CNS SPECTRUMS

CME Review Article

A New Era in the Diagnosis and Treatment of Tardive Dyskinesia

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After completing this activity, you should be better able to:

- Identify and differentiate patients at risk for tardive dyskinesia during routine examination
- Apply evidence-based tools and strategies for the early identification and diagnosis of patients with tardive dyskinesia.
- Formulate appropriate, treatment regimens for patients with tardive dyskinesia

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A new era in the diagnosis and treatment of tardive dyskinesia

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Abstract

Tardive dyskinesia (TD) is a heterogeneous, hyperkinetic movement disorder induced by dopamine-receptor blocking agents that presents a unique challenge in the treatment of psychosis. Although acceptance of TD as a serious consequence of antipsychotic treatment was resisted initially, subsequent research by many investigators in psychopharmacology contributed to a rich store of knowledge on many aspects of the disorder. While basic neuroscience investigations continue to deepen our understanding of underlying motor circuitry, past trials of potential treatments of TD focusing on a range of theoretical targets were often inconclusive. Development of newer antipsychotics promised to reduce the risk of TD compared to older drugs, but their improved tolerability unexpectedly enabled an expanding market that paradoxically both increased the absolute number of patients at risk and diminished attention to TD which was relegated to legacy status. Fortunately, development and approval of novel vesicular monoamine transporter inhibitors offered evidence-based symptomatic treatment of TD for the first time and rekindled interest in the disorder. Despite recent progress, many questions remain for future research including the mechanisms underlying TD, genetic predisposition, phenomenological diversity, whether new cases are reversible, how to implement best practices to prevent and treat TD, and whether the development of novel antipsychotics free of the risk of TD is attainable. We owe our patients the aspirational goal of striving for zero prevalence of persistent symptoms of TD in anyone treated for psychosis.

Clinical implications

- Anyone prescribed a dopamine-receptor blocking agent for whatever reason and sustained length of time is at risk of developing potentially irreversible tardive dyskinesia manifested by abnormal involuntary movements that range in phenomenology, severity, and impact.
- Tardive dyskinesia can range from subtle movements in one body area that may be mildly embarrassing and resemble common mannerisms to painful, disfiguring, or generalized movements that are stigmatizing and incapacitating.
- A rational strategy for management includes screening at all clinical visits, documenting abnormal movements, discussion of treatment options with patients and caregivers, modification of psychotropic medications, and consideration of specific antidyskinetic treatment with vesicular monoamine transporter inhibitors.

Introduction

In 1957, a few years after chlorpromazine was first given to patients with psychosis,[1] Schonecker et al[2] reported 3 elderly women who developed persistent dyskinesias after treatment. Subsequent observations confirmed the occurrence of a complex phenomenological picture of abnormal movements that were distinguished from previously described drug-induced movements by a delayed onset and persistence after antipsychotics were discontinued.[3-6]

Despite initial resistance, the significance of tardive dyskinesia (TD) became a major impetus for developing drugs effective against psychotic symptoms without affecting motor circuitry.[7] While extensive research by many prominent groups established the clinical and epidemiological dimensions of TD,[8-18] the landmark study of clozapine by Kane et al[19] served as a proof-of-concept for industry stakeholders in developing new drugs that preserved and extended antipsychotic efficacy while reducing the risk of TD and other drug-induced movement disorders. Paradoxically, success of the subsequent new antipsychotics extended risk of TD to more patients as the proliferation of new drugs, indications, and off-label use exploded. While awareness of TD waned among psychiatrists,[20,21] TD continued to occur and remained a concern among movement disorder specialists.[22-25]

More recently, industry-sponsored clinical trials led to the approval of two novel vesicular monoamine transporter-2 (VMAT2) inhibitors, valbenazine and deutetrabenazine,[26-31] with

more favorable pharmacokinetic properties than tetrabenazine which had long been recognized as effective in suppressing TD movements.[22,32-34] Availability of these evidence-based treatments prompted renewed industry support for research on TD. We sought to briefly summarize new evidence for detecting, diagnosing, and treating TD.

