

Spectrum of tardive syndromes: clinical recognition and management

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ABSTRACT

Tardive syndrome (TS) refers to a group of delayed onset disorders characterised by abnormal movements and caused by dopamine receptor blocking agents (DRBAs). Classical tardive dyskinesia is a specific type of oro-buccal-lingual dyskinesia. However, TS may exist in other forms—for example, stereotypy, dystonia, and akathisia—and frequently occur in combination. The onset typically is insidious and after reaching its maximum severity it often stabilises. Frequently reported risk factors are age, dose and duration of neuroleptic exposure, the use of conventional DRBAs, and co-existing mood disorders. This review highlights the broad spectrum of TS, not limited to classical tardive dyskinesia, as well as the clues for its recognition. Despite challenges in the treatment of TS, dictated by the different phenomenology, severity of TS and the need for ongoing neuroleptic treatment, the authors provide evidence based recommendations for patient management, which is not restricted to only withdrawal of the offending neuroleptics or the selection of an alternative medication, such as clozapine. In a minority of cases with significant functional disability, symptomatic or suppressive treatments should be considered. Recently, there has been a resurgence of stereotactic pallidal surgery for the treatment of TS. Although the efficacy of both pallidotomy and pallidal deep brain stimulation in dystonia has been encouraging, the evidence is still limited.

The ‘discovery’ of tardive dyskinesia (TD) occurred more than five decades ago, about 5 years after the introduction of neuroleptic drugs into psychiatry. The original description of persistent abnormal involuntary movements induced by neuroleptic agents was published in a paper by Schonecker in 1957.¹ Since then, the phenomenon of TD alerted physicians and the public to its iatrogenicity and to its medicolegal impact, further enhancing clinical awareness of a potential negative and delayed impact of these useful drugs on the nervous system. While tardive syndromes (TS) encompass all aspects of abnormal movements, tardive dyskinesia (TD) specifically refers to classical oro-buccal-lingual dyskinesia associated with ‘piano playing’ finger movements. The involuntary movements of various phenomenology associated with neuroleptic agents are classified as TS, including classic oro-buccal-lingual dyskinesia, stereotypy, dystonia, akathisia, tics, myoclonus, tremor, and parkinsonism. TS is now accepted as a separate and unique entity as a result of the principal adverse effect of long term treatment with conventional antipsychotic agents. In this review, we discuss the clinical issues related to TS, including clinical

recognition of various phenomenologies of TS, not limited to TD, and the practical management of this condition. Basic common principles of management of TS are also provided. When possible, preventive measures should be considered such as avoiding the use of neuroleptics when alternative treatments are available, limiting the course of neuroleptic treatment, and carefully watching for the earliest signs of TS. Once TS has developed, therapeutic choices often include the discontinuation of neuroleptics in patients with TS (if possible), and a determination of which medications may be considered for suppressing TS. In medically intractable cases, severe disability may force the need for chemodervation or surgical intervention.

CLASSIFICATION OF TS

TD refers to a group of disorders characterised by predominantly late onset and sometimes persistent involuntary movements (or a sensation of restlessness), which are caused by exposure to dopamine receptor blocking agents (DRBAs). The first international congress of movement disorders defined TD as a hyperkinetic movement that develops during treatment with neuroleptics or within 6 months of stopping the offending agent, and it must persist for at least 1 month after discontinuing all neuroleptics. A somewhat different definition by the American Psychiatric Task Force requires 3 months of exposure to a DRBA for diagnosis of TD.^{2,3} The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria specifies the shortest duration of exposure to DRBAs of at least 1 month in individuals ≥ 60 years. The French term ‘tardive’ is used to denote its late onset during the course of neuroleptic therapy, and ‘dyskinesia’ refers to unnatural movements which may or may not be involuntary. Generally, TD does not appear until after 1 or 2 years of continued neuroleptic treatment, and almost never before 3 months. Because virtually all types of movement disorders have been associated with neuroleptic therapy, and this identical clinical syndrome can be induced by other agents in addition to neuroleptics (box 1), the term ‘tardive dyskinesia’ is confusing and problematic. Traditionally and historically, the term ‘tardive dyskinesia’ was used to describe a specific type of movement, characterised by oro-buccal-lingual dyskinesias.⁴ There are several phenomenological distinct types of abnormal movements and they are classified into classical tardive dyskinesia, tardive stereotypy, tardive dystonia, tardive akathisia, tardive tremor, tardive myoclonus, and tardive tourettism (box 2).⁵ It remains unclear if tardive

Box 1 Drugs that are commonly associated with tardive syndromes

1. Phenothiazines
 - a. Chlorpromazine
 - b. Triflupromazine
 - c. Thioridazine
 - d. Mesoridazine
 - e. Trifluoperazine
 - f. Prochlorperazine
 - g. Perphenazine
 - h. Fluphenazine
 - i. Perazine
2. Thioxanthenes
 - a. Chloprothixene
 - b. Thiothixene
3. Butyrophenones
 - a. Haloperidol
 - b. Droperidol
4. Diphenylbutylpiperidine
 - a. Pimozide
5. Dibenzazepine
 - a. Loxapine
6. Dibenzodiazepine
 - a. Clozapine
 - b. Quetiapine
7. Thienobenzodiazepine
 - a. Olanzapine
8. Substituted benzamides
 - a. Metoclopramide
 - b. Tiapride
 - c. Sulpiride
 - d. Clebopride
 - e. Remoxipride
 - f. Veralipride
9. Indolones
 - a. Molindone
10. Pyrimidinone
 - a. Risperidone
11. Tricyclic antidepressants
 - a. Amoxapine
12. Calcium channel blockers
 - a. Flunarizine
 - b. Cinnarizine

