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A Review and Update on Tourette Syndrome: Where Is the Field Headed?

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Abstract Tourette syndrome (TS) is a childhood onset neurologic disorder with manifestations including multiple motor and phonic tics, and in most cases a variety of behavioral comorbidities such as attention deficit hyperactivity disorder, obsessive compulsive disorder, and other impulse control disorders. Although it is considered a hereditary disorder, likely modified by environmental factors, genetic studies have yet to uncover relevant causative genes and there is no animal model that mimics the broad clinical phenomenology of TS. There has been a marked increase in the number of neurophysiological, neuroimaging, and other studies on TS. The findings from these studies, however, have been difficult to interpret because of small sample sizes, variability of symptoms across patients, and comorbidities. Although anti-dopaminergic drugs are the most widely used medications in the treatment of TS, there has been increasing interest in other drugs, behavioral therapies, and surgical approaches including deep brain stimulation. Herein, we review the current literature and discuss the complexities of TS and the challenges in understanding its pathophysiology and in selecting the most appropriate treatment. We also offer an expert's view of where the field of TS may be headed.

Keywords Tourette syndrome · Tic disorders · Neurodevelopmental disorders · Movement disorders

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Introduction

Tourette syndrome (TS) is a complex, childhood-onset, neurodevelopmental disorder characterized by motor and phonic tics and a variety of behavioral manifestations, particularly obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD). Jean-Martin Charcot, widely considered the founder of modern clinical neurology, gave Georges Albert Gilles de la Tourette, one of his pupils, credit for recognizing the disorder by naming it TS [1]. In his 1885 paper, Tourette provided a clear description of nine patients suffering from a "malady of tics" [2]. Although the syndrome had previously been described in case reports by Seprenger and Heinrich in 1498, by Itard in 1825 [3], by Trousseau in 1873 [4], and by Hughlings Jackson in 1884 [5], Tourette recognized the clinical features, including motor and phonic tics, echolalia (repeating what others say), echopraxia (mimicking other's actions), coprolalia (shouting of obscenities or profanities), and its hereditary nature. TS is a complex entity presenting challenges for both the clinician and the researcher. The complexity is highlighted by the variations in individual clinical manifestations, the fluctuations in severity and frequency of symptoms, and the common behavioral comorbidities. Although the pathogenesis of TS is still not fully understood, it is now widely recognized that TS likely results from a multitude of genetic and environmental factors. Since its original description, an increasing number of publications have drawn attention to diagnostic, genetic, imaging, physiological,

and therapeutic discoveries related to TS [6]. Many unanswered questions and research challenges, however, still remain. In this review, we present an overview of the clinical features, the neurobiology, the pathogenesis, and treatment options for TS. We will offer expert insights into where TS research and care is headed over the next decade.

Clinical Features

The clinical hallmark of TS is sudden, repetitive movements (motor tics) and vocalizations and other sounds (phonic tics). These tics have varying degrees of intensity and frequency and may be of short or long duration. The frequency, intensity, and course of tics can be quite variable in individual patients and across patient populations [7, 8]. Tics are subclassified into simple and complex categories. Simple motor tics involve individual muscles or groups of muscles, whereas complex tics consist of more coordinated and sequenced movements, which may in some cases be socially inappropriate [9]. Common simple motor tics include eye blinking, head, neck, or limb jerking, sustained mouth opening, or shoulder rotation, whereas examples of complex motor tics include touching, hitting, gyrating, bending, copropraxia (gesturing and touching of genitalia), other socially inappropriate behaviors, and self-injurious behaviors. Examples of common simple phonic tics are grunting, squeaking, coughing, sniffing, snorting, and throat clearing. Complex phonic tics include meaningful utterances and vocalizations, such as echolalia, coprolalia, and palilalia (repeating one's own words) [10]. Although coprolalia has been characterized as a cardinal feature of TS, it occurs in only 10–19 % of individuals [11].

It is common for tics to be exacerbated during periods of anticipation, stress, excitement, or fatigue and to be reduced when concentrating on mental or physical tasks. Several studies have documented that tics may persist during all stages of sleep [12]. Tics are considered to be involuntary, but can also be voluntarily suppressed [13]. This ability to volitionally inhibit tics is useful for differentiating TS from other hyperkinetic movement disorders. Following voluntary tic suppression, patients may experience a rebound "release" of tics, and this release has been frequently reported as worse than the baseline symptoms [14].

