement of neuroleptic treatment in psychiatry
- Current evidence supports a lower TD risk for second-generation antipsychotics (SGA) than for first-generation antipsychotics (FGA)
- However TD remains a significant treatment issue
- New treatment approaches to persistent TD are in development

Jankelowitz SK. *Neuropsychiatric Disease and Treatment*. 2013;9:1371-80.
Schonecker M. *Nervenarzt.*1957;28:550–3.

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
- Similar movement disorders were described before dopamine antagonist medications existed

Of note, dyskinesias can first appear after neuroleptic cessation and may disappear several weeks later; these symptoms, called withdrawal dyskinesia, reflect the action of neuroleptics to suppress or mask dyskinesia

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.
Jeste DV & Wyatt RJ. *Am J Psychiatry.* 1981;138:297-309.

Tardive Dyskinesia: Pathophysiology

- 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
  - Also contributory are possible abnormalities of striatal GABA neurons and degeneration of striatal cholinergic interneurons
  - SGAs may cause less TD because they have less impact on the basal ganglia and are less likely to cause postsynaptic dopamine hypersensitivity
- Oxidative stress created from chronic antipsychotic use
- 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.

Tardive Dyskinesia: Epidemiology

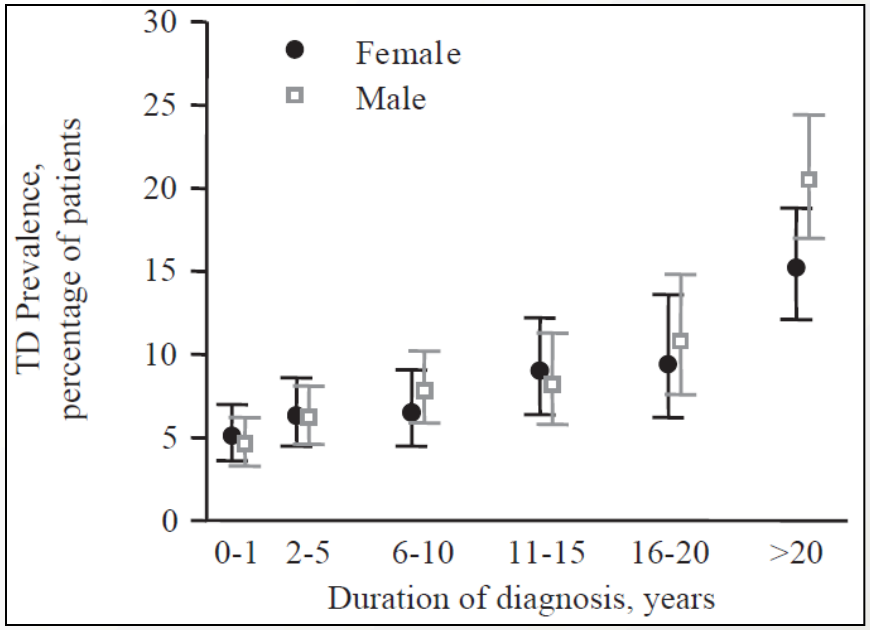
Data from Correll & Schenk (2008)	Number of Studies	Number of Patients	FGAs	SGAs
Incidence/year	12	28,051	5.5%	3.9%
Prevalence	4	2,088	32.4%	13.1%

