TD NEWS+VIEWS
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Unmasking the Impact of Tardive Dyskinesia on Patients' Lives

CLINICAL

Assessing Tardive Dyskinesia and Its Impact on Patients and Clinicians

Even subtle tardive dyskinesia (TD) movements can significantly impact patients' lives and hinder mental health management. Evaluating TD impact, regardless of severity, is crucial for appropriate treatment.

CASE STUDY

Recognizing the Significance of Detecting Subtle Movements of Tardive Dyskinesia in a Patient Diagnosed With Major Depressive Disorder

For patients with mood disorders on antipsychotics, clinicians must assess movements and their impact and appropriately treat them upon TD diagnosis.

TREATMENT

AUSTEDO XR®: A Once-Daily Treatment Option for Adult Patients With Tardive Dyskinesia

Explore the clinical data from the pivotal and long-term, open-label extension (OLE) studies as well as key findings from real-world patients' experience with AUSTEDO XR.

EXPERT COMMENTARY

Expert Commentary With Rakesh Jain, MD, MPH

Clinical Professor - Mental Wellness - Psychiatry
Austin, Texas

In this conversation, Dr Jain discusses the impact of TD on patients, noting impairment beyond movement severity, and highlights insights from the IMPACT-TD Registry study along with real-world experiences using AUSTEDO XR.

This newsletter is produced by Teva Pharmaceuticals, and Dr Jain was compensated by Teva for his insights.

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.

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

ANTICHOLINERGIC OVERUSE

Assessing Tardive Dyskinesia and Its Impact on Patients and Clinicians

Even when the movements associated with TD are subtle, they can have a significant impact on patients' lives and interfere with the management of underlying mental health conditions. Uncovering the presence and consequences of TD, no matter the severity, can lead to appropriate treatment of patients with this disorder.

Overview of TD

TD is a persistent, typically irreversible, hyperkinetic movement disorder resulting from chronic exposure to antipsychotics and other dopamine receptor blocking agents (eg, antiemetics or prokinetics).[1-3] In the United States, TD affects approximately 785,000 patients.[4] In truth, though, **TD may be underdiagnosed and undertreated**. Only around 15% of patients with TD receive a formal diagnosis, and fewer than 6% of patients are treated with vesicular monoamine transporter 2 (VMAT2) inhibitors, the only medication approved by the US Food and Drug Administration for TD.[4] In a study of patients with probable TD, less than half were formally diagnosed, despite having lived with the impact of TD for 5 years.[4]

TD affects ~785,000 patients—most are not diagnosed, and even fewer are treated.

Impact of TD

The impact of TD, even when movements are mild, reaches into many aspects of patients' lives. This is reflected in the IMPACT-TD Registry study, an ongoing, real-world, longitudinal study evaluating the impact of TD on patients.[5] In an interim analysis of clinician-reported data from 286 patients, 98% of patients experienced the impact of TD on some aspect of their lives.[5] Importantly, **more than half of patients with mild TD experienced moderate to severe impacts on social, psychological, physical, and vocational areas of life**. In fact, 54% of patients with very mild TD, as assessed by the Clinician's Global Impression of Severity, and 61% of patients with mild TD experienced moderate to severe impact.[5]

A challenge in evaluating the impact on patients is that **clinicians might perceive mild TD movements differently from how patients experience them**.[5] This contrast is exemplified below, where a patient describes the impact of mild TD with and without sound. Without audio, simply watching the patient's movements might not indicate any impact, but when sound is included, the significant impact becomes clear **(Videos 1 and 2)**.

A Real Patient Describes the Extensive Impact of Mild TD

Video 1. Patient's Movements (no sound)
The visual assessment of TD is mild

Click here to view video

Video 2. Patient Impact From TD (with sound)
The verbal description of TD indicates significant impact

Click here to view video

Patient images used with permission.

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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More than half of patients with very mild to mild TD experience moderate to severe impact, influencing their social, psychological, and emotional well-being.

The IMPACT-TD Registry study also showed that approximately 74% of patients with an Abnormal Involuntary Movement Scale score of 1 to 6 experienced a moderate to severe impact of TD on their lives.[5] The impact of TD was particularly acute in the psychosocial aspects of life (eg, embarrassment in social situations, impacting the ability to enjoy things they do for fun) **(see video 3)**.[6]

TD may also adversely affect the clinician's ability to manage the patient's underlying mental health condition. In an online survey of 269 patients, nearly 50% of patients reported that because of TD, they skipped doses of their antipsychotic medication, and nearly 40% stopped taking their antipsychotic altogether. Over 20% advised others not to take an antipsychotic medication. Moreover, 36% of patients reported they stopped going to the doctor to treat their underlying condition due to TD **(Figure 1.1)**.[7] The experiences reported by these patients demonstrate the **difficulty of managing underlying mental health conditions when TD is present**.