Identifying and stratifying risk for TD during routine examination

Incidence and prevalence

A guiding principle for antipsychotic treatment is that anyone prescribed a dopamine-receptor blocking agent for whatever reason and sustained length of time is at risk for developing potentially irreversible TD manifested by abnormal involuntary movements that range in phenomenology, severity, and impact. TD is not uncommon. In general, the incidence of new cases of TD is reported to be approximately 3% to 5% annually, rising cumulatively at this rate for at least the first 3–5 years of antipsychotic treatment.[35-39] However, annualized rates of TD should not be misinterpreted as meaning TD occurs only after exposure of a year or more, as TD may occur within a few weeks in vulnerable patients.[2,40-43] The prevalence of TD in populations of treated patients is reported to average approximately 20% to 30%.[35,36]

Risk factors

Keeping the dictum of universal vulnerability in mind, there are varying degrees of risk to consider. Advancing age is the strongest predictor of TD, such that antipsychotics should be prescribed cautiously in people 45 years or older.[44-48] The incidence and prevalence of TD among older adults may reach 15% to 30% annually and 50% to 60%, respectively.[44,49] Sex, race, and ethnicity are less consistent risk factors as contrasting prescribing practices affecting demographic groups may be one of many confounding variables.[45-47,50-53] Schizophrenia, which like aging predisposes to spontaneous dyskinesias,[7,54-58] confers a high risk of TD. Severity of positive, negative, and cognitive symptoms has been associated independently with TD,[45,46,59] although confounded by higher dosing and longer use of potent agents with frequent noncompliance in patients with more severe symptoms of chronic schizophrenia. Developmental disorders and mood disorders, primarily bipolar disorder, also may confer risk.[60-62] But more women and older patients with depression who receive intermittent treatment with antipsychotics during episodic relapses may confound the association with mood disorders.[6,46,47,62,63]

TD is associated with medical co-morbidities as well.[58] In particular, diabetes has been implicated in increasing the risk of TD in some but not all studies.[45,58,64] However, this association and other medical co-morbidities may represent an artifact of the concomitant metabolic side effects of antipsychotics experienced by older and chronically treated patients rather than supporting diabetes as a risk factor for TD.

Pharmacogenetic studies of TD are preliminary but offer promise of identifying risk for TD.[65] Association studies of TD have focused on polymorphisms of genes related to metabolism of antipsychotics, neurotransmitter receptors, transporter proteins, and genes involved in synaptic plasticity, oxidative stress, and inflammation. One interesting candidate is SLC18A2 which encodes the vesicular monoamine transporter-2, the target of VMAT2 inhibitors. Detection of SLC18A2 variants might allow identification of alterations in VMAT2 function informing the use of VMAT2 inhibitors and antipsychotics to prevent or treat TD. Studies to date have not yet provided consistent evidence that would support the implementation of genetic testing to predict TD in clinical practice.

The risk of TD differs among antipsychotics. Drugs classified as second-generation antipsychotics (SGAs) have consistently shown a reduced risk of TD compared with first-generation antipsychotics (FGAs).[36,37,56,66-68] The true risk differential may not be as great as initially thought, ranging from one-quarter to two-thirds of the risk of FGAs.[47,69-72] Several meta-analyses have shown that relative risk may have more to do with D2-receptor blocking potency of individual antipsychotics rather than the year a drug was introduced.[73,74] Patients receiving higher cumulative doses for longer duration are intuitively at greater risk,[47,56,75] although clinicians should remain vigilant given that even short-term treatment with low doses may induce TD in vulnerable patients.[76] So, for example, prolonged high doses of haloperidol predictably cause TD, whereas the risk of TD with clozapine is significantly diminished.[69,77]

The relative risk of long-acting injectable antipsychotics compared to oral agents is unclear but likely similar, with newer SGAs less likely than FGAs to cause TD in some but not all studies.[78-81] Studies of long-acting injectable agents have suggested that guaranteed continuous administration of antipsychotics may actually decrease the risk of TD compared with intermittent treatment resulting from "drug holidays," symptom-driven administration or patient nonadherence.[82-85]