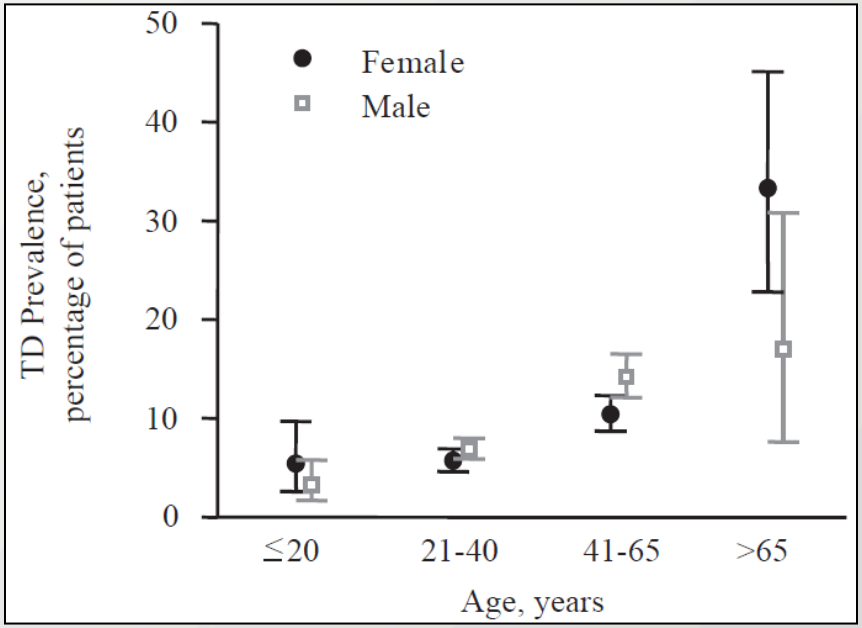
- However, in a small study of 80 non-elderly schizophrenic patients who received SGAs for >1 year without any previous exposure to FGAs, a current or history of TD and/or tardive dystonia associated with SGA was identified in 28 (35%) subjects
- In a prospective study of 352 initially TD-free outpatients, 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)
  - **The incidence and prevalence TD was similar to previous findings at this site in the 1980s**

Correll CU & Schenk EM. *Curr Opin Psychiatry*. 2008;21:151-6.
Ryu S et al. *J Clin Psychopharmacol*. 2015;35:13-21.
Woods SW et al. *J Clin Psychiatry*. 2010;71:463-74.

Tardive Dyskinesia: Epidemiology

- Similar results around the world: outpatients with schizophrenia from Africa and the Middle East, Asia, Central and Eastern Europe, and Latin America





Kasper S et al. *Schizophrenia Research*. 2006; 81:139-43.

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]

Citrome L et al. *American Journal of Managed Care*. 2007;13(Suppl):1-12.

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

- Observer-rated 12-item anchored scale that takes 5-10 minutes
- 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

		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 et al. *American Journal of Managed Care*. 2007;13(Suppl):1-12.

Abnormal Involuntary Movement Scale (AIMS): Caveats

- Volitional or psychotic mannerisms, tics, and drug-induced parkinsonism must be distinguished from TD and can coexist with TD in the same patients
- 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
- Clinicians should be vigilant because patients may not complain of TD symptoms; many are unaware of their own dyskinesias
- Even with routine, careful examination, TD can be difficult to detect early, because the antipsychotic agents that cause the underlying pathology can also mask the emergence of symptoms

Citrome L et al. *American Journal of Managed Care*. 2007;13(Suppl):1-12.
Khouzam HR. *Postgrad Med*. 2015;127:726-37.

Tardive Dyskinesia: Lack of Awareness is Common

- 607 patients in a state mental hospital in Singapore were assessed using the 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.

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

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

1. Ask the patient to remove shoes and socks
2. Ask the patient whether there is anything in his/her mouth (e.g., gum, candy, etc.) and if there is, to remove it
3. 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?
4. 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
5. Have the patient sit in a hard chair with hands on her/his knees, legs slightly apart, and feet flat on the floor
   - Look at entire body for movements while in this position

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

6. 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
7. Ask the patient to open her/his mouth
   - Observe tongue at rest within mouth
   - Do this twice
8. Ask the patient to protrude her/his tongue
   - Observe abnormalities of tongue in movement
   - Do this twice
* 9. 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

*Activated movements

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

10. Flex and extend the patient's left and right arms (one at a time)
    - Note any rigidity and rate on separate scale if applicable
11. Ask the patient to stand up
    - Observe in profile
    - Observe all body areas again, hips included

*12. Ask the patient to extend both arms outstretched in front with palms down
    - Observe trunk, legs, and mouth

*13. Have the patient walk a few paces, turn, and walk back to chair
    - Observe hands and gait
    - Do this twice

*Activated movements

Abnormal Involuntary Movement Scale (AIMS): Rating Facial and Oral Movements

For ratings, use the highest severity observed.
0=None; 1=Minimal, may be extreme normal;
2=Mild; 3=Moderate; 4=Severe

1. Muscles of Facial Expression:
   - Movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing
2. Lips and Perioral Area:
   - Puckering, pouting, smacking
3. Jaw:
   - Biting, clenching, chewing, mouth opening, lateral movement
4. Tongue:
   - Rate only increases in movement both in and out of mouth, NOT inability to sustain movement

