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CHILD AND ADOLESCENT DISORDERS (T D BENTON, SECTION EDITOR)

Advances in the Treatment of Tourette's Disorder

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Abstract
Purpose of Review This article was written in order to bring the reader up to date with developments that have occurred in the treatment of Tourette disorder (TD) over the last 5 years.
Recent Findings Despite the fact that TD has been recognized for over a century, the understanding of the underlying mechanisms remains poor. There has been limited development in the last 5 years for new therapeutic options.
Summary Aripipazole is the only newly approved pharmaceutical therapy for TD in the last 5 years, although several medications are under active study. For the most severely affected individuals, there is increasing experience with surgical interventions. One of the most promising areas of research is the work of genetic consortiums currently looking into identifying the underlying pathogenetic basis which in turn will hopefully lead to the development of safer and more effective therapies.

Keywords Tourette · Therapy · Treatment · Current

Introduction

Tourette syndrome (TS) is a heterogeneous neuropsychiatric disorder with onset in childhood. It is defined by chronic motor and verbal tics, but other features are often present and sometimes more interfering [1]. Although first described by Georges Albert Edouard Brutus Gilles de la Tourette more than 130 years ago, understanding the pathophysiology, genetics, and treatments is still a work in progress [2].

Tics are defined by sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. In the DSM-V, this constellation of symptoms is referred to as Tourette disorder (TD) under the following conditions: there must be at least one vocal (e.g., humming, snorting, echolalia, and coprolalia) and multiple motor tics. These manifestations are not necessarily concurrent—waxing and waning frequency is the rule—but they must be present for more than a year with onset prior to age 18 years and not attributable to another medical condition or secondary to medication or substance abuse. This is a condition that affects all ethnic groups and affects more boys than girls (with a ratio of more than 4:1). The mean age of onset is under 7 years [3] and motor tics typically precede the onset of vocal tics. Most often, tics have a waxing and waning course with discrete bouts lasting weeks to months. Exacerbations can be associated with stress, illness, injury, or other challenges, but there is often no clear precipitant. Whether or not treatment is initiated in childhood, most affected individuals experience a resolution or reduction in tic frequency by young adulthood; about 20% of patients have persistent symptoms requiring chronic therapy [4]. TD is associated with a multitude of neuropsychiatric comorbidities in about 50–90% of those affected. These include obsessive-compulsive disorder (OCD), anxiety disorders, attention deficit hyperactivity disorder (ADHD), and depression [5]. When these conditions are comorbid with TD, they often cause distressing and disabling effects to the patient that may be more significant than the tics themselves and require equal or more attention. Individuals with TD often have family histories associated with TD, with studies showing higher concordance among monozygotic twins as compared to dizygotic twins [6]. Despite numerous large-scale population-based genetic studies, we are only beginning to identify

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the specific susceptibility genes associated with this disorder [7•].

The pathophysiology of this disorder is incompletely understood; however, the proposed mechanisms involve both functional and structural changes in the corticostriatal–thalamocortical circuitry in the basal ganglia, as well as the dopaminergic nigrostriatal pathways [8]. The neurochemical basis involves a complicated interaction of noradrenergic, serotoninergic, histaminergic, glutaminergic, GABAergic, and cholinergic systems [9]. These complex interactions contribute to the lack of specific drug targets that can be effective at treating this disorder as too many neurotransmitter systems are involved. A major strategy that promises to define the etiology of TD has involved genetics. It has always been accepted that the majority of cases are inherited, but it is clear that TD results most likely from multifactorial genetic and environmental factors. New technologies in the last decade from genome-wide association studies to whole-exome sequencing have been applied, and are leading to new knowledge including candidate genes and involvement of unsuspected neural systems, especially through large-scale collaborative projects that are studying international cohorts of well-defined families with new-onset disease as well as multigenerational involvement [10, 11].

