Tardive Dyskinesia: Challenges in Screening, Diagnose and Treatment

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Definition and Symptoms

The American Psychiatric Association defines Tardive Dyskinesia (TD) as involuntary athetoid or choreiform movements generally of the tongue, lower face, jaw and extremities (may involve the pharyngeal, diaphragmatic, or trunk muscles). Tardive dyskinesia is an iatrogenic condition that arises following extended use of antipsychotic and other dopamine-related medications. It is characterized by repetitive, involuntary muscle movements throughout the body.TD develops in association with the use of neuroleptic medication for at least a few months. Symptoms persist over 4-8 weeks.[1,2]

When beginning treatment with dopamine D2 receptor antagonists, physicians must thoroughly examine all patients to identify movement problems. The clinical manifestations of tardive dyskinesia include the involuntary movements of the tongue, neck, facial muscles, truncal musculature, and limbs. When it comes to buccolingual movements, which include masticatory muscles, lip-smacking, tongue protrusion, perioral movements, chewing movements, or a puffing of cheeks, these characteristics define buccolingual movements. At times, it may be difficult to differentiate these motions from the stereotypical posture that is observed in people who suffer from chronic psychosis. Tardive dyskinesia is also associated with nonmotor features, including akathisia and pain. On the other hand, people who have been exposed to dopamine D2 receptor blockage for an extended period may get tardive dyskinesia. The beginning of tardive dyskinesia is a gradual process that can be difficult to identify because the early stages of the condition only indicate a slight deviation from the norm regarding movement. Tardive dyskinesia can become apparent anywhere from one to six months after the beginning of treatment with a dopamine receptor antagonist. Diagnosing acute or chronic dyskinesias might be difficult when a thorough history is not considered. To make an accurate diagnosis of tardive dyskinesia, it is helpful to have a comprehensive history of movement abnormalities and medications. Anti-dopaminergic drugs have the potential to cause a variety of disorders, including the following[3,4]:

1. Tardive akathisia
2. Tardive orofacial dyskinesia

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3. Tardive dystonia
4. Tardive blepharospasm
5. Tardive tics

Prevalence

For individuals who are being treated with antipsychotics, the lifetime prevalence of TD is predicted to be between 16 and 50%. The majority of cases of tardive dyskinesia (87%) are irreversible, even following the discontinuation of the offending medication. Patients and clinicians may not be aware of TD because antipsychotic medications might hide symptoms, patients may not be conscious of dyskinesia symptoms, or physicians may have limited experience with dissociative disorder. The hypokinetic effects of antipsychotic drugs might cause signs of TD to be masked, and these symptoms may not become apparent until after therapy is reduced, switched, or discontinued. As a result of the increased utilization of atypical antipsychotics for the treatment of a wide range of psychiatric illnesses, such as obsessive-compulsive disorder, eating disorders, and post-traumatic stress disorder, a more significant number of patients may be at risk for TD. Also, a person's risk for TD may be increased by other risk factors, such as age, the presence of a movement disorder that was present prior to the onset of the condition, and the use of other medications, such as antiemetics. Even though atypical antipsychotics, which differ in their potential of causing TD in comparison to conventional antipsychotics, are being used more frequently, the burden of TD continues to be significant. To this day, just a few literature publications explain the clinical characteristics of people who have TD, even though its frequency has been widespread.[5]

Risk factors

Unmodifiable risk factors[6]:

1. Older age
2. Female sex
3. White and African descent
4. Longer illness duration
5. Intellectual disability and brain damage
6. Negative symptoms of schizophrenia

7. Mood disorders
8. Cognitive symptoms in mood disorders
9. Gene polymorphisms involving antipsychotic metabolism and dopamine functioning.

Modifiable risk factors[6]:

1. Diabetes
2. Smoking, Alcohol/substance abuse
3. Treatment related
4. Dopamine receptor blocker
5. Higher cumulative and current antipsychotic dose or plasma levels
6. Early Parkinsonian adverse events
7. Treatment-emergent akathisia
8. Anticholinergic co-treatment

Impacts

TD can have a wide-ranging impact. An increase in the severity of psychopathology, an increase in the rates of comorbidities, an increase in the risk of mortality, and a decrease in treatment results are some of the cumulative impacts that TD can have on patients who have major mental illness. Not only can TD have a detrimental impact on motor skills like speech, walking, and respiration, but it can also have an adverse impact on cognitive functions like verbal memory and processing. There is also the possibility that TD will result in emotions of stigmatization, social disengagement, the loss of job, and increased consumption of healthcare resources.[7]

