REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

VIDEO CONTENT AVAILABLE ONLINE

Tics and Tourette Syndrome

By Harvey S. Singer, MD, FAAN

ABSTRACT

PURPOSE OF REVIEW: The purpose of this article is to present current information on the phenomenology, epidemiology, comorbidities, and pathophysiology of tic disorders and discuss therapy options. It is hoped that a greater understanding of each of these components will provide clinicians with the necessary information to deliver thoughtful and optimal care to affected individuals.

RECENT FINDINGS: Recent advances include the finding that Tourette syndrome is likely due to a combination of several different genes, both low-effect and larger-effect variants, plus environmental factors. Pathophysiologically, increasing evidence supports involvement of the cortical–basal ganglia–thalamocortical circuit; however, the primary location and neurotransmitter remain controversial. Behavioral therapy is first-line treatment, and pharmacotherapy is based on tic severity. Several newer therapeutic agents are under investigation (eg, valbenazine, deutetrabenazine, cannabinoids), and deep brain stimulation is a promising therapy.

SUMMARY: Tics, defined as sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations, are essential components of Tourette syndrome. Although some tics may be mild, others can cause significant psychosocial, physical, and functional difficulties that affect daily activities. In addition to tics, most affected individuals have coexisting neuropsychological difficulties (attention deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety, mood disorder, disruptive behaviors, schizotypal traits, suicidal behavior, personality disorder, antisocial activities, and sleep disorders) that can further impact social and academic activities or employment.

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(4, MOVEMENT DISORDERS): 936–958.

Address correspondence to Dr Harvey S. Singer, Professor of Neurology and Pediatrics, Johns Hopkins Hospital, Rubenstein Child Health Building, 200 N Wolfe St, Ste 2141 Baltimore, MD 21287, *hsinger@jhmi.edu*.

RELATIONSHIP DISCLOSURE:
Dr Singer serves as a consultant for Abide Therapeutics, Inc; Cello Health BioConsulting; ClearView Healthcare Partners; Teva Pharmaceutical Industries Ltd; and Trinity Partners, LLC. Dr Singer receives publishing royalties from Elsevier and research/grant support from the Tourette Association of America.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Singer discusses the unlabeled/investigational use of baclofen, botulinum toxin, cannabidiol, clonazepam, clonidine, deutetrabenazine, ecopipam, fluphenazine, guanfacine, nabiximols, risperidone, sulpiride, tetrabenazine, Δ-9-tetrahydrocannibinol, tiapride, topiramate, and valbenazine.

INTRODUCTION

Tourette syndrome, also known as Gilles de la Tourette syndrome or Tourette disorder, is a complex, childhood-onset neuropsychiatric condition that includes multiple phenotypic motor and vocal tics. The condition is named after the French physician Georges Gilles de la Tourette, who in 1885 reported nine patients with the "maladie of tics."[1] Before Tourette's report, motor and vocal tics had been reported in the context of witchcraft, in well-known historical individuals, and in the medical literature by Jean Itard in 1825.[2]

Tourette syndrome affects children, adolescents, and adults worldwide and represents only one entity in a spectrum of tic disorders ranging from a provisional form to those associated with general medical conditions. Although some tics may be mild, others can result in psychosocial, physical, and functional difficulties that affect social activities, academic achievements, and employment performance. Comorbid or co-occurring conditions are common in patients with Tourette syndrome, the most common being obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), anxiety, mood disorders, disruptive behaviors, learning difficulties, and alterations of sleep. The underlying pathophysiology, in terms of both anatomic localization and the primary neurochemical abnormality, remains unclear. Therapeutically, behavioral therapy is the first-line option, followed by various standard and emerging pharmacologic treatments and, finally, deep brain stimulation.

TIC PHENOMENOLOGY

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations (phonic productions).

Categories and Types

Tics are classified into two larger categories (motor and phonic), with each being subdivided into a simple and complex grouping. Brief, rapid, abrupt jerklike, nonrhythmic movements that involve only a single muscle or localized group are considered simple (eye blink, head jerk, shoulder shrug) (**VIDEO 3-1**,[3] *links.lww.com/CONT/A284*). In contrast, complex tics involve either a cluster of simple actions or a more coordinated pattern of movements. Complex motor tics can be nonpurposeful (facial or body contortions) (**VIDEO 3-2**, *links.lww.com/CONT/A285* and **VIDEO 3-3**, *links.lww.com/CONT/A286*) or appear purposeful but actually serve no purpose (touching, hitting, smelling, jumping, bending, imitating observed movements [echopraxia], and making obscene gestures [copropraxia]). They may have a dystonic quality (oculogyric movements, sustained mouth opening, body posturing, torticollis) or have a tonic character (prolonged tensing of abdominal muscles, immobility, staring), labeled by some as *blocking tics*.[4] In approximately 4% to 5% of patients, self-injurious ("malignant") tics can cause myelopathies, ocular damage, or body injuries.[5,6]

Simple vocal tics include various sounds and noises (grunts, barks, hoots, hollers, moans, groans, sniffs, and throat clearing) (**VIDEO 3-4**, *links.lww.com/CONT/A287* and **VIDEO 3-5**, *links.lww.com/CONT/A288*). Complex vocalizations (**VIDEO 3-6**, *links.lww.com/CONT/A289*) involve linguistically meaningful vocalizations and utterances; the repetition of words, syllables, or phrases; echolalia (repeating other people's words); palilalia (repeating one's own words); or coprolalia (obscene words or profanity). Although coprolalia is commonly associated with Tourette syndrome, only a small minority (about 10% to 19%) of individuals with Tourette syndrome have this symptom.[7,8] Vocal alterations can also include pauses and hesitations in speech, word interjections, changes in tone/pitch, and prolongations of words.

While the distinction between motor and vocal tics is often emphasized, some vocalizations can be secondary to a nasal, pharyngeal, chest, or abdominal motor tic. For example, a rapid contraction of the chest or abdomen can lead to the expulsion of air and production of a simple vocalization. Although it has been suggested that tics can mimic almost any movement or sound, uncommon tics

have included anterior-posterior movements of the external ear, sign language tics, palatal movements, air swallowing, vomiting, and retching.

Characteristics

Tics have several characteristics that are useful in identifying their presence, including precipitating factors, a waxing and waning pattern, admixture of new and old tics, a premonitory urge that resolves when the tic is done, reduction when engrossed, and variable severity. They can range from infrequent and unnoticed to very frequent, intense, intrusive, and even self-injurious. Tics are exacerbated by stress, anxiety, excitement, anger, fatigue, elevated temperatures, or infections.[9,10] These conditions, however, do not account for more prolonged changes in tic severity.[11] Tics are reduced when the individual is concentrating on a physical or mental task or sleeping. Although most parents and patients report that tics do not occur while sleeping, polysomnograms have identified their presence in all phases of sleep.[12] About 90% of adults[13] and 37% of children[14] report a premonitory urge/sensation just before a motor or phonic tic. Vaguely defined as an urge, mounting tension, pressure, itch, or feeling, it is generally localized to the region of the tic and resolves when the tic is permitted to occur.[15] Many individuals can briefly suppress their tics, although this effort may trigger an exacerbation of premonitory sensations or a sense of increased internal tension.

Tic disorders are more common in males than in females (ratio of 3:1 to 4:1) and usually begin between the ages of 4 and 8. Motor tics usually precede vocal tics, with initial simple motor tics involving the face, head, or neck. Tics can be highly variable and fluctuate, and an individual's tic repertoire evolves over time. Statistically, the maximum severity of tics tends to occur between 8 and 12 years of age,[16] with tics declining in severity throughout the teenaged to early adulthood years.[16,17] An approximate rule of thirds suggests that one-third of tics disappear, one-third improve, and one-third continue to fluctuate.[18] Although many adults have reported the resolution of tics, formal assessments have indicated otherwise.[19] Assumptions that adult tic severity can be predicted by childhood tic severity, childhood fine motor skills, and reduced childhood MRI caudate volumes require additional confirmation. Tics can persist into adulthood and, for some, can be severe and debilitating.[20] In addition, symptom worsening has occurred in adults after prolonged periods of clinical remission.[21] Adult-onset tic disorders (formally, other specified tic disorder with onset after age 18 years) have been reported and often include severe symptoms, greater social morbidity, and poorer response to medications compared to childhood-onset tic disorders.[22]

Neurologic examination and neuroimaging studies are typically normal. "Soft" neurologic findings may include coordination issues, synkinesis (involuntary muscular movements accompanying voluntary movements), and motor restlessness, especially in individuals with ADHD.

DIAGNOSIS

The diagnosis of a tic disorder is based on historical features and observation of the tics; there is no definitive diagnostic laboratory test. Tics must be differentiated from drug-induced movements (akathisia, dystonia, parkinsonism), obsessive-compulsive behaviors, hyperactivity, antisocial behaviors, and stereotypies.[23] In contrast to tics, which are commonly associated with a premonitory urge,

compulsions are complex activities that are performed to prevent or relieve anxiety, are executed in a rigid pattern, and may be done in response to an obsession. Motor stereotypies typically have an earlier onset, fixed pattern, rhythmic quality, prolonged duration, and lack of a premonitory urge and stop abruptly with distraction.[24] Individuals with stuttering may also have an array of nonspeech motor ticlike behaviors, including eye blinking, ocular deviation, head jerks, and limb and trunk movements.[25] In practice, repetitive sniffing, throat clearing, and coughing tics are often mistakenly attributed to allergies, sinusitis, or pulmonary issues; eye blinking tics are mistakenly thought to stem from ophthalmic problems; and ocular tics are confused with opsoclonus. Psychogenic disorders that present with ticlike movements can arise in childhood but are more common in adults; they are also more common in females than in males.[26] Nevertheless, it may be difficult, at times, to distinguish a functional movement in an individual with preexisting typical tics. Clues helpful in identifying a psychogenic movement include predisposing factors, the lack of a premonitory sense, inability to briefly suppress the tics, other functional movements, and the lack of response to otherwise effective therapies.

