TD NEWS+VIEWS
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On the Front Line: Helping Advanced Practice Providers to Recognize, Assess, and Treat Tardive Dyskinesia

CLINICAL

Empowering Mental Health Advanced Practice Providers to Screen, Diagnose, and Appropriately Treat Tardive Dyskinesia

This article offers psychiatric-mental health advanced practice providers (APPs) an overview of tardive dyskinesia (TD) and examines its impact on patients' lives.

SCREENING AND ASSESSMENT

Uncovering, Identifying, and Addressing Tardive Dyskinesia: Strategies for Assessment and Treatment

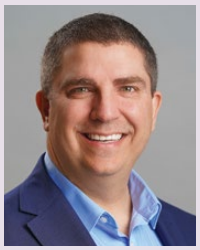
In patients receiving antipsychotics, it is important to screen and assess TD movements as well as understand the impact to appropriately treat it.

TREATMENT

Once-Daily AUSTEDO XR for Tardive Dyskinesia: Information for Advanced Practice Providers

Review the role of AUSTEDO XR in the treatment of adults with TD.

EXPERT COMMENTARY



Expert Commentary With Jeremy Schreiber, MSN, APRN, PMHNP-BC

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This newsletter is produced by Teva Pharmaceuticals, and Jeremy Schreiber was compensated by Teva for his insights.

In this conversation, Jeremy Schreiber discusses the role of APPs in screening, assessing, and treating TD. He details the impact of TD on patients and explores the potential implications of once-daily AUSTEDO XR for clinicians and their patients.

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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CLINICAL

Empowering Mental Health Advanced Practice Providers to Screen, Diagnose, and Appropriately Treat Tardive Dyskinesia

Approximately 1 in 4 adults in the United States experiences a mental illness.[1] At the same time, there has been a decrease in the number of psychiatrists, underscoring the importance of a robust workforce of healthcare professionals, including psychiatric-mental health APPs, composed of nurse practitioners (NPs) and physician assistants (PAs).[2,3] This article provides mental health APPs with an overview of TD, a movement disorder resulting from exposure to antipsychotic drugs.[4] It also explores the multifaceted impact of TD on patients' lives.

The Growing Role of NPs and PAs in Mental Healthcare

In 2023, it was estimated that approximately **59 million US adults, or 23% of the adult population, experienced a mental illness**, and nearly half of those individuals did not receive treatment.[1] Mental healthcare clinicians can range from psychiatrists, psychologists, NPs, and PAs to social workers, and from solo practitioners to multidisciplinary teams.[5-7]

Compounding this crisis is a **growing shortage of psychiatrists**, with projections from the US Health Resources and Services Administration (HRSA) predicting a deficit of 18,000 to 21,000 professionals by 2030, suggesting that an expanding number of people of all ages will have unmet behavioral health needs.[1,2] Due to this accelerating demand for mental healthcare professionals, **NPs and PAs are an increasingly vital resource for managing patients with mental health disorders**.[3] According to the HRSA, 11,310 new NPs and PAs are expected to join the workforce by 2030, highlighting the essential role of these providers in meeting the rising demand for mental healthcare and mitigating the shortage of psychiatrists.[8]

NPs and PAs play a critical role in addressing the growing need for mental healthcare in the midst of the mental health crisis.

Overview and Clinical Presentation of TD

Dopamine receptor blocking agents such as atypical and typical antipsychotics are commonly used to treat a variety of psychiatric disorders. It is known that they may cause side effects, including movement disorders such as TD, drug-induced parkinsonism (DIP), akathisia, and dystonia.[9]

TD is a persistent, typically irreversible, hyperkinetic movement disorder that affects approximately 785,000 individuals in the US.[4,10,11] Despite this prevalence, **TD may be underdiagnosed and undertreated**, with approximately 15% of patients receiving a formal diagnosis and less than 6% being treated with vesicular monoamine transporter 2 (VMAT2) inhibitors, the only FDA-approved treatments for TD.[11-13] **While TD primarily affects the face, it can also impact any part of the body, including the trunk and extremities (Video 1.1).**[14]

Video 1.1. Clinical Presentations of TD

Click here to view video

Patient images used with permission.

Impact of TD on Patients' Lives

According to an online survey of patients, **TD can hinder a clinician's ability to manage a patient's underlying mental health condition**.[15]

- 48% reported they skipped doses of an antipsychotic medication or took less than the doctor instructed
- 39% reported they stopped taking antipsychotic medication altogether
- 36% stopped going to the doctor for treatment of their underlying condition
- 21% advised someone else not to take an antipsychotic medication

One of the challenges in assessing the impact of TD on patients is that the **clinician's perception of mild movements may not equal the patient's experience of impact**.[16] The disconnect between movement severity, as observed by the clinician, and impact, as experienced by the patient, is illustrated in **Videos 1.2 and 1.3**.

Any presentation of TD can have a profound impact on various aspects of patients' lives such as their capacity to carry out daily tasks, maintain productivity, and engage in social activities.[17-19] **TD manifestations such as these can complicate the management of the underlying mental health disorder.**[20]

Video 1.2. Patient's Movements (No Sound)

The visual assessment of TD is mild

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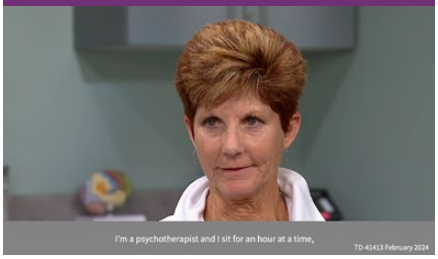
Video 1.3. Patient Impact From TD (With Sound)

The verbal description of TD indicates significant impact



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> The clinician's perception of mild TD movements may not equal the patient's experience of impact.