The effect of other prescription drugs or substance abuse on the risk of TD is less clear. Anticholinergic drugs have often been associated with TD. While anticholinergics acutely exacerbate TD symptoms and withdrawal may improve TD,[63,86] it remains unclear whether they are risk factors for the development of TD.[6] As they are commonly started or maintained in patients with drug-induced parkinsonism and other acute movement disorders, which are themselves associated with TD,[87,88] the association between anticholinergics and TD may simply reflect people with predisposition to all movement disorders. The effects of nicotine and smoking on the risk and severity of TD are unclear and confounded by changes in plasma levels of antipsychotics induced by hydrocarbons in cigarette smoke.[6,86,89,90] Although other psychotropic agents often used concurrently with antipsychotics induce a variety of abnormal movements, for example, tremor, ataxia, or myoclonus, their influence on the risk of TD has not been well studied.[62,91] While the development of TD-like movements with serotonin reuptake inhibitors or other antidepressants used as monotherapy is theoretically possible and has been reported in rare cases, whether irreversible movements can occur in the absence of dopamine receptor blockers is still controversial.[91,92] Finally, drugs used in other medical specialties that have dopamine receptor blocking properties, for example, metoclopramide, prochlorperazine, flunarizine, or cinnarizine, are associated with the risk of TD and should not be overlooked.[93]

Evidence-based strategies and tools for the diagnosis of patients with TD

Phenomenology

Although the symptoms of TD are mild and affect the orofacial region in 60% to 80% of cases,[6] manifestations can be complex

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Table 1. Phenomenology of Tardive Dyskinesia

Stereotypy:	Repetitive, rhythmic, patterned, pseudo-purposeful movements
	Examples: chewing, lip licking or puckering, truncal rocking, hand rubbing
Chorea:	Irregular, random, brief, flowing movements
	Examples: Fidgety or dancelike movements of toes or fingers, tongue darting, diaphragmatic effects on respiration
Dystonia	Repetitive, sustained, pulling, twisting, movements or postures
	Examples: Torticollis, pleurothotonus, jaw trismus, grimacing, blepharospasm, laryngeal/pharyngeal spasms
Akathisia:	Restlessness with urge to move
	Examples: Difficulty sitting or standing still, pacing, walking in place, leg-swinging or crossing, toe-tapping
Tics:	Abrupt, brief, jerk-like, compulsive movements preceded by a premonitory urge
	Examples: Eye blinking, jerking neck and limb movements, vocalizations
Myoclonus:	Sudden, brief, shock-like movements
	Examples: Spontaneous or stimulus-sensitive
Sensory symptoms:	Pain, anxiety or fatigue
	Examples: Associated with sustained postures or repetitive movements, oral or genital burning pain

taking a variety of phenomenological forms that can range widely in severity and impact (Table 1).[6,94,95] The variety of movements has generated discussion of whether the term "tardive dyskinesia" should be restricted to the classic oral-buccal-lingual movements as opposed to a more encompassing term such as "tardive syndromes."[25,96] TD movements can affect any striated or voluntary muscle group and are most often described as stereotyped or choreiform, but can appear as dystonia, akathisia, tics, or myoclonus. TD may have a sensory component as well, typically pain accompanying movements. The notion that these different forms represent phenotypic manifestations of the same underlying process is supported by the fact that they often occur concurrently in the same patient, for example, approximately 10% of patients with classic TD also have tardive dystonia.[94,97] While it is unclear to what extent different forms of TD predict different treatment response or prognosis, it is critical for clinicians to be able to distinguish TD from acute and reversible drug-induced movement disorders which respond oppositely to TD (Table 2).[94] But it is important to note that acute movements can also co-exist in patients with TD raising challenging treatment questions.[50] In patients receiving antipsychotics, at least 20% to 30% may have two or more drug-induced movement disorders, and 13% and 5%, respectively, of those with TD may simultaneously have parkinsonism or akathisia.[50,98,99]

Diagnostic criteria

Standardized diagnostic criteria for TD in DSM5-TR include a concise description of clinical signs and require exposure to antipsychotics of at least 3 months (1 month for patients over

