TD NEWS+VIEWS
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The Importance of Differentiating Tardive Dyskinesia from Drug-Induced Parkinsonism: Steering Clear of Inappropriate Anticholinergic Use

ANTICHOLINERGIC OVERUSE

Overuse of Anticholinergics in Psychiatry: Consequences for Patients With Tardive Dyskinesia

Anticholinergics are still being prescribed to treat or prevent tardive dyskinesia (TD), even though they have been shown to worsen the disorder.

CASE STUDY

Consequences of Misdiagnosis and Anticholinergic Use: Recognizing the Need to Distinguish Tardive Dyskinesia From Other Drug-Induced Movement Disorders

Observation of differences between TD and drug-induced parkinsonism may lead to appropriate treatment for each.

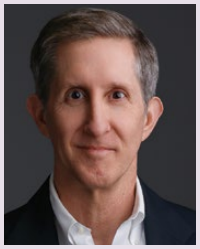
TREATMENT

AUSTEDO XR®: A Once-Daily Treatment for Tardive Dyskinesia

Vesicular monoamine transporter 2 (VMAT2) inhibitors are the only approved treatments for patients with TD. Take a deep dive into the role AUSTEDO XR can play in the treatment of TD.

EXPERT COMMENTARY

Expert Commentary With Jonathan Meyer, MD, and Daniel Kremens, MD, JD



Jonathan Meyer, MD
Psychiatrist
San Diego. California

Daniel Kremens, MD, JD
Movement Disorder Specialist
Philadelphia, Pennsylvania

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INDICATIONS AND USAGE

AUSTEDO XR® (deutetrabenazine) extended-release tablets and AUSTEDO® (deutetrabenazine) tablets are indicated in adults for the treatment of chorea associated with Huntington's disease and for the treatment of tardive dyskinesia.

IMPORTANT SAFETY INFORMATION

Depression and Suicidality in Patients with Huntington's Disease: AUSTEDO XR and AUSTEDO can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidality and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation. AUSTEDO XR and AUSTEDO are contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.

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Overuse of Anticholinergics in Psychiatry: Consequences for Patients With Tardive Dyskinesia

Tardive dyskinesia (TD) is a persistent, typically irreversible, hyperkinetic movement disorder, resulting from chronic exposure to antipsychotics that affects approximately 785,000 patients in the United States.[1-4]

The term "extrapyramidal symptoms," or EPS has a long history of being used to describe all drug-induced movement disorders (DIMDs) experienced by patients taking antipsychotics.[1,5,6] These include acute syndromes, developing within hours or days of treatment (eg, dystonia, akathisia, and drug-induced parkinsonism [DIP]) as well as tardive syndromes, occurring after a continued period of treatment (eg, TD, tardive dystonia, and tardive akathisia).[7] Although these syndromes are often lumped together, they are each distinct movement disorders, with different underlying causes and, consequently, different treatment approaches. For instance, TD and DIP are common movement disorders occurring in up to 1 of 3 patients taking antipsychotics, but their distinction may often be misunderstood.[1,8,9] However, treatment for DIP can worsen TD and vice versa.[1,9] Therefore, it is critical to differentiate TD from other DIMDs, particularly DIP, in order to guide appropriate treatment for patients.

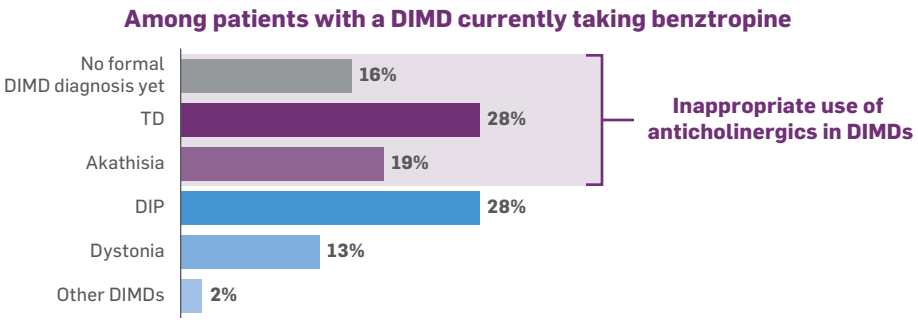
Overuse of Anticholinergics in DIMDs: Evidence From Real-World Practices

Psychiatric clinicians continue to use anticholinergics broadly to treat or prevent EPS.[10] This can negatively impact patients with TD. While anticholinergics are appropriate for treating DIP and acute dystonia, they can make TD movements worse.[1,9] In fact, the prescribing information for benztropine, a widely prescribed anticholinergic, warns that antiparkinsonism agents do not alleviate symptoms of TD and may, in some instances, exacerbate them.[11]

As a result, the American Psychiatric Association (APA) treatment guidelines and the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed, Text Revision (DSM-5-TR) warn that anticholinergics should not be used to prevent or treat TD.[12,13] Instead, vesicular monoamine transporter 2 (VMAT2) inhibitors are recommended as first-line treatment for TD that has an impact on the patient, regardless of the severity of movements.[13]

Despite these recommendations, a significant number of patients with TD continue to be treated with anticholinergic medications, reflecting a critical need for increasing awareness of this issue.[10] Results from a survey of high prescribers of benztropine for TD (33 psychiatrists and 13 nurse practitioners [NPs]/physician assistants [PAs]) found that 30% of patients with a DIMD were currently taking benztropine.[4] Among these patients, up to 63% were inappropriately prescribed anticholinergics, including 28% of patients with TD **(Figure 1.1)**.[4]

Figure 1.1. Breakdown of Benztropine Patients by DIMD[4]



IMPORTANT SAFETY INFORMATION (CONTINUED)

Contraindications: AUSTEDO XR® (deutetrabenazine) extended-release tablets and AUSTEDO® (deutetrabenazine) tablets are contraindicated in patients with Huntington's disease who are suicidal, or have untreated or inadequately treated depression. AUSTEDO XR and AUSTEDO are also contraindicated in: patients with hepatic impairment; patients taking reserpine or within 20 days of discontinuing reserpine; patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing MAOI therapy; and patients taking tetrabenazine or valbenazine.

