

Tardive Dyskinesia: What Are We Missing?

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Learning Objectives

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

Faculty Disclosures

- **Dr. Citrome:** Speakers Bureau—Acadia, Alkermes, Allergan, AstraZeneca, Janssen, Jazz, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva; Consultant—Acadia, Alexza, Alkermes, Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Forum, Genentech, Janssen, Jazz, Lundbeck, Merck, Medivation, Mylan, Neurocrine, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, Teva, Valeant, Vanda; Stockholder—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer.
- **Dr. McEvoy:** Advisory Board—Neurocrine, Teva; Research Grants—Alkermes, Avanir, Boehringer Ingelheim, Otsuka, Teva.

Disclosure

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

Diagnosing Tardive Dyskinesia in Clinical Practice

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Overview

- Tardive dyskinesia (TD) is a syndrome characterized by persistent choreoathetoid movements 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

Tardive Dyskinesias

- Tardive dyskinesias (TDs) are involuntary movements of the tongue, lips, face, trunk, and extremities that occur in patients treated long-term with dopamine antagonist medications
- Similar movement disorders were described before dopamine antagonist medications existed
- The use of dopamine antagonist medications increased the incidence of TD (by approximately 15% over background levels)

Brasic JR. *Medscape Drugs, Diseases & Procedures*. Aug 12, 2015.
Lerner V, Miodownik C. *Curr Psychiatry Rep*. 2011 Aug;13(4):295-304.

Tardive Dyskinesia Continued Concern

- Thousands of patients are left with TD as a legacy of past treatment
- The “indications” for dopamine antagonist antipsychotic medications have expanded, and large numbers are receiving these medications (adjunctive treatment in depression, conduct disorder, agitation associated with cognitive decline or following traumatic brain injury)
- The pathophysiology of TD is not well understood
- TD, once established, has proved to be irreversible in most cases

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

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.

TD in the CATIE Schizophrenia Trials

- Subjects with TD were older, had a longer duration of receiving antipsychotic medication, and were more likely to have been receiving a conventional antipsychotic and an anticholinergic agent
- Diabetes mellitus (DM) and hypertension did not predict TD, whereas substance abuse significantly predicted TD
- Differences in cognitive functioning were not significant after controlling for baseline covariates
- The TD subjects also had higher ratings of psychopathology, EPSE, and akathisia

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

TD in the Elderly

- 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-naïve 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.

Tardive Dyskinesias 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 hypersensitive system
- Neurodegeneration secondary to lipid peroxidation or excitotoxic mechanisms may be involved

Brasic JR. *Medscape Drugs, Diseases & Procedures*. Aug 2, 2015.

Tardive Dyskinesias

Brain-Derived Neurotrophic Factor (BDNF)

- 80 schizophrenia patients with TD were compared with 45 schizophrenia patients without TD, as well as with 45 age- and sex-matched normal controls
- The patients with TD had lower plasma BDNF levels than patients without TD, and lower BDNF levels than normal controls
- In the patients with TD, plasma BDNF levels were inversely correlated with AIMS total score, and with PANSS negative subscore

Tan YL. *Schizophr Res.* 2005 May 1;74(2-3):263-70.
Barcelos RC et al. *Neurotox Res.* 2010 Apr;17(3):228-37.

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) Instructions for Performing the Exam

1. Ask the patient whether there is anything in his/her mouth (gum, candy, etc.) and if there is, 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

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

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.

Diagnosing TD: Schooler-Kane Criteria

1. At least 3 months of cumulative antipsychotic drug exposure
2. Abnormal Involuntary Movement Scale:
 - At least 3=moderate in ≥ 1 area, or at least mild=2 in ≥ 2 areas
3. Absence of other causal conditions

Schooler NR, Kane JM. *Arch Gen Psychiatry*. 1982;39(4):486-7.

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 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