Table 2. Comparison of Tardive Dyskinesia and Drug-Induced Parkinsonism

Characteristic	Tardive dyskinesia	Drug-induced parkinsonism
Clinical signs	Heterogeneous hyperkinetic movements of the face, neck, trunk and extremities	Hypokinetic movements of bradykinesia and rigidity, plus tremors
Associated features	Forms include stereotypy, chorea, dystonia, akathisia, tics, myoclonus, pain	Masked facies, gait disturbance, postural instability, drooling
Onset after antipsychotics	Weeks-years (incidence 3%-5%/year)	Days-weeks (50%-75% occur within 1 month, 90% within 3 months)
Reversibility	Resolves in no more than 2%-5% of established cases after drug cessation; Early cases may allow for reversal in 50%-75% with long-term follow-up; Maintenance antipsychotics may mask symptoms in up to 67%	Resolves in weeks-months after drug cessation; May persist or predict Parkinson's disease in up to 15%
Pharmacologic responses;		
↑Antipsychotic	Improves (suppresses)	Worsens
↓Antipsychotic	Initial worsening; Possibly improves overtime	Improves
↑Anticholinergic	Worsens; Tardive dystonia may improve	Improves
↓Anticholinergic	Improves; Tardive dystonia may worsen	Worsens
VMAT2 inhibitor	Improves (suppresses)	Worsens
Amantadine	May improve?	Improves

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age 60) or occurring within 4 weeks of withdrawal from oral agents or 8 weeks from long-acting agents.[100] In ICD-10-CM, TD is formally coded as "drug-induced subacute dyskinesia" but is poorly defined and often miscoded under other and unspecified drug-induced movement disorders or neglected entirely in recorded databases.[58,101,102] The best known and widely accepted operationalized criteria are the Schooler-Kane research criteria which posit the presence of at least moderate movements in one area or mild in two areas on the Abnormal Involuntary Movement Scale (AIMS) that are not caused by another etiology and are associated with at least 3 months of antipsychotic exposure.[103] Glazer et al[104] proposed a lower threshold for diagnosis, with movements meeting a total AIMS score of three with at least one area rated as mild. Use of higher diagnostic thresholds on the AIMS in past epidemiologic studies may have underestimated the true extent of TD since recent evidence suggests that even mild movements in one body area are diagnostic for TD.[40,105] Basing diagnosis on the number of areas recorded on the AIMS also may be problematic because the orofacial region is overweighted and differentiating overflow movements between the jaw, lips, and tongue as distinct areas is challenging.[40,105]

Differential diagnosis

The most common movement disorders for clinicians to distinguish from TD are spontaneous dyskinesias and other drug-induced movement disorders. Unusual movements including compulsions, mannerisms, and stereotypies comprise a core symptom dimension of schizophrenia.[24,55,57,106,107] People with depression or mania are similarly characterized by abnormal movements or catatonic signs.[108] Aging itself predisposes to abnormal movements, especially in the orofacial region and when edentulousness occurs.[48,57] These observations prompted studies comparing the incidence of spontaneous dyskinesias to TD, suggesting that antipsychotics reveal or facilitate the appearance of abnormal movements in people who are naturally predisposed to their eventual occurrence.[13,109]

Given the contrasting responses to treatment (Table 2), it is also important to differentiate acute reversible drug-induced movements, induced by use of illicit or prescription drugs, from TD. While the phenomenology between some forms of TD and acute movements, for example, dystonia or akathisia, may be similar, temporal correlation with antipsychotic treatment helps distinguish between them.[6,24,94,110,111] TD is more likely to be delayed after antipsychotic treatment initiation, and often appears or worsens and can persist after drug dose reduction or discontinuation. Psychotropic drugs other than antipsychotics are also associated with abnormal movements.[24,62,91,112,113] Lithium, antidepressants, and anticonvulsants may cause tremors while antidepressants and stimulants may also cause or worsen akathisia, tics, and TD. However, in nearly all these cases, the movements are acute and reversible with drug discontinuation whereas dopamine-receptor blockers appear to be uniquely associated with persistent or irreversible movements.[92]

Finally, the differential diagnosis of movement disorders in general is extensive across the spectrum of pathological etiologies.[6,95] Although overlooking any of these neurological or systemic disorders could be tragic, they are mostly rare and irreversible, and are best evaluated in collaboration with medical or neurological consultants. Clues that may indicate an underlying etiology are worth keeping in mind (Table 3).[40]

Table 3. Clues to Alternative Etiologies in the Differential Diagnosis of Tardive Dyskinesia

