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Tremor and Other Hyperkinetic Movements

Reviews

An Update on Tardive Dyskinesia: From Phenomenology to Treatment

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Abstract

Tardive dyskinesia (TD), characterized by oro-buccal-lingual stereotypy, can manifest in the form of akathisia, dystonia, tics, tremor, chorea, or as a combination of different types of abnormal movements. In addition to movement disorders (including involuntary vocalizations), patients with TD may have a variety of sensory symptoms, such as urge to move (as in akathisia), paresthesias, and pain. TD is a form of tardive syndrome—a group of iatrogenic hyperkinetic and hypokinetic movement disorders caused by dopamine receptor-blocking agents. The pathophysiology of TD remains poorly understood, and treatment of this condition is often challenging. In this update, we provide the most current information on the history, nomenclature, etiology, pathophysiology, epidemiology, phenomenology, differential diagnosis, and treatment of TD.

Keywords: Tardive syndrome, tardive dyskinesia, dystonia, akathisia, dopamine receptor-blocking agents, neuroleptics

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History and Definitions

TD is a group of delayed-onset iatrogenic movement disorders of various phenomenology caused by dopamine receptor-blocking agents, also referred to as neuroleptics. In some cases, the movement disorder may be accompanied by sensory phenomenon such paresthesias, pain and an inner urge to move. Neuroleptic medications were introduced in the early 1950s and revolutionized the treatment of schizophrenia and other psychiatric disorders. Just a few years later, however, neuroleptics were recognized as a cause of abnormal involuntary movements. The first report of orofacial stereotypic involuntary movements, referred to as "paroxysmal dyskinesia," in a patient treated with the phenothiazine derivative megaphen was published in 1957.[1]

The term "tardive dyskinesia" (TD) was first introduced in 1964 by Faurbye, highlighting the delay between the initiation of treatment with the offending drug and the onset of the abnormal movements (hence, the name "tardive").[2] The term is now used to define any tardive hyperkinetic movement disorder, such as stereotypy, akathisia, dystonia, tremor, tics, chorea, and myoclonus. On the other hand, some physicians reserve the term TD exclusively for oro-bucco-lingual stereotypy, which has caused confusion in the medical literature. Because many patients present with a combination of different phenomenologies, which may include a movement disorder as well as sensory symptoms, the term "tardive syndrome" is more appropriate when referring to all tardive disorders, manifested by any combination of hyperkinetic or hypokinetic movement disorders, as well as sensory symptoms that may be phenomenologically distinct but sharing the same etiological background (recent exposure to dopamine receptor-blocking agents [DRBAs]). We suggest that the term "classic tardive dyskinesia" should be used for oro-bucco-lingual stereotypy when it manifests as an isolated or predominant tardive syndrome.[3]

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for at least 3 months (or 1 month in patients age 60 years or older) or within 4 weeks of withdrawal from an oral medication (or within 8 weeks of withdrawal from a depot medication).[4] The disorder should persist for at least 1 month after discontinuation of an offending drug to qualify as TD. Some experts consider exposure to DRBAs within 1 year prior to the onset of tardive syndrome as being causally related. Withdrawal emergent syndrome was first described in 1973 by Polizos et al[5] as choreic movements in children after abrupt discontinuation of long-term use of an antipsychotic drug. The symptoms usually manifest during the first few days or weeks after discontinuation of the offending DRBA.

Etiology

TD results from chronic exposure to DRBAs, such as some antipsychotics (typical and atypical neuroleptics), tricyclic antidepressants (e.g., amoxapine), and antiemetics and other medications used for gastrointestinal disorders (e.g., metoclopramide and promethazine) (Table 1). The first generation "typical" neuroleptics with high dopamine D_2 receptor occupancy have been reported to have a higher risk of causing TD than the second- or third-generation medications, often referred to as "atypical" antipsychotics, with low D_2 receptor occupancy, such as clozapine and quetiapine. It is now well recognized, however, that even atypical antipsychotics can cause TD.[6] There are also relatively rare cases of movement disorders, clinically indistinguishable from DRBA-induced TD, that have been reported to be associated with the use of antidepressants, such as certain selective serotonin reuptake inhibitors (SSRIs) or selective serotonin norepinephrine reuptake inhibitors (SNRIs).[7,8] The mechanism of TD caused by SSRIs or SNRIs is unclear. Some authors have hypothesized that increased levels of serotonin might inhibit striatal neurons and produce a antidopaminergic effect similar to DRBAs.[7,8] Further epidemiologic and animal model studies are needed to clarify the role of SSRIs in TD. Rare cases of TD were also associated with lithium.[9] Calcium channel blockers, such as cinnarizine and flunarizine, are relatively common causes of tardive syndromes in some countries.[10]