Differential Diagnosis

Clinicians often encounter spontaneous dyskinesias and other drug-induced movement disorders, which are the most prevalent types of movement disorders that need to be differentiated from TD. Accurate diagnosis and effective treatment of tardive dyskinesia (TD) are essential, as its symptoms can significantly disrupt the lives of both patients and their caregivers. Unconventional behaviours such as compulsions, quirks, and stereotypies are fundamental aspects of schizophrenia. Individuals experiencing depression or mania exhibit comparable symptoms, such as atypical movements or catatonic behaviours. The ageing process increases the likelihood of

experiencing irregular movements, particularly in the face and mouth, especially when a person is missing teeth. These discoveries led to investigations that compared the occurrence of spontaneous dyskinesias to TD. These studies suggested that antipsychotics can bring out or make it easier for abnormal movements to arise in individuals who are already prone to experiencing them. To accurately distinguish between acute reversible drug-induced movements caused by illicit or prescribed drugs and TD, it is crucial to consider the differing reactions to treatment.[8,9]

The similarity in phenomenology between certain types of TD and acute movements, such as dystonia or akathisia, can be differentiated by the temporal association with antipsychotic medication. Tardive dyskinesia (TD) is a condition that is more prone to being postponed following the commencement of antipsychotic medication. It frequently manifests or intensifies and can endure even after reducing the drug dosage or stopping its use. Abnormal movements can also be linked to psychotropic medicines, except antipsychotics. Lithium, antidepressants, and anticonvulsants may cause tremors, while akathisia, tics, and TD may be caused or exacerbated by antidepressants and stimulants. However, the movements are sudden in almost all of these situations and may be reversed by stopping medicine use. On the other hand, dopamine-receptor blockers are specifically linked to movements that are long-lasting or cannot be reversed. Ultimately, a wide range of potential causes for movement abnormalities can be classified into various pathological origins. While neglecting these neurological or systemic problems would be unfortunate, they are generally uncommon and irreversible. It is advisable to assess them in partnership with medical or neurological experts.[8]

Diagnostic Criteria and Evaluation

DSM-5[1]:

1. Involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles).
2. Symptoms develop in association with the use of neuroleptic medication for at least a few months.

Schooler-Kane criteria

Dr Kane and his colleague, Nina R. Schooler, PhD, developed a more in-depth set of diagnostic criteria for TD, known as the Schooler-Kane criteria, originally intended for research settings but has been widely used in clinical practice. The first of the 3 Schooler-Kane criteria is that the patient must have at least three months of antipsychotic exposure, which may be continuous or discontinuous. Second, the patient must exhibit abnormal, involuntary movements of moderate or greater severity in 1 or more body regions or mild severity in 2 or more body regions, according to a rating scale such as the AIMS. Third, the patient must be free of other conditions that may cause abnormal, involuntary movements. A patient who meets all three criteria has probable TD. Further evaluations are necessary to determine if movements improve, worsen, or stay the same if dosing changes and when movements and medication have or have not been present.[10]

Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale (AIMS) identifies tardive dyskinesia and monitors its progression in patients. This tool is highly beneficial for clinicians monitoring the long-term effects of neuroleptic medications and for researchers examining the impacts of these therapies. The Abnormal Involuntary Movement Scale (AIMS) is conducted at regular intervals of three to six months to assess and track the patient's progress about the occurrence of Tardive Dyskinesia (TD). TD typically manifests in patients approximately three months after the commencement of neuroleptic treatment. However, in elderly individuals, TD might manifest within a month. The FDA recently approved pharmacological treatment options for tardive dyskinesia.[11]

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			

Treatment

Once the symptoms of TD become apparent, discontinuing the medicine may not result in resolution. Indeed, this is a technique for distinguishing between TD and Parkinsonism. While parkinsonism can often be alleviated by stopping or reducing the dose of the responsible medication, the same does not apply to TD. Furthermore, anticholinergic medications commonly employed for the treatment of parkinsonism are deemed ineffectual for TD and perhaps harmful (20). Studies investigating the natural progression of TD have found that remission rates vary significantly. This variability is primarily due to differences in the rates at which individuals continue to take antipsychotic drugs, which suggests that these medications can effectively hide the presence of ongoing TD.[12]

