An Update on the Diagnosis and Management of Tic Disorders

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Abstract

Tic disorders (TDs) are a group of common neuropsychiatric disorders of childhood and adolescence. TDs may impact the physical, emotional, and social well-being of the affected person. In this review, we present an update on the clinical manifestations, pathophysiology, diagnosis, and treatment of TDs. We searched the PubMed database for articles on tics and Tourette syndrome. More than 400 articles were reviewed, of which 141 are included in this review. TDs are more prevalent in children than in adults and in males than in females. It may result from a complex interaction between various genetic, environmental, and immunological factors. Dysregulation in the cortico-striato-pallido-thalamo-cortical network is the most plausible pathophysiology resulting in tics. TD is a clinical diagnosis based on clinical features and findings on neurological examination, especially the identification of tic phenomenology. In addition to tics, TD patients may have sensory features, including premonitory urge; enhanced and persistent sensitivity to non-noxious external or internal stimuli; and behavioral manifestations, including attention deficit hyperactivity disorders, obsessive-compulsive disorders, and autism spectrum disorders. Clinical findings of hyperkinetic movements that usually mimic tics have been compared and contrasted with those of TD. Patients with TD may not require specific treatment if tics are not distressing. Psychoeducation and supportive therapy can help reduce tics when combined with medication. Dispelling myths and promoting acceptance are important to improve patient outcomes. Using European, Canadian, and American guidelines, the treatment of TD, including behavioral therapy, medical therapy, and emerging/experimental therapy, has been discussed.

Keywords: Attention deficit hyperactivity disorder, cortico-striato-pallido-thalamo-cortical network, tetrabenazine, tic disorders, Tourette syndrome

What are Tic Disorders?

Tic disorders (TDs) are a group of common neuropsychiatric disorders of childhood and adolescence, characterized by sudden, rapid, recurrent, stereotyped, non-rhythmic, non-goal-directed movements, or vocalizations that can be voluntarily suppressed to a variable extent and are preceded by an urge.[1,2] In addition to the premonitory urge and voluntary suppressibility, variability over time, fluctuating nature, distractibility, and suggestibility are commonly observed in TD.[1,2] After ruling out TD related to drugs, Huntington's disease, post-viral encephalitis, and other secondary causes, primary TD can be grouped into provisional TD, chronic motor or vocal TD, or Tourette's syndrome (TS), provided the onset of tics is below 18 years of age.[3] Whereas provisional TD includes tics with a duration of less than 1 year, those with a duration of more than 1 year are grouped under chronic motor or vocal TD. TS is diagnosed in the presence of multiple motor tics along with at least one vocal tic lasting for more than 1 year.[3]

Usually, TDs are benign but can result in social embarrassment, physical discomfort, emotional impairment, or employment issues, thereby affecting daily activities, including school performance. Along with motor problems, patients with TD manifest several non-motor features. They are often associated with attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, impulse control disorders, and sleep disturbances, which may further enhance the suffering of these patients.[4] Therefore, the management of TD requires a multidisciplinary approach involving neurologists, psychiatrists, psychologists, and behavioral therapists. In this review, we present an update on the clinical manifestations, pathophysiology, and management of TD. Methods for developing this review are detailed in Box 1.

History of TD and Tourette Syndrome

Although Sprenger and Kraemer reported motor and phonic tics in a priest in 1489,[5] it was in 1825 that Jean-Marc Gaspard Itard reported a case of a noblewoman with involuntary movements and vocalizations including echolalia and coprolalia.[5] Subsequently, in 1885, Dr. Jean-Martin Charcot labeled the same disease "de la Tourette syndrome," based on the work of his resident, Dr. Georges Gilles de la Tourette, who reported

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Box 1: Search strategy

We identified articles through MEDLINE/PUBMED literature searches by using the search terms "Tic disorders," OR "Tourette syndrome" AND "epidemiology," "pathology," "diagnosis," "treatment," AND "prognosis" from 1980 to present. We used European, Canadian, and American national guidelines to construct this review, in addition to published systematic reviews. Where possible, we selected the most recent articles and the articles with the most robust level of evidence (such as randomized controlled trials and meta-analyses). We reviewed more than 400 citations, of which 141 are included in this review.

nine patients with TD.[5] They described childhood onset, the presence of motor and vocal tics, and the fluctuating nature of the disease as well as its tendency to develop chronicity. Their description also included behavioral abnormalities, including ADHD and OCD.[5] Because many of the clinical features of TD were also observed in psychiatric disorders, including hysteria, many physicians considered it a primarily psychiatric disorder.[5,6] Work by subsequent researchers and movement disorder clinicians established TD as a primarily neurological disorder. In his initial description, Dr. Georges Gilles de la Tourette suspected a neurodegenerative basis for TDs, which was later rejected.[6]

How Common are Tic Disorders?

TDs are more prevalent in children than in adults and in males than in females (M: F = 2.4:1).[3,7] Assessing the prevalence of TD is challenging due to fluctuating symptoms, differing presentations, limited awareness, and under-diagnosis of mild TD cases. Thus, larger population-based observational studies are needed to accurately determine TD's prevalence.