The onset of both motor and phonic tics frequently is preceded by premonitory urges, described as a buildup of tension, pressure, or energy localized to the tic region, or a general psychological tension, associated with a pressing need to act. Some examples of premonitory urges are muscle tension, nasal stuffiness, and dry throat—all preceding the tic. Executing the tic relieves these inner sensations and results in a feeling of relief. Tics have been described by some experts as a "voluntary response to an involuntary sensation" [8]. About 90 % of adults with TS report the occurrence of premonitory urges [15, 16], whereas 37 % in the pediatric population report similar sensations [17]. Recent studies showed that certain urges could be selectively associated with tics (e.g., physical sensations), and similarly some urges could be associated with obsessive compulsive symptoms (e.g., feelings of unease and urgency) [18].

The lifetime prevalence of any psychiatric comorbidity among individuals with TS is reported to be 66 % [19]. Seventy-two percent of TS patients meet the criteria for OCD and ADHD [20]. Fifty-eight percent of the TS population had two or more psychiatric disorders including autism spectrum disorders, depression, personality disorder, anxiety disorder, or self-injurious behavior [19, 21]. These symptoms add to the complex comorbidities associated with TS, and these comorbidities can impact quality of life (Fig. 1).

The clinical course of TS is variable, and the average age at onset of motor tic is 5.6 years [22]. Phonic tics typically follow the onset of motor tics, but sniffing, coughing, and other sounds may precede tics but are often initially wrongly attributed to "allergies." Studies have revealed that the severity of symptoms usually peaks just before puberty [23]; in one study, the peak was at a mean of 10.6 years [23]. The majority of patients with TS achieve complete or near complete remission of tics by 21 years of age, but in 10–20 % of TS cases, the symptoms fluctuate, persist, or worsen [24]. Figure 1 summarizes the natural history of TS [23, 24] and the associated comorbid conditions. The average age at onset of ADHD has been shown to precede tic symptoms (~3 years old), whereas the onset for OCD and the peak age of OCD severity occur 3–4 years following tic onset and peak tic severity [22]. ADHD and OCD symptoms usually persist to a variable degree through adulthood.

The estimated prevalence of TS ranges from 3 to 9 per 1000 in school-age children [23, 24]. The prevalence is higher in males compared to females, with the ratio varying from 2:1

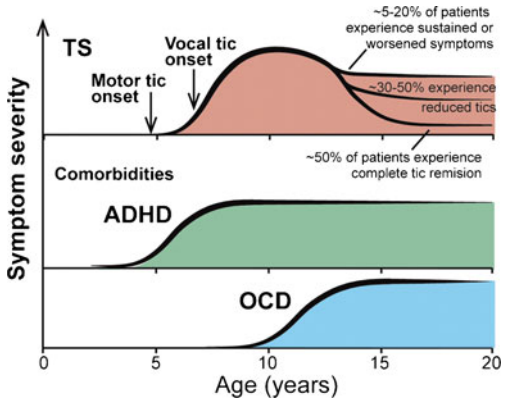

Fig. 1 The clinical course of TS and coexisting disorders. The *vertical axis* represents the approximate "amount" the disorder affects a TS patient. TS symptom severity peaks around age 11 years, and ~50 % of patients experience complete or near to complete tic remission. Thirty to 50 % experience significantly reduced symptom severity, whereas 5–10 % of patients will experience sustained or worsened symptoms

to 4:1 [25••]. The number of diagnosed cases in the USA is lower among African Americans and Hispanic Americans, yet this may be related to differences in access to care [26].

Although TS is not a degenerative disorder, it can be socially crippling and motor tics may be painful, severe, and even life threatening. It has been estimated that 5 % of TS patients will be admitted to hospitals each year due to tic-related injuries, self-injurious behavior, uncontrollable violence, or suicidal ideation with or without suicide attempts [27]. Such "malignant" cases have been associated with greater severity of motor symptoms and the presence of two or more behavioral comorbidities.

Clinical Features: Where Is the Field Headed?

An important focus of research on clinical features has been aimed at better understanding the mysterious premonitory urges of TS. The idea that interoceptive awareness could be a strong predictor of premonitory urges has been proposed. The association of greater tic severity to higher rates of premonitory urges has recently been shown. The high levels of interoceptive awareness have been hypothesized to reflect a self-attentive capacity to perceive urges [28]. Experts have focused on this clinical feature as important to better understand TS, but also to develop improved treatment paradigms. One group has been recording from pre-motor human cortex in an effort to define and use the premonitory urge as a potential treatment approach [29].

Another clinical focus will likely be on the improved characterization of comorbidities, which cause most of the heterogeneity in clinical features across patients. Comorbidities define "types of TS" as TS only, TS + OCD, and TS + OCD + ADHD [30], which has raised questions as to whether these should be considered a continuum of the phenotype. The next decade will likely bring clarity to the issue of TS-associated comorbidities, and this improved understanding will fill an important knowledge gap as the field moves toward more effective treatments.

