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Diagnosis and management of tardive dyskinesia: from research to clinical practice

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Summary. Tardive dyskinesia (TD) is a chronic, often disabling hyperkinetic movement disorder associated with prolonged use of dopamine receptor blocking agents (DRBAs), particularly antipsychotics (APs) for psychiatric disorders such as schizophrenia and bipolar disorder. It manifests as abnormal, involuntary movements, often involving the orofacial region, extremities, or trunk, and is associated with significant physical and psychosocial impairment. TD is primarily linked to dopamine receptor hypersensitivity, oxidative stress, and genetic susceptibility, with a higher prevalence in patients treated with first-generation APs. However, second-generation APs (SGAs) have not eliminated the risk entirely, particularly in older adults and those with prolonged exposure. Diagnosis relies on clinical assessments such as the Abnormal Involuntary Movement Scale (AIMS) and comprehensive neurological evaluations. Treatment guidelines emphasize early detection, prevention through minimal effective doses of APs, and the use of VMAT2 inhibitors (vesicular monoamine transporter 2 inhibitors) as a first-line therapy in moderate-to-severe cases. VMAT2 inhibitors reduce dopamine signaling dysregulation without directly blocking D2 receptors, effectively managing symptoms in many patients. For treatment-resistant cases, deep brain stimulation and other non-pharmacological interventions offer promising alternatives. Current research underscores the complexity of TD's pathophysiology and the need for personalized approaches. Future directions include developing biomarkers for risk stratification, refining therapeutic strategies, and optimizing long-term outcomes through multidisciplinary care.

Key words. Antipsychotic-induced movement disorders, dopamine receptor blocking agents, hyperkinetic movement disorders, tardive dyskinesia, VMAT2 inhibitors.

Diagnosi e gestione della discinesia tardiva: dalla ricerca alla pratica clinica.

Riassunto. La discinesia tardiva (TD) è un disturbo del movimento ipercinetico cronico e spesso invalidante, associato all'uso prolungato di agenti bloccanti i recettori della dopamina (DRBA), principalmente antipsicotici (AP) utilizzati per trattare schizofrenia e disturbo bipolare. Si manifesta con movimenti involontari anomali, spesso localizzati nella regione orofacciale, alle estremità o al tronco, e comporta un impatto significativo sulla salute fisica e psicosociale. La TD è legata principalmente all'ipersensibilità dei recettori dopaminergici, allo stress ossidativo e a fattori genetici, con una prevalenza maggiore nei pazienti trattati con antipsicotici di prima generazione. Tuttavia, anche gli antipsicotici di seconda generazione (SGA) non hanno eliminato completamente il rischio, soprattutto nei pazienti anziani e in trattamenti prolungati. La diagnosi si basa su valutazioni cliniche, come la scala Abnormal Involuntary Movement Scale (AIMS), e su un esame neurologico approfondito. Le linee guida terapeutiche si concentrano sulla prevenzione tramite dosi minime efficaci di AP e sull'uso precoce di inibitori VMAT2 (inibitori del trasportatore vescicolare delle monoamine di tipo 2), considerati il trattamento di prima linea nei casi moderati e severi. Gli inibitori VMAT2 modulano la disregolazione della segnalazione dopaminergica senza bloccare direttamente i recettori D2, offrendo una gestione efficace dei sintomi nella maggior parte dei pazienti. Nei casi resistenti al trattamento, la stimolazione cerebrale profonda e altre opzioni non farmacologiche rappresentano alternative promettenti. Le ricerche attuali evidenziano la complessità della patofisiologia della TD e la necessità di approcci personalizzati. Le prospettive future includono lo sviluppo di biomarcatori per la stratificazione del rischio, il miglioramento delle strategie terapeutiche e l'ottimizzazione degli esiti a lungo termine attraverso cure multidisciplinari.

Parole chiave. Agenti bloccanti i recettori della dopamina, discinesia tardiva, disturbi del movimento indotti da antipsicotici, disturbi del movimento ipercinetico, inibitori VMAT2.