Findings From the IMPACT-TD Registry Study

Historically, it was believed that the severity of TD movements dictated the overall impact on the patient. However, more recently it has become evident that **movement severity is only part of the equation, and TD can have a broader impact on patients' lives**.[21] To more fully comprehend the impact of TD, **the IMPACT-TD Registry study** was established to systematically collect data across various domains of patients' lives. This study was the **first of its kind**, and its objective was to significantly enhance the understanding of TD.[22]

A key finding from this interim analysis was that **patients with symptoms that were considered mild**, based on measurements taken by a healthcare professional, **can experience a moderate to severe impact of TD**. Notably, this study revealed that 54% of patients with very mild or 61% with mild TD (based on the Clinical Global Impression of Severity of TD) experienced a moderate to severe impact on the clinician IMPACT-TD global score. Furthermore, approximately 74% of patients with an Abnormal Involuntary Movement Scale (AIMS) score of 1 to 6 reported moderate to severe impact from TD.[16]

Additionally, the **impact of movements extended into the social, psychological, physical, and vocational/educational/recreational dimensions of**

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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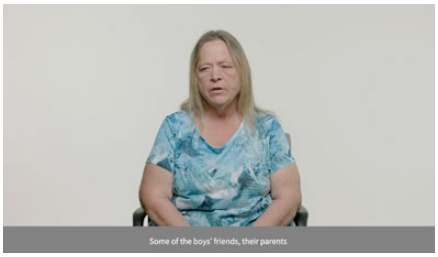
patients' lives, with 83% indicating moderate to severe impact in at least 1 domain.[16] Patients have reported that TD had an impact on the following[23]

- ~60% said their movements prevented them from leaving the house
- >75% reported feeling embarrassed in social situations
- >60% said movements impacted their sleep
- >50% reported their movements limited them at work

Presented below are testimonials from patients conveying the impact of TD in their own words across various domains studied in the IMPACT-TD Registry study **(Videos 1.4-1.7)**.

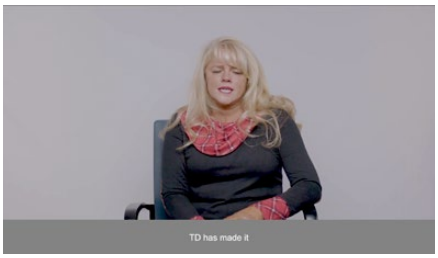
The IMPACT-TD Registry study revealed that more than half of patients with mild TD symptoms experienced a moderate to severe impact, affecting the social, psychological, physical, and vocational/educational/recreational aspects of their lives.

Video 1.4. Social Domain



Click here to view video

Video 1.5. Psychological/Psychiatric Domain

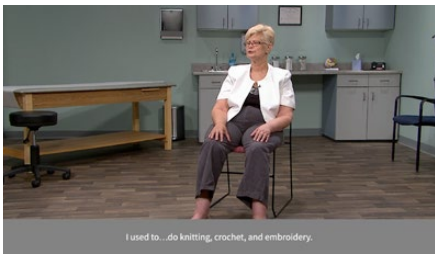


Click here to view video

Video 1.6. Physical Domain

Click here to view video

Video 1.7. Vocational/Educational/Recreational Domains



Click here to view video

Patient images used with permission.

Assessing the Impact of TD in Clinical Practice

Managing patients treated with antipsychotics involves not only screening for and assessing TD movements but also understanding the wider impact TD has on patients, their families, and caregivers.[24-26] There may also be a discrepancy between the severity of movements observed by the clinician and the impact as experienced by the patient.[16] Thus, it is essential to **look** for any abnormal movements and **ask questions** to gauge the impact of these movements at every clinical encounter **(Figure 1.1)**.[18,24,27,28]

Per American Psychiatric Association (APA) Guidelines, VMAT2 inhibitors are recommended if TD has an impact on the patient, regardless of the severity of movements.[25]

Summary

- Amid the mental health crisis and psychiatrist shortage in the US, the demand for mental healthcare professionals is growing[1-3]
- Psychiatric mental health NPs and PAs have a critical role in filling this gap[3]
- In recent years, the number of antipsychotic prescriptions has increased, resulting in an increased prevalence of TD, a hyperkinetic and often irreversible movement disorder[4,10,11]

IMPORTANT SAFETY INFORMATION (CONTINUED)

QTc Prolongation: AUSTEDO XR® (deutetrabenazine) extended-release tablets and AUSTEDO® (deutetrabenazine) tablets 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.

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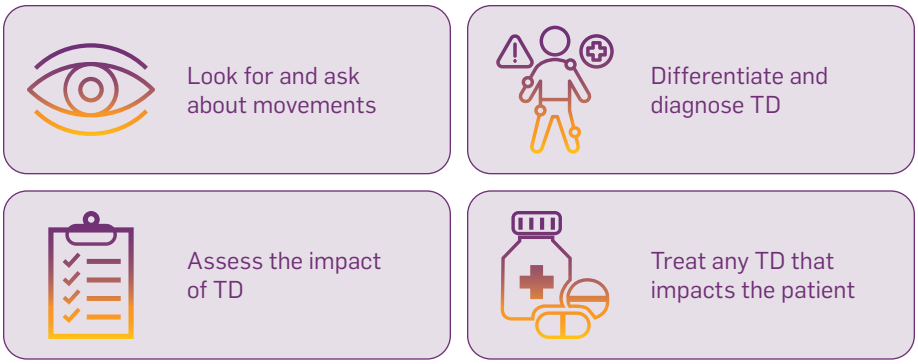
Figure 1.1. In all patients with current or previous exposure to antipsychotics[4,18,25,29]



Managing patients on antipsychotics requires not only screening for and evaluating TD movements but also comprehending the impact on patients and their social circle.

Summary (continued)

- Data from the groundbreaking IMPACT-TD Registry study shows that TD movements, regardless of severity, can impact patients across the social, psychological, physical, and vocational/educational/recreational aspects of their lives[16]
- Assessment of TD impact should be performed at every clinical visit[24]
- The APA Guidelines support treatment of TD that has an impact on the patient with VMAT2 inhibitors, regardless of severity of movements[25] ■

SCREENING AND ASSESSMENT

Uncovering, Identifying, and Addressing Tardive Dyskinesia: Strategies for Assessment and Treatment

Tardive dyskinesia (TD) is a hyperkinetic movement disorder that can arise in patients taking antipsychotics or other dopamine receptor blocking agents and significantly impacts their lives.[1,2] As a result, it is critical to identify, accurately diagnose, and appropriately treat TD that has an impact on the patient.[1,3]

Screen for Movements in Patients Taking Antipsychotics at Every Clinical Encounter

