Tourette's Syndrome

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Tourette's syndrome is a movement disorder most commonly seen in school-age children. The incidence peaks around preadolescence with one half of cases resolving in early adulthood. Tourette's syndrome is the most common cause of tics, which are involuntary or semi-voluntary, sudden, brief, intermittent, repetitive movements (motor tics) or sounds (phonic tics). It is often associated with psychiatric comorbidities, mainly attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. Given its diverse presentation, Tourette's syndrome can mimic many hyperkinetic disorders, making the diagnosis challenging at times. The etiology of this syndrome is thought to be related to basal ganglia dysfunction. Treatment can be behavioral, pharmacologic, or surgical, and is dictated by the most incapacitating symptoms. Alpha$_2$-adrenergic agonists are the first line of pharmacologic therapy, but dopamine-receptor–blocking drugs are required for multiple, complex tics. Dopamine-receptor–blocking drugs are associated with potential side effects including sedation, weight gain, acute dystonic reactions, and tardive dyskinesia. Appropriate diagnosis and treatment can substantially improve quality of life and psychosocial functioning in affected children. (*Am Fam Physician.* 2008;77(5):651-658, 659-660. Copyright © 2008 American Academy of Family Physicians.)

▶ **Patient information:** A handout on Tourette's syndrome, written by the authors of this article, is provided on p. 659.

In 1885, Georges Gilles de la Tourette described the major clinical features of the syndrome that now carries his name. Tourette's syndrome is one of the most common causes of motor and phonic tics. This childhood-onset movement disorder is commonly associated with obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and other psychiatric comorbidities. The perception of Tourette's syndrome has evolved from a psychological disorder to one with biologic, genetic, and imaging features more consistent with a neurologic disorder.

Presentation

Tics are involuntary or semi-voluntary, sudden, brief, intermittent, repetitive movements (motor) or sounds (phonic)[1] that are classified as simple or complex *(Table 1)*. Simple motor tics involve a single muscle or group of muscles and may be brief (clonic), more prolonged (dystonic), or sustained, such as an isometric contraction (tonic). Such tics are often easy to camouflage as voluntary movements and are frequently unnoticed. Complex motor tics produce a more coordinated movement mimicking normal motor function. They often occur out of their normal context or in inappropriate situations, thus calling attention to the person because of their exaggerated, forceful, and repetitive nature. Socially inappropriate movements, including obscene gestures (copropraxia) or imitating another's gestures (echopraxia), can be particularly bothersome.

Simple phonic tics can also be disguised and are often meaningless utterances or noises. Complex phonic tics are words or phrases, including obscenities (coprolalia), echoing what others say (echolalia), and repeating one's own utterances (paliphrasia).

Tics are transiently suppressible and suggestible. They may improve with concentration or distraction and may worsen with stress, fatigue, or excitement.[2] Tics may be relatively absent while a child plays video games or may occur immediately on casual mention. Prolonged suppression of tics causes an inner tension that may lead to a more dramatic tic or burst of tics. Children may experience a "release" of tic activity on returning home from school, and the severity of symptoms may vary in different environments. About 80 percent of patients note a premonitory sensation such as paresthesia or dysesthesia (e.g., burning or itching of the eyes before eye

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Alpha$_2$-adrenergic agonists are useful in treating patients with Tourette's syndrome, although they improve tics to a lesser degree than dopamine-receptor–blocking drugs. Clonidine (Catapres) also tends to improve sleep and attention. Guanfacine (Tenex) has the same pharmacologic mechanism as clonidine, but displays a more benign side-effect profile.	B	19
Dopamine-receptor–blocking drugs are the most effective treatment for tics. Haloperidol (Haldol) and pimozide (Orap) have been studied most extensively but are infrequently used because of potential side effects.	B	21-25, 27-30
Fluphenazine (Prolixin; brand no longer available) displays a more benign safety profile than haloperidol or pimozide, but has been studied in controlled trials to a lesser degree.	B	25, 26
Tetrabenazine (investigational) is a promising dopamine-depleting drug; controlled trials are ongoing.	B	31
Medically refractory motor and disabling phonic tics such as coprolalia can be ameliorated by botulinum toxin (Botox) injections.	B	32-34
Deep brain stimulation is being used at an increasing rate for medically refractory tics in Tourette's syndrome.	B	12