Abnormal Involuntary Movement Scale (AIMS): Rating Extremity and Trunk Movements

For ratings, use the highest severity observed.
0=None; 1=Minimal, may be extreme normal;
2=Mild; 3=Moderate; 4=Severe

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).
6. Lower (legs, knees, ankles, toes):
   - E.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot
7. Neck, shoulders, hips:
   - E.g., rocking, twisting, squirming, pelvic gyrations

Abnormal Involuntary Movement Scale (AIMS): Global Judgements

For ratings, use the highest severity observed.
0=None; 1=Minimal, may be extreme normal;
2=Mild; 3=Moderate; 4=Severe

8. Severity of abnormal movements
9. Incapacitation due to abnormal movements
10. Patient's awareness of abnormal movements (rate only patient's report)

Abnormal Involuntary Movement Scale (AIMS): Dental Status

11. Current problems with teeth and/or dentures? Y N
12. Does patient usually wear dentures? Y N

Schooler-Kane Criteria

- By itself, the AIMS examination does not diagnose TD
- In 1982 Schooler and Kane developed 3 diagnostic criteria for TD:
  1. At least 3 months of cumulative antipsychotic drug exposure
  2. Presence of at least moderate abnormal involuntary movements in 1 or more body area(s) or mild movements in 2 or more body areas
     - Using the AIMS scoring at least 3 (moderate) in ≥1 area, or at least 2 (mild) in ≥2 areas
  3. Absence of other conditions that might produce involuntary movements.
- An alternative definition for TD is the Glazer-Morgenstern criteria: AIMS total score >3, with at least 1 body area rated >2, at two successive visits

Schooler NR, Kane JM. *Arch Gen Psychiatry*. 1982;39:486-7;
Morgenstern H & Glazer WM. *Arch Gen Psychiatry*. 1993;50:723-33.

Tardive Dyskinesia: Continued Concern

- Thousands of patients are left with TD as a legacy of past treatment
- The pathophysiology of TD is not well understood
- TD, once established, has proved to be irreversible in most cases
- 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.

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

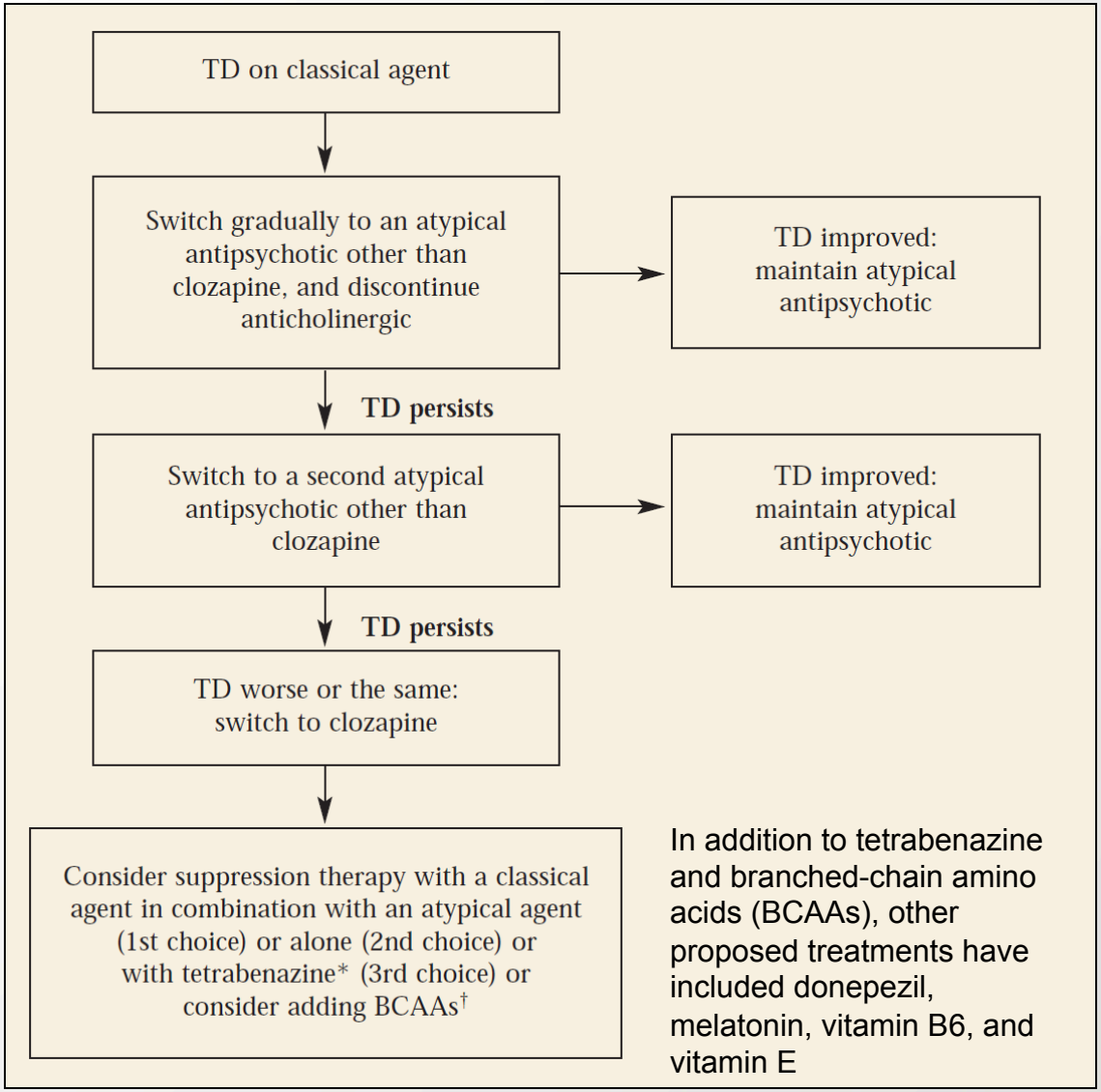
Caroff SN et al. *Current Psychiatry*. 2011;10(10): 23-32.