A meta-analysis reported provisional TD being the most common type of TD in children, with a prevalence of 2.99% (1.60%–5.61%). The prevalence of TS was 0.77% (0.39%–1.51%), four times higher in boys (1.06%) as compared to girls (0.25%). The prevalence of TS in adults was 0.05% (0.03%–0.08%).[7] In a subgroup analysis including school-based studies, the prevalence of chronic vocal tics, chronic motor tics, and TD not otherwise specified was 0.69% (0.49%–0.97%), 1.65% (0.64%–4.28%), and 0.79% (0.28%–2.21%), respectively.[7] In DSM-5, the terminology "tic disorder not otherwise specified" has been substituted with "other specified tic disorder" or "unspecified tic disorder."[3] A separate study evaluated the community samples and reported provisional TD in 11%–20% of school-going children, TS in 0.26%–3.8%, chronic TD in 0.5%–3%, and chronic vocal TD in up to 0.9% of children.[8] An Indian study reported the prevalence rate of TD being 0.04% and a male: female ratio of 4.5:1.[9]

Who Develops TD?

A patient's susceptibility to develop TD may result from a complex interaction between various genetic, environmental, and immunological factors [Table 1].[10-14] TD and TS are polygenic hereditary disorders, with multiple genes being implicated to date. A Swedish population-based cohort study estimated the heritability of TS to be between 0.58 and 0.77.[15] Whereas the concordance rate for TD is 77%–94% in monozygotic and 23% in dizygotic twins, the concordance rate for TS is 53%–56% and 8% in mono- and dizygotic twins, respectively.[16,17]

Table 1: Risk factors for tic disorders and Tourette syndrome

Non-modifiable risk factors[10]	Modifiable risk factors
• Age (Childhood to adolescence)[3,7]	• Low socioeconomic status[18]
• Sex (M:F=2.4:1)[3,7]	• Pre- and perinatal factors
• Positive family history/Genetic mutations (*CNTNAP2* gene, *NLGN4* gene, *SLITRK1* gene, *HDC* gene, *IMMP2L* gene, *ASH1L* gene)[10]	- Maternal stress during pregnancy[19]
	- Nausea and vomiting in the first trimester of pregnancy[19]
	- Low birth-weight*[20]
	- Gestational age*[20,21]
	- Prenatal maternal smoking*[21]
	- Prenatal maternal alcohol and cannabis use[22]
	- Parity[22]
	- Inadequate weight gain during pregnancy[22]
	- Parental (especially maternal) psychiatric disorders[23]
	- Nuclear family with poor parental relationship[24]
	• Immunological
	- PANDAS and PANS[14]
	- increased inflammatory lymphocytes, proinflammatory cytokines, microglial activation, and dysregulated immunoglobulin synthesis, as well as decreased regulatory T-lymphocytes[11,12]
	- a 30% higher incidence of TS in male offspring of mothers with autoimmune diseases[13]

*Inconclusive results in studies. ASH1L gene: ASH1-like histone lysine methyl transferase gene; CNTNAP2 gene: contactin-associated protein 2 gene; HDC gene: histidine decarboxylase gene; IMMP2L gene: inner mitochondrial membrane peptidase subunit 2 gene; M: F=male: female; NLGN4 gene: neuroligin 4 X-linked gene; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS: pediatric acute neuropsychiatric syndromes; SLITRK1 gene: SLIT and NTRK-like family member 1 gene; TD: tic disorders; TS: Tourette syndrome

What is the Pathophysiology of TD?

Dysregulation in the cortico-striato-pallido-thalamo-cortical (CSPTC) network is the most plausible pathophysiology resulting in TD.[25] Evidence from several studies supports CSPTC network dysfunction in TD.[26] Post-mortem studies have reported a reduction in inhibitory neurons in the striatum,[27] along with a drop in globus pallidus externus (GPe), and an increase in the globus pallidum internus (GPi) neurons among TS patients.[28] Brain imaging studies have revealed smaller striatum and globus pallidum volumes in TS cases.[29,30] Recent studies have also investigated changes in functional connectivity and brain anatomy in TS patients,[31] including a study that found a link between hippocampal volume and tic severity.[32] In addition, another study found altered connectivity between the cerebellum, frontal, cingulate, and sensorimotor cortices, suggesting

dysfunction in cortico-basal ganglia-cerebellar networks in TS.[33] Lastly, a resting-state functional MRI (fMRI) study demonstrated age-specific connectivity changes in TD patients.[34]

White-matter structural connectivity changes have also been observed in TD patients, including lower connections between the caudate nucleus and anterior-dorsolateral-frontal cortex.[35] In addition, connections between the supplementary motor area (SMA) and basal ganglia (BG) were inversely correlated with tic severity, whereas connections between the motor cortex and striatum/thalamus were positively correlated with tic severity.[36-38] Another study found increased basal ganglia-cortical and thalamocortical connectivity but reduced connections within the cortico-cerebellar network and between certain cortical regions.[39] Genetic alterations in the *SLITRK1* gene have also been identified in TD patients.[40,41] *SLITRK1*, also known as the *SLIT* and *NTRK*-like family gene, encodes a vital single-pass transmembrane protein involved in neuronal development, impacting neurite growth and synapse formation. Its regulated expression influences the maturation of corticostriatal-thalamocortical circuits. Thus, altered *SLITRK1* expression may disrupt neural circuits in the basal ganglia and cortex, leading to imbalances in dopamine and glutamate neurotransmitter systems, thereby contributing to motor symptoms in TS and TD; however, exact mechanisms remain unclear.[41]