Moreover, early-onset longitudinal studies will be crucial to uncover clinical features that point towards remission of the disease versus those that point to a lifelong disorder.

Diagnosis

Tic disorders are identified and diagnosed through a careful history documenting childhood onset, neurological examination, recognition of the broad spectrum of motor and behavioral phenomenology, and family history. The diagnostic criteria for TS were modified in 2012 by the fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-V). This publication is the primary diagnostic reference for Mental Health professionals practicing in the USA and Canada [31]. The new diagnostic criteria for TS and other tic disorders are summarized in Table 1. A diagnosis of TS is made when both motor and vocal tics have been present at some time during the patient's history (criterion A) and have been persistent for greater than a year (criterion C). The age at onset of tics must occur before the age of 18 years (criterion B). The presence of comorbid disorders (e.g., ADHD, OCD), though common, is not a requirement for the diagnosis of TS. Other potential causes of tics including drug-induced or associated other medical conditions such as Huntington's disease should be eliminated prior to a formal diagnosis of TS (criterion D).

Although tics may be confused with other hyperkinetic movement disorders such as chorea, myoclonus, stereotypies, dystonia, or epileptic seizures [32], most neurologists and

Table 1 Differential diagnosis of tic orders

DSM V classification of tic disorders					
Diagnostic features	Tourette syndrome (category 1)	Persistent (chronic) motor or vocal tic disorder (category 2)	Provisional tic disorder (category 3)	Other tic disorders (category 4)	
				Other specified tic disorder	Unspecified tic disorder
Tic type (criterionA)	Multiple motor and one or more vocal tics (not necessarily concurrent)	Single or multiple motor or vocal tics (not both)	Single or multiple motor and/or vocal tics	*The clinician records the specific reason that the presentation does not meet the criteria for a tic disorder or any other neuro-developmental disorder.*	*The clinician chooses not to communicate the specific reason that the presentation does not meet the criteria for a tic disorder or any other neuro-developmental disorder, and/or there is insufficient information to make a more specific diagnosis.*
Duration (criterionB)	>1 year since onset	>1 year since onset	<1 year since onset		
Onset (criterion C)	Before age 18 years	Before age 18 years	Before age 18 years		

Criterion D. None of the disturbances attributable to the physiological effect of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, post-viral encephalitis)

psychiatrists can differentiate tics based on the history, the examination, and the ability to suppress tics as well as the presence of premonitory urges. *Chorea*, in contrast to TS, represents continuous, non-stereotyped motor movements, which randomly involve different body parts and are not associated with premonitory urges. *Motor stereotypies*, such as hand waving or rotating, can be differentiated from tics based on predictability, prolonged duration (seconds to minutes), constant repetitive movements without variability, and the occurrence in the same body region. Stereotypies can be exacerbated by physical activities, lack a premonitory urge, and generally abate with distraction. Stereotypies have an earlier age at onset compared to TS (<3 years of age). *Dystonia* is the simultaneous sustained contracture of both agonist and antagonist muscles, and dystonia usually results in a distorted posture or movement and may be frequently triggered by voluntary movements. *Myoclonus* is differentiated from tics by its rapidity, difficulty in suppression, and absence of a premonitory urge. Presentations differentiating *obsessive-compulsive* behaviors from tics include a cognitively based and goal-directed drive, precise numbers of repetitions of the movements, and persistence until a "just right" feeling is achieved.

Diagnosis: Where Is the Field Headed?

The biggest challenge in this area has been to address the frequent multiyear delay in establishing an accurate diagnosis. Additionally, Scharf et al. [19] recently refined the population prevalence estimate of 0.3–0.9 % in children and reported that clinically referred cases had prevalence estimates that were lower than those derived from population-based samples. Study sample size, which is likely a proxy for the case assessment method, and the use of DSM-IV-TR diagnostic criteria were the major sources of heterogeneity in diagnosis. Experts generally agree that TS is common and that making an earlier diagnosis has the potential to impact outcome. Chronic multiple tic disorders have a higher prevalence, and though controversial, the field may be slowly moving toward merging these diagnoses.

Genetics

Several lines of evidence suggest that genetic factors are primary contributors to the etiology of TS. Careful family studies have found tics or a history of tics occurring in a majority of parents [25••], and in many cases TS is bilineally transmitted (both parents are affected to some degree) [33]. First-degree relatives are at significantly higher risk of developing TS when compared to controls [34]. Studies with twins have revealed concordance rates of TS to be 53–56 % in monozygotic twins, compared to a considerably lower rate of 8 % in dizygotic twins [35]. One study showed a heritability point estimate of 0.58 for TS (and 0.37 for OCD) using genome-wide complex trait analysis (GCTA) [36, 37].

Despite all the lines of evidence implicating multiple genes and chromosomal regions in the pathogenesis of TS, no causative gene mutation or common variant has been uncovered that can account for the majority of TS cases [38]. The Tourette Syndrome Association International Consortium for Genetics (TSAICG) has been conducting genome screens in large cohorts (110 individuals in 1999 [39] and 2040 individuals in 2007 [40]). Several international collaborative efforts are currently underway, including the European Society for the Study of Tourette Syndrome (ESSTS) [41], TSAICG [42] and the more recent Tourette International Collaborative Genetics (TIC Genetics) study [40, 41]. Interpretation of these results is, however, complicated partly because of heterogeneous presentation, presence of comorbidities, bilineal transmission, diversity of genotypes, and complex interaction with various environmental factors.

Genetics: Where Is the Field Headed?

It is likely that, over the next decade, genome-wide association and other genetic studies conducted across multiple centers will uncover important genetic clues that will advance our understanding of pathogenesis and treatment of TS.

Neuroinflammation

A role for environmental factors, especially infections, in the presentation and exacerbation of tics has been postulated as early as 1929 [43]. There were many early case reports showing an association between childhood sinusitis and the onset of TS [44]. More recently, post-streptococcal autoimmunity has been postulated as a potential environmental trigger [45–47]. Also, tics have been shown to be neurological manifestations of rheumatic fever associated with Sydenham's chorea, and this has been suggested as a potential model for TS pathophysiology. Swedo and colleagues coined the term PANDAS [48, 49], for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, and Mell et al. [50] provided epidemiologic evidence supporting PANDAS. While the hypothesis has stimulated clinical and basic research, it has led to considerable scientific controversy [51]. Criticism of reported results has been leveled for a variety of reasons including that approximately two thirds of study participants in PANDAS clinical trials have undergone selective recruitment. There were also issues with small sample sizes and few or no controls [52–55]. The debates over PANDAS have evolved to include an expanded clinical entity named PANS (Pediatric Acute-onset Neuropsychiatric

Syndrome) [54]. This term has been used to refer to a subgroup of children with abrupt onset OCD symptoms and other acute onset symptoms such as urinary frequency or enuresis, separation anxiety, etc.

Neuroinflammation: Where Is the Field Headed?

Experts have suggested a need for a broader concept of childhood acute neuropsychiatric symptoms (CANS) [56]. It is now widely recognized that a broad spectrum of movement disorders can possibly be associated with antibodies and inflammation. It is likely that TS is not one disease and that different entities may emerge as we begin to separate tics into different phenotypes based on genetics, pathogenesis, and clinical presentation. Future directions should involve large-scale epidemiologic studies and centralized registries with standardized and longitudinal data collection strategies, as well as randomized, controlled clinical trials of novel therapies. Many experts believe that most, if not all, cases of PANDAS and associated neuropsychiatric manifestations are actually tics and possibly fit the criteria for TS.

Pathophysiology

Neurophysiology

The classical models of cortico-striatal-thalamocortical circuits (CSTC) have provided frameworks for uncovering the neurophysiological basis for the manifestations of involuntary tic. The hypotheses that arise from these models suggest that the basal ganglia likely modulate behavior through a mechanism that involves changing cortical excitability through the "direct" and "indirect" basal ganglia pathways (see Fig. 3a). The direct pathway, from the striatum to the globus pallidus interna (GPi) and the substantia nigra (SNr), excites the cortex through the disinhibition of the thalamus. The indirect pathway, from the striatum to the globus pallidus externa (GPe) to the subthalamic nucleus (STN), inhibits the thalamic projections [57]. Based on these models, it has been hypothesized that tics result from competing motor patterns. According to this hypothesis, focal aberrations in the striatum cause excessive inhibition of the GPi and SNr in the direct pathway, thereby causing an involuntary motor command to be executed in the cortex due to excessive disinhibition (see Fig. 3b).

There has been a lack of human electrophysiological studies and especially a lack of studies targeting circuits. One study has found normal pre-movement (Bereitschaftspotential) in TS patients prior to execution of tics suggesting that some components of tics may be mediated via volitional pathways [58]. Further studies, however, are needed to determine whether the characteristic premonitory sensations are in any way related to this physiologic finding or whether it represents an abnormality in motor-sensory integration [59].

Deep brain stimulation (DBS) surgery offers a unique opportunity to invasively record from TS-related brain areas to study physiological abnormalities in TS. Moreover, next-generation DBS devices, such as the NeuroPace RNS and Medtronic Activa PC+S, are facilitating chronic recordings from stimulation electrodes. Most human neurophysiology studies point to low-frequency (<10 Hz) activity during tics in the ventralis oralis (VO) complex [60] or centromedian nucleus (CM) of the thalamus [61–63]. Similar activity was not present in the thalamus during voluntary mimicking of the tics [64] or during tic suppression [65•, 66].