Box 2 Classification of tardive syndromes

1. Tardive dyskinesia
2. Tardive stereotypy
3. Tardive dystonia
4. Tardive akathisia
5. Tardive tourettism
6. Tardive myoclonus
7. Tardive tremor
8. Tardive parkinsonism

varies widely in the literature, reflecting the heterogeneity of the groups being observed as well as the various assessment methods used, an average prevalence among neuroleptic treated patients, corrected for the prevalence of spontaneous dyskinesia, is estimated to be between 20–40%.^{6–9} In addition to TD, there are few studies about prevalence of other movement disorders as part of TS. Tardive dystonia has a prevalence of between 2–16% of neuroleptic treated patients.^{10–11} The prevalence of tardive akathisia, tics, myoclonus, and tremor have been reported as 22%, 4%, 1%, and 30%, respectively.¹⁰

Ageing appears to be a critical risk factor for developing TD, as the incidence increases from 5% in the younger age group (<40 years old) to 12% or higher in the older age group (≥40 years old).¹² In general, at least 20% of patients treated with typical neuroleptics are affected with TD and approximately 5% are expected to develop TD during each year of neuroleptic treatment. Female gender may be a risk factor although this is not supported by incidence studies. Patients with existing movement disorders are at greater risk of developing TD with continued use of antipsychotics. Total neuroleptic load, the dose and duration of use, is considered to be a risk factor. Neuroleptics, both typical and atypical agents, induce the upregulation of D₂ receptor binding, which is associated with the development of TD. However, typical neuroleptics carry a greater risk than atypical agents.^{13–15} Indeed, all atypical neuroleptics have a high serotonin-to-dopamine receptor blockade ratio in the brain, and this high serotonergic blockade is thought to play a role in reducing acute extrapyramidal symptoms. Other reported risk factors are race, a diagnosis of a mood disorder, cognitive impairment, the presence of negative symptoms, alcohol and substance abuse, the use of antiparkinsonian agents and lithium, early extrapyramidal symptoms, illness awareness, diabetes, and lastly, HIV seropositive status¹⁶ (box 3).

parkinsonism truly exists. The term ‘classical tardive dyskinesia’ will be used in this review to denote a characteristic oro-buccal-lingual dyskinesia. Although detailed and somewhat impractical, this differentiation into specific abnormal movements gives physicians additional clues to identify a specific aetiology, pathophysiologic mechanism, and specific treatment protocols in certain subgroups of populations. The combination of more than one type of hyperkinetic movements (eg, stereotypy and dystonia) strongly suggests the diagnosis of TD.

EPIDEMIOLOGY AND RISK FACTORS OF TS

The most compelling evidence supporting the association between neuroleptics and TD comes from epidemiologic studies. In general, TD is the most frequently observed disorder in TS. These studies have also determined risk factors, including age, duration of treatment, and gender. While the prevalence of TD

Classical TD

Classical TD comprises a phenomenologically distinct syndrome of TS, is the most common persistent adverse reaction to prolonged neuroleptic medication, and was the first to be identified. General characteristics are frequently observed to resemble normal movement patterns, such as chewing (rumination), bridling (retraction of the corners of the mouth), grasping or ‘piano-playing’ movements; however, patients perform these movements involuntarily. Orofacial movements especially may be temporarily suppressed by patients themselves or when engaged in voluntary activities, such as talking or chewing. Interestingly, many patients with classical TD do not even notice their involuntary movements unless their attention is drawn to them by others.

The facial muscles, particularly the perioral and oral muscles, are commonly affected in classical TD.^{4–17} Dyskinesia of the

Box 3 Risk factors of tardive syndromes

1. Older age (young age in case of tardive dystonia)
2. Female gender
3. African American population
4. Typical neuroleptics
5. Higher dose and longer duration of neuroleptic use
6. Pre-existing mood disorders
7. Cognitive impairments
8. Presence of negative symptoms
9. Alcohol and substance abuse
10. Use of antiparkinsonian agents and lithium
11. Early extrapyramidal symptoms
12. Diabetes
13. HIV seropositive status

tongue is characterised by a slow and repetitive retraction, or a sweeping tongue movement within the oral cavity, producing a bulge in the cheek, referred to as the 'bonbon sign'.¹⁸ When the patient is asked to extend the tongue, irregular, worm-like contractions of the tongue muscles are frequently observed. Grimacing, with a lifting or arching of eyebrows or frowning, can also be a symptom of classical TD. Most patients exhibit uncoordinated flexion/extension movements of individual fingers, somewhat resembling guitar or piano playing movements. Dyskinesias of the legs—'stamping movements'—give the impression of slowly walking in place or shifting body weight from one foot to the other.¹⁸ Dyskinesia of the diaphragm may lead to an irregular, uneven rhythm of speech or uncontrollable grunting and groaning. Other movements that have been described in classical TD include hip-rocking movements, to-and-fro movements of the upper torso, head nodding, and flexion/extension movements of the toes, wrists, and ankles.

