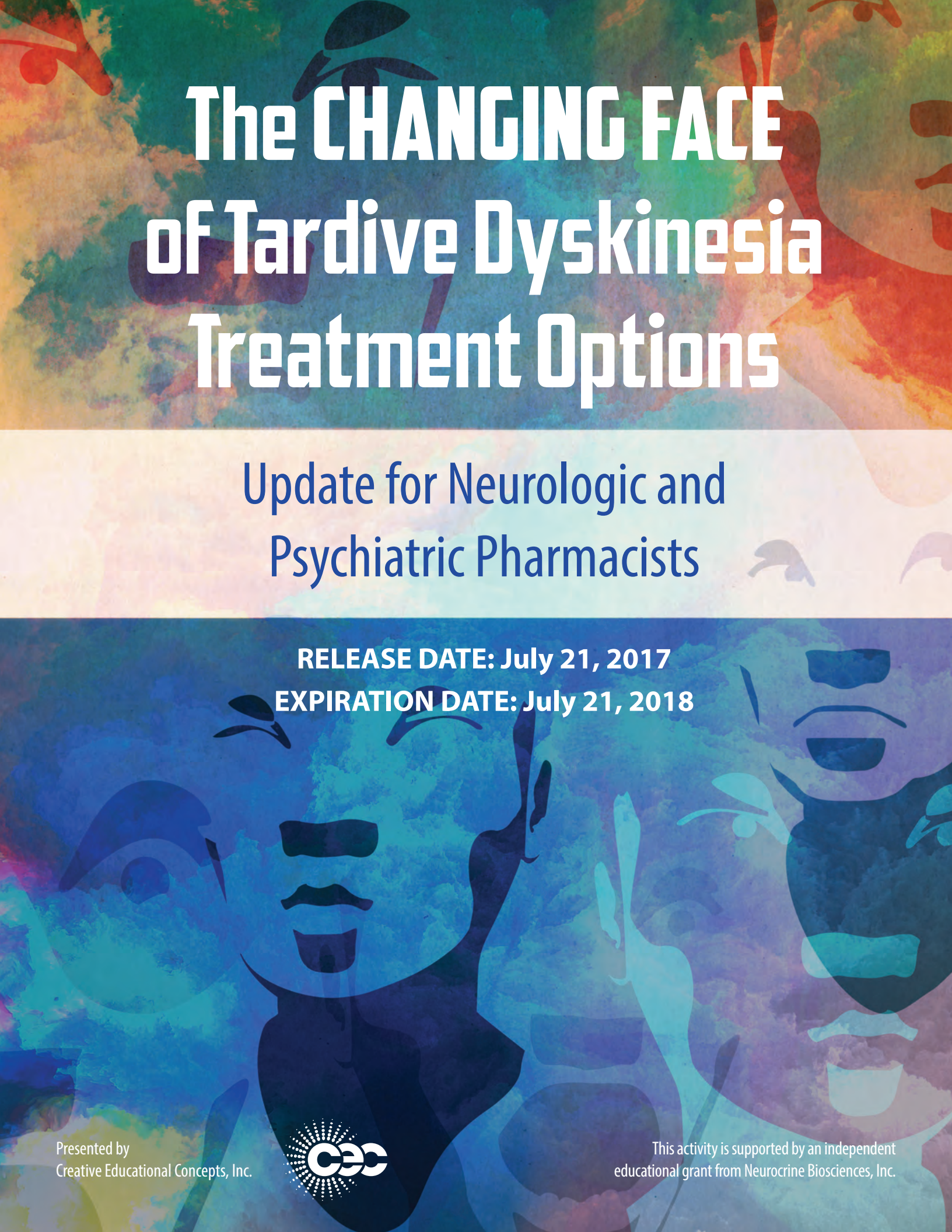

The CHANGING FACE of Tardive Dyskinesia Treatment Options

Update for Neurologic and Psychiatric Pharmacists

RELEASE DATE: July 21, 2017

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Presented by
Creative Educational Concepts, Inc.

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MEDIA

Online monograph

TARGET AUDIENCE

This activity is designed to meet the educational needs of psychiatric and neurologic pharmacists who treat patients with tardive dyskinesia (TD).

ACTIVITY DESCRIPTION

Psychiatric and neurologic pharmacists are actively involved in the care of patients with long-standing psychiatric illness, many of whom receive antipsychotic medications for extended periods of time. Trained specialty pharmacists have been shown to assess abnormal movements at a skill level comparable to trained physicians and are ideally positioned to assist in the documentation of AIMS/DISCUS scores for the patient at risk. They also may be a primary provider for treatment decisions or part of the treatment team and can guide optimal medication selection. CPNP attendees will review new data with clinical experts and interact via patient cases to ensure they are current with their assessment techniques and knowledgeable about new treatment options.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based activity, participants should be able to:

1. Outline risk factors for development of tardive dyskinesia in the psychiatric setting.
2. Assess new onset or progression of movement symptoms in patients at risk for tardive dyskinesia.
3. Identify treatment options for tardive dyskinesia in the psychiatric patient, using evidence-based and emerging therapies with the highest degree of demonstrated efficacy and safety.

AGENDA

5 minutes	Pre-test
50 minutes	Monograph: The Changing Face of Tardive Dyskinesia Treatment Options: Update for Neurologic and Psychiatric Pharmacists
5 minutes	Post-test/Evaluation

FACULTY DISCLOSURES

In accordance with the Food and Drug Administration, the speakers have disclosed that there is the potential for discussions concerning off-label uses of a commercial product/device during this educational activity.

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INSTRUCTIONS

To receive a statement of credit, you must:

- Review the full content of the activity and reflect upon its teaching.
- Complete the questions and evaluation at the end of the activity.
- Obtain a passing score of 70% on the post-test. You will have two (2) opportunities to complete the post-test.