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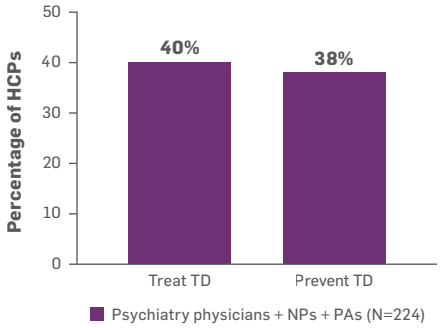
Additionally, this report demonstrated that healthcare professionals (HCPs) most frequently use benztropine long-term, with up to 93% of patients with TD being on benztropine for more than 3 months.[4] While ~50% of survey respondents reported that they were very familiar with tardive syndromes or agreed with statements related to differentiated diagnosis of TD and DIP, and 37% understand that anticholinergic drugs are not effective for the treatment of TD, less than one-third seemed concerned that prescribing them may exacerbate TD and would discontinue anticholinergic treatment if they suspected a patient had TD.[4]

In a second survey by Chepke et al, ~40% of psychiatry HCPs (151 psychiatrists and 98 NPs/PAs) reported using benztropine to prevent or treat TD **(Figure 1.2)**.[10] Additionally, they were more inclined to continue using benztropine for more than 6 months, with a significantly higher percentage continuing for more than 12 months.[10]

These studies demonstrate that even with a proper diagnosis of TD, patients are still frequently prescribed benztropine, highlighting that broad and inappropriate use of anticholinergics in patients with TD persists in psychiatry, despite recommendations that it can worsen symptoms.

Figure 1.2. Real-World Benztropine Usage Patterns in Movement Disorders Among Surveyed Psychiatry HCPs[4]



~40% of HCPs reported using benztropine to treat or prevent TD[10]

Figure 1.3. Reported Reasons for Prescribing Benztropine to Patients With TD[4]

Efficacy/Patient reports helpful	41%
Multiple or unconfirmed diagnosis	24%
Insurance/cost	24%
Refill prescription	9%
Tolerability	9%

"The patient does not want to change"

"It has historically been used, and some patients find it to be effective"

"When the diagnosis is not clear, it tends to be effective"

"To help sort out whether the person has EPS or TD"

Why Do Psychiatric HCPs Continue to Prescribe Anticholinergics?

Compiled results from the behaviors and attitudes of high prescribers of benztropine for TD indicated that patients reporting it as helpful, and multiple or unconfirmed diagnoses were among the most frequent reasons for prescribing anticholinergics **(Figure 1.3)**.[4]

Another possible reason outlined in this report was that respondents were following teaching habits learned during medical school or from more experienced attending physicians who endorse the use of anticholinergics for any movement disorder.[4] Additionally, some prescribers may be unwilling to deprescribe the medication, fearing it would hurt their relationship with patients.[4] Others lack motivation to change prescribing habits.[4] Finally, providers may still prescribe anticholinergics over standard-of-care therapies due to the lack of understanding of APA recommendations around the treatment of TD. In fact, Chepke et al found that less than 40% of psychiatric HCPs were somewhat or very familiar with the APA 2020 guidelines.[10] However, of HCPs who reported being at least somewhat familiar, the majority agreed that VMAT2 inhibitors are the first-line treatment for TD.[10]

Educating clinicians on the importance of deprescribing anticholinergics in patients with TD is required and has previously been accomplished in a community

mental health setting.[14] Critical reasons to consider deprescribing anticholinergics include that they are not indicated to treat or prevent TD, can make TD symptoms worse, and are inappropriate for many older adults.[11-13,15] For patients taking an anticholinergic, it is recommended to gradually reduce anticholinergic therapy to lessen the potential impact on TD symptoms.[9] VMAT2 inhibitors are the only FDA-approved treatment for TD and are recommended as first-line treatment for TD that has an impact on the patient, regardless of severity of movements.[12]

Summary

- Although the APA treatment guideline and DSM-5-TR caution against using anticholinergics, such as benztropine, to treat or prevent TD, anticholinergics are still being overused in psychiatry settings, because of patients reporting their use as helpful, inertia (eg, absence of motivation to change prescribing habits), lack of understanding of APA recommendations, or self-perpetuating prescribing patterns from more senior staff and attending physicians who support the use of anticholinergics for any movement disorders[4,10,12,13]
- The APA recommends that patients who have TD that has an impact on the patient be treated with a reversible inhibitor of the VMAT2, regardless of the severity of movements[13]
- Implementing standard protocol or guidelines in clinical practices may influence prescribing patterns toward deprescribing anticholinergics and implementing habits for the use of VMAT2 inhibitors for patients with TD ■

CASE STUDY

Consequences of Misdiagnosis and Anticholinergic Use: Recognizing the Need to Distinguish Tardive Dyskinesia From Other Drug-Induced Movement Disorders

Antipsychotic drugs used to treat patients with psychotic (eg, schizophrenia) and mood (eg, bipolar disorder and major depressive disorder) disorders can cause abnormal involuntary movements. Historically, the term "extrapyramidal symptoms (EPS)" has been used broadly in psychiatry and product labeling to refer to all these drug-induced movements. As a result, it is well entrenched in the psychiatry lexicon.

However, it is now widely recognized that drug-induced movement disorders (DIMDs), which include tardive dyskinesia (TD), drug-induced parkinsonism (DIP), akathisia, and dystonia, are distinct conditions with specific symptoms, different underlying mechanisms, and subsequently different treatment approaches. As a result, the broad use of EPS to describe any DIMD is inadequate and can lead to poor outcomes for patients.