Introduction

Tardive dyskinesia is a persistent and often disabling hyperkinetic movement disorder associated with prolonged exposure to dopamine receptor blockers, particularly antipsychotics (APs) used to treat psychiatric disorders such as schizophrenia and bipolar disorder. Research suggests that second-generation APs have a lower risk of tardive dyskinesia than first-generation APs[1]. Tardive syndromes can manifest in a variety of ways, including oro-buccal-lingual stereotypy, akathisia, dystonia, tics, tremor, and chorea[2]. Tardive dyskinesia (TD) is the most common tardive syndrome and is characterized by abnormal involuntary movements, typically manifesting as involuntary continuous orofacial movements and movements of the extremities or trunk[3]. It is a serious, potentially permanent neurological hyperkinetic movement disorder that occurs after months or years of psychotropic medication use[4]. Despite the expectation that atypical APs would reduce the prevalence of TD, data show that TD remains a significant challenge due to the persistent nature of its symptoms and resistance to various treatment modalities, including AP discontinuation[5]. It is important to note that TD can occur independently of AP use: in the pre-AP era, spontaneous dyskinesia was observed in patients with psychosis[6] and prolonged use of metoclopramide and prochlorperazine can also lead to TD due to their dopamine antagonist properties[7].

In addition, TD often transiently worsens after cessation of the causative DRBA[8]. The etiopathogenesis of TD remains unclear, although it is associated with long-term AP use[9]. While the new generation of atypical AP agents may potentially eliminate concerns about TD in the future, it currently remains a significant clinical problem for patients, their caregivers, and physicians[10]. The effects of antipsychotics are inherently multidimensional, encompassing diverse neurobiological targets that extend beyond dopamine receptor modulation. These include immunomodulatory actions, particularly on microglia, as well as interactions with neuroactive steroids and inflammatory pathways, which may contribute to symptom improvement in schizophrenia spectrum disorders[11,12]. Effective management of TD is critical, as variants such as tardive dystonia and tardive akathisia tend to be more severe and challenging to treat than typical TD[13]. Tardive dystonia consists of sustained muscle contractions and irregular postures, whereas tardive akathisia consists of motor restlessness and subjective discomfort. AP drug withdrawal rarely benefits patients with these variants[13], but reserpine, first-generation VMAT2 inhibitors, β-blockers, benzodiazepines, or clozapine may benefit certain patients[14]. Patients with focal tardive dystonia may also improve with local injection of botulinum neurotoxin.

It is also essential to differentiate TD from other movement disorders. The differential diagnosis of TD is based on several factors, including a history of exposure to dopamine receptor blocking agents (DRBAs), the duration of such exposure, the specific characteristics of the movement abnormalities, and a history of related systemic or neurologic conditions[2,8].

In summary, TD is a complex and challenging movement disorder associated with long-term use of AP medications. While advances have been made in the understanding and managing TD, further research is needed to improve treatment outcomes and quality of life for individuals affected by this condition.

Materials and methods

This narrative review synthesizes current evidence on TD, focusing on its diagnosis, pathophysiology, and management strategies. The authors conducted a comprehensive literature search using PubMed, Scopus, and Web of Science databases for articles published through September 2024. The search strategy combined terms related to "tardive dyskinesia", "VMAT2 inhibitors", "dopamine receptor blockers", "antipsychotic-induced movement disorders", and their variants. We included peer-reviewed studies, clinical trials, systematic reviews, and meta-analyses that addressed TD's epidemiology, etiology, clinical features, and treatment options. Priority was given to publications from the past decade, although seminal older papers were included when relevant. The search was limited to English-language publications. We focused particularly on high-quality evidence, including randomized controlled trials, meta-analyses, and current clinical practice guidelines. Special attention was paid to studies examining the efficacy and safety of VMAT2 inhibitors, as these represent the newest approved treatments for TD. The narrative synthesis of the literature aims to provide clinicians with practical, evidence-based guidance for the diagnosis and management of TD.

Overview of the paper

This article provides a comprehensive review of the current understanding of TD, a persistent and often disabling movement disorder associated with prolonged exposure to dopamine receptor blockers, particularly AP drugs[15]. We discuss the epidemiology, risk factors, pathophysiology, clinical features, diagnostic criteria and tools, and treatment of TD[16,17].