Tardive stereotypy

Stereotypy, which is defined as a seemingly purposeful, coordinated but involuntary, repetitive, ritualistic gesture, mannerism or utterance, was reported by Stacy *et al.*,^{19 20} and Miller *et al.*²¹ to be the most common form of TD. Some experts suggested that tardive stereotypy is probably a more appropriate term than classical TD to describe the repetitive, rather than random, movements. However, the stereotypic movements in classical TD are very characteristic and similar in almost all patients with this disorder, differentiating it from other types of stereotypies seen in patients with autism and psychosis.²²

Tardive dystonia

Since the earliest reports of TD, a variety of involuntary movements, in addition to the well known oro-buccal-lingual

masticatory movements, have been described, including dystonia. The term 'tardive dystonia' was defined by Burke *et al* to represent an involuntary movement predominated by dystonia and associated with the use of DRBAs.²³ For reasons not fully understood, young adults seem to be particularly susceptible to this disorder.¹⁹ According to Burke *et al*, dystonia must be present for more than a month and occur either during ongoing treatment with a DRBA or within 3 months of its discontinuation.²³ Although choreiform movements may occur, the principal movement must be dystonia. Dystonic movements in tardive dystonia are strikingly different from the classical TD. Firstly, dystonic movements, defined as a syndrome of sustained muscle contractions frequently causing twisting and abnormal postures, tend to be action specific. They occur consistently with certain actions and do not exhibit clear-cut periodicity as classical TD. Secondly, many patients with dystonia note that their movements can be partially controlled by simple tactile manoeuvres, termed sensory tricks or 'geste antagoniste', such as touching the chin to alleviate torticollis.²⁴ Third, tardive dystonia occurs more often among men than women, the gender at greater risk for classic TD.²⁵ Finally, the shorter duration for neuroleptic exposure develops tardive dystonia and it tends to occur in populations with a lower age of onset when compared with other TS.^{10 26}

Without a reliable history, tardive dystonia may be indistinguishable from idiopathic torsion dystonia, including sensory tricks and distribution of dystonia. However, there are some different features for identification of these disorders (table 1). Tardive dystonia has a special predilection for cranial and cervical muscles. When it affects the neck, it usually results in retrocollis (figure 1), in contrast to laterocollis or torticollis in idiopathic cervical dystonia. When involving the trunk, it usually produces severe scoliosis or opisthotonic posturing (figure 2). When involving the upper limbs, internal rotation of the arms, extension of the elbows, and flexion of the wrists are common postures in tardive dystonia.²⁶ The legs are only infrequently involved. Tardive dystonia often occurs with other TS, while idiopathic torsion dystonia rarely does.

Tardive akathisia

Akathisia refers to a feeling of inner restlessness and jitteriness that is often manifested by semi-purposeful movements. Subjectively, the most common complaint is the inability to keep the legs still which are associated with vague inner tension, unease, or anxiety. Objectively, patients are seen rocking from foot to foot, walking in place, grunting, moaning, or trunk rocking. In addition to its common occurrence as an acute adverse effect of neuroleptics, akathisia can become chronic (tardive akathisia).²⁷ Not surprisingly, tardive akathisia usually coexists with classic TD. The mean age of onset is 58 years, as the age of onset of patients to whom neuroleptics are administered typically is younger than those taking other agents.¹⁰

Table 1 A comparison of tardive dystonia and idiopathic torsion dystonia

Clinical features	Tardive dystonia	Idiopathic torsion dystonia
Cervical dystonic posture	Retrocollis	Torticollis, laterocollis
Axial dystonic posture	Opisthotonic posturing	Lateral twisting of trunk
Unique characteristics: internal rotation of the arms, extension of the elbows, and flexion of the wrists	Frequent in young men	None
Leg involvement	Less frequent	Frequent in primary generalised dystonia
Dystonia after voluntary action	Reduced	Exacerbated
Coexist with other tardive syndromes	Frequent	None



Figure 1 A patient with tardive dystonia presenting with retrocollis.

Although earlier evidence indicated a potential increased risk of suicide among patients with tardive akathisia, evidence on this association is still conflicting and requires a long term prospective study to address this issue.²⁸

Tardive tics

Tics are brief, repetitive, temporarily suppressible movements or sounds. There are usually premonitory sensations preceding motor or vocal tics. Tics have been reported to occur in patients after exposure to DRBAs. Besides older age of onset and history of neuroleptic exposure, they are clinically indistinguishable from Tourette's syndrome.

Tardive myoclonus

Postural myoclonus was also observed in approximately 25% of psychiatric patients who had been taking neuroleptics for at least 3 months (tardive myoclonus). It usually is prominent myoclonus in the upper extremities and is accompanied by other TS.²⁹

Tardive tremor

Tardive tremor was first described by Jankovic.^{4 30} The existence of tardive tremor has been the subject of case reports.³⁰ High amplitude, moderate frequency, postural and resting tremor have been observed in some patients who were exposed to neuroleptics, but without signs of parkinsonism.

