Tardive Dyskinesia: New Treatments for an Old Ailment

ARS PRE QUESTIONS

Tardive Dyskinesia: New Treatments for an Old Ailment

Learning Objectives

- Discuss the diagnosis and prevalence of Tardive Dyskinesia (TD).
- Implement evidence based management strategies for TD, including innovative treatments.

Overview

- Phenomenology and Etiology
- Differential Diagnosis
- Prevalence and Incidence
- Assessment
- Treatment
- Summary and Conclusions

Phenomenology and Etiology

Background

- Tardive dyskinesia (TD) is a syndrome characterized by persistent involuntary choreoathetoid movements of the tongue, lips, face, trunk, and extremities developing after long-term treatment with dopamine-DAD2 blocking (e.g., antipsychotic) agents
- Current evidence supports a lower, but non-zero, TD risk with second-generation antipsychotics (SGA) than with first-generation antipsychotics (FGA)
- However TD remains a significant treatment issue
- The Abnormal Involuntary Movement Scale (AIMS) is the accepted screening and measurement tool for TD

Waln O, Jankovic J. *Tremor Other Hyperkinet Mov (N Y)*. 2013; 3: tre-03-161-4138-1.

Tardive Dyskinesias 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 (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.

Differential Diagnosis

Tardive Dyskinesia Diagnosis

- In typical cases, TD is characterized by involuntary, repetitive orofacial movements, often accompanied by choreiform movements of the upper extremities.
  - Screen regularly with AIMS scale for the presence of suspicious movements
- Other tardive syndromes, such as dystonia, akathisia, tics, tremor, or myoclonus, may occur alone or co-exist with the dyskinetic movements.
  - Thus, diagnose TD
    - based on movement disorder symptoms
    - based on Temporal association with antipsychotic exposure
    - After consideration of other etiologies!!!

Tardive Dyskinesia Diagnosis

- In typical cases, TD characterized by involuntary, **repetitive orofacial movements**, often accompanied by choreiform movements of the upper extremities.
- Diagnose with confidence if you see:
  - Tongue protrusions, fly catcher tongue.
  - Isolated smacking, puckering
  - Mouth/jaw opening, closing, lateral movements
- Think twice if you see:
  - Any severe or rapidly evolving syndrome
  - Vivid piano player movements only
  - Localized, fixed dystonia only
  - Isolated dyskinesia of lower body
- …and if you cannot work out the time sequence of psychiatric symptoms, antipsychotic exposure and movement disorder

FIRST VIDEO HERE

Tardive Syndromes
– Think outside of the box-

- Copulatory Dyskinesia
- Respiratory Dyskinesia
- Retrocollis and other localized dystonias
- Axial Dystonia
- Tardive Tourette
- Tardive Akathisia
- …….almost any involuntary / abnormal movement, which developed in temporal association with antipsychotic exposure
- BUT not all abnormal movements in patients receiving antipsychotic medication are tardive dyskinesia

Tardive Syndromes: Syndromal Differential Diagnosis

- Mannerisms (semi-purposeful movements)
- Stereotypies (repetitive complex movements)
- Tics (quick, repetitive movements)
- Myoclonus (quick, may be irregular)
- Dystonias (sustained or repetitive muscle contraction)
- Fasciculations (high frequency movements, e.g., of tongue)
- Mirror movements (contralateral movements upon activation, e.g. of fingers)

Tardive Syndromes: Diagnostic Differential Diagnosis

- Chorea
  - Morbus Huntington (age: 25-50 years, begins with psychiatric symptom (depression, suicidality, impulsivity)
  - Sydenham's Chorea (youth, post-streptococcal infection (<6 months), concomitant OCD, impulsivity, ADHD, depression possible, duration: 5-15 weeks)
  - Benign familial Chorea (Chromosome 14, no overt psychiatric symptoms)
  - Metabolic (uremia, hypo/hyper Na, hypo/hyper parathyreoidism)
  - Inflammatory (HSV, Varicella, MMR, etc,)
  - Lupus erythematodes (sudden onset chorea, with psychiatric symptoms)
  - Substance-induced (antipsychotics, anticholinergics, antiepileptics, psychostimulants (amphetamine, methcathinone, methylphenidate), methadone, steroids, manganese, toluene, aluminum)

Prevalence and Incidence

TD Prevalence Meta-Analysis

- 41 studies: n=11,493, mean age=42.8 years, male=66.4%, schizophrenia-spectrum disorders=77.1%
- The global mean TD prevalence was 25.3% (95%CI=22.7-28.1%).
- Rates were lower with current SGA treatment (20.7%; 95%CI=16.6-25.4%, N=5,103) vs. current FGA treatment (30.0%; 95%CI=26.4-33.8%, N=5,062; p=0.002).
- Lower TD prevalence of SGA relative to FGA was also confirmed in the subgroup of studies assessing and directly comparing ≥2 antipsychotic classes/combinations:
  - SGAs vs. FGAs (risk ratio=0.80; 95%CI=0.67-0.95, p=0.011);
  - SGAs vs. FGA+SGA (risk ratio=0.80, 95%CI=0.71-0.90, p<0.001).
- TD prevalence with SGAs was especially low in the 4 studies reporting on patients without prior FGA treatment: 7.2%
- Moderators of TD in the prevalence meta-analysis: older age, longer illness duration, early EPS, African-American ethnicity

Carbon M et al. *J Clin Psychiatry* - in press

TD Incidence Meta-Analysis: FGAs vs SGAs

- 26 studies: n=9,157, mean age=38.7 years, male=65.1%, schizophrenia-spectrum disorders=23 of 26 studies, mean follow-up duration: 1.6 years
- Treatment-emergent TD with SGAs: 2.2% in 4380 person years
- Treatment-emergent TD with FGAs: 6.3% in 1982 person years
- Annualized TD rates were lower with SGAs relative to FGAs (rate ratio (RR)=0.37;
- CI=0.28-0.48; p<0.0001)
- The dose of the FGA comparator (below vs. above 500mg chlorpromazine equivalent), did not significantly moderate this difference (p=0.29)
- FGA-SGA TD rate ratios did not differ between SGA subgroups and persisted independently within each subgroup (all comparisons p<0.01)
- Moderator analyses for age, sex, illness duration, study region and anticholinergic use were non-significant.