The burden of TD on patients and healthcare systems is reviewed, highlighting its impact on quality of life, social stigma, and economic costs[18,19]. Current guidelines for managing TD are reviewed, focusing on prevention strategies, dose reduction or discontinuation of causative agents, and the use of VMAT2 inhibitors[20,21]. Recent advances in understanding the pathophysiology of TD are also reviewed, including the role of dopamine receptor hypersensitivity, GABA insufficiency, oxidative stress, and neuronal toxicity[22-26]. We used a narrative approach for this review. The literature search was conducted using specific keywords such as "tardive dyskinesia", "VMAT2 inhibitors", "dopamine receptor blockers", and "antipsychotic-induced movement disorders". We searched databases, including PubMed, Scopus, and Web of Science, for studies published through September 2024. The search aimed to identify relevant clinical trials, reviews, and meta-analyses focusing on tardive dyskinesia's epidemiology, pathophysiology, and management. Although this review is not systematic, we have carefully selected the most relevant literature to support our discussion and expert opinion. We conclude with expert opinions on future directions for research and treatment, emphasizing the need for improved prevention, early detection, and individualized management of TD in clinical practice.

Epidemiology

The risk of developing TD differs between first-generation APs (FGAs) and second-generation APs (SGAs)[27]. Multiple studies and meta-analyses have consistently shown that SGAs are associated with a lower risk of TD compared to FGAs, with a cumulative annual incidence of 5.4%-7.7% with FGAs compared to 0.8%-3.0% with SGAs[27]. A meta-analysis by Carbon et al. (2017) reported that global mean TD prevalence was 25.3% across all studies, with lower rates in patients treated with SGAs (20.7%) compared to those treated with FGAs (30.0%)[27,28]. The reduced risk of TD with SGAs is related to their lower affinity for dopamine D2 receptors and their effects on other neurotransmitter systems, such as serotonin[29,30]. However, it is important to note that the advantage of SGAs over FGAs in terms of TD risk may not be as substantial as initially believed, and TD can still occur with SGAs, particularly in vulnerable populations such as older adults and those with a longer duration of AP exposure[22,30,31]. In addition, some studies have suggested that the risk of TD may vary between SGAs, with risperidone and olanzapine possibly having a lower risk than other SGAs[29,32,33]. Other antipsychotics, such as aripiprazole, brexpiprazole, cariprazine, and lurasidone, are less commonly associated with TD, although they may predispose patients to other side effects, such as akathisia.

Sex differences in the risk of TD have been reported in some studies, with a higher prevalence in women compared with men, especially in older age groups[34,35]. A meta-analysis by Yassa and Jeste[34] found that the prevalence of TD was 26.6% in women and 21.6% in men, with the sex difference being more pronounced in patients over 50 years of age. However, other studies have not found significant sex differences in the risk of TD57. Older age is a well-established risk factor for TD, with higher prevalence and incidence observed in older patients[34,36]. The risk of TD appears to increase significantly after age 50, with some studies suggesting a cut-off age of 55 years[34,36]. A prospective study by Jeste et al.[36] found that the incidence of TD was 25% in patients aged 55 years and older compared to 10% in younger patients.

Despite the reduced risk with SGAs, TD remains a significant concern in patients requiring long-term AP treatment, and regular monitoring for the onset of TD symptoms is critical for early detection and management[31].

Etiology and pathophysiology

The etiology of TD is multifactorial, involving a complex interplay of genetic predisposition, oxidative stress, and neurochemical imbalances, particularly in the dopaminergic system[37]. Chronic blockade of dopamine receptors, particularly D2 receptors, by dopamine receptor blockers such as APs is thought to lead to compensatory upregulation and hypersensitivity of these receptors, contributing to TD[32,33]. Genetic factors, including polymorphisms in genes related to dopamine receptors, drug metabolism, and oxidative stress, may influence an individual's susceptibility to developing TD21. Candidate gene studies in TD have identified a number of promising leads, including CYP2D6, DRD2, SLC18A2, HTR2A, and HSPG2. Other genes, particularly in the γ-aminobutyric acid (GABA) and glutamate systems, may be worthy of additional interrogation, especially given the observed co-transmission of dopamine and GABA through vesicular co-packaging by VMAT2 in striatal dopaminergic neurons[37].

Oxidative stress, resulting from an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, has been implicated in the pathogenesis of TD[38]. Chronic exposure to DRBAs may increase dopamine turnover and oxidative stress in the basal ganglia, resulting in neurotoxicity and neuroinflammation[38,39]. These pathophysiological mechanisms, along with age-related changes in the brain and other environmental factors, may collectively contribute to the development of TD in susceptible individuals[32,33].