Tardive parkinsonism

As noted above, the category of tardive parkinsonism is questionable but it has been used to describe the movements of some patients who had persistent parkinsonian features several months after neuroleptic discontinuation.³¹

DIFFERENTIAL DIAGNOSIS OF TS

The development of dyskinesias in a psychiatric patient is often attributed to neuroleptic therapy. Although neuroleptic exposure may be the cause of involuntary movements in the majority



Figure 2 Axial dystonia and opisthotonic posturing in tardive dystonia.

of psychiatric patients, other possibilities should always be considered since dyskinesias are symptoms or signs of neurological dysfunction and may stem from a variety of disparate neurological or medical disorders (box 4).³² Furthermore, many neurological disorders, such as Huntington's disease or Wilson's disease, may initially manifest themselves by isolated neuropsychiatric syndromes, preceding the onset of motor abnormalities by many years.³³

Dyskinesias are symptoms or may represent a syndrome, but they are not a diagnosis. There are no definitive clinical, laboratory, or electrophysiological criteria for the diagnosis of neuroleptic induced TD. However, some clues, if present, may provide an alternative diagnosis other than TD: (1) a rapidly deteriorating course; (2) constant unilateral manifestation; (3) the presence of additional neurological signs, such as dementia, sensory abnormalities, or urinary incontinence; and (4) the appearance of other physical symptoms or signs, such as jaundice, fever, skin rash, etc.

Huntington's disease (HD) is the major challenge for a differential diagnosis of TD because abnormal movements in both disorders can be phenomenologically identical and both can initially present with neuropsychiatric symptoms without motor abnormalities. However, careful observations of motor abnormalities in HD reveal different patterns, which may help distinguish it from TD. In HD, choreic movements are random, flowing from one part of the body to the other, and frequently

Box 4 Differential diagnosis of tardive syndromes

1. Classical tardive dyskinesia
 - a. Huntington's disease
 - b. Hepatolenticular degeneration
 - c. Drug induced dyskinesias
 - i. Levodopa
 - ii. Tricyclic antidepressants
 - iii. Selective serotonin reuptake inhibitors
 - iv. Serotonin and norepinephrine reuptake inhibitors
 - v. Lithium
 - vi. Phenytoin
 - d. Edentulous orodyskinesia
 - e. Spontaneous orofacial dyskinesias
 - f. Stroke
 - g. Immune chorea
2. Tardive dystonia
 - a. Primary dystonia
 - b. Heredodegenerative dystonia—for example, Wilson's disease
 - c. Secondary dystonia
3. Tremor
 - a. Parkinsonian tremor
 - b. Essential tremor
 - c. Cerebellar tremor
 - d. Enhanced physiologic tremor
 - e. Idiopathic tremor

superimposed by semi-purposeful movements in an attempt to mask involuntary movements. In contrast, choreic movements in TD are more likely to be slow, stereotypic and repetitive, often in the oral region. Furthermore, gait abnormalities, described as a stuttering choreic gait, more frequently occur with HD. Importantly, eye movement abnormalities in HD such as slow saccades have been frequently observed. Before the discovery of the HD gene, a definite diagnosis of HD would be made in the presence of: (1) a positive family history consistent with autosomal dominant inheritance; (2) progressive motor disability; and (3) mental disturbances including cognitive decline, affective disturbances, and/or changes in personality. Furthermore, in HD, progressive atrophy of the caudate nucleus is frequently observed, which is not seen in TD.^{34 35} Despite these clinical criteria, misdiagnosis occurs fairly frequently. The availability of the HD gene, especially its pathogenic mutation, has made it easier to distinguish TD from HD.

Among various dystonic syndromes, Wilson's disease figures prominently in the differential diagnosis of tardive dystonia. Although dystonia in both conditions frequently affects craniocervical regions, the presence of retrocollis or axial dystonia is highly suggestive of tardive dystonia, while oromandibular dystonia is more common in Wilson's disease (figure 3). Wilson's disease is an autosomal recessive disorder and can present with a myriad of manifestations, ranging from psychiatric illness to various types of movement disorders. Wilson's disease should be considered in adolescents and adults younger than 40 years with the following: (1) elevated liver enzymes found incidentally or in the context of an acute hepatitis episode; (2) dysphagia or dysarthria not explained by other neurological disorders; (3) patients with any types of movement disorders; (4) patients with psychiatric symptoms and liver disease; (5) adolescents with mood disorders and minor



Figure 3 Characteristic jaw opening dystonia in Wilson's disease.

elevations of liver transaminase; (6) patients with Coombs negative haemolytic anaemia; and (7) patients with unexplained liver cirrhosis and hepatic failure.³⁶ Until recently, the genetic basis of Wilson's disease confirmed the link to one of the transport proteins with a defect in a P-type ATP (ATPase) involving the transport of copper across the trans-Golgi and into transport vesicles.^{37 38}

Withdrawal emergent syndrome, typically seen in children, is identical to classical TD manifested in adults with the exception of the more generalised movements.³⁹ This syndrome is referred to as withdrawal dyskinesia, occurring after an acute withdrawal of long term use of antipsychotics. In contrast to classical TD, the random hyperkinesias seen in this syndrome primarily involve the limbs, neck, and trunk, and seldom the lower facial region, developing within a few days after discontinuation of antipsychotics. The course of illness in withdrawal emergent syndrome is shorter and more benign than classical TD and typically disappears after 3 months.