Pathophysiology

Pathophysiology of TD remains poorly understood, but it is believed to be the result of chronic blockade of dopamine receptors, particularly D_2 and possibly D_3, by DRBAs. "Typical" antipsychotics tightly bind

Table 1. Medications With the Potential to Cause Tardive Syndromes

Benzisothiazole (ziprasidone)
Benzisoxazole (iloperidone)
Butyrophenones (haloperidol, droperidol)
Calcium channel blockers (flunarizine, cinnarizine)
Dibenzazepine (loxapine, asenapine)
Dibenzodiazepine (clozapine, quetiapine)
Diphenylbutylpiperidine (pimozide)
Indolones (molindone)
Lithium
Phenothiazines (chlorpromazine, triflupromazine, thioridazine, mesoridazine, trifluoperazine, prochlorperazine, perphenazine, fluphenazine, perazine)
Pyrimidinone (risperidone, paliperidone)
Quinolinone (aripiprazole)
Substitute benzamides (metoclopramide, tiapride, sulpiride, clebopride, remoxipride, veralipride, amisulpride, levosulpiride)
Serotonin reuptake or serotonin norepinephrine reuptake inhibitors (duloxetine, citalopram)
Thienobenzodiazepine (olanzapine)
Thioxanthenes (chlorprothixene, thiothixene)
Tricyclic antidepressants (amoxapine)

The medications are listed alphabetically.

and remain attached to D_2 receptors for a longer time (a few days) than "atypical" agents. Therefore, they have a stronger antipsychotic effect but much higher propensity to cause TD than "atypical" antipsychotic drugs, which have a relatively low degree of D_2 receptor antagonism and rapid (12–24 hours after a single dose) dissociation from the D_2 receptors, thus presumably explaining the lower risk of TD.[11] In addition to dopamine, other neurotransmitter receptors may be important in determining a drug's propensity to facilitate TD, especially 5-hydroxytryptamine 2 (5-HT_2) receptors that are widely distributed in the striatum and are thought to be involved in modulating motor activity by interaction with dopaminergic neurotransmission.[12] High 5-HT_2 receptor-blocking activity of "atypical" antipsychotics, combined with their low D_2 receptor occupancy, has been thought to be protective against TD because of a relative lack of D_2 receptor upregulation.[12,13]

One of the most prominent theories about TD pathogenesis is that chronic exposure to the neuroleptics results in D_2 receptor upregulation with postsynaptic dopamine receptor supersensitivity. This theory is difficult to prove but is supported by the common observation that increased DRBA dose can temporarily alleviate the symptoms of TD, and the abrupt withdrawal of an offending drug can exacerbate or even cause TD. Because D_2 receptors are inhibitory receptors expressed on medium-spiny neurons that project onto the indirect pathway, their hypersensitivity can result in disinhibition of the globus pallidus internus and subthalamic nucleus, producing a variety of hyperkinetic movement disorders.[14] On the other hand, the dopamine receptor supersensitivity and receptor upregulation theory cannot explain why TD often persists for years or even decades after discontinuation of the offending DRBA, since theoretically the dopamine receptors lacking continuous blockade would be expected to decrease in numbers due to downregulation.

Another theory of TD pathogenesis, supported by animal studies (mice, rats, primates), proposes that damaged or dysfunctional striatal γ-aminobutyric acid (GABA)-containing neurons lead to GABAergic hypofunction and degeneration of the striatal fast-spiking GABAergic interneurons that regulate balance between direct and indirect basal ganglia pathways.[15–17]

According to the recently proposed "maladaptive synaptic plasticity" hypothesis, D_2 receptor hypersensitivity and degenerative changes in the neurons caused by increased oxidative stress can result in secondary effects on the synaptic plasticity of glutamatergic synapses on striatal interneurons, causing imbalance between direct and indirect basal ganglia pathways and thus producing abnormal output to the sensorimotor cortex.[14] Maladaptive cortical synaptic plasticity, coupled with abnormal basal ganglia output, may lead to the formation of miscoded motor programs and abnormal movements.