Clinical features

The symptoms of TD (figure 1) can vary in severity and significantly impact the quality of life of affected individuals. Common manifestations include repetitive, involuntary movements such as facial grimacing, tongue protrusion, lip smacking, and rapid eye blinking[2,40]. These abnormal movements predominantly affect the orofacial region but can also extend to involve the trunk and extremities, leading to more generalized motor impairment[2,40]. Individuals with TD may encounter challenges in daily activities such as eating, speaking and walking. They may also face social stigma and isolation due to the visible nature of the symptoms[41]. The presentation of TD symptoms can range from mild and intermittent movements to severe, continuous, and disabling manifestations[2,40]. Illustrative cases demonstrate a spectrum of TD manifestations, from isolated perioral movements to generalized chorea and dystonia affecting multiple body regions[2,42]. Oro-bucco-lingual dyskinesia, often considered the classic form of tardive dyskinesia, was observed in 72% of cases[2]. Tardive tremor affected 30% of the patients, while 22% experienced tardive akathisia, and 16% suffered from tardive dystonia[2]. Less common manifestations included tardive tics and myoclonus, affecting 4% and 1% of patients, respectively[2]. Additionally, 35% of individuals presented with a combination of two or more tardive syndromes[2]. The impact of TD on daily functioning and quality of life is substantial, with patients reporting physical discomfort, emotional distress, and limitations in social and occupational engagement[41].

Diagnosis

The diagnosis of TD (figure 2) relies primarily on a comprehensive clinical assessment, which includes a detailed history of exposure to dopamine receptor-blocking agents and a thorough neurological examination to identify characteristic involuntary movements[2,4,43]. The Abnormal Involuntary Movement Scale (AIMS) (Appendix 1) is a validated tool commonly used (particularly in clinical research) to assess the severity of TD symptoms, with scores ranging from 0 (no dyskinesia) to 4 (severe dyskinesia) across 12 items evaluating involuntary movements in various body regions (including face, extremities, and trunk), as well as overall severity, impact and awareness of abnormal movements[44,45]. Items 1 through 7 quantify abnormal movements involving the face, extremities, and trunk[45]. An AIMS score ≥2 in 2 or more body areas or a score of 3 or 4 in at least 1 body region indicates an abnormal hyperkinetic movement like TD, according to Schooler-Kane criteria[45]. Additional diagnostic tools such as the Extrapyramidal Symptom Rating Scale (ESRS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS) offer further insights into TD severity and its impact on daily functioning[46,47]. Clinical history and physical examination play a crucial role in confirming the diagnosis of TD and differentiating it from other movement disorders that may present similarly, such as Huntington's disease, primary dystonia or Wilson's disease[2,4]. A thorough differential diagnosis is essential to ensure appropriate management and treatment of the underlying condition[48] (Appendix 2).

Burden of disease

The impact of TD on patients is substantial, affecting their physical, emotional, and social well-being. The involuntary movements associated with TD can lead to stigmatization, social withdrawal, and a decline in quality of life[48,49]. Individuals with TD often experience embarrassment, social isola-

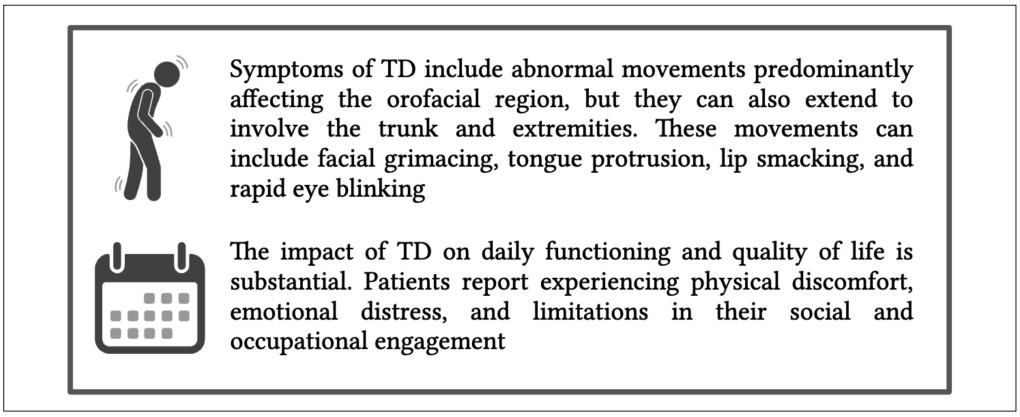

Figure 1. Symptoms of Tardive Dyskinesia (TD).