Tardive Dyskinesia: Risk Factors to Consider

- Risk factors for TD include female sex, older age, higher drug dose, long-term treatment, 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**
- 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)
- 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.

Tardive Dyskinesias: Management



In addition to tetrabenazine and branched-chain amino acids (BCAAs), other proposed treatments have included donepezil, melatonin, vitamin B6, and vitamin E

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.

Tardive Dyskinesia Treatments: 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.

Tardive Dyskinesia: Off-Label Treatments

Drug	Possible dosage	Common side effects
Tetrabenazine	12.5 mg twice daily titrated to a maximum of 150 mg/d in 2 or 3 divided doses	Somnolence, insomnia, depression, and akathisia
Reserpine	≥0.25 mg 4 times daily, to 8 mg/d	Depression, diarrhea, dizziness, somnolence
Vitamin E	400 units/d to 1,600 units/d	Dosages >3,000 units can cause symptoms of hypervitaminosis, which include nausea, weakness, and intestinal cramps
Melatonin	2 to 10 mg daily for 4 to 6 weeks	Drowsiness
Vitamin B_6	100 to 400 mg/d for 4 to 8 weeks	Sensory neuropathic syndromes
Donepezil	5 to 10 mg/d for 6 weeks	Nausea, diarrhea, insomnia, fatigue, vomiting
Medications are in order by most recent evidence		

- Other off-label interventions found to be potentially helpful as per the American Academy of Neurology include clonazepam and ginkgo biloba, as well as possibly amantadine
  - Found *not* helpful were diltiazem, galantamine and eicosapentaenoic acid
- Surgical interventions are a last resort: deep brain stimulation of globus pallidus interna and lesioning surgeries like pallidotomy