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 579 or http://www.aafp.org/afpsort.xml.

tics, throat "tickling" or discomfort before throat clearing, or muscular tension before shoulder shrugging)[2] before a motor or phonic tic occurs; the sensation is temporarily relieved after the movement.[1] Patients may execute tics repeatedly until they feel "just right," lending them a compulsive quality.

Tics occurring intermittently for one to 12 months are referred to as transient tic disorder, the prevalence of which is 3 to 15 percent.[3] In patients with Tourette's syndrome, tics wax and wane over days, weeks, or months, such that patients experience new tics or regain old ones.[2] Diagnostic criteria for Tourette's syndrome *(Table 2)*[4,5] highlight the presence of multiple tic types, the total duration of symptoms, and age at onset before 18 years. Males are five times more likely to be affected, and the prevalence may approach 0.72 percent.[6] Typically, tics start around eight years of age, peak in preadolescence, and decline in early adulthood. Complete resolution occurs by age 18 in 50 percent of patients with Tourette's syndrome.[2] This natural history is thought to parallel the process of nigrostriatal innervation in the developing brain,[7] implicating Tourette's syndrome as a neurodevelopmental disorder.

More than 50 percent of children with Tourette's syndrome experience a psychiatric comorbidity,[8] commonly ADHD by age four and OCD by age seven.[1] Depression, anxiety, and behavioral problems may be at least as disruptive as tics or can exacerbate them. Executive dysfunction from ADHD can disrupt school performance. For example, children may have difficulty with initiating, planning, sequencing, and prioritizing assigned tasks such as homework or projects, leading to incomplete work or careless errors. Because OCD and ADHD are commonly associated with tics, children presenting with either disorder alone should be questioned

Table 1. Examples of Common Tics

Simple motor	**Complex motor**	**Simple phonic**
Clonic	Burping	Blowing
Eye blinking	Copropraxia	Coughing
Head jerking	Echopraxia	Grunting
Nose twitching	Head shaking	Hiccupping
Dystonic	Hitting	Screaming
Blepharospasm	Jumping	Sniffing
Blocking tic	Kicking	Squeaking
Bruxism	Retching	Sucking
Oculogyric movements	Smelling objects	Throat clearing
Shoulder rotation	Throwing	**Complex phonic**
Sustained jaw opening	Touching	Coprolalia
Torticollis	Trunk bending	Echolalia
Tonic	Vomiting	Paliphrasia
Abdominal contraction		
Blocking tic		
Limb extension		
Limb flexion		