Neurophysiology: Where Is the Field Headed?

Recent advances in technology capable of recording from multiple cortical and subcortical regions simultaneously within the brain of awake human will soon facilitate testing of the TS circuit hypotheses. Much of the current understanding of TS physiology has been based on studies in anesthetized patients or inadequate animal models.

Neuroimaging

Structural imaging studies have suggested that smaller caudate nucleus volumes correlated with severity of tics in patients with TS followed longitudinally [67]. A recent longitudinal study revealed that, in young adolescents with persistent tics, there was a decrease in left putamen volume and changes in diffusivity in right caudate nucleus, thalamus, and frontal lobe [68]. Connectivity studies have shown decreased projections between the caudate nucleus and the lateral frontal cortex [69]. These findings support a cortical disinhibition theory for TS as well as the idea that there are underlying aberrations in the striatum.

Imaging studies have also revealed changes outside of the TS striatum. These include reduced cortical thickness in motor, pre-motor, pre-frontal, and lateral orbitofrontal cortical areas [70] and structural alterations in somatosensory pathways [71] and in the corpus callosum [72]. Comorbidity studies with OCD and ADHD have revealed decreased gray matter volume in the lateral frontal cortex (inferior frontal gyrus) [73]. Abnormal cortical development in TS is supported by other imaging studies that have found abnormal structural patterns of cortical sulci which correlated with severity of clinical symptoms [74–76]. One study compared sulcal depth, length, and thickness of gray matter in 52 adult patients with TS and 52 matched controls [77•]. Patients with TS had lower depth and reduced thickness of gray matter in the pre- and post-central as well as superior, inferior, and internal frontal sulci, bringing further support for abnormal brain development.

Functional imaging studies are challenging to perform in patients with TS largely due to motion artifacts. Nevertheless, functional imaging studies of tic generation suggest increased activity in the supplementary motor association areas [78] and motor pathways [79] as well as a decreased activity in CSTC circuits responsible for motor control [80]. A resting state fMRI study revealed abnormal activity in the CSTC circuits, in pre-motor, sensorimotor, and cingulate cortices, and in the medial thalamus [81].

Neuroimaging: Where Is the Field Headed?

There are substantial difficulties in capturing motion artifact-free images in TS patients. Structural and functional neuroimaging will however be critical for elucidating the understanding of this circuit disorder. Neuroimaging may offer the intriguing possibility of parsing individual clinical manifestations into specific causative brain regions, and early-onset longitudinal studies can provide insight into the role of brain development in the manifestations and the natural history of TS. Moreover, neuroimaging can allow the study of response to various treatments. Consortia, such as the one set up by the Tourette Syndrome Association, which pool multiple scans from multiple institutions, will likely aid in filling a large knowledge gap in TS neuroimaging.

Neurochemistry

Many studies of drug trials [82], imaging [83], and human sample analysis [84, 85] have collectively led to the hypothesis of neurochemical abnormalities in TS [86, 87]. The most common neurochemical hypothesis of TS is dopaminergic dysfunction, based initially on the observation that dopamine receptor-blocking drugs (neuroleptics) were most effective in reducing tics. While some studies have found abnormalities of dopamine transporter binding capacity [88] and increases of cortical [89, 90] and striatal [91] dopamine receptors, no dopaminergic hyperinnervation has been demonstrated by PET studies [92].

Neurochemistry: Where Is the Field Headed?

Dopamine is no longer considered the exclusive neurotransmitter involved in TS. Studies have demonstrated that serotonergic pathways play an important role in the pathophysiology of TS [93]. Other hypotheses include imbalances in noradrenergic, glutamatergic, serotonergic, opioid, cholinergic, and GABA-ergic systems [84, 85, 94, 95]. A recent study by Xu et al. [96••] showed that ablation of ~50 % of cholinergic interneurons in the striatum of mice led to TS-like stereotypies, thus implicating striatal cholinergic system in TS. The most compelling observation related to neurochemical abnormalities in TS is the finding, based on PET ligand studies, of decreased density of receptors to GABA, an inhibitory neurotransmitter, in the striatum, globus pallidus, thalamus, and amygdala and increased binding in the SNr, posterior cingulate cortex, and cerebellum. This is consistent with the hypothesis of GABA-ergically mediated disinhibition as the main neurotransmitter underpinning TS. A recent study has also brought attention to deficiencies in histamine as a rare cause of TS [97]. We will likely observe clarification of the neurochemical bases of TS over the next 5–10 years.