The "neurodegenerative hypothesis" of TD is supported by the irreversibility of the symptoms after discontinuation of the offending drug.[18] Proponents of this hypothesis suggest that neuroleptics could increase lipid peroxidation and free radical formation, leading to the neuronal damage and therefore degeneration of the different neurotransmitter systems. Structural changes in the brain, including neuronal loss and gliosis in the basal ganglia after prolonged exposure to neuroleptics, were identified in animal studies and postmortem neuropathological examinations of the brains of TD patients.[19] The neurodegenerative hypothesis eventually merged with the oxidative stress hypothesis. Accordingly, blockade of dopamine receptors leading to increased dopamine turnover is thought to be associated with increased free radical formation by monoamine oxidase and also with auto-oxidation of dopamine molecules into free radicals and quinines.[18,20] Increased production of free radicals, coupled with impairment of the antioxidant system leading to increased oxidative stress, was reported with chronic neuroleptic administration.[21] This oxidative stress hypothesis[20,22] is supported by the finding that plasma activity of manganese superoxide dismutase, one of the main enzymes involved in the antioxidant defense mechanism, is elevated in TD patients compared with the subjects on neuroleptics without TD or normal controls.[23] The level of enzyme activity in TD patients correlated with TD clinical symptom severity. A polymorphism in the superoxide dismutase gene was also associated with TD.[20]

Interestingly, most patients taking antipsychotic medications for years do not develop TD, and patients with TD caused by exactly the same medication regimen might have a very broad range of TD severity and phenomenology. These observations might be explained by individual, possibly genetic, susceptibility for TD.[14,20,24] Several gene candidates have been implicated in the predisposition for TD, including genes coding for the dopamine D_3 receptor,[25] D_2 receptor,[26] serotonin 5-HT_{2A} receptors,[27] manganese superoxide dismutase,[23] catechol-*O*-methyltransferase (COMT),[28] and several other genes with various degrees of association with TD.[14,20] In addition, cytochrome P450 (CYP2D6), which affects drug metabolism, may influence the risk for TD.[29] A meta-analysis of 20 studies from 1976 to 2007 estimated pooled odds ratios (ORs) of TD associated with COMT, DRD2, and MnSOD gene polymorphisms.[28] Among 382 TD and 707 non-TD patients exposed to DRBAs, two variants of the COMT gene were found to be protective against TD (ORs 0.63 and 0.66). Analysis of MnSOD gene polymorphism in 134 TD and 546 non-TD patients identified two protective gene variants with ORs of 0.37 and 0.49. Two DRD2 gene variants were found to predispose for TD (ORs 1.30 and 1.80) in the pooled population of 297 TD and 467 non-TD patients. An analysis of DRD3 gene polymorphism in a pooled sample of 317 TD and 463 non-TD patients identified the DRD3gly gene variant as a factor increasing susceptibility for TD (pooled OR 1.33).[25] A 5-HT_{2A} gene variant (T102C) was associated with a higher risk of developing TD in 221 schizophrenic patients (OR 0.44).[27]

Epidemiology

TD prevalence is estimated to be 20–50% of all patients treated with neuroleptics, but it varies among different age groups and published studies, with prevalence increasing with advanced age.[4] The largest review involving 56 studies and 34,555 subjects treated with neuroleptics, yielded an average TD prevalence of 20%.[30] Although TD prevalence in patients treated with metoclopramide has been less studied, the published data indicate a prevalence ranging from less

than 1% to 10%.[31] The incidence of neuroleptic-induced TD is lower among younger individuals (3–5% per year) and higher in middle-aged and elderly patients, particularly women, reaching incidence rates as high as 30% after 1 year of cumulative exposure to neuroleptics. Incidence of TD was lower in patients treated with second-generation neuroleptics (risperidone, olanzapine, quetiapine, amilsulpride, and ziprasidone), with the total annual incidence rate ranging from 0.8% in patients younger than 50 years to 5.3% in those older than 50 years.[32] Although previous studies suggest that both genders are equally susceptible to TD, postmenopausal women might have a higher risk of developing TD.[4] The latter observation might be explained by the fact that estrogen modulates dopamine-mediated behaviors and exhibits an antioxidant effect, thus potentially protecting against TD.[20,33] TD is the exception to the age-related increase in incidence of tardive syndrome, which tends to occur more often in young male patients. Besides age and gender, other less convincing demographic and medical risk factors include African-American race,[34] pre-existing movement disorders, brain damage, cognitive impairment, total DRBA load (composed of the dose and the duration of drug exposure), mood disorder, presence of negative schizophrenia symptoms, alcohol and drug abuse, and diabetes mellitus.[35,36]

