CNS Spectrums (2018), **23**, 370–377.
doi:10.1017/S1092852917000542

REVIEW ARTICLE

Tardive dyskinesia: motor system impairments, cognition and everyday functioning

Martin Strassnig,[1]* *Amie Rosenfeld,*[1] *and Philip D. Harvey*[2]

[1] Department of Integrated Medical Science, Florida Atlantic University, Charles Schmidt College of Medicine, Boca Raton, Florida
[2] Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida

The recent approval of treatments for tardive dyskinesia (TD) has rekindled interest in this chronic and previously recalcitrant condition. A large proportion of patients with chronic mental illness suffer from various degrees of TD. Even the newer antipsychotics constitute a liability for TD, and their liberal prescription might lead to emergence of new TD in patient populations previously less exposed to antipsychotics, such as those with depression, bipolar disorder, autism, or even attention deficit hyperactivity disorder. The association of TD with activity limitations remains poorly understood. We review potential new avenues of assessing the functional sequelae of TD, such as the performance of instrumental activities of daily living, residential status, and employment outcomes. We identify several mediating aspects, including physical performance measures and cognition, that may represent links between TD and everyday performance, as well as potential treatment targets.

Received 14 June 2017; Accepted 1 August 2017; First published online 7 September 2017

Key words: Tardive dyskinesia, motor function, cognition, physical performance, disability.

Introduction

Tardive dyskinesia (TD) is a syndrome that subsumes a variety of iatrogenic movement disorders. It is mostly caused by antipsychotic medications to treat schizophrenia and other major mental disorders, along with certain drugs for gastrointestinal disorders (e.g., metroclopramide) and neurological disorders (e.g., dopamine agonists). There are also some other established risk factors for developing TD that are not drug-related. Age seems consistently associated with the development, persistence, and progression of TD. Women appear to be at increased risk for TD.[1] Moreover, spontaneous dyskinesias in medication-naïve patients with schizophrenia and rarely, in the general population, have been reported.[2,3] The defining characteristics of TD include its delayed onset—hence the name "tardive"—signifying a delay of weeks to months until symptoms appear, and dyskinetic (abnormal, involuntary) movements. Depending on the severity, tardive dyskinesia can have a quite adverse functional impact that can be debilitating, stigmatizing, and associated with increased mortality.

* Address correspondence to: Martin Strassnig, Department of Integrated Medical Science, Florida Atlantic University, Charles Schmidt College of Medicine, 777 Glades Road, Boca Raton, Florida 33431.
(Email: mstrassnig@health.fau.edu)

TD has long been considered irreversible. Partly for that reason, "atypical" antipsychotics were developed with their purported "atypicality" squarely aimed at reducing or eliminating the motor side effects prevalent with the classic antipsychotic drugs, including TD. Yet despite widespread adoption of atypical antipsychotics in lieu of the older drugs, TD remains highly prevalent.[4] Recent estimates have found that the current prevalence of TD is as high as 13.1% in those exposed to atypicals as compared to 32.4% for classic antipsychotics.[5] Some argue that the TD prevalence with classic and atypical antipsychotics is even more similar.[6] For example, a recent metaanalysis reporting on the prevalence of TD symptoms in inpatients estimated that a quarter of all patients (25.3%) had symptoms of TD, with 20.7% of those exposed to atypical antipsychotics and 30% of those exposed to the "older" antipsychotics. This compares to a prevalence of around 20.5% of TD *prior* to the availability of the newer antipsychotics.[7] Moreover, the hypothesized reduction in TD incidence with "atypical" agents was not found in the CUtLASS nor the CATIE trial, both of which were independently funded, with differing explanations according to viewpoint.[8] The association of atypical antipsychotics is especially noteworthy now that these agents enjoy widespread use in conditions not involving the treatment of psychosis,

qsuch as anxiety disorders, mood disorders, developmental disorders, and sleep disorders.[9,10]