Correll CU, et al, oral presentation at the ICOSR meeting, San Diego, March 24-28, 2017

TD in the Elderly: FGAs

- The cumulative rates of tardive dyskinesia were 25%, 34%, and 53% after 1, 2, and 3 years of cumulative antipsychotic treatment in a group of 261 neuroleptic-naive patients aged 55 or above identified at the time they were starting antipsychotic drug treatment
- A greater risk of tardive dyskinesia was associated with history of ECT treatment, higher mean daily and cumulative antipsychotic doses, and presence of extrapyramidal signs early in treatment
- Tardive dyskinesia rates for patients beginning treatment with conventional antipsychotics in their fifth decade or later are three to five times what has been found for younger patients, despite treatment with lower doses

Woerner M et al. *Am J Psychiatry*. 1998 Nov;155(11):1521-8.

TD in the Elderly: SGAs

Neuropsychopharmacology (2011), 1–9

www.neuropsychopharmacology.org

Incidence of Tardive Dyskinesia with Risperidone or Olanzapine in the Elderly: Results from a 2-Year, Prospective Study in Antipsychotic-Naïve Patients

Margaret G Woerner[1], Christoph U Correll[1,2], Jose Ma J Alvir[3], Blaine Greenwald[1,2], Howard Delman[1] and John M Kane*[1,2]

[1]The Zucker Hillside Hospital, North Shore—Long Island Jewish Health System, Glen Oaks, NY, USA; [2]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA; [3]Pfizer Pharmaceuticals, New York, NY, USA

Tardive dyskinesia (TD) rates with second-generation antipsychotics (SGAs) are considered to be low relative to first-generation antipsychotics (FGAs), even in the particularly vulnerable elderly population. However, risk estimates are unavailable for patients naïve to FGAs. Therefore, we aimed to determine the TD incidence in particularly vulnerable, antipsychotic-naïve elderly patients treated with the SGA risperidone or olanzapine. The present work describes a prospective inception cohort study of antipsychotic-naïve elderly patients aged ⩾55 years identified at New York Metropolitan area in-patient and out-patient geriatric psychiatry facilities and nursing homes at the time of risperidone or olanzapine initiation. At baseline, 4 weeks, and at quarterly periods, patients underwent assessments of medical and medication history, abnormal involuntary movements, and extra-pyramidal signs. TD was classified using Schooler–Kane criteria. Included in the analyses were 207 subjects (age: 79.8 years, 70.0% female, 86.5% White), predominantly diagnosed with dementia (58.9%) or a major mood disorder (30.9%), although the principal treatment target was psychosis (78.7%), with (59.4%) or without (19.3%) agitation. With risperidone ($n = 159$) the cumulative TD rate was 5.3% (95% confidence interval (CI): 0.7, 9.9%) after 1 year (mean dose: 1.0 ± 0.76 mg/day) and 7.2% (CI: 1.4, 12.9%) after 2 years. With olanzapine ($n = 48$) the cumulative TD rate was 6.7% (CI: 0, 15.6%) after 1 year (mean dose: 4.3 ± 1.9 mg/day) and 11.1% (CI: 0, 23.1%) after 2 years. TD risk was higher in females, African Americans, and patients without past antidepressant treatment or with FGA co-treatment. The TD rates for geriatric patients treated with risperidone and olanzapine were comparable and substantially lower than previously reported for similar patients in direct observation studies using FGAs. This information is relevant for all patients receiving antipsychotics, not just the especially sensitive elderly.

Neuropsychopharmacology advance online publication, 20 April 2011; doi:10.1038/npp.2011.55

Assessment

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

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

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)
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

*Activated movements

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

*Activated movements

Second Video Here

Abnormal Involuntary Movement Scale (AIMS) Scoring

- Score the highest amplitude or frequency in a movement on the 0-4 scale, not the average
- Score Activated Movements the same way; do not lower those numbers as was proposed at one time
- A POSITIVE AIMS EXAMINATION IS A SCORE OF 2 IN TWO OR MORE BODY REGIONS or a SCORE OF 3 OR 4 IN A SINGLE BODY REGION