A study of 100 patients with tardive syndromes reported the following frequencies of different types of movement disorders: 72% had oro-bucco-lingual dyskinesia (classic TD), 30% had tardive tremor, 22% had tardive akathisia, 16% had tardive dystonia, and 4% and 1% had tardive tics and myoclonus, respectively; 35% of the patients had a combination of two or more tardive syndromes.[37]

Clinical Course and Phenomenology of Tardive Syndromes

The symptoms of TD usually first appear after 1–2 years of continuous exposure to a DRBA and almost never before 3 months.[36] Severity of TD ranges from mild involuntary movements often unnoticed by a patient to a disabling condition. TD has an insidious onset; it usually evolves into a full syndrome over days and weeks, followed by stabilization of the symptoms, and a chronic but waxing and waning course. TD tends to persist for years or decades in the majority of patients, even after elimination of the offending drug. In some patients it can remit completely or partially a few years after discontinuation of a causative medication or even while continuing DRBA treatment. In one study, 33% of the patients experienced remission of their TD 2 years after discontinuation of the offending drug.[38] Other studies, however, have reported much lower rates of remission. In one study, only 5 out of 42 (12%) patients achieved remission following discontinuation of DRBAs (for up to 6.7 years).[39] Interpretation of spontaneous remission rates in TD patients who continue treatment with DRBAs might be complicated by the fact that DRBAs can suppress or mask the dyskinesia.[35] The rate of remission of TD without discontinuation of DRBAs was reported to be 2.5% per year, which was only slightly higher than the remission rate following discontinuation or reduction of the DRBA dose.[35,40] Another study found that permanent discontinuation of DRBAs in TD patients increased the chance of remission by fourfold after 8.5 years of follow-up (22% out of 54 patients withdrawn from DRBAs vs. 5.8% from 52 patients who continued taking DRBAs).[19] Several studies have concluded that longer duration of exposure to DRBAs prior to discontinuation decreases the chances of remission of TD.[19] On the other hand, TD may be precipitated by a dose reduction or sudden withdrawal of neuroleptics, especially in children (withdrawal emergent syndrome),[41] with the symptoms manifesting during the first few days or weeks after DRBA discontinuation. In contrast to other TD syndromes, withdrawal emergent syndrome is typically encountered almost exclusively in children and is self-limiting, typically completely resolving over several weeks.

Tardive syndrome can manifest as a variety of phenomenologically distinct abnormal movements or their combination. The spectrum of tardive syndrome includes stereotypy, dystonia, akathisia, tics (tardive tourettism), myoclonus, tremor, or chorea (Table 2). Besides these iatrogenic hyperkinetic movement disorders, DRBA can also cause other delayed-onset neurological conditions, such as drug-induced or tardive parkinsonism and neuroleptic malignant syndrome.[42,43]

Classic TD (Video 1) manifests as involuntary stereotypic movements in the oro-bucco-lingual region, such as lip smacking or pursing, chewing, facial grimacing, and tongue movements inside the mouth or tongue popping out; thus, it is often termed "oro-bucco-lingual stereotypy."[44] Patients with classic TD may also have stereotypic movements involving the limbs or trunk; however, oro-bucco-lingual stereotypy remains the leading phenomenology of this syndrome.

The term "*tardive stereotypy*" is often used to describe the seemingly purposeful, repetitive, and coordinated movements sometimes giving the appearance of ritualistic gestures or mannerisms (Video 2).[45] Although oro-bucco-lingual stereotypy of classic TD is the most common form of tardive stereotypy, some patients also have limb stereotypies, manifested as repetitive foot tapping, complex stereotypic piano-playing finger and toe movements, and hand rubbing. Trunk stereotypy is typically manifested by repetitive rocking and swaying body movements.