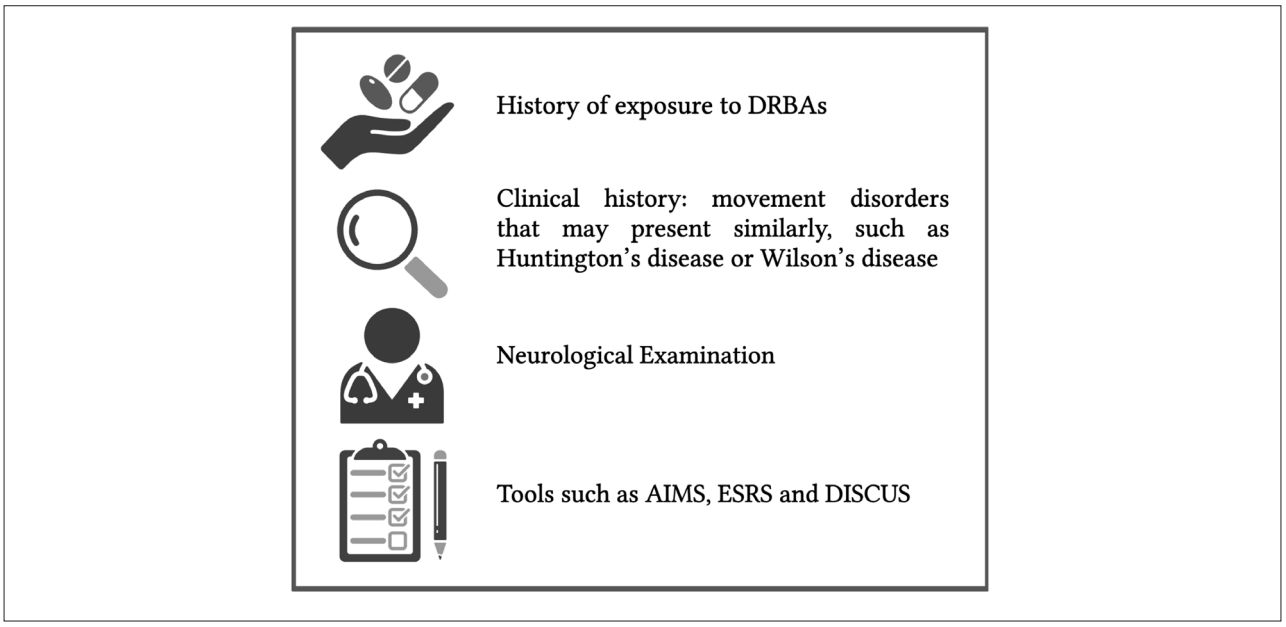

Figure 2. Diagnosis of Tardive Dyskinesia (TD).
Legend: DRBAs= dopamine receptor blocking agents; AIMS= Abnormal Involuntary Movement Scale; ESRS= Extrapyramidal Symptom Rating Scale; DISCUS= Dyskinesia Identification System: Condensed User Scale.

tion, and difficulties in daily activities such as eating, speaking, and walking[48,49]. The psychological burden of TD is significant, with patients reporting higher rates of depression, anxiety, and low self-esteem[1,48]. Furthermore, the economic consequences of TD include increased healthcare costs due to ongoing management and potential disability[49]. Patients with TD demonstrate higher rates of healthcare resource utilization, including more frequent visits to healthcare providers, increased use of emergency services, and longer hospital stays compared to those without TD[41,49]. TD's social and economic impacts extend beyond the individual patient, affecting their families and the healthcare system as a whole[41,49].

Guidelines

The management of TD is directed by the latest clinical guidelines that emphasize early detection and the use of the lowest effective dose of AP medications. The American Academy of Neurology (AAN) and the American Psychiatric Association (APA) provide recommendations for assessing and treating TD, advocating for regular screening and considering VMAT2 inhibitors as treatment options[45,48]. The AAN guidelines underscore the importance of monitoring for TD signs and suggest the use of VMAT2 inhibitors when appropriate[45,48]. APA guidelines recommend that all patients receiving AP medications should be regularly monitored for movement disorders[45,48]. The APA recommends that patients treated with FGAs be monitored every 6 months, while patients on SGA drugs should be evaluated every 12 months[45,48]. According to the APA guidelines, a closer monitoring for abnormal movements should be performed for patients at increased risk for TD (e.g., older adults, presence of affective disorder) receiving AP medications[45,48]. These high-risk patients should be assessed for movement disorders every 3 months if taking FGAs or every 6 months if receiving SGAs[45,48].