For instance, TD and DIP are common DIMDs, but they are quite distinct from each other. TD is characterized by an excess of movements that are irregular, jerky, and unpredictable. On the other hand, parkinsonism is characterized by a paucity or slowness of movement and may be accompanied by rigidity. When involuntary abnormal movements occur, they are typically rhythmic (ie, tremors). It is critically important to differentiate between DIP and TD because treatment approaches for these movement disorders are different. Anticholinergics are indicated to treat DIP, but they can worsen TD. Because of this, failure to differentiate TD from DIP can result in inappropriate treatment.

The American Psychiatric Association (APA) treatment guidelines and *Diagnostic and*

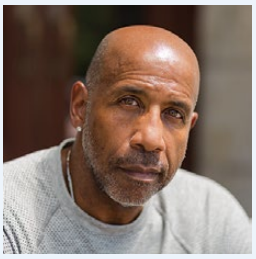
Anticholinergics, such as benztropine, should not be used in patients with TD because they can worsen symptoms.

Statistical Manual of Mental Disorders, 5th ed, Text Revision (DSM-5-TR) warn that anticholinergics, such as benztropine, should not be used in patients with TD because they can worsen symptoms. Instead, the APA recommends vesicular monoamine transporter 2 (VMAT2) inhibitors, the only FDA-approved treatment, as first-line treatment for TD that has an impact on the patient, regardless of severity of movements.

This case study features James, a 55-year-old man who was prescribed a long-acting injectable (LAI) typical antipsychotic to treat schizophrenia. Following the development of abnormal finger movements, James was diagnosed with EPS and initiated on benztropine, a commonly prescribed anticholinergic. When his symptoms worsened, James was reevaluated and diagnosed with TD. After gradual discontinuation of benztropine, he was prescribed a VMAT2 inhibitor.

James's case highlights the importance of differentiating TD from other DIMDs and the consequences of using anticholinergic medication to treat a patient with TD.

Case study: James, a 55-year-old man with schizophrenia and a misdiagnosis of EPS



Not an actual patient.

Medical History

James is 55 years old, lives independently, and receives care at a community mental health center (CMHC). He was diagnosed with schizophrenia at the age of 24 and is supported by a local Assertive Community Treatment team. For many years, he had been treated with an LAI typical antipsychotic.

Presenting Issue

The case manager at the CMHC noticed that James had developed some abnormal, involuntary finger movements and suggested he mention these to his clinician at his next psychiatric appointment. After examination, James's clinician diagnosed the abnormal movements as EPS. James was initiated on benztropine at 1 mg and titrated up to 2 mg twice daily. During this time, the finger movements persisted, and James began to experience involuntary grimacing.

TD Diagnosis and Assessment of Impact

The worsening of James's symptoms while on anticholinergic treatment prompted his clinician to reassess his diagnosis.

James's abnormal movements

- Originally started after long-term exposure to a typical antipsychotic medication
- Worsened with anticholinergic treatment
- Were irregular and jerky, affecting his fingers and face

Based on these symptoms, which are consistent with the DSM-5-TR criteria, James's clinician diagnosed him with TD and then used the Abnormal Involuntary Movement Scale (AIMS) to assess the severity of his movements.

The clinician then asked James about how the movements impacted his day-to-day life. James reported that he felt lonely, like people were avoiding him because of his TD movements. He also had some difficulty holding objects, like a spoon or his toothbrush, because of the finger movements, which made it challenging to perform some routine activities.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex reported in association with drugs that reduce dopaminergic transmission, has been observed in patients receiving tetrabenazine. The risk may be increased by concomitant use of dopamine antagonists or antipsychotics. The management of NMS should include immediate discontinuation of AUSTEDO XR and AUSTEDO; intensive symptomatic treatment and medical monitoring; and treatment of any concomitant serious medical problems.

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Treatment Decisions

To manage James's TD, the clinician took the following approach:

1. James was switched from a typical to an atypical antipsychotic, which may have less propensity to cause abnormal movements. His schizophrenia symptoms remained stable, but his TD persisted
2. Benztropine dose was gradually reduced over 1 to 4 months from 2 mg twice a day (BID) to 1 mg BID and then discontinued
3. James was started on a VMAT2 inhibitor, the only FDA-approved treatment for TD. The APA recommends VMAT2 inhibitors as first-line treatment for TD that has an impact on the patient, regardless of movement severity

Treatment Outcomes

Once on the VMAT2 inhibitor, James experienced reduced jerky finger movements and facial grimacing. With a reduction in movements, he was able to eat with utensils and brush his teeth with less difficulty.

The APA recommends VMAT2 inhibitors as first-line treatment for TD that has an impact on the patient, regardless of severity of movements.

Discussion: Key Learnings From This Case Study

- James's initial diagnosis of EPS and treatment with anticholinergics worsened his TD movements
- An accurate diagnosis of TD helped James get appropriate treatment
- Anticholinergics, such as benztropine, should not be used to treat or prevent TD
- The APA recommends that TD symptoms that have an impact on the patient, regardless of severity, should be managed with a VMAT2 inhibitor
- James's case study highlights the consequences of failing to differentiate and accurately diagnose TD and using an anticholinergic, like benztropine, to treat patients with TD ■

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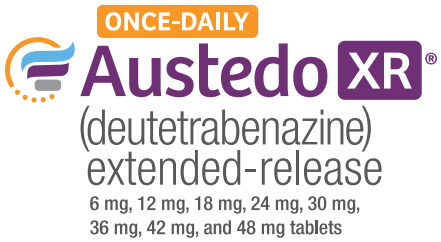