TD can also involve the respiratory muscles of the upper airways, chest, and diaphragm, causing gasping, stridor, interrupted flow of speech, paradoxical breathing, dyspnea on exertion, and other respiratory symptoms similar to those seen in some patients with primary dystonia and defined as "dystonic respiratory dysregulation."[46] TD patients can also exhibit irregular breathing with episodes of hypoventilation and hyperventilation, audible respiratory noises that might look very alarming but in most cases do not cause any medical problem, and other noises, such as continuous humming or moaning.[47]

Tardive akathisia (Video 2) is a feeling of inner restlessness involving the whole body or certain body parts; it is usually uncomfortable to the patients and sometimes disabling.[48] The patients often have repetitive and stereotypical movements (rocking in a chair, crossing/uncrossing of legs when sitting, pacing on a spot, shifting weight from one foot to another when standing, face or scalp touching or scratching) in an attempt to relieve feelings of restlessness. The movements sometimes resemble limb and trunk stereotypies of TD without akathisia, but

Table 2. Spectrum of Tardive Syndromes

Classic Tardive Dyskinesia	Isolated or Predominant Oro-bucco-lingual Dyskinesia (stereotypy)
Tardive stereotypy	Seemingly purposeful, repetitive and coordinated movements in the limbs or trunk (if the face is mainly involved, would be considered as classic TD)
Tardive dystonia	Focal, segmental or generalized dystonia (classic features are retrocollis, opisthotonic trunk posturing, arm extension)
Tardive akathisia	Feeling of restlessness, inability to stay still, intense inner urge to move
Tardive tics (tardive tourettism)	Clinically indistinguishable from tics in Tourette syndrome but much older age of onset
Tardive tremor	Postural, kinetic, and rest tremor (typically high amplitude and low frequency)
Tardive myoclonus	Prominent postural myoclonic jerks in upper extremities
Tardive chorea	Usually accompanies classic TD in adult patient
Tardive parkinsonism	Rest tremor, bradykinesia, rigidity persisting for months/years after discontinuation of DRBAs; normal DAT SPECT
Withdrawal emergent syndrome	Generalized chorea (no or minimal involvement of oro-bucco-lingual region) in children after sudden discontinuation of DRBAs; self-limiting condition
Neuroleptic malignant syndrome	Fever, rigidity, mental status change, hyperthermia, elevated CK, leukocytosis
Tardive pain	Chronic painful oral and genital sensations

Abbreviations: CK, creatine kinase; DAT, dopamine transporter; DRBA, dopamine receptor-blocking agent; SPECT, single photon emission computerized tomography TD, tardive dyskinesia.

tardive stereotypy lacks the sensory component of akathisia. Repetitive vocalizations such as moaning and grunting are also common features of akathisia.

Tardive Dystonia (Video 3) can be focal (usually cranial dystonia affecting jaw, tongue, and facial muscles), segmental, or generalized, closely resembling idiopathic dystonia but with a few distinctive features.[36,39] Axial TD is typically manifested by opisthotonic posturing, scoliosis, and retrocollis. Tardive limb dystonia usually presents as adduction and pronation of arms in the shoulders, extension at elbows, and flexion of the wrists.

Tardive chorea as the only manifestation of TD is quite rare and usually accompanies oro-bucco-lingual stereotypy in adult patients with TD. Because chorea by definition is a random jerk-like movement, the term "rhythmic chorea," sometimes applied to tardive

Video 1. **Classic Tardive Dyskinesia.** A 77-year-old woman developed symptoms 2 weeks after sudden discontinuation of prochlorperazine 10 mg daily that she had been taking for a year. The video demonstrates classic oro-bucco-lingual stereotypy and mild extremity stereotypies.

Video 2. **Tardive Akathisia and Tardive Stereotypy.** A 34-year-old man with paranoid schizophrenia treated with haloperidol 10 mg daily for 2.5 years and lurasidone 80 mg daily for 6 months developed restlessness, inability to stay still, and abnormal hand movements. The video demonstrates extreme restlessness and hand-rubbing stereotypies.

Video 3. **Tardive Dystonia.** A 42-year-old man with mood disorder treated with ziprasidone 60 mg daily developed mild facial grimacing and tapered off ziprasidone over 2 weeks followed by worsening and generalization of abnormal movements. Video demonstrates cervical dystonia with retrocollis and torticollis to the left, jaw-opening dystonia, blepharospasm, truncal dystonia with opisthotonic trunk posturing, proximal arms dystonia with arm extension and internal rotation, and proximal legs dystonia.

chorea, is not appropriate as many TD patients actually have stereotypy.