Hyperkinetic movements, identified as spontaneous dyskinesia, may occur in some elderly individuals without any known causes.⁴⁰ Interestingly, these spontaneous movements are found much more frequently among neuroleptic naïve schizophrenic patients than among older non-psychiatric patients and patients with other psychiatric diagnoses. Whether the presence of spontaneous dyskinesia is intrinsic to the pathophysiology of schizophrenia or a manifestation of brain damage remains to be elucidated. In addition to neuroleptics, late onset dyskinesias can be induced by tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).⁴¹ In patients with Parkinson's disease, levodopa, and to a lesser extent the dopamine agonists, can induce dyskinesia, with a fluctuating course and peripheral distribution.^{42–45} Occasionally, poorly fitted dentures or loss of teeth can produce bucco-oral movements, mimicking orofacial dyskinesias.^{46–48}

NATURAL HISTORY OF TS

TD typically begins several years after the initiation of neuroleptic treatment. However, a period of 3 months is generally regarded as the minimum period to include the vast majority of patients in whom neuroleptics play an essential role as a causative agent. Older patients appear to develop symptoms more quickly than younger patients, perhaps as a result of

neurobiological changes associated with ageing.⁴⁹ In general, TD has an insidious onset, later reaching its maximal severity rapidly, and then stabilises. Although different reports have shown the natural history of TD to persist, improve, or to have an unpredictable course, the most common course of TD by far is waxing and waning of mild-to-moderate symptoms over many years. Significant worsening after a period of stabilisation is unusual. Clinical manifestations may be precipitated by a dose reduction or withdrawal of neuroleptics, especially the first several weeks,^{5 50} or by concomitant administration of anticholinergics or antidepressants.⁵¹ Five per cent to 10% of patients on long term neuroleptics develop symptoms that are severe enough to notably impair functioning. Orofacial dyskinesias can cause difficulty in eating, resulting in weight loss. Similarly, only 11% of patients improve, and remissions, if they occur, usually appear within 1–2 years after discontinuation. About 50% of patients have had relatively persistent symptoms over the course of 5 years.⁵² These data may suggest that continued treatment with neuroleptics after the development of TD is probably a reasonable option for many patients.

PATHOPHYSIOLOGY OF TS

Despite extensive research on the mechanisms of action of neuroleptics, the specific pathophysiological processes underlying movement disorders remain incompletely understood. While patients with genetic predisposition for movement disorders, neurodegenerative disorders, or pre-existing brain injury may be more susceptible in developing TS, the most accepted theories suggest that chronic exposure of neuroleptics resulted in a combination of postsynaptic dopamine receptor hypersensitivity, abnormalities of striatal GABA (γ -aminobutyric acid)-containing neurons, and degeneration of striatal cholinergic interneurons.⁵³ Chronic blockade with neuroleptics may result in D₂ receptor upregulation and increased sensitivity of the dopamine receptors.⁵⁴ In addition, the findings of degeneration of neurons in the striato-pallidal and striato-nigral GABA-aminergic pathways combined with cholinergic interneurons were also observed in animal models of TD.^{55 55 56}

MANAGEMENT OF TS

Since, by definition, TD is an iatrogenic disorder, the best management is prevention. Patients should be advised of the inherent risk of developing TD before commencing drug therapy with neuroleptics. Once a TD is encountered, removal of the aetiological agent should be seriously considered. Importantly, early detection and discontinuation of DRBAs provide a higher chance for remission, although younger age is associated with a better chance of remission.⁵⁷ Most experts recommend neuroleptic withdrawal only in those who can tolerate it.³ Unfortunately, the best treatment for many psychiatric disorders is the long term administration of neuroleptics. Therefore, dose reductions and the use of the smallest effective dose is generally recommended as the next step.³

Atypical versus typical neuroleptics

As a result, patients with TD should have a greater likelihood of TD remission on atypical neuroleptics.^{58–62} Other than risperidone, little information is available on the use of atypical neuroleptics in TD.⁶³ Recently, one multicentre, double blind trial found significant improvement of anti-dyskinetic scores in risperidone treated schizophrenic patients greater than either haloperidol or placebo. Risperidone treated patients at 6 mg per day showed the most beneficial effect on TD, with greater

efficacy in the oro-buccal-lingual than the limb area.⁶⁴ Unlike the conventional and other atypical neuroleptics, clozapine is a relatively weak D₂ receptor blocker, and a number of small studies have demonstrated a reduction in involuntary movements for a short period with clozapine in both classical TD and tardive dystonia.^{65–71} Several smaller studies reported improvement of TD after switching typical neuroleptics to olanzapine and quetiapine. Overall, the cumulative data conclude that risperidone has been shown to be effective in the treatment of TD, mainly buccolinguo-masticatory dyskinesia, over an 8 week period.⁶⁴ Regarding clozapine, it does not worsen TD and may improve it. Despite limited evidence, some experts recommended switching from a typical neuroleptic to an atypical neuroleptic without distinguishing among atypical agents.⁷² However, the decision should be based on a consideration of both the benefits and the risks to the patient for each treatment option. With atypical agents, the possible benefits of TD reduction must be balanced against the risk of side effects, including sedation, weight gain, diabetes, agranulocytosis, and psychiatric exacerbation.