Video 3. A Patient Describing the Impact of TD Across the 4 Domains Assessed in the IMPACT-TD Registry Study

Click here to view video

Patient images used with permission.

Figure 1.1. Impact of TD on Management of Underlying Condition

TD can undermine the management of underlying mental health conditions.

Assessing the Impact of TD

The American Psychiatric Association (APA) recommends **treating patients when their TD negatively impacts them, regardless of severity**.[8]

Unfortunately, clinicians don't always have a full picture of the impact of TD on their patients. In one online survey, 154 patients with TD and 150 clinicians were asked to rate the impact of TD on 4 domains; psychological/emotional, physical, professional, and social. Patients reported a greater awareness of the impact of TD than clinicians. While patients and clinicians both reported similar impact of TD in the psychological and emotional domain, patients reported a significantly greater level of impact across all domains compared with clinicians. Nearly twice as many patients reported their physical domain was impacted as clinicians. These data highlight the **need for increased dialogue between patients with TD and their clinicians to assess the impact of TD on patients**.[9]

What can clinicians do to have a deeper understanding of the impact of TD on the lives of their patients? Once a patient has been diagnosed, it is important to ask about the impact at every clinical visit.[10] **Consider identifying the consequences**

IMPORTANT SAFETY INFORMATION (CONTINUED)

Clinical Worsening and Adverse Events in Patients with Huntington's Disease: AUSTEDO XR and AUSTEDO may cause a worsening in mood, cognition, rigidity, and functional capacity. Prescribers should periodically re-evaluate the need for AUSTEDO XR or AUSTEDO in their patients by assessing the effect on chorea and possible adverse effects.

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of TD across the 4 domains: psychological/psychiatric, social, physical, and vocational/educational/recreational.[11] Talking with caregivers, family, and friends may also be helpful in identifying the impact of TD.[11] Specific questions related to each domain may include the following[11,12]:

- How bothered are you by negative reactions to your TD by your friends or family?
- Have you experienced feelings of low self-esteem or embarrassment because of your TD?
- Do you have trouble eating or falling asleep?
- How often does your TD impact your ability to perform your job?

Consider the Impact-TD scale as a guide in clinical practice to assess the impact of TD. **Click here** to view the article.

The Importance of Assessing the Impact of TD in Clinical Practice

There are many reasons why it is important for you, as a healthcare professional, to routinely assess the impact of TD in your clinical practice. First, TD can affect your ability to manage your patients' ongoing mental health conditions.[7] In addition, **TD can profoundly impact your patients, influencing their ability to perform daily functions, be productive, and socialize**.[5] Finally, the APA Guidelines recommend treating patients with TD when the condition negatively impacts them, even if the movements are mild.[8] **Routine assessment of both the presence and consequences of TD**, through careful questioning and listening, **can illuminate the impact of TD** on your patients and lead to appropriate treatment.[11,12] ■

Ask the right questions and listen to your patients to uncover the impact of TD.

CASE STUDY

Recognizing the Significance of Detecting Subtle Movements of Tardive Dyskinesia in a Patient Diagnosed With Major Depressive Disorder

Prescriptions of antipsychotics have increased over time, driven by the use of atypical antipsychotics for mood disorders, including major depressive disorder (MDD). **While these drugs are essential for many patients with MDD, they can also cause tardive dyskinesia (TD)**, a persistent, often irreversible, hyperkinetic movement disorder, which can have a profound impact on patients' ability to perform daily activities, be productive, and socialize.

Patients with mood disorders are often highly functioning and can be severely impacted by even subtle movements. While all patients taking antipsychotic drugs are at risk of developing TD, **mood disorder has been recognized as an additional risk factor**. Consequently, clinicians should closely monitor subtle movement changes and assess their impact to ensure patients receive appropriate treatment.

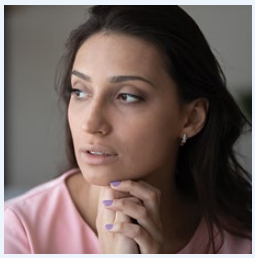
In this case study, Carol was prescribed an atypical antipsychotic following a severe depressive episode and subsequently developed TD. After experiencing episodes of mouth twitches and repetitive blinking, Carol became concerned about how the movements would impact the way she was perceived

at work. After she sought a second opinion, her clinician diagnosed TD and noted its impact on her life, subsequently offering treatment with a vesicular monoamine transporter 2 (VMAT2) inhibitor.