Advances in the Management of TD

Currently, the treatments for TD are symptomatic rather than curative and the natural history is favorable. The goal of therapy is not elimination of all tics, but rather emphasizes amelioration of disability associated with tics and/or associated comorbidities. The first and perhaps most important step in the treatment course is education about the condition, including discussion about the prognosis with the patient and family, teachers, caregivers, and employers when appropriate. Even when children first come to medical attention and the condition is very mild, all benefit from education about the disorder; increased awareness may increase resilience, promote prevention, and prompt early intervention before symptoms worsen or before the situation becomes critical. Patients and families need to know that both medications and non-pharmacologic interventions are available for tics and/or the co-occurring problems when they cause significant impairment and contribute to a poor quality of life. Consequences of untreated or inadequately treated TD can be serious including significant psychiatric risks such as depression and suicide [12].

Significant advances in the treatment of TD have evolved from the days of Gilles de la Tourette from approaches such as the application of leeches, cooling of the body, massages, thoracic compressions, tongue traction, static electricity to the phrenic nerve, spinal manipulations, and sea voyages, and use of valerian, cocoa, arsenic, quinine, atropine, chlorine, and chloral hydrate to today's use of cognitive behavioral therapy, pharmacologic agents, and deep brain stimulation [13].

Behavior Therapy

The first line of therapy for TD is often cognitive behavioral therapy. This behavioral therapy intervention is demonstrated to be the most effective in reducing tic severity. It is called comprehensive behavioral interventions for tics (CBIT). This therapy involves training patients to be more aware of their tics through performing a competing behavior when they feel premonitory urges. This has been shown in RCTs and meta-analyses to reduce tic frequency with a similar effect size to antipsychotic medications [14]. This short-term approach is a form of habit reversal therapy (HRT) that includes psychoeducation, awareness training, generalization training, self-monitoring with relaxation training, behavioral rewards, motivational procedures, and social supports [15]. This training is performed until it becomes habit or second nature. The time course for treatment response is different for different individuals. Even after a treatment course, it is important to tell patients that they may still have tics but hopefully they are reduced to a less socially disabling severity [16]. It has also been noted that patients feel better and more in control—even in cases where there is no objective reduction in tics. A recent review of these and other behavioral therapies and the role of these non-pharmacologic interventions including exposure and response prevention as first-line treatments suggests that internet-based (video call) and telehealth approaches may facilitate wider accessibility [17•]. Despite its effectiveness, CBT is not appropriate for all children. When the child is too young to benefit, or when they are unmotivated, in situations where appropriate therapy cannot be accessed for any reason or in those cases where disabling tics remain refractory, then pharmacologic agents should be considered.

Pharmacologic Agents

Progress in drug development for TD has been frustratingly slow over the past five decades. Haloperidol was the first drug shown to reduce tics and was approved for use in adults with TD in 1969 and in children in 1974 [18]. This came about by serendipity in the days when severe TD was typically treated in inpatient psychiatric facilities and newly discovered antipsychotics had a dramatic response. This led to a major shift toward a neurobiologic versus a functional basis for the condition with widespread interest in the use of other dopamine D2 receptor blockers that were thought to decrease the dopaminergic influence from the substantia nigra and ventral tegmentum to the basal ganglia. Pimozide was approved by the FDA in 1984—the first under a new orphan drug act to expedite new therapies for rare medical conditions. Subsequently,

haloperidol and pimozide were joined by aripiprazole in 2014 as the only FDA-approved drugs for TD [19•]. In addition to the above agents, there is extensive clinical experience with non-neuroleptic medications. Despite the off-label usage, many clinicians start treatment for TD with one of the adrenergic agents, clonidine or guanfacine, when medication is considered for mild to moderate tic disorder.

Considerations when initiating pharmacotherapy should begin with correct diagnosis of TD and comorbid psychiatric disorders, and safety and side effect profiles. Consideration for treating the comorbidities should be emphasized when choosing a drug. Please note that many of these medications are off-label and considerations of side effects should be made when used in the pediatric population (please refer to Table 1).