In classical TD, involuntary movements often are not disabling or even bothersome to the patients and many of them seem unaware of the movements. However, the families often tend to be more distressed or upset than the patients. If this is the case, symptomatic therapy is rarely indicated although other management should be directed at trying to encourage the development of spontaneous remission or improvement through adjustment of neuroleptics as described above. Alternatively, some patients are severely distressed by the movements, and functional disabilities occur which interfere with speech and feeding including biting lips, and irregular respiration. Severe TD most commonly occurs in younger men (<40 years) and older women (over 65 years), and often has a component of dystonia. Treatment of severe TD requires continued neuroleptic therapy concomitantly with serial trials of suppressive agents.

Generally, suppressive therapy with neuroleptics is successful in 75% of patients, but the long term safety has not been demonstrated. There are no validated guidelines to follow when choosing a suppressive agent since not a single agent has been successful in large scale, double blinded, randomised controlled trials.⁷³ Selection should be based on the underlying psychiatric diagnosis, risk/benefit analysis, potential side effects, and interaction with other medications. In general, therapeutic trials have attempted to manipulate one of the following neurotransmitters, including dopamine, GABA, acetylcholine, norepinephrine, and serotonin. Based on the dopamine hypersensitivity hypothesis, both typical and atypical neuroleptics may be effective in suppressing TD.⁷⁴ While its efficacy in short term suppression has been clearly demonstrated, the therapeutic efficacy of long term suppression (more than 8 weeks) remains unclear. High potency neuroleptics have been observed to have more suppressive effect than those of lower potency.⁷⁴ Although overall results have varied, significant improvement, particularly with dystonic features, has been observed with clozapine and risperidone.^{64 67 75}

Dopamine depleting agents

The strategy of depleting dopamine without exposing the brain to DRBAs has been shown to reduce TD symptoms. Reserpine and tetrabenazine (not available in the USA) inhibit the vesicular monoamine transporter and thereby deplete presynaptic stores of dopamine. Studies of dopamine depleting medications suggest that they may alleviate symptoms in up to 50% of patients with TD.⁷⁴ Tetrabenazine has a quicker onset and

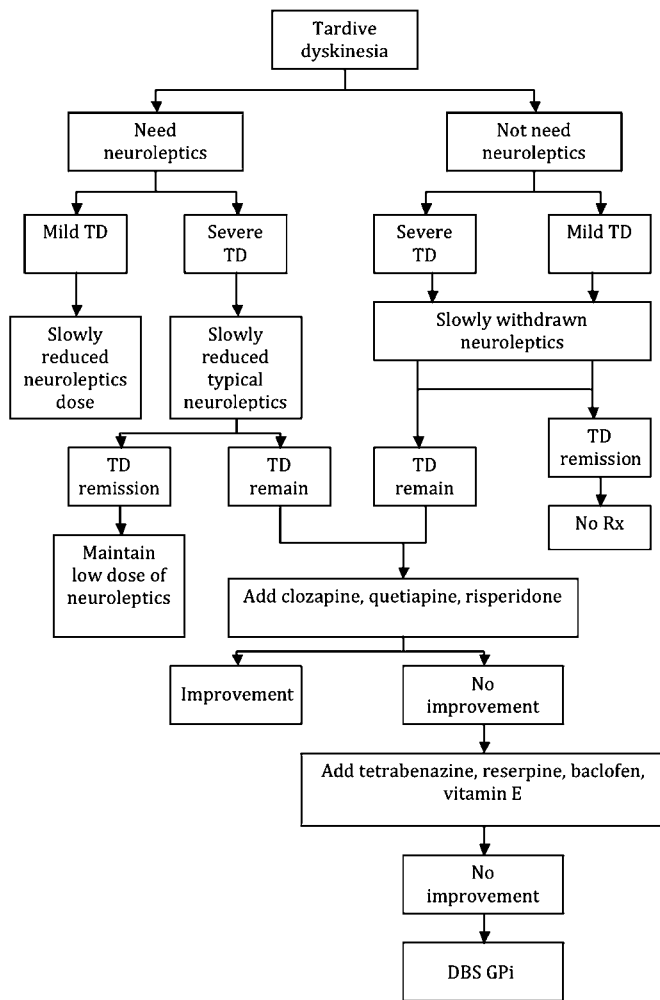


Figure 4 Algorithm in the management of tardive dyskinesia. DBS, deep brain stimulation; ECT, electroconvulsive therapy; GPI, globus pallidus interna; Rx, treatment; TD, tardive dyskinesia.

shorter duration of action, with fewer peripheral catecholamine depleting effects than reserpine. In addition, both agents have not been implicated in causing TD. While larger, well controlled studies are needed to validate the efficacy of tetrabenazine, the limited available data support its use for TD suppression.⁷⁶