Tardive dyskinesia (TD) continues to be a difficult clinical issue for patients undergoing treatment with antipsychotic medicines. Despite a drop in incidence following the introduction of SGAs, the risk of TD remains high even after treatment with SGAs. The significance of the impact on quality of life, treatment adherence, and recovery should not be overlooked. Prescribing physicians must not only communicate the risk of TD with patients who are treated with antipsychotic medicines, but they must also be knowledgeable about the various therapy options to address these severe symptoms. TD continues to be a therapy option that is not utilized to its full potential. Patients with persistent symptoms of psychosis are already not receiving enough prescriptions for this medication. This is due to various obstacles, such as the requirement for regular blood monitoring and the significant risks of neutropenia and myocarditis. Additionally, there are more common but still problematic side effects, including weight gain, tachycardia, sialorrhea, and constipation.[12]

Enhanced education regarding the safe and efficient management of these obstacles could potentially result in increased availability of clozapine for patients who do not respond to alternative antipsychotic medicines. If psychiatrists acquire greater proficiency and ease in prescribing clozapine, its potential application as a therapy for TD could be contemplated. Indeed, there have been suggestions to transition to clozapine monotherapy as an initial strategy for managing TD.[12]

The more recent VMAT2 inhibitors seem to possess the most compelling data for the nonclozapine therapy of TD. The most prevalent obstacles to utilizing these agents are their tolerability and cost. It is important to be cautious of the possibility of Qtc prolongation when

using VMAT2 inhibitors, particularly when they are used alongside antipsychotics or CYP2D6 inhibitors. This is because all three VMAT2 inhibitors are metabolized through this pathway. However, these drugs seem to provide substantial advantages to those suffering from incapacitating TD.[12]

Additional medications, such as clonazepam, amantadine, and Gingko biloba, have limited supporting evidence. However, they may offer some advantages for certain patients, particularly those who are unable to tolerate or have other medical reasons to avoid clozapine or the VMAT2 inhibitors. Surgical and neurostimulatory methods may be contemplated as a last resort in challenging situations. However, the existing evidence mostly consists of individual case reports, mainly focusing on tardive dystonia. Therefore, the effectiveness of these procedures for individuals with TD is still uncertain.[12]

Valbenazine for Tardive Dyskinesia

Valbenazine (VBZ) is an FDA-approved medication that specifically inhibits VMAT2 and is used to treat tardive dyskinesia (TD) in adults. The beta isomer acts as an antagonist of the D2 dopamine receptor, leading to drowsiness and parkinsonism. The alpha isomer functions as a VMAT2 inhibitor, which is the desired mechanism of action for treating TD. Valbenazine is a refined precursor of the alpha isomer, which gives it a strong preference for inhibiting VMAT2 while minimizing the likelihood of causing unwanted side effects through binding to other receptors. Additionally, it undergoes a slower breakdown process, resulting in a prolonged half-life, which permits once-daily dosing. A phase 3 randomized, double-blind, placebo-controlled trial was conducted to compare the effects of valbenazine to a placebo. The experiment focused on individuals with moderate to severe TD who also had a history of mood disorders. The results of the trial indicated that valbenazine led to improvement in the symptoms of TD in these patients. During six weeks, patients were randomly assigned to receive one of three treatments: a daily dose of placebo, 40 mg of valbenazine, or 80 mg of valbenazine. After six weeks, there were notable decreases in AIMS scores in both the 80 mg group and the 40 mg group as compared to the placebo.[13]

VBZ have been approved by the FDA for symptomatic treatment of tardive dyskinesia. The FDA indicates that potential negative responses encompass balance difficulties, headaches, anticholinergic effects, akathisia, vomiting, nausea, and arthralgia. The prevailing adverse

reactions have primarily consisted of drowsiness and lengthening of the QT interval. Notable medication interactions that have a major impact on clinical outcomes include Monoamine Oxidase Inhibitors (MAOIs), potent CYP3A4 inhibitors, potent CYP3A4 inducers, and digoxin. While there is a lack of extensive evidence on the impact of valbenazine in pregnant and breastfeeding individuals, studies conducted on rats indicate a potential rise in the occurrence of stillborn offspring and deaths of newborn pups. Pregnant women should be informed about the potential hazards, and lactating women should be warned against taking Valbenazine while breastfeeding. No studies have been conducted to assess the effectiveness and safety of Valbenazine in children. Valbenazine is deemed to be safe for use in the geriatric population and individuals with mild to severe renal impairment without requiring any modifications to the dosage. While Valbenazine is not primarily eliminated through the kidneys, it should be avoided in individuals with severe renal impairment.58 In individuals with moderate to severe hepatic insufficiency, it is necessary to decrease the dosage of Valbenazine. Valbenazine is presently accessible in capsule form with two dosage options: 40 mg or 80 mg, to be consumed once per day.58 While short-term trials have demonstrated the safety and effectiveness of valbenazine, further research is required to investigate its long-term consequences.[13,14]