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

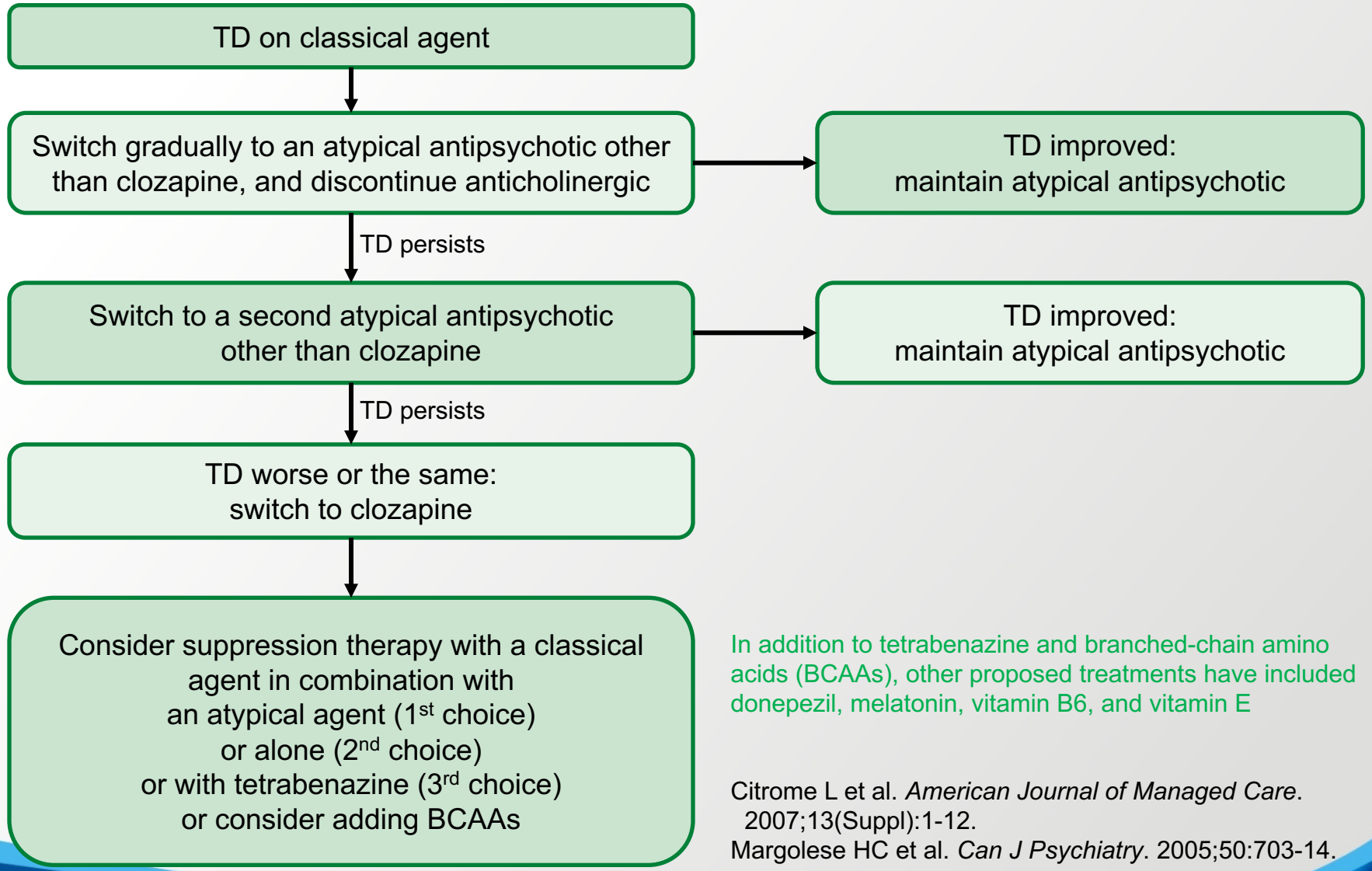
Classifying TD: Schooler-Kane Criteria

- 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.

Treatment

Tardive Dyskinesia: Management Circa 2007



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: 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

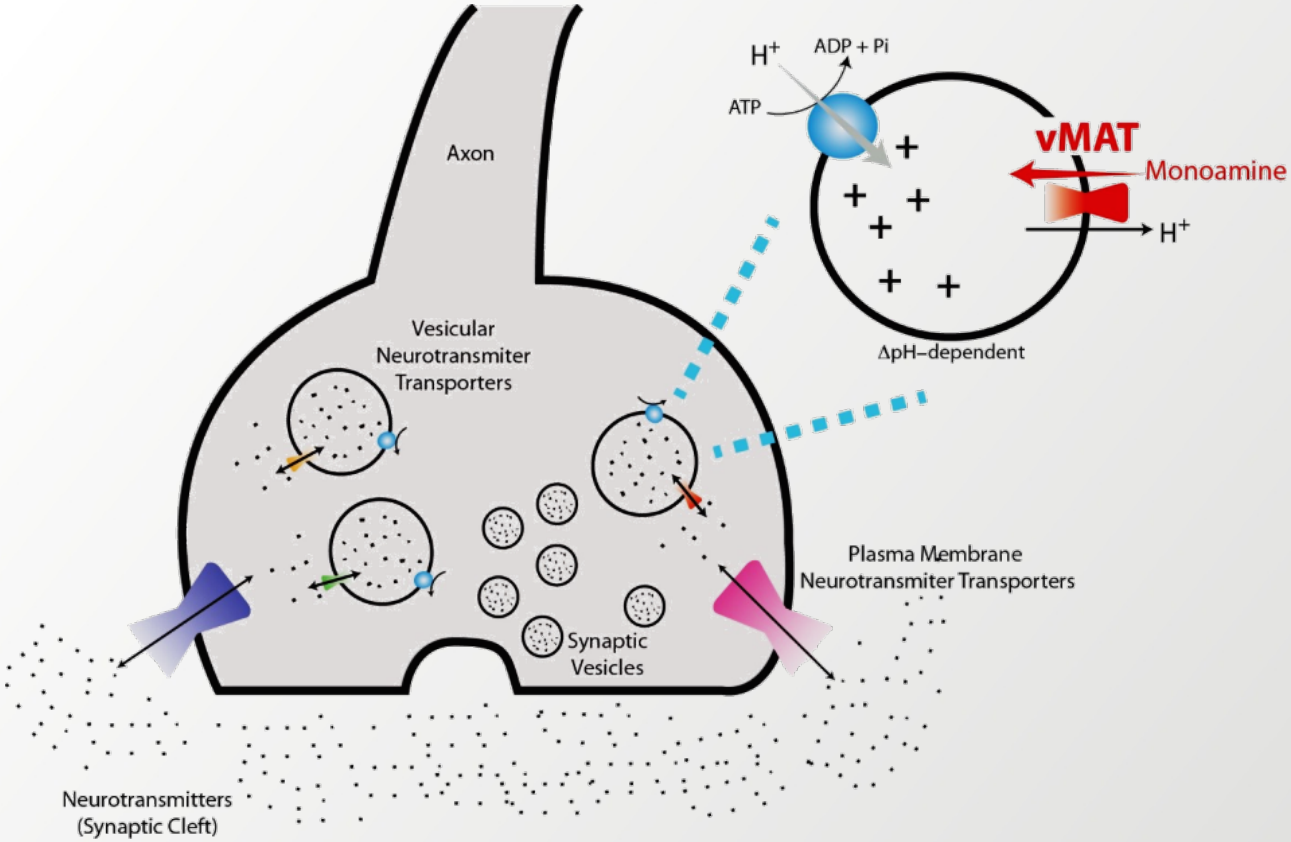
Kaspar R & Ellingrod VL. *Current Psychiatry.* 2014;13(3):44-6.
Bhidayasiri R et al. *Neurology.* 81:463-9.
Kim J et al. *Drugs in Context*. 2014;3:212259.