In terms of treatment strategies, APA recommends VMAT2 inhibitors for patients with moderate to severe or disabling TD associated with AP therapy[45,48]. Both guidelines stress the significance of early detection and minimal effective AP doses to reduce the risk of TD development[45,48]. Best practices for monitoring include regular clinical assessments and standardized rating scales such as the AIMS.[45,48] Early intervention strategies, such as AP dose reduction, switching to lower-risk APs, or initiating VMAT2 inhibitors, are crucial in preventing or alleviating the long-term consequences of TD[45,48]. Indeed, switching from an FGA, particularly haloperidol, to an SGA with a lower D2 affinity, such as clozapine or quetiapine, may reduce TD symptoms[48].

Regarding VMAT2 inhibitors, there is good evidence to support a favourable benefit-risk profile for novel VMAT2 inhibitors as a treatment option for TD[48]. Novel VMAT2 inhibitors should be considered as first-line treatment for TD[48]. Instead, there is limited evidence for the use of first-generation VMAT2 inhibi-

tors for the treatment of TD[48]. The current evidence suggests that, while first-generation VMAT2 inhibitors may be helpful for TD, their use is associated with more adverse effects than novel VMAT2 inhibitors[48].

An interdisciplinary approach involving collaboration among psychiatrists, neurologists, and primary care providers is essential for the optimal management of TD and the underlying psychiatric condition.

Treatment

The treatment of TD involves various approaches and considerations. One approach to managing TD is to discontinue AP treatment or reduce its dosage. However, these options may not always be feasible due to the potential risk of exacerbation of symptoms or negative impact on psychiatric status[50]. Recommendations for treating TD, including the use of adrenergic uptake inhibitors and AP agents, are provided in systematic reviews[48]. Introducing new treatments, such as VMAT2 inhibitors, has revitalized interest in recognizing and managing TD[45,48]. The pharmacological approach to treating TD has explored various medications and interventions to alleviate symptoms and improve patient outcomes. VMAT2 inhibitors have shown promise in managing TD, with studies highlighting their efficacy and safety profiles[45,48,51].

Additionally, the use of botulinum toxin injections has been considered in the treatment of TD, particularly in cases of focal dyskinesia[2]. The botulinum toxin acts at the alpha motoneuron nerve terminals at the injected site exerting its effect as local muscle relaxant[52]. The efficacy and tolerability of VMAT2 inhibitors for TD have been systematically reviewed, shedding light on their potential as a treatment option[45,48]. VMAT2 inhibition works by reducing dopamine stimulation without directly blocking D2 receptors. This mechanism decreases the overstimulation of D2 receptors in the indirect pathway, which in turn reduces inhibition of the "stop" signal.

Additionally, VMAT2 inhibition benefits in the direct pathway by amplifying "go" signals, as dopamine's effects on D1 receptors are enhanced[53]. Furthermore, vitamin E's role in treating TD has been investigated, with meta-analyses aiming to determine its effectiveness in alleviating symptoms[54]. Vitamin E may help reduce the damage caused by the overproduction of cytotoxic free radicals and may prevent or lessen the severity of TD, especially in individuals who have experienced the onset of the condition within the past five years[54]. The use of anticholinergic medications should be discouraged, and it may worsen TD. Moreover, case studies suggest that neurostimulation via deep brain stimulation (DBS) or repetitive transcranial magnetic stimulation (rTMS) may be an effective option in severe, refractory cases of TD[55]. An interdisciplinary approach involving psychiatrists, neurologists, and primary care providers is crucial for the optimal management of TD and for selecting appropriate pharmacological interventions tailored to individual patient needs.