Cholinergic versus anticholinergic agents

The observations that parkinsonian symptoms can be improved by dopamine agonists or cholinergic antagonists have implicated the 'imbalance' between acetylcholine and dopamine to induce dyskinesias. As a result, numerous studies have been conducted since 1970 to examine the efficacy of cholinomimetic agents or acetylcholinesterase inhibitors.^{77–79} Unfortunately, a systematic review of cholinergic agents was unable to demonstrate its clear-cut value in ameliorating dyskinesias. Currently, only donepezil has demonstrated some benefit in suppressing TD.^{80–82} Likewise, anticholinergics do not help or may actually worsen TD and discontinuation may be helpful in some patients. The only exception is tardive dystonia, which may improve with high doses of trihexyphenidyl.⁷⁵

GABA agonists

No clear evidence has been reported that GABA agonists, benzodiazepines, are effective in suppressing TD.⁸³ However, 40–50% of patients reported favourable outcome with clonazepam or diazepam, mainly with dystonic symptoms.^{84–85}

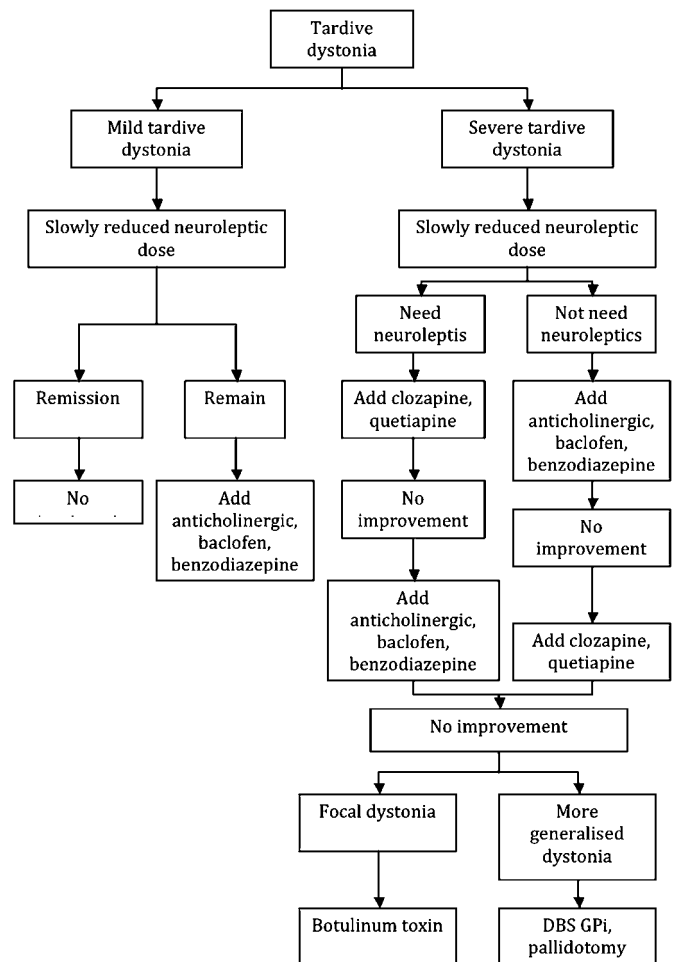


Figure 5 Algorithm in the management of tardive dystonia. DBS, deep brain stimulation; GPI, globus pallidus interna.

Baclofen, a GABA_B agonist, brought about significant improvements as a suppressive agent in TD when it was combined with neuroleptic agents.^{86–87}

Botulinum toxin

In addition to primary torsion dystonia, chemodenervation with botulinum toxin, mainly type A, was also considered as a treatment for tardive dystonia.^{88–90} The response to botulinum toxin in tardive patients was no different than the response in other forms of dystonia.⁹¹

Antioxidants

Chronic neuroleptic exposure has been shown to increase the turnover of dopamine in the brain, which subsequently leads to production of cytotoxic free radicals. Thus, vitamin E has been proposed as an effective treatment for TD by neutralising free radicals. While positive effects have been observed in patients with relatively recent onset (within 5 years), a recent large multicentre study found no significant improvement of TD with vitamin E at a daily dose of 1600 mg.^{92–94} Therefore, there still is no consistent evidence for suppressive benefits of vitamin E in TD. Additions to vitamin E, other antioxidants such as melatonin, vitamin B6, or eicosapentaenoic acid, are unproven in efficacy for suppressing TD.

Surgical treatment

Recently, there have been many studies for surgical intervention in patients with TS, mainly dystonia. The optimal target of

lesioning or deep brain stimulation is the globus pallidus internus. As a result, the efficacy of both pallidotomy and pallidal deep brain stimulation had shown improvement in several case reports among tardive dystonia patients. The motor beneficial effects were similar for oro-buccal-lingual dystonia and axial as well as limb dystonia.^{95–98} However, pallidal surgical procedures are appropriate for severe disabling tardive dystonia patients unresponsive to other forms of therapy.