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

https://lookfordiagnosis.com/mesh_info.php?term=Vesicular+Monoamine+Transport+Proteins&lang=1

Tetrabenazine: Limitations

- Short serum half-life leads to frequent dosing with high peaks (Cmax)
- 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 (DHTBZ), 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 (a stable, non-radioactive, non-toxic, and naturally occurring isotope of hydrogen) in place of hydrogen at the sites of primary metabolism results in metabolic clearance being slowed
  - Less frequent dosing (BID vs. TID) and lower Cmax values
  - Comparable drug exposure with half the dose of tetrabenazine
  - Similar to tetrabenazine, there are α and β enantiomers and each gives rise to two isomers of a DHTBZ metabolite
- Breakthrough Therapy Designation from the FDA for the treatment of TD
- Also being studied for Huntington Disease and Tourette Syndrome
  - Current status: FDA issued a Complete Response Letter in May 2016 regarding SD809 for the treatment of Huntington Disease

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. *Teva Pharmaceutical Industries Ltd*. http://infoviewer.infodesk.com/infodisplay/item/8c88a7239111447b93129cb62d70cdf1.html?CU=tev3845&APP=3

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
- Results: AIMS score (LS mean change from baseline to Week 12): deutetrabenazine -3.0; placebo -1.6; P=0.019

Anderson KE et al. Poster P8-004, APA Annual Meeting, May 14-18, 2016, Atlanta, GA

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

All Subjects

Categorical Outcome	Placebo (n=59)	Deutetrabenazine (n=58)	NNT (95% CI)
CGIC response: "Very much improved" or "Much Improved"	40.4%	48.2%	13 (ns)
PGIC response: "Very much improved" or "Much improved"	29.8%	42.9%	8 (ns)

Baseline AIMS ≥ 6

Categorical Outcome	Placebo (n=49)	Deutetrabenazine (n=48)	NNT (95% CI)
CGIC response: "Very much improved" or "Much Improved"	34.7%	52.1%	6 (ns)
PGIC response: "Very much improved" or "Much improved"	28.6%	45.8%	6 (ns)

Treatment with deutetrabenazine did not result in any reports of depression or suicidal ideation and showed low rates of other psychiatric adverse events, such as anxiety and insomnia, which have been reported with tetrabenazine.

CGIC, Clinical Global Impression of Change; CI, confidence interval; NNT, number needed to treat; PGIC, Patient Global Impression of Change

Anderson KE et al. Poster P8-004, APA Annual Meeting, May 14-18, 2016, Atlanta, GA

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

Treatment-Emergent Adverse Events Occurring in at Least 4% of Patients in Either Treatment Group

Preferred Term	Deutetrabenazine (n=58) n (%)	Placebo (n=59) n (%)
AnyTEAE	41 (70.7)	36(61.0)
Somnolence	8(13.8)	6(10.2)
Headache	4 (6.9)	6(10.2)
Fatigue	4 (6.9)	5 (8.5)
Insomnia	4 (6.9)	1(1.7)
Anxiety	3 (5.2)	4 (6.8)
Diarrhea	3 (5.2)	3(5.1)
Akathisia	3 (5.2)	0(0.0)
Dry mouth	2 (3.4)	6(10.2)
Upper respiratory tract infection	2 (3.4)	4 (6.8)
Dizziness	2 (3.4)	3(5.1)
Rash	1(1.7)	3(5.1)

Anderson KE et al. Poster P8-004, APA Annual Meeting, May 14-18, 2016, Atlanta, GA

Deutetrabenazine for TD
Phase III Trial: AIM-TD (NCT02291861)

- 12-week, randomized, double-blind, placebo-controlled, fixed-dose (8 weeks; after 4-week titration), comparing SD-809 12, 24, or 36 mg or placebo, twice daily for patients with moderate to severe TD
  - AIMS rating (primary outcome) improved from baseline to week 12 by -3.3 points for 36 mg (P=0.001), -3.2 points for 24 mg (P=0.003) and -2.1 for 12 mg (P=NS), compared to -1.4 in placebo.
  - CGI-TD change rating improved by -0.5 for 36 mg (P=0.011) and by -0.6 for 24 mg (P=0.002).
  - CGI-TD responder rates (key secondary outcome: “much/very much improved”) were significantly higher than placebo with 24 mg (P=0.014), withy trend-level superiority for the 36 mg dose (P=0.059).