The CSPTC network that governs TD can be divided into two categories: expression networks and control networks.[42] Expression networks mediate TD symptoms, comorbid symptoms, and additional brain state changes, leading to naturally occurring and experimentally induced behaviors.[42] The sensorimotor cortex, putamen, GP, substantia nigra, subthalamic nucleus, thalamus, and ventral tegmental area correlate with the expression and severity of spontaneous tics.[43,44] Studies have reported activation of pre- and primary motor cortices and limbic and sensory areas before tic onset, followed by aberrant enhanced motor activity within and outside the CSPTC circuit during tic expression.[45-50] Experiments with rats have suggested that the involved body part in tics may be related to the site of the striatum involved. Involvement of the anterior or posterior part of the striatum can result in forelimb or hind limb tics, respectively.[51]

Premonitory urges, a sensation felt before tic expression, are not well understood. They may have a causal relationship with tics or be an independent symptom. Multiple neuroimaging studies, including both fMRI and PET, highlight the role of sensory and limbic regions in generating premonitory urges.[45,52,53] For instance, in an fMRI study by Neuner *et al*.,[45] activation was observed in various motor and sensory regions such as pre- and primary motor cortices, sensory areas (parietal operculum), putamen, and limbic and para-limbic areas (anterior cingulate, insula, and amygdala) before tics emerged. Similarly, a PET study demonstrated links between tic occurrence, premotor and primary motor cortex activity, and correlated striatal activity.[53] Functional connectivity of the right dorsal anterior insula and the left dorsomedial prefrontal cortex had been reported to have a positive correlation with urge severity.[54] Associated disorders, including ADHD and OCD, have also been linked to dysregulation of CSPTC circuits.[42] Local disinhibition of the central associative-limbic part of the striatum and nucleus accumbens leads to ADHD, whereas central and ventral parts of the anterior striatum result in OCD.[55-57]

Control networks govern voluntary tic suppression and behavioral states such as stress and arousal affecting symptom expression.[42] Frontal cortex involvement in modulating BG activity is believed to play a role in tic suppression.[58] An fMRI study backed this by indicating that frontal cortex activity relates to heightened caudate nucleus activity, which in turn links to lowered activity in the GP, putamen, and thalamus.[58] MR spectroscopy studies suggest that tic suppression may result from local tonic inhibition via extracellular GABA within SMA.[59] Ganos *et al*.[60] reported differences in the abilities of various body parts to suppress tics, with tic inhibition being inversely related to their proportion of somatotopic representation in the brain.

How Do We Diagnose TD?

TD is a clinical diagnosis. It is based on clinical features and findings on neurological examination, especially the identification of tic phenomenology.

Age of onset and sex differences

TD usually begins in childhood between 3 and 10 years of age, with peak severity at 9–11 years.[61] Symptoms tend to decrease with age. Studies from different parts of the world have reported TD and TS to be 2–10 times more common in males as compared to females.[62,63] The sex difference in TD may be related to the possible neuroendocrine involvement, including that of the hypothalamo-pituitary-gonadal axis.[64]

Clinical manifestation of TD

Motor features

The defining feature of TD is the presence of tics. It can be simple or complex in nature. Simple tics involve a single muscle group or body part, such as eye blinking, facial grimacing, shrugging, sniffing, grunting, coughing, and throat clearing.[3,4] In contrast, complex tics engage multiple muscle groups and can involve body twisting, repeating actions or words from others (echopraxia or echolalia), repeating one's own actions or words (palipraxia or palilalia), or making socially inappropriate gestures or utterances (copropraxia or coprolalia).[3,4] Vocal tics are tics arising from repetitive movements of nasal, pharyngeal, laryngeal, or respiratory muscles, leading to the production of sound.[65] Simple motor tics are most commonly seen at onset, with eye tics being reported in more than 90% of TS patients.[66] As the disease progresses, additional tics appear in a rostrocaudal manner, with craniofacial tics being common followed by truncal

tics and then involving the limbs. Vocal tics usually appear later.[4] Tics can be briefly suppressed voluntarily, followed by a rebound urge.[4]

Based on phenomenology, motor tics can be grouped into "clonic tics," that is, sudden, rapid, brief jerky movements such as eye blinking and head jerking; "tonic tics," that is, isometric muscle contractions such as truncal and limb muscle tightness; "dystonic tics," that is, briefly sustained abnormal posture such as dystonic neck posturing; and "blocking tics," that is, a brief pause while speaking or moving with normal sensorium.[67,68]

Clinical course of tics

Tics usually occur as spells, and their frequency, phenomenology, and severity may fluctuate over time and can be precipitated by emotional factors.[69,70] Traditionally, it was believed that recently started tics would go away within a year, but recent studies reported that 90% of affected children are left with tics even after a year.[71] Better control of tics in situations with immediate reward was linked with less severe tics.[72] The fluctuation of tics and their severity over time has been widely studied, and the duration of tic occurrence has been reported to manifest in clusters, with intervening periods either being tic-free or having tics of significantly lower severity.[65] A fractal pattern of time distribution with alternating periods of tics and no/less severe tics has been hypothesized.[73] The severity of tics usually reduces during the second decade, and remission has been reported in 17%–65% of patients in various follow-up studies of TD.[65,74] Children with severe tics, reduced caudate volume, and visuomotor skill deficiency are factors associated with clinically bothersome tics in adulthood.[74,75] Another study involving children with TS at a Danish clinic reported that the severity of tics, ADHD, and OCD in early adulthood was correlated with the severity scores of these conditions later in life.[76]