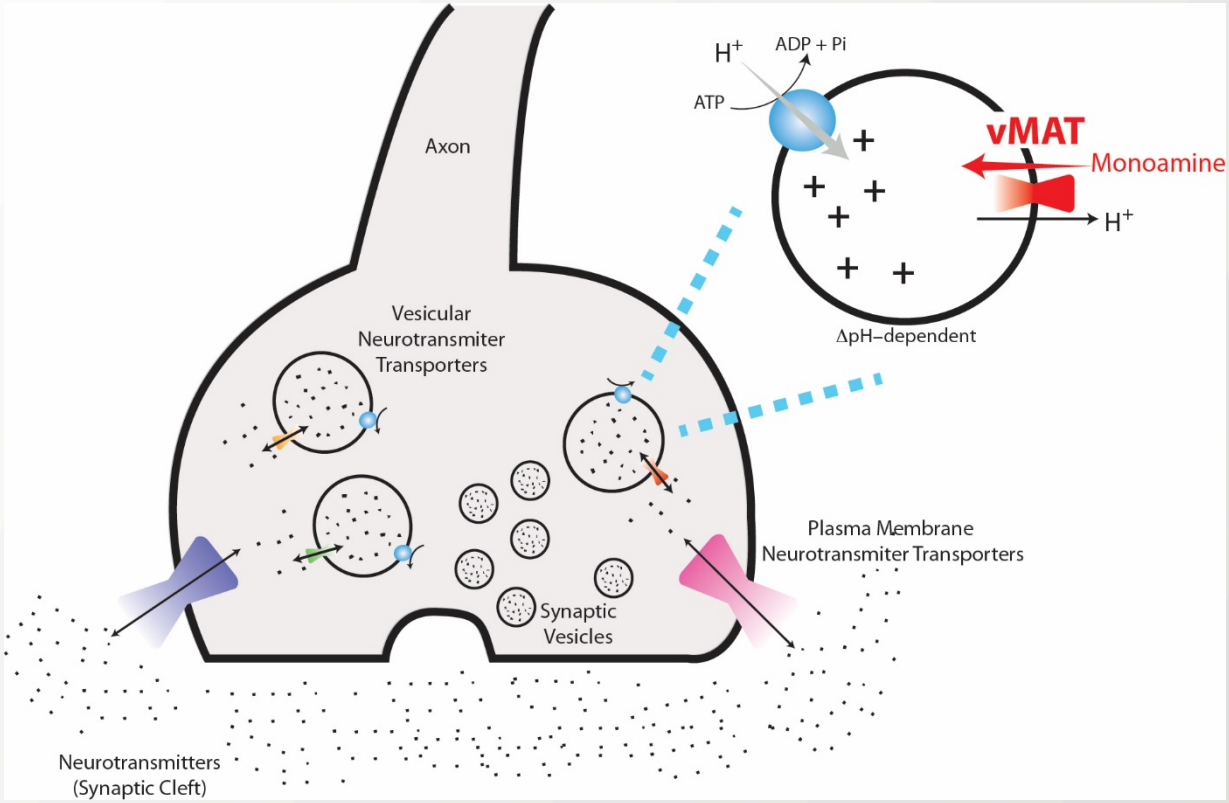
Kaspar R & Ellingrod VL. *Current Psychiatry.* 2014;13(3):44-6.
Bhidayasiri R et al. *Neurology.* 81:463-9.
Kim J et al. *Drugs in Context*. 2014;3:212259.

Tetrabenazine

- Tetrabenazine was approved in 2008 as an orphan drug for the treatment of choreiform movements associated with Huntington's Disease
  - Launched at $34.25 for a 12.5 mg tablet and $68.50 for a 25 mg tablet
- Tetrabenazine is a reversible and specific inhibitor of vesicular monoamine transporter-2 (VMAT-2), a transporter that packages neurotransmitters (preferentially dopamine) into vesicles for release into the synapse
- Tetrabenazine is the current treatment of choice 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;45:525-31.
Citrome L. *Current Psychiatry*. 2014;13(5):24.

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

Tetrabenazine: Limitations

- Short serum 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
  - The two derivatives of β-tetrabenazine are antagonists at the dopamine D2 receptor and can induce sedation and parkinsonism; side effects are more pronounced in the presence of CYP2D6 inhibitors
- The FDA label for tetrabenazine carries a boxed bolded warning for depression and suicide risk

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.

Deutetrabenazine (SD-809)
A Better Tetrabenazine ?