This case underscores the importance of assessing the impact of TD, regardless of the severity of movements, especially in patients with mood disorders like Carol.

Clinicians should carefully assess and monitor even minor, subtle changes in movement and, importantly, inquire about the effects of these abnormal movements to ensure that appropriate treatment is offered to these patients.

Case Study: Carol, a 36-year-old woman, undergoing treatment with an antidepressant and an atypical antipsychotic for the management of MDD



Not an actual patient.

Medical History

Carol is recently engaged and being considered for partnership in a major accounting firm. She was diagnosed with MDD at the age of 29 and was treated with an antidepressant. Following a severe depressive episode, **she began adjunctive treatment with an atypical antipsychotic** and has since remained stable for several years.

Carol expressed concern about how her movements may impact her daily activities, specifically at work, and how this could influence her chances for promotion.

Presenting Issue

Recently, she has noticed abnormal movements, including mouth twitches and repetitive eye blinking, which were noticed by a colleague who then made a joke about illicit drug use. She told her psychiatric clinician she had been feeling anxious about both wedding planning and her partnership interviews. The clinician acknowledged her comments and movements; however, **the clinician noted that the movements were mild and did not ask further questions or see a need for additional investigation**.

Impact on Daily Activities

No clinical studies have been conducted to evaluate the effects of treating TD on the outcomes discussed here.

Carol told her coworkers that she had dry eyes to explain the excessive blinking, but the **movements in her mouth and hands would worsen during stressful meetings and near important deadlines**. She was concerned about her movements worsening during her upcoming partnership interviews, which could **impact her chances of being promoted**. Her awareness of these movements was affecting her daily life and contributing to her anxiety. As a result, she sought a second opinion to have her concerns about the movements addressed.

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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TD Diagnosis and Assessment of Impact

During the clinical examination, her new clinician observed excessive blinking and slight puckering of the lips as she waited to begin the session and inquired if Carol was aware of the movements. **Carol acknowledged them and expressed worry about the worsening of movements in her hands and mouth under stress, and their potential impact on her career.** She also mentioned experiencing jaw pain, which indicated additional orofacial involvement. The clinician conducted an activation maneuver and observed mild "piano playing" in her fingers. Based on these observations, **the clinician diagnosed TD and, recognizing its impact on the patient, prepared for a discussion about treatment**.

Treatment Decisions

The American Psychiatric Association (APA) recommends treatment of TD that has an impact on the patient, regardless of the severity of movements. Based on the impact of movements on Carol's life, she and her clinician discussed appropriate treatment. **To manage Carol's TD, her clinician started treatment with a VMAT2 inhibitor, the only FDA-approved treatment for TD, without making any adjustments to her current regimen of antidepressant and adjunctive antipsychotic therapy.**

Outcomes

Carol's movements improved with treatment ahead of her partnership interviews and wedding. As a result of the reduction in movements, Carol **felt more at ease in social situations**, such as her wedding. Throughout ongoing conversations with her clinician, Carol understood that TD typically persists, potentially requiring lifelong treatment. To that end, she plans to continue treatment while regularly seeing her new psychiatric provider to manage her MDD.

Discussion: Key Learnings From This Case Study

- Antipsychotic medications prescribed for mood disorders such as MDD can lead to the development of TD, which is characterized by abnormal, involuntary movements
- Small, subtle movements associated with TD can negatively impact daily activities, and may worsen the mood of patients with MDD
- It is critical that providers ask questions to uncover the impact of subtle movements on their patients' lives
- APA guidelines recommend VMAT2 inhibitors—the only FDA-approved treatment for TD—if TD has an impact on the patient, regardless of the severity of movements
- Carol's case study highlights the need for clinicians to carefully assess movements and their impact in patients with mood disorders who are taking antipsychotics, and appropriately treat TD that has an impact on the patient ■

After being diagnosed with TD, Carol began taking a VMAT2 inhibitor. She experienced a reduction in movements, and as a result, felt more comfortable in social and work environments.