TREATMENT

AUSTEDO XR: A Once-Daily Treatment for Tardive Dyskinesia

Tardive dyskinesia (TD) and drug-induced parkinsonism (DIP) are distinct movement disorders. Both are caused by exposure to antipsychotics but they have different underlying causes and different treatment approaches.[1,2] Vesicular monoamine transporter 2 (VMAT2) inhibitors are recommended by the American Psychological Association (APA) as first-line treatment for TD that has an impact on the patient regardless of severity of movements, and are the only treatment for TD approved by the US Food and Drug Administration (FDA).[3] In contrast, anticholinergics that are used to treat DIP are not approved for TD.[4,5] Despite this, a significant number of patients with TD are treated inappropriately with anticholinergics.[6]

Because treatment for one condition can worsen the other, it is critical to differentiate TD from DIP and treat each appropriately.[1,2]

The Role of AUSTEDO in the Treatment of TD

ARM-TD and AIM-TD: Pivotal Clinical Trials

The efficacy and safety of AUSTEDO in the treatment of TD was evaluated in 2 pivotal clinical trials, ARM-TD and AIM-TD.[7,8]

ARM-TD was a randomized, double-blind, parallel-group study in adult patients with TD. In this flexible-dose clinical trial, patients' doses were titrated to an individualized dosage that reduced abnormal movements and was tolerated by the patient. Patients were randomized 1:1 to receive AUSTEDO twice daily (BID) or placebo.[7]

AIM-TD was a randomized, double-blind, placebo-controlled, phase 3 clinical trial in adult patients with TD. Patients were randomly assigned 1:1:1:1 to receive 1 of 3 fixed doses of AUSTEDO (12 mg/day, 24 mg/day, or 36 mg/day) or placebo.[8]

For both ARM-TD and AIM-TD, the primary efficacy endpoint was change in Abnormal Involuntary Movement Scale (AIMS) score from baseline to Week 12.[7,8]

RIM-TD: Long-Term Maintenance Study

RIM-TD was an open-label study evaluating the efficacy of AUSTEDO as a long-term maintenance therapy in patients with TD who successfully completed either the ARM-TD or AIM-TD clinical trials. Enrolled patients discontinued the study drug for at least 1 week before beginning AUSTEDO (12 mg/day) and titrated for up to 6 weeks. The dose was adjusted once per week to identify a dose that adequately controlled dyskinesia and was tolerated by the patient.[9]

Primary Efficacy Data: ARM-TD and AIM-TD

Patients receiving AUSTEDO in both the ARM-TD and AIM-TD studies achieved significant improvement in AIMS total scores compared with patients receiving placebo.[7,8] Data did not suggest substantial differences in efficacy across various demographic groups.[4]

In the ARM-TD study, patients receiving AUSTEDO achieved a reduction of 3.0 points from baseline to Week 12 compared with 1.6 points for patients receiving placebo, and a treatment effect of -1.4 points (P=0.019) when compared with

IMPORTANT SAFETY INFORMATION (CONTINUED)

Parkinsonism: AUSTEDO XR and AUSTEDO may cause parkinsonism in patients with Huntington's disease or tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. The risk of parkinsonism may be increased by concomitant use of dopamine antagonists or antipsychotics. If a patient develops parkinsonism, the AUSTEDO XR or AUSTEDO dose should be reduced; some patients may require discontinuation of therapy.

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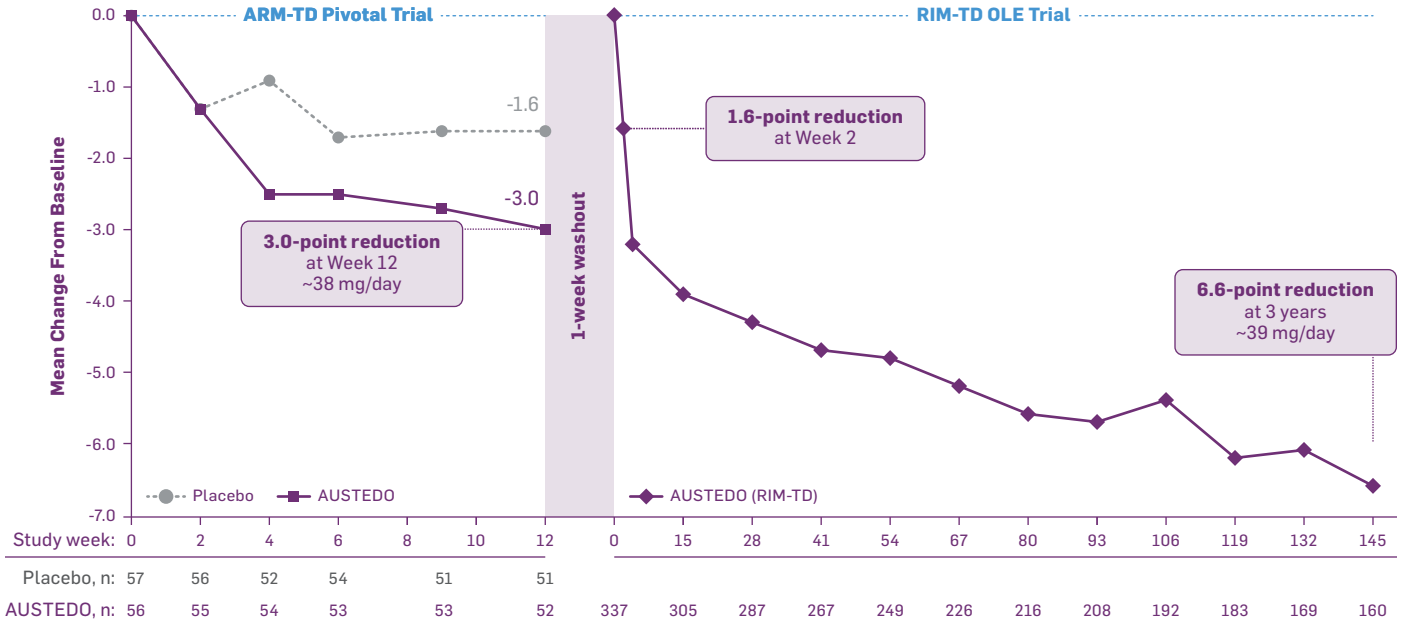
Figure 3.1. Rapid Response as Early as Week 2.* Increasing Improvement Observed Over 3 Years in an OLE Study†



Patients in the ARM-TD and RIM-TD studies received the AUSTEDO® (deutetrabenazine) tablets BID formulation.
*Response observed as early as Week 2 in the placebo-controlled studies.
†71% of patients at Week 145 saw improvement relative to Week 15.
OLE, open-label extension.

placebo **(Figure 3.1)**. The mean dose of AUSTEDO at the end of the treatment period was 38.3 mg/day.[7]

The results from ARM-TD were consistent with the results in AIM-TD at Week 12. In AIM-TD, patients receiving AUSTEDO 36 mg/day achieved a reduction of 3.3 points from baseline to Week 12, compared with 1.4 points for patients receiving placebo, and a treatment effect of -1.9 points (*P*=0.001) when compared with placebo.[8]

Long-Term Data: RIM-TD

During the overall treatment period, a reduction in mean AIMS total scores was observed from baseline through Week 145, with 67% of patients achieving ≥50% improvement in AIMS score through Year 3 **(Figure 3.1)**.[9]

Safety and Tolerability Profile

The most common adverse reactions occurring in patients treated with AUSTEDO (>3% and greater than placebo) were nasopharyngitis and insomnia. One or more adverse reactions resulted in a reduction of the dose of study medication in 4% of patients treated with AUSTEDO and in 2% of patients treated with placebo.[4] The adverse reactions occurring in patients treated with AUSTEDO (12-48 mg per day) (≥2%) are summarized in **Figure 3.2**.

Once patients were titrated to their maintenance dose, the following adverse reactions were no longer reported: dry mouth and nausea in AIM-TD and somnolence and dry mouth in ARM-TD.[10] Adverse reactions in the 3-year RIM-TD study were comparable to the 12-week ARM-TD and AIM-TD studies, with no new safety signals identified over the course of the study.[9]

Adverse reactions with AUSTEDO XR® (deutetrabenazine) extended-release tablets are expected to be similar to those with AUSTEDO BID.[4]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Sedation and Somnolence: Sedation is a common dose-limiting adverse reaction of AUSTEDO XR and AUSTEDO® (deutetrabenazine) tablets. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, until they are on a maintenance dose of AUSTEDO XR or AUSTEDO and know how the drug affects them. Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

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Figure 3.2. Safety and Tolerability Profile

Placebo-Controlled TD Studies: Adverse Reactions Reported in ≥2% of Patients Treated With AUSTEDO

Adverse Reaction	AUSTEDO (n=279)	Placebo (n=131)
Headache	5%	8%
Somnolence	4%	7%
Diarrhea	4%	4%
Nasopharyngitis	4%	2%
Fatigue	4%	5%
Insomnia	4%	1%
Anxiety	4%	5%
Upper respiratory tract infection	3%	4%
Dry mouth	3%	5%
Nausea	2%	7%
Weight increased	2%	3%
Urinary tract infection	2%	2%
Depression/Dysthymic disorder	2%	1%
Akathisia/Agitation/Restlessness	2%	1%
Arthralgia	2%	1%

Figure 3.3. VMAT2 Inhibitor Dosing Recommendations and Considerations

Coadministration per Pathway	Recommended Maximum Daily Therapeutic Dose	
	Deutetrabenazine	**Valbenazine**
Strong CYP3A4/5 inducer	No dose restriction	Concomitant use not recommended
Strong CYP3A4/5 inhibitor		40 mg
Strong CYP2D6 inducer	36 mg	40 mg
Strong CYP2D6 metabolizer		

No trials comparing AUSTEDO XR and Ingrezza® have been conducted. Their differences should not be construed to imply differences in safety, efficacy, or clinical outcome.

Considerations for Patients on Concomitant Medications

To limit possible drug-drug interactions, it is important to consider metabolic pathways when choosing a treatment for TD, particularly in patients who are taking medications for comorbidities. AUSTEDO XR is metabolized primarily by CYP2D6, with minor contributions from CYP3A4/5 and other enzymes to form several minor metabolites.[4] It has a range of dosing options for patients on concomitant medications and has the most dosing options for patients taking common strong cytochrome P450 (CYP) inhibitors or inducers **(Figure 3.3)**.[4,11] Even patients taking strong CYP inducers or inhibitors can titrate up to 36 mg/day, and no dose adjustments are required when taking AUSTEDO XR with P-glycoprotein (P-gp) substrates such as calcium channel blockers, statins, and antimicrobials.[4,12]

AUSTEDO is the only VMAT2 inhibitor indicated for TD with no recommendations against concomitant use with CYP3A4/5 inducers or inhibitors and may be considered for patients with TD who are receiving CYP3A4/5 inducers.[4,11]

Flexible, Once-Daily Dosing (24-48 mg/day)

AUSTEDO XR is available as a once-daily, extended-release tablet. The recommended starting dose of AUSTEDO XR for patients with TD is 12 mg/day and may be increased at weekly intervals by 6 mg/day,

IMPORTANT SAFETY INFORMATION (CONTINUED)

Hyperprolactinemia: Tetrabenazine elevates serum prolactin concentrations in humans. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of AUSTEDO XR and AUSTEDO.