- The incorporation of deuterium in place of hydrogen at the sites of primary metabolism results in metabolic clearance being slowed, allowing less frequent dosing (BID vs. TID) with lower C_{max} values occurring after each dose (because a smaller dose will suffice to provide continuous exposure), and the combination of lower C_{max}, less dramatically fluctuating serum levels, and less rapid rise after a dose will provide better tolerability
- Comparable drug exposure with half the dose of tetrabenazine
- Breakthrough Therapy Designation from the FDA for the treatment of TD
- Also being studied for Huntington Disease and Tourette Syndrome

Stamler D. *Auspex Pharmaceuticals*. June 22, 2013. www.auspexpharma.com/wp-content/uploads/2013/12/D-Stamler-Auspex-HDSA-2013-0621-FINAL.pdf.
Teva Pharmaceutical Industries Ltd. http://www.tevapharm.com/news/teva_announces_breakthrough_therapy_designation_for_sd_809_granted_by_fda_for_the_treatment_of_tardive_dyskinesia_11_15.aspx.
Stamler D, et al. *Movement Disorders*. 2013;28(Suppl1):S271-2.

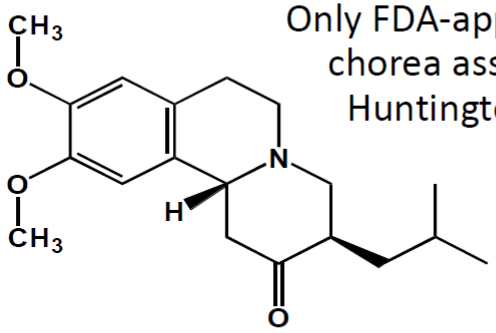
Deutetrabenazine

- Deuterium is a stable, non-radioactive, non-toxic, and naturally occuring isotope of hydrogen to design improved variations of existing drugs
  - We all have about 1-2 gm of deuterium in our bodies
- It has the same size and shape as a hydrogen atom, and differs only in forming very slightly stronger chemical bonds
- The removal of a hydrogen atom attached to a carbon atom is the first and rate-limiting step in the metabolism of many drugs
  - If the hydrogen that is removed in the first step of the metabolic process is replaced by deuterium, the metabolic process is slowed by a factor of up to 8-fold

Stamler D. *Auspex Pharmaceuticals*. June 22, 2013. www.auspexpharma.com/wp-content/uploads/2013/12/D-Stamler-Auspex-HDSA-2013-0621-FINAL.pdf.
Auspex Pharmaceuticals. December 2014. http://files.shareholder.com/downloads/AMDA-2IEHYZ/0x0x797219/01a86e01-44d4-4ee0-9fb2-69537c486954/Piper%20Jaffray%20Presentation%2012-2-14.pdf
Zacks Small-Cap Research. November 12, 2014. http://s1.q4cdn.com/460208960/files/ASPX_Initiation-Report-November-2014_Napodano_v001_s99ij4.pdf

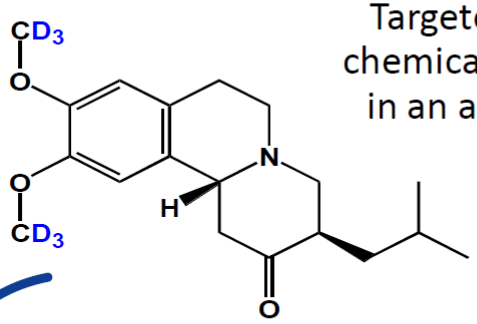
Deutetrabenazine

XENAZINE® (Tetrabenazine)



Only FDA-approved drug for chorea associated with Huntington's disease

SD-809 (Deutetrabenazine)

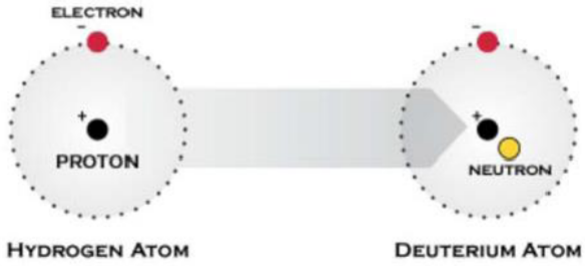


Targeted deuterium chemical modifications in an approved drug

DEUTERIUM

What is it?

A non-toxic, naturally occurring form of hydrogen (H) with twice the molecular weight.



Advantages of D Substitution:

- No change in shape, size, charge, or target pharmacology of small molecules
- Can improve PK: 8x stronger C-D bond attenuates metabolism and increases half life
- Confers several potential advantages
  - Less frequent dosing
  - Reduced interpatient variability in drug metabolism
  - Improved tolerability
  - Reduced drug interactions
  - Reduced genotyping

Auspex Pharmaceuticals. December 2014. http://files.shareholder.com/downloads/AMDA-2IEHYZ/0x0x797219/01a86e01-44d4-4ee0-9fb2-69537c486954/Piper%20Jaffray%20Presentation%2012-2-14.pdf.