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ACCREDITATION

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This knowledge-based activity is approved for 1.0 contact hour (0.10 CEUs) of continuing pharmacy education credit (0245-0000-17-007-H01-P).

Pharmacy credit will be reported directly to the National Association of Boards of Pharmacy® (NABP®) CPE Monitor electronic CE tracking system.

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This activity is complimentary.

SUPPORTING ORGANIZATION

This activity is sponsored by Creative Educational Concepts, Inc. (CEC) and is supported through an independent educational grant from Neurocrine Biosciences, Inc.

BACKGROUND

Extrapyramidal symptoms (EPS) are side effects associated with both first (FGA) and second generation antipsychotics (SGA), but may also occur with other medications including the gastrointestinal agent metoclopramide. EPS can take the form of pseudoparkinsonism, dystonia, akathisia, and tardive dyskinesia (TD). The presence of EPS provides a potential barrier between patient and physician expectations and can promote treatment non-adherence.

TD Risk Factors

- Increased age (higher incidence and lower remissions over age 50)
- African-American race
- History of acute EPS with antipsychotics (Parkinsonism, dystonia, akathisia)
- Female gender
- Postmenopausal
- Head injury
- Substance abuse
- Concurrent affective/mood disorder
- Concurrent medical disease (diabetes)
- Use of antipsychotics in high doses
- Exposure to antipsychotics over time

Saltz BL, et al. *JAMA*. 1991; Ganzini L, et al. *Psychopharmacol Bull*. 1992; Woerner MG, et al. *Am J Psychiatry*. 1993; Woerner MG, et al. *Am J Psychiatry*. 1998; Chan HY, et al. *J Clin Psychiatry*. 2010; Müller T. *Expert Opin Investig Drugs*. 2015.

Tardive dyskinesia has long been considered a chronic form of EPS that if not addressed and allowed to progress, may become irreversible and debilitating. TD is associated with a reduced quality of life, functional impairment, and historically any treatments have largely been unsuccessful. A recent 41-study meta-analysis examined published studies from 2000 to 2015 comparing outcomes from patients taking FGA and SGA agents.[1] In total, 11,493 patients were included in the study that resulted in an estimated global TD prevalence of 25.3%.[1] Patients currently being treated with SGAs were associated with a 20.7% prevalence rate of TD while patients currently treated with FGAs experienced a 30% prevalence rate ($p=0.002$).[1] This study also reported that the TD prevalence rate was lower in patients never treated with a FGA (7.2%) compared to those that had been treated with a FGA (23.4%, $p<0.001$).[1] Interestingly, the TD prevalence rate was estimated to be 22.7% in patients concurrently treated with a FGA and SGA.[1] Increased rates of TD were also associated with increased age, duration of illness, and prior EPS symptoms. Many other risk factors exist for TD including female gender, substance abuse, and concurrent mood disorder.[2,3,4,5,6] These numbers are slightly different from a published study that examined data from 2004 to 2008 and suggested TD prevalence rates of 13.1% for SGA treated patients and 32.4% for FGA treated patients.[7]

The evolution of SGAs and increased use brought with it expectations to reduce the presence of EPS and the potential elimination of TD when compared to FGA treated patients. However, expanded use of antipsychotics for other mental health conditions such as bipolar and anxiety disorders has exposed an increased number of patients to FGAs and SGAs who are potentially more susceptible to side effects than patients with schizophrenia. Cost considerations at some institutions also continue to drive the use of FGA agents over SGAs. There is a general sense that in new clinical trials, TD is under reported because of an increased focus on metabolic outcomes, shorter duration of treatment, and the lack of a FGA comparator. Additionally, medication non-adherence may be suggestive of more TD side effects and loss of patients to further follow-up. Another consideration is that because of antipsychotic associated bradykinesia and rigidity, there may be a masking of the clinical presentation of TD through increased muscle stiffness and a reduction in choreoathetotic movements.

Since the development of new onset TD has not been eliminated, there is a continued need for clinical assessment and monitoring for the presence or worsening of EPS symptoms and specifically the development of TD. In order to offer a good assessment one must not only understand the clinical presentation, but also some of the basic and fundamental principles to provide an environment that is conducive to providing an accurate evaluation.

The clinical presentation of TD usually involves initial dyskinetic movements in the lips or tongue with a progression to include additional oral and facial movements (e.g. chewing, grimacing, blinking, and lip smacking). This can also progress to movements more writhing in nature and witnessed in the face, neck, back, trunk, and extremities.[8,9,10,11,12] Significant progression can lead to impairment in speaking, eating, walking, and breathing. Historically, treatment has focused on being able to suppress symptoms to a level that does not dramatically impair one's ability to function, however traditional treatment approaches (antipsychotic dose reduction, change from FGA to SGA, and discontinuation of anticholinergics) while appropriate, have not proven to be curative.

ASSESSMENT

When preparing to conduct a movement disorder assessment it is important to introduce yourself and explain the purpose of the assessment to the patient. Providing a comfortable environment including adequate space and furniture with good lighting and a comfortable temperature will help reduce barriers associated with the examination. The examination itself should be adapted somewhat to the patient based upon any physical limitations or existing psychiatric symptoms. When preparing to conduct an examination, the examiner should also have in mind what type of cognitive and motor based distraction techniques will be utilized to help better assess and unmask movement disorder related symptoms.

Conducting a movement disorder assessment requires that you consistently follow a number of basic principles. This includes ensuring that an adequate time period for observation occurs and to continue to rate each area over the course of an examination, not just the time spent on a specific area or region. In addition, it is important to establish a personal "normal" as there is no one right way to conduct an exam but to improve consistency it is imperative to develop a fluent examination process. The only true way to improve is to conduct multiple ratings over time and to work with experienced raters who can guide and provide mentorship through the process, even conducting assessments separately and comparing and discussing findings.[13,14]

There are two primary TD psychometric assessment tools that are utilized in clinical practice. These include the Dyskinesia Identification System Condensed User Scale (DISCUS) and the Abnormal Involuntary Movement Scale (AIMS).