Table 2. Diagnostic Criteria for Tic Disorders

Diagnostic and Statistical Manual of Mental Disorders, *4th ed.*[4]	*Tourette's Syndrome Classification Study Group*[5]
Tourette's syndrome	**Tourette's syndrome**
Both multiple motor tics *and* one or more phonic tics must be present at some time, although not necessarily concurrently	Both multiple motor tics *and* one or more phonic tics must be present at some time during the illness, although not necessarily concurrently
The tics must occur many times a day (usually in bouts) nearly every day or intermittently over more than one year, during which time there must not have been a tic-free period of more than three consecutive months	Tics must occur many times a day, nearly every day, or intermittently throughout a period of more than one year; the anatomic location, number, frequency, type, complexity, or severity of tics must change over time
The onset occurs before 18 years of age	The onset occurs before 21 years of age
The disturbance must not be caused by the direct physiologic effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease, postviral encephalitis)	Involuntary movements and noises must not be explainable by other medical conditions
	Motor tics, phonic tics, or both, must be witnessed directly by a reliable examiner at some point during the illness or be recorded by videography or cinematography
Transient tic disorder	**Transient tic disorder**
Single or multiple motor and/or phonic tics (e.g., sudden, rapid, recurrent, nonrhythmic, stereotypic motor movement or vocalizations) are present	This disorder is characterized by single or multiple motor and/or phonic tics
The tics occur many times a day, nearly every day, for at least four weeks, but for no longer than 12 consecutive months	The tics occur many times a day, nearly every day, for at least two weeks, but for no longer than 12 consecutive months, although the disorder began more than one year earlier
The onset occurs before 18 years of age	The anatomic location, number, frequency, complexity, or severity of tics changes over time
The disturbance is not caused by the direct physiologic effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease, postviral encephalitis)	Patient has no history of Tourette's syndrome or chronic motor or phonic tic disorders
Criteria have never been met for Tourette's syndrome or chronic motor or phonic tic disorder	The onset occurs before 21 years of age
Specify if this is a single or recurrent episode	Motor tics, phonic tics, or both must be witnessed directly by a reliable examiner at some point during the illness or be recorded by videography or cinematography

Information from references 4 and 5.

about the coexistence of tics. Intellectual abilities are distributed normally in patients with Tourette's syndrome, but neuropsychological features such as dysgraphia, dyslexia, learning disabilities, and impaired visuomotor integration may pose educational obstacles.[9] Tics and/or comorbidities may cause a decline in grades and lead to disciplinary action at school. Children can become withdrawn and socially isolated, and may have poor self-esteem because of their symptoms and teasing by peers.

Differential Diagnosis

In most patients with Tourette's syndrome, the birth and developmental histories are normal. The neurologic examination is also normal other than the presence of tics (although these are often suppressed in the clinic); therefore, diagnostic testing provides little additional information. Atypical presentations should prompt a broader differential diagnosis *(Table 3)* and appropriate testing, especially when tourettism is associated with mental retardation, abnormal birth and development, or autistic spectrum disorders.[10] Causes of secondary tics and tourettism are listed in *Table 4*.

Other movement disorders may be misinterpreted as tics, including chorea (e.g., Sydenham's chorea), dystonia (e.g., blepharospasm, focal hand or foot dystonia), and myoclonus (e.g., myoclonic epilepsy), but these differ by lack of a premonitory urge, sense of relief on completion of the movement, suppressibility, and suggestibility *(Table 3)*. Myoclonus is a faster, sudden, involuntary jerking of the muscles. Chorea is characterized by involuntary movements that travel between body parts in a random, unpredictable fashion, whereas Tourette's syndrome involves a number of discrete tics or tic patterns that are repeated in a predictable and stereotypic

manner. Dystonia is a sustained contraction of muscles that produces an abnormal posture. It may improve with a sensory trick, or geste antagoniste, in which touching the affected or adjacent body part can relieve the posture. Symptoms do not wax and wane. Restless legs syndrome (RLS) and Tourette's syndrome involve movements initiated by an urge or uncomfortable sensation and followed by a sense of relief. However, RLS mainly affects the lower extremities, increases with inactivity, worsens at night, and does not share comorbidities. Treatment-related akathisia, chorea, dystonia, tremor, and movements related to OCD (e.g., slapping, self-mutilation) and ADHD (e.g., nonstereotypic generalized movements) should be differentiated from worsening tics.[11]

Etiology

Tics and comorbidities improve with the use of selective serotonin reuptake inhibitors (SSRIs) and dopamine-receptor–blocking drugs, thereby implicating dopaminergic and serotonergic neurotransmission in Tourette's syndrome pathophysiology.[7] The high density of dopaminergic and serotonergic neurons in the striatum and presence of tics in other disorders with striatal dysfunction suggest that Tourette's syndrome is a basal ganglia disorder. Reports of improvement after deep brain stimulation of the globus pallidus interna or thalamus further support this hypothesis,[12] as do data from imaging studies. Volumetric imaging shows smaller caudate volumes in patients with Tourette's syndrome, and functional imaging studies reveal abnormalities in the basal ganglia and associated cortical areas during tic activity.[7] Tics may result from aberrant activation of a discrete group of striatal neurons that share functional homogeneity (matrisomes); multiple tics result from dysfunction in multiple matrisomes. The exact cause of this activation remains unknown, but it may be caused in part by increased striatal dopaminergic innervation.[7]