TD is a typically irreversible hyperkinetic movement disorder resulting from chronic exposure to typical and atypical antipsychotics or other dopamine receptor blocking agents (eg, antiemetics, prokinetics).[1,4-7] TD can impact patients' lives and undermine the stability of their underlying mental health condition.[2,8] As a result, expert consensus **recommends that patients taking antipsychotics be screened for movements at every visit regardless of the risk of TD**.[9]

Abnormal movements in **TD can affect any part of the body, but most often impact the face**, causing lip puckering, grimacing, and tongue protrusion. Movements are also often seen in the trunk and limbs.[1] Screening can be conducted unobtrusively as patients enter the consultation room and engage in conversation.[10] Clinicians can also **empower their**

entire office staff to be aware of these movements, recognize them in patients, and report observations to the provider. Because patients can temporarily mask the movements of TD, it may be necessary to employ **activation maneuvers to uncover them (Video 2.1)**.[10,11]

Effective management includes using the **Abnormal Involuntary Movement Scale (AIMS) exam to make careful examination of movements** affecting various body regions and **asking detailed questions** to understand the impact of movements and the severity experienced by patients.[3,8,12] Since patients might not be fully aware of their movements or the effects they have, it may be helpful to seek feedback from caregivers regarding any abnormal movements.[8]

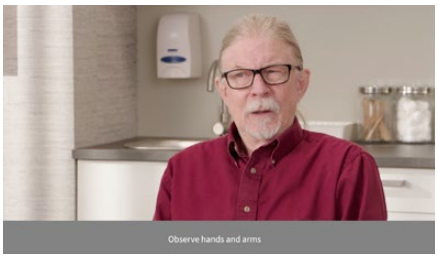
Differentiate TD From Other Drug-Induced Movement Disorders

Drug-induced movement disorders (DIMDs) include TD, drug-induced parkinsonism (DIP), akathisia, and dystonia.[13] Historically, these disorders were all classified as **"extrapyramidal symptoms" or EPS, a now-outdated classification** that misdirects the need for a specific diagnosis.[1,13-15] DIMDs have distinct pathophysiological mechanisms and clinical manifestations, necessitating different treatment approaches.[1,13,16] **It is critical that TD is differentiated from DIP since treatment for one can worsen the other.**[16,17]

TD and DIP are different disorders with different causes **(Video 2.2)**[1,16]

- **DIP is a hypodopaminergic state:** the acute blockade of dopamine receptors caused by some antipsychotics leads to a reduction in postsynaptic dopamine signaling. Reduced signaling results in decreased movement and other symptoms associated with DIP[15,16]
- **TD is a hyperdopaminergic state:** it is thought that chronic blockade of dopamine receptors results in the upregulation of dopamine receptor function. This is possibly due in part to hypersensitivity or upregulation of dopamine receptors. This upregulation results in increased dopamine signaling, which manifests as the excessive movement characteristic of TD[1,16]

Video 2.1. Activation Is Used to Help Reveal Movement in Areas Not Being Activated



Click here to view video

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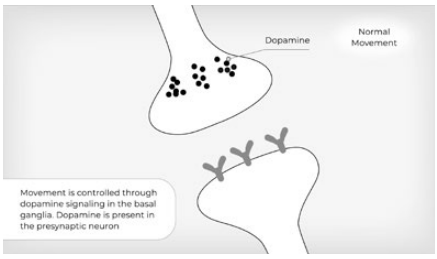
Video 2.2. TD and DIP Are Different Disorders With Different Causes



Click here to view video

TD and DIP show differences in the onset of symptoms[16]

- **DIP** usually develops within **a few days or weeks of**[16,17]
  - Starting or increasing the dosage of an antipsychotic
  - Reducing the dosage of a medication used to treat EPS (eg, anticholinergics)
- **TD** develops **after using an antipsychotic for at least a few months**[17]
  - TD movements may appear after discontinuing, changing, or reducing the medication dosage; if symptoms persist for longer than 4 to 8 weeks, then the patient is considered to have TD. Older adults may develop TD symptoms in a shorter period of medication usage

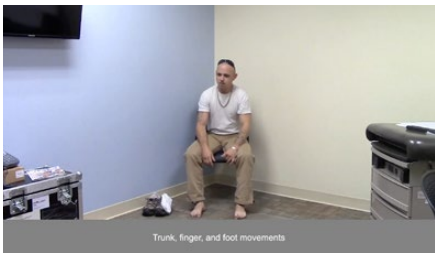
In patients receiving antipsychotics, it's important to screen and assess TD movements and understand the impact.

Key features that differentiate TD from DIP include the nature and frequency of movements[16,18]

- **TD is characterized by an excess of movements** that are irregular, jerky, and unpredictable; TD movements are accompanied by normal muscular tone **(Video 2.3)**[17-19]
- **DIP is characterized by a paucity of movement** and, in some cases, rigidity. When movements occur, they are typically rhythmic **(Video 2.4)**[15,18,20]

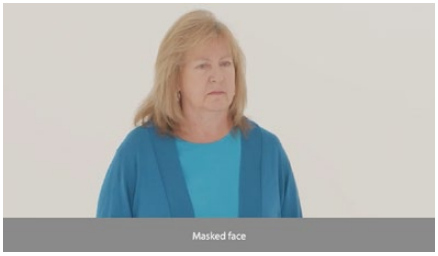
Whether the patient has TD or DIP should be carefully determined based on a differential diagnosis since treatment for one can worsen the other.

Video 2.3. Irregular, Unpredictable, Jerky, and Twitchy Movements in TD



Click here to view video

Video 2.4. Tremors and Masked Face in DIP



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AIMS Is the Standard Scale for Quantifying TD Movements

The AIMS is a structured exam widely used to **screen for and monitor TD symptoms**, consisting of 2 parallel processes[3,9]

- Following instructions to systematically observe and ask about movements in patients taking antipsychotics
- Scoring the severity of observed movements on a 12-item scorecard

The American Psychiatric Association (APA) recommends all at-risk patients undergo an assessment with a structured instrument such as the AIMS and suggests **patients at high risk be assessed at a minimum of every 6 months, while lower-risk patients should be assessed at least every 12 months**. High-risk patients include individuals older than 55 years; women; individuals with a mood disorder, substance use disorder, intellectual disability, or central nervous system injury; individuals with high cumulative exposure to antipsychotic medications; and patients who experience acute dystonic reactions, clinically significant parkinsonism, or akathisia. Abnormal involuntary movements can also emerge or worsen with antipsychotic medication. Patients should also be assessed if a new onset or exacerbation of preexisting movements is detected at any visit.[3]

AIMS exam items 1 to 7 assess the severity of involuntary movements across body regions, while items 8 through 12 address global severity, patient awareness and distress, and dental issues. **While AIMS items 9 and 10 quantify the impact of TD, determining the severity of impact requires further qualitative assessment.**[21,22]

Each of the first 7 items is scored on a 0-to-4 scale[23]

0: None (not present)

1: Minimal (may be extreme normal [abnormal movements occur infrequently and/or are difficult to detect])

2: Mild (abnormal movements occur infrequently and are easy to detect)

3: Moderate (abnormal movements occur frequently and are easy to detect)

4: Severe (abnormal movements occur almost continuously and/or are of extreme intensity)

The AIMS exam quantifies movements, but TD of any severity that impacts the patient should be treated.