Treatment

A critical step in TS treatment is to provide education to the patient, parents, caregivers, and peers about the condition [98, 99]. This is important in establishing appropriate expectations and optimal treatment strategies and in creating more informed relationships [100]. A comprehensive evaluation of comorbid psychiatric conditions is also essential for treatment. A common strategy is to tailor therapy to address the symptoms (tics or comorbidities), which are likely contributing to problems of daily functioning or impacting quality of life. Treatment of TS comorbidities may diminish tic severity [22].

Several rating scales for tics have been developed to facilitate the assessment and monitoring of symptoms and to measure treatment outcomes. Two of the most commonly used scales are the Yale Global Tic Severity Scale (YGTSS) [101] and the Modified Rush Tic Rating Scale (MRTRS) [102]. Discrepancies between these outcome measures have been reported across TS studies [103, 104], and this may be due to the fluctuation of tics and the difficulty in precise measurement of the phenomenon. Additionally, measures for OCD, ADHD, self-injurious behavior, and other comorbidities are important since these symptoms may impact quality of life even more than simple motor and vocal tics.

Treatment decisions are often guided by individual needs and the experience of clinicians. It is common for clinicians to adopt a sequential approach to TS [6], in order to improve the risk-benefit ratio for any intervention. Following family education, behavioral and pharmacological approaches may be addressed. Occasional medication refractory cases may lead to discussion of surgical treatment strategies. Figure 2 provides an outline and summary of TS management. Treatment should be tailored in each case. If easily accessible, behavioral therapy such as Comprehensive Behavioral Intervention for Tic Disorders (CBIT), which may include habit reversal training (HRT), can be offered to the patients as a first line of treatment. The aim of such behavioral approach is to facilitate control of tics by disrupting the pattern of premonitory urges and the relief sensation that follows the execution of some tics. Two randomized controlled trials reported that HRT reduced tic severity with an outcome improvement of 10.5 points (out of 100) on the YGTSS at 5 months [105, 106]. Two multisite studies have demonstrated the efficacy of CBIT

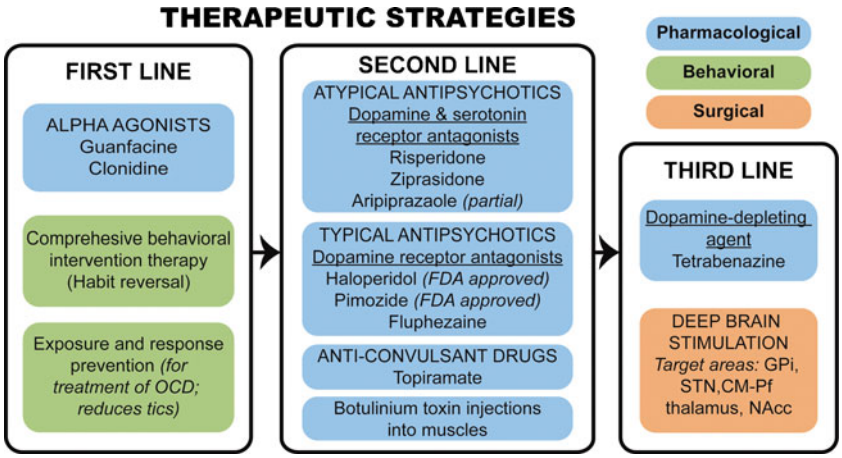

Fig. 2 A generalized flowchart of therapeutic strategies for TS compiled from literature. Therapies should be tailored to each patient's symptoms and needs, with priority given to the most disabling symptom (tic or comorbidity). This table is an illustration of potential medications and treatments, but is not a comprehensive list, as we recognize, for example, that many different dopamine blockers may be utilized

especially in mild to moderate TS populations [107, 108] and have suggested behavioral therapy as a safe first-line treatment for TS [6]. This treatment approach may be combined with exposure and response prevention therapy, especially if severe OCD is present [109, 110]. These trials have collectively demonstrated the superiority of CBIT over supportive psychotherapy in improving tic severity in children [107] and adults [108] as rated by the YGTSS (3.7 points mean group difference after 10 weeks of treatment). A systematic review of behavior therapy in TS highlights that there are no studies directly comparing the efficacy of behavioral therapies with pharmacotherapies for tics [111]. A meta-analysis of eight randomized controlled trials involving 438 subjects with TS concluded that CBIT produced moderate treatment effects and participants receiving CBIT were more likely to exhibit a treatment response compared to control interventions [112].

There is a paucity of standardized, large evidence-based drug trials in TS [113]. Pharmacologically, often the first line of TS treatment are the alpha agonists guanfacine [114] and clonidine [115]. These drugs are reasonable choices for mild to moderate tics and in general have been associated with few adverse effects (e.g., drowsiness, dry mouth). Antipsychotic drugs that act by blocking dopamine receptors (neuroleptics) are usually as second-line pharmacological treatments, although their beneficial effects in TS have been documented since the 1960s [116]. These drugs, however, can lead to adverse reactions such as drowsiness, severe weight gain, excessive sedation, parkinsonism, akathisia, and even tardive dyskinesia [83], and most experts try to reserve their use for cases when more conservative approaches fail.