• Abnormal movements atypical for tardive dyskinesia
• Localizing neurological or systemic medical signs or symptoms
• Sudden onset, rapidly progressive or generalized course
• Family history of abnormal movements or neurodegenerative disorders
• Unrelated temporal association with dopamine receptor blocking agents
• Presence of alternative drugs or substance abuse associated with abnormal movements
• Abnormal laboratory or neuroimaging findings
• Unexpected treatment failure, intolerability, or resistance of movements

Screening tools and policies

Regular screening to detect early signs of TD is critical. Among a number of rating instruments proposed for screening and monitoring, the AIMS achieved high interrater reliability and near-universal acceptance as the standard tool in clinical trials and epidemiology research, in clinical practice settings, and by regulatory agencies.[114] Based on a standardized examination, the AIMS scale measures the objective severity of abnormal movements across seven selected muscle groups ranging from normal to severe judged on the basis of quality, amplitude, frequency, anatomic distribution, and duration of abnormal movements observed during the examination.[115,116]

Opportunities to extend its usefulness have received renewed attention. For example, shortcomings of the AIMS include; whether a total summed score obscures the distribution of symptoms; the value of a single global score; and lack of consensus on a minimal clinically important difference to assess the significance of change scores.[105,117,118] Awareness, incapacitation, and dental items have not been standardized and are less reliable. The AIMS is weighted toward orofacial movements and does not provide information about phenomenology which can have a major impact on prognosis as well as tolerability.[119] While more comprehensive rating scales measuring all abnormal movements have been suggested for research or specialty settings, time constraints in a busy clinical practice support the need for simplified screening tools. Evidence suggests that the major reason for noncompliance with screening is lack of sufficient time.[105] Therefore, a number of efforts have been undertaken to validate brief screening tools or virtual procedures,[120-123] and to instruct patients and caregivers on self-examination to detect early signs.[124-126]

Another area not covered by the AIMS is the impact of TD. The impact of TD is critical in determining how severity and changes in abnormal movements affect functioning and quality of life.[120,127] While severe TD may impair functioning in all affected people, even mild TD may have profound effects on an individual.[128] Recent studies have documented the impact of TD and piloted the use of rating scales that incorporate functional measures. Additional evidence is needed on the predictive validity of AIMS scores in determining the effect of TD on functioning and quality of life.[105]

Finally, a screening tool is only as effective as the reliability with which it is applied. Guidelines and institutional policies vary in how often screening with AIMS should occur.[129] Previous policies

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mandating screening on an annual basis are insufficient and likely to miss a significant number of cases precluding early intervention and potential reversal.[40] Questions about TD and visual inspection for abnormal movements should be added to screening assessments of side effects at every clinical visit.

Formulating individualized treatment plans for patients with tardive dyskinesia

Once TD is diagnosed, a logical sequence of management decisions follows.[63,130] First, assessment of the severity, distribution, and phenomenology of TD should be conducted by documenting a complete AIMS examination. Assessment of the functional impact should be conducted by asking concrete, descriptive questions on awareness and impact on self-esteem and limitations in health, social and occupational functioning. Second, a differential diagnosis should be considered to rule out spontaneous dyskinesias or other acute drug-induced movements, with specialist consultation if the diagnosis is uncertain or other rare neurological disorders are suspected. Once TD is confirmed, a discussion should take place with patients and caregivers to inform them of the diagnosis, prognosis, and treatment options.

It is important to consider the natural course of TD in deciding on subsequent treatment decisions. Abnormal movements fluctuate with activation, anxiety, relaxation, inattention, or distraction, they can be suppressed by voluntary action, and they disappear during sleep. TD severity can fluctuate over the course of a day or between clinical visits. In patients with TD at baseline randomized to receive SGAs in one large-scale trial, 76% met the criteria for TD at some or all subsequent visits, 24% did not meet the criteria at any visit, 32% showed more than 50% improvement in TD, while 7% showed more than 50% worsening of AIMS scores.[59] The relationship to treatment is informative, as 5% to 67% of patients may have TD that is covert or masked by ongoing antipsychotic treatment and only becomes apparent after drug discontinuation.[7] Withdrawal dyskinesia is defined by a movement first observed after treatment cessation that subsides within 4-12 weeks after antipsychotic discontinuation.[100] Withdrawal dyskinesias that subside after drug discontinuation do not necessarily require specific treatment. The distinction between withdrawal dyskinesia and incipient TD may be arbitrary and more likely, withdrawal dyskinesias are on a continuum with persistent TD. In other words, early TD may be reversible after drug discontinuation, but may become irreversible after a variable period of time if antipsychotics are continued.