Valbenazine is synthesized by combining the alpha isomer of tetrabenazine, which is the most potent and selective active metabolite, with valine. This combination enables a sustained release and quick activation of (+) alpha dihydrotetrabenazine ((+)-alpha HTBZ). Valbenazine reversibly inhibits VMAT2, a transmembrane protein responsible for absorbing and accumulating various monoamines, such as dopamine, in presynaptic vesicles inside the central nervous system (CNS). Valbenazine and its metabolites have a minimal affinity for VMAT1, a peripheral location. Valbenazine and its metabolites, particularly (+)-alpha HTBZ, have been demonstrated to selectively block VMAT2, which hinders dopamine uptake into synaptic vesicles. Consequently, this increases dopamine breakdown by monoamine oxidase (MAO) in the cytoplasm of the presynaptic neuron. As a result, there is a general reduction in the amount of dopamine present in the presynaptic cells located in the motor striatum.62 This enables a therapeutic reduction in the level of dopaminergic activation in the indirect pathway of the motor striatum, as opposed to the inhibition of dopamine D2 receptors. Prolonged utilization of antipsychotic medications that inhibit the D2 receptors in the indirect pathway of the motor striatum increases the number and heightened sensitivity of these receptors. The number is 63. Suppose the D2 receptor antagonist

dosage is escalated in response to TD. In that case, it may temporarily alleviate symptoms but at the expense of a general escalation in TD and other neurological symptoms. The number is 64.[13]

Valbenzine (VBZ) is a potent and specific VMAT2 inhibitor that can bind to VMAT2 receptors and reverse its effects. It produces metabolites that only have an affinity for VMAT2 receptors, which helps to reduce any negative side effects. The activation of a prodrug of DBZ occurs by hydrolysis rather than relying on hepatic metabolism. Several randomized, double-blinded, placebo-controlled trials have shown that patients who were given VBZ experienced notable improvement in TD compared to those who received a placebo. While three studies have demonstrated short-term improvement in trials conducted over six to 12 weeks, additional studies have been conducted for up to 52 weeks to assess the long-term effects.[12]

The KINECT series of trials, presented in Figure 1, have yielded the majority of the evidence. During the 6-week KINECT experiment, VBZ did not improve either AIMS or Clinical Global Impression of Change–Tardive Dyskinesia (CGI-TD) ratings compared to the placebo (41). In the extensive KINECT2 study, individuals were randomly assigned to receive either a placebo or VBZ, with the dosage gradually increased to a maximum of 75 mg per day, based on their capacity to tolerate the medication and their response to it. After a 6-week period of observation, the average severity score for AIMS decreased by 3.6 points for VBZ, while it only decreased by 1.1 points for the placebo group ($p<0.001$). The VBZ group had a considerably higher proportion of responders (>50% reduction in AIMS from baseline) compared to the placebo group (48.9% versus 18.2%, $p<0.001$).[12]

Comparable findings were observed in KINECT 3 for both brief (43) and extended (44) experiments. During the 6-week experiment, the individuals were randomly assigned to one of three groups: placebo, VBZ 40 mg/day, or VBZ 80 mg/day, with an equal number of participants in each group. The discrepancy in the least-squares average change from baseline to week 6 was -3.2 points in the VBZ 80 mg/day group, -1.9 points in the 40 mg/day group, and -0.1 in the placebo group. This corresponds to a number required to treat (NNT) of 3.2 (rounded to 4) for the 80 mg/day VBZ group.[12]