The DISCUS was developed in 1991 and consists of 15-items that assess seven different regions of the body that includes the following: face; eyes; oral; lingual; head/neck/trunk; upper limb; lower limb.[15] All items are scored on a scale of zero through 4, with "0" representing no symptoms present and a "4" representing a severe level of symptoms. The assessment tool itself is not diagnostic, but rather aids in the identification and severity of symptoms and allows for continued assessment over time. The DISCUS is considered both reliable and validated with a cut-off score of "5" correctly differentiating TD from non-TD in a majority of cases.

The AIMS was developed in 1976 by researchers in the Psychopharmacology Research Branch at the National Institute of Mental Health specifically for the assessment of patients treated with antipsychotic medication.[16] The assessment tool is not diagnostic, but like the DISCUS, is used to identify and assess the severity of TD related abnormal movements. The AIMS consists of 12-items with items assessing the orofacial region (questions 1-4), extremities (question 5 – 7), and global assessment (questions 8-10). In addition, Questions 11 and 12 are utilized to assist in the identification of any confounding variables related to abnormalities with teeth and dentures. Questions 1 through 10 are scored on a scale of zero through 4, with "0" representing no symptoms present and a "4" representing a severe level of symptoms. Symptoms that are considered to be "mild" are thought to be too persistent to be normal, while "moderate" symptoms present with an increased frequency and amplitude, and "severe" symptoms suggest the region being evaluated is in constant motion. When evaluating the findings from the AIMS, there is not a well-established guideline for the interpretation of scoring. While assessment items 1-7 can be totaled, it primarily serves to establish a personal standard and the score is not diagnostic itself. Reducing scores by a point from "activation" related movements is also no longer considered a standard assessment procedure.

AIMS Severity Scale

- For Items 1 – 10 the following rating scale is used:
  - Score of 0 = no abnormalities
  - Score of 1 = minimal, may be extreme normal
  - Score of 2 = mild
  - Score of 3 = moderate
  - Score of 4 = severe
- Frequency, amplitude, and quality of movement are considerations

Guy WG. *EDCEU Assessment Manual for Psychopharmacology.* 1976.

"Research criteria" do exist when considering if TD is present.[17] This includes that the patient being assessed is on an antipsychotic for a minimum of three months (one month if > 60 years of age), there is an absence of contributing factors or conditions, and an AIMS score of mild in two or more body regions or a score of moderate in one body region is suggestive of the presence of TD.

There are a number of clinical pearls to remember when conducting a movement disorder assessment. As previously mentioned, creating a comfortable environment

Considerations in Assessing for Tardive Dyskinesia – Schooler/Kane Criteria (AIMS)

- Minimum of 3 months of antipsychotic treatment
- Absence of contributing factors or conditions
- AIMS score of 2 (mild) in 2 or more body parts or a score of 3 (moderate) in 1 body region

Schooler NR and Kane JM. *Arch Gen Psychiatry.* 1982.

Clinical Pearls of the AIMS Examination

- Ask the patient to open their mouth and observe any abnormal movements with their tongue in their mouth and also extended*
- Ask for specified activation movements to allow for identification of unsuppressed movements
- Flex and extend each arm
- Ask the patient to stand
- Ask the patient to extend their arms
- Ask the patient to walk*

**Repeat this observation twice.*

and clear communication are imperative. The clinician should identify any contributing variables, assess the patient for any problems with teeth or dentures, and ask the patient if they have noticed any abnormal movements specifically in their face, mouth, hands, or feet. If the patient affirms abnormalities the level of "annoyance" should also be reported. When seated, it is important that the patient be relaxed, sitting in a firm chair that preferably has no arms, and with their hands on their knees at the start of the assessment process. Another helpful reminder is to have patients remove their shoes in order to be able to best identify and assess any abnormal movements in their feet.

Throughout the course of the assessment period the evaluator should ask the patient to complete a number of tasks through simple commands. Many of these tasks are repeated to allow for complete and accurate assessment. When completing an AIMS examination it is important to remember that "hand tremor" should not be rated as that is more consistent with a pseudoparkinsonian tremor though it should be documented in the notes section.

There are multiple benefits from using movement disorder rating scales for clinical monitoring. Being consistent and doing regular assessments will provide objective data to make good clinical decisions, it will serve as a tool to make evidence based decisions, and will offer legal support and documentation for treatment interventions. Both the DISCUS and the AIMS are validated rating tools for the assessment of TD. These scales are also both reliable and if the rater is consistent in their assessment approach, the results will be reproducible. Lastly, when utilizing these scales remember to "rate up" if you are in doubt and when completing an assessment, "rate what you see" not what you think the diagnosis is.

TREATMENT

Traditionally, the treatment of TD has been limited in treatment choices to reduce or resolve symptoms. In many cases, if TD symptoms begin to develop and an anticholinergic (e.g. benztropine) is a part of the treatment regimen, discontinuation is recommended. The SGA's have provided a few treatment options as well and clozapine, quetiapine, and iloperidone possess lower suggested rates of associated risk for EPS and specifically TD.[18,19]

A number of additional treatment options for TD have been considered, but robust and consistent data are lacking.[18-29] Gingko biloba, amantadine, and clonazepam all have moderate amounts of data suggesting some benefit at reducing TD symptoms but they are not widely utilized. Botulinum toxin has also been studied and may offer benefit for some orofacial TD movements.