Treatment of TD is challenging and is often unsatisfactory since there are no specific antidyskinetic drugs. The severity of TD and the absolute necessity for neuroleptics often dictates the treatment approach for the disorder. Since withdrawal of the offending drug may bring full remission in some instances, this option should always be considered in all patients if at all possible. If not, as is usually the case, then a drug that may permit passive healing should be considered. While clozapine is a good choice, it is logistically difficult to use and risperidone or quetiapine might be considered as an alternative. In mild cases that do not warrant treatment, adding vitamin E may be worthwhile albeit still unproven. The doses of atypical neuroleptics should be kept as low as possible. With limited current evidence and the lack of formal guidelines, the use of suppressive agents is highly individualised. Each expert may have a different strategy and there may not be a generalised approach for all circumstances. Often, a trial of different drugs is needed before an effective one is found. The decision regarding which suppressive agent should be chosen requires a consideration of the benefits and risks to the patient for each treatment option. The algorithms shown in figures 4 and 5 are provided as a guide based on scientific rationale and evidence-based information (figures 4 and 5). However, it is important to bear in mind several abovementioned factors when selecting suppressive medications and customise therapy to the needs of the individual patient.

CONCLUSION

TS refers to a group of delayed onset movement disorders, not limited to classical TD, caused by DRBAs. While the most frequent manifestation of TS is characterised by oro-buccal-lingual dyskinesias, TS may exist in other forms, including

Main messages

- ▶ Tardive syndromes (TS) refer to a group of disorders characterised by predominantly late onset and sometimes persistent involuntary movements, which are caused by exposure to dopamine receptor blocking agents. Therefore, there are several phenomenological distinct types of abnormal movements in TS, not limited to classical tardive dyskinesia (TD).
- ▶ Recognition of different forms of TS is critically important since the differential diagnosis as well as management can be vastly different.
- ▶ Potential red flags to alternative diagnosis other than TD include a rapidly deteriorating course, constant unilateral manifestation, the presence of additional neurological signs, and the appearance of other physical symptoms or signs, such as jaundice, fever, skin rash.
- ▶ Management of TS is complex and needs to be individualised. However, discontinuation or reduction of neuroleptic dosages should be considered first, followed by suppressive or specific therapies if symptoms are severe.

Current research questions

- ▶ What are the preventive strategies in patients who are exposed to DRBAs and are considered to be at risk of developing tardive syndromes?
- ▶ What are the incidences of extrapyramidal syndromes in typical and atypical neuroleptics?
- ▶ Why do patients who are exposed to DRBAs manifest different types of abnormal movements? For example, some may experience classical tardive dyskinesia while others suffer from dystonia.
- ▶ Are there additional risk factors of tardive syndromes that we are not aware of?
- ▶ Which suppressive agents are considered most effective in reducing the severity of dyskinesia and dystonia?

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stereotypy, dystonia, akathisia, tics, myoclonus, tremor, and possibly parkinsonism. Many risk factors for TS have been identified, including older age, female gender, African American ethnicity, typical neuroleptics of higher dosages, longer duration of neuroleptics exposure, and pre-existing mood or psychiatric disorders. With the increasing use of neuroleptics by multiple medical specialists, TD will continue to pose a clinical dilemma and remain a major public health issue in psychiatry. Further understanding of the pathophysiology of TD will lead to further advances in discovering newer agents with lower propensity to cause TD and effective therapeutic agents to reduce symptoms. Lastly, physicians should always remind themselves of the adage ‘primum non nocere’ (first, do not harm) when prescribing any medicine.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)**1. Which of the following are useful clinical signs in differentiating patients with classical tardive dyskinesia from Huntington's disease?**

- A. Limited attention
- B. Poor frontal lobe function
- C. Slow saccadic eye movement
- D. Impersistence of tongue protrusion
- E. Piano playing movements

2. Suppressiv agents for tardive dyskinesia should be considered only if:

- A. Symptoms predominantly involve axial structures
- B. The severity impairs activities of daily livings as well as increased care giver burden
- C. The discontinuation of neuroleptics is not possible
- D. Replacement of typical with atypical neuroleptics is not possible
- E. There is a high likelihood that the tardive syndromes will be permanently abolished

3. The best management of patients with tardive syndromes is:

- A. Prevention
- B. To use the minimal dose as patient can tolerate
- C. To combine the use of neuroleptics with anticholinergics
- D. To prescribe neuroleptics on an intermittent basis even though patients require continuous therapy for suppression of psychiatric symptoms
- E. To inform possible risks and benefits of neuroleptics to patients before its introduction

4. Chemodervation with botulinum toxin may be considered in patients with tardive syndrome who experience:

- A. Focal dystonia
- B. Axial generalised dystonia
- C. Retrocollis
- D. Medically intractable generalised dystonia
- E. Tongue dystonia with severe dysphagia

5. Clozapine should be used with extreme caution because of:

- A. Severe drowsiness
- B. Its propensity to cause extrapyramidal syndrome
- C. Its unique adverse event of agranulocytosis
- D. Its interaction with other neuroleptics resulting in neuroleptic malignant syndrome
- E. The risk of worsening dystonia

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ANSWERS

1. A (F); B (T); C (T); D (T); E (F)
2. A (F); B (T); C (F); D (F); E (F)
3. A (T); B (F); C (F); D (F); E (T)
4. A (T); B (F); C (T); D (F); E (F)
5. A (F); B (F); C (T); D (F); E (F)



Spectrum of tardive syndromes: clinical recognition and management

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