Deutetrabenazine for TD
Phase II/III Trial (ARM-TD, NCT02195700)

- Randomized, double-blind, placebo-controlled, parallel-group study of 117 patients globally (104 patients completed the study) with moderate to severe TD
- Enrolled patients received either SD-809 or placebo, twice daily, titrated to optimal dosage over the course of 6 weeks, and then administered at that dose for another 6 weeks for a total treatment of 12 weeks
- The primary efficacy endpoint was the change in AIMS from baseline at week 12 scored by blinded, central video raters
  - The study results show patients taking deutetrabenazine achieved an improvement of 3.0 points on the AIMS score from baseline to end of therapy compared to 1.6 points in placebo ($p = 0.0188$)
  - Study results also demonstrated a favorable safety and tolerability profile of deutetrabenazine, including low rates of depression, somnolence, insomnia and akathisia

Teva Pharmaceutical Industries Ltd. June 16, 2015. http://www.businesswire.com/news/home/20150616005822/en/Teva-Advances-Pipeline-Movement-Disorder-Assets-Announcement.

Deutetrabenazine for TD
Phase III Trials in Progress

- AIM-TD (NCT02291861): Randomized, double-blind, placebo-controlled, fixed-dose, parallel-group study patients with moderate to severe TD
  - Enrolled patients to receive either SD-809 12, 24, or 36 mg or placebo, twice daily for 12 weeks; dose titrated for 4 weeks to target randomized dose and then dose is maintained for an additional 8 weeks
  - The primary efficacy endpoint is change in AIMS from baseline at week 12
- RIM-TD (NCT02198794): Open-label, 54-week safety study in patients with moderate to severe TD
  - Dose titrated for 6 weeks until optimal dose is reached and then dose is maintained for the duration of the study

ClinicalTrials.gov. Jan 31, 2016. https://clinicaltrials.gov/ct2/show/NCT02291861.
ClinicalTrials.gov. Jan 13, 2016. https://clinicaltrials.gov/ct2/show/NCT02198794.

Valbenazine

- A novel, highly selective, vesicular monoamine transporter 2 inhibitor
- Orally active compound with 2 active metabolites, NBI-98782 and NBI-136110, all three have VMAT2 binding
- Designed to deliver the active metabolites in a controlled fashion
- Designed to limit off-target receptor binding
- Half life of 20 hours allowing QD dosing

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine

- The hypothesis is that dosing parent molecule with a highly selective and potent active metabolite will result in both reduced pharmacokinetic variability and improved safety profile
- Breakthrough Therapy Designation from the FDA for the treatment of TD
- Results of 3 studies available (KINECT 1, Phase II study, press releases; KINECT 2, Phase II study, published; KINECT 3, Phase III study, press releases)
- Also being studied in Tourette syndrome

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase II Trial (KINECT 1, NCT01688037)

- 6-week, double-blind, placebo-controlled study
- 109 male and female adult subjects with moderate or severe tardive dyskinesia were randomized
- One cohort took 50 mg valbenazine for 6 weeks and the other group received 100 mg in the first 2 weeks, then the patients were down titrated to 50 mg for the final 4 weeks of this study
- The primary study end point was a comparison of placebo versus valbenazine effects on the AIMS scores at the end of week 6
  - 50 mg did not significantly improve AIMS scores
  - 100 mg reduced symptoms, when scored via a blinded central video AIMS assessment at the end of the 100 mg dosing interval

Muller T. *Expert Opin Investig Drugs*. 2015;14:737-42.