Subsequent prescribing decisions begin with re-evaluating antipsychotic treatment. Maintenance of current treatment may be justified in patients with severe psychiatric illness at high risk for relapse who are stable on current antipsychotic therapy but have mild, localized TD with minimal subjective impact. In most cases, TD is not progressive even with continued antipsychotic treatment, although symptoms may worsen in some cases.[59] Patients should provide informed consent and should be carefully monitored for any signs of progression.

Ideally, antipsychotics could be tapered off. In patients without an underlying psychotic disorder, for example, those who develop TD while taking adjunctive dopamine antagonists for depression, antipsychotic treatment could be safely tapered.[62] However, patients with schizophrenia, bipolar disorder, or psychotic depression may incur a significant risk of relapse and require ongoing maintenance treatment.[131] More research on the early mechanisms underlying onset leading to permanence of TD are needed. Meanwhile, early detection and reconsidering antipsychotic treatment for patients who could be safely treated by other means is prudent to account for the possibility of reversible TD after drug discontinuation, whereas established TD is unlikely to resolve.

However, complete and permanent reversibility beyond the withdrawal period is controversial and may be uncommon. Early studies suggested that after withdrawal from FGAs, approximately 33% to 53% of patients experience worsening of dyskinesias initially, while 36% to 55% may show improvement over time.[132] In a meta-analysis, Soares and McGrath reported that 37.3% of patients assigned to placebo across studies showed some improvement of TD, but concluded that evidence was insufficient to support antipsychotic drug cessation or dose reduction in view of the risk for psychotic relapse.[133] While recent surveys suggest as few as 2% to 5% of patients show resolution of TD without specific treatment even when followed-up for a few years after antipsychotic withdrawal,[134,135] earlier studies reported remission a few months to years after drug cessation in 50% to 75% of patients provided that TD was detected early.[83,136-138] These early reports suggest that further studies of antipsychotic cessation in nonpsychotic patients as a management option for new-onset cases of TD are needed.

Another option is the dose reduction of antipsychotics. Evidence is mixed on whether dose reduction improves TD which in fact may temporarily worsen on decreased dosages.[139-141] Recent evidence suggests that dose reduction like drug cessation may contribute to psychotic relapses and possible re-hospitalization, further limiting this treatment option for TD without additional evidence.[102]

If maintenance treatment is necessary or if a patient requests a change from the agent that caused TD, switching to more potent antipsychotics or FGAs may temporarily suppress TD in up to 67% of patients, although limiting remission of TD and exacerbating parkinsonism and other acute drug-induced movements.[132,142-144] Several studies of SGAs have shown a reduction in TD severity, with some studies showing greater suppression, lesser suppression, or no difference compared with FGAs.[59,95,141,145] In fact, studies of SGAs in suppressing TD have shown approximately a 3-4 point average decrease in total AIMS severity scores which is comparable to decreases in recent trials of VMAT2 inhibitors.[15,59,142,146-149] Among SGAs, some studies have highlighted evidence that clozapine significantly reduces symptoms of moderate to severe TD, especially dystonic movements, suggesting that it should be considered an alternative antipsychotic in patients with TD who may not be responding to other approaches.[146,148,150,151] However, switching any antipsychotics may incur the risk of destabilizing psychiatric symptoms in an otherwise stable patient.[152]

If anticholinergic drugs have been prescribed, a decision about continuation or tapering should be considered. Anticholinergic drugs are not effective as a treatment for TD; in fact, they may worsen TD acutely, such that improvement in TD severity ratings have been noted in up to 60% of patients withdrawn from these agents.[132,143,153-155] But caution should be taken in reducing anticholinergics if acute drug-induced movements (eg, parkinsonism, dystonia) or tardive dystonia are present as these disorders could re-emerge or worsen after withdrawal.[155] Amantadine may be a reasonable alternative to anticholinergics in patients with both TD and parkinsonism, especially if they are