With successful treatment interventions for TD lacking, further study has led to the development of new agents with unique mechanisms of action to counter the effects of TD. Recent focus has been the vesicular monoamine transporter-2 (VMAT2) as it is present in both the central nervous system (CNS) and peripheral regions while its counterpart VMAT1 is found peripherally and within sympathetic ganglia. VMAT2 is the only neuronal transporter identified that is responsible for the transport of monoamines from cellular cytosol sites to synaptic vesicles, specifically in the striatum and limbic regions.[6] Newer TD treatments target the VMAT2 to inhibit its activity and ability to deliver monoamine concentrations to the synaptic cleft.

The first VMAT2 inhibitor studied was tetrabenazine (TBZ) which is a reversible inhibitor. It was originally used for the

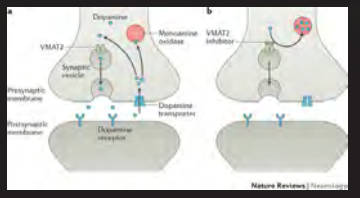
Additional Treatment Interventions for TD

Agent	Proposed Mechanism	Evidence	Level of Evidence
Gingko biloba	Antioxidant	Shown to improve AIMS scores over 12 weeks	Moderate for use[1]
Amantadine	Dopamine agonist	Shown to improve AIMS scores in patients treated with concurrent antipsychotics	Moderate for use[2]
Clonazepam	Potentiation of GABA	Improved dyskinesia scores over course of 12 weeks to 9 months	Moderate for use[3]
Vitamin E	Antioxidant	Mixed results showing benefit	Limited Data
Pyridoxine	Antioxidant	Case reports and small studies report benefit, 26-week study showed improvement in ESRS scores	Limited Data[4]
Melatonin	Antioxidant	Questionable clinical benefit	Limited Data[5]

[1]Zhang WF, et al. *J Clin Psychiatry*. 2011; [2]Pappa S, et al. *Clin Neuropharmacol*. 2010; [3]Thaker GK, et al. *Am J Psychiatry*. 1990; [4]Lerner V, et al. *Am J Psychiatry*. 2001; [5]Nelson K, et al. *Ann Pharmacother*. 2003; Bhidayasiri R, et al. *Neurology*. 2013; Rana AQ, et al. *Drug Des Devel Ther*. 2013.

Vesicular Monoamine Transporter 2 (VMAT2): Proposed Role in TD

- VMAT2 – responsible for monoamine transport from cellular cytosol into synaptic vesicles
- VMAT2 inhibitors bind to distinct sites on the protein and inhibit its activity, thereby reducing monoamine concentrations in the synaptic cleft



Muller T. *Expert Opin Investig Drugs*. 2015.

Additional Treatment Interventions for TD

Agent	Proposed Mechanism	Evidence	Level of Evidence
Botulinum toxin	Blocks acetylcholine release and develops axonal sprouting, reduced muscle contraction	Potential benefit in orofacial TD with consistent antipsychotic dose	Limited Data[1]
Zonisamide	Enhanced GABA release	Limited data suggests improved AIMS scores	Limited data[2]
Levetiracetam	Binds vesicle protein 2A, N-type calcium channel blockade, reduced neurotransmitter release	Limited data suggests improved AIMS scores, 26-week trial demonstrated significant reductions in AIMS	Limited data[3,4]
Branched chain amino acids	Increases ratio of aromatic amino acids and suppresses neurotransmitter synthesis	Mixed results, improved AIMS scores in some studies	Weak evidence for use[5]
Omega-3 fatty acids	Improved neurotransmission and neuroprotection	Limited data, non-significant benefit	Moderate evidence against use

[1]Slotema CW, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; [2]Iwata U, et al. *J Neurol Sci*. 2012; [3]Bona JR. *J Clin Psychopharmacol*. 2006; [4]Woods SW, et al. *J Clin Psychiatry*. 2008; [5]Richardson MA, et al. *J Clin Psychiatry*. 2004; Bhidayasiri R, et al. *Neurology*. 2013; Rana AQ, et al. *Drug Des Devel Ther*. 2013.

Deutetrabenazine

- VMAT2 reversible inhibitor
- Deutetrabenazine is a novel molecule structurally related to tetrabenazine
  - Incorporates deuterium in lieu of hydrogen at 1º metabolism sites
  - Deuteration of TBZ results in a more than 2-fold increase in systemic exposure to total (α+β)-HTBZ, a near doubling of half-life and only minor increases in C_{max}
  - The increased half-life of total (α+β)-HTBZ allows for administration of lower doses of deutetrabenazine compared with TBZ, thus permitting comparable plasma exposure with lower peak and higher trough concentrations
- BID dosing
- Under FDA review for tardive dyskinesia (Breakthrough Therapy Designation; PDUFA 8/30/17); FDA approval for Huntington's disease on 4/4/17

Huntington Study Group. *JAMA*. 2016; Stamler D, et al. *Neurology*. 2013.

treatment of schizophrenia in the 1970's but later gained approval for the treatment Huntington's disease in 2009.[30] TBZ has limitations, as it requires a dosing titration strategy and is dosed three times a day. TBZ also is associated with sedation, the development of parkinsonian symptoms, dysphagia, hypotension, and depression and suicidality (boxed warning).

Subsequently, deutetrabenazine was developed and is structurally related to TBZ however deuterium is incorporated into the molecule instead of hydrogen bonds at the primary metabolic sites which are more difficult to break. The resultant effect is the near doubling of half-life, minimal increase in C_{max} and overall increased systemic exposure (increased area under the curve) to drug when dosed twice daily.[31,32] Deutetrabenazine gained FDA approval for Huntington's disease in April of 2017 and is under review (August 2017) for a TD indication.[33]

There are currently two 12-week studies of deutetrabenazine examining its use to treat TD. The ARM-TD study is a 12-week, double-blind, placebo controlled trial in adults with TD that includes a 6-week titration phase and a 6-week maintenance phase.[34] There is also an AIMS responder subanalysis. The AIM-TD study is a 12-week, double-blind, placebo controlled dose finding study comparing placebo, 12 mg, 24 mg, or 36 mg dosed twice daily and titrated over a 4-week period and maintained for an additional 8 weeks.[35] A third study, the RIM-TD study is also under way which is an open-label design, 54-week safety study.