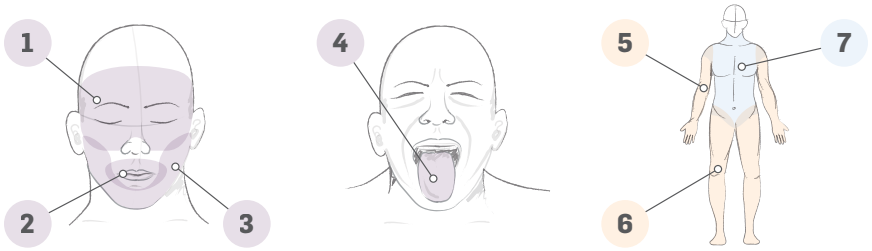
The AIMS total score is the sum of items 1 to 7 and can range from 0 to 28 **(Figure 2.1)**.

Ultimately, **TD that impacts the patient, regardless of severity, should be treated**, with vesicular monoamine transporter 2 (VMAT2) inhibitors, if it has an impact on the patient, regardless of severity of movements.[3]

Ask the Right Questions and Listen to Your Patients to Uncover the Impact of TD

While the AIMS exam quantifies movements, the **severity of TD can only be fully understood by considering the impact** these movements have on the patients, regardless of their amplitude or frequency, in the various aspects of their daily lives. Therefore, it is crucial to ask **appropriate questions and actively listen to your patients** to grasp the impact of TD, particularly because clinicians may underestimate how TD movements, particularly those that are subtle, can impact patients' lives.[25] As a result, investigating the consequences of TD across 4 domains—psychological/psychiatric, social, physical, and vocational/educational/recreational—is essential. This can be achieved by **asking questions to gauge the severity of the impact in each area (Figure 2.2)**.[8,12] Receiving information from caregivers, family, and friends can also be helpful in determining the impact of TD on patients' lives.[8]

Figure 2.1. Items 1 to 7 Assess the Severity of Involuntary Movements Across Body Regions[22-24]



MOVEMENT RATINGS		SCORE
Facial & Oral Movements	1. Muscles of facial expression	0 1 2 3 4
	2. Lips and perioral area	0 1 2 3 4
	3. Jaw	0 1 2 3 4
	4. Tongue	0 1 2 3 4
Extremity Movements	5. Upper (arms, wrists, hands, fingers)	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes)	0 1 2 3 4
Trunk Movements	7. Neck, shoulders, hips	0 1 2 3 4
Global Judgments	8. Severity of abnormal movements overall	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4
	10. Patient awareness of abnormal movements	0 1 2 3 4
Dental Status	11. Current problems with teeth/dentures?	No Yes
	12. Are dentures usually worn?	No Yes

SCORING

0	1	2	3	4
None	Minimal	Mild	Moderate	Severe

Consider the IMPACT-TD Scale as a guide in clinical practice to assess the impact of TD.

Click here to access.

Ask insightful questions to uncover the impact of TD that extends beyond the degree of movements.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Sedation and Somnolence: Sedation is a common dose-limiting adverse reaction of AUSTEDO XR® (deutetrabenazine) extended-release tablets 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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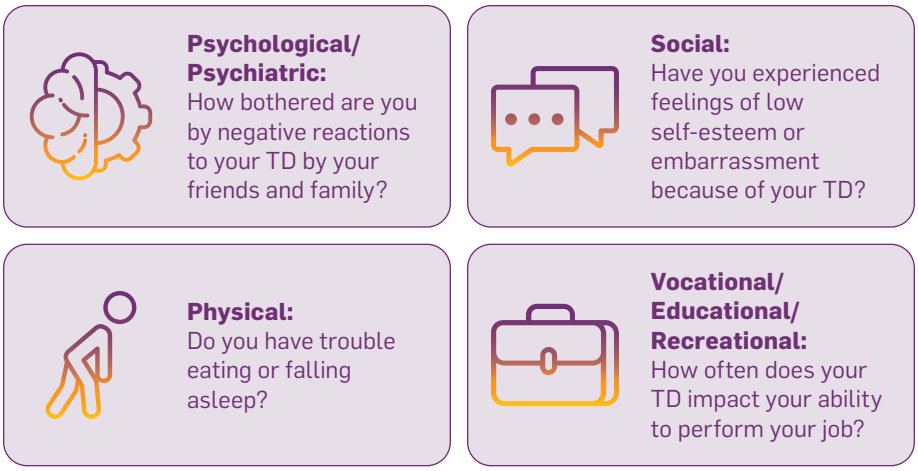
Figure 2.2. Sample Questions to Reveal the Impact of TD[8,12]



Following the AIMS Instructions Can Help Identify Signs of DIP

The AIMS procedure contains elements that can also help clinicians identify DIP. These include[1,23]

- Unobtrusive observance of the patient at rest and during activation maneuvers when the clinician may note rhythmic tremor
- A close watch of the patient's gait, during which the HCP might identify a lack of arm swing or shuffling of the feet, indicative of DIP
- Assessing rigidity, which is an important component of the AIMS procedure, can help identify rigidity associated with DIP

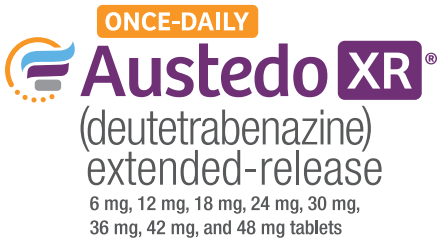
Because DIP and TD may co-occur, testing for parkinsonian rigidity is an important corollary to the AIMS exam as rigidity may partially or completely mask dyskinesia.[10]

To further your knowledge and practice your scoring skills, click here visit ConnecTD.