Atypical antipsychotic drugs have been preferred by some experts over typical antipsychotic therapies, presumably because of a better adverse event profile and a lower risk of tardive dyskinesia [117]. Although haloperidol and pimozide are the only two drugs currently approved by the Food and Drug Administration (FDA) for the treatment of TS, fluphenazine appears to be possibly more effective and better tolerated [118].

Tetrabenazine, a dopamine-depleting agent, has been used to control motor and phonic tics [119–121], but well-designed controlled trials have not been reported. Tetrabenazine is considered by some experts to be more effective and safer than conventional neuroleptics, although it may be associated with dose-related side effects such as drowsiness, depression, parkinsonism, and restlessness.

Other medications, such as topiramate, have been less studied, but may also improve tic severity [122]. In patients with focal motor or phonic tics, injections with botulinum toxin into the affected muscles usually provides 3–4 months of relief with minimal side effects [123]. A summary of drugs and dosages used to treat TS is presented in Table 2.

In cases of "malignant" TS and for patients unresponsive to pharmacological or behavioral therapy, DBS has been increasingly used to treat not only tics but also associated OCD [124] High-frequency DBS (>100 Hz) modulates basal ganglia-thalamo-cortical circuits and may suppress motor and phonic tics (Fig. 3). In the 1970s, Rolf Hassler reported stereotactic lesioning of the thalamus and basal ganglia as a way to modulate abnormal brain circuits and to suppress tic-related behavior [125]. The most beneficial target for TS DBS has yet to be determined. According to the Tourette Syndrome Association International DBS Database and Registry Study Group since 1999, 120 patients have been reported across 13 countries to have undergone TS DBS therapy, and most have reported significant clinical improvements [126•]. The most commonly targeted structures have been the centromedian-parafascicular complex (CM-PF) of the thalamus (approximately 70 patients) and the motor and non-motor portions of the GPi (approximately 30 patients). Determination of optimal targets will require controlled studies performed in large cohorts, as well as standardization of surgical methods and outcome assessments. The Tourette Syndrome Association International Deep

Table 2 Pharmacotherapy used in the treatment of TS: empirical support and dosing guidelines (Adapted from Scahill et al. (2006))

Medication	Type	Empirical support	(Uncorrected) improvement over placebo (%)	Starting dose (mg)	Usual dose range (mg/day)
Haloperidol	Antipsychotic	Good	66	0.25–0.5	1–4
Pimozide	Antipsychotic	Good	39–58	0.5–1.0	2–8
Risperidone	Antipsychotic	Good	35–50	1.0–3.0	1.0–3.0
Botulinum toxin	Non-antipsychotic/ anti-convulsant	Fair	40	30–300 units in single or several focal sites	
Clonidine	Non-antipsychotic	Fair	35	0.025–0.05	0.1–0.3
Guanfacine	Non-antipsychotic	Fair	30–37	0.5–1.0	1–3
Fluphenazine	Antipsychotic	Fair	N/A	0.5–1.0	1.5–10
Pergolide	Non-antipsychotic	Fair	35	0.025	0.1–0.4
Tiapride	Antipsychotic	Fair	44	50–150	150–500
Ziprasidone	Antipsychotic	Fair	35	10–20	20–100
Aripiprazole	Antipsychotic	Fair	N/A	2.5–5.0	10–20
Baclofen	Non-antipsychotic	Minimal	N/A	10	40–60
Flutamide	Non-antipsychotic	Minimal	N/A	250	750
Mecamylamine	Non-antipsychotic	Minimal	N/A	2.5	2.5–7.5
Nicotine patch	Non-antipsychotic	Minimal	N/A	7	7–21
Olanzapine	Antipsychotic	Minimal	N/A	2.5–5.0	2.5–12.5
Quetiapine	Antipsychotic	Minimal	N/A	25–50	75–150
Sulpiride	Antipsychotic	Minimal	N/A	100–200	200–1000
Tetrabenazine	Non-antipsychotic	Minimal	N/A	25	37.5–150

Brain Stimulation Database and Registry Study Group has also recently updated the recommendations for selection of candidates for TS DBS [126•]. The revised guidelines require a DSM-V diagnosis of TS by an expert clinician and have removed the previously suggested age limit of 25 years, with the specification that a multidisciplinary team approach should be employed [127]. A local Ethics Committee or Institutional Review Board consultation is recommended for patients younger than 18 years of age and for those with urgent indications. TS patients with DBS implants may be at an increased risk for hardware malfunction (such as fractures of the leads or lead extensions) due to head and neck snapping tics [128].