In the ARM-TD study, adults with moderate to severe TD who had a history of using dopamine receptor antagonists (antipsychotics or gastrointestinal) for at least 3 months (one month if > 60 years of age) were eligible. In order to be included, subjects had to have AIMS scores of 6 or more in total for items 1 through 7 at the time of screening. Deutetrabenazine was initiated via titration (maximum daily dose = 48 mg; dosed twice daily) over 6 weeks and then

maintained for an additional 6 weeks. The primary outcome measure was the change in AIMS score from baseline to Week 12. Secondary outcome measures included the Clinical Global Impression of Change (CGIC) and the Patient Global Impression of Change (PGI-C).

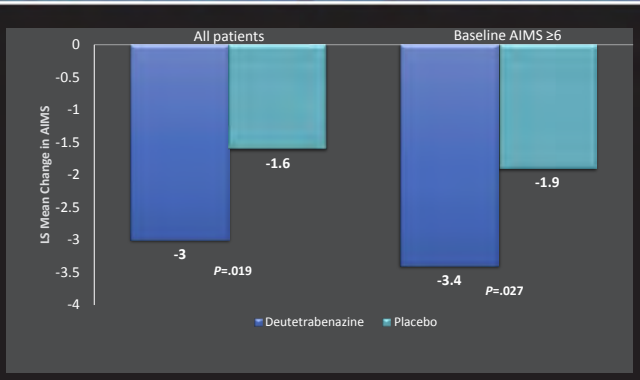
Deutetrabenazine Clinical Trials

- ARM-TD (NCT02195700; Phase II/III)
  - 12-wk, DBRPC study of adults
  - 6-wk of titration plus 6-wk of maintenance
  - AIMS responder subanalyses
- AIM-TD (NCT02291861; Phase III)
  - 12-wk, DBRPC study
  - Dose-finding of placebo, 12, 24, or 36 mg BID titrated over 4 wks and maintained for 8 additional wks
- RIM-TD (NCT02198794; Phase III)
  - Open-label, 54-wk safety study

DBRPC=double-blind, randomized, placebo-controlled

www.clinicaltrials.gov.

ARM-TD: Results



Anderson KE, et al. Presented at the 2016 American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA.

ARM-TD: Adverse Events

Adverse Event	Deutetrabenazine (N=58) N (%)	Placebo (N=59) N (%)
Any Treatment Adverse Events	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)

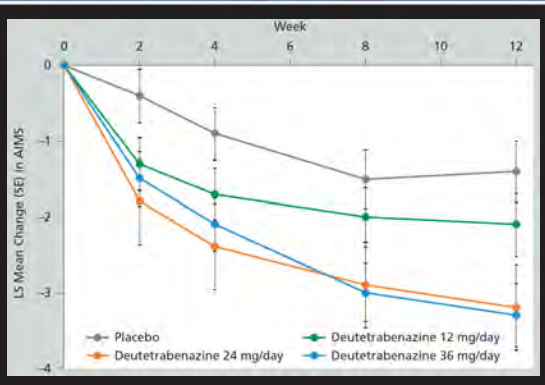
Anderson KE, et al. Presented at the 2016 American Psychiatric Association Annual Meeting; May 2016; Atlanta, GA.

There were no statistically significant demographic differences between the placebo and deutetrabenazine treatment groups with the baseline AIMS in the deutetrabenazine group being 9.7 ± 4.1 and 9.6 ± 3.8 in the placebo group.[34] The mean decrease in AIMS score for the deutetrabenazine group was 3.4 points and 1.9 points for placebo (p=0.027).[34] The CGI-C and PGIC were both improved for deutetrabenazine compared to placebo, though the results were not statistically significant.[34] Deutetrabenazine was well tolerated with somnolence, headache, fatigue, and insomnia being reported as the most common side effects.[34]

The AIM-TD study was also a 12-week, placebo controlled study of adult patients with moderate to severe TD and who had a history of using dopamine antagonists for at least 3 months (one month if > 60 years of age). In order to be included, subjects had to have AIMS scores of 6 or more in total for items 1 through 7 at the time of screening. Deutetrabenazine was titrated on a twice-daily dosing schedule to a total daily fixed dose of either 12 mg, 24 mg, or 36 mg over 4-weeks. Subjects were then maintained on this dose for an additional 8-weeks. The primary outcome measure was also the same as the ARM-TD study examining the change in AIMS score from baseline to Week 12.

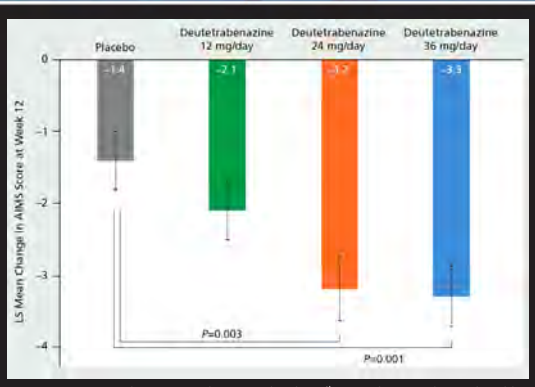
Response was observed for all deutetrabenazine treatment groups by Week 2, with significant improvement noted at Week 12 for all treatment groups when compared to placebo.[35] The mean change in AIMS scores was 3.3 points for the 36 mg/day group, 3.2 points for the 24 mg/day group, and 2.1 points for the 12 mg/day group.[35] Deutetrabenazine was well tolerated, with headache, diarrhea, and nasopharyngitis being the more commonly reported adverse events. Depression was reported in 1% of the 12 mg/day group and in 4% of the 24 mg/day group.[35]

AIM-TD: Results
Change in AIMS Score by Treatment Group



Anderson KE, et al. Presented at the 29th US Psychiatric and Mental Health Congress, 2016.