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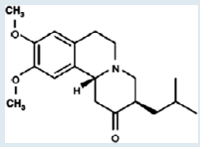
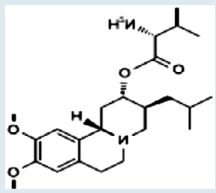
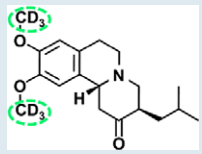
Table 4. Comparison of VMAT2 Inhibitors

Medication	Tetrabenazine	Valbenazine	Deutetrabenazine
			
Mechanisms	Reversibly binds VMAT2	Reversibly and selectively binds VMAT2	Reversibly binds VMAT2
Initial daily dose (mg)	12.5	40	12
Maximum daily dose (mg)	150	80	48
Dosing frequency	TID	Once daily	BID
Half-life (h)	5-7	15-22	9-10
Taken with food	With or without	With or without	With
Hepatic impairment	Contraindicated	Dose 40 mg	Contraindicated
Renal impairment		Not recommended in severe impairment	
Cytochrome enzymes	Genotyping CYP2D6 for doses >50 mg; Maximum daily dose 50 mg in CYP2D6 poor metabolizers or with CYP2D6 inhibitors	40 mg dose in CYP2D6 poor metabolizers, or with CYP3A4 or CYP2D6 inhibitors; not recommended with CYP3A4 inducers	Maximum daily dose 36 mg in CYP2D6 poor metabolizers or with CYP2D6 inhibitors
Side effects	Somnolence, akathisia, parkinsonism, depression, ↑QTc, contraindicated in suicidal patients	Somnolence, fatigue, headache, parkinsonism, ↑QTc, monitor digoxin	Somnolence, fatigue, headache, parkinsonism, ↑QTc, contraindicated in suicidal patients

at risk for adverse anticholinergic effects; it is now marketed in a long-acting formulation and evidence suggests it may have beneficial effects on both dyskinesias and parkinsonism.[154,156] It is also helpful to recall that some studies have suggested that patients with TD are heterogeneous in response to pharmacological agents.[10,17]

If TD remains a significant problem once antipsychotic treatment is optimized, specific antidyskinetic treatment with VMAT2 inhibitors should be considered. Numerous and mostly flawed past clinical trials of agents engaging diverse pharmacological targets yielded inconclusive or negative results.[141,143,157-159] In contrast, recent trials have provided robust evidence on the efficacy and tolerability of valbenazine and deutetrabenazine (Table 4). Like tetrabenazine, these drugs act to deplete dopamine and thereby reduce the severity of TD by inhibiting VMAT2 in nerve terminals, which ordinarily protects dopamine from the metabolic breakdown by transporting monoamines into protective vesicles. Despite a paucity of controlled trials, tetrabenazine is efficacious for the treatment of TD based on observational studies, but is limited by a short half-life and side effects of sedation, parkinsonism, akathisia, and depression.[22,160,161] Valbenazine and deutetrabenazine were designed with improved pharmacokinetics to allow for a longer half-life and reduced fluctuations associated with differences in genetic metabolic rate and drug interactions. Rigorous short and long-term trials have confirmed that both drugs are more effective than placebo in reducing severity of TD and are likely better tolerated than tetrabenazine.[26-29,162-165] Although both are effective compared to placebo, valbenazine has the advantage of simple titration and once-a-day dosing, whereas deutetrabenazine may allow for smaller increments of titration. Variability of response to VMAT2 inhibitors based on phenomenology has yet to be tested, but earlier trials suggested that both tardive dystonia and tardive akathisia also improve with these drugs.[166-168]

If TD does not respond to one VMAT2 inhibitor or side effects emerge, a second VMAT2 inhibitor could be tried. Among other agents that have not met the threshold of evidence to justify approval, some may have efficacy for subgroups of patients with TD. Cholinergic agents (acetylcholine precursors, cholinesterase inhibitors) have been tried with inconclusive results, but emerging drugs targeting specific cholinergic receptors may be worth exploring.[86,169] GABA-ergic drugs have questionable benefits in reducing TD and are limited by side effects.[141,143,170] For example, although clonazepam has been rated as probably improving TD and is commonly used, it is limited by its potential for abuse and significant hazards of sedation, ataxia, and cognitive impairment, especially in older adults.[157] Evidence that dopaminergic blockade results in excess dopamine turnover and oxidative free radical formation formed the rationale for trials of antioxidants albeit with limited support to date.[141] For example, although vitamin E appeared promising as a treatment for TD in early pilot studies, a subsequent definitive large-scale randomized controlled trial failed to show a significant effect on TD compared to placebo.[171] Amantadine, an N-methyl-D-aspartate receptor antagonist with dopaminergic and anticholinergic properties, has undergone preliminary testing as a treatment for TD and may have value in patients with concurrent TD and parkinsonism.[141,154,156] In tardive dystonia,