Genetic factors influence Tourette's syndrome; relatives of patients with Tourette's syndrome have increased rates of tics, OCD, and ADHD.[13] There are high concordance rates in monozygotic, but not dizygotic, twins.[14] Segregation analyses supported an autosomal-dominant hypothesis,[15] but investigators now favor intermediate modes of inheritance or a polygenic model.[7] Another possibility is bilineal transmission, because a history of tics and/or comorbidities may be found in both maternal and paternal family members.[13] Recently, alterations in the gene sequence of SLITRK1 were associated with some cases of Tourette's syndrome.[16] The SLITRK1 gene encodes a protein that can influence dendritic growth in animal models, but the actual relationship to symptoms of Tourette's syndrome remains unclear.

Table 3. Differential Diagnosis of Tics

Characteristic of tic	*Differential diagnosis*
Abrupt	Chorea
	Myoclonus
	Paroxysmal dyskinesia
	Seizure
Improves with concentration	Akathisia
	Psychogenic
Increases with stress	Most hyperkinesias
Multifocal/migratory	Chorea
	Myoclonus
	Paroxysmal dyskinesia
Patient unaware	Chorea
	Seizure
Premonitory sensation (or urge)	Akathisia
	Dystonia
Present during sleep	Myoclonus (segmental)
	Painful legs/moving toes
	Periodic limb movements of sleep
	Seizure
Suppressible	Chorea
	Restless legs syndrome
	Stereotypy

Treatment

A detailed history with attention to the presence and severity of various features is crucial in the management of patients with Tourette's syndrome, because tics and comorbidities are interrelated and may influence each other. The goal of treatment

should be to improve social functioning, self-esteem, and quality of life. Complete resolution of symptoms is often not achieved. Treatment should be individually tailored *(Table 5)*, and a combination of drugs may be required. General principles for the treatment of Tourette's syndrome–related symptoms are presented in *Table 6*.

Behavioral therapy and counseling can improve patients' understanding of the condition; can improve their self-esteem and social functioning; and can reduce tics or other maladaptive behaviors. Widely used techniques include awareness training, assertiveness training, cognitive therapy, relaxation therapy, and habit reversal therapy.[17,18] Education of family, teachers, classmates, and other school personnel helps create an accepting environment for a child with Tourette's syndrome who may otherwise be teased, ridiculed, disciplined, or simply told to "stop it." Appropriate school modifications should be implemented when needed.[9] Further information for patients, families, and educators and links to local support groups are available on the Tourette's Syndrome Association Web site (http://www.tsa-usa.org) and on the Worldwide Education and Awareness for Movement Disorders Web site (http://www.wemove.org).

If tics severely affect a child's social functioning or self-esteem, or if the tics are painful or self-injurious, medical treatment is warranted. The decision to initiate pharmacologic intervention must be balanced with the potential risks and reassessed regularly. Parents and patients should participate in treatment decisions. Haloperidol (Haldol) and pimozide (Orap) are approved by the U.S. Food and Drug Administration (FDA) for treatment of tics and Tourette's syndrome, although haloperidol is often avoided because of its less favorable side effect profile. Other medications are also effective *(Table 7)*. Alpha$_2$-adrenergic agonists such as clonidine (Catapres) and guanfacine (Tenex) are good first-line medications when symptoms are mild. Clonidine is available as a pill or transdermal patch, and may also improve anxiety, insomnia, hyperactivity, and impulsivity in patients who have Tourette's syndrome with