AIM-TD: Results
Analysis of Change in AIMS Score at Week 12



Anderson KE, et al. Presented at the 29th US Psychiatric and Mental Health Congress, 2016.

AIM-TD: Adverse Events

Adverse Event	Deutetrabenazine 12 mg/day (N=74), [n,%]	Deutetrabenazine 24 mg/day (N=73), [n,%]	Deutetrabenazine 36 mg/day (N=74), [n,%]	Placebo (N=72), [n,%]
Any Treatment Emergent Adverse Event	35 (47)	31 (42)	38 (51)	34 (47)
Headache	5 (7)	2 (3)	5 (7)	4 (6)
Diarrhea	1 (1)	3 (4)	5 (7)	2 (3)
Nausea	1 (1)	1 (1)	1 (1)	7 (10)
Nasopharyngitis	4 (5)	3 (4)	2 (3)	1 (1)
Anxiety	3 (4)	2 (3)	3 (4)	2 (3)
Fatigue	1 (1)	2 (3)	3 (4)	1 (1)
Somnolence	0	1 (1)	3 (4)	3 (4)
Depression	1 (1)	3 (4)	1 (1)	0
Dry Mouth	3 (4)	0	2 (3)	0
Muscle Spasms	0	0	3 (4)	0
Hypertension	0	0	3 (4)	1 (1)

Anderson KE, et al. Presented at the 29th US Psychiatric and Mental Health Congress, 2016.

An additional VMAT2 inhibitor, valbenazine, recently gained FDA approval for the treatment of TD (April 2017).[36] Valbenazine is a valine ester of dihydrotetrabenazine and does not directly impact dopamine$_1$ or dopamine$_2$ receptors.[36,37] Valbenazine also has two active metabolites that are selective for VMAT2 (NBI-98782 and NBI-136110).[36,37] The estimated half-life is 20 hours and the pharmacokinetic profile results in a low peak:trough concentration ratio which may offer some advantages with regards to fewer concentration related side effects.[36,37] Valbenazine was specifically approved for TD on April 11, 2017 and is also being studied in Tourette's syndrome.[36]

There are four primary valbenazine clinical trials evaluating treatment outcomes in patients diagnosed with TD. The first is the KINECT 1 study, a 6-week, double-blind placebo controlled trial examining the effect of valbenazine 100 mg as assessed by changes in AIMS scores.[38] The KINECT 2 study is also a 6-week, double-blind placebo controlled trial examining the effect of valbenazine dosed 25 mg to 75 mg daily as assessed by changes in AIMS scores, but also included an extensive evaluation of psychiatric stability.[39,40] The KINECT 3 study is another 6-week, double-blind placebo controlled trial examining the use of 40 mg or 80 mg of valbenazine.[41,42,43] The primary efficacy measure was the change in AIMS score and includes a long-term extension for a total of 52 weeks. The KINECT 4 study is a long term open-label study.

Valbenazine Clinical Trials

- KINECT 1 (NCT01688037; Phase II)
  - 6-wk, DBRPC study in adults
  - 100 mg dose reduced symptoms on AIMS score
- KINECT 2 (NCT01733121; Phase II)
  - 6-wk, DBRPC dose-titration study of adults on 25-75 mg
  - Psychiatric stability analysis
- KINECT 3 (NCT02274558; Phase III)
  - 6-wk, DBRPC study of adults on 40 or 80 mg
  - 52-week, long-term extension study
- KINECT 4
  - Open-label (with dose escalation/reduction) based on efficacy/tolerability

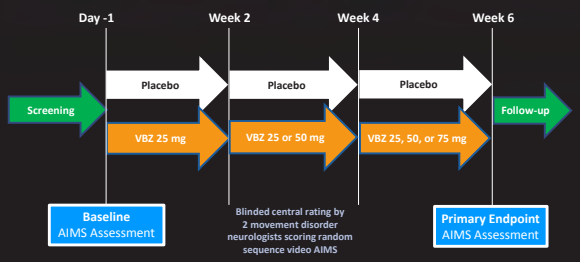
DBRPC=double-blind, randomized, placebo-controlled www.clinicaltrials.gov.

The KINECT 2 study included adult subjects diagnosed with schizophrenia, schizoaffective or a mood disorder, or a gastrointestinal disorder. In order to be included in the study subjects had to have antipsychotic or metoclopramide associated TD for a minimum of 3 months. Subjects were also required to score as moderate to severe symptoms (Item 8) on the AIMS and were required to be psychiatrically stable with a Brief Psychiatric Rating Scale (BPRS) score under 50. Subjects were then randomized to placebo or 25 mg of valbenazine once daily for two weeks. At Week 2 subjects could be increased to 50 mg daily of valbenazine and again at Week 4 to a maximum of 75 mg daily of valbenazine. Dosing adjustments (increase or decrease) were at the discretion of the blinded clinician's judgment. The severity of TD was determined by the AIMS total score (items 1 through 7) with the primary outcome measure being the change in AIMS from baseline to end of Week 6. Secondary outcome measures included the Clinical Global Impression of Change-TD Scale (CGI-TD).