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some evidence suggests that anticholinergics, botulinum toxin, or neurosurgical procedures may be beneficial.[95,167,168]

Looking ahead

The explosive growth in promotion and prescribing of antipsychotics is likely to continue, resulting in more cases of TD. There is a compelling need for education among practitioners about conservative use of antipsychotics, the risks of TD, and screening and monitoring policies and instruments. In addition, research and development of antipsychotics that target novel brain targets (trace amine-associated receptor 1 agonists, serotonin agonists and serotonin/opioid antagonists, muscarinic receptor agonists) that lack dopamine receptor affinity may offer promise as effective antipsychotics without movement disorder liability.[78]

Meanwhile, VMAT2 inhibitors are likely to transform the treatment of TD and renew interest in TD research.[172] Although trials of VMAT2 inhibitors offer clear evidence of efficacy and tolerability in suppressing TD, their impact on real-world outcomes merits additional investigation. There are as yet no head-to-head prospective trials comparing VMAT2 inhibitors, SGAs, or other antidyskinetic agents.[160,173] In addition, continuing studies of the social, psychological, and economic impact of TD are likely to provide crucial evidence to better inform cost–benefit treatment decisions in the near future.[174]

The interaction between the VMAT2 inhibitors and antipsychotics has also raised interesting questions.[175] For example, adding VMAT2 inhibitors early in treatment for first-episode patients may allow lower doses of antipsychotics to be used possibly reducing the risk of TD. However, dopamine depletion, like denervation, may theoretically add to the risk of TD from antipsychotic-induced dopamine receptor blockade.[63,176] In addition, by suppressing TD symptoms without blocking dopamine receptors, these agents might allow patients who do not require maintenance antipsychotics to tolerate drug withdrawal and therefore facilitate natural reversal of the mechanisms underlying TD over time.[177] As suggestive evidence, approximately 25% to 30% of patients enrolled in long-term extension studies of valbenazine continued to show a reduction of TD even 4 weeks after withdrawal from valbenazine.[178] In patients without the need for maintenance antipsychotics, long-term withdrawal studies may provide answers in the future.

Conclusion

The availability of novel VMAT2 inhibitors has transformed the treatment of TD. These findings need to be tested in real-world settings over the long term and taken into consideration as part of a broader, practical treatment algorithm that provides a stepwise approach to the management of patients affected by TD. Availability of these treatments may also rekindle interest in TD and the need for re-education and implementation of standardized practice guidelines. Additional research should include investigations of underlying pathophysiological mechanisms, variations in phenomenology, genetic predisposition, and the efficacy of other novel antipsychotic and antidyskinetic drugs, especially those targeting non-dopaminergic mechanisms, with the ultimate goal of achieving prevention, reversibility, and remission of TD symptoms.

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Posttest Study Guide

The posttest can only be submitted online. The below posttest questions have been provided solely as a study tool to prepare for your online submission.

1. Which of the following is the greatest risk factor for developing tardive dyskinesia in patients prescribed a dopamine receptor blocking agent?
   A. Age
   B. Diabetes
   C. Genetic predisposition
   D. Weight

2. According to the DSM5-TR, how long is a patient over the age of 60 required to be on an antipsychotic before being diagnosed with tardive dyskinesia?
   A. 1 week
   B. 1 month
   C. 3 months
   D. 8 months
   E. 12 months

3. Assuming a patient continues to present tardive dyskinesia symptoms despite optimizing their antipsychotic treatment, which two drugs act as VMAT-2 inhibitors to deplete the concentration of dopamine in a synaptic vesicle?
   A. Amantadine/Clonazepam
   B. Amantadine/Clozapine
   C. Benztropine mesylate/Valbenazine
   D. Clonazepam/Tetrabenazine
   E. Deutetrabenazine/Valbenazine

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