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ONCE-DAILY
Austedo XR®
(deutetrabenazine)
extended-release
6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, 42 mg, and 48 mg tablets

TREATMENT

AUSTEDO XR®: A Once-Daily Treatment Option for Adult Patients With Tardive Dyskinesia

TD, a hyperkinetic movement disorder caused by antipsychotics, affects multiple aspects of patients' lives and undermines the stability of their underlying mental health disorders.[1,2] Even **mild symptoms can have a significant impact extending into social, psychological, and emotional aspects of patients' lives**.[3,4] The prevalence of TD is growing, owing to the increased use of antipsychotics for patients with mood disorders. These patients tend to have a greater awareness of abnormal movements and the impact they have on their lives.[2,7,8] The American Psychiatric Association (APA) Guidelines recommend **vesicular monoamine transporter 2 (VMAT2) inhibitors for the treatment for TD if it has an impact on the patient, regardless of the severity of movements**.[9] Additionally, VMAT2 inhibitors are recommended for the treatment of TD without the need to modify the antipsychotic dose.[9-11]

AUSTEDO XR is a VMAT2 inhibitor approved in the US for the treatment of adults with TD.[11] This article reviews efficacy and safety data from the pivotal and long-term, open-label extension (OLE) studies. Then it delves into key findings from a real-world survey that evaluated patients' experience with AUSTEDO XR, including perceived ease of use and effects on social and emotional well-being.

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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ARM-TD and AIM-TD Study Designs

The efficacy and safety of AUSTEDO® (deutetrabenazine) tablets in the treatment of TD was evaluated in 2 pivotal clinical trials, ARM-TD (Aim to Reduce Movements in Tardive Dyskinesia) and **AIM-TD** (Addressing Involuntary Movements in Tardive Dyskinesia).[12,13]

ARM-TD was a 12-week, randomized, double-blind, placebo-controlled trial in which doses of AUSTEDO were titrated to an individualized dose that reduced abnormal movements and was tolerated. After screening, patients were randomized 1:1 to receive AUSTEDO twice daily (BID) or placebo.[13]

AIM-TD was a 12-week, randomized, double-blind, placebo-controlled trial in which patients received AUSTEDO 0 mg (placebo), 12 mg/day, 24 mg/day, or 36 mg/day.[11,12]

The primary efficacy endpoint in both trials was the change in Abnormal Involuntary Movement Scale (AIMS) total score from baseline to Week 12.[6,11-13]

ARM-TD and AIM-TD: Key Efficacy Endpoints

Patients who received AUSTEDO demonstrated a **rapid response as early as Week 2 and achieved a significant and meaningful reduction in TD severity at Week 12**.[6,11,13] In ARM-TD, patients receiving AUSTEDO demonstrated a statistically significant improvement in AIMS total score, with a reduction of 3.0 points from baseline to Week 12, compared with 1.6 points in the placebo group (treatment effect of -1.4 points, *P*=0.019) **(Figure 3.1)**.[6,13] At Week 12, 94% of patients were taking a dose of ≥30 mg/day.[6]

At Week 12 in AIM-TD, AIMS total score was reduced by 3.3 points from baseline in patients taking AUSTEDO 36 mg/day vs 1.4 points in patients taking placebo (treatment effect of –1.9 points, *P*=0.001).[11,12]

RIM-TD: Study Design and Key Efficacy Endpoint

RIM-TD (Reducing Involuntary Movements in Participants With Tardive Dyskinesia) was an open-label study designed to evaluate **long-term treatment of TD with AUSTEDO for up to 3 years**, following completion of ARM-TD or AIM-TD. Among the patients evaluated, 337 patients were in treatment at baseline and 160 patients remained on treatment through the end of Week 145.[14] The mean overall compliance rate was nearly 90% at 3 years.[6]

At Week 145, 87% of patients were taking a dose of ≥30 mg/day.[6]

Patients who received AUSTEDO achieved significant and meaningful reduction in TD severity at Week 12.

Figure 3.1. ARM-TD: Significant and Meaningful Reduction in TD Severity at Week 12[6,13]

Patients in the ARM-TD study received the AUSTEDO BID formulation.

Baseline AIMS total scores were similar between AUSTEDO and placebo: AUSTEDO 9.7 (SD, 4.1); placebo 9.6 (SD, 3.8).

LS, least squares; SD, standard deviation; SE standard error.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Sedation and Somnolence: Sedation is a common dose-limiting adverse reaction of AUSTEDO XR® (deutetrabenazine) extended-release tablets and AUSTEDO. 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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At baseline, concurrent diagnoses included schizophrenia (50%), schizoaffective disorder (10%), bipolar disorder (17%), and depression (19%).[6]

Increasing improvement in AIMS total score was observed over 3 years in the OLE study.[14] Specifically, 71% of patients at Week 145 saw improvement relative to Week 15 (Figure 3.2).[6]

Consistent outcomes were observed, regardless of the underlying condition.[6]

Increasing improvement in AIMS total score was observed in an OLE study.

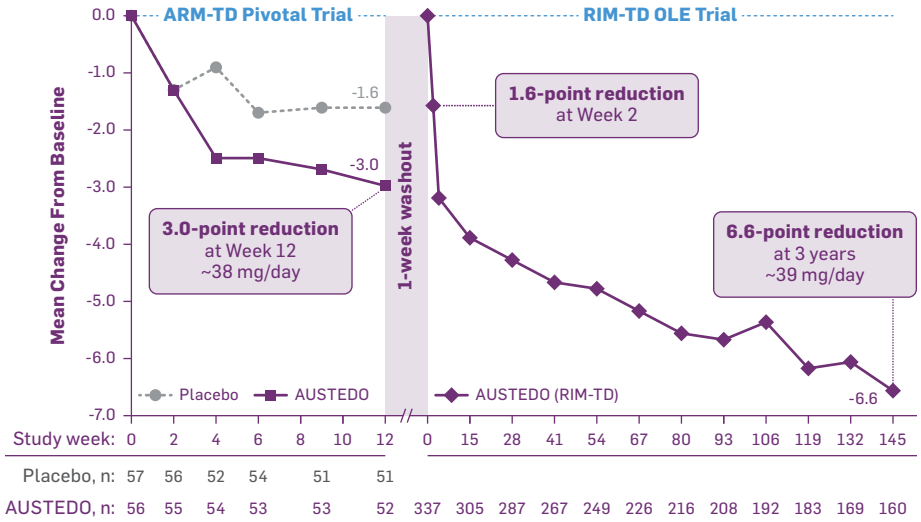
Safety and Tolerability Profile

Across both placebo-controlled studies in patients with TD, the **most common adverse reactions reported in patients treated with AUSTEDO** (>3% and greater than placebo) **were nasopharyngitis and insomnia**.[11] The adverse reactions occurring in patients treated with AUSTEDO (12-48 mg per day) (≥2%) are summarized in **Figure 3.3**.

Discontinuation due to adverse events (AEs) occurred in 4% of patients taking AUSTEDO compared with 3% of patients treated with placebo.[12] Four percent of patients required dose reduction of AUSTEDO due to AEs compared with 2% of patients taking placebo.[11] Once patients were titrated to their maintenance dose, several AEs were no longer reported, including dry mouth and nausea in AIM-TD and somnolence and dry mouth in ARM-TD.[6]

No new safety signals were identified in RIM-TD, and AEs were comparable with those in the 12-week clinical trials.[14] Results were consistent across patient subgroups, including those with psychotic disorders such as schizophrenia and schizoaffective disorder, as well as those with mood

Figure 3.2. AIMS Score Reduction in Pivotal and OLE Studies[6,11,13,14]



Patients in the ARM-TD and RIM-TD studies received the AUSTEDO BID formulation.

Baseline AIMS total scores were similar between AUSTEDO and placebo: AUSTEDO 9.6 (SD, 4.1); placebo 9.6 (SD, 3.8).

Figure 3.3. Placebo-Controlled TD Studies: Adverse Reactions Reported in ≥2% of Patients Treated With AUSTEDO[6,11,*]

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%

*Patients in the AIM-TD and ARM-TD studies received the AUSTEDO BID formulation.[6,11]

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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disorders like depression and bipolar disorder, and other disorders.[15]

Adverse reactions with AUSTEDO XR® (deutetrabenazine) extended-release tablets are expected to be similar to AUSTEDO® (deutetrabenazine) tablets BID.[11]

AEs in RIM-TD were similar to those reported in ARM-TD and AIM-TD.

Real-World Survey Assessing Experience With AUSTEDO XR

A prospective, cross-sectional survey of 118 patients with TD was conducted between July 2, 2024, and August 2, 2024, to assess patients' experience with AUSTEDO XR, including perceived ease of use and effects on social and emotional well-being. Interim results from this survey found that more than **50% of patients reported improved social and emotional well-being as a result of movement reduction with AUSTEDO XR**. Patients reported greater self-esteem (66%), less embarrassment (73%) and anxiety (59%), and better overall emotional well-being (77%) **(Figure 3.4)**. In addition, **98% of patients said taking once-daily AUSTEDO XR was easy, and 95% planned to continue taking AUSTEDO XR**.[16]

Consider the Potential for Drug-Drug Interactions When Choosing a VMAT2 Inhibitor

It is crucial to consider patient comorbidities and the medications they may be taking, as the potential exists for drug interactions when selecting a VMAT2 inhibitor. AUSTEDO XR is metabolized primarily by CYP2D6, with minor contributions from CYP3A4/5 and other enzymes to form several minor metabolites.[11] However, there are **no dose restrictions up to 36 mg/day for patients starting AUSTEDO XR (Figure 3.5)**.[11] Moreover, no dose adjustments to P-gp substrates, which may include some calcium channel blockers, statins, and antimicrobials, are required when taking AUSTEDO XR.[11,17]

AUSTEDO XR is the only VMAT2 inhibitor indicated for TD with no recommendations against concomitant use with strong CYP3A4/5 inducers or inhibitors.[11,18]

AUSTEDO XR: Flexibility for Effective and Tolerable Control

AUSTEDO XR has the most once-daily dosing options of any VMAT2 inhibitor.[11,18] The recommended starting dose of AUSTEDO XR for patients with TD is 12 mg/day, which may be increased at weekly intervals by 6 mg/day until desired symptom control is tolerably achieved.[11] The average daily dose in clinical trials was >36 mg/day, and 52% of patients were taking between 36 mg/day and 48 mg/day at Week 145 in the long-term study.[12,14] AUSTEDO XR should be swallowed whole. Tablets should not be chewed, crushed, or broken. **AUSTEDO XR may be taken with or without food (Figure 3.6).**[11]

A real-world survey indicated that patients experienced improved social and emotional well-being as a result of movement reduction with AUSTEDO XR.

Figure 3.4. >50% of Patients Reported Improved Social and Emotional Well-Being as a Result of Movement Reduction With AUSTEDO XR[16]

In a real-world survey, patients reported improvement in other areas of life as a result of movement reduction with AUSTEDO XR[16]

- Greater self-esteem and less embarrassment
- Less anxiety and better overall emotional well-being
- Feeling more comfortable with social activities, including
  - Spending time with family and friends
  - Speaking to others
  - Going to work and school

98%
said taking once-daily AUSTEDO XR was easy

95%
of patients planned to continue taking AUSTEDO XR

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.

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No dose restrictions up to 36 mg/day for patients starting AUSTEDO XR.

Figure 3.5. Dosing Recommendations and Considerations for VMAT2 Inhibitors[11,18]

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.

Figure 3.6. Dosing Options for AUSTEDO XR[6]

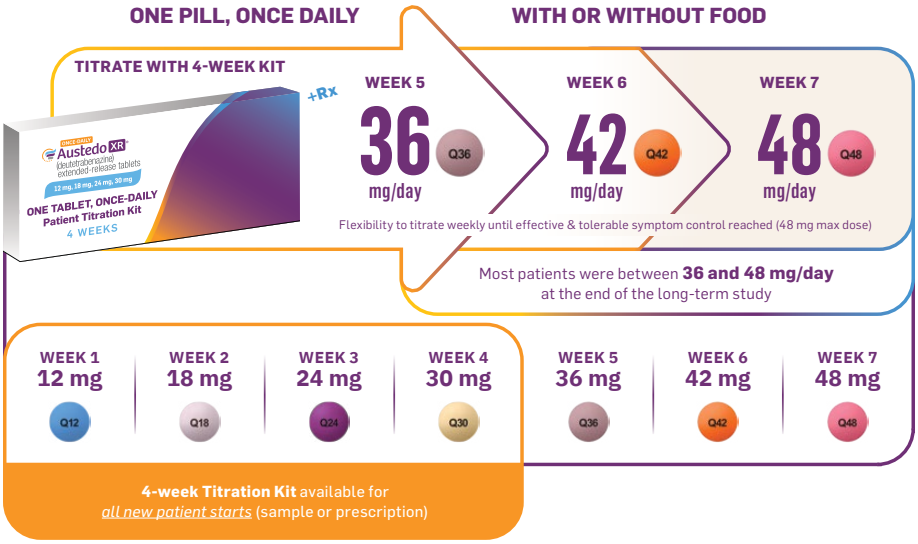


Image shown is not actual 4-week Titration Kit. Tablets not shown to actual size.

AUSTEDO XR has the most once-daily dosing options for any VMAT2 inhibitor, allowing for effective and tolerable symptom control.