Study	Study design	Population	Exposure	Primary endpoint	Efficacy results	Adverse events
KINECT 2 (42) N=100 (58% with schizophrenia or SCAD), mean baseline AIMS score=8.0	6-week randomized, double-blind study of VBZ vs. PBO	Moderate to severe TD diagnosis at study entry (assessed via video by movement disorder specialists) among patients with psychiatric stability (BPRS<50) and history of DRBA use	NBI–98854 (VBZ) at a starting dosage of 25 mg once daily, increased by 25 mg every 2 weeks until reaching maximum dosage of 75 mg/day	Change in AIMS score from baseline to week 6	AIMS score improved by −3.6 in the VBZ group vs. −1.1 points in PBO group. A significantly greater percentage of responders (>50% reduction in AIMS from baseline) present in VBZ vs. PBO group (48.9% vs. 18.2%, p<0.001)	Most common adverse events in VBZ vs. PBO group were fatigue (9.8% vs. 4.1%), headache (9.8% vs. 4.1%), constipation (3.9% vs. 6.1%) and urinary tract infection (3.9% vs. 6.1%), respectively.
KINECT 3 (43) N=227 (65% with schizophrenia or SCAD), mean baseline AIMS score=10.0	6-week double-blind study, randomized 1:1:1 to PBO, VBZ 80 mg/day, or VBZ 40	Moderate to severe TD diagnosis at study entry (assessed via video by movement disorder specialists), history of DRBA use >3 months	VBZ at 40 mg/day or 80 mg/day	Change in AIMS score from baseline to week 6	Mean least-squares AIMS score improved by −3.2 in the VBZ 80 mg/day group, −1.9 in the 40 mg/day group, and −0.1 in PBO group. NNT=4 for the VBZ 80 mg/day group.	Most common adverse events VBZ 40 mg/day group vs. VBZ 80 mg/day group vs. PBO group were somnolence (5.6%, 5.1%, and 3.9%), akathisia (4.2%, 2.5%, and 1.3%), and dry mouth (6.9%, 0%, and 1.3%), respectively.

Figure 1. Efficacy and safety analysis data for VBZ

The KINECT3 extension study consisted of a 42-week phase where the VBZ extension was conducted, followed by a 4-week period where the participants stopped taking VBZ to cleanse their system. In total, the trial lasted for 52 weeks. Participants who were first given a placebo were randomly assigned to either 40 mg/day or 80 mg/day. Participants who were already taking 40 mg or 80 mg of VBZ continued to take these dosages. The gains in AIMS and CGI-TD scores were sustained throughout the follow-up period, demonstrating a continued and lasting improvement in TD. During week 48, the average changes in AIMS scores were -4.8 in the 80 mg/day group and -3.0 in the 40 mg/day group. This difference was statistically significant, with a p-value of less than 0.001. As anticipated, these enhancements were capable of being reversed, as the scores reverted to their original levels after discontinuing the use of VBZ.[12]

KINECT 4 conducted a comprehensive assessment of the prolonged impacts of VBZ over 48 weeks. In this unblinded study (N=167), the treatment was started at 40 mg per day and then raised to 80 mg per day during the fourth week, depending on the individual's capacity to tolerate the medication and their response to it. This was done to replicate real-life clinical scenarios. The average improvement in AIMS score for the group taking 40 mg/day was 10.2 points, whereas the group taking 80 mg/day had an average improvement of 11.0 points. The study reported that 90% of the patients had a therapeutic response, defined as a greater than 50% improvement on the AIMS scale. Throughout the extension period, 69.2% of patients experienced at least one adverse event, with headache being the most prevalent (7.2% for the 40 mg/day group and 6.9% for the 80 mg/day

group). The discontinuation rate as a result of any adverse event was 15.7%. 14.6% of the subjects experienced severe adverse events, with syncope being the sole severe event that occurred in more than two participants (N=3). The administration of VBZ therapy did not cause or exacerbate parkinsonism or akathisia, as assessed using the Simpson-Angus Scale and the Barnes Akathisia Rating Scale. No significant changes in vital signs or ECG parameters were reported during the extended experiment. Among the participants, 5.1% reported having suicidal thoughts. Out of these, five individuals discontinued therapy due to suicidal thoughts or actions. However, the investigators at the site determined that these incidents were unlikely to be caused by VBZ. It is observed that a small number of participants experienced a decline in scores on the Columbia Suicide Severity Rating Scale for suicidal thoughts, even though about one-third of them had a history of suicidal tendencies. This study provided more evidence to confirm the enduring safety and effectiveness of VBZ, particularly in elderly patients. Upon dichotomizing patients at the age of 55, no notable disparities were observed between the older and younger groups in terms of both effectiveness and harmful occurrences.[12]

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