Expert opinion and conclusions

In summary, tardive dyskinesia (TD) remains a challenging disease to manage, with significant implications for patients, their caregivers, and healthcare systems. Advances in understanding the pathophysiology of TD, including the role of dopamine receptor hypersensitivity, GABA insufficiency, and oxidative stress, have led to targeted treatments such as VMAT2 inhibitors. VMAT2 inhibitors offer hope for better management of TD symptoms and improved patient outcomes. However, challenges remain in optimizing TD prevention, early detection, and individualized treatment in clinical practice. Future research should focus on identifying predictive biomarkers of TD susceptibility and treatment response, comparing the long-term efficacy and safety of VMAT2 inhibitors, and exploring novel therapeutic approaches such as deep brain stimulation and transcranial magnetic stimulation. Expert evidence highlights the importance of regular screening for TD (through regular use of the AIMS scale in clinical practice, as it is a simple, rapid and reliable tool for diagnosis and monitoring of TD), using the lowest effective dose of APs, and considering VMAT2 inhibitors for patients with moderate to severe TD. Recommendations for clinical practice include adopting a prevention-oriented approach, educating patients and caregivers about the risk of TD, and collaborating with movement disorder specialists for complex cases.In terms of managing TD in current clinical practice, experts suggest a stepwise approach[56,57]. First, prevention strategies should be employed, such as using the lowest effective dose of antipsychotics and regularly monitoring for early signs of TD using the AIMS scale[56]. If TD is detected, the offending antipsychotic should be discontinued or switched to a lower-risk alternative, such as clozapine or quetiapine, if clinically feasible[57]. For patients with moderate to severe TD, VMAT2 inhibitors should be considered as first-line pharmacological treatment[57]. Novel VMAT2 inhibitors have demonstrated efficacy in reducing TD severity and are generally well-tolerated[58,59]. In cases where TD is refractory to pharmacological interventions, non-pharmacological options such as deep brain stimulation may be explored in collaboration with movement disorder specialists[60]. Management of tardive TD requires routine assessment of its impact on daily functioning and quality of life using tools like the Impact of TD Scale. An integrative, interdisciplinary approach – combining psychiatrists, neurologists, and primary care providers – should ad-

Recommendations for assessing TD impact in clinical practice.
Routinely assess the impact of TD on patients' daily functioning and quality of life as part of standard care, in addition to assessing TD severity.
Use a standardized, easy-to-administer tool such as the Impact of TD Scale to systematically assess the frequency and distress associated with specific functional consequences of TD symptoms.
Key domains to assess include social, physical, psychological, and cognitive functioning, as well as activities of daily living.
Incorporate the patient's perspective on the impact of TD into treatment, decision-setting, decision-making, and goal-setting.
Managing TD requires an integrative approach with routine impact assessments, interdisciplinary care, patient-centered treatment, and prevention strategies to minimize its burden and improve outcomes.
Collaborate with interdisciplinary teams, including psychiatrists, neurologists, and primary care providers, to optimize TD management and address the multifaceted impact of TD on patients' lives.
Consider alternative analyses of Abnormal Involuntary Movement Scale (AIMS) data, such as effect size and minimal clinically significant difference, to improve TD assessment's clinical relevance and interpretability in practice.

dress motor, psychological, and social aspects of TD. Incorporating the patient's perspective into treatment decisions fosters individualized care. Prevention and early detection, alongside personalized pharmacological and non-pharmacological strategies, are critical for minimizing TD's burden and improving outcomes. Alongside pharmacological management, it is crucial to educate and support patients and their caregivers[56]. This includes informing them about the potential risk of TD with long-term antipsychotic use, the importance of regular monitoring, and the available treatment options. Patients should be encouraged to report any involuntary movements to their healthcare providers promptly[54]. In summary, the management of TD in current clinical practice involves a combination of prevention, early detection, individualized pharmacological and non-pharmacological interventions, and patient and caregiver education. By adopting these strategies, clinicians can work toward minimizing the burden of TD and improving the quality of life for patients with this challenging condition.

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Appendix 1. Tardive dyskinesia: diagnosis and management: an expert opinion

AIMS examination procedure

Either before or after completing the Examination Procedure, observe the patient unobtrusively, at rest (e.g., in the waiting room). The chair to be used in this examination should be a hard, firm one without arms.