Clinical Picture and Treatment

The clinical picture of TD involves involuntary, repetitive, non-goal-directed movements of the motor system, including orofacial, buccal, lingual, neck, extremity, trunk, and respiratory muscles. Tardive dyskinesia can be accompanied by one or a combination of the following: tardive dystonia, akathisia, tremors, and tics (these symptoms can also occur alone). Typical motor patterns include tongue thrusting, lip smacking, lip pursing, grimacing and chewing movements, rocking of the trunk, pelvic thrusting, rotation of the ankles or legs, marching in place, irregular respiration, and repetitive sounds (e.g., humming or grunting).[11]

Tardive dyskinesia, with its characteristic delayed onset, must be distinguished from acute drug-induced movement disorders, including dystonia, akathisia, and parkinsonism. It is well known that patients who react to antipsychotics with acute extrapyramidal symptoms have a greater risk for developing TD later in the treatment course, and that TD and extrapyramidal symptoms may coexist.

The pathophysiology of TD is complex and not fully understood. Potential mechanisms include a dopamine "hypersensitivity" due to chronic blockade of dopamine receptors by antipsychotics, resulting in an upregulation of postsynaptic dopamine receptors.[12] The GSK3B polymorphism is a vulnerability marker for TD in schizophrenia.[13] Other potential mechanisms implicated include such neurochemical hypotheses as disturbed balance between the dopamine and cholinergic systems, dysfunction of striatonigral gamma aminobutyric acid dysfunction (GABAergic neurons, excitotoxicity), and oxidative stress.[14]

Tardive dyskinesia movements can be voluntarily suppressed for brief periods of time. Relaxation or sedation and sleep eliminate TD. Anxiety, stress, agitation, or distraction may worsen TD movements. The relative instability of TD symptoms makes them a challenge to objectively evaluate and foster introduction of bias in clinical observations.

Evidence-based treatment guidelines[15] suggest that several pharmacological treatments may be helpful in ameliorating tardive syndromes, including clonazepam and Ginkgo biloba, followed by amantadine and tetrabenazine. Insufficient evidence exists for omega-3 fatty acids (fish oil), melatonin, vitamin E, vitamin B_6, levetiracetam, piracetam, beta blockers, acetazolamide, bromocriptine, thiamine, baclofen, selegiline, nifedipine, buspirone, electroconvulsive therapy, α-methyldopa, reserpine, anticholinergics, and amantadine or for changes in antipsychotic dosing, all of which have met with varying success.[16] Clozapine has the lowest risk among the antipsychotics to cause TD and has been reported to improve or suppress TD symptoms. It is unclear whether the reduction in TD is due to removing dopamine D_2 receptor blockade in exchange for D_4 blockade, or if clozapine has an actual anti-TD effect.[17] Interventional procedures such as botulinum toxin injections can be successful but must be repeated frequently. Surgical approaches including brain stimulation of the globus pallidus[18] and pallidotomy are reserved for the most severe cases, and they can have partial success.

There are many people who have conditions where no antipsychotics are required. There are now many instances in which antipsychotics are prescribed off-label to ameliorate symptoms other than psychosis. In these instances, alternative treatment routes can often be implemented, and the risk/benefit, even for atypical medications, appears to argue against their use for many conditions (e.g., anxiety disorders, attention deficit hyperactivity disorder).

Tetrabenazine and Novel Derivatives

Tetrabenazine is a dopamine-depleting agent, initially developed in the 1950s and approved for the treatment of psychoses in several European countries, until phenothiazines were developed and successfully introduced.[19] The mechanism of action of tetrabenazine is associated with the activity of VMAT, a vesicular monoamine transporter responsible for transport of cytosolic monoamines (serotonin, dopamine, norepinephrine, histamine) into synaptic vesicles in monoaminergic neurons.[20] There are two subtypes of VMAT: VMAT1 is mainly found in neuroendocrine cells and VMAT2 in the CNS. Tetrabenazine is a potent VMAT2 blocker, binding reversibly to VMAT2, interrupting its function. Due to its fairly rapid metabolism, tetrabenazine is usually administered two to three times a day. Tetrabenazine has been available on an off-label basis for the treatment of TD for many years, despite its limited use. Tetrabenazine was approved in 2008 for the treatment of movements associated with Huntington's disease and has been used off-label for the treatment of TD. Several small studies have been carried out to examine the effect of tetrabenazine on tardive dyskinesia. Dosing constraints, costs, potential development of depressive and anxiety symptoms, confusion, dizziness, and parkinsonism have limited its use.