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Figure 3.4. Flexibility to Titrate Dosing for Effective and Tolerable Control

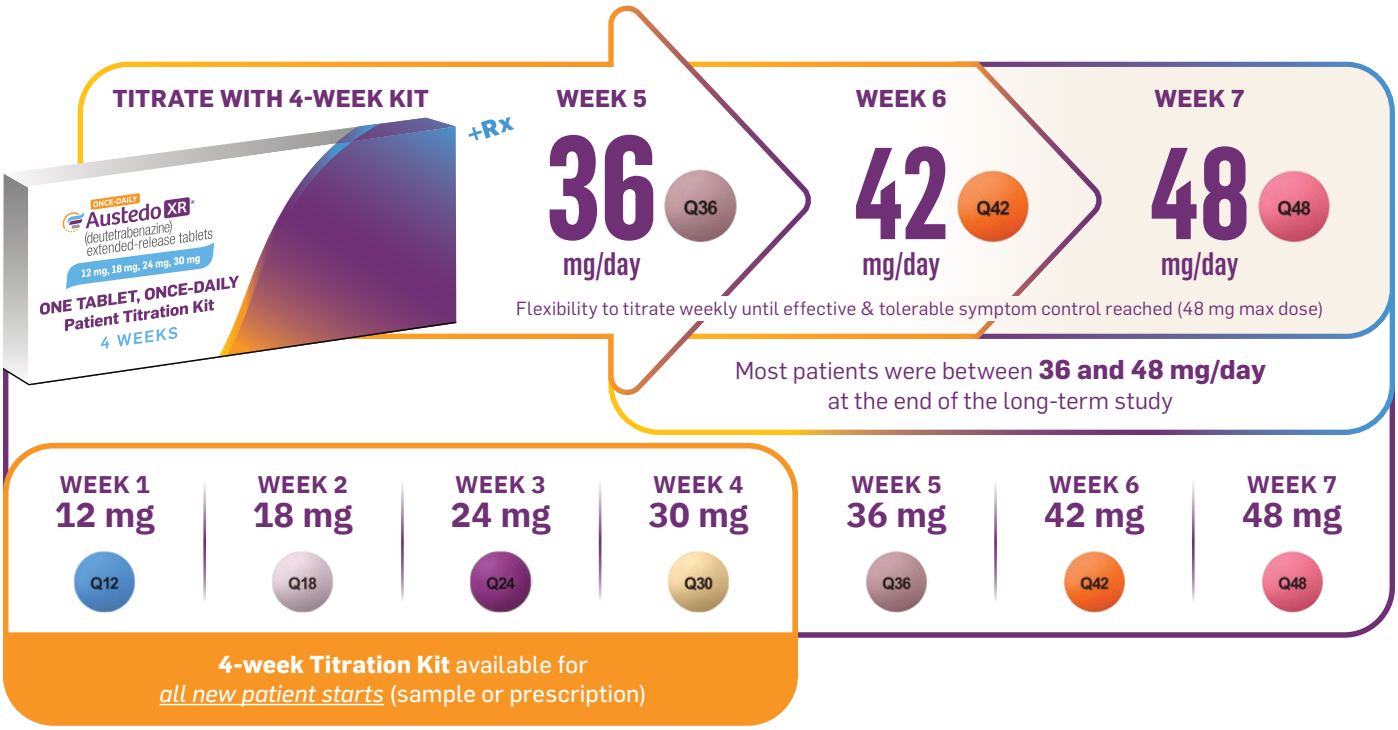

Image shown is not actual 4-week Titration Kit. Tablets not shown to actual size.

providing the flexibility to titrate as needed to achieve effective and tolerable symptom control. The maximum recommended daily dosage is 48 mg **(Figure 3.4)**.[4]

In a real-world survey, 98% of patients treated with once-daily AUSTEDO XR® (deutetrabenazine) extended-release tablets reported that taking it was very easy, and 95% of patients reported that they planned to continue treatment with AUSTEDO XR.[13]

Real-World Survey of Patients Taking AUSTEDO XR

In addition to patients reporting satisfaction with using AUSTEDO XR, patients also reported improvements in other areas of life as a result of movement reduction, including greater self-esteem, less embarrassment and anxiety, and overall better emotional well-being. Patients also reported feeling more comfortable with social activities, including spending time with family and friends, speaking to others, and going to work and school.[13]

Summary: Demonstrated Results With Once-Daily Dosing

VMAT2 inhibitors are the recommended first-line treatment for patients with TD.[3] It is critical to differentiate TD from other movement disorders and treat it appropriately.[4,5] It is also important to consider the metabolic pathways for all of a patient's prescribed treatments when identifying an appropriate treatment.[1,2] AUSTEDO XR is a VMAT2 inhibitor that has demonstrated efficacy and safety in the treatment of TD, with no recommendations against concomitant use with CYP3A4/5 inducers or inhibitors.[4,7,8] The flexible, once-daily dosing possible with AUSTEDO XR allows for individualized treatment to achieve effective and tolerable control.[4] ■

IMPORTANT SAFETY INFORMATION (CONTINUED)

Binding to Melanin-Containing Tissues: Deutetrabenazine or its metabolites bind to melanin-containing tissues and could accumulate in these tissues over time. Prescribers should be aware of the possibility of long-term ophthalmologic effects.

Please see additional Important Safety Information throughout and click here for full Prescribing Information, including Boxed Warning.

Expert Commentary With Jonathan Meyer, MD, and Daniel Kremens, MD, JD

Jonathan Meyer, MD
Psychiatrist
San Diego. California

Daniel Kremens, MD, JD
Movement Disorder Specialist
Philadelphia, Pennsylvania

This newsletter is produced by Teva Pharmaceuticals, and Dr Jonathan Meyer and Dr Daniel Kremens were compensated by Teva for their insights.

Q: Can you speak to the importance of antipsychotic medication as a treatment option for patients with schizophrenia and mood disorders?

Dr Meyer: For people with schizophrenia spectrum disorders, antipsychotics are a foundational therapy. There are also many patients with other diagnoses who need these therapies. We've come to recognize the role of these agents in treating mood disorders, including bipolar depression and major depressive disorder.

Q: When patients take antipsychotics, what is the risk of developing a movement disorder? What types of movement disorders do you see most often?