1. Ask the patient whether there is anything in his/her mouth (i.e., gum, candy, etc.) and if there is, remove it.
2. Ask the patient about the current condition of his/her teeth. Do teeth bother the patient now?
3. Ask the patient whether he/she notices any movements in his/her mouth, face, hands, or feet. If yes, ask the patient to describe them and to indicate to what extent they currently bother the patient or interfere with his/her activities.
4. Have patient sit in chair with hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position).
5. Ask patient to sit with hands hanging unsupported. If male, between legs; if female and wearing a dress, hanging over knees. (Observe hands or other body areas).
6. Ask patient to open his/her mouth. (Observe the tongue at rest within the mouth). Do this twice.
7. Ask patient to protrude his/her tongue. (Observe abnormalities of tongue movement). Do this twice.
8. Ask patient to tap his/her thumb, with each finger as rapidly as possible for 10 to 15 seconds; first with right hand, then with left hand. (Observe facial and leg movements).
9. Flex and extend patient's left and right arms (one at a time).
10. Ask patient to stand up. (Observe the patient in profile. Observe all body areas again, hips included).
11. Ask patient to extend both arms out in front, palms down. (Observe trunk, legs, and mouth).
12. Have patient walk a few paces, turn, and walk back to the chair. (Observe hands and gait). Do this twice.

Administration time

- **Administration time:** the AIMS test generally takes about 10 to 15 minutes to complete. This includes both the interview and the physical examination of the patient.

Frequency of administration

- **Initial baseline measurement:** when first diagnosing or identifying symptoms of tardive dyskinesia, the AIMS should be administered to establish a baseline.
- **Follow-up assessments:**
- **Monthly:** for patients who are at a higher risk of developing TD (e.g., those on antipsychotic medications), it is recommended to conduct the AIMS monthly for the first year.
- **Every 3 to 6 months:** after the first year, if the patient remains on the medication, the AIMS can be administered every 3 to 6 months. This helps to monitor for the emergence or progression of symptoms.

Clinical Judgment

- **More frequent monitoring:** in cases where there is a change in medication, an increase in dosage, or a change in the patient's clinical status, more frequent monitoring may be warranted.
- **Less frequent monitoring:** for patients who have been stable over a long period without any signs of TD, the frequency may be reduced based on clinical judgment.

Regular use of the AIMS allows healthcare providers to detect TD early and make necessary adjustments to the patient's treatment plan, potentially mitigating the severity of the disorder.

Abnormal Involuntary Movement Scale (AIMS)

Instructions: Complete the examination procedure before making ratings. Circle score for each item.

Patient Name:	Date:	None	Minimal, may be extreme normal	Mild	Moderate	Severe
Facial and Oral Movements						
1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks; Include frowning, blinking, smiling, grimacing		0	1	2	3	4
2. Lips and Perioral Area e.g., puckering, pouting, smacking		0	1	2	3	4
3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement		0	1	2	3	4
4. Tongue Rate only increases in movement both in and out of mouth, NOT inability to sustain movement		0	1	2	3	4
Extremity Movements						
5. Upper (arms, wrists, hands, fingers) Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous); athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic).		0	1	2	3	4
6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot		0	1	2	3	4
Trunk Movements						
7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations		0	1	2	3	4
Global Judgments						
8. Severity of abnormal movements		0	1	2	3	4
9. Incapacitation due to abnormal movements		0	1	2	3	4
10. Patient's awareness of abnormal movements (rate only patient's report) 0 = not aware; 1 = aware, no distress; 2 = aware, mild distress; 3 = aware, moderate distress; 4 = aware, severe distress		0	1	2	3	4
Dental Status						
11. Current problems with teeth and/or dentures?		No	Yes			

Appendix 2. Tardive dyskinesia: diagnosis and management: an expert opinion

Resume table.

Step	Key points
Diagnosis	- Exposure to dopamine receptor blocking agents (DRBAs) for ≥3 months (≥1 month if age >60)
	- Presence of involuntary movements of tongue, face, lips, trunk, and extremities
	- Differential diagnosis to exclude other movement disorders
Assessment	- Use Abnormal Involuntary Movement Scale (AIMS) for screening and severity assessment
	- Consider Extrapyramidal Symptom Rating Scale (ESRS) for comprehensive evaluation
	- Regular screening: every 3-6 months for patients on first-generation antipsychotics, every 6-12 months for second-generation antipsychotics
Treatment	- Prevention: use lowest effective dose of antipsychotics
	- Consider discontinuation or dose reduction of offending agent if possible
	- Consider switching to clozapine for moderate evidence of symptom improvement - Consider use of a VMAT2 inhibitor - Explore non-pharmacological options (e.g., deep brain stimulation) for refractory cases