The AIMS exam includes steps that can assist clinicians in differentiating DIP from TD.

Summary

- All patients taking antipsychotics should be screened for TD movements at every clinical encounter, regardless of the risk of TD[3,9]
- TD and DIP have different causes[1,15,16]
  - In DIP, acute dopamine receptor blockade reduces dopamine signaling, leading to decreased movement (ie, hypodopaminergic state)
  - In TD, chronic dopamine receptor blockade results in upregulation of dopamine receptor function, leading to increased dopamine signaling and excessive movements (ie, hyperdopaminergic state)
- TD and DIP differ in symptom onset[16]
  - DIP usually emerges within a few weeks to months of starting antipsychotic treatment[16,17]
  - TD develops after using an antipsychotic for at least a few months[17]
- Anticholinergics are indicated for the treatment of DIP but can worsen TD symptoms[16,17]
- AIMS is a clinician-rated scale that helps quantify the degree of TD movements[8,9,12,21-23]
  - Items 1 to 7 assess the severity of involuntary movements across body regions
  - Items 9 and 10 quantify the impact of TD
  - Determining the severity of impact requires further qualitative assessment by asking the appropriate questions and actively listening to your patients
- APA Guidelines recommend VMAT2 inhibitors, if TD has an impact on the patient, regardless of severity of movements[3]
- The AIMS procedure contains elements that can also help clinicians identify DIP[1,23] ■



TREATMENT

Once-Daily AUSTEDO XR for Tardive Dyskinesia: Information for Advanced Practice Providers

Tardive dyskinesia (TD) is a persistent hyperkinetic movement disorder caused by prolonged exposure to dopamine receptor blocking agents, including antipsychotics.[1-3] Even **mild TD movements can significantly impact various aspects of patients' lives, extending into the social, psychological, and emotional domains**.[4,5] The American Psychiatric Association (APA) Guidelines **recommend vesicular monoamine transporter 2 (VMAT2) inhibitors, like AUSTEDO XR, for treating TD if it has an impact on the patient, regardless of severity of movements**.[6,7] The goal of this article is to inform advanced practice providers on how to treat TD by offering an overview of AUSTEDO XR, a once-daily treatment option for adults with this disorder. To that end, key efficacy and safety data from the pivotal clinical trials with AUSTEDO® (deutetrabenazine) tablets are presented. This article further highlights real-world evidence from a survey assessing patients' experiences with AUSTEDO XR and reviews recommendations and considerations for patients taking concomitant medications, as well as AUSTEDO XR dosing options.

ARM-TD, AIM-TD, and RIM-TD: Study Designs

The efficacy and safety of AUSTEDO 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).[8,9]

- ARM-TD was a 12-week, randomized, double-blind, placebo-controlled trial in which doses 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[9]
- 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[7,8]

The primary efficacy endpoint in both trials was the change in Abnormal Involuntary Movement Scale (AIMS) total score from baseline to Week 12.[7-10]

RIM-TD (Reducing Involuntary Movements in Participants With TD), an open-label study, was designed to evaluate **long-term treatment 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.[11] The mean overall compliance rate was nearly 90% at 3 years.[10]

ARM-TD, AIM-TD, and RIM-TD: Key Efficacy Endpoints

In the placebo-controlled trials, 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**.[7,9,10]

- 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

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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effect of –1.4 points, *P*=0.019) **(Figure 3.1, left graph)**.[9,10] At Week 12, 94% of patients were taking a dose of ≥30 mg/day, and the average daily dose was ~38 mg[9,10]

- In AIM-TD, AUSTEDO significantly reduced AIMS total score by 3.3 points from baseline in the 36 mg/day arm compared with a reduction of 1.4 points with placebo at Week 12 (treatment effect of –1.9 points, *P*=0.001).[7,8] The average daily dose was ~39 mg[8]

In the open-label extension (OLE) study, **increased improvement in AIMS total score was observed over 3 years, with 71% of patients at Week 145 seeing improvement relative to Week 15 (Figure 3.1, right graph)**.[10,11] At Week 145, 87% of patients were taking a dose of ≥30 mg/day and the average daily dose was ~39 mg.[10,11]