Dr Meyer: Treatment with any dopamine antagonist, including antipsychotics, will incur risks for movement disorders, including drug-induced parkinsonism (DIP), akathisia, dystonia, and tardive dyskinesia (TD). **While some movement disorders occur during the initial stages of treatment or when treatment is modified, TD occurs after long-term treatment with an antipsychotic and requires different and specific approaches to treatment.**

There is a recently approved therapy for schizophrenia that does not inhibit dopamine receptors, and, as a result, does not carry the same risk for TD, but it is not approved for patients with mood disorders, who are the majority of patients taking antipsychotics.

Dr Kremens: I agree that movement disorders are common in people taking antipsychotics. Looking specifically at TD, it's thought that about 30% of patients taking typical antipsychotics, about 7% of patients taking atypical antipsychotics without prior exposure to typical antipsychotics, and about 21% of patients taking atypical antipsychotics where their prior exposure is unspecified will develop TD. DIP is also common in people who are taking not just antipsychotics but other dopamine receptor blocking agents.

Q: Why is it important to evaluate and treat these movement disorders?

Dr Meyer: As a psychiatrist, I am concerned about TD because it can undermine the long-term psychiatric stability of my patients. **Although no clinical studies have been conducted to evaluate the impact of treating TD on patients, I have seen the impact of treatment on patients in my clinic.** In some cases, patients have reported that they stopped

taking antipsychotic medication regularly when they developed TD. **Not only does TD impact the patient physically, affecting their daily function, but it can also have profound impacts on their psychosocial functioning.**

Dr Kremens: I'd like to add that although some people may think of movement disorders as only impacting the patient, **they can have a significant impact on caregivers**—they tend to have higher scores on caregiver burden scales, and have reported that **TD has an impact on their daily activities, psychological well-being, and social or professional life.**

Q: Why is the term extrapyramidal symptoms, or EPS, still so widely used in psychiatry?

Dr Meyer: Partly, it's just historical precedent. The terms have been around for decades, and even though there are many people in psychiatry and neurology who are united in saying that this is an outdated term that doesn't accurately describe the different drug-induced movement disorders, the US Food and Drug Administration (FDA) is still wedded to it. When drugs are approved, they still use this terminology in their package insert. **It's unfortunate that the FDA still perpetuates what we think is outdated terminology, but I think as long as they continue to use it, we're going to have an uphill battle to try to get people to stop using it.**

Dr Kremens: I think it's also important to point out that it's not just the FDA. It's still being used in training programs, and **I see psychiatric residents still talking about EPS.** As you pointed out—EPS is an outdated term for a host of different movement disorders typically associated with drug exposure.

Instead of using the term EPS, we should be differentiating these disorders—this person has acute dystonia, this person has DIP, this person has TD—because the treatments are different, and **the term EPS may be contributing to the overuse of anticholinergic therapies in patients where that treatment is not appropriate.**

Q: What are the consequences of the use of the term EPS, and what do these consequences mean for outcomes for patients?

Dr Kremens: In the old days, everyone reached for anticholinergic therapies for EPS, thinking that they're treating either acute dystonia or DIP. This could lead to mistreatment of many other conditions. Anticholinergics, for example, aren't an appropriate treatment for TD and can make TD movements worse.

I think the emergence of vesicular monoamine transporter 2 (VMAT2) inhibitors for the treatment of TD has brought to the forefront the fact that these really are different disorders, and there are different treatments that are appropriate for many patients that would have previously fallen into the category of EPS.

I also think it's important to mention that, going forward, psychiatric providers are going to have to think carefully regarding the use of anticholinergics such as benztropine because a therapy for schizophrenia was recently approved that works in a cholinergic pathway and may increase the frequency or severity of anticholinergic adverse reactions when used concomitantly with other drugs that produce these reactions.

Q: How familiar are psychiatric providers with the differences between TD and DIP?

Dr Kremens: There hasn't been a lot of time or formal training devoted to teaching psychiatric providers the difference between these movement disorders. I think this was because, in the past, there

were no effective treatments for TD. There was almost a psychic blindness that developed to seeing movements, particularly TD. The patient needed to stay on the psychiatric medication, so if you diagnosed TD, there was very little you could do about it beyond switching the patient to a different antipsychotic.

Now that we have effective therapies, people are realizing that it's really important to see this movement disorder, understand it, and treat it.

Q: What do they need to understand in order to successfully make the differential diagnosis?

Dr Kremens: It's especially important for psychiatric providers to realize that, for the vast majority of these abnormal movements, they will be able to make the diagnosis, and they don't need fellowship training or specialty training to do it. Yes, there may be the rare cases where people have a very unusual movement or where patients may have both TD and DIP, but in general, tardive movements can be easily diagnosed.

TD is a hyperkinetic movement disorder, so we would expect to see excessive, fidgety movements. Although movements can occur anywhere in the body, the vast majority are going to be oral-buccal-lingual symptoms. These include things like excessive blinking, grimacing, lip puckering, lip smacking, and eyebrow furrowing. In the body, you're going to typically see movements in the hands—the so-called piano-playing fingers—or in the feet. Sometimes you can see abnormal movements in the trunk as well.

DIP, on the other hand, is a hypokinetic movement, so we would expect movements to be slow. Instead of having a lot of facial movement, they may have a paucity of facial movement. It may also be associated with tremor, which is a rhythmic, rather than fidgety, movement.

On a very gross level, which I think is very translatable to general practice, TD movements are fast and fidgety, generally involving the face, and Parkinsonian movements are rhythmic and slow. If you look for these features and keep those big things in mind, it will help you to identify the vast majority of movements correctly.

Dr Meyer: In addition to the features Dr Kremens mentioned, the time course usually helps distinguish DIP from TD as well: **DIP typically emerges quickly after a patient is either started on a new drug or a dose is increased, while TD begins later in the course of exposure—typically after at least 3 months, except in older individuals where it may occur after only one month of drug exposure.**

And I would emphasize that psychiatric providers are fully capable of differentiating a rhythmic, regular movement from the jerky, irregular movements of TD. They have been treating DIP for decades, in many cases without referring their patients to a neurologist. There may be instances where you need to refer a patient to a movement disorder specialist, but the vast majority of cases can be handled by a psychiatric provider.