Table 4. Causes of Secondary Tics and Tourettism

Type of tics	*Causes*
Basal ganglia insult	Ischemic or hemorrhagic stroke
	Postinfectious (encephalitis)
	Posttraumatic
Coexistent with another movement disorder	Dystonia
	Essential tremor
	Myoclonus
	Restless legs syndrome
Exposure to drugs or toxins	Cocaine
	Stimulants
	Tardive tics (exposure to neuroleptics)
Genetic/chromosomal	Choreoacanthocytosis
	Down syndrome
	Huntington's disease
	Klinefelter syndrome
	Neurofibromatosis
Other neurologic disorder	Dementia
	Headache
	Myoclonic epilepsies
	Seizures
	Static encephalopathy
Peripherally induced	Following trauma
Pervasive developmental disorder	Asperger's syndrome
	Autistic spectrum disorders
Psychogenic tics	Conversion, with family history of tics/Tourette's syndrome
	Precipitated by stressor
Structural	Arnold-Chiari malformation
	Corpus callosum dysgenesis
	Craniosynostosis

Table 5. Treatment Options for Patients with Tourette's Syndrome

Nonpharmacologic therapy

Reassurance and environmental modifications

Identification and treatment of triggers

Cognitive behavior therapy

Pharmacologic therapy

Alpha$_2$-adrenergic agonist or clonazepam (Klonopin)

Dopamine-receptor–blocking drugs

Other medications: topiramate (Topamax), tetrabenazine (investigational), baclofen (Lioresal Intrathecal solution for injection—only form of brand available)

Other therapies

Botulinum toxin (Botox)

Deep brain stimulation

NOTE: *Options are listed in order of increasing severity of symptoms.*

Table 6. General Principles for the Treatment of Patients with Tourette's Syndrome

Identify the most disabling symptoms and address these first
Determine if symptoms are severe enough to warrant treatment (e.g., psychosocial or school dysfunction, poor self-esteem, teasing by peers)
Determine if nonpharmacologic therapies apply (e.g., cognitive behavior therapy, counseling, habit reversal training)
Unless symptoms are florid or obvious dysfunction is present, start with the mildest agents first (e.g., alpha$_2$-adrenergic agonists, topiramate [Topamax])
If stimulants worsen tics, initiate treatment of tics first, then reintroduce the stimulant
Do not start more than one agent at a time
Have a high index of suspicion for comorbid obsessive-compulsive disorder, depression, or anxiety, and treat as necessary
Assess for classroom modifications or accommodations, if needed

ADHD.[19] Side effects (including sedation and hypotension) are less common with guanfacine than with clonidine, but both medications are usually well tolerated in patients with Tourette's syndrome.[19,20]

Dopamine-receptor–blocking drugs remain the most effective pharmacologic treatment for tics[21] *(Tables 5 and 7)*. Haloperidol and pimozide are FDA-approved for this indication.[22-24] Pimozide was found to be more effective and better tolerated, but it may prolong the QT interval, necessitating periodic electrocardiography. Fluphenazine (Prolixin—brand no longer available) is a commonly used dopamine-receptor–blocking drug because of better safety and tolerability, but no controlled studies exist in the medical literature.[25,26] Typical neuroleptics are associated with tardive dyskinesia, although this is rarely reported in patients with Tourette's syndrome.[27] The atypical dopamine-receptor–blocking drugs such as risperidone (Risperdal) and olanzapine (Zyprexa) carry less risk of tardive dyskinesia and can be effective in the treatment of Tourette's syndrome[28,29]; however, potential side effects include sedation and weight gain. Dopamine-receptor–blocking drugs can cause acute dystonic reactions such as oculogyric crisis, jaw fixation, torticollis, and opisthotonic posturing. Acute dystonic reactions usually occur at initiation of therapy[30] and can be successfully managed by coadministration of anticholinergics. Dopamine-receptor–blocking drugs can be used with alpha$_2$-adrenergic agonists, and atypical agents may enhance standard treatments for depression and OCD.