ClinicalTrials.gov. Jan 23, 2017. https://clinicaltrials.gov/ct2/show/NCT02291861; http://www.biospace.com/News/teva-announces-positive-top-line-data-from-second/433356.

Deutetrabenazine for TD
Phase III Trial in Progress

- 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 21, 2017. https://clinicaltrials.gov/ct2/show/NCT02198794.

Valbenazine (NBI-98854)

- A novel, highly selective, vesicular monoamine transporter 2 inhibitor
- Orally active compound with 2 active metabolites,(+)α-DHTBZ and the oxidative metabolite of (+)α-DHTBZ, 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
- Breakthrough Therapy Designation from the FDA for the treatment of TD
- 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)

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)

Across measures of psychopathology, there was generally no increase in psychopathology or suicidality with valbenazine; psychiatric status remained stable or improved in subjects with underlying schizophrenia, schizoaffective disorder, depression or bipolar disorder.

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.
Lindenmayer JP et al. Poster P8-071, APA Annual Meeting, May 14-18, 2016, Atlanta, GA.

Valbenazine for TD
Phase II Trial (KINECT 2)

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

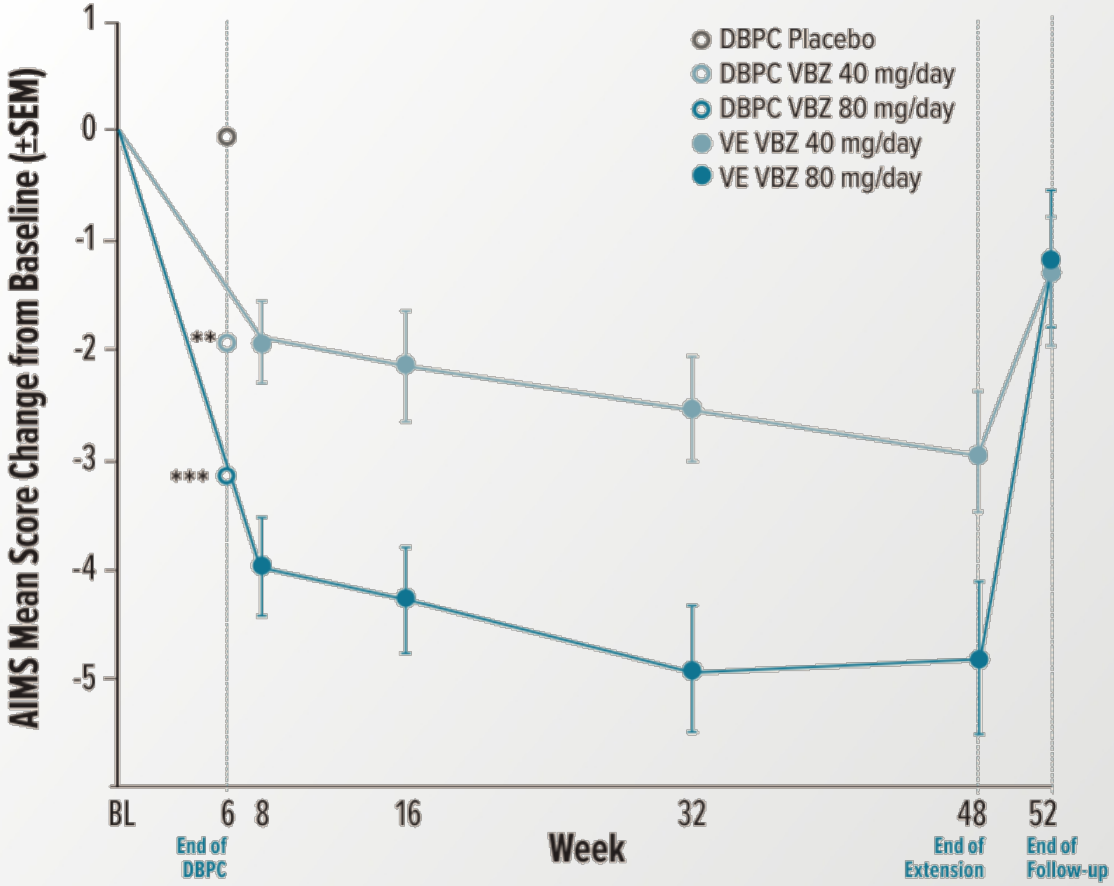
O'Brien CF et al. *Movement Disorders*. 2015. 30: 1681–7.

Valbenazine for TD
Phase III Trial (KINECT 3, NCT02274558)

- 6-week, double-blind, placebo-controlled, parallel, fixed-dose study of valbenazine 40 and 80 mg
  - Subjects eligible to continue for an additional 42 weeks (subjects on placebo re-randomized to 40 or 80 mg)
- 234 moderate to severe TD patients with schizophrenia, schizoaffective disorder, bipolar or major depressive disorder
- Study completion rate was 89% for valbenazine 80 mg, 83% for valbenazine 40 mg, and 91% for placebo
- 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
- Results: AIMS score (LS mean change from baseline to Week 6, MMRM): valbenazine 80 mg, -3.2; placebo, -0.1; $P<0.001$; effect size, $d=0.90$

Hauser RA et al. Presentation, AAN Annual Meeting, April 15-21, 2016, Vancouver, BC, Canada.;
Marder S et al. Poster P9-082, APA Annual Meeting, May 14-18, 2016, Atlanta, GA.

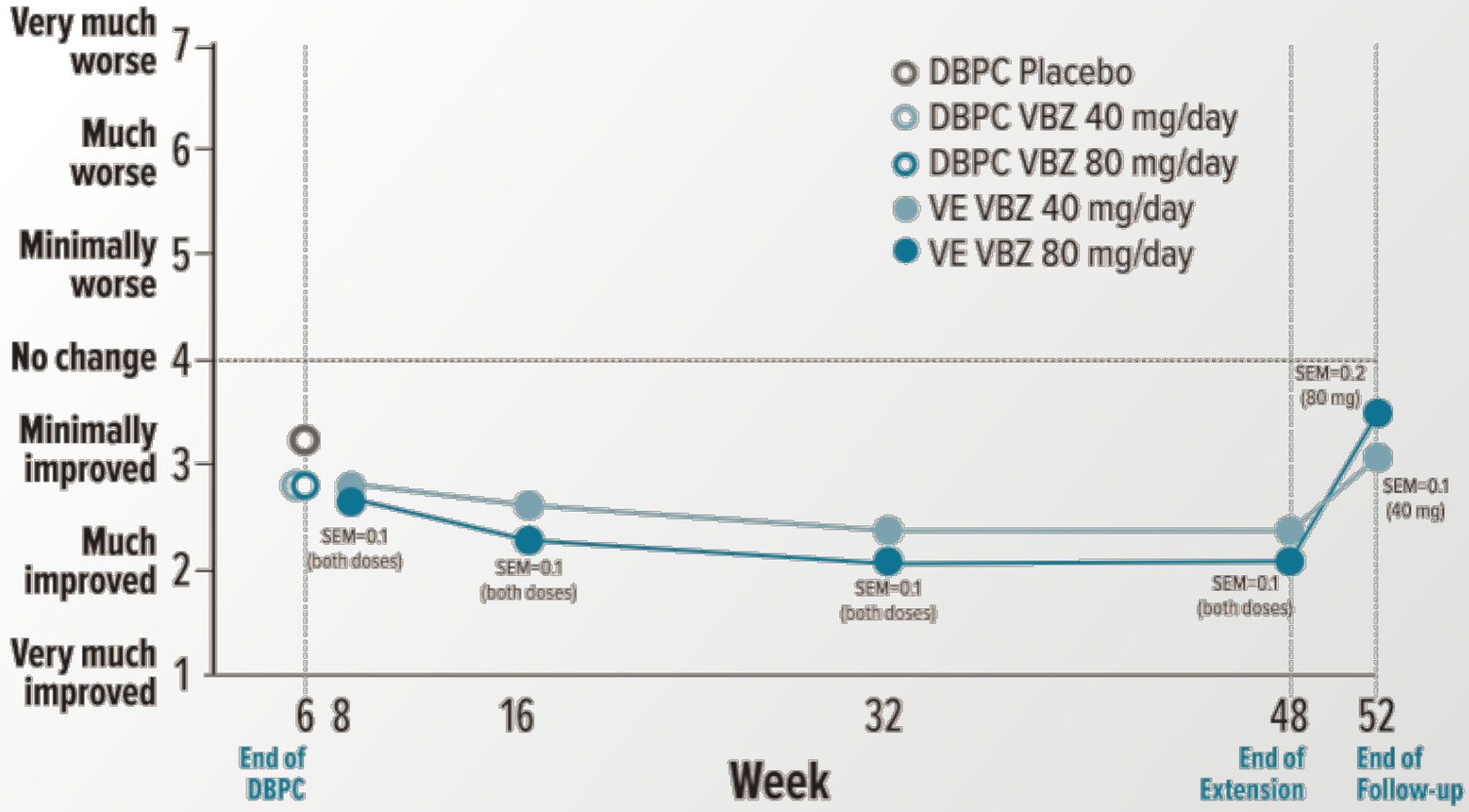
Valbenazine for TD - Phase III Trial (KINECT 3): AIMS Scores by Study Visit in Extension Phase (ITT)



t end of DBPC: **P<0.01; ***P<0.001 vs. placebo (statistical significance met for 80 mg/day based on the predefined fixed-sequence testing procedure); results based n least squares mean change from DBPC baseline using a mixed-effects model for repeated measures.
E and drug-free follow-up periods; results based on arithmetic mean changes, with no imputation for missing values or significance testing between dose groups.
IMS, Abnormal Involuntary Movement Scale; BL, baseline; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean;
BZ, valbenazine; VE, valbenazine extension.

Grogoriadis D et al. Poster presentation Annual ACNP Meeting, December 4-8, 2016,Hollywood, FL.