Repetitive transcranial magnetic stimulation (rTMS) targeting the supplementary motor areas (SMA) at a rate of 1 Hz has been shown to improve symptoms in children [129, 130]. Studies of this therapy have been limited by small numbers and a lack of control conditions [131].

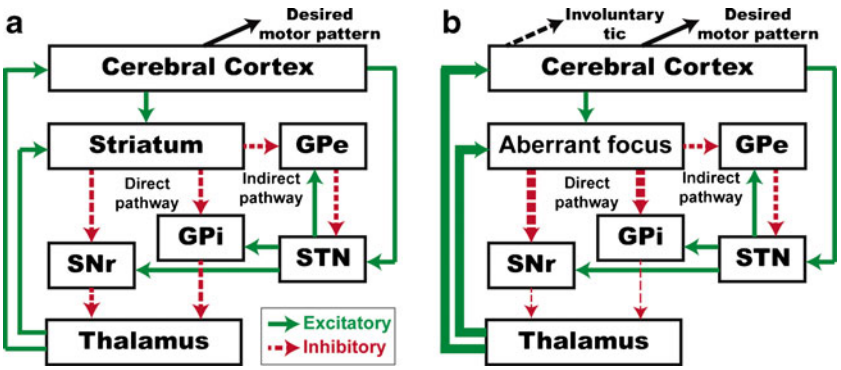

Fig. 3 **a** The cortico-striatal-thalamocortical circuits under normal conditions. Desired motor patterns are disinhibited by the direct pathway, and competing motor patterns are suppressed by the indirect pathway. Abbreviations: *GPi* globus pallidus pars interna, *SNr* substantia nigra pars reticulata, *STN* subthalamic nucleus. **b** A cortico-striatal-thalamocortical hypothesis regarding TS (adapted from Albin and Mink [63]). The relative activity of projections is represented by *line thickness*. When aberrant groups of striatal neurons with inhibitory projections onto the SNr and GPi become inappropriately active, thalamocortical circuits in turn are disinhibited. This leads to undesired competing motor patterns in the cortical output, such as involuntary tics

Treatment: Where Is the Field Heading?

CBIT therapy administered in person or through telemedicine has been evolving as an important part of the treatment armamentarium for mild to moderate tics. Many experts are also using tetrabenazine as opposed to classical neuroleptic drug treatments. DBS is a promising approach for malignant and severe medication refractory cases. The way we administer DBS will likely change over the next decade. A recent long-term study demonstrated the potential of scheduled TS DBS of less than 2 h of stimulation per day, and closed-loop responsive DBS approaches may be feasible in the TS population [132]. Closed-loop DBS strategies use neurophysiological or neurochemical feedback to deliver stimulation only when pathological activity is detected in order to reduce adverse effects of DBS and to increase battery life [133].

Conclusion

There is an abundance of future directions for research in the TS field. On the clinical side, it will be important to better understand premonitory urges, to characterize variations in TS phenotypes, and to better characterize comorbidities. Gene discovery will be applied to larger cohorts, and we will more effectively separate different clinical and genetic phenotypes of TS. More electrophysiological studies will be needed, especially in human patients performing intraoperative tasks, or through advanced DBS devices capable of recording brain signals and correlating them to awake human behavior. The manifestations of TS, which are paroxysmal, present a unique opportunity to develop responsive closed-loop neurotechnologies designed to suppress tics. All of these approaches should be conducted with the goal of developing new and improved therapies to improve the quality of life for those suffering from TS.

Looking to the future, there is a dire need for increased knowledge, awareness, and specialist care for both children and adults with TS. The First World Congress on TS and Tic Disorders was held in London in 2015, which promoted outreach and advocacy for the disorder and highlighted the important advances in all areas of TS.

Search Strategy and Selection Criteria

The authors searched PubMed for peer-reviewed articles published from 2000 to January 2015. The search terms "Tourette syndrome," "Tourette," "tic," "involuntary movement," "involuntary vocalizations," "neurodevelopmental disorders," "neuropsychiatric disorders," "movement disorders," "comorbidities," "OCD," "ADHD," "genetics," "pathophysiology," "PANDAS," "diagnosis," "treatment," "neurophysiology," "neuroimaging," and "deep brain stimulation" were used. Additional articles were identified by searching the reference lists of identified articles. Only papers in English were reviewed, with the exception of historical papers published in French. Articles were selected mostly from the past decade, but included older articles that were considered highly relevant to this review and to the history of TS. Review papers were included that provided insightful and comprehensive overviews on relevant aspects of Tourette syndrome.

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Compliance with Ethical Standards

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- •• Of major importance

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