The recent approval of two novel tetrabenazine analogs for the treatment of TD[21] has brought with it a renewed interest in TD and its consequences. Deutetrabenazine is an analog of tetrabenazine, with six hydrogen atoms replaced by deuterium atoms. This slows the drug's metabolism and allows for once- or twice-daily dosing depending on the total dose, with a half-life of 9–10 hours. Its major circulating metabolites are α-dihydrotetrabenazine [HTBZ] and β-HTBZ). The liver

https://doi.org/10.1017/S1092852917000542 Published online by Cambridge University Press

enzymes involved in metabolism includes CYP2D6, with minor contributions from CYP1A2 and CYP3A4/5. Valbenazine[22] is a prodrug and an ester of [+]-α-dihydrotetrabenazine with the amino acid L-valine. It is extensively hydrolyzed in the liver to an active metabolite, α-dihydrotetrabenazine. Plasma protein binding of valbenazine is over 99%, and that of dihydrotetrabenazine is about 64%. The half-life of both valbenazine and dihydrotetrabenazine is 15–22 hours, allowing for once-daily dosing. The relevant liver enzymes involved in inactivation are CYP3A4, CYP3A5, and CYP2D6. The metabolites of deutetrabenazine and valbenazine are thought to be reversible and selective VMAT2 inhibitors. The major side effects include somnolence, agitation, and QTc prolongation. Both deutetrabenazine and valbenazine, just like the parent compound tetrabenazine, are projected to be quite costly, and improvements that go beyond reductions in abnormal involuntary movements to generalized improvement in everyday functioning may significantly add to the current value proposition.

Impact of Tardive Dyskinesia on Everyday Functioning

It is quite clear that tardive dyskinesia can have a significant impact on affected individuals' ability to carry out the activities of daily living, although the exact pattern of impairment associated with TD has never been determined. Over 30 years ago, Yassa and Jones[23] proposed to classify complications of tardive dyskinesia into medical and psychological complications. We will expand the context of this classification to capture a wider array of potential impairments, most of which can be quantified with performance-based measures so that an accurate and objective assessment of the individual's limitations can be obtained.

Motor System Impairments

The pattern ("topograpy") of dyskinesia is important for differentiating its functional impact. Truncal TD, for example, impacts gait and posture and may also exert its detrimental impact quite broadly by interfering with the activities of daily living (ADLs) that require standing or moving, such as grooming, dressing, toileting, bathing, ambulating, and transport. In contrast, orofacial TD would not have a significant impact on these tasks but would perhaps affect speech, which is required for effective interpersonal interactions or getting and keeping a job. The potential differential functional impact on motor system performance related to the topography of TD has never been determined. This leaves the field with a diffuse notion that TD is detrimental to the performance of ADLs without knowing its exact impact and, consequently, what can be done to counteract or compensate for these specific deficits. Previously suggested quantitative instrumental assessments of TD have included accelerometers, electromyography, forge gauges, position transducers, and Doppler ultrasound, and have assessed various expressions of TD in isolation,[24] but a comprehensive assessment with performance-based measures other than using rating scales has never been completed.

Gait and Posture

Broad-based gait, spastic gait, pelvic gyration, difficulty standing, abnormal arm swing, manneristic gait, dancing, and duck-like gait in addition to other features of TD have been observed,[25] with prevalence estimates ranging from 27 to 59% of those affected with TD.[26–28]

Gait speed, cadence, step length, posture, arm swing, gait initiation, turning, and gait efficiency can all be impaired with TD, and such secondary impairments as limited joint range of motion, loss of lower extremity power/strength, or lack of endurance may ensue, further worsening the performance on gait-related everyday activities. Moreover, severe gait abnormalities may pose a fall risk, with associated morbidity and mortality. Gait can be comprehensively assessed in several ways, including 3D motion detectors combined with electromyography, or a gait analysis walkway that allows for temporospatial gait analysis. The interrelationship between gait and cognition suggests that gait assessments can provide a window into an understanding of the influence of cognitive function on motor performance under a cognitive load, using dual-task gait assessments (e.g., walking while performing an attention-demanding task).[29]