Non-motor features

Sensory features

Tics are associated with sensory symptoms:

i) Premonitory urge: It is the unpleasant sensation appearing before tic onset, which gets relieved immediately following the tic movement. The premonitory urge sensation can be either somatic, such as itch, or psychosomatic, such as a feeling of restlessness or inner tension.[65] The body location of premonitory urge usually coincides with that of motor tics. Although a child may not report the premonitory urge, its awareness increases with age.[65]

ii) Enhanced and persistent sensitivity to non-noxious external or internal stimuli:[65] TD patients manifest an enhanced sensitivity to external stimuli in visual, tactile, auditory, and olfactory domains.[77]

iii) Voluntary suppressibility: TD patients exhibit voluntary suppressibility of their tics to a variable extent. Increased voluntary suppression may enhance the severity of the premonitory urge.[78]

Behavioral features

TDs have several associated behavioral manifestations.[4,65,69,79] More than three-fourths of TS and more than half of TD cases have at least one coexisting behavioral problem such as ADHD, OCD, autism spectrum disorders, anxiety, depression, rage, impulse control disorders (e.g. self-harm or self-injurious behavior (SHB or SIB)), sleep disorders, or conduct disorders.[79-83] Among these disorders, OCD and ADHD are the most common, affecting 11%–80% and 20%–90% of TD and TS patients, respectively.[79,80,84] Whereas non-tic OCD manifests as an obsession for cleanliness, tic-related obsessive-compulsive symptoms include obsession to maintain symmetry, counting, or doing a socially inappropriate behavior.[65]

The nature of behavioral features varies by gender, with boys more likely to experience rage attacks, conduct disorder, ADHD, and learning issues, and girls more likely to experience OCD and SHB or SIB.[74-76] Behavioral features may make the diagnosis, treatment, and prognosis of TD more challenging. It also interferes with children's ability to learn, adapt socially, and develop their personalities and psychological qualities.[74,75]

Clinical diagnostic criteria for TD

The presence of motor and/or vocal tics, duration of illness, age at tic onset, and absence of secondary causes are important to diagnose different types of TD as per DSM-V criteria [Table 2].[3] TDs are hierarchical in order (i.e., TS, followed by CTD, followed by provisional TD, followed by the other specified and unspecified TDs) such that once a TD at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made.

Which Other Involuntary Movements can Mimic Tics?

Tics should be differentiated from other neurological conditions such as dystonia, chorea, athetosis, hamiballismus, seizures, myoclonus, tremor, and functional tics [Table 3].[85] Most TD cases are primary and idiopathic, with no direct cause or specific biomarkers. Neurologic examination will be typically unremarkable in such patients. However, in children with ADHD, soft neurologic signs such as poor fine-motor coordination and restlessness may be present.[86]

What Tests or Investigations are Available to Help Diagnose TD?

Primary TD is a clinical diagnosis, and electroencephalogram, neuroimaging, psychological evaluation, and lab tests are mainly used to diagnose comorbidities or exclude other disorders, including secondary causes of TD [Table 4].[67,85,87-91] Secondary TD should be suspected if tics appear suddenly in older children, worsen rapidly, or are accompanied by other neurological symptoms. In such cases, screening tests such as blood tests and neuroimaging should be performed to determine the cause. Early identification and treatment

Table 2: Diagnostic classification of tic disorders according to DSM-5*[3]

Tourette Syndrome (TS)	Persistent (Chronic) Motor or Vocal Tic Disorder	Provisional Tic Disorder
• Presence of two or more motor and at least one vocal tics; these may manifest at different times during the illness. • Tics may fluctuate in frequency but must persist for ≥1 year since onset • Onset before 18 years of age • Symptoms not related to any drug/substance intake or another medical condition such as Huntington's disease, or post-viral encephalitis	• Presence of one or more motor or vocal tics, but not both motor and vocal • Tics may fluctuate in frequency but must persist for ≥1 year since onset • Onset before 18 years of age • Symptoms not related to any drug/substance intake or another medical condition such as Huntington's disease, or post-viral encephalitis • Never met the criteria for TS	• Presence of one or more motor and/or vocal tics • Tics present for <1 year since onset • Onset before 18 years of age • Symptoms not related to any drug/substance intake or another medical condition such as Huntington's disease, or post-viral encephalitis • Never met the criteria for TS or persistent (chronic) motor or vocal tic disorder

*In addition to the above three classes, patients may have characteristic symptoms of tic disorders causing functional impairment but do not meet complete criteria for tic disorders or any other neurodevelopmental disorder. The reason for not meeting the criteria may be specified ("Other specified tic disorders") or not available ("Unspecified tic disorders"). DSM-V=Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition, e.g.,=example, TS: Tourette syndrome

of secondary TD is important to prevent potential long-term consequences.

How is TD Treated?