Chorea can be seen in children following sudden withdrawal from a DRBA as part of the so-called *withdrawal emergent syndrome* (Video 4).[41] This is a self-limiting condition, typically manifesting days or weeks after DRBA discontinuation as generalized chorea that markedly differs from the more common tardive stereotypy. The movements in withdrawal emergent syndrome involve mainly trunk and limbs, and rarely the oral region, as opposed to classic TD.

Tardive tics, or tardive tourettism (Video 5), is clinically very similar to motor and phonic tics typically associated with Tourette syndrome, but the age at onset is usually much older.[49]

Tardive tremor (Video 5) manifests as postural, kinetic, and resting oscillatory movement (tremor) in the limbs with a frequency from 3 to 5 Hz and typically of high amplitude. In the absence of parkinsonian features, it is responsive to dopamine-depleting drugs such as tetrabenazine (TBZ) (see below).[50]

Tardive myoclonus usually presents as prominent postural spontaneous or stimulus-sensitive jerk-like movement (myoclonus) in the upper extremities.[51]

Tardive parkinsonism is a controversial entity that refers to parkinsonian features persisting several months, years, or indefinitely after cessation of DRBA therapy. Some patients with parkinsonism who do not improve after DRBA discontinuation might be found to have evidence of presynaptic dopaminergic deficit as indicated by reduced density of dopamine transporter (DAT) on ^{123}I-ioflupane single-photon emission computerized tomography (SPECT), suggesting that they have an underlying Parkinson's disease (PD) that became symptomatic, or unmasked, after DRBA exposure.[52,53] There are three possible scenarios of parkinsonian features in the context of ongoing or past history of DRBA exposure: 1) parkinsonian features are present while being treated with DRBAs but resolve within weeks after its discontinuation (drug-induced parkinsonism); 2) parkinsonian features are present during DBRA treatment and persist for years after discontinuation of the offending drug, and DAT SPECT is normal (tardive parkinsonism); 3) parkinsonian features persist indefinitely (longer than several months or years after DRBA discontinuation, and DAT SPECT is abnormal (underlying PD unmasked by exposure to DRBA). On the other hand, patients with parkinsonism in the context of ongoing or recent DRBA exposure who have normal ^{123}I-ioflupane SPECT studies represent true drug-induced parkinsonism or tardive parkinsonism if the symptoms persist for months or years after discontinuation of an offending DRBA. A 15-year prospective population-based study of 2,991 elderly subjects estimated a 3.2-fold higher risk of developing clinically probable PD in subjects with a history of exposure to neuroleptics compared to elderly individuals never exposed to DRBAs, although the mechanism remains unclear.[54]

Video 4. **Withdrawal Emergent Syndrome.** An 11-year-old boy with Tourette syndrome and behavioral problems treated with olanzapine 30 mg daily and fluphenazine 5 mg daily had all his medications suddenly discontinued, and 1–2 weeks later developed mild piano-playing finger movements with rapid progression to generalized chorea. The symptoms gradually resolved over the next 2 months with no treatment.

Video 5. **Tardive Tics and Tardive Tremor.** A 37-year-old man with history of gastroesophageal reflux disease treated with metoclopramide (20-30 mg/day) for 9 months developed facial tics and hands tremor (postural and kinetic) that persisted for 2 years after discontinuation of the medication. The patient also has left leg stereotypy.

Tardive gait is another characteristic feature of TD. Gait changes can vary from "dancing" gait (repetitive short steps on toes followed by a long stride) to "duck-like" gait (wide-based and unsteady, with short stride length and mild steppage features).[55] TD can also interfere with normal gait because of axial and arm dystonia.[45]

Neuroleptic malignant syndrome (NMS) is a rare complication of neuroleptic treatment that can occur within days to months after the initial exposure to the DRBA. It typically manifests as a combination of fever, rigidity, mental status changes, elevated body temperature, autonomic dysfunction, elevated serum creatine kinase, and leukocytosis, although presence of all symptoms is not required for to make a diagnosis.[43] NMS can be caused by exposure to any DRBA, including typical and atypical neuroleptics in either stable or escalating doses, or by sudden withdrawal of dopaminergic medications.[43,56] NMS can range from a relatively mild and self-limiting condition to a life-threatening disorder.