Postural Stability

Postural dynamics in patients with TD is impaired, as measured with force plate platforms, with irregular anterior–posterior motion noted.[30] The dimension of the center of pressure in tardive dyskinetic individuals is systematically lower than in normal controls, translating into a discrepancy between the variability and stability of posture,[31] an independent predictor of hip fractures.[32] Self-efficacy is reduced in people with poor balance, also impacting everyday activities.[33]

Speech, Dentition, Respiration

The most commonly encountered motor speech disorder in TD is dysarthria, which can affect any combination of these speech subsystems (i.e., respiration, phonation, articulation, and velopharyngeal control). Irrespective of the subsystems involved, any type of dysarthria tends to result in reduced intelligibility and naturalness of speech, impacting on the person's effectiveness to

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communicate and quality of life.[34,35] Motor speech disorders can be assessed in various ways, from using commonly available structured rating scales to computerized acoustic and physiologic measures that give a detailed analysis of the speech process.

Such dental problems as attritions and abfractions are very frequent in people with TD,[36,37] as are pain from myalgia, temporomandibular joint dysfunction, traumatic lesions, tooth wear, and impaired retention of prosthetic devices.[38,39] Respiratory movements may be affected, with altered rhythmic patterns leading to hyperventilation and hypoventilation.[40] Reflexive grunting, snorting, and gasping as well as shortness of breath have been reported, along with dyspnea, respiratory alkalosis, chest pain, and muscle spasms.[41,42]

Swallowing Difficulties

Tardive dyskinetic/dystonic movements involving the tongue and also associated with oromandibular dystonia/dyskinesias have been reported to interfere with food intake, requiring assistance. Esophageal dyskinesia has been reported,[43] as have loss of coordination of the tongue and muscles of mastication, dyskinetic movements of the pharynx, delayed swallow reflex, and poor laryngeal elevation, with diaphragmatic involvement in severe cases.[44]

Fine Motor Skills

A reduction in upper extremity function and fine motor skills is a common consequence of TD. Upper extremity TD, even when mild, causes difficulties with such everyday tasks as writing, self-care, and fine object manipulation. These types of tasks that require more complex organizational and sensorimotor skills, the "instrumental activities of daily living" (IADLs), include the ability to use the phone, shopping, meal preparation, housekeeping, laundry, handling finances, and managing transportation. These crucial tasks require reaching and grasping, moving objects, using tools and money, writing, or interacting with technology, and they are all necessary for people to live fully independent lives in the community.

Difficulty in manipulating objects with appropriate speed and dexterity impacts such diverse activities as work, recreation, dressing, and eating. The impaired ability to use a smartphone and handwriting dysfluency, previously reported in patients with TD,[45] can have detrimental effects on one's social and employment activities.

Motor deficits during development may represent an endophenotype for schizophrenia,[46] although its specificity is limited in relation to other serious mental disorders,[47] and TD may amplify these underlying deficits, compounding the impact. Formal assessments of crucial fine motor skills utilizing pegboard tests or similarly accurate measures such as finger tapping and spiral drawing have not been carried out in patients with TD.

Strength/Power/Flexibility

Lower extremity strength, power, and flexibility are crucial elements required for the performance of ADLs and IADLs. We have recently shown that a simple measure of lower extremity strength, the ability to rise from a chair, predicts disability in a sample of patients with schizophrenia and bipolar disorder.[48] Tardive dyskinesia may impair the generation of well-modulated force and compound these strength deficits. Moreover, the ability to maintain a sustained force output was found to be inversely proportional to the amount of force generated in people with TD,[49] impairing static/positional strength. Tardive dyskinesia can also cause a reduced range of motion due to contractures, accompanied by reduced joint flexibility. None of these factors (strength, power, or flexibility) have been assessed formally in TD independently or as they relate to everyday functioning, with a plethora of measures available.