Q: How do you approach differentiating the movements that you notice in your patients?

Dr Meyer: I start with a global impression of the person and their movement: is it rhythmic, regular, slow, fast, jerky, or irregular? Where is it presenting?

Then I look at the time course of onset: Is this something which presented relatively soon after a dose increase, within the expected time frame of the kinetics of the preparation? Or is this something which appeared out of the blue or insidiously, without respect to ongoing treatment changes?

And then lastly, I check if there have been other changes in treatment and how they may have impacted the movements. For example, consider a patient with mild dyskinesia who discontinued their antipsychotic. Did the movements worsen, as can happen with TD?

IMPORTANT SAFETY INFORMATION (CONTINUED)

Contraindications: AUSTEDO XR and AUSTEDO are contraindicated in patients with Huntington's disease who are suicidal, or have untreated or inadequately treated depression. AUSTEDO XR and AUSTEDO are also contraindicated in: patients with hepatic impairment; patients taking reserpine or within 20 days of discontinuing reserpine; patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing MAOI therapy; and patients taking tetrabenazine or valbenazine.

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Or did they improve, which you would expect with DIP? Similarly, a patient's response to an adjunctive anticholinergic may also indicate which movement disorder they have, as this treatment can make TD movements worse but will improve DIP.

Dr Kremens: I'd like to add that a very good examination for movement disorders can be done via telepsychiatry, and with additional camera positioning, examination of all 7 items on the Abnormal Involuntary Movement Scale, or AIMS, test should be possible.

The one item that may be difficult to test is rigidity. If you have a patient with paucity of movements and you're trying to identify if this person is slow for other reasons—maybe they're on sedating medications, for example—but they don't have a tremor, it may be necessary to follow up in person.

Q: How do you treat TD versus DIP, and do you reference any guidelines that support your decisions?

Dr Kremens: When I was just starting out, there was no FDA-approved treatment for TD. We would tell patients to stop or reduce the medication. I came to learn from my psychiatric colleagues that this was extraordinarily frustrating because most of the time, they had worked months to years to get this patient stable, and now all of a sudden I was telling them that they were going to have to stop or change this medicine.

Thankfully, with VMAT2 inhibitors we now have 2 FDA-approved, first-line treatments for TD that don't impact the psychiatric treatment of these patients.

Multiple guidelines—including the American Psychiatric Association (APA), the American Academy of Neurology, and a consensus panel of experts—have recommended VMAT2 inhibitors as first-line therapy for TD.

Dr Meyer: If you have a schizophrenia spectrum disorder, the idea of stopping the medication does not seem feasible, and even many people with mood disorders may need this medicine for psychiatric stability.

Now that we have FDA-approved treatments for TD, the reflex to stop the antipsychotic is not appropriate in many circumstances.

VMAT2 inhibitors were studied in people with severe mental illnesses. Depending on the study, 60% or more of the individuals had schizophrenia spectrum disorders, and the vast majority of the other subjects in these studies had a mood disorder, especially bipolar disorder. In the studies for each drug, the medication was added to existing medications, so there's no reason to change underlying therapy when you add either of the approved VMAT2 inhibitors.

Q: Why do you think that the use of anticholinergics for TD is so widespread?

Dr Meyer: I think it was a lack of understanding of the balance between dopamine and acetylcholine in the various pathways within the striatum. Because of that misunderstanding, there was a thought that if it's a movement disorder caused by D2 blockade, it should respond to an anticholinergic.

Now we understand the vast differences between the pathophysiology of TD and DIP and the alteration in the cholinergic-dopaminergic balance. Out of sympathy, I would also say there was probably an aspect of desperation. You had very little to offer people for TD prior to 2017 in the US. There was a hope that maybe this would make the situation better.

Dr Kremens: I agree. Many of them were trained that benztropine is the appropriate treatment for EPS, and TD fell under the EPS term. We now know that these are separate movement disorders, and that the use of anticholinergics in a patient with TD can make the condition worse.

Q: Given that VMAT2 inhibitors like AUSTEDO XR® (deutetrabenazine) extended-release tablets are the only

FDA-approved treatments for TD, what might you say to your colleagues regarding the importance of differentiating TD from other DIMDs and treating it appropriately?

Dr Kremens: The APA Guidelines for Schizophrenia indicate that moderate to severe TD should be treated, and that even mild TD should be treated if it is impacting the patient. **So, it's incumbent upon us to look for movements, and if we see them, determine the impact that it's having on our patients.** It's not for us to make the decision for them. Ask the patient, their family, and their caregivers about the impact of TD movements, and then make an appropriate decision about treatment with VMAT2 inhibitors.

Dr Meyer: I'll end by saying that there's no minimum score to diagnose TD. If there's an abnormal movement which looks like TD and it is having an impact on the patient, then that patient should be offered appropriate treatment. Often, patients who were not offered treatment and its potential benefits may have minimized the impact of their TD.

It is important for psychiatric providers to ask about the impact of TD across all domains of a patient's life—physical, psychological, social, vocational, educational, and recreational. Examples of questions to ask might be: Do other people notice? Do people at the group home make fun of you? Is your family not able to take you out to a meal or to church or a family gathering because of your movement disorders? Asking the right questions and probing your patients on different aspects of their life can help uncover the impact of TD even in patients who are not fully aware of their movements or who have a lack of insight into their condition.

And reinforce that treatment for TD can be added on to their current medication regimen without making any changes. Don't accept the first no as the end of the conversation; make it an ongoing discussion. Over time, people may decide that they want to consider treatment for TD.

I think it's important that we act as advocates for our patients. ■

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To further your knowledge of anticholinergic overuse and differentiating DIP from TD, please click here to visit ConnecTD.