Patients with TD usually do not need specific treatment if tics are not distressing. Supportive care, education for patients and their families, and reassurance are sufficient. These include discussing the natural course, potential triggers, and therapy options. Psychoeducation and supportive therapy can help reduce tics when combined with medication. Dispelling myths and promoting acceptance are important to improve patient outcomes [Box 2].[5,67,92-97]

TD management requires a multidisciplinary approach. To assess the severity of TD and monitor treatment effectiveness, various objective standardized tools have been created such as the Yale Global Tic Severity Scale (YGTSS),[98] the Gilles de la Tourette Syndrome Health-Related Quality of Life Scale (GTS-QOL),[99] and the Premonitory Urge for Tics Scale (PUTS).[100] The commonly used scale, YGTSS, assesses motor/vocal tic symptoms, tic severity, and functional impairments through a semi-structured clinical interview. A total score of less than 25 is considered mild, 25–50 is moderate, and 51–100 is severe.[98]

The management of TD has been addressed by various consensus guidelines, including European Clinical Guidelines for TS and TD, Canadian guidelines for the evidence-based treatment of TD, and the most recent American Academy of Neurology Practice Guideline Recommendations for Treatment of TS and Chronic TD.[101-107] These guidelines suggest that patients with mild TD can benefit from medical education, psychological support, and regular follow-ups, whereas moderate-to-severe TD should be treated with a combination of behavioral therapy (BT) and pharmacological and surgical treatment, along with medical education and psychological support. Thus, three principal treatment options for TD include BT, medical treatment, and surgical interventions.[101-107]

Behavioral therapy

BT is the recommended first-line treatment for TD due to its lack of side effects.[101-107] This includes exposure and response prevention (ERP), habit reversal therapy (HRT), and comprehensive behavioral intervention for tics (CBIT). ERP involves exposing patients to the unpleasant sensation associated with premonitory urge and simultaneously teaching habituation to urge and tic prevention.[108] HRT, one of the earliest forms of BT, involves training in awareness, competing response, and habit control.[109] It has evolved into CBIT, which includes psychoeducation, relaxation training, rewards, and functional interventions.[108] Studies have shown the effectiveness of these therapies in reducing tics, with benefits persisting in 74% of participants even a year later.[110] A recent

Box 2: Myths and truths about tics[5,67,92-97]

Myth (s)	Truth (s)
TD/TS is caused by stress or neglect	TD/TS has a strong genetic basis Stress may be a risk factor, but not the sole causative factor
Tics may become a continuous disorder	Tics mostly remain an intermittent disorder
Tics are found in childhood only and do not appear in adulthood.	Majority (up to 80%) of children with tics may have persistent tics in adulthood or have recurrence of tics in adulthood after initial remission in childhood[67,94]
Adulthood tics are mostly due to secondary causes	Most common cause of adulthood tics are recurrence of childhood tics[67]
Tics are absent during sleep	Tics may persist during and have been shown to be present during all stages of sleep[95]
Tic disorder is a motor disorder	Tic disorder has significant sensory and behavioral manifestations
Motor problems remain the major troubling problem for patients with tic disorder	A significant proportion of TD patients are troubled primarily by behavioral symptoms including ADHD and OCD.
All patients with tics need to be treated.	Nearly 20% of patients with TD do not require treatment. Education of patients, caregivers, and teachers along with reassurance may suffice[5,96,97]
Pharmacological therapy is the only treatment to improve tics	A significant proportion of tics respond to behavioral therapy

ADHD: attention deficit hyperkinetic disorder;
OCD: obsessive-compulsive disorder; TD: tic disorders; TS: Tourette syndrome

Table 3: Common differential diagnoses of tic disorder[85]