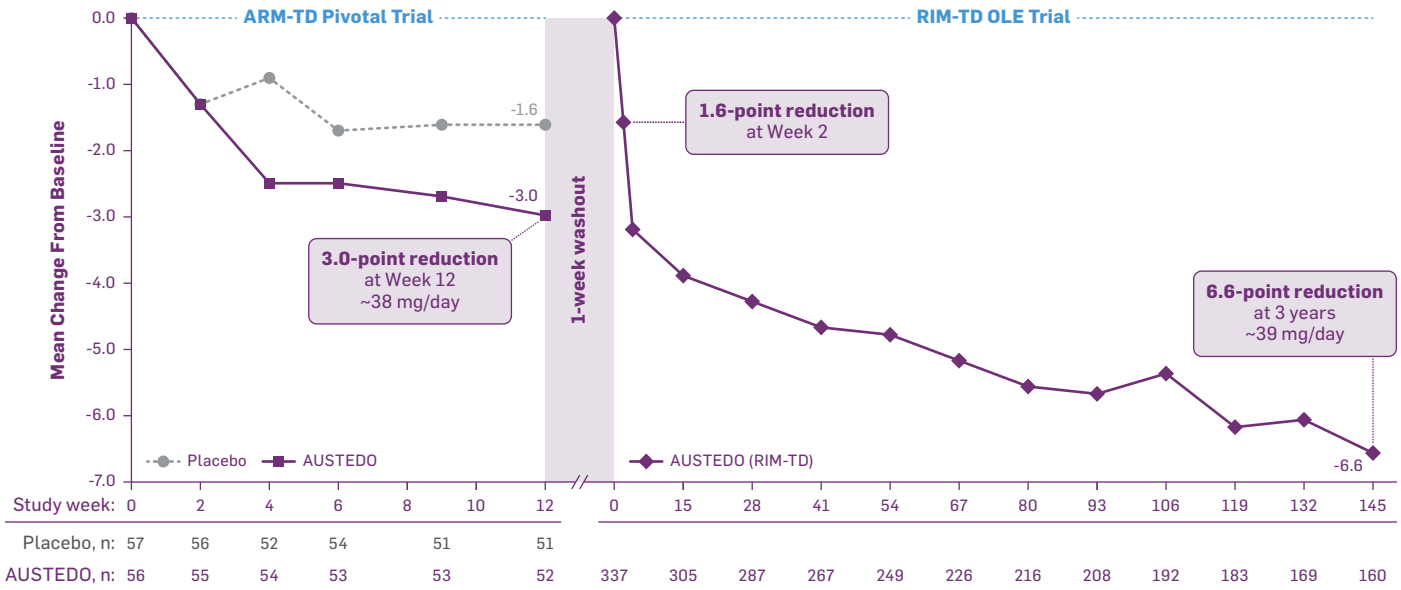
Safety and Tolerability Profile

The **most common adverse reactions reported across both placebo-controlled studies in patients with TD treated with AUSTEDO** (>3% and greater than placebo) **were nasopharyngitis and insomnia**.[7] Adverse reactions occurring in patients treated with AUSTEDO (12-48 mg/day) (≥2%) are summarized in **Figure 3.2**.

Discontinuation due to adverse events (AEs) occurred in 4% of patients compared with 3% of patients treated with placebo.[8] Four percent of patients required dose reduction of AUSTEDO due to

Patients who received AUSTEDO in the pivotal placebo-controlled trials demonstrated a rapid response as early as Week 2 and achieved a significant and meaningful reduction in TD severity at Week 12.

Figure 3.1. Change in AIMS Score at Week 12 (ARM-TD) and Week 145 (RIM-TD)[7,9-11]



ARM-TD, Aim to Reduce Movements in Tardive Dyskinesia; OLE, open-label extension; RIM-TD, Reducing Involuntary Movements in Participants With TD.

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.

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Figure 3.2. Adverse Reactions Reported in ≥2% of Patients With TD Treated With AUSTEDO® (deutetrabenazine) tablets in Placebo-Controlled Studies[7,10,*]

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.[6,7,10,11]

AEs compared with 2% of patients taking placebo.[7] 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.[10]

No new safety signals were identified in RIM-TD, and AEs were comparable with those in the 12-week clinical trials.[11]

Adverse reactions with AUSTEDO XR® (deutetrabenazine) extended-release tablets are expected to be similar to AUSTEDO BID.[7]

Insights From a Real-World Survey of Patients With TD Taking AUSTEDO XR

In addition to clinical data, real-world evidence of patient-reported

AEs in RIM-TD were comparable with those reported in ARM-TD and AIM-TD.

experiences may help inform discussions about treatment with your patients. This was highlighted in a prospective, cross-sectional survey involving 118 patients with TD, which assessed patients' experiences 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 3.3)**. In addition, 98% of patients said taking once-daily AUSTEDO XR was easy, and 95% planned to continue taking AUSTEDO XR **(Figure 3.3)**. Furthermore, **86% liked the ability to adjust their dose up or down with their doctor and >60% reported taking AUSTEDO XR in the morning**.[12]

IMPORTANT SAFETY INFORMATION (CONTINUED)

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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Interim results from a real-world survey of 118 patients taking AUSTEDO XR for TD found that more than 50% of patients reported improved social and emotional well-being as a result of movement reduction with AUSTEDO XR.

Figure 3.3. Patients Reported Improvement in Other Areas of Life as a Result of Movement Reduction With AUSTEDO XR[12]

- 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

Figure 3.4. No Dose Restrictions up to 36 mg/day for Patients Starting AUSTEDO XR[7,14]

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.

AUSTEDO XR is the only VMAT2 inhibitor indicated for TD with no dose restrictions for—or recommendations against—concomitant use with strong CYP3A4/5 inducers or inhibitors.[7,14]

Dosing Recommendations and Considerations for VMAT2 Inhibitors

Patients with TD may also be taking medications to treat nonpsychiatric comorbidities in addition to medication to stabilize their mental health condition. In order to reduce the risk of drug-drug interactions, it is critical that clinicians are aware of the patient's medication regimen and consider metabolic pathways when selecting a VMAT2 inhibitor to treat TD. AUSTEDO XR is metabolized primarily by CYP2D6, with minor contributions from CYP3A4/5 and other enzymes to form several minor metabolites.[7] **When potential drug interactions with CYP3A4 or CYP2D6 are considered, AUSTEDO XR offers flexibility with several dosing options, allowing adjustments up to 36 mg/day (Figure 3.4).**[7] Moreover, no dose adjustments to P-glycoprotein substrates (eg, calcium channel blockers, statins, and antimicrobials) are required when taking AUSTEDO XR.[7,13]

Dosing Options for AUSTEDO XR

AUSTEDO XR offers a variety of therapeutic doses, providing flexibility to achieve effective and tolerable symptom control.[7] The recommended starting dose of AUSTEDO XR for patients with TD is 12 mg/day, which may be increased

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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at weekly intervals by 6 mg/day.[7] 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.[8,11] In separate pharmacokinetic studies, increased plasma levels of AUSTEDO® (deutetrabenazine) tablets correlated with higher potential for treatment success, but not AEs.[15,16]

AUSTEDO XR® (deutetrabenazine) extended-release tablets should be swallowed whole. Tablets should not be chewed, crushed, or broken. AUSTEDO XR may be taken with or without food **(Figure 3.5)**.[7]

AUSTEDO XR offers a variety of therapeutic doses, providing flexibility to achieve effective and tolerable symptom control when accounting for potential drug-drug interactions.