Valbenazine for TD
Phase II Trial (KINECT 2, NCT01733121)

- 6-week, double-blind, placebo-controlled, dose-titration study
- 102 male and female adult subjects with moderate or severe tardive dyskinesia were randomized
- Valbenazine or placebo was given once per day starting at 25 mg and then escalated by 25 mg to a maximum of 75 mg based on dyskinesia and tolerability assessment
  - 76% of valbenazine subjects and 80% of placebo subjects reached the maximum allowed dose
- The primary efficacy endpoint was the change in AIMS from baseline at week 6 scored by blinded, central video raters

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase II Trial (KINECT 2)

TABLE 2. AIMS change from baseline at week 6 (mITT)

	Placebo (n = 44)	NBI-98854 (n = 45)
Mean (SD)	−1.1 (3.7)	−3.6 (3.5)
Median	−0.5	−3.0
LS mean (SEM)[a]	−0.2 (1.1)	−2.6 (1.2)
95% Confidence interval	(−2.4, 2.0)	(−4.9, −0.3)
LS mean difference (SEM)	−2.4 (0.7)	
95% Confidence interval	(−3.7, −1.1)	
p-value	0.0005	

[a]Least-squares (LS) mean (standard error of the mean [SEM]) based on the analysis of covariance (ANCOVA) model using the modified intent-to-treat (mITT) set, with baseline AIMS dyskinesia total score value as a covariate and treatment group and disease category as fixed effects.
Abbreviations: AIMS, Abnormal Involuntary Movement Scale; SD, standard deviation.

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase II Trial (KINECT 2)

Categorical Outcome	Placebo (n=44)	Valbenazine (n=45)	NNT (95% CI)
Responder rate (≥50% improvement in AIMS from baseline)	8 (18.2%)	22 (48.9%)	**4 (2-9)**
CGI-TD response: "Very much improved" or "Much Improved"	7 (15.9%)	30 (66.7%)	**2 (2-3)**
PGIC response: "Very much improved" or "Much improved"	14 (31.8%)	26 (57.8%)	**4 (3-17)**

Abbreviations: AIMS, abnormal involuntary movement scale; CGI-TD, Clinical Global Impression of Change–TD scale; CI, confidence interval; NNT, number needed to treat; PGIC, Patient Global Impression of Change

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase II Trial (KINECT 2)

TABLE 4. Incidence of treatment-emergent adverse events experienced by ≥2 subjects

Adverse Event	Placebo (n = 49) n (%)	NBI-98854 (n = 51) n (%)
Fatigue	2 (4.1%)	5 (9.8%)
Headache	2 (4.1%)	5 (9.8%)
Decreased appetite	0	4 (7.8%)
Nausea	2 (4.1%)	3 (5.9%)
Somnolence	1 (2.0%)	3 (5.9%)
Dry mouth	0	3 (5.9%)
Vomiting	0	3 (5.9%)
Constipation	3 (6.1%)	2 (3.9%)
Urinary tract infection	3 (6.1%)	2 (3.9%)
Sedation	1 (2.0%)	2 (3.9%)
Back pain	0	2 (3.9%)
Dizziness	2 (4.1%)	0

O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase III Trials (KINECT 3 and 4)

- KINECT 3 (NCT02274558): randomized, double-blind, placebo-controlled, parallel, fixed-dose study of valbenazine 40 and 80 mg in 234 moderate to severe TD patients with schizophrenia, schizoaffective disorder, bipolar or major depressive disorder
  - Double-blind, placebo-controlled, treatment period for 6 weeks
  - Double-blind, valbenazine treatment period for additional 42 weeks
  - The primary efficacy endpoint was the change in AIMS from baseline at week 6 in the 80 mg once-daily dosing group compared to placebo as assessed by central blinded video raters
    - AIMS ratings was reduced 3.1 points more than placebo ($p<0.0001$)
    - Both 40 mg and 80 mg superior to PBO on AIMS and CGI-TD
- KINECT 4 (NCT02405091): A separate open-label study to evaluate the safety and tolerability of valbenazine administered once daily for a total of 48 weeks of treatment is in progress

PR Newswire. Oct 8, 2015. http://www.prnewswire.com/news-releases/neurocrine-announces-positiv
results-from-phase-iii-kinect-3-study-of-nbi-98854-in-tardive-dyskinesia-300156384.html.
ClinicalTrials.gov. Jan 7, 2016. https://clinicaltrials.gov/ct2/show/study/NCT02405091

Tardive Dyskinesia: Summary

- Prevent if possible
- Screen with scheduled AIMS exams, especially in the older population
- TD is still common
- Treat as quickly as possible after it appears
- Reliable, effective, and now well tolerated, treatments are being developed for persistent TD