Physical Capacity

The physical capacity of people with varied TD topography has not been examined. We know that people with persistent mental illness have reduced physical capacity, at times to the point of interfering with daily activities.[50] TD-related impairments may compound physical capacity limitations. There are numerous ways to assess a person's overall physical capacity, or functional level, which include but are not limited to isometric strength, aerobic capacity, lifting capacity, and positional endurance. Simple assessments include the six-minute walk test and various treadmill and ergometer testing protocols.

Cognitive Impairments

There is a plethora of literature available that associates tardive dyskinesia with cognitive impairments. Waddington *et al.*[51] carried out the initial, very well-controlled observations linking TD with cognition and found that the localized onset of orofacial movements but not truncal TD was predictive of cognitive dysfunction.[50] Deterioration of cognition in relation to emerging orofacial tardive dyskinesia was also noted.[51] These observations have been confirmed by several other studies.[52–56]

Age appears to amplify the effect. The pattern of a correlation between orofacial TD and cognitive impairment was also found in a well-characterized sample of elderly institutionalized patients in the United States,[57] while correlations were less clear in younger patients.[58] Similarly, modest correlations were reported between

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dyskinesias and cognition[59] present before the onset of TD.[60] Others found that patients with TD showed more preexisting cognitive impairments than non-TD controls.[61]

More recent evidence continues to implicate orofacial TD with greater cognitive impairment as compared to those without TD,[62] including specific memory impairment that was associated with orofacial TD but not with limb/truncal TD.[63] In contrast, results from the CATIE schizophrenia trial did not reveal specific associations between subtypes or the global presence of TD and cognitive impairment.[64] However, the patients in the CATIE trial had previously been and still were receiving a substantial mix of antipsychotic treatments with markedly different TD risks, as described above. In the classic Waddington studies, all patients were started on conventional antipsychotic medications in doses larger than those used currently.

The heterogeneity of the cognitive tests used may make it difficult to compare results across studies. Recent advances in cognitive testing methodology have made it possible to accurately and efficiently assess cognition with brief and repeatable PDA (personal digital assistant) app-based programs, such as the BACS (Brief Assessment of Cognition), which could increase the homogeneity of assessments and clarify their correlates.

There is also preliminary evidence that basal ganglia volumes are reduced in patients with TD as compared to patients without, in line with observations that orofacial TD may represent a marker of compromised cerebral systems that mediate spatial memory, such as the frontal–striatal–thalamic systems.[65,66]

Lack of Awareness

Despite the striking motor manifestations that can comprise the TD syndrome, many patients appear to be unaware of their TD.[67] Lack of awareness of tardive dyskinesia is a common feature in schizophrenia and is stable over time.[68] Some authors have investigated a link between poor insight into clinical symptoms and poor awareness of TD, but they have concluded that poor insight and TD awareness are not closely related.[69] Others have described the lack of awareness as "total lack of concern" and have linked it to cognitive impairment.[70] Cognitive deficits appear to indeed be associated with a lack of awareness of TD.[71] Discrepancies between self-assessment and actually measured performance have been noted before in patients with severe mental illness, with patients with greater unawareness of cognitive limitations having the greatest functional deficits.[72] In that way, unawareness of TD may be an extension of this lack of self-assessment capability across the clinical, cognitive, and functional domains and may require specific attention to properly direct the focus of treatment.

Other Complications

Suicide rates may be increased in people with severe TD, although this seems incongruent with the lack of awareness described above.[70] Pain has been reported in association with TD,[73,74] in that chronic musculoskeletal spasms and pain are possible sequelae of repetitive TD movements.[75,76] Social stigma and reduced quality of life are common.[77] Caregiver burden has not been evaluated in adequate detail but may be substantial in some cases.

Measuring the Detrimental Effect of TD on Everyday Functioning

Adequate everyday functioning is a prerequisite to independence in residence, gainful employment, and fulfillment of social interactions. In mental illness, determinants of everyday functioning include cognitive deficits and symptoms, along with such other predictors as health and physical functioning.[78] Individuals with persistent mental illness often have a poor diet, sedentary behavior, little or no physical exercise, and persistent smoking, and are treated with obesogenic atypical antipsychotics, indefinitely as long as they are adherent. This background provides for an unhealthy environment that results in high rates of obesity and physical health consequences, including poor physical performance, which all adversely impact everyday functioning.