Figure 3.5. Flexibility to Titrate Dosing for Effective and Tolerable Control[10]

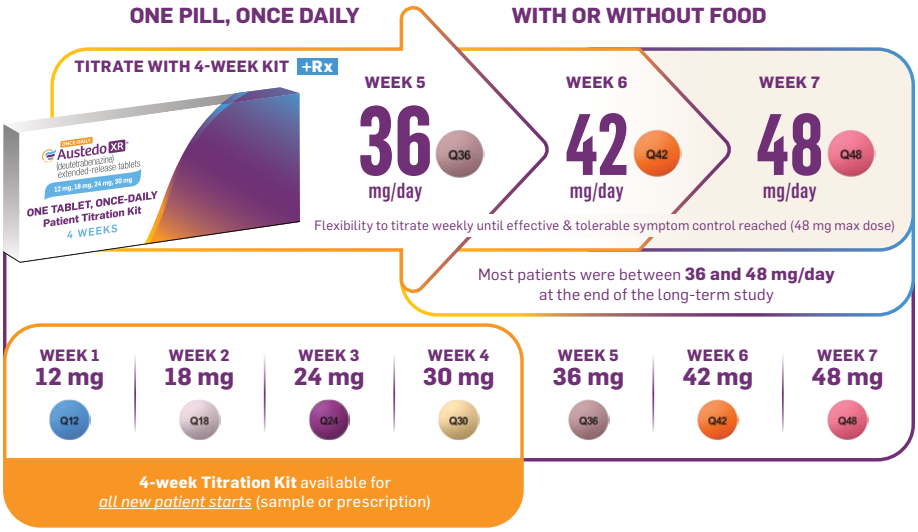

Image shown is not actual 4-week Titration Kit. Tablets not shown to actual size.

Summary

- Patients treated with AUSTEDO in the ARM-TD and AIM-TD placebo-controlled studies achieved significant and meaningful reduction in TD severity at Week 12[7-9]
- Increasing improvement in AIMS score was observed over 3 years in RIM-TD, with 71% of patients at Week 145 seeing improvement relative to Week 15[10,11]
- The most common AEs for AUSTEDO (3% and greater than placebo) in placebo-controlled studies in patients with TD were nasopharyngitis and insomnia. Adverse reactions with AUSTEDO XR are expected to be similar to AUSTEDO[7]
- Additionally, patients expressed satisfaction with the convenience of AUSTEDO XR as a once-daily tablet, appreciating the flexibility of taking it with or without food and at various times throughout the day[12]
- The flexible, once-daily dosing with AUSTEDO XR enables patients to titrate as needed to achieve effective and tolerable symptom control[7] ■

EXPERT COMMENTARY

Expert Commentary With Jeremy Schreiber, MSN, APRN, PMHNP-BC

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Q: What role do advanced practice providers (APPs), particularly mental health nurse practitioners (NPs), play in psychiatry and in caring for patients with tardive dyskinesia (TD)? In what ways do you foresee this role evolving in the coming years due to the increasing shortage of psychiatrists?

A: APPs often serve as frontline clinicians treating patients in a variety of settings, including clinics they own and operate, as well as those managed by counselors and psychiatrists. Their work spans community mental health centers and private practices as well as inpatient and outpatient facilities. **APPs are already heavily involved in assessing, diagnosing, and treating patients with TD across various healthcare settings.** Given the ongoing shortage of psychiatrists, **I believe their roles will evolve**, and we might see them conducting more research and even serving as primary investigators on clinical trials. They will also play a crucial role in educating other NPs and physician assistants, particularly new graduates or those transitioning into psychiatry. Additionally, they may be taking on executive and leadership roles, overseeing large healthcare organizations, and managing other healthcare providers.

APPs play a crucial role in treating patients with TD, and their responsibilities are anticipated to expand in the coming years to help mitigate the increased demand for mental health services.

Q: What would you say to your colleagues to address the issue of underdiagnosis of TD and help move the needle toward improved identification and appropriate treatment?

A: In the United States, **TD is often undiagnosed and untreated**, with approximately 15% of patients with TD receiving a formal diagnosis and less than 6% of patients being treated with vesicular monoamine transporter 2 (VMAT2) inhibitors, the only FDA-approved treatment for TD.

What I'd like my colleagues to understand is that **even mild movements can have a significant impact on patients' lives**. Moreover, the impact of TD may extend beyond the patient; individuals close to someone, such as spouses, parents, children, or friends, are often affected and they may also become more isolated. It is thus **critical to recognize TD and treat it appropriately**.

In my experience, a key reason for the high rate of TD underdiagnosis is that **clinicians may not be aware of the guidelines provided by professional organizations** such as the American Psychiatric Association (APA). Awareness of the guidelines is one thing, but implementing them into clinical practice is another challenge altogether. **To enhance**

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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TD diagnosis, I think we should integrate these guidelines into our patient evaluation charts.

Q: How often do you screen for TD movements in your practice?
A: Expert consensus recommends that **patients taking antipsychotics should be screened for movements at every visit regardless of the risk for TD**. In addition, the **APA recommends assessment with a structured instrument such as the Abnormal Involuntary Movement Scale (AIMS) at a minimum of every 6 months in patients at high risk of TD and at least every 12 months in other patients, as well as if a new onset or exacerbation of preexisting movements is detected at any visit**. High-risk patients include individuals older than 55 years; women, including post-menopausal females; individuals with a mood disorder, substance use disorder, intellectual disability, or central nervous system injury; individuals with high cumulative exposure to antipsychotic medications, particularly high-potency dopamine D2 receptor antagonists; and patients who have experienced other movement disorders such as acute dystonic reactions or clinically significant parkinsonism. TD develops after using an antipsychotic for at least a few months, although elderly persons may develop TD symptoms in a shorter period of medication usage. Personally, **I conduct standardized screenings every 3 months for high-risk patients and every 6 months for everyone else**.

Expert consensus recommends that patients taking antipsychotics should be screened for movements at every visit regardless of the risk of TD.

Q: What questions do you ask your patients to try to determine if and how TD is impacting their lives?
A: My approach centers on understanding patients' personal goals and their desired way of living and recognizing that many face challenges and have developed coping strategies for managing TD. When assessing impact with patients, I ask direct questions such as "Are you avoiding the store?" or "Do you find socializing difficult?" I also inquire if their family, friends, or coworkers have commented on increased feelings of embarrassment during social or family gatherings. Sometimes, individuals experience challenges with certain activities, particularly if they involve hand movements. Therefore, I might ask if they have difficulties with tasks like buttoning a shirt, using zippers, holding silverware, or engaging in activities requiring fine hand movements. They might not notice that they spill things more often or need extra time to get dressed. It is critical to realize that **patients who have been managing their symptoms for a long time may not fully realize how much these issues affect their daily lives until they experience improvement**. Therefore, it's important to treat the symptoms and then ask patients to reflect on how the reduction in movements has impacted their ability to perform day-to-day activities that were previously difficult.