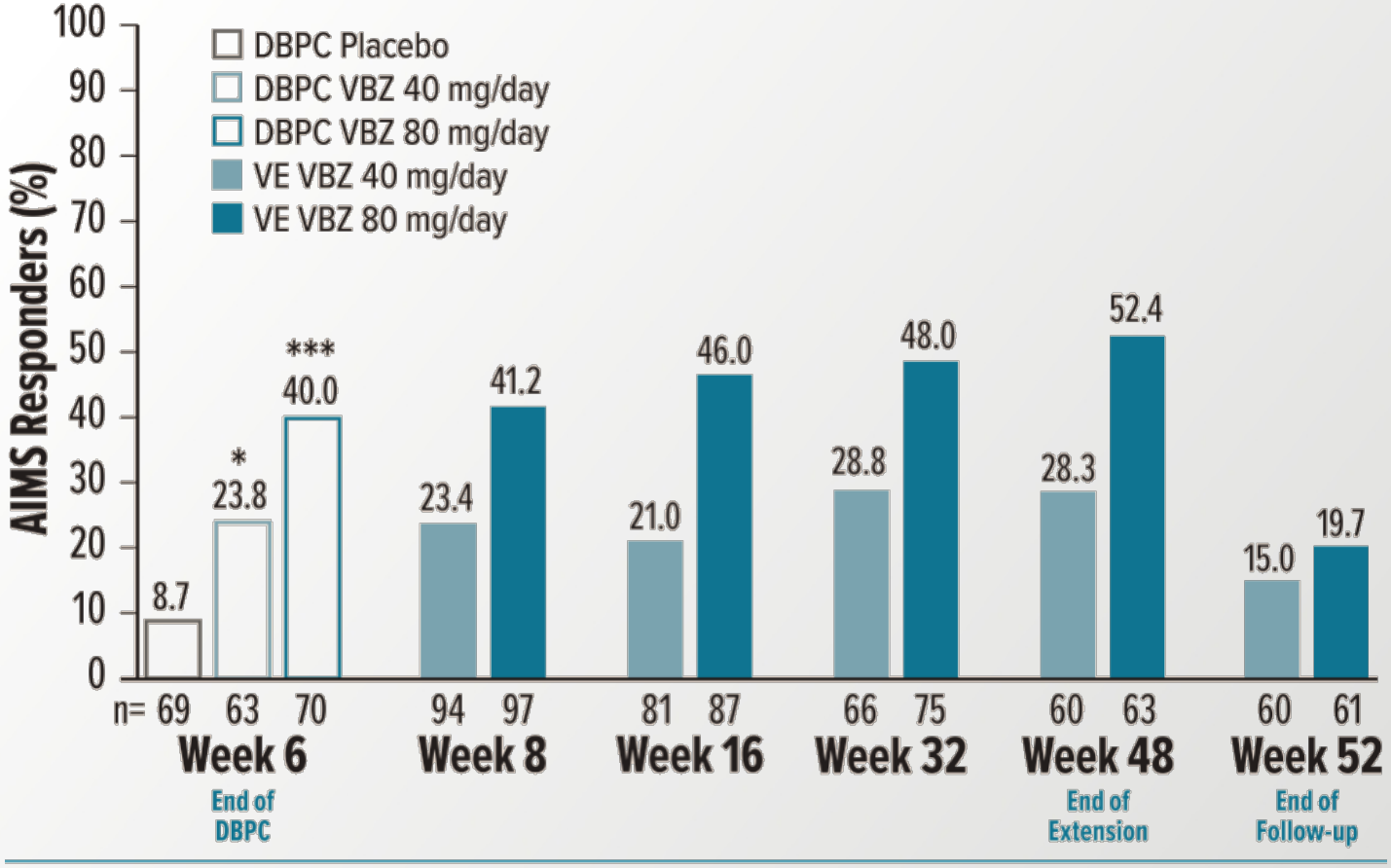
Valbenazine for TD - Phase III Trial (KINECT 3): CGI-TD Scores by Study Visit in Extension Phase (ITT)



At end of DBPC: no statistical difference between valbenazine (80 or 40 mg/day) and placebo; based on least squares mean scores using a mixed-effects model for repeated measures.
VE and drug-free follow-up periods: results based on arithmetic mean scores with no imputation of missing values or significance testing between dose groups.
CGI-TD, Clinical Global Impression of Change-Tardive Dyskinesia; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean; VBZ, valbenazine; VE, valbenazine extension.

Grogoriadis D et al. Poster presentation Annual ACNP Meeting, December 4-8, 2016, Hollywood, FL.