Tardive pain was described by Ford et al[57] in 1994 as a chronic painful oral and genital sensation in patients exposed to DRBAs who had TD. Dopamine-depleting medications used to treat motor symptoms of TD were effective in reducing painful sensations.

Diagnosis and Differential Diagnosis of TD

The diagnosis of TD is based on the patient's history of exposure to DRBAs, characteristic clinical presentation, and exclusion or other conditions with similar phenomenology.

Differential diagnosis of TD should include primary neurological conditions that can be manifested by various dyskinesias among other symptoms, such as Huntington's disease, Wilson's disease, neuroacanthocytosis, prion diseases, neurodegeneration with brain iron accumulation,[58] Sydenham chorea, systemic lupus erythematosus, antiphospholipid antibody syndrome,[59] anti-*N*-methyl-D-aspartate receptor encephalitis,[60] and other autoimmune diseases.[61] Additional diagnostic work-ups such as neuroimaging, genetic testing, and metabolic and immune panels might be necessary if historical events or the course of clinical manifestations suggest the possibility of an alternative diagnosis besides TD. Orofacial dyskinesia can be observed in elderly individuals with poor dentition and without any neurological disorder (edentulous dyskinesia).[62] Dyskinesia can occur in patients taking levodopa or dopamine agonists, but it is a short-lived condition that remits as soon as the medication wears off.

Tardive tremor needs to be differentiated from tremor in patients with PD, essential tremor, and dystonic tremor. Lack of other parkinsonian features (rigidity, bradykinesia, gait abnormality) differentiates tardive tremor from PD. In some more challenging cases, DAT SPECT might be useful in the differential diagnosis because there is no presynaptic dopaminergic deficit in tardive tremor or tardive parkinsonism; therefore, DAT SPECT is expected to be normal, as opposed to reduced DAT density typically observed in PD. History of DRBA exposure, lack of family history of tremor, and lack of sensitivity of tremor to alcohol might help differentiate tardive tremor from essential tremor. Improvement with TBZ can be observed in tardive tremor but not with essential or PD-related tremor. In fact, tremor in PD would be expected to worsen with TBZ. Dystonic tremor in the limbs is usually irregular, asymmetrical, position-related, and associated with dystonic posturing of the limb; although dystonia might be mild and difficult to recognize during the examination. Other drug-induced tremors, caused by multiple medications including antidepressants, neuroleptics, lithium, antiepileptics, amiodarone, beta-adrenergic agonists, and central nervous system (CNS) stimulants, should be also considered.[63] These tremors usually have higher frequencies than tardive tremor, are dose dependent, and resolve within weeks after discontinuation of the offending drug.

Management of TD

Prevention of TD is paramount; therefore, strict selection of patients to be treated with DRBAs is prudent medical practice. DRBAs should be avoided whenever possible by choosing alternative medications with lower potential to cause TD. Furthermore, long-term treatment with DRBAs should be avoided, but, if absolutely necessary, it should be accompanied by frequent re-assessments of the need to continue treatment and high vigilance and monitoring for early symptoms and signs of TD.

The main aspect of TD treatment is removal of a causative drug whenever possible, but slow taper is recommended as sudden withdrawal is more likely to precipitate TD or withdrawal emergent syndrome.[41] There is a large body of evidence that supports the notion that that the sooner the offending medication is discontinued, the more likely it is that TD will gradually resolve.[19] If a patient requires continuous treatment with antipsychotics, the newer generation of "atypical" neuroleptics, such as quetiapine and clozapine, may be useful alternatives, although essentially all typical and atypical neuroleptics carry a risk of TD.[6] Restarting or increasing the dose of a causative DRBA or a similar agent can reduce TD, but this strategy should be avoided whenever possible and reserved only as an emergency solution for the most severe cases that require immediate control of the involuntary movements. High doses of clozapine and quetiapine have been reported to alleviate TD symptoms,[64] but these drugs should not be used for long-term treatment of TD. It is likely that atypical neuroleptics in high doses can demonstrate D_2 receptor-blocking quality, acting as typical DRBAs, even causing TD.[6]