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

Take Home Messages

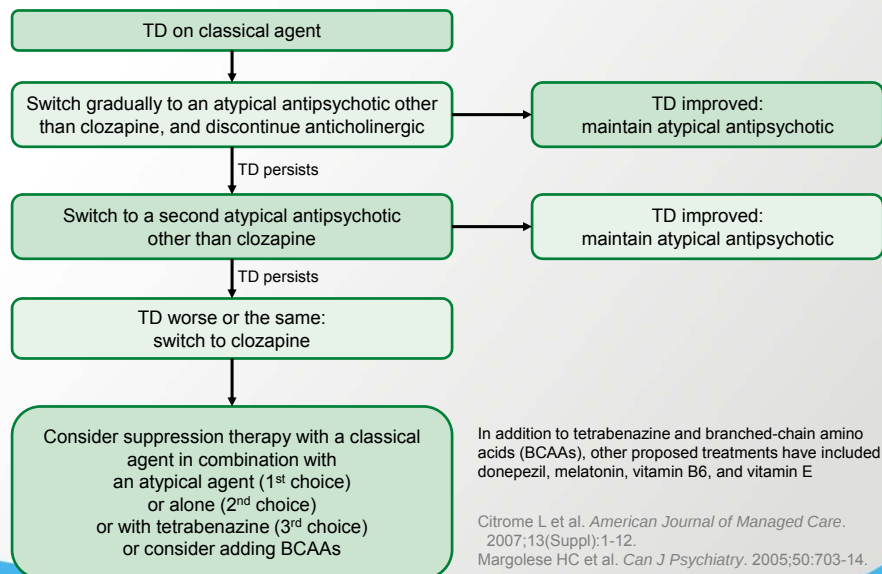
- AIMS is gold standard for detecting TD and quick
- TD is still present with 2nd generation antipsychotics and underdiagnosed
- Always ask about problems with teeth or dentures before doing the AIMS examination
- Optimize dose of antipsychotics to reduce EPS which is associated with TD

Recent Advances in the Management of Tardive Dyskinesia (TD)

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Tardive Dyskinesia: Management Circa 2007



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 B₆	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

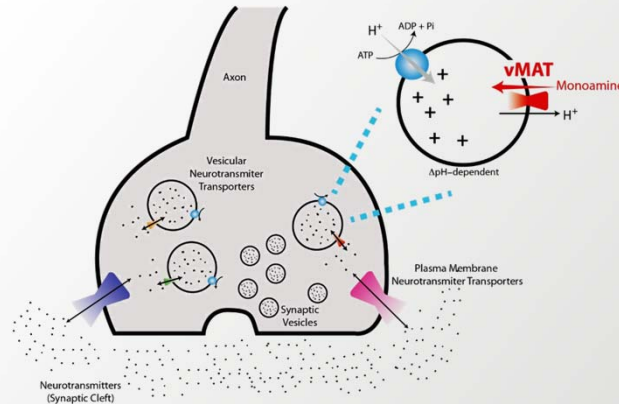
Kaspar R & Ellingrod VL. *Current Psychiatry*. 2014;13(3):44-6.
 Bhidayasiri R et al. *Neurology*. 81:463-9.
 Kim J et al. *Drugs in Context*. 2014;3:212259.

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 (C_{max})
- 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 C_{max} 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)
	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 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 (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, 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
- Results: AIMS score (LS mean change from baseline to Week 6, ANCOVA): valbenazine, -3.6; placebo, -1.1; $P=0.0005$

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)

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)

Adverse Events (Safety Population)

	Placebo n=76	VBZ 40 mg n=72	VBZ 80 mg n=79
Summary of AEs, n(%)			
Any serious AE	3(3.9)	4(5.6)	6(7.6)
Discontinuation due to AE	2(2.6)	2(2.8)	3(3.8)
Any TEAE	34(44.7)	28(38.9)	39(49.4)
TEAEs by Preferred Term, n(%)^a			
Somnolence	3(3.9)	3(4.2)	4(5.1)
Akathisia	1(1.3)	3(4.2)	2(2.5)
Arthralgia	1(1.3)	1(1.4)	3(3.8)
Dry mouth	1(1.3)	4(5.6)	0(0.0)
Vomiting	0(0.0)	0(0.0)	3(3.8)
Dyskinesia	0(0.0)	0(0.0)	3(3.8)
Urinary tract infection	3(3.9)	3(4.2)	0(0.0)

^a reported in $\geq 3\%$ of subjects in either valbenazine group at an incidence greater than placebo.
AE, adverse event; TEAE, treatment-emergent adverse event; VBZ, valbenazine.
Marder S et al. Poster P9-082, APA Annual Meeting, May 14-18, 2016, Atlanta, GA.

Valbenazine for TD Phase III Trials in Progress

- KINECT 4 (NCT02405091): Open-label study to evaluate the safety and tolerability of valbenazine administered once daily for a total of 48 weeks of treatment

ClinicalTrials.gov. Jan 7, 2016. <https://clinicaltrials.gov/ct2/show/study/NCT02405091>

Treatment of Tardive Dyskinesia: Summary

- Prevent if possible
- Screen with scheduled AIMS exams, especially in the older population
- Treat as quickly as possible after it appears
- New treatments are being developed for persistent TD
 - Deutetrabenazine (SD-809)
 - Valbenazine (NBI-98854)

Thank you!

Q&A session