At the end of 6-weeks, a significant reduction in mean AIMS score was observed in the active treatment arm (-3.6 ± 3.5 points) compared to placebo (-1.1 ± 3.7 points, $p<0.0005$).[39] In addition, the "response" (≥ 50% reduction in AIMS from baseline) was greater in the valbenazine treatment group compared to placebo (48.9% vs. 18.2%,

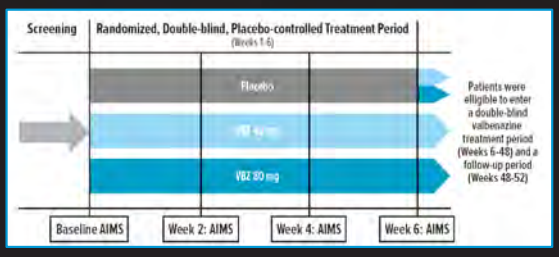
p=0.0022).[39] The number of responders was also greater with the CGI-TD in the valbenazine treatment group (66.7% vs. 15.9%, p < 0.0001).[39] The most common reported adverse events included fatigue, headache, decreased appetite, nausea/vomiting, somnolence, and dry mouth.[39]

KINECT 2: Study Design



O'Brien CF, et al. *Mov Disord*. 2015.

KINECT 3: Study Design



At the Week 6 visit, subjects initially randomized to placebo were re-randomized to VBZ 40 mg or 80 mg. Subjects initially randomized to VBZ 40 mg or 80 mg remained at their current dose. Subjects initially randomized or re-randomized to VBZ 80 mg received 40 mg for the first week.

Factor SA, et al. *Mov Disord*. 2016; Factor SA, et al. Presented at the 20th Annual International Congress of Parkinson's Disease and Movement Disorders Meeting; June 2016; Berlin, Germany.

KINECT 2: Results

Variable	Placebo (N=44) N(%)	Valbenazine (N=45) N(%)	P-value	NNT (95% CI)
Mean Change AIMS (SD)	-1.1 (3.7)	-3.6 (3.5)	.0005	
AIMS Response at Week 6 (MITT)	8 (18.2)	22 (48.9)	.0022	4 (2-9)
Mean CGI-TD (SEM)	3.1 (0.1)	2.3 (0.1)		
LS Mean CGI-TD (SEM)	3.1 (0.3)	2.2 (0.3)		
CGI-TD Responder (ITT)	7 (15.9)	30 (66.7)	<.0001	2 (2-3)
Mean PGIC (SEM)	2.9 (0.1)	2.2 (0.1)		
LS Mean PGIC (SEM)	3.3 (0.3)	2.6 (0.3)		
PGIC Responders	14 (31.8)	26 (57.8)	.0011	4 (3-17)

O'Brien CF, et al. *Mov Disord*. 2015.

KINECT 2: Results

Adverse Event	Placebo (N=49) N (%)	Valbenazine (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%)

O'Brien CF, et al. *Mov Disord*. 2015.

The KINECT 3 study included adult subjects diagnosed with schizophrenia, schizoaffective or a mood disorder, or a gastrointestinal disorder. In order to be included in the study subjects had to have antipsychotic or metoclopramide associated TD for a minimum of 3 months. Subjects were also required to score as moderate to severe symptoms (Item 8) on the AIMS and were required to be psychiatrically stable as determined by one of the following psychometric measures: ≤ 50 on the BPRS; ≤ 70 on the Positive and Negative Syndrome Scale (PANSS); a total score ≤ on the Calgary Depression Scale for Schizophrenia; a total score ≤ 10 on the Young-Mania Rating Scale (YMRS); or a score < 13 on the Montgomery-Asberg Depression Rating Scale (MADRS).

Subjects were randomized to receive placebo, valbenazine 40 mg/day, or valbenazine 80 mg/day given once daily. The primary efficacy measure was the change in AIMS score (items 1 through 7) for the 80 mg/day group compared to placebo at Week 6. The principle secondary outcome measure was the change in CGI-TD at Week 6. (Hauser) Subjects completing the 6 week study were given the opportunity to participate in a 42-week extension study to receive either 40 mg/day or 80 mg/day of valbenazine.

At Week 6, the AIMS score decreased significantly for the 80 mg/day valbenazine treatment group when compared with placebo (-3.2 vs. -0.1 points, p < 0.001) with a corresponding effect size of 0.90.[41,42,43] The AIMS scores also

decreased significantly for the 40 mg/day valbenazine treatment group compared to placebo (-1.9 vs. -0.1 points, p=0.002) and an effect size of 0.52.[41,42,43] Statistically significant change from placebo was noted for both the 40 mg/day and 80 mg/day valbenazine treatment groups at Weeks 2, 4, and 6.[41,42,43] The number of subjects achieving "response" (≥ 50% reduction from baseline) on the AIMS was also significant for the 40 mg/day (23.8%, p=0.02) and 80 mg/day valbenazine groups (40.0%, p<0.001) when compared to the placebo group response rate of 8.7%.[41,42,43] No significant difference was noted for either treatment group compared to placebo for the CGI-TD when using the intent-to-treat analysis, however using the per-protocol group did result in significant changes for both the 40 mg/day and 80 mg/day valbenazine treatment groups (p=0.011, p=0.011).[41,42,43] The most commonly reported adverse events for the combined 40 mg/day and 80 mg/day treatment groups included somnolence, akathisia, and dry mouth.[41,42,43] Of note, suicidal ideations were reported in 4.2% of the 40 mg/day group and 1.3% of the 80 mg/day group compared to 5.3% in the placebo group.[41,42,43]

Also of note, at the completion of 6-weeks, psychiatric stability was maintained as determined by the PANSS, Calgary Depression Scale for Schizophrenia, MADRS, and YMRS.[41,42,43]