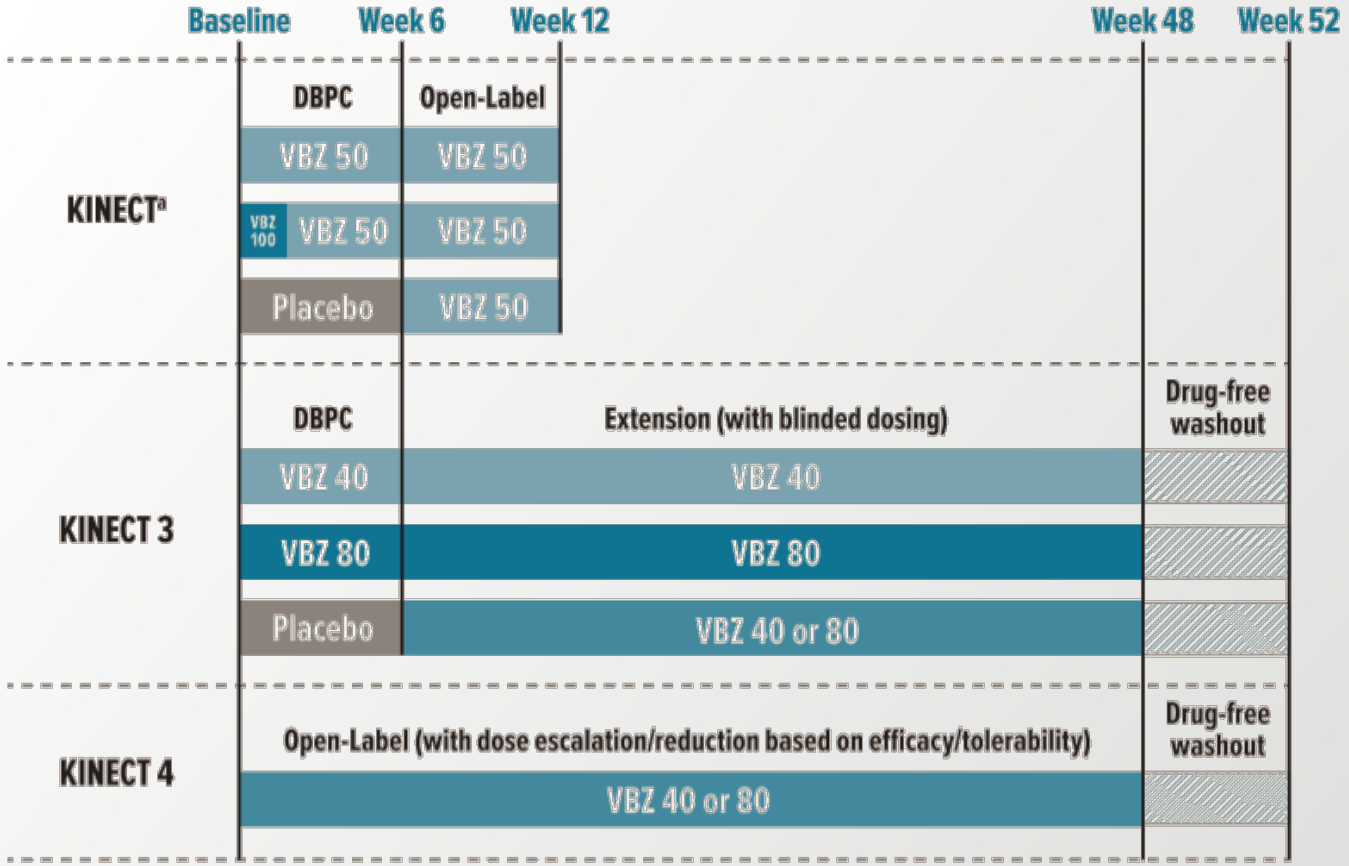
Valbenazine for TD - Phase III Trial (KINECT 3): AIMS 50% Reduction Responder by Study Visit in Extension Phase (ITT)



t end of DBPC: *P<0.05, ***P<0.001 vs. placebo, based on a 2-sided Cochran-Mantel-Haenszel analysis.
/E and drug-free follow-up periods: no significance testing between doses were performed.
IMS, Abnormal Involuntary Movement Scale; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; VBZ, valbenazine; VE, valbenazine extension.

Grogoriadis D et al. Poster presentation Annual ACNP Meeting, December 4-8, 2016, Hollywood, FL.

Valbenazine for TD – Pooled Data from 3 Long-term Studies
Adverse Effects (Safety Population)



[a]KINECT, 100 mg for 2 weeks.
KINECT and KINECT 3 are completed. Enrollment for KINECT 4 is completed; estimated completion for primary data analysis is mid-2017.
DBPC, double-blind placebo-controlled; VBZ, valbenazine.

Remington G et al. Poster presentation Annual ACNP Meeting, December 4-8, 2016, Hollywood, FL.

Valbenazine for TD – Pooled Data from 3 Long-term Studies
Adverse Effects (Safety Population)

	Valbenazine Dose Groups		
	40 mg (n=200)	80 mg (n=230)	All Subjects (N=430)
Summary of AEs, %			
Any TEAE	61.0	71.3	66.5
Any serious AE[a]	11.5	16.5	14.2
Discontinuation due to AE	16.0	13.5	14.7
AE leading to dose reduction	5.0	8.3	6.7
TEAEs by preferred term, %[b]			
Headache	7.0	8.3	7.7
Urinary tract infection	7.5	7.4	7.4
Somnolence	7.5	5.2	6.3
Fatigue	7.0	3.5	5.1
Suicidal ideation[c]	4.5	4.8	4.7
Dizziness	3.0	5.2	4.2
Diarrhea	3.0	4.8	4.0
Nasopharyngitis	3.0	4.3	3.7
Constipation	3.5	3.9	3.7
Depression	5.0	2.2	3.5
Vomiting	3.5	3.5	3.5
Anxiety	3.5	3.5	3.5
Fall	3.5	3.0	3.3
Dry mouth	4.0	2.2	3.0

[a]Serious AEs that occurred in ≥1% of all subjects were schizophrenia (1.2%) and suicidal ideation (1.2%).
[b]Reported in ≥3% of all valbenazine-treated subjects.
[c]Includes spontaneous patient-reported TEAEs and worsening in any Columbia-Suicide Severity Rating Scale suicidal ideation category (items 1-5).
AE, adverse event; TEAE, treatment-emergent adverse event.

Remington G et al. Poster presentation Annual ACNP Meeting, December 4-8, 2016, Hollywood, FL.

Summary and Conclusions

- Prevent if possible
  - Confirm and document the indication for dopamine antagonist antipsychotic medications
  - Use conservative maintenance doses
  - Consider the use of second generation antipsychotic medications, especially in those at high risk for EPSE
  - Inform patients and caregivers of the risk
  - Assess for incipient signs of TD regularly (every 3 months) using the AIMS
- Screen with scheduled AIMS exams
- Consider differential diagnoses
- Manage as quickly as possible after it appears
- New treatments are being developed for persistent TD
  - Deutetrabenazine (SD-809)
  - Valbenazine (NBI-98854)

Caroff SN et al. *Curr Psych*. 2011. 10(10) 23-32.

ARS POST QUESTIONS

Q&A

Thank You