Table 7. Commonly Used Oral Pharmacologic Agents in the Treatment of Patients with Tics

Medications	*Initial dosage*	*Goal dosage*	*Maximum dosage*
Noradrenergic drugs			
Clonidine (Catapres)	0.05 mg at bedtime	0.1 mg three times daily	0.2 mg three times daily
Guanfacine (Tenex)	0.5 mg at bedtime	1 mg twice daily	1 mg three times daily
Dopamine-receptor–blocking drugs			
Fluphenazine (Prolixin—brand no longer available)	0.5 mg at bedtime	1 mg three times daily	3 mg three times daily
Olanzapine (Zyprexa)	1.25 mg at bedtime	2.5 mg twice daily	5 mg twice daily
Pimozide (Orap)	0.5 mg at bedtime	1 mg twice daily	3 mg twice daily
Risperidone (Risperdal)	0.25 mg at bedtime	1 mg twice daily	2 mg twice daily
Dopamine-depleting drugs			
Tetrabenazine (investigational)	12.5 mg at bedtime	25 mg three times daily	50 mg three times daily
Other drugs			
Baclofen (Lioresal Intrathecal solution for injection—only form of brand available)	5 mg daily	10 mg three times daily	20 mg three times daily
Clonazepam (Klonopin)	0.25 mg at bedtime	0.5 mg three times daily	1 mg three times daily
Topiramate (Topamax)	25 mg at bedtime	100 mg daily	200 mg daily

There are few alternatives to alpha$_2$-adrenergic agonists and dopamine-receptor–blocking drugs *(Table 7)*. Topiramate (Topamax) is an antiepileptic drug that may potentiate inhibitory neurotransmission of γ-aminobutyric acid, thus reducing abnormal neuronal firing in the basal ganglia. A multicenter, double-blind, placebo-controlled trial is currently underway, but open-label experience at our center suggests that this drug is safe and effective in treating tics and could be considered as an alternative to dopamine-receptor–blocking drugs. Tetrabenazine, a monoamine-depleting medication, has also been used successfully and extensively in patients with Tourette's syndrome at our institution.[31] Topiramate may cause weight loss and tetrabenazine is weight neutral; neither causes tardive dyskinesia. No double-blind, placebo-controlled study of tetrabenazine in Tourette's syndrome has been conducted, and availability of the drug is currently limited to a few centers. However, FDA approval of tetrabenazine for a different indication, chorea in Huntington's disease, has been obtained.

Medically refractory motor and phonic tics may require referral to specialty centers. The exact mechanism by which botulinum toxin (Botox) affects Tourette's syndrome is unknown, but it can reduce tics and premonitory sensations.[32,33] Disabling phonic tics, including coprolalia, can improve with vocal cord injections.[34] For truly severe and refractory cases of Tourette's syndrome, deep brain stimulation is an emerging therapy, but case reports have demonstrated beneficial effects at different stimulation sites, using differing selection criteria and outcome measures.[12]

Comorbid ADHD, OCD, and other mood disorders should be treated when necessary. Stimulants such as methylphenidate (Ritalin) are the mainstay of therapy for ADHD, even in patients with Tourette's syndrome. Because ADHD often precedes onset of tics, treatment with stimulants may be perceived as "causing" tics. However, persistent tic activity after discontinuation of the stimulant indicates the presence of a comorbid tic disorder, typically Tourette's syndrome. Results of a recent large study conducted by the Tourette's Syndrome Study Group suggest that long-term use of methylphenidate is safe and does not exacerbate tics.[19] Nonstimulants such as atomoxetine (Strattera) can improve both ADHD and tics,[35] but clinical experience varies. OCD and mood disorders are commonly treated with SSRIs, but Tourette's syndrome–associated OCD can prove refractory, and augmentation with dopamine-receptor–blocking drugs or tricyclic antidepressants may be needed.[36]

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