Hyperkinetic movements	Characteristic features	
Tics	• Brief, rapid, jerky, non-rhythmic, semi-voluntary; present at rest and continues with action • Paroxysmal, multi-focal, stereotypic movements or vocalizations • Preceded by premonitory urge and voluntarily suppressible • Severe tics may persist during sleep • Onset in childhood (below 10 years of age) and more common in males • Cranio-caudal progression	
	Characteristic features	
	Similarities with tics	**Differences from tics**
Akathisia	• Premonitory uncomfortable feeling or a sensory urge, relieved with motor acts • Paroxysmal movements • Movements are usually stereotyped, non-rhythmic, and paroxysmal • May vocalize including moaning • May affect an isolated body part • Transient voluntary suppressibility	• Patient unable to sit still • Rate of movement slower than tics • Usually complex movements, e.g., truncal rocking, touching head, walking back and forth in the room • Akathitic moaning may be continual* • Akathisia associated with tardive dyskinesia can be rhythmic
Athetosis	• Non-rhythmic • Present at rest and continues during action • Decreased during sleep	• Slow, writhing, continuous movements • Usually involves hands, fingers, toes and feet • Lack of premonitory urge and voluntary suppressibility • Overflow (athetosis in a body part can start following voluntary use of another body part)
Absence seizures with eyelid myoclonia	• Sudden, brief involuntary movements including eye blinking, lip smacking • Occurs in childhood	• Behavioral arrest; motionless stare • Automatism like eyelid blinking, lip smacking • Lack of premonitory urge and voluntary suppressibility
Ballism	• Sudden; non-rhythmic • Decreased during sleep • Partial voluntary suppressibility	• Large-amplitude, flinging, continual*, involuntary movements of proximal limbs • Rate of movement slower than tics • Usually unilateral, known as hemi-ballism • Lack of premonitory urge
Chorea	• Sudden, brief, non-rhythmic, ill-sustained involuntary movements • Decreased during sleep • Partial voluntary suppressibility • Occasional involuntary phonation e.g., sniffing and groaning in Huntington's disease and neuro-acanthocytosis • Present at rest and continues during action	• Random movements (uncertain timing, direction, and location) and flow from one body part to another • Rate of movement slower than tics • Non-stereotyped, continual* movements • Parakinesia – the involuntary movements are included in quasi-purposeful movements • Motor impersistence • Lack of premonitory urge
Dystonia	• Repetitive, non-rhythmic • Occasional tics have sustained muscle contraction (dystonic tics) • Occasional vocalization including moaning in oromandibular dystonia • Decreased during sleep • Some dystonia present at rest and continues during action • Partial voluntary suppressibility	• Sustained muscle contraction causing continuous posturing and/or tremor • Patterned movements • Rate of movement slower than tics • More forceful than tics • Lack of premonitory urge • Occasionally suppressible by sensory tricks • Severe dystonia may persist during sleep • Some dystonia present only during action or while doing a specific task
Myoclonus	• Sudden, brief, jerky, ill-sustained movements • Usually decreased during sleep • Present at rest and continues during action	• Continual* or continuous • Ocular and spinal myoclonus may persist during sleep • May be focal, multifocal, or generalized • Lack of premonitory urge and voluntary suppressibility
Stereotypies	• Non-goal-directed, non-rhythmic, repetitive movement or vocalization • Some stereotypies may be paroxysmal • Decreased during sleep • More voluntary suppressibility than tics	• Voluntary, continual*, patterned • May be rhythmic • Lack of premonitory urge • Distractible

Contd...

Table 3: Contd...

	Characteristic features	
	Similarities with tics	**Differences from tics**
Tremor	• May be precipitated by rest or action • Decreased during sleep • Partial voluntary suppressibility	• Rhythmic, regular, continuous, patterned • Rate of movement slower than tics • Lack of premonitory urge • Some tremors present only during action or while doing a specific task
Functional tics	• Sudden, brief, non-rhythmic, ill-sustained movements • Decreased during sleep	• Adulthood onset; more common in young females • Precipitated by trauma • Lack of premonitory urge and suppressibility • Other functional neurological symptoms • Arms and trunk commonly involved

*Continual=occurring repeatedly; Continuous=occurring without stopping

Table 4: Secondary causes of tics[67,85,87-91]

Group	Disorders
Inherited disorders	• Huntington disease • Primary dystonia • Neuroacanthocytosis • Neurodegeneration with brain iron accumulation • Tuberous sclerosis • Wilson disease
Chromosomal disorders	• Down syndrome • Kleinfelter syndrome • XYY karyotype • Fragile X syndrome • Triple X and 9p mosaicism • Partial trisomy 16 • 9p monosomy • Beckwith–Wiedemann syndrome
Developmental disorders	• Static encephalopathy • Intellectual disability syndromes • Autistic spectrum disorders
Infections	• Encephalitis • Creutzfeldt–Jakob disease • Neurosyphilis • Sydenham disease • Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) • Coronavirus disease-19[90]
Drugs & Toxins	• Amphetamines • Carbon monoxide • Cocaine • Antiepileptics – Carbamazepine, Lamotrigine, Phenytoin, phenobarbital, levetiracetam, lacosamide[91] • Levodopa • Methylphenidate • Antipsychotics, and other dopamine receptor–blocking drugs
Others	• Head trauma • Stroke • Schizophrenia

meta-analysis reported that both CBIT and antipsychotics had comparable benefits in Tourette syndrome.[111] Group behavioral therapies can be cost-effective and provide patients the opportunity to interact and support each other. An open-label controlled trial of combined HRT and ERP in adults with TS showed a significant reduction in tic severity in 67% of participants, with no significant difference between individual and group therapies.[112]

Medical therapy

Medical therapy for TD should only be considered if BT fails or is not accessible, or for severe, violent tics.[101-107] The goal is to reduce tic frequency and severity to a manageable level, considering factors such as efficacy, safety, cost, and convenience, as well as the severity of tics and comorbidities.[107] Four groups of drugs are available based on TD's neurotransmitter dysfunctions:[107]

1. **Anti-dopaminergic agents:** Presynaptic dopamine depletion by vesicular monoamine transporter-2 (VMAT-2) inhibitors (tetrabenazine, deutetrabenazine, and valbenazine), D2 receptor blockers (haloperidol, pimozide, aripiprazole, risperidone, fluphenazine, and tiapride), dopamine and serotonin receptor antagonist (lurasidone), and D1 receptor antagonist (ecopipam)
2. **Noradrenergic agents:** Presynaptic alpha-2 receptor agonist (clonidine and guanfacine) and noradrenalin reuptake inhibitor (bupropion)
3. **GABAergic drugs**: Antiepileptics (topiramate, benzodiazepines, levetiracetam) and baclofen
4. **Cannabinoids:** Tetrahydrocannabinol (THC), cannabidiol, and dronabinol

Table 5 lists the therapeutic dose, side effects, and usage recommendations of drugs that can be used in the management of TD. Despite numerous drug options, only three are FDA-approved for treating TS: haloperidol for children over 3 years, pimozide for those over 12, and aripiprazole for ages 6–18.[113]

Various alternative treatments, including nutritional supplements (e.g. calcium, magnesium, coenzyme Q10, fish oil, gastrodin, and vitamins B, C, D, and E), chiropractic, meditation, acupuncture, hypnosis, homeopathy, and biofeedback, have also been reported to have success in reducing tics.[10]

Table 5: Commonly used medications for management of Tic disorders

Class of drug	Name of drug	Mechanism of action	Starting dose	Maximum dose	Side effects	Level of evidence[107]
			Adrenergic agents			
Alpha adrenergic agonist	Clonidine[114-117]	Reduce central noradrenergic activity by stimulating α-2 receptors which are responsible for the regulation of noradrenaline by negative feedback	0.025–0.05 mg/day	0.3–0.4 mg/day (divide up to 4 times a day)	Sedation, bradycardia, hypotension, light-headedness, tiredness, irritability, dry mouth	Level B
	Guanfacine[118]		0.5–1.0 mg/day	1.0–4.0 mg/day	Fatigue, QTc prolongation, drowsiness, dry mouth, headache, irritability	Level B
			GABAergic agents			
Anticonvulsant Agents	Topiramate[119]	GABAergic activity enhancer and kainate/AMPA Glutamate receptor blocker	25 mg/day	50–200 mg/day	Headache, diarrhea, abdominal pain, drowsiness, cognitive slowing, kidney stones, weight loss	Level B
	Levetiracetam[120]	GABAergic activity enhancer	20 mg/kg/day (250 mg/d)	60 mg/kg/day (2000 mg/d)	Irritability and somnolence	Limited Data available
	Clonazepam[121,122]	GABAergic activity enhancer by acting on benzodiazepine receptors	0.25–0.5 mg/day	2 mg/day in 2 divided doses	Sedation and drowsiness	Limited data available
Anti-spasticity Agent	Baclofen[123]	GABA B receptor agonist	10 mg/day (weekly increase by 10 mg)	80 mg/day	Sedation and drowsiness	Limited data available
			Anti-dopaminergic agents			
Typical neuroleptics/ anti-psychotic medications	Haloperidol*[122,124]	D2 receptor antagonist	0.5 mg/day (weekly increase by 0.25–0.5 mg)	2–10 mg/day	Extrapyramidal side effects Lethargy Increased appetite Hepatic insufficiency	Level C
	Pimozide*[125,126]	D2 receptor antagonist	0.05 mg/kg/day	0.2 mg/kg/day (not exceeding 10 mg/day)	Arrhythmia (QT prolongation), hypotension	Level C
Atypical neuroleptics/ anti-psychotic medications	Aripiprazole*[127,128]	Partial agonist of dopaminergic (D2, D3, and D4 receptor) and serotonergic (5-HT1A and 5-HT2C) receptors	1.25–2.5 mg/day	20 mg/day divided into two doses	Sedation, fatigue, extrapyramidal side effects (tardive dyskinesia)	Level C Safer cardiovascular profile[10]
	Risperidone[129]	D2 and 5-HT2 receptor antagonist (5-HT2 receptor antagonist at low doses and D2 antagonist at high doses)	0.25 mg/day	1.0–4.0 mg/day	Sedation, extrapyramidal symptoms (e.g., acute dystonic reactions, parkinsonism, akathisia), orthostatic hypotension, hyperprolactinemia, gynecomastia, weight gain	Level C
	Ziprasidone[130]	D2 and 5-HT2 receptor antagonist	5–10 mg/day	40 mg/day	Dose-dependent QTc interval prolongation	Level C
	Fluphenazine[131]	D1, D2 receptor antagonist	0.5 mg/day	12 mg/day	Drowsiness, weight gain, akathisia, acute dystonia, depression (Lesser side effects compared to haloperidol)	Limited data available

Contd...

Table 5: Contd...

Class of drug	Name of drug	Mechanism of action	Starting dose	Maximum dose	Side effects	Level of evidence[107]
Dopamine depleters	Tetrabenazine[132]	Deplete presynaptic dopamine by blocking the VMAT2	12.5 mg/day	75 mg/day in 3 divided doses	Drowsiness, depression, akathisia, parkinsonism	Limited data available Useful in refractory TD cases[97]
	Deutetrabenazine[132,133]	Deplete presynaptic dopamine by blocking the VMAT2	6 mg/day	36 mg/day in 2 divided doses	Fatigue, headache, irritability, somnolence, hyperhidrosis, diarrhea, nasopharyngitis	Limited data available Useful in refractory TD cases[97]
	Valbenazine[132]	Deplete presynaptic dopamine by blocking the VMAT2	40 mg/day	80 mg/day	Somnolence, anticholinergic effects, balance disorders, headache, akathisia, vomiting, arthralgia	Limited data available Useful in refractory TD cases[97]
Dopamine receptor antagonist	Ecopipam[134]	D1/D5 receptor antagonist	12.5–25 mg/day	50 mg/day for weight <34 kg; 100 mg/day for weight >34 kg	Headache, insomnia, fatigue, somnolence Overall better side effect profile	Limited data available Useful in refractory TD cases[97]