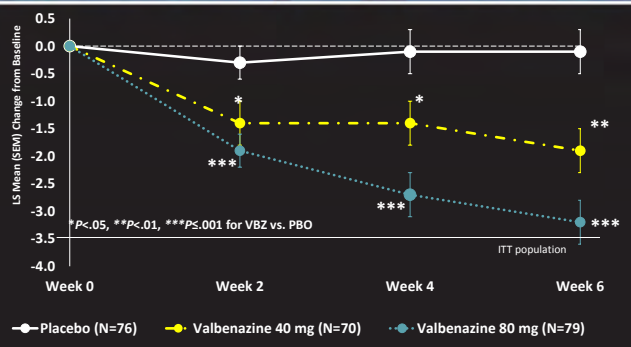
Upon the completion of the long-term extension study at 48 weeks, the valbenazine 40 mg/day treatment group noted a mean decrease of 3.0 points and the 80 mg/day group noted a mean decrease of 4.8 points. At the completion of 48-weeks, a 4-week washout was conducted that demonstrated a return to baseline levels for AIMS in both treatment groups.[44]

When looking at the pooled safety data from the three different KINECT trials, somnolence (10.9%), anticholinergic effects (5.4%), and balance disorders/fall (4.1%) are the most common adverse events.[36]

CONCLUSION

Tardive dyskinesia has one newly approved treatment option as of April 11, 2017 (valbenazine) and another that will be reviewed for approval in August of 2017 (deutetrabenazine). Initial trials with both agents are positive suggesting efficacy and favorable tolerability. Valbenazine is available through specialty pharmacies and is currently available as a 40 mg capsule and is recommended to be initiated at 40 mg once daily with the potential to be

KINECT 3: AIMS Score Change by Study Visit



Factor SA, et al. *Mov Disord*. 2016; Factor SA, et al. Presented at the 20th Annual International Congress of Parkinson's Disease and Movement Disorders Meeting; June 2016; Berlin, Germany.

KINECT 3: Adverse Events

Adverse Event	Placebo (N=76) N(%)	VBZ 40 mg (N=72) N(%)	VBZ 80 mg (N=79) N(%)
Any Event	33 (43.4)	29 (40.3)	40 (50.6)
Any Event Leading to Discontinuation	4 (5.3)	4 (5.6)	5 (6.3)
Somnolence	3 (3.9)	4 (5.6)	4 (5.1)
Akathisia	1 (1.3)	3 (4.2)	2 (2.5)
Suicidal Ideation	4 (5.3)	3 (4.2)	1 (1.3)
Arthralgia	1 (1.3)	1 (1.4)	3 (3.8)
Dry Mouth	1 (1.3)	5 (6.9)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	3 (3.8)
Dyskinesia	0 (0.0)	0 (0.0)	3 (3.8)
Anxiety	0 (0.0)	1 (1.4)	2 (2.5)
Urinary Tract Infection	3 (3.9)	3 (4.2)	0 (0.0)
Weight Increase	0 (0.0)	1 (1.4)	2 (2.5)

Factor SA, et al. *Mov Disord*. 2016; Factor SA, et al. Presented at the 20th Annual International Congress of Parkinson's Disease and Movement Disorders Meeting; June 2016; Berlin, Germany.

Valbenazine Adverse Events: Pooled Data

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

Adverse Reaction	Placebo (N=183)	VBZ (N=262)
Somnolence	4.2%	10.9%
Anticholinergic effects	4.9%	5.4%
Balance disorders/fall	2.2%	4.1%
Headache	2.7%	3.4%
Akathisia	0.5%	2.7%
Vomiting	0.6%	2.6%
Nausea	2.1%	2.3%
Arthralgia	0.5%	2.3%

Valbenazine Prescribing Information, April 2017.

increased to 80 mg once daily after one week.[36] In the presence of moderate to severe hepatic impairment the dose if valbenazine should not be increased above 40 mg/day.[36] Additional consideration should be given to dosing if administered with strong CYP450 3A4 inducers or inhibitors or use with CYP 2D6 poor metabolizers.[36] It is also recommended that valbenazine use be avoided in congenital long QT syndrome or arrhythmia associated with prolong QT interval.[36] Valbenazine may be taken with our without food.

Deutetrabenazine does not yet have an indication for tardive dyskinesia with an FDA review date scheduled for August 2017. Deutetrabenazine was approved for Huntington's disease on April 4, 2017 and is available through specialty pharmacies.[33] Deutetrabenazine carries a warning to monitor for depression and suicidality.[33] Currently for Huntington's disease treatment it is available as a 6 mg, 9 mg, and 12 mg tablet.[33] In the treatment of Huntington's disease it is recommended to be initiated at 6 mg daily with weekly 6 mg increases up to a tolerated dose that reduces chorea and a maximum of 48 mg per day.[33] The maximum recommended dose with CYP450 2D6 inhibitors is 36 mg per day and when daily doses reach a total of 12 mg/day deutetrabenazine should be given in two divided doses.[33] Deutetrabenazine is recommended to be given with food.

Valbenazine Practical Issues

- Available May 2017 through specialty pharmacies
- Dose Availability: 40 mg capsule
- Initiate at 40 mg po daily; may increase to 80 mg po daily at one week
  - Maintain at 40 mg if CYP2D6/3A4 poor metabolizer or severe hepatic impairment
  - Reduce dose to 40 mg with strong CYP3A4 inhibitors
  - Avoid use with strong CYP3A4 inducers
  - Consider dose reduction in CYP2D6 poor metabolizers (based on tolerability)
- Take with or without food
- Procurement: http://inbracesupportprogram.com

Valbenazine Prescribing Information & Product Website, April 2017.

Deutetrabenazine Practical Issues

- FDA Approval for Huntington's Disease 4/4/17
- Under FDA review for Tardive Dyskinesia, PDUFA 8/30/17
- Warning for depression and suicidality
- Dose Availability: 6 mg, 9 mg, 12 mg tablets
- Initiate at 6 mg po daily, titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum daily dose of 48 mg
  - In use with strong CYP2D6 inhibitors the maximum recommended dose is 36 mg per day
  - Total daily doses of 12 mg or above should given in two divided doses
- Take with food

Deutetrabenazine Prescribing Information & Product Website, April 2017.

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