It is important to treat TD symptoms and then ask patients to reflect on how the reduction in movements has impacted their day-to-day activities.

Q: To what extent are you continuing to use telepsychiatry services? Do you have any advice for colleagues who evaluate movement disorders during telehealth/telepsychiatry appointments?
A: I continue to utilize telepsychiatry services, although my practice is primarily office-based and in-person,

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® (deutetrabenazine) extended-release tablets and AUSTEDO® (deutetrabenazine) tablets; intensive symptomatic treatment and medical monitoring; and treatment of any concomitant serious medical problems.

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It is important to maintain the standard of care and screen for TD at every clinical encounter, including telehealth sessions.

with most of my providers and myself working from the office. **It is possible to effectively assess movements during telehealth visits by following a few best practices.** First, it's essential to ensure the patient is in a well-lit area. If possible, have someone assist with holding or positioning the camera to capture a full body view of the patient. This setup can be beneficial, especially if you need to zoom in on a specific area for closer examination. To reduce reflections and improve the assessment of facial movements, I request that patients remove their glasses and provide an unobstructed view of their face. Additionally, providing enough floor space for the patient to walk from point A to point B can allow you to observe their gait by zooming out. Most importantly, **whether in telehealth or in the office, remember to focus on your patients rather than just on the computer or notes**.

Q: Although the APA Guidelines and DSM-5-TR caution against using anticholinergics, such as benztropine, to treat or prevent TD, they are still overused or inappropriately prescribed in psychiatry settings. What would you say to your colleagues to help change this mindset and use VMAT2 inhibitors, which are indicated and FDA-approved to treat TD, instead?

A: First and foremost, I would urge them to "STOP!" prescribing anticholinergics for TD, given that the prescribing information for benztropine warns that antiparkinsonism agents do not alleviate the symptoms of TD and may, in fact, worsen them. While anticholinergics may be suitable for other conditions, such as acute dystonia or drug-induced parkinsonism (DIP), they may exacerbate TD symptoms. **In my experience, doing nothing would be better than prescribing anticholinergics for TD.** However, rather than taking no action, I recommend using the FDA-approved VMAT2 inhibitors, which can effectively reduce movements in patients with TD. So, it is **critical to accurately diagnose TD and treat it appropriately**.

Q: What do you think are important clinical features of AUSTEDO XR as a once-daily treatment for adults with TD?

A: First, AUSTEDO has a **demonstrated efficacy and safety profile**, established in 2 randomized, placebo-controlled clinical trials. The most common adverse reactions reported in patients with TD treated

The efficacy and safety profile of AUSTEDO was demonstrated in the pivotal placebo-controlled clinical trials.

with AUSTEDO (>3% and greater than placebo) were nasopharyngitis and insomnia. Second, **increasing improvement in AIMS total score was observed through 3 years** in an open-label extension (OLE) study, with 71% of patients at Week 145 seeing improvement relative to Week 15. Finally, patient-reported ease of use with AUSTEDO XR was highlighted in a real-world survey, **in which 98% of patients said taking once-daily AUSTEDO XR was easy, and 95% planned to continue taking AUSTEDO XR**.

Q: How do you discuss initiating treatment with AUSTEDO XR with your patients?

A: When speaking with patients, I make it a priority to explain the diagnosis and its underlying causes. At times, I use YouTube videos or other resources on my computer to show them what the condition looks like and why it occurs. I educate my patients on the chronic nature of TD and the need to stay on treatment. Then, I discuss treatment

IMPORTANT SAFETY INFORMATION (CONTINUED)

Akathisia, Agitation, and Restlessness: AUSTEDO XR and AUSTEDO may increase the risk of akathisia, agitation, and restlessness. The risk of akathisia may be increased by concomitant use of dopamine antagonists or antipsychotics. If a patient develops akathisia, the AUSTEDO XR or AUSTEDO dose should be reduced; some patients may require discontinuation of therapy.

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options. If I am going to offer a patient AUSTEDO XR® (deutetrabenazine) extended-release tablets, I will note what was observed in the clinical trials and explain what they can expect with treatment. I will then talk about **how we will titrate the dose of their medication until we find a dose that is tolerable and achieves desired symptom control**.

Usually, **I start my patients on the 4-week Titration Kit**. In the real-world START study, patients and physicians reported treatment success with the 4-week Titration Kit that was consistent with pivotal studies, as well as overall satisfaction with the Titration Kit and ease of following the titration schedule. Additionally, **over 90% of patients adhered to the Titration Kit, with the majority reaching a dosage >24 mg/day by Week 4**.

Q: Could you provide an example of how you have used AUSTEDO XR in your clinical practice?

A: One of my patients with a long history of mood disorders was diagnosed with TD. She was unemployed and somewhat isolated, with limited family contact. Initially, she was on AUSTEDO® (deutetrabenazine) tablets BID but later transitioned to AUSTEDO XR. TD prevented her from being able to paint as a hobby, because the movements interfered with her ability to hold a brush. **Treatment with AUSTEDO XR significantly reduced her movements, and as a result, she was able to hold a paintbrush and paint with less difficulty**, providing her with a renewed sense of purpose. My patient's experience is not an isolated case. In fact, results from a real-world survey showed that more than 50% of patients reported improved social and emotional well-being as a result of movement reduction with AUSTEDO XR. I was grateful that by treating my patient's TD movements, I could help her do something again that brought her joy. **We, as healthcare professionals, can and should be champions for our patients.**

It is part of our role as healthcare professionals to treat TD movements that have an impact on our patients.

Key Learning Points

- APPs often serve as frontline clinicians to assess, diagnose, and treat patients with TD across various healthcare settings
- In the United States, TD is often underdiagnosed and undertreated
- All patients taking antipsychotics should be screened for TD movements at every clinical encounter, regardless of the risk for TD
- Anticholinergics may exacerbate TD movements and should not be used to treat or prevent this disorder
- AUSTEDO XR is an FDA-approved once-daily treatment for TD with
  - Demonstrated efficacy and safety profile
  - Long-term results demonstrated in an OLE study
  - Patient-reported satisfaction and ease of use
  - Patient-reported improvements in emotional and social well-being as a result of reduction in movements ■

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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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CLINICAL: Empowering Mental Health Advanced Practice Providers to Screen, Diagnose, and Appropriately Treat Tardive Dyskinesia

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