Specific Tic Diagnoses

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), includes five tic categories[27]:

- ***Provisional tic disorder*** designates an individual whose tics (motor or vocal) have been present for less than 1 year since first tic onset, and onset is before age 18 years. The disturbance cannot be attributable to the psychological effects of a substance or other medical conditions. For example, tics can result as a direct consequence of a variety of neurodegenerative disorders (eg, neuroacanthocytosis, Huntington disease, neurodegeneration with brain iron accumulation), neurocutaneous syndromes, and Creutzfeldt-Jakob disease.[3,28] Tics have also been reported in association with infections, Sydenham chorea, toxins (carbon monoxide), stroke, head and peripheral trauma, and surgery. Drugs reported to induce tics include cocaine, lamotrigine, and neuroleptics.[29] Significant data exist refuting the concept that stimulant medications are precipitating agents for tics.[30]
- ***Chronic motor or vocal tic disorder*** indicates the presence of either motor or vocal tics, but not both, for longer than 1 year, without regard for tic frequency. Onset is before 18 years of age, and tics cannot be attributed to the use of drugs or other medical condition. Note that multiple characteristics overlap in individuals with chronic motor tic disorder and individuals with Tourette syndrome.[31]
- ***Tourette disorder*** is also called Tourette syndrome, and both have very similar formal criteria,[27,32] except that when originally proposed, the age of onset for Tourette syndrome was before 21 years of age as compared to before 18 years of age for Tourette disorder. Other criteria include the presence of multiple motor tics and at least one vocal tic, a waxing and waning course, a duration of longer than 1 year, and tics that are neither substance-induced nor due to a general medical condition.

The last two categories apply to tic disorders that cause clinical distress/impairment but do not meet criteria for either of the aforementioned three tic disorders or any neurodevelopmental disorder.

- ***Other specified tic disorder*** is a diagnosis used when the clinician chooses to communicate the reason why the individual failed to meet the criteria for a tic disorder, (eg, other specified tic disorder with an age of onset of older than 18 years).
- ***Unspecified tic disorder*** is a diagnosis used when the criteria for a tic disorder are not met, and there is insufficient information to make a more specific diagnosis.

KEY POINTS

- Tics have several characteristics that are useful in identifying their presence, including precipitating factors, a waxing and waning pattern, admixture of new and old tics, a premonitory urge that resolves when the tic is done, reduction when engrossed, and variable severity.
- Tics can be highly variable and fluctuate, and an individual's tic repertoire evolves over time.
- The diagnosis of a tic disorder is based on historical features and observation of the tics; no definitive diagnostic laboratory test has yet been established.

TIC RATING SCALES

The Yale Global Tic Severity Scale, a semistructured clinical interview, is the most widely used tic severity assessment instrument.[33] It consists of the Total Tic Score, composed of five separate ratings (number, frequency, intensity, complexity, and interference) on a scale of 0 to 5 for both motor (maximum of 25 points) and vocal (maximum of 25 points) tics, and the Tic Impairment Score, a ranking of impairment based on the impact of the tic disorder on self-esteem, family life, and social acceptance (maximum of 50 points). Although tic severity might be expected to correlate with impairment, studies have shown that this is not necessarily the case.[17] The Gilles de la Tourette Syndrome Health-Related Quality of Life Scale is a 27-item patient-reported Tourette syndrome–specific scale with psychological, physical, obsessional, and cognitive subscales.[34] The Premonitory Urge for Tics Scale characterizes and quantifies premonitory urges.[35]

EPIDEMIOLOGY

Simple tics are relatively common in childhood, with reports of prevalence (the number of cases in the population at a given time) being 6% to 12% (range of 4% to 24%).[36,37] For Tourette syndrome, which occurs worldwide with common features in all cultures and races, prevalence estimates have been variable, with estimates ranging from 0.3% to 1%. In two meta-analyses, prevalence in children was 0.52%[38] and 0.77%[39] but increased to 1.06% when only boys were considered.[39] Another estimate is that an additional 1% to 3% of children and adolescents have a mild unidentified form. The variations in reported prevalence are believed to be associated with differences in assessment methods and measures. Several studies have documented that Tourette syndrome is common in children with autistic spectrum disorders[40]; however, no correlation with the severity of autistic symptoms has been seen. Mortality rates are reportedly higher in Tourette syndrome and chronic motor or vocal tic disorder, irrespective of the presence of comorbidities.[41] Parents of children with chronic tic disorders have higher rates of psychiatric illnesses, greater in mothers than fathers, although whether this is associated with parental stress or environmental, genetic, or other factors is unclear.[42]

COMORBIDITIES

Most individuals with Tourette syndrome (an estimated 86% to 90%) have at least one comorbid/coexisting neuropsychological problem.[43] These additional issues add an extra clinical burden, and, for some, the clinical impact may be greater than that caused by tics. Health-related quality of life assessments have shown that outcome is predicted by the presence of comorbidities, such as ADHD and obsessive-compulsive disorder (OCD), rather than tic severity.[44,45] Coexisting neuropsychological issues add a significant additional burden to patients with Tourette syndrome or chronic motor or vocal tic disorder.[44,46] It has also been suggested that less severe tic phenotypes have lower rates of comorbidity.[47] In a study examining parent attribution of impairment in home activities, non–tic-related concerns were a greater problem.[48]

Longitudinal studies in patients with Tourette syndrome have suggested a decline in both ADHD and OCD during adolescence although other psychopathologies persist.[17] Recognizing the common presence and detrimental

effect of coexisting problems, physicians caring for patients with tic disorders must be knowledgeable about and continually assess for them.

Attention Deficit Hyperactivity Disorder

ADHD symptoms (inattentiveness, hyperactivity-impulsivity, or both) usually precede the onset of tics by 2 to 3 years. ADHD is reported to affect about 50% (range of 21% to 90%) of referred patients with Tourette syndrome.[49] In patients with tics, the addition of ADHD symptoms correlates with increased deficits in the ability to plan, working memory, and inhibitory control and increased psychosocial and school difficulties, aggressiveness, disruptive behaviors, emotional problems, functional impairment, and learning disabilities.[50,51] Tourette syndrome and ADHD are not believed to be alternative phenotypes of a single underlying genetic cause but rather to have a shared genetic susceptibility and overlap in their underlying neurobiology.[43,52]

Obsessive-Compulsive Disorder

Obsessive-compulsive behaviors usually emerge during early adolescence, several years after the onset of tics, although an earlier age of onset has been suggested.[43,53] The *DSM-5* criteria for OCD require that obsessions, compulsions, or both occupy at least 1 hour per day or cause significant clinical distress or functional impairment. A lifetime comorbid diagnosis of OCD is present in about 50% of patients with Tourette syndrome; symptoms typically becoming more severe at a later age.[54,55] In Tourette syndrome, obsessive-compulsive behaviors usually include a need for order or routine and a requirement for things to be symmetric or "just right." Hence, the execution of tics must occur in a particular fashion and sequence (eg, number of times, order, both sides of the body) and often requires a certain "just right" sense/feeling before stopping. Other common obsessive-compulsive behaviors include counting; arranging; ordering; hoarding; touching; tapping; rubbing; checking for errors; and a higher frequency of aggressive, sexual, religious, and symmetry-related obsessions. In contrast, in OCD without tics, individuals typically have contamination and cleaning compulsions. Genetic associations between OCD and Tourette syndrome are complex, with a higher degree of heritability in both conditions (refer to the Genetics section later in this article).

Anxiety and Mood Disorders

The prevalence of anxiety and depression in Tourette syndrome is variable depending on the ages evaluated and methodologies used. For example, the presence of generalized anxiety disorder in subjects with Tourette syndrome has ranged from 19% to 80%, with increased rates in children and youth with Tourette syndrome.[53] A high-risk period for anxiety issues begins at age 4, and a high-risk period for mood disorders begins at age 7.[43] The presence of depression in patients with Tourette syndrome has correlated positively with earlier onset and a longer duration of tics.[56] Suicidality, both thoughts and attempts, also has a higher prevalence in Tourette syndrome.[57] Hence suicidal behavior should be monitored closely, especially in individuals with a history of persistent tics beyond young adulthood, suicide attempts, and psychiatric issues. The presence of ADHD is claimed to mediate anxiety and disruptive behaviors, whereas individuals with comorbid OCD are more likely to have a mood disorder.[43]

KEY POINTS

- Simple tics are relatively common in childhood, with reports of prevalence (the number of cases in the population at a given time) being 6% to 12% (range of 4% to 24%).
- Most individuals with Tourette syndrome have at least one comorbid/coexisting neuropsychological problem.
- Coexisting neuropsychological issues add a significant additional burden to patients with Tourette syndrome or chronic motor or vocal tic disorder.

CASE 3-1

A 9-year-old boy presented for a neurologic consultation for tics. He had developed eye-blinking tics at age 7 and subsequently gradually developed a variety of other motor tics, including head turning, neck stretching, and facial grimacing, and vocal tics that included throat clearing and grunting sounds. Over the years, his tics had a waxing and waning course. They were worse when he was stressed or fatigued. Nothing clearly made them better, and they were not present during sleep. He denied having a premonitory urge. At the time of evaluation, motor tics were occurring approximately once per hour but at times more frequently. The movements were not interfering with his daily activities. Vocal tics occurred about once every 3 hours, were quieter than his normal voice, and did not interfere with his communication. He had received only a few comments in the academic setting, his tics were not causing any physical issues nor disrupting his classroom, and he had been on no prior tic-suppressing therapy.

The patient had a history of attention deficit hyperactivity disorder since age 4 and was started on a stimulant medication (amphetamine) at age 6 years and 9 months. He had no history of obsessive-compulsive behaviors, anxiety, or mood issues. He did, however, have disruptive behaviors, with yelling, crying out, and banging on objects, and was easily angered when he did not get his way.

The patient was the product of an uncomplicated pregnancy and delivery, his early development was normal, and his general health was good. His family history was positive for childhood tics in his father. His neurologic examination was normal other than the occasional tics that were observed.

COMMENT

This case illustrates a typical presentation of a child with Tourette syndrome, with gradual onset and evolving course of both motor and vocal tics and with tics causing only a limited psychosocial or physical effect. This patient also had attention deficit hyperactivity disorder and disruptive behaviors; most patients with Tourette syndrome have at least one comorbidity, which may have a significant effect on quality of life. He also had a positive family history, with his father having had childhood tics. Although this patient's tics began after the initiation of a stimulant medication, these medications have not been scientifically proven to cause tics, and no changes were recommended in this patient. Tic-suppressing therapy should be reserve for individuals whose tics are causing psychosocial, physical, functional, or other difficulties. If needed, Comprehensive Behavioral Intervention for Tics (CBIT) should be tried before tic-suppressing pharmacotherapy is considered. Tics generally improve in the teenage and early adulthood years.

Disruptive Behaviors

Disruptive behaviors, including episodic outbursts, rage, and difficulty with aggression, are common in patients with Tourette syndrome.[43,58] Episodic behavioral outbursts and anger control problems are reported in 25% to 70% of Tourette syndrome populations.[59] The role of other comorbidities as a causative factor for disruptive behaviors is unclear. Self-injurious behavior in Tourette syndrome has been shown to correlate with impulsivity and impulse control.[60]

Other Neuropsychological Symptoms

Poor self-concept, reduced self-esteem, antisocial activities, oppositional behaviors, schizotypal traits, and personality disorders are more frequent in individuals with Tourette syndrome. Their cause, however, appears to be more strongly related to psychiatric comorbidities, family, or economic issues than to tic severity.[61,62] Approximately two-thirds of patients with Tourette syndrome had abnormal scores on the Child Behavior Checklist; identified clinical problems included obsessive-compulsive behaviors, aggressiveness, hyperactivity, immaturity, withdrawal, and somatic symptoms.[63] No evidence has shown that patients with Tourette syndrome are more likely to engage in criminal behavior than those without Tourette syndrome.[64]

Academic Difficulties

Intellectual function is typically normal in Tourette syndrome; however, some children have executive function issues, differences between performance and verbal IQ testing, impairment of visual-perceptual achievement, and a reduction of visual-motor skills.[46] A variety of factors account for poor school performance in children with Tourette syndrome, including disruptive tics, psychosocial difficulties, ADHD, OCD, learning disabilities, and use of medications.[51,65] Individuals with Tourette syndrome or chronic motor or vocal tic disorder are more likely to academically underachieve, even after accounting for various comorbidities.[66]

Sleep Disorders

Sleep disorders, including difficulties falling and staying asleep, restlessness, arousals, and parasomnias, are common in Tourette syndrome.[67,68] Sleep issues have been associated with the presence of comorbidities such as ADHD, anxiety, mood disorders, or OCD[69]; however, others have suggested that sleep problems in Tourette syndrome are not fully explainable by these associated conditions.[67] The effective management of sleep problems has been reported to improve tic control in both severity and impact on life (CASE 3-1).[70]

ETIOLOGY

The precise etiology for Tourette syndrome remains undetermined; however, there is strong agreement that it is associated with polygenic and environmental vulnerability factors.

Genetics

Tourette syndrome is currently classified as a polygenic inherited disorder, suggesting that a combination of a variety of genes (some common, some with a low effect or rare, and others having a larger effect) and environmental factors are all involved in its transmission.[71–73] An inherited nature for Tourette

KEY POINT

- **Tourette syndrome is currently classified as a polygenic inherited disorder, suggesting that a combination of a variety of genes (some common, some with a low effect or rare, and others having a larger effect) and environmental factors are all involved in its transmission.**

syndrome is supported by findings, including a population-based heritability estimate of 0.77 (a value of 1 indicating 100% heritability), a 15-fold increased risk of developing Tourette syndrome/chronic motor or vocal tic disorder in siblings of individuals with Tourette syndrome, a positive family history for tics in about one-half of patients, and monozygotic twins having an 86% concordance rate with chronic motor or vocal tic disorder compared to 20% in dizygotic twins.[74] A genetic predisposition is also believed to increase tic severity and the rate of comorbidities and psychosocial and educational difficulties.[75]

A variety of explanations have been put forth to explain why no definitive causative gene mutation or risk allele has been identified, with possibilities including phenotypic and genotypic heterogeneity, variations in polygenic burden, rare mutations (inherited or de novo), epigenetic factors, and gene-environment interactions.[76] The list of suggested prenatal and perinatal epigenetic risk factors is extensive: limited perinatal care, maternal nausea and vomiting, low birth weight, reduced 5-minute Apgar scores, thimerosal use during the pregnancy, maternal emotional stress, and smoking. Limitations to these studies include the use of retrospective data and clinic-derived rather than epidemiologically derived samples.

Recognizing the absence of definitive risk genes for Tourette syndrome, several potential susceptibility genes have been suggested but not confirmed including the *SLITRK1* gene, located at 13q31.1, and a mutation located in the gene encoding L-histidine decarboxylase *(HDC)*. Genome-wide investigations of copy number variations have identified two significant loci: deletions in *NRXN1* (encodes neurexin 1) and duplications of *CNTN6* (encodes contactin). In a large genome-wide association study, no single marker attained significance; however, the single-nucleotide polymorphism with the strongest signal was located within an intron of *COL27A1* (encodes collagen-α1 chains).[77] In another study, the top single-nucleotide polymorphism associated with Tourette syndrome was an intergenic region distal to *NTN4*, which encodes an axon guidance protein that is expressed in the developing striatum.[78] In an expanded whole-exome sequencing study, de novo variants carried more risk in individuals with unaffected parents, *CELSR3* was identified as a risk gene, and genes mutated in Tourette syndrome were enriched for those relating to cell polarity.[71] Additional studies are required to confirm a link between potential susceptibility genes and the underlying neurobiology of Tourette syndrome.

Tourette syndrome and OCD are clinically associated, and each is highly heritable, suggesting a potential shared genetic liability.[79,80] Nevertheless, specific shared gene variants have been difficult to identify. For example, evidence of 16p13.11 deletions is stronger in OCD than in Tourette syndrome. In contrast, a significant overlap of de novo sequence variants was identified between Tourette syndrome and OCD and of de novo copy number variants between Tourette syndrome and autistic spectrum disorder.[71] An analysis of shared heritability in 23 different neurologic and psychiatric disorders suggested that a significant proportion of Tourette syndrome polygenic heritability is shared with OCD, ADHD, and migraine.[73]

Possible Autoimmune Disorder

Although supporting data are very limited, several immune-mediated mechanisms, including microglial dysfunction, reduced numbers of regulatory T cells, altered gamma globulin, and an increased response to pathogens, have been proposed as

potential contributing etiologic factors for tics.[81] Tic symptoms have also been claimed to be associated with a preceding group A β-hemolytic streptococcal infection, known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). In PANDAS, it is hypothesized that streptococcal-induced polyreactive antibodies, through the process of molecular mimicry, recognize and disrupt either neuronal extracellular surface or intracellular antigens. The existence of PANDAS and its proposed therapy are extremely controversial.[82,83]

KEY POINT

● The existence of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and its proposed therapy are extremely controversial.

PATHOPHYSIOLOGY

Pathophysiological models of Tourette syndrome typically include the disruption of specific circuits involved in motor activity and their associated neurotransmitters.

Circuits

A series of parallel cortical–basal ganglia–thalamocortical circuits provide a framework for understanding the pathophysiology of tics and associated behaviors (FIGURE 3-1).

CORTICOSTRIATAL CONNECTIONS. The three major corticostriatal circuits thought to be involved with Tourette syndrome symptomatology are the association, motor, and limbic circuits. The broad association circuit comprises two major components. The first is a circuit linking dorsolateral Brodmann areas 9 and 10 with the dorsolateral head of the caudate. This pathway is involved with executive functions (flexibility, organization, constructional strategy, verbal and design fluency), motor planning (sequential and alternating reciprocal motor tasks), and goal-directed behaviors. The second component is a lateral orbitofrontal circuit linking the inferior lateral prefrontal cortex (Brodmann areas 11 and 12) with the ventral medial caudate. This circuit is associated with obsessive-compulsive behaviors, personality changes, mania, disinhibition, and irritability. The motor circuit originates from the supplementary motor area and premotor cortex and projects to the putamen in a somatotopic distribution. This pathway is involved with habitual behaviors and is therefore favored by some to be the anatomical site associated with the production of tics. The limbic circuit arises from the anterior cingulate gyrus and projects to the ventral striatum, which also receives input from the amygdala, hippocampus, medial orbitofrontal cortex, entorhinal area, and perirhinal cortex. The ventral striatum (nucleus accumbens and olfactory tubercle) serves as the integrating site for information pertaining to emotion, motivation, vigor, reward, attention, and autonomic factors.

STRIATAL–GLOBUS PALLIDUS–THALAMIC CONNECTIONS. The striatal–globus pallidus–thalamic connections model is a simplistic model that fails to fully recognize the complex interactions between components and focuses on "direct" and "indirect" pathways. The direct pathway transmits striatal information monosynaptically from medium-sized spiny neurons containing dopamine D_1 receptors to the globus pallidus internus/substantia nigra pars reticulata region, where it has an inhibitory effect. In contrast, the indirect pathway conveys information from medium-sized spiny neurons containing dopamine D_2 receptors to the globus pallidus externus, from the globus pallidus externus to the subthalamic nucleus, and then to the globus pallidus interna/substantia nigra pars reticulata, where it has an activating effect. Neurons in the globus pallidus

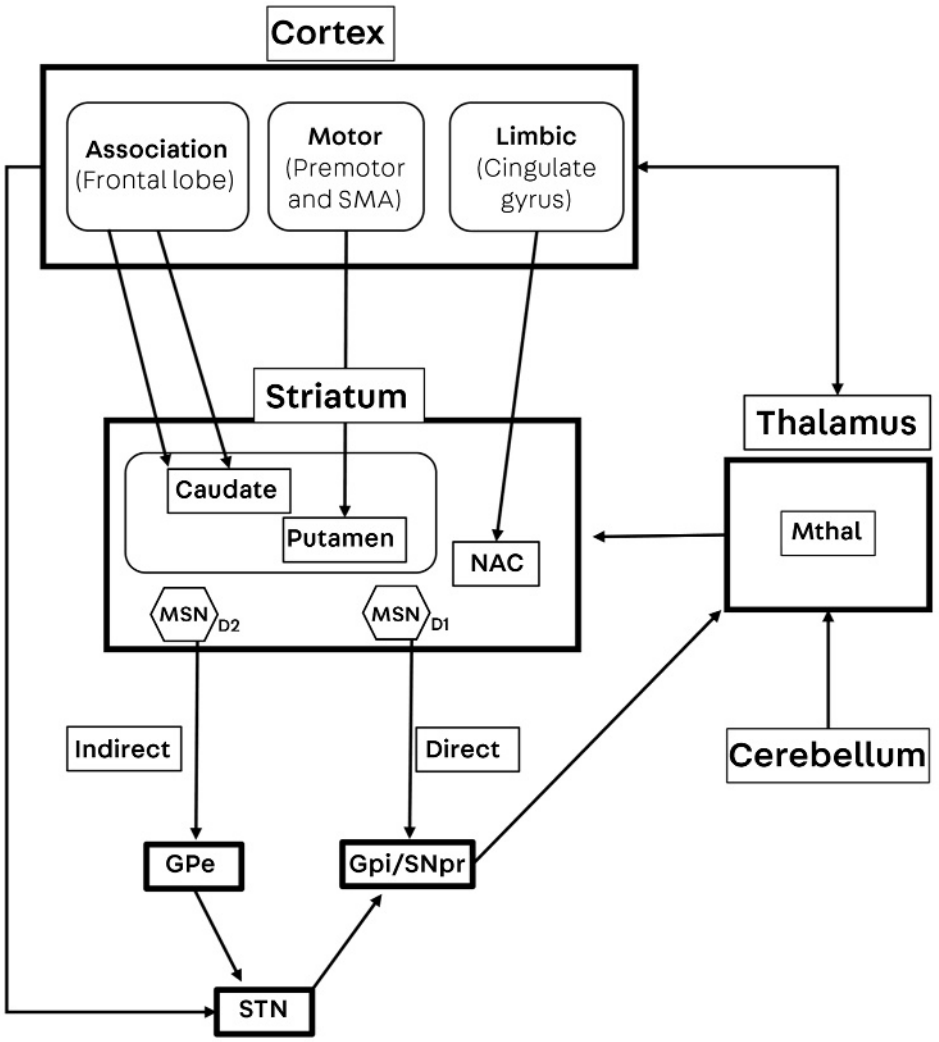

FIGURE 3-1

Cortical–basal ganglia–thalamocortical circuit.

D_1 = dopamine D_1 receptor; D_2 = dopamine D_2 receptor; GPe = globus pallidus externus; GPi = globus pallidus internus; Mthal = motor thalamus; MSN = medium-sized spiny neuron; NAC = nucleus accumbens; SMA = supplementary motor area; SNpr = substantia nigra pars reticulata; STN = subthalamic nucleus.

internus/substantia nigra pars reticulata region, in turn, affect the firing of cells in the thalamus that project to the cortex. In sum, the direct pathway facilitates motor activity via disinhibition of thalamocortical neurons and the indirect pathway reduces motor activity by increasing the inhibition of thalamocortical neurons.

THALAMUS. The motor thalamus is part of a closed loop, receiving input from cortical association, premotor, and motor areas; basal ganglia; and the cerebellum (dentate nucleus). In addition, short subcortical loops exist between the thalamus and striatum.

Possible Location of the Abnormality

Direct and indirect evidence is available to support hypotheses that implicate various individual components of the cortical–basal ganglia–thalamocortical

circuit as the primary anatomic abnormality in Tourette syndrome.[3,84] Nevertheless, identification of the true primary site remains an area of active discussion.

CORTEX. Evidence supporting a primary cortical involvement in tics includes the following:

- A frequent association of tics with neuropsychiatric comorbidities
- A preceding sensory premonitory urge that is associated with activation of several cortical regions
- Postmortem studies demonstrating changes in dopamine transporter and D_2 receptor densities in the frontal cortex not identified in the striatum
- Volumetric MRI studies showing larger dorsal prefrontal and parietooccipital areas; changes in prefrontal, frontal, sensorimotor, cingulate and temporal areas; and alterations of the corpus callosum
- Functional connectivity studies showing increased connections between cortical–basal ganglia networks and widespread immature functional connectivity
- Areas of cortical hypermetabolism in positron emission tomography (PET) studies
- Reduced inhibition within the motor cortex
- Animal models showing that disruption of cortical activity leads to ticlike behaviors

BASAL GANGLIA. Evidence supporting basal ganglia involvement in Tourette syndrome includes its association with other movement disorders; postmortem studies showing reduced density of parvalbumin-positive interneurons, choline acetyltransferase–positive cholinergic interneurons, and medium-sized spiny neurons in the striatum; and animal models demonstrating that the disruption of the glutamate/GABA balance within the striatum causes ticlike behaviors. In contrast, imaging studies of the caudate and putamen have been variable. For example, individual reports have suggested putamen volumes were smaller in children and adults, larger in children, asymmetric, or contained only white matter changes.

OTHER. Preliminary imaging and animal model studies also provide support for involvement of the amygdala, hippocampus, ventral striatum, thalamus, midbrain, and cerebellum. A favored proposal suggests the presence of a complex circuit in which a failure anywhere within the cortical–basal ganglia–thalamocortical circuit, or even one involving inputs to the circuit, can lead to an aberrant message arriving at the primary motor cortex and enabling the tic.[84]

Neurotransmitter Abnormality

Strong evidence supports involvement of cortical–basal ganglia–thalamocortical circuits in the pathophysiology of tic disorders. Several neurotransmitters, including dopamine, glutamate, GABA, serotonin, acetylcholine, norepinephrine, endogenous cannabinoids, opioids, histamine, and adenosine, are active participants within these circuits and may be dynamic factors in the pathophysiology of tics. Hence, an additional area of controversy is whether a specific neurotransmitter or combination of neurotransmitters is relevant in the pathogenesis of tics. Several published reviews discuss the evidence supporting individual neurotransmitter abnormalities in Tourette syndrome.[84,85] In general, data used to support a particular neurotransmitter hypothesis are derived from clinical responses to specific classes of medications; genetic protocols; CSF, blood,

KEY POINTS

- A series of parallel cortical–basal ganglia–thalamocortical circuits provide a framework for understanding the pathophysiology of tics and associated behaviors.
- Identification of the true primary site of anatomic abnormality in Tourette syndrome remains an area of active discussion.

or urine measurements; imaging protocols (magnetic resonance spectroscopy, PET, single-photon emission computed tomography [SPECT]); and a limited number of neurochemical assays on postmortem brain tissues.

Strong neurochemical evidence in Tourette syndrome supports a dopaminergic abnormality, either presynaptic and postsynaptic dysfunctions, or a favored intrasynaptic abnormality involving the phasic (stimulus-induced) release of dopamine.[86] Despite this claim, investigations in humans and animal models have identified imbalances in other neurotransmitter systems. Thus, when trying to determine a primary neurotransmitter abnormality in Tourette syndrome, it is important to recognize that within complex integrated circuits, a change in one neurotransmitter has a significant effect on the function of other interconnected transmitters. Additionally, within a multitransmitter interconnected system, a successful pharmacotherapy does not necessarily indicate that the primary neurotransmitter abnormality is being targeted.

TREATMENT

The establishment of an effective therapeutic plan requires the careful initial assessment of tics, determining the presence of co-occurring issues, and clarifying the resulting impairment of each issue. Further, it is essential to clarify whether tics or associated problems, such as ADHD, OCD, anxiety, school problems, or behavioral disorders, represent the greatest impairment.

The first step in treatment (FIGURE 3-2) is education of the patient, his/her family, and the school or workplace about the diagnosis, its potential coexisting issues, and indications for therapy. Tics have no cure and fluctuate, and supportive

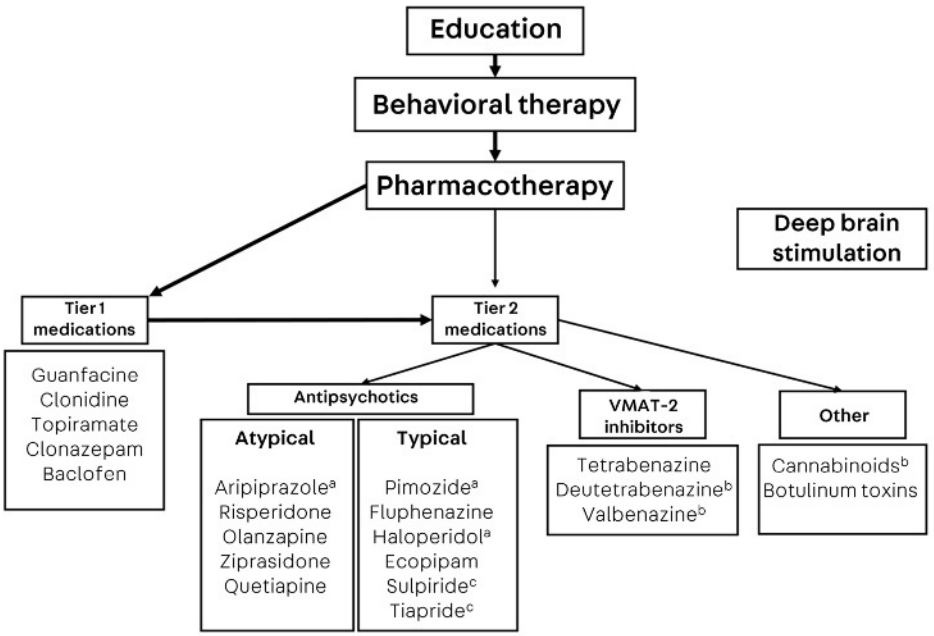

FIGURE 3-2

Approaches to the treatment of tics.

VMAT-2 = vesicular monoamine transporter-2.

[a] Approved by the US Food and Drug Administration for the treatment of tics.

[b] Medications are under investigation.

[c] Medications are not available in the United states.

care is often sufficient for many individuals with milder tics. Specific criteria for initiating behavioral or pharmacologic tic-suppressing therapy include the presence of psychosocial problems (eg, loss of self-esteem; peer problems; difficulty participating in academic, work, family, social, and after-school activities), tic-induced musculoskeletal/physical difficulties, and disruption of classroom/work settings. The goal of treatment is to reduce tics to a degree at which they are no longer causing significant problems.

Nonpharmacologic Treatments

Randomized blinded controlled trials have established the safety and efficacy of habit reversal training for tics. Various practice guidelines have also suggested that habit reversal training should be the first-line intervention for tics.

The treatment program now known as CBIT includes three major components: (1) awareness training to make the patient more aware of his/her tics and the premonitory urge, (2) competing response training to provide a substitutive behavior to perform as soon as the tic or urge appears, and (3) functional intervention (self-monitoring, relaxation training, and contingency management) to help identify changes in daily activities that could be beneficial in reducing tics.[87,88] CBIT has been shown to be beneficial in several large studies and is particularly appealing given its safety and lack of side effects. Recognizing a deficiency of trained therapists, the use of telemedicine and home-based parent-directed therapy are being assessed. Exposure and response prevention, another behavioral technique, asks the patient to experience the urge to tic while actively suppressing tics.

Many families and patients with tics have been attracted to the use of various complementary or alternative medicines,[89–92] including numerous natural supplements (eg, vitamins B, C, and E; magnesium; calcium; flaxseed and fish oil; omega-3 fatty acids; and herbal medicines). To date, however, evidence regarding the efficacy or safety of complementary or alternative medicine treatments for tics is limited. Acupuncture, self-hypnosis, and plum blossom needle therapy also have very limited support. A randomized controlled trial with biofeedback failed to produce a clinical effect greater than placebo. Since many complementary or alternative medicines are pursued independent of a physician's suggestion, an active and open discussion of these therapies is recommended.

Pharmacotherapy

Recommendations regarding the sequence of pharmacologic therapy vary. In general, a two-tiered approach to the use of pharmacotherapy is recommended for treating tics with use of tier 1 medications for milder tics and use of tier 2 medications reserved for more difficult to control symptoms (FIGURE 3-2). Therapeutic agents should initially be prescribed at their lowest effective dosage and gradually increased as needed. Patients should be carefully followed and have periodic evaluations assessing medication efficacy, side effects, and the requirement for continued therapy. Recognizing that treatment is symptomatic, if tics remain under good control for a significant period, a gradual taper of the medication during a nonstressful time should be considered. Currently, only pimozide, haloperidol, and aripiprazole have US Food and Drug Administration (FDA) approval for use as tic-suppressing agents. The extent of supporting evidence for medications has been reviewed, and individual drug selection is often based on physician experience.[91]

KEY POINTS

- It is important to recognize that within a multitransmitter interconnected system, a successful pharmacotherapy does not necessarily indicate that the primary neurotransmitter abnormality is being targeted.
- The establishment of an effective therapeutic plan for Tourette syndrome and tics requires careful initial assessment of tics, determining the presence of co-occurring issues, and clarifying the resulting impairment of each issue.
- The first step in treatment of Tourette syndrome is education of the patient, his/her family, and the school or workplace about the diagnosis, its potential coexisting issues, and indications for therapy.
- Specific criteria for initiating behavioral or pharmacologic tic-suppressing therapy include the presence of psychosocial problems, tic-induced musculoskeletal/physical difficulties, and disruption of classroom/work settings.
- Various practice guidelines have suggested that habit reversal training, more specifically Comprehensive Behavioral Intervention for Tics (CBIT) should be the first-line intervention for tics.
- In general, a two-tiered approach to the use of pharmacotherapy is recommended for treating tics, with use of tier 1 medications for milder tics and use of tier 2 medications reserved for more difficult to control symptoms.

TIER 1 MEDICATIONS. As a category, tier 1 medications are less effective in suppressing tics but have fewer and generally less significant side effects. Medications in this category typically include clonidine, guanfacine, topiramate, clonazepam, and baclofen. Therapeutically, the two α-adrenergic agonists (clonidine and guanfacine) have beneficial effects for both tic suppression and treatment of ADHD.[93] A study comparing extended-release guanfacine to placebo did not, however, confirm a clinically meaningful effect size within the guanfacine group.[94] The efficacy of anticonvulsants is varied; topiramate, a broad-spectrum anticonvulsant medication, was superior to placebo in reducing tics,[95] whereas levetiracetam was not beneficial.[96] Clonazepam is often prescribed for tics, despite limited studies confirming its tic-suppressing effect. Baclofen, a GABA-B receptor agonist, has been variably effective as a treatment for Tourette syndrome.[97]

TIER 2 MEDICATIONS. As a category, tier 2 medications are more effective in suppressing tics than tier 1 medications but are associated with more significant side effects that frequently limit their usefulness. Medications in this category include the dopamine receptor antagonists (typical and atypical antipsychotics) and the vesicular monoamine transporter-2 inhibitors. Several recent reviews provide updates on the efficacy and safety of these therapies.[98,99] Long-term side effects seen in patients receiving either typical or atypical antipsychotics include weight gain, sedation, drowsiness, hyperprolactinemia, extrapyramidal symptoms, including tardive dyskinesia, and QTc prolongation. It has been suggested that tardive dyskinesia is less common in patients with Tourette syndrome treated with atypical antipsychotics as compared to typical antipsychotics.

Typical antipsychotics are primary dopamine antagonists that are further subdivided based on their effect on either the D_1 or D_2 receptor. The two FDA-approved antipsychotics in this category, pimozide and haloperidol, are both D_2 antagonists. Pimozide is generally preferred because of fewer side effects. Sulpiride and tiapride have been beneficial in European trials but are not available in the United States. A new D_1 receptor antagonist, ecopipam, has been effective in small Tourette syndrome trials in both adults and children.[100] Fluphenazine, a combined D_1 and D_2 receptor inhibitor, has also been shown to be effective in several small studies and a retrospective chart review.[101]

Atypical antipsychotics are characterized by a relatively greater affinity for 5-hydroxytryptamine 2 ($5\text{-}HT_2$) receptors than for D_2 receptors, a reduced potential for extrapyramidal side effects, and a possible benefit for behavioral comorbidities (anxiety, mood, disruptive behaviors). In this category, aripiprazole and risperidone are the two most widely studied medications for tics.[98] Aripiprazole, FDA approved for tics, has a different mechanism from the others, being a partial agonist at dopamine receptors.

Vesicular monoamine transporter-2 inhibitors exert their effect by blocking the transport of dopamine into presynaptic vesicles, thereby depleting levels at the synaptic terminal. Tetrabenazine has been shown to be beneficial in open-label trials,[98] although concerns exist about its use in individuals with depression and suicidality. Two new vesicular monoamine transporter-2 inhibitors approved for use in tardive dyskinesia are currently being evaluated for the treatment of tics. Deutetrabenazine, a deuterated form of tetrabenazine, has a longer half-life and improved absorption. Valbenazine, a purified parent drug of the (+)-α-isomer of tetrabenazine, has a half-life of about 24 hours.

Preliminary studies suggest that both valbenazine and deutetrabenazine have fewer side effects than tetrabenazine, but which will be more effective for tic suppression remains undetermined.

Other Medications

Several small studies and case reports have suggested that cannabinoids may have a beneficial effect on tics in patients with Tourette syndrome.[102,103] Pharmacologic approaches have included smoking marijuana or using extracts from the cannabis plant, including Δ-9-tetrahydrocannibinol (THC), cannabidiol, and nabiximols (combinations of THC and cannabidiol). The most common side effects are sedation, dizziness, headaches, a "high" (euphoria feeling), red eyes, increased appetite, psychosis, depression, and cognitive impairment.[84] Several reviews, however, have emphasized the lack of evidence with regard to the use of cannabinoids and the requirement for additional testing. A second investigative approach to cannabinoid therapy involves attempts to modulate the brain's existing endocannabinoid system.

Botulinum toxin has a beneficial chemodenervation effect on severe localized tics (eg, violent head thrusts), dystonic motor tics, and vocal tics and reduces the premonitory sensory component (CASE 3-2).[104,105]

Brain Stimulation

Repetitive transcranial magnetic stimulation is a noninvasive technique that uses brief repetitive intense magnetic fields generated by a coil placed over the scalp to produce an electromagnetic field in the underlying brain region. Several small trials in Tourette syndrome using low-frequency inhibiting repetitive transcranial magnetic stimulation (1 Hz) suggest that it can have a beneficial effect, especially if the supplementary motor area is targeted.[106] A single double-blind randomized placebo trial, however, showed no significant difference between active and sham treatment.[107] A small study using cathodal transcranial direct current stimulation was unsuccessful in two-thirds of patients with severe tics.[108]

Deep brain stimulation is a stereotactic treatment that has significant potential for the treatment of tics.[109,110] The centromedian parafascicular complex of the thalamus and anteromedial globus pallidus internus have been the most commonly stimulated sites, but the optimal target has yet to be determined. Although most reports describe a beneficial effect, interpretation is confounded by variations in methodologies, differences in complications, variable use of standard outcome measures, and the lack of a control population. Suggested criteria for the use of deep brain stimulation in patients with tics include the following:

- Disabling tics with a Yale Global Tic Severity Scale score of more than 35/50
- Failed behavioral therapy (CBIT)
- Failed medication trials from pharmacologic groups including α-adrenergic agonists (guanfacine, clonidine) and dopamine antagonists (including one typical and one atypical antipsychotic), plus one additional category (vesicular monoamine transporter-2 inhibitors)
- Evaluation by a multidisciplinary team (eg, neurologist, neurosurgeon, psychiatrist, neuropsychologist, deep brain stimulation programmer)
- Treated and stable comorbid conditions[110]

KEY POINT

- Deep brain stimulation is a stereotactic treatment that has significant potential for the treatment of tics.

Deep brain stimulation for patients younger than 18 years of age should have additional institutional approval (CASE 3-2).

CONCLUSION

Tourette syndrome is a heterogeneous disorder with variable and fluctuating motor and vocal tics as well as frequent co-occurring neuropsychiatric

CASE 3-2

A 19-year-old man was referred for a second opinion regarding the treatment of Tourette syndrome. He was diagnosed with Tourette syndrome at 8 years of age. His history included numerous intermittent and fluctuating motor tics (ocular deviations, forceful head jerks, shoulder shrugs, facial and body contortions, abdominal jerks, hitting, jumping, and copropraxia) and vocal tics (coprolalia, echolalia, palilalia, shouts, and screams).

Over the past several weeks, his tics had dramatically increased without a clear precipitating event. Both motor and vocal tics were occurring every few minutes. The motor tics were extremely forceful and complex and included violent head flexion and extension movements that were causing persistent neck discomfort. Recent x-rays of his neck were normal. His vocal tics were very loud and interfered with his social activities. He had recently left college and returned home because of his discomfort.

He was on 20 mg/d aripiprazole after clonidine, guanfacine, pimozide, haloperidol, and risperidone had failed to control his tics. He was also on sertraline and clonazepam for anxiety and obsessive-compulsive disorder.

On examination, he was extremely anxious and had frequent motor tics, including very painful exaggerated head thrusts, and coprolalia. Neurologic examination showed marked discomfort with neck flexion and extension and cervical spine tenderness. Tone, strength, sensation, and reflexes were normal.

COMMENT

Although many tics have a benign course, a sudden worsening of symptoms, such as in this patient, is not unusual. Exacerbations are often associated with increased stress, fatigue, anxiety, illness, or the use of certain medications. At times, however, no clear precipitating event may be identified. As in this patient, tics can be extremely violent, and movements of the head and neck can cause cervical dislocations, myelopathies, and subdural hematomas. Tics that are potentially self-injurious require immediate attention.

Both typical and atypical antidepressants had failed for this patient, but he had never been prescribed a trial of a vesicular monoamine transporter-2 inhibitor, which he was then treated with. Because of the potential for further self-injury and the need for gradual adjustment of his medications, he also received cervical muscle botulinum toxin therapy. If further treatment is required, deep brain stimulation is a promising therapeutic option.

conditions. While tics are the defining symptom, for some, the presence of comorbid conditions may be a greater impairment. Providing education to the affected individual and others in his or her life is essential. If tics are causing psychosocial or physical problems or frequent disruptions within the school, home, or work environment, behavioral and pharmacologic therapies may be beneficial. Tics have no cure; behavioral therapy (CBIT) is considered first-line therapy, and pharmacotherapy should be based on tic severity. If required, appropriate therapies should be initiated for co-occurring conditions. Ongoing follow-up is essential to monitor the patient's progress, adjust therapy, and assess for side effects. Tourette syndrome is currently believed to be a polygenic inherited disorder, and the discovery of additional susceptibility genes is expected. Although controversy regarding the precise anatomic localization and neurotransmitter abnormality is ongoing, progress is being made. It is expected that a better understanding of the genetics and pathophysiologic mechanism in Tourette syndrome will lead to improved care and newer therapies.

VIDEO LEGENDS

VIDEO 3-1
Tourette syndrome. Video shows a boy with Tourette syndrome demonstrating frequent blinking, alternating facial contractions, tongue protrusions, and mouth openings.
links.lww.com/CONT/A284

VIDEO 3-2
Dystonic tics. Video shows a girl exhibiting facial tics manifested by repetitive sustained contractions of facial muscles, resulting in grimacing and neck muscle contractions typical of dystonic tics.
links.lww.com/CONT/A285

VIDEO 3-3
Repetitive complex movements. Video shows a boy with Tourette syndrome displaying repetitive, complex movements produced by contractions of his shoulder and trunk muscles, preceded by an intense premonitory sensation of a chill.
links.lww.com/CONT/A286

VIDEO 3-4
Dystonic, vocal, and holding (blocking) tics. Video shows a boy with Tourette syndrome exhibiting a dystonic extension of his neck associated with repetitive expiratory grunting sounds. In addition, he demonstrates a holding (blocking) tic, during which time he stops breathing and is completely motionless.
links.lww.com/CONT/A287

VIDEO 3-5
Complex motor and phonic tics. Video shows a 17-year-old girl with severe Tourette syndrome exhibiting complex motor tics and loud screaming phonic tics.
links.lww.com/CONT/A288

VIDEO 3-6
Complex motor and phonic tics. Video shows a boy with severe Tourette syndrome exhibiting complex motor and loud phonic tics, including coprolalia.
links.lww.com/CONT/A289

USEFUL WEBSITE

TOURETTE ASSOCIATION OF AMERICA
The Tourette Association of America provides educational materials and information about research efforts, support groups, and other services to assist patients and their families in coping with the problems associated with Tourette syndrome.
tourette.org

REFERENCES

1 Gilles dela Tourette G. Étude sur une affection nerveuse caractèrisée par de l'incoordination motrice accompagnée d'écholalie et de coprolalie (jumping, latah, myriachit). Paris: Aux bureaux du Progrès médical : V.-A. Delahaye et Lecrosnier; 1885. 68 p. (Publications du Progrès médical).

2 Kushner HI. Medical fictions: the case of the cursing marquise and the (re)construction of Gilles de la Tourette's syndrome. Bull Hist Med 1995;69(2):224–254.

3 Singer HS. Tics and Tourette syndrome. In: Singer HS, Mink J, Gilbert DL, Jankovic J. Movement disorders in childhood. 2nd ed. London, UK: Elsevier, 2016:81–109.

4 Cavanna AE, Robertson MM, Critchley HD. Catatonic signs in Gilles de la Tourette syndrome. Cogn Behav Neurol 2008;21(1):34–37. doi:10.1097/WNN.0b013e318165a9cf.

5 Robertson MM, Trimble MR, Lees AJ. Self-injurious behaviour and the Gilles de la Tourette syndrome: a clinical study and review of the literature. Psychol Med 1989;19(3):611–625. doi:10.1017/S0033291700024211.

6 Cheung MY, Shahed J, Jankovic J. Malignant Tourette syndrome. Mov Disord 2007;22(12):1743–1750. doi:10.1002/mds.21599.

7 Freeman RD, Zinner SH, Müller-Vahl KR, et al. Coprophenomena in Tourette syndrome. Dev Med Child Neurol 2009;51(3):218–227. doi:10.1111/j.1469-8749.2008.03135.x.

8 Robertson MM, Eapen V, Singer HS, et al. Gilles de la Tourette syndrome. Nat Rev Dis Primers 2017;3:16097. doi:10.1038/nrdp.2016.97.

9 Lin H, Katsovich L, Ghebremichael M, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. J Child Psychol Psychiatry 2007;48(2):157–166. doi:10.1111/j.1469-7610.2006.01687.x.

10 Hoekstra PJ, Steenhuis MP, Kallenberg CG, Minderaa RB. Association of small life events with self reports of tic severity in pediatric and adult tic disorder patients: a prospective longitudinal study. J Clin Psychiatry 2004;65(3):426–431.

11 Horesh N, Zimmerman S, Steinberg T, et al. Is onset of Tourette syndrome influenced by life events? J Neural Transm (Vienna) 2008;115(5):787–793. doi:10.1007/s00702-007-0014-3.

12 Cohrs S, Rasch T, Altmeyer S, et al. Decreased sleep quality and increased sleep related movements in patients with Tourette's syndrome. J Neurol Neurosurg Psychiatry 2001;70(2):192–197. doi:10.1136/jnnp.70.2.192.

13 Kwak C, Dat Vuong K, Jankovic J. Premonitory sensory phenomenon in Tourette's syndrome. Mov Disord 2003;18(12):1530–1533. doi:10.1002/mds.10618.

14 Banaschewski T, Woerner W, Rothenberger A. Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. Dev Med Child Neurol 2003;45(10):700–703. doi:10.1017/S0012162203001294.

15 Prado HS, Rosário MC, Lee J, et al. Sensory phenomena in obsessive-compulsive disorder and tic disorders: a review of the literature. CNS Spectr 2008;13(5):425–432. doi:10.1017/S1092852900016606.

16 Shprecher DR, Gannon K, Agarwal N, et al. Elucidating the nature and mechanism of tic improvement in tourette syndrome: a pilot study. Tremor Other Hyperkinet Mov (N Y) 2014;4:217. doi:10.7916/D8TH8JQQ.

17 Groth C, Mol Debes N, Rask CU, et al. Course of Tourette syndrome and comorbidities in a large prospective clinical study. J Am Acad Child Adolesc Psychiatry 2017;56(4):304–312. doi:10.1016/j.jaac.2017.01.010.

18 Erenberg G, Cruse RP, Rothner AD. The natural history of Tourette syndrome: a follow-up study. Ann Neurol 1987;22(3):383–385. doi:10.1002/ana.410220317.

19 Pappert EJ, Goetz CG, Louis ED, et al. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology 2003;61(7):936–940. doi:10.1212/01.WNL.0000086370.10186.7C.

20 Jankovic J, Gelineau-Kattner R, Davidson A. Tourette's syndrome in adults. Mov Disord 2010;25(13):2171–2175. doi:10.1002/mds.23199.

21 Schaefer SM, Chow CA, Louis ED, Robakis D. Tic exacerbation in adults with Tourette syndrome: a case series. Tremor Other Hyperkinet Mov (N Y) 2017;7:450. doi:10.7916/D8FF3Z1Q.

22 Eapen V, Lees AJ, Lakke JP et al. Adult-onset tic disorders. Mov Disord 2002;17(4):735–740. doi:10.1002/mds.10180.

23 Kompoliti K, Goetz CG. Hyperkinetic movement disorders misdiagnosed as tics in Gilles de la Tourette syndrome. Mov Disord 1998;13(3):477–480. doi:10.1002/mds.870130317.

24 Mahone EM, Bridges D, Prahme C, Singer HS. Repetitive arm and hand movements (complex motor stereotypies) in children. J Pediatr 2004;145(3):391–395. doi:10.1016/j.jpeds.2004.06.014.

25 Van Borsel J, Tetnowski JA. Fluency disorders in genetic syndromes. J Fluency Disord 2007;32(4):279–296. doi:10.1016/j.jfludis.2007.07.002.

26 Baizabal-Carvallo JF, Jankovic J. The clinical features of psychogenic movement disorders resembling tics. J Neurol Neurosurg Psychiatry 2014;85(5):573–575. doi:10.1136/jnnp-2013-305594.

27 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Washington, DC: American Psychiatric Association, 2013.

28 Jankovic J, Mejia NI. Tics associated with other disorders. Adv Neurol 2006;99:61–68.

29 Kim DD, Barr AM, Chung Y, et al. Antipsychotic-associated symptoms of Tourette syndrome: a systematic review. CNS Drugs 2018;32(10): 917–938. doi:10.1007/s40263-018-0559-8.

30 Friedland S, Walkup JT. Meta-assurance: no tic exacerbation caused by stimulants. J Am Acad Child Adolesc Psychiatry 2015;54(9):706–708. doi:10.1016/j.jaac.2015.06.018.

31 Saccomani L, Fabiana V, Manuela B, Giambattista R. Tourette syndrome and chronic tics in a sample of children and adolescents. Brain Dev 2005;27(5):349–352. doi:10.1016/j.braindev.2004.09.007.

32 Definitions and classification of tic disorders. The Tourette Syndrome Classification Study Group. Arch Neurol 1993;50(10):1013–1016.

33 Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28(4):566–573. doi:10.1097/00004583-198907000-00015.

34 Cavanna AE, Schrag A, Morley D, et al. The Gilles de la Tourette syndrome–quality of life scale (GTS-QOL): development and validation. Neurology 2008;71(18):1410–1416. doi:10.1212/01.wnl.0000327890.02893.61.

35 Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with tic disorders. J Dev Behav Pediatr 2005;26(6): 397–403. doi:10.1097/00004703-200512000-00001.

36 Kurlan R, McDermott MP, Deeley C, et al. Prevalence of tics in schoolchildren and association with placement in special education. Neurology 2001; 57(8):1383–1388. doi:10.1212/WNL.57.8.1383.

37 Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 2: tentative explanations for differing prevalence figures in GTS, including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes. J Psychosom Res 2008;65(5):473–486. doi:10.1016/j.jpsychores.2008.03.007.

38 Scharf JM, Miller LL, Gauvin CA, et al. Population prevalence of Tourette syndrome: a systematic review and meta-analysis. Mov Disord 2015;30(2): 221–228. doi:10.1002/mds.26089.

39 Knight T, Steeves T, Day L, et al. Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol 2012;47(2):77–90. doi:10.1016/j.pediatrneurol.2012.05.002.

40 Canitano R, Vivanti G. Tics and Tourette syndrome in autism spectrum disorders. Autism 2007;11(1):19–28. doi:10.1177/1362361307070992.

41 Meier SM, Dalsgaard S, Mortensen PB, et al. Mortality risk in a nationwide cohort of individuals with tic disorders and with tourette syndrome. Mov Disord 2017;32(4):605–609. doi:10.1002/mds.26939.

42 Leivonen S, Scharf JM, Mathews CA, et al. Parental psychopathology and Tourette syndrome/chronic tic disorder in offspring: a nationwide case–control study. J Am Acad Child Adolesc Psychiatry 2017;56(4):297–303.e4. doi:10.1016/j.jaac.2017.01.009.

43 Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry 2015;72(4):325–333. doi:10.1001/jamapsychiatry.2014.2650.

44 Cavanna AE, Rickards H. The psychopathological spectrum of Gilles de la Tourette syndrome. Neurosci Biobehav Rev 2013;37(6):1008–1015. doi:10.1016/j.neubiorev.2012.10.011.

45 Storch EA, Merlo LJ, Lack C, et al. Quality of life in youth with Tourette's syndrome and chronic tic disorder. J Clin Child Adolesc Psychol 2007;36(2): 217–227. doi:10.1080/15374410701279545.

46 Channon S, Pratt P, Robertson MM. Executive function, memory, and learning in Tourette's syndrome. Neuropsychology 2003;17(2):247–254. doi:10.1037/0894-4105.17.2.247.

47 Khalifa N, Knorring AL. Psychopathology in a Swedish population of school children with tic disorders. J Am Acad Child Adolesc Psychiatry 2006;45(11):1346–1353. doi:10.1097/01.chi.0000251210.98749.83.

48 Stiede JT, Alexander JR, Wellen B, et al. Differentiating tic-related from non-tic-related impairment in children with persistent tic disorders. Compr Psychiatry 2018;87:38–45. doi:10.1016/j.comppsych.2018.07.017.

49 Comings DE, Comings BG. A controlled study of Tourette syndrome. I. Attention-deficit disorder, learning disorders, and school problems. Am J Hum Genet 1987;41(5):701–741.

50 Termine C, Luoni C, Fontolan S, et al. Impact of co-morbid attention-deficit and hyperactivity disorder on cognitive function in male children with Tourette syndrome: a controlled study. Psychiatry Res 2016;243:263–267. doi:10.1016/j.psychres.2016.06.048.

51 Huckeba W, Chapieski L, Hiscock M, Glaze D. Arithmetic performance in children with Tourette syndrome: relative contribution of cognitive and attentional factors. J Clin Exp Neuropsychol 2008; 30(4):410–420. doi:10.1080/13803390701494970.

52 Stewart SE, Illmann C, Geller DA, et al. A controlled family study of attention-deficit/hyperactivity disorder and Tourette's disorder. J Am Acad Child Adolesc Psychiatry 2006;45(11): 1354–1362. doi:10.1097/01.chi.0000251211.36868.fe.

53 Martino D, Ganos C, Pringsheim TM. Tourette syndrome and chronic tic disorders: the clinical spectrum beyond tics. Int Rev Neurobiol 2017; 134:1461–1490. doi:10.1016/bs.irn.2017.05.006.

54 Gaze C, Kepley HO, Walkup JT. Co-occurring psychiatric disorders in children and adolescents with Tourette syndrome. J Child Neurol 2006; 21(8):657–664. doi:10.1177/08830738060210081301.

55 Lombroso PJ, Scahill L. Tourette syndrome and obsessive-compulsive disorder. Brain Dev 2008; 30(4):231–237. doi:10.1016/j.braindev.2007.09.001.

56 Rickards H, Robertson M. A controlled study of psychopathology and associated symptoms in Tourette syndrome. World J Biol Psychiatry 2003; 4(2):64–68. doi:10.3109/15622970309167953.

57 Storch EA, Hanks CE, Mink JW, et al. Suicidal thoughts and behaviors in children and adolescents with chronic tic disorders. Depress Anxiety 2015;32(10):744–753. doi:10.1002/da.22357.

58 Budman CL, Rockmore L, Stokes J, Sossin M. Clinical phenomenology of episodic rage in children with Tourette syndrome. J Psychosom Res 2003;55(1):59–65. doi:10.1016/S0022-3999(02)00584-6.

59 Mol Debes NM. Co-morbid disorders in Tourette syndrome. Behav Neurol 2013;27(1):7–14. doi:10.3233/BEN-120275.

60 Mathews C, Waller J, Glidden D, et al. Self injurious behaviour in Tourette syndrome: correlates with impulsivity and impulse control. J Neurol Neurosurg Psychiatry 2004;75(8):1149–1155. doi:10.1136/jnnp.2003.020693.

61 Silvestri PR, Baglioni V, Cardona F, Cavanna AE. Self-concept and self-esteem in patients with chronic tic disorders: a systematic literature review. Eur J Paediatr Neurol 2018;22(5):749–756. doi:10.1016/j.ejpn.2018.05.008.

62 Cavanna AE, Robertson MM, Critchley HD. Schizotypal personality traits in Gilles de la Tourette syndrome. Acta Neurol Scand 2007;116(6): 385–391. doi:10.1111/j.1600-0404.2007.00879.x.

63 Ghanizadeh A, Mosallaei S. Psychiatric disorders and behavioral problems in children and adolescents with Tourette syndrome. Brain Dev 2009;31(1): 15–19. doi:10.1016/j.braindev.2008.03.010.

64 Jankovic J, Kwak C, Frankoff R. Tourette's syndrome and the law. J Neuropsychiatry Clin Neurosci 2006; 18(1):86–95. doi:10.1176/jnp.18.1.86.

65 Singer HS, Schuerholz LJ, Denckla MB. Learning difficulties in children with Tourette syndrome. J Child Neurol 1995;10(suppl 1):S58–S61. doi:10.1177/08830738950100S112.

66 Pérez-Vigil A, Fernández de la Cruz L, Brander G, et al. Association of Tourette syndrome and chronic tic disorders with objective indicators of educational attainment: a population-based sibling comparison study. JAMA Neurol 2018; 75(9):1098–1105. doi:10.1001/jamaneurol.2018.1194.

67 Lee WT, Huang HL, Wong LC, et al. Tourette syndrome as an independent risk factor for subsequent sleep disorders in children: a nationwide population-based case-control Study. Sleep 2017;40(3). doi:10.1093/sleep/zsw072.

68 Ghosh D, Rajan PV, Das D, et al. Sleep disorders in children with Tourette syndrome. Pediatr Neurol 2014;51(1):31–35. doi:10.1016/j.pediatrneurol.2014.03.017.

69 Kirov R, Kinkelbur J, Banaschewski T, Rothenberger A. Sleep patterns in children with attention-deficit/hyperactivity disorder, tic disorder, and comorbidity. J Child Psychol Psychiatry 2007;48(6):561–570. doi:10.1111/j.1469-7610.2007.01729.x.

70 Ghosh D, Rizkala A, Khuhro A. Management of sleep problems helps improve tic control in children with Tourette Syndrome/chronic tic disorder. Poster presented at: 47th Child Neurology Society Meeting; Chicago IL, Annals of Neurology, 84: issue 522, Oct 2018, S370.

71 Wang S, Mandell JD, Kumar Y, et al. De novo sequence and copy number variants are strongly associated with Tourette disorder and implicate cell polarity in pathogenesis. Cell Rep 2018;24(13): 3544. doi:10.1016/j.celrep.2018.12.024.

72 Fernandez TV, State MW, Pittenger C. Tourette disorder and other tic disorders. In: Geschwind DH, Paulson HL, Klein C, editors. Handbook of Clinical Neurology. Amsterdam, the Netherlands: Elsevier, 2018:343–354.

73 Brainstorm Consortium; Anttila V, Bulik-Sullivan B, et al. Analysis of shared heritability in common disorders of the brain. Science 2018;360(6395): 048991. doi:10.1126/science.aap8757.

74 Mataix-Cols D, Isomura K, Pérez-Vigil A, et al. Familial risks of Tourette syndrome and chronic tic disorders. A population-based cohort study. JAMA Psychiatry 2015;72(8):787–793. doi:10.1001/jamapsychiatry.2015.0627.

75 Pauls DL, Abramovitch A, Rauch SL, Geller DA. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci 2014;15(6):410–424. doi:10.1038/nrn3746.

76 Georgitsi M, Willsey AJ, Mathews CA, et al. The genetic etiology of Tourette syndrome: large-scale collaborative efforts on the precipice of discovery. Front Neurosci 2016;10:351. doi:10.3389/fnins.2016.00351.

77 Scharf JM, Moorjani P, Fagerness J, et al. Lack of association between SLITRK1var321 and Tourette syndrome in a large family-based sample. Neurology 2008;70(16 pt 2):1495–1496. doi:10.1212/01.wnl.0000296833.25484.bb.

78 Lai Wing Sun K, Correia JP, Kennedy TE. Netrins: versatile extracellular cues with diverse functions. Development 2011;138(11):2153–2169. doi:10.1242/dev.044529.

79 Browne HA, Hansen SN, Buxbaum JD, et al. Familial clustering of tic disorders and obsessive-compulsive disorder. JAMA Psychiatry 2015;72(4):359–366. doi:10.1001/jamapsychiatry.2014.2656.

80 Yu D, Mathews CA, Scharf JM, et al. Cross-disorder genome-wide analyses suggest a complex genetic relationship between Tourette's syndrome and OCD. Am J Psychiatry 2015;172(1):82–93. doi:10.1176/appi.ajp.2014.13101306.

81 Martino D, Zis P, Buttiglione M. The role of immune mechanisms in Tourette syndrome. Brain Res 2015;1617:126–143. doi:10.1016/j.brainres.2014.04.027.

82 Gilbert DL, Mink JW, Singer HS. A pediatric neurology perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. J Pediatr 2018;199:243–251. doi:10.1016/j.jpeds.2018.04.035.

83 Singer HS. Autoantibody-associated movement disorders in children: proven and proposed. Semin Pediatr Neurol 2017;24(3):168–179. doi:10.1016/j.spen.2017.08.003.

84 Augustine F, Singer HS. Merging the pathophysiology and pharmacotherapy of tics. Tremor Other Hyperkinet Mov 2018;8:595. doi:10.7916/D8H14JTX.

85 Singer HS. The neurochemistry of Tourette syndrome. In: Martino D, Leckman JF, editors. Tourette syndrome. London, UK: Oxford University Press, 2013. *oxfordmedicine.com/view/10.1093/med/9780199796267.001.0001/med-9780199796267-chapter-13*. Accessed June 5, 2019.

86 Singer HS, Szymanski S, Giuliano J, et al. Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. Am J Psychiatry 2002;159(8):1329–1336. doi:10.1176/appi.ajp.159.8.1329.

87 Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010;303(19):1929–1937. doi:10.1001/jama.2010.607.

88 Wile DJ, Pringsheim TM. Behavior therapy for Tourette syndrome: a systematic review and meta-analysis. Curr Treat Options Neurol 2013;15(4):385–395. doi:10.1007/s11940-013-0238-5.

89 Kompoliti K, Fan W, Leurgans S. Complementary and alternative medicine use in Gilles de la Tourette syndrome. Mov Disord 2009;24(13):2015–2019. doi:10.1002/mds.22724.

90 Sharp AN, Singer HS. Standard, complementary, and future treatment options for tics. Curr Dev Disord Rep 2018;5(2):101–107. doi:10.1007/s40474-018-0138-1.

91 Pringsheim T, Holler-Managan Y, Okun MS, et al. Comprehensive systematic review summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology 2019;92(19):907–915. doi:10.1212/WNL.0000000000007467.

92 Kumar A, Duda L, Mainali G, et al. A comprehensive review of Tourette syndrome and complementary alternative medicine. Curr Dev Disord Rep 2018;5(2):95–100. doi:10.1007/s40474-018-0137-2.

93 Singer HS. Treatment of tics and tourette syndrome. Curr Treat Options Neurol 2010;12(6):539–561. doi:10.1007/s11940-010-0095-4.

94 Murphy TK, Fernandez TV, Coffey BJ, et al. Extended-release guanfacine does not show a large effect on tic severity in children with chronic tic disorders. J Child Adolesc Psychopharmacol 2017;27(9):762–770. doi:10.1089/cap.2017.0024.

95 Yang CS, Zhang LL, Zeng LN, et al. Topiramate for Tourette's syndrome in children: a meta-analysis. Pediatr Neurol 2013;49(5):344–350. doi:10.1016/j.pediatrneurol.2013.05.002.

96 Smith-Hicks CL, Bridges DD, Paynter NP, Singer HS. A double blind randomized placebo control trial of levetiracetam in Tourette syndrome. Mov Disord 2007;22(12):1764–1770. doi:10.1002/mds.21615.

97 Singer HS, Wendlandt J, Krieger M, Giuliano J. Baclofen treatment in Tourette syndrome: a double-blind, placebo-controlled, crossover trial. Neurology 2001;56(5):599–604. doi:10.1212/WNL.56.5.599.

98 Mogwitz S, Buse J, Wolff N, Roessner V. Update on the pharmacological treatment of tics with dopamine-modulating agents. ACS Chem Neurosci 2018;9(4):651–672. doi:10.1021/acschemneuro.7b00460.

99 Quezada J, Coffman KA. Current approaches and new developments in the pharmacological management of Tourette syndrome. CNS Drugs 2018;32(1):33–45. doi:10.1007/s40263-017-0486-0.

100 Gilbert DL, Murphy TK, Jankovic J, et al. Ecopipam, a D1 receptor antagonist, for treatment of tourette syndrome in children: a randomized, placebo-controlled crossover study. Mov Disord Aug;33(8):1272–1280. doi:10.1002/mds.27457.

101 Wijemanne S, Wu LJ, Jankovic J. Long-term efficacy and safety of fluphenazine in patients with Tourette syndrome. Mov Disord 2014;29(1):126–130. doi:10.1002/mds.25692.

102 Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 2015;313(24):2456–2473. doi:10.1001/jama.2015.6358.

103 Kanaan AS, Jakubovski E, Müller-Vahl K. Significant tic reduction in an otherwise treatment-resistant patient with Gilles de la Tourette syndrome following treatment with nabiximols. Brain Sci 2017 26;7(5): pii: E47. doi:10.3390/brainsci7050047.

104 Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol 2000;57(8):1190–1193. doi:10.1001/archneur.57.8.1190.

105 Vincent DA Jr. Botulinum toxin in the management of laryngeal tics. J Voice 2008;22(2):251–256. doi:10.1016/j.jvoice.2006.08.014.

106 Grados M, Huselid R, Duque-Serrano L. Transcranial magnetic stimulation in Tourette syndrome: a historical perspective, its current use and the influence of comorbidities in treatment response. Brain Sci 2018;8(7). pii: E129. doi:10.3390/brainsci8070129.

107 Landeros-Weisenberger A, Mantovani A, Motlagh MG, et al. Randomized sham controlled double-blind trial of repetitive transcranial magnetic stimulation for adults with severe Tourette syndrome. Brain Stimul 2015;8(3):574–581. doi:10.1016/j.brs.2014.11.015.

108 Behler N, Leitner B, Mezger E, et al. Cathodal tDCS over motor cortex does not improve Tourette syndrome: lessons learned from a case series. Front Behav Neurosci 2018;12:194. doi:10.3389/fnbeh.2018.00194.

109 Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. JAMA Neurol 2018;75(3):353–359. doi:10.1001/jamaneurol.2017.4317.

110 Schrock LE, Mink JW, Woods DW, et al. Tourette syndrome deep brain stimulation: a review and updated recommendations. Mov Disord 2015;30(4):448–471. doi:10.1002/mds.26094.