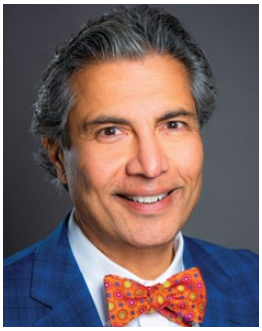
Summary

- The APA guidelines recommend VMAT2 inhibitors for the treatment of TD that has an impact on the patient, regardless of the severity of movements[9]
- AUSTEDO XR is a once-daily VMAT2 inhibitor approved for the treatment of adults with TD[11]
- Significant and meaningful symptom reduction was demonstrated with AUSTEDO and increased improvement over 3 years was seen in the OLE study, with 71% of patients at Week 145 experiencing improvement relative to Week 15[6,14]
- The most common adverse reactions for AUSTEDO (3% and greater than placebo) in controlled clinical studies in patients with TD were nasopharyngitis and insomnia
- Adverse reactions with AUSTEDO XR are expected to be similar to AUSTEDO[11]
- In a real-world survey, patients reported improved social and emotional well-being as a result of movement reduction with AUSTEDO XR[16]
- The flexible, once-daily dosing possible with AUSTEDO XR allows for individualized treatment to achieve effective and tolerable control[11] ■

IMPORTANT SAFETY INFORMATION (CONTINUED)

Common Adverse Reactions: The most common adverse reactions for AUSTEDO (>8% and greater than placebo) in a controlled clinical study in patients with Huntington's disease were somnolence, diarrhea, dry mouth, and fatigue. The most common adverse reactions for AUSTEDO (4% and greater than placebo) in controlled clinical studies in patients with tardive dyskinesia were nasopharyngitis and insomnia. Adverse reactions with AUSTEDO XR extended-release tablets are expected to be similar to AUSTEDO tablets.

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



EXPERT COMMENTARY

Expert Commentary With Rakesh Jain, MD, MPH

Clinical Professor - Mental Wellness - Psychiatry
Austin, Texas

This newsletter is produced by Teva Pharmaceuticals, and Dr Jain was compensated by Teva for his insights.

In this conversation, Dr Jain discusses the impact of tardive dyskinesia (TD) on patients, emphasizing the substantial impairment that can occur beyond the severity of abnormal movements themselves. He also highlights important findings from the IMPACT-TD Registry study and shares real-world experiences with the use of AUSTEDO XR® (deutetrabenazine) extended-release tablets.

Q: Based on your experience, how does TD impact various aspects of patients' lives?

A: Traditionally, it was thought that the severity of TD movements determined the overall impact on the patient. **However, in the last decade, it has become clear that the severity of movements is only part of the picture.** In fact, TD can have a **broader impact on patients' lives, leading to significant impairment in critical areas**. These include physical challenges related to speech, swallowing, or breathing; social implications, including the substantial stigma attached to abnormal movements; and psychological impact, such as hopelessness or anger. In my experience, patients with TD **may feel a sense of betrayal toward both their clinician and the medication that caused this condition**. They might feel let down by their own minds and bodies, which may no longer be able to perform simple tasks, and they may encounter stigmatization from others as a result of their abnormal movements. This creates the perfect storm that leads to the functional impairment that many patients face. As a result, American Psychiatric Association (APA) Guidelines state that TD that impacts patients should be treated, regardless of severity of movements.

Q: How does TD impact patients with mood disorders such as bipolar disorder and major depressive disorder?

A: In the early stages of my career, I only encountered TD in individuals with schizophrenia. Now, it's becoming more prevalent in individuals with mood disorders who rely on medications that can cause TD. In fact, the use of atypical antipsychotics to treat mood disorders is thought to be the primary cause of the increasing rates of TD in the United States. These individuals may experience a more severe impact from TD because they are often highly functioning and therefore more aware of even small movements. Additionally, some may discontinue their medication due to feelings of betrayal and the mistaken belief that it will halt the progression of TD. This has the potential to destabilize their underlying mental health disorder. Therefore, **it's essential for clinicians to raise awareness among our patients and colleagues about the high**

potential for TD in this population, engage in more careful screening by looking and asking about movements, and treating patients if TD impacts their lives.

Q: What impact does TD have on caregivers?

A: Individuals close to someone with TD, such as spouses, parents, children, or friends, are often affected. Caregivers can experience the burden of TD in various ways. They may need to help the patient with daily activities, such as meal preparation and driving, and they may experience psychological distress, such as anxiety or worry. Caregivers may also face social repercussions due to the patient's TD, such as strained friendships, or they may withdraw from social activities. I like to use the term **"meta-metastatic disease"** to accurately capture the far-reaching and profound effects of TD on both the individual and their social network.

In a way, TD can be described as a "meta-metastatic disease," affecting both the patients and their social networks.