First-line pharmacotherapies that should be initiated are the α-adrenergic agonists such as guanfacine and clonidine. These are often used with comorbid ADHD. A commonly used second-line agent is topiramate, which has demonstrated efficacy for TD and a more favorable side effect profile than the atypical agents. Atypical antipsychotics such as aripiprazole and risperidone are recommended as third-line agents given their lower risk of extrapyramidal side effects than haloperidol. Botulinum toxin injections have been used successfully for painful, problematic motor tics [20]. Cannabinoids have been used successfully as shown in some case reports but there is no evidence base to support its use; there have been no quality studies and further investigation is needed prior to recommendations for use [21•].

The most common comorbidity with TD is ADHD which affects approximately 60% of individuals, and sometimes is much more disabling than the associated tics. There has been controversy regarding the use of stimulant medications in the presence of TD, with the Physicians' Desk Reference suggesting that stimulants are contraindicated in the presence of a personal or family history of TD. This is not supported by the weight of evidence from the natural history of the co-existing conditions (ADHD symptoms typically precede tics by 1 to 2 years long after introduction of methylphenidate and amphetamine medication) to numerous studies that have documented the precipitation, worsening, improvement, and

Table 1 Pharmacologic therapies used in Tourette disorder

Drugs or agent	Mechanism of action	Indication	Adverse effects	Dosage guidelines
Guanfacine	α2-Adrenergic agonists	Moderate tics	Sedation, dizziness, fatigue, hypotension, irritability	1–7 mg QHS for extended-release formulation 0.5–2 mg BID for immediate-release formulation
Clonidine				0.1–0.4 mg daily in divided doses
Risperidone	Atypical antipsychotic (dopamine D2-antagonist, 5HT2 serotonin agonist)	Moderate to severe tics	Sedation, weight gain, akathisia	0.1–4 mg
Aripiprazole				1–20 mg
Ziprasidone				20–80 mg
Haloperidol	Typical antipsychotics (dopamine D2-antagonist)	Moderate to severe tics	Sedation, weight gain, muscle stiffness, dystonia, tremor, parkinsonism, cardiac conduction problems	0.5–10 mg
Pimozide				2–10 mg
Fluphenazine				1–10 mg
Topiramate	Anticonvulsant Blocks voltage-dependent sodium channels Exact-unknown	Moderate tics Headaches	Cognitive slowing, word-finding difficulties, tingling in extremities	25–200 mg
Levetiracetam	Unknown mechanism		Irritability, depression	500–5000 mg
Oxcarbazepine	Blocks voltage-sensitive sodium channels		Sedation, hyponatremia, dizziness	300–3000 mg
Clonazepam	Benzodiazepine GABA–A receptor modulators	Moderate to severe tics	Sedation, irritability, hypersalivation	0.25–4 mg
Tetrabenazine	Dopamine-depleting agent	Moderate to severe tics	Sedation, depression, parkinsonism	12.5–100 mg
Deutetrabenazine				18–36 mg
Baclofen			Sedation, weakness	5–60 mg
Botulinum toxin injection	Blocks acetylcholine release at neuromuscular junctions	Disabling tics especially involving the eyelids and neck muscles	Weakness, hoarseness, dysphagia, aspiration	Variable depending on muscle size 5–50 units

neutral effects on the tics which show that appropriate dosing of stimulants does not exacerbate or worsen tic frequency and benefits outweigh potential adverse effects in these patients [22]. Many clinicians prefer to treat tics with adrenergic agents, which are also FDA approved (at least the extended-release versions of both guanfacine and clonidine) for ADHD. While there are definitely benefits of non-stimulants from 24/7 coverage to avoidance of appetite and growth issues, unfortunately, they are less effective for the core symptoms of ADHD, both in terms of likelihood of symptom reduction (approximately 50 vs 90%) and efficacy [23].

Stimulation and Surgical Therapies

Despite adherence to behavioral therapy and the addition of pