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Tourette Syndrome: Evolving Concepts

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ABSTRACT: Tourette syndrome is a common childhood-onset neurobehavioral disorder characterized by multiple motor and phonic tics affecting boys more frequently than girls. Premonitory sensory urges prior to tic execution are common, and this phenomenon helps to distinguish tics from other hyperkinetic movement disorders. Tourette syndrome is commonly associated with attention deficit hyperactivity disorder, obsessive-compulsive disorder, learning difficulties, and impulse control disorder. The pathophysiology of this complex disorder is not well understood. Involvement of basal ganglia-related circuits and dopaminergic system has been suggested by various imaging and postmortem studies. Although it is considered a

genetic disorder, possibly modified by environmental factors, an intense search has thus far failed to find causative genes. Symptomatic treatment of tics chiefly utilizes various alpha adrenergic agonists, antidopaminergic drugs, topiramate, botulinum toxin, and deep brain stimulation. Habit reversal therapy and other behavioral approaches may be a reasonable option for some cases. Improved understanding of Tourette syndrome should lead to better symptomatic and more effective pathogenesis-targeted therapies. © 2011 Movement Disorder Society

Key Words: attention deficit disorder; obsessive compulsive disorder; tics; Tourette syndrome

Tourette syndrome (TS) should be more appropriately named “Gilles de la Tourette syndrome,” after the French neurologist who described this neurological and behavioral disorder in 1885. In his initial monograph, Georges Albert Édouard Brutus Gilles de la Tourette, a 28-year-old student of Jean-Martin Charcot, described 9 patients who exhibited brief involuntary movements (motor tics): 6 made noises (phonic tics), 5 shouted obscenities (coprolalia), 5 repeated the words of others

(echolalia), and 2 mimicked others' gestures (echopraxia).¹ Traditionally credited with the first comprehensive report of this neurobehavioral disorder, Gilles de la Tourette actually was not the first to describe the disorder that now bears his name, as a detailed account of the most typical features was published 12 years earlier by Parisian physician Armand Trousseau.¹ Although the hereditary nature of the disorder was recognized early, the etiology was initially ascribed to psychogenic causes until the 1960s, when the beneficial effects of neuroleptic drugs in the treatment of tics began to be recognized. TS is now considered a neurologic disorder manifested by motor and phonic tics usually starting during childhood and often accompanied by a variety of behavioral comorbidities such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), poor impulse control, and other behavioral problems.² Despite improved understanding of TS, the disorder is still often wrongly labeled as “mental” and is currently included in the ICD-9 classification in the category of “mental disorders” (codes 290–319), although some physicians use the code 333.3—tics of organic origin. As a result of the misrepresentation of TS as a “mental disorder,” payments for TS-related services are often denied by insurance companies. According to the criteria outlined by the *Diagnostic and Statistical Manual of Mental*

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Disorders, Fourth Edition (DSM-IV), currently under revision as DSM-V (<http://www.dsm5.org>), to make a diagnosis of definite TS: (1) both multiple motor and 1 or more phonic tics must be present at some time during the illness, although not necessarily concurrently; (2) the tics must occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year without a tic-free period of more than 3 consecutive months; (3) the onset must be before age 18 years; and (4) the disturbance must not be due to the direct physiological effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington disease or postviral encephalitis).

Despite increased educational efforts, the diagnosis of TS often is still made not by pediatricians or other physicians but by the patients themselves or their families as a result of information obtained from the media or the Internet. By supplementing scientific articles with videos, the *Movement Disorders* journal (MDJ) over the past quarter century has played a key role in informing physicians, particularly neurologists, about the rich phenomenology associated with TS. Many patients, however, remain undiagnosed, or their symptoms are wrongly attributed to habits, allergies, asthma, dermatitis, hyperactivity, nervousness, and many other conditions.

Phenomenology

Tics, the clinical hallmark of TS, are sudden, rapid, recurrent, nonrhythmic motor movements (motor tics) or sounds (phonic tics). Although the diagnosis of TS requires the presence of both motor and phonic tics, this division seems rather arbitrary, as phonic tics are actually motor tics that involve oral, nasal, pharyngeal, laryngeal, and respiratory musculature. Contractions of these muscles may produce sounds by moving air through the nose, mouth, or throat. In many cases, such as clicking of teeth or other clicking sounds produced by movement of the palate, no air flow is required to produce the sound.³ Because many of the sounds produced by TS patients do not involve vocal cords, the term *phonic tic*, rather than *vocal tic*, is preferable. Except for tics, the neurologic examination in patients with TS is usually normal.

There has been increasing recognition of the heterogeneous clinical phenomenology of tics in TS. Tics may be simple or complex. Simple motor tics involve only 1 group of muscles, causing a brief, jerklike movement. They are usually abrupt in onset and rapid (clonic tics), but they may be slower, causing a briefly sustained abnormal posture (dystonic tics) or an isometric contraction (tonic tics).² Examples of simple clonic motor tics include blinking, head jerking, and as described in the MDJ, palatal myoclonus.³ Simple dystonic tics include blepharospasm, oculogyric movements, bruxism, sustained mouth opening, torticollis, and shoulder

rotation. Simple tonic tics are exemplified by abdominal or limb muscle tensing without actual movement. Dystonic tics should be distinguished from dystonia, which is usually more continuous and patterned, but as pointed out in an MDJ article, the 2 disorders can rarely coexist.⁴ Some TS patients also manifest sudden and transient cessation of all motor activity (blocking tics) without alteration of consciousness.

Complex motor tics consist of coordinated, sequenced movements resembling normal motor acts or gestures that are inappropriately intense and timed. Examples of complex motor tics are repetitive touching, throwing, hitting, jumping, kicking, and trunk bending. Instances of copropraxia, such as gesturing “the finger” and grabbing one’s genitalia, are also examples of complex motor tics. Repetitive vomiting, retching, and air swallowing may also represent complex tics. Complex motor tics may be difficult to differentiate from compulsions, which frequently accompany tics, particularly in TS.

Simple phonic tics typically consist of sniffing, throat-clearing, grunting, squeaking, screaming, coughing, blowing, sucking, and burping sounds. Complex phonic tics include linguistically meaningful utterances and verbalizations, such as the shouting of obscenities or profanities (coprolalia), repetition of someone else’s words or phrases (echolalia), and repetition of one’s own utterances, particularly the last syllable, word, or phrase in a sentence (palilalia). Coprolalia, perhaps the most recognizable and certainly one of the most distressing symptoms of TS, is actually present in a minority of patients with TS. In a study of 597 individuals with TS from 7 countries, coprolalia occurred at some point in the course of the disease in 19.3% of males and 14.6% of females and copropraxia in 5.9% of males and 4.9% of females.⁵

The finding that in many cases tics have more than just motor features has received increasing attention. Both motor and phonic tics are often preceded by premonitory sensations, and as discussed in MDJ articles, this is a feature that is very helpful in differentiating tics from other hyperkinesias such as dystonia, myoclonus, and chorea.^{6–8} The premonitory phenomenon consists of either localizable sensations or discomforts in the region of the tic, such as a feeling of “tension” or “tightness” in the neck that is relieved by stretching of the neck or an uncomfortable feeling in the throat that is relieved by throat clearing or grunting or by a more generalized urge to move. Patients who have OCD associated with TS tend to have more bodily sensations occurring either before or during the patient’s performance of the repetitive behaviors as well as mental sensations including urges, energy release (mental energy that builds up and needs to be discharged), and “just right” perceptions.

Tics vary in frequency and intensity and often change distribution. TS patients can suppress tics

completely for brief periods or partially while in school or in public and release them when they come home. Suppressibility, suggestibility, and exacerbation with stress are some of the characteristics of tics that may lead to a wrong diagnosis of a psychogenic disorder. In contrast to the common belief, it is now clear that motor and phonic tics may persist during all stages of sleep.⁹

Interest has focused on trying to identify fundamental physiological disturbances that underlie the full clinical expression of TS. An important link between motor and behavioral manifestations of TS is the loss of impulse control. Many behavioral problems, which can be explained by loss of normal inhibitory mechanisms (disinhibition), are manifested by poor impulse control. It is as though the TS patients have lost their ability to suppress vestiges of primitive behavior. Poor impulse control might also explain the inability to control anger, as a result of which many patients have frequent and sometimes violent temper outbursts and rages. Rarely, TS patients exhibit inappropriate sexual aggressiveness and antisocial, oppositional, and even violent behavior. Although TS patients usually feel and often express remorse for their inappropriate behavior, the various offensive acts that accompany TS are often misunderstood and misinterpreted by the legal system.¹⁰

Natural History

The natural history of TS has not been well studied, and careful prospective longitudinal studies are needed to better elucidate the course of the condition. The average age at onset of tics is 5.6 years, and the tics usually become most severe at age 10; by 18 years of age, half of patients are tic-free.¹¹ In one of the best longitudinal studies, 46 children with TS underwent a structured interview at a mean age of 11.4 years and again at 19.0 years.¹² The mean "worst-ever" tic severity score was 31.6 of a possible 50 on the Yale Global Tic Severity Scale (YGTSS) and occurred at a mean age of 10.6 years. By the time of the second interview, mean YGTSS score decreased to 10. This prospective longitudinal study also showed that only 22% continued to experience mild or greater tic symptoms (YGTSS score ≥ 10) at follow-up, whereas nearly one third were in complete remission of tic symptoms at follow-up. The peak OCD severity occurred 2 years after peak tic severity, and, interestingly, a 10-point increase in baseline IQ increased the risk of OCD symptoms at follow-up by 2.8 fold.

Although TS is usually considered a childhood disease, the symptoms may also occur in adults. The clinical features may differ somewhat in patients with adult presentation. In 1 study published recently in the MDJ, 43 adults with TS were found to have significantly more facial and truncal tics, as well as a greater

prevalence of substance abuse and mood disorders, but fewer phonic tics and lower rates of ADHD and oppositional behavior than children with TS.¹³ During the course of TS, phonic and complex motor tics, self-injurious behaviors, and ADHD tend to improve, but facial, neck, and trunk tics dominate the adult TS phenotype. Thus, adult TS appears to largely represent a reemergence or exacerbation of childhood-onset TS.

Although TS is rarely disabling, recent studies have drawn attention to the troublesome and even serious nature of the disorder in some patients. In addition to causing embarrassment adversely affecting interpersonal and social interactions, tics can be painful and, as pointed out in 2 MDJ articles, TS can be quite severe and even life threatening.^{14,15} For example, cervical tics may be so forceful and violent, so-called whiplash tics, that they may cause secondary neurologic deficits such as cervical artery dissection and compressive and noncompressive cervical myelopathy.¹⁶ Of 332 TS patients seen at 1 TS clinic during a 3-year period, 17 (5.1%) met criteria for "malignant TS," defined as ≥ 2 emergency room visits or ≥ 1 hospitalizations for TS symptoms or its associated behavioral comorbidities.¹⁴ The patients exhibited tic-related injuries, self-injurious behavior, uncontrollable violence and temper, and suicidal ideation or attempts. Compared with patients with nonmalignant TS, those with malignant TS were significantly more likely to have a personal history of OCD, complex phonic tics, coprolalia, copropraxia, self-injurious behavior, mood disorder, suicidal ideation, and poor response to medications.

Etiology of Tics and Tourettism

As noted above, the vast majority of tics in adults represent recurrences of childhood-onset tics, but when tics first appear during adulthood, this should prompt a search for secondary causes, such as infection, trauma, stroke, drugs, and central and peripheral injury (Table 1).^{17,18} A variety of lesions in the frontal-limbic-subcortical circuits have been reported to cause tics or other features of TS, so-called secondary tourettism. A hypothesis that TS might occur as part of an autoimmune response following streptococcal infection has not been supported by recent studies.¹⁹

Pathology

Postmortem brain neuropathological studies have been rare in TS, and no pathological findings thus far have satisfactorily explained the condition. Early neuropathological and neurochemical studies of postmortem TS brains have identified reduced dynorphin-like positive woolly fibers in the globus pallidus, reduced cortical and striatal levels of cyclic AMP, and

TABLE 1. Causes of tics

A. Primary	
1.	Tourette syndrome
2.	Transient motor or phonic tics (<1 year)
3.	Chronic motor or phonic tics (>1 year)
B. Secondary	
1.	Inherited
a.	Huntington's disease
b.	Primary dystonia
c.	Neuroacanthocytosis
d.	Neurodegeneration with brain iron accumulation
e.	Tuberous sclerosis
f.	Wilson's disease
2.	Infections: encephalitis, Creutzfeldt-Jakob disease, neurosyphilis, Sydenham's disease
3.	Drugs: amphetamines and other CNS stimulants, cocaine, carbamazepine, phenytoin, phenobarbital, lamotrigine, antipsychotics, and other dopamine receptor-blocking drugs (tardive tics, tardive tourettism)
4.	Toxins: carbon monoxide
5.	Developmental: static encephalopathy, mental retardation syndromes, chromosomal abnormalities, autistic spectrum disorders (Asperger syndrome)
6.	Chromosomal disorders: Down syndrome, Klinefelter syndrome, XYY karyotype, fragile X syndrome, triple X and 9p mosaicism, partial trisomy 16, 9p monosomy, paracentric inversion, 15q13;q22.3, Beckwith-Wiedemann syndrome
7.	Head and peripheral trauma
8.	Other: stroke, neurocutaneous syndromes, schizophrenia, neurodegenerative diseases
C. Related manifestations and disorders	
1.	Stereotypies/habits/mannerisms/rituals
2.	Self-injurious behaviors
3.	Motor restlessness
4.	Akathisia
5.	Compulsions
6.	Excessive startle
7.	Jumping Frenchman, "ragin' Cajuns" of Louisiana, latah of the Malays, and myriachit of Siberia

increased dopamine uptake sites in both the caudate and the putamen, the latter findings suggesting that enhanced dopaminergic innervation of the striatum might underlie TS.² A more recent study identified an increased number of neurons in the globus pallidus internum (GPi) and externum (GPe) and caudate nucleus, as well as an increased number of neurons positive for the calcium-binding protein parvalbumin in the GPi but a decreased number in the other 2 regions.²⁰ These findings suggest that a possible developmental defect in the migration of GABAergic neurons in the basal ganglia with resultant imbalance in the functional dynamics of the cortico-striato-thalamic circuit may be present in TS. It is clear that more post-mortem brain studies are needed to better clarify the true neuropathology of TS.

Epidemiology

TS had long been considered a rare condition manifested by severe and bizarre symptoms. However, in

the past 25 years there has been a major shift in views about the prevalence of the condition and its severity. A major factor in this change was the occurrence starting in the 1980s of family studies in which investigators went out into the community to interview and examine members of large kindreds affected by TS. The researchers were surprised to find that, contrary to patients seen by physicians for TS, those affected in the community usually had mild tics that were frequently unrecognized by the individuals themselves, and medical attention was often not sought. Further recognition of the common and often mild nature of TS and tics came from epidemiologic studies of community populations, such as schoolchildren.²¹ Recent reviews concluded that the overall worldwide prevalence of TS in children is about 1%.^{22,23} The condition appears and is similarly manifest in all cultures but does appear to be rarer in individuals of black African descent.²² About 20% to 30% of schoolchildren experience at least transient tics, and children with academic problems requiring special education have a significantly higher rate of tics, suggesting that tics might be linked to abnormal brain development.²¹

Genetics

Concepts regarding the hereditary characteristics of TS have evolved substantially over time, and the specific inheritance pattern still remains uncertain.²⁴ Although initial segregation analysis studies of TS families suggested autosomal dominant transmission, the hereditary pattern is now thought to be more complex, with the transmission of a variety susceptibility loci, often in a bilineal (from maternal and paternal sides) fashion.²⁵ Extensive research efforts have been devoted to identifying the genetic loci involved in TS. To date, only a few have been reported, including the *SLITRK1* gene (which codes for a neuronal transmembrane molecule)²⁶ and the L-histidine decarboxylase (*HDC*) gene (which codes for the rate-limiting enzyme in histamine biosynthesis).²⁷ These genes, however, appear to account for only a small number of cases. In a recent genome-wide screening, TS was reported to be associated with recurrent exonic copy-number variants.²⁸ Although potentially important, this study has many limitations, and the data have to be interpreted cautiously.²⁹ As with many other neuropsychiatric disorders, the detailed genetics of TS has proven extremely difficult to decipher.

Pathogenesis

Striatal postsynaptic dopamine receptor supersensitivity has long been thought to be present in TS, partly supported by the finding of reduced levels of the dopamine metabolite homovanillic acid in the cerebrospinal

fluid of patients and the known response of tics to drugs that block dopamine receptors or deplete dopamine. The advent of modern neuroimaging techniques has yielded some helpful information about the underlying neurotransmitter abnormalities. Increased binding to presynaptic dopamine transporter sites in ventral striatum was observed in a postmortem neurochemical study,³⁰ and a SPECT study in TS patients found similar results.³¹ Potential medication effects and case heterogeneity, however, have confounded some neuroimaging studies in TS. Some prior PET studies have reported increased synaptic dopamine release,³² but more recent studies provided no evidence of increased dopaminergic innervation of the striatum, based on [11C] dihydrotetrabenazine and [11C] methylphenidate binding.³³ Another recent PET study identified reduced D2 and D3 receptor binding in the frontal cortex and thalamus.³⁴ A variety of brain regional volumetric changes have been reported in neuroimaging studies of TS, but the findings have been inconsistent, confounded by psychiatric comorbidities, and generally identifiable only in group comparisons and not for individual patients. Reduced gray matter in the frontal lobes with loss of normal left-greater-than-right asymmetry³⁵ and increased gray matter in the midbrain³⁶ have been reported. Caudate volumes have been reported to significantly inversely correlate with tic severity,¹² and loss of the normal left-greater-than-right basal ganglia asymmetry has been seen.³⁵ Clearly, more research is needed to clarify the brain morphologic and neurochemical disturbances specific to TS.

Pathophysiology

Some functional imaging studies and physiological investigations have begun to elucidate underlying pathophysiology of tics and TS. A recent PET study suggested that the metabolic pattern most closely linked to TS consisted of reduced resting activity of the striatum and orbitofrontal cortex associated with relatively increased activity in the premotor cortex and cerebellum.³⁷ Another PET investigation found robust activation of the cerebellum, insula, thalamus, and putamen at the time TS patients released their tics.³⁸ These studies provide support for the disturbance of motor control in the frontal cortex-striatum-thalamus-cortex pathways that has generally been considered to underlie TS and other movement disorders. Tics have been hypothesized to represent a failure of cortical inhibition of unwanted motor programs generated in the basal ganglia.³⁹ In addition to reduced excitability of cortical inhibitory activity, suggested by transcranial magnetic stimulation (TMS), when TMS was combined with diffusion tensor magnetic resonance imaging, relatively weak left-to-right interhemispheric inhibition was found, providing evidence of abnormal functional inter-

hemispheric connectivity across the corpus callosum in TS.⁴⁰ These and other studies suggest that “disinhibition” is an important mechanism of tics and possibly may also account for poor impulse control and other behavioral problems associated with TD.

Treatment

Before discussing available treatments, it is important to emphasize the importance of evaluating for secondary causes and assessing psychosocial factors and comorbid neuropsychiatric conditions.^{41,42} The appropriate approach to managing patients with tic disorders was reviewed in a recent MDJ article.⁴¹ In the 1960s the observed response to antipsychotic drugs that act as dopamine receptor antagonists (neuroleptics) both transformed the etiologic view of TS from a psychodynamic disturbance to an organic neurochemical disorder and suggested the likelihood of an underlying disturbance of dopamine neurotransmission. The efficacy of antipsychotic drugs was established in several controlled clinical trials. Today, the only FDA-approved medications for TS remain the classical antipsychotics haloperidol and pimozide. However, many experts are reluctant to use these and other typical neuroleptics because of numerous potential side effects, such as drowsiness, weight gain, school phobia, and hepatic and cardiac abnormalities. Interestingly, the feared complication of neuroleptic drug use, tardive dyskinesia, appears to occur relatively rarely in treated TS patients, perhaps because of the already abnormal state of their dopamine receptors and evidence of neuroplasticity, particularly in young individuals.⁴¹ Nevertheless, this complication can occur in children,⁴³ although it is more common in adult TS patients, in whom drugs such as tetrabenazine, a presynaptic depletor of dopamine not previously associated with tardive dyskinesia, may be preferable (Fig. 1).^{42,44}

Controlled trials have established the modest tic-suppressing efficacy of the alpha agonists clonidine and guanfacine,⁴⁵ and these appear to be good therapeutic choices, especially for patients with mild to moderate tic severity. Guanfacine is generally preferred over clonidine because it tends to cause less sedation and can be administered in fewer daily doses (Fig. 1).⁴¹ Several of the newer antipsychotic drugs (risperidone, olanzapine, quetiapine, aripiprazole) have been reported to demonstrate tic-suppressing effects in TS patients, but they seem to be less effective than the classical neuroleptics. As discussed in a recent MDJ article, although the risk of tardive dyskinesia may be lower with the second- and third-generation neuroleptics, this complication can still occur with these drugs, including aripiprazole, which seems to be most effective of the atypical neuroleptics in suppressing tics.⁴⁶ The anticipated tolerability advantages of the atypical

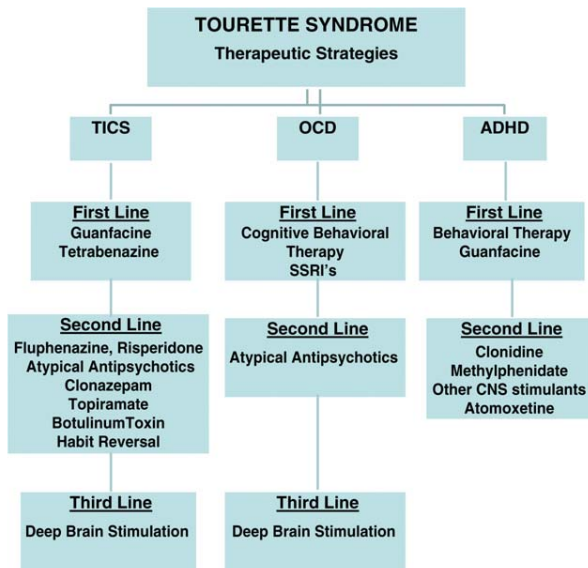


FIG. 1. This proposed algorithm is based on the authors' interpretation of evidence-based literature and their own experience. The approach to each patient with TS must be individualized and specifically tailored to the management of the most troublesome symptoms.

(second- and third-generation) neuroleptics compared with the classical antipsychotics have not been clearly realized because patients treated with these newer drugs frequently experience sedation, weight gain, and other adverse effects usually attributed to the classical neuroleptics.⁴⁷ Other medications that may be helpful in lessening tics include clonazepam and topiramate.⁴⁸ Tetrabenazine, another medication with reported tic-suppressing efficacy, is emerging as a leading drug in the treatment of tics associated with TS, even though evidence based on double-blind controlled trials is lacking.^{42,49,50} The role of tetrabenazine in treating childhood movement disorders, including TS, was summarized in an MDJ article.⁴⁹ Possible adverse effects of tetrabenazine include drowsiness, depression, parkinsonism, and akathisia, but all these side effects are dose related and resolve with reduction in daily dosage. In addition to having a low risk of tardive dyskinesia, tetrabenazine has another advantage over neuroleptics in that it does not seem to cause as much weight gain.⁵¹ Local intramuscular injections of botulinum toxin at the site of bothersome tics (eg, eyelids, neck) have proven effective for patients with a few particularly disabling tics.^{52,53}

A form of cognitive-behavioral therapy (habit reversal) has recently been reported to lessen tics in patients with TS.⁵⁴ However, because of the need for compliance by patients and parents and the lack of specially trained therapists and adequate insurance coverage, the widespread applicability of this approach remains to be determined.

In the past few years, a dramatic change in therapeutic options to be considered for patients with

severe, medication-refractory TS has been the introduction of deep brain stimulation (DBS) surgery.^{55,56} In addition to central nuclei of the thalamus,⁵⁷⁻⁶⁰ other targets reported to be effective in DBS treatment of TS are the GPi,^{61,62} subthalamic nuclei, and other structures.⁶³ The optimal location for electrode placement, the effects of DBS on behavioral comorbidities such as OCD and ADHD, and other DBS issues have not been fully studied.⁶⁴ Guidelines to optimal patient selection criteria for DBS and pre- and postoperative assessments have been published in the MDJ.⁶⁵

In addition to the treatment of tics, management of patients with TS usually involves the use of medications for neurobehavioral comorbidities such as ADHD, OCD, and impulse control disorder (Fig. 1).^{44,66} A randomized controlled trial showed that despite warnings in pharmaceutical company literature and by pharmacists, the stimulant drug methylphenidate is effective and well tolerated (without worsening tics) in the treatment of ADHD in children with tics.⁶⁷ Several different preparations of central nervous system stimulants, including long-acting, once-daily dosing preparations of methylphenidate and amphetamine and their derivatives, have been found to be effective in the treatment of ADHD associated with TS.⁶⁹ Clonidine and guanfacine can also improve ADHD in children with tics.^{45,67} Atomoxetine, a selective norepinephrine reuptake inhibitor, was shown to be effective for ADHD and well tolerated by children with tics.⁷⁰ Cognitive-behavioral therapy, selective serotonin reuptake inhibitor medications, and atypical antipsychotics are now proven and available therapies for TS patients with disabling OCD. Deep brain stimulation is also available for patients with refractory, severe OCD (Fig. 1).

Future Directions

Major advances in the understanding of TS will require more in-depth knowledge about the role of the basal ganglia and their connections to the frontal cortex and other brain structures in the pathophysiology of the complex neurobehavioral features associated with TS. Clarification of the role of genetic factors in tics and comorbid disorders will also be important. Perhaps a major clue toward research directions is the observation that most patients with TS experience an improvement or resolution of their tics in their late teens and early twenties. Such research may also unravel the mystery of why some individuals experience recurrence of symptoms in mid-life or even later. Elucidating the changes in neurodevelopmental events and neuroplasticity during the course of TS should provide important insights into the underlying mechanisms and potential therapeutic avenues.⁷¹ More effective and better tolerated therapies are clearly needed.

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