The dopamine-depleting drugs reserpine and TBZ inhibit vesicular monoamine transporter (VMAT) at the presynaptic membrane of the nerve terminal; thus exposing monoamines to monoamine oxidase, which results in depletion of the synaptic pool of monoamines.[65–67] Reserpine has slow onset and a prolonged duration of action that should be taken into consideration while changing the dose. It blocks both types of VMAT: VMAT1 found peripherally and VMAT2 present in CNS. TBZ has quicker onset and shorter duration of effect. It selectively inhibits VMAT2 and therefore does not have peripheral catecholamine-depleting side effects, such as orthostatic hypotension and gastrointestinal side effects.[67] TBZ is currently considered a first-line agent and the most effective medication to treat persistent and disabling TD. Previous studies at the Baylor College of Medicine reported marked or moderate improvement of abnormal movement intensity and amplitude in up to 95% of patients with TD.[67] This

Table 3. Treatment of Tardive Dyskinesia

Medication	Starting Daily Dose	Daily Dose Range
Slow Taper of an Offending DRBA		
Dopamine-depleting medications		
Tetrabenazine[67]	12.5–25 mg	25–200 mg (typical therapeutic dose 50–75 mg)
Reserpine[86]	0.25 mg	0.75–8 mg
Amantadine[86]	100 mg	100–300 mg
GABA agonistic medications		
Clonazepam[86]	0.5 mg	1–4 mg
Baclofen[73]		20–120 mg
Valproic acid[73]		900–1500 mg
Anticholinergic medications		
Trihexyphenidyl[87]	1 mg	4–20 mg
Less studied/might be effective medications (donepezil, lithium, antioxidants, zonisamide, vitamin B6, melatonin, zolpidem, propranolol)		
Chemodenervation with botulinum toxin injections		
Surgical treatment (deep brain stimulation)		

Abbreviations: DRBA, dopamine receptor-blocking agent.

medication is usually well tolerated; however, with higher doses that are often needed to control the symptoms of TD, it can cause side effects such as depression, lethargy, akathisia, and parkinsonism.[67] However, all these side effects are dose related, and no documented case of TBZ-induced TD has been reported. Serious side effects such as severe hyperthermia, NMS, acute dystonic reaction, and suicide are rare. Alpha-methylparatyrosine (AMPT) is a competitive inhibitor of tyrosine hydroxylase, an important enzyme in dopamine synthesis. It is not very effective as monotherapy but can enhance the antidopaminergic effect of dopamine-blocking drugs when used in combination.[68] AMPT is rarely used in the treatment of TD.

Other less studied medications may also provide various degrees of symptomatic improvement in TD, but these observations are based on small open-label studies and case reports (Table 3). The list of such medications includes amantadine, possibly acting as a glutamate receptor-blocking agent,[69] GABA agonistic medications, including benzodiazepines, baclofen, valproic acid,[70–73] donepezil acting as a cholinomimetic,[74] lithium,[75] antioxidants,[76,77] zonisamide,[78] vitamin B6,[79] melatonin,[80] and zolpidem[81] From our experience, zolpidem and propranolol might be the most effective treatments for tardive akathisia,[81] which is often refractory to medical therapy including TBZ; however, larger studies of the use of zolpidem in TD and tardive akathisia are required. Anticholinergic medications such as trihexyphenidyl or ethopropazine can be effective in tardive dystonia,[39] but they may exacerbate classic and other forms of TD. Dopamine agonists and levodopa are not effective in TD and can exacerbate an underlying psychiatric disorder. The only exceptions are tardive parkinsonism and NMS, which are often managed with dopamine agonists if discontinuation of a DRBA alone is not sufficient.

Chemodenervation with botulinum toxin injections into the muscles causing disabling but focal dyskinesia is also often used in the treatment of TD, particularly tardive dystonia.[82,83] Surgical treatment, including pallidotomy and pallidal deep brain stimulation, is reserved for the most severe and medication-resistant cases of TD.[84]

Withdrawal emergent syndrome is a self-limiting condition that often does not require treatment.[41] For faster recovery or if the abnormal movements are very uncomfortable for a patient, DRBA can be reinstituted and tapered off gradually.

Prompt and gradual withdrawal of neuroleptic at the first signs of NMS is the main intervention to manage this condition. In mild cases, discontinuation of the offending drug along with supportive symptomatic care might be sufficient. In more severe cases of NMS, treatment with levodopa, dopamine agonists, dantrolene, steroids, and benzodiazepines can be used in parallel with intravenous hydration and careful observation.[43] Electroconvulsive therapy may be used in some drug-resistant and refractory cases of NMS.[85]

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