Q: Why do some healthcare providers not fully assess the impact of TD, and what might you say to convince them to make the assessment of impact routine?

A: Until recently, the assumption in psychiatry was that TD was primarily found in community mental health centers, state hospitals, and in individuals with schizophrenia. It wasn't until a decade ago that we realized that TD is present in every practice. Additionally, there was a misconception that atypical antipsychotics had resolved the issue of TD, when in fact they are now recognized as drivers of new cases. The reluctance to address TD primarily stems from **discomfort in assessing and differentiating TD from other movement disorders**. Furthermore, I believe that clinicians **may lack familiarity with the use of vesicular monoamine transporter 2 (VMAT2) inhibitors** and may hold misconceptions regarding their use, whether it is necessary to discontinue antipsychotics, and potential side effects.

Ultimately, we can encourage our colleagues to adopt the **"see something, do something"** principle—recognizing TD movements and the potential impact on patients and initiating the appropriate therapy.

Q: What makes the IMPACT-TD Registry study so significant, and what are some of the key findings?

A: This study is truly unique and the **first of its kind worldwide**, contributing significantly to our understanding of TD. The data demonstrate the **consistency of impairment levels among patients with TD**, irrespective of the severity of movements, and this distinct characteristic makes TD stand out among other movement disorders. Additionally, the study establishes the chronic nature of TD, providing long-term insights into our patients' experiences. This highlights the continuous and pervasive nature of the disorder and emphasizes the need for ongoing treatment. Thus, this study is likely to be regarded as **a landmark study in our understanding of TD**.

The IMPACT-TD Registry study offers valuable real-world insights into how TD movements affect various aspects of patients' lives beyond just movement severity.

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.

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

Q: Do you have any guidance for your colleagues who are more hesitant to titrate to effective and tolerable symptom control? What steps are necessary to make progress in this area?

A: Psychiatry clinicians tend to start low and go slow. Clinicians may be treating TD with the lowest dose that improved some movements for the patient, assuming that this minimal level is the therapeutic target. I would like to encourage them to **consider impairment as their benchmark, and if the patient continues to experience impairment in some aspect of their life, the clinician should consider continuing to increase the dose**. An important feature of AUSTEDO XR® (deutetrabenazine) extended-release tablets is that it provides a range of therapeutic doses and offers **flexibility to achieve effective and tolerable control**. In pharmacokinetic studies, increased plasma levels correlated with higher potential for treatment success, as measured by Clinical Global Impression of Change and Patient Global Impression of Change scales, but not higher potential for adverse events.

Q: What are some of the key findings from the real-world survey that evaluated satisfaction and experience with AUSTEDO XR? What are the clinical implications of these findings?

A: Most participants reported that their abnormal movements improved compared with how they felt before treatment with AUSTEDO XR. They also noted that this reduction had a **positive impact on their lives and daily activities**. In addition, they appreciated the flexibility of taking AUSTEDO XR with or without food and at different times of the day. However, there was also some indication of suboptimal dosing, underscoring the potential for additional improvement in some patients.

Overall, this real-world study demonstrated that, **as movements improve, there is a genuine potential for enhancement in the individual's life beyond merely suppressing the movement**. This progress is not only inspiring for the prescribing clinician but also for the entire clinical team, as it reflects improvements in movement severity, social interaction, and physical functioning.

In a real-world survey, >50% of patients reported improved social and emotional well-being as a result of movement reduction with AUSTEDO XR.

Key Learning Points

- TD significantly impacts patients' lives, causing substantial impairment in physical, social, and psychological aspects
- Clinicians should be more aware of the rising prevalence of TD in patients with mood disorders, owing to the increased use of atypical antipsychotics
- APA Guidelines recommend VMAT2 inhibitors for TD that has an impact on the patient, regardless of the severity of movements
- Clinicians' hesitation to fully address the impact of TD may stem from difficulties in differentiating TD from other drug-induced movement disorders and misconceptions related to VMAT2 inhibitors
- The IMPACT-TD Registry study is groundbreaking, offering unique insights into the impact of TD movements on the physical, social, psychological, and vocational aspects of patients' lives
- Most participants in the survey who were asked about experience with AUSTEDO XR reported an overall satisfaction and noted that the reduction in abnormal movements had a positive impact on patients' lives and daily activities ■

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QTc Prolongation: AUSTEDO XR and AUSTEDO may prolong the QT interval, but the degree of QT prolongation is not clinically significant when AUSTEDO XR or AUSTEDO is administered within the recommended dosage range. AUSTEDO XR and AUSTEDO should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

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

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