Tardive dyskinesia may serve to compound these impairments and amplify problems with everyday functioning directly through a further worsening of physical performance, or indirectly, through worsening cognition, promoting a cycle of a lack of engagement in the community or in a group of patients that already suffers from an inherently impaired cognition and engagement as a result of their mental illness.

In this context, neither the (potentially accretive) spectrum of motor system impairments associated with TD (e.g., strength/power/balance, gait, or fine motor performance) nor (additional) TD-related cognitive impairments have been examined systematically for their impact on everyday functioning. The available literature[79] mainly relies on case series and clinical observations to determine the impact of TD, broadly defined, but does not delineate specific areas of impairment. There is a need for objective, reliable, and sensitive measures that can be employed for assessing the subtle differential motor effects of TD on motor skills relevant for everyday activities. Similarly, there is a need to determine the potential interactions with cognitive impairments, a main driver of disability in the SMI (serious mental illness) population. It is entirely possible that the relative topography of TD (e.g., orofacial TD worsening cognition versus limb/truncal TD worsening motor

https://doi.org/10.1017/S1092852917000542 Published online by Cambridge University Press

performance) is mediated through different mechanisms, and that the effects of orofacial and limb/truncal TD may have an additive impact on everyday functioning.

Performance-based measures of the aspects of TD such as those suggested above may also serve a different purpose: objective methods show a higher prevalence of TD when compared to use of rating scales.[80] Trained raters, utilizing standard rating scales, may underestimate the prevalence of some motor abnormalities. This is particularly relevant for clinical trials designed to test pharmacotherapies for treating existing TD to circumvent the potential bias introduced by voluntary suppression of TD, as well as detecting subclinical changes in motor function that are not picked up with rating scales.[45,81]

Moreover, with two novel treatments (valbenazine and deutetrabenazine) now available, their exact impact on most aspects of motor performance and cognition has not been investigated as of yet. Improvements in motor performance and cognition, and especially accretive or even interactive improvements, can potentially lead to significant improvements in aspects of everyday functioning, thus reducing disability.

Conclusions

There are no specific data about the impact of various aspects of the tardive dyskinesia syndrome on crucial areas of everyday functioning. Performance-based assessments have rarely been utilized to characterize the differential impact of the topographically and functionally differing motor system impairments associated with TD, nor have the cognitive deficits associated with TD been assessed systematically with standardized cognitive measures. Measured comprehensively, this would aid in assessing the relationship between the variety of motor deficits and cognitive impairment associated with TD and their impact on different areas relevant to everyday functioning beyond other factors that are already operative. The potentially accretive effects of motor and cognitive impairments associated with TD in context of obesity, reduced physical functioning, and underlying cognitive impairments inherent in persistent mental illness may be substantial.

Previously thought of as untreatable, TD remains prevalent despite the advent of antipsychotics initially deemed "atypical" and their increasing use for mental health conditions that do not involve psychosis. With the advent of two novel TD medications, valbenazine and tetrabenazine, improvements in everyday functioning can potentially be achieved. Pharmacological improvements of TD could translate into cognitive and motor performance gains, accretive and potentially interactive, directly improving everyday functioning. There is a potential for modest but significant reductions in TD-associated disability. Demonstrating these reductions in disability will be critical for the value proposition of these new pharmacological TD treatments.

Disclosures

Philip Harvey has the following disclosures. Abbvie: personal fees; Akili: personal fees; Allergan: personal fees; Boehringer-Ingelheim: personal fees; Forun Pharma: personal fees; Genetech: personal fees; Otsuka Digital Health: personal fees; Lundbeck: personal fees; Sanofi: personal fees; Sunovion: consultant, personal fees.

Martin Strassnig reports other disclosures from TEVA Pharmaceuticals, outside the submitted work (equity).

Amie Rosenfeld does not have any conflicts of interest to disclose.

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https://doi.org/10.1017/S1092852917000542 Published online by Cambridge University Press