*US FDA approved[131]. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, D: day, D-1,2,3,4,5: Dopamine receptors 1,2,3,4,5, GABA: Gama amino butyric acid, 5-HT: 5-Hydroxytryptamine, kg: kilograms, MOA: Mechanism of action, TD: Tic disorders, VMAT-2: vesicular monoamine transporter-2 (VMAT-2) inhibitors

Treatment of comorbid behavioral manifestations[97]

Comorbid with ADHD (TD + ADHD)

Alpha 2 receptor agonists such as clonidine, guanfacine, and atomoxetine hydrochloride are the preferred initial treatment. Due to its tic-aggravating tendency, methylphenidate may be considered as a secondary option.[97]

Comorbid with OCD (TD + OCD)

The most supported and recommended treatment for TD + OCD is cognitive BT (CBT) combined with ERP. As for medication options, selective serotonin reuptake inhibitors (SSRIs) such as sertraline are the preferred first-line pharmacological agents. Tricyclic antidepressants (clomipramine) and risperidone can be considered as secondary options.[97]

Emerging/experimental therapies

Brain stimulation

It consists of two major categories: non-invasive brain stimulation (NIBS) and invasive deep brain stimulation (DBS) techniques. NIBS includes transcranial magnetic stimulation, transcranial direct current stimulation, and peripheral nerve stimulation [Table 6].[135,136] DBS, with electrodes targeting the thalamus, globus pallidus internus, and other nearby structures, have been reported to be beneficial in drug-refractory tics.[136,137] According to 2015 guidelines for selection of TS patients for DBS, five conditions need to be fulfilled: (1) diagnosis of TS as per DSM-V criteria; (2) tic causing significant disability in life; (3) YGTSS severity is ≥35 for at least 1 year or tics leading to ≥2 emergency department visits or 1 hospitalization; (4) failure of at least three different medication classes and BT for at least 4–12 weeks; and (5) OCD are stable for at least 6 months.[136] Studies have shown moderate evidence of the effectiveness of these interventions in severe, drug-resistant TD. Table 6 illustrates the principles of action of these interventions in TD.[135,136]

Botulinum toxin injection

By inhibiting acetylcholine release at the neuromuscular junction, botulinum toxin injection results in temporary relaxation of injected muscles. It is useful in refractory focal motor and phonic tics.[138-141] Botulinum toxin may be used, especially targeting 1–2 muscles overactive due to tics.

What is the Prognosis of TD?

The prognosis of TD is generally favorable. Most TD children can lead healthy lives as adults. However, some may experience persistent tic symptoms and associated co-morbidities. Approximately 50% of pediatric TD patients attain full remission during their adolescent or adult years, and an additional one-third (30%) observe noticeable improvement. Merely one-fifth (up to 20%) continue to exhibit tics into adulthood. However, a minuscule proportion (5%–10%), particularly when accompanied by other comorbidities, not only experience deterioration but also develop severe manifestations of TD.[76,80,97] Factors such as family history of mental disorders, childhood stress, high tic severity, smaller

Table 6: Principles of action and targets of various emerging interventions in TD[135,136]

Name of procedure	Mechanism of action	Comments
TMS[135]	Repetitive transcranial magnetic simulation at low frequencies of 1 Hz leads to inhibitory modulation Target: SMA; bilateral parietal cortex	Useful for treatment-resistant TD and comorbidities such as OCD
tDCS[135]	It uses constant, low current delivered via electrodes attached directly to the scalp. Cathodal stimulation decreases cortical excitability Target: SMA; left motor cortex	It is cheap, portable, easy to administer, does not need specialized training
Peripheral nerve stimulation[135]	Transcutaneous nerve stimulations with alpha or mu (8–14 Hz) and beta (15–30 Hz) frequency band, are associated with suppression of movement Target: Vagus nerve; median nerve	It can be combined with breathing exercises for tic reduction
DBS[136,137]	Inhibitory modulation by electrical impulses generated from Intracranial implanted electrode Target: Centromedian thalamus, anterior globus pallidus internus, nucleus accumbens, and anterior internal capsule	Useful in refractory TD; 30%–50% improvement in tics following DBS
Botulinum toxin injection[138-141]	It inhibits acetylcholine release at the neuro-muscular junction, leading to temporary relaxation of injected muscles	Useful in refractory focal tics such as blinking, facial movements, neck jerking, and disabling coprolalia or loud vocal tics

DBS: deep brain stimulation; HZ: hertz; OCD: Obsessive-compulsive disorders; SMA: Supplementary motor area; TD: Tic disorders; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation

caudate volume, and poor fine-motor control influence the prognosis.[80,97]

Conclusion

TD is a common hyperkinetic movement disorder, primarily affecting the pediatric age group. It is important to have a detailed history regarding the onset, frequency, severity, alleviating and exacerbating factors of tics, followed by a thorough evaluation for underlying behavioral comorbidities. Management of TD needs collaborative and individualized therapy in the form of patient and family education, clinical assessment, and discussion of treatment options, such as behavioral therapies, drugs, and their adverse effect profile. A small percentage of TD patients who do not respond to BT and medication may benefit from surgical treatment including DBS.

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Conflicts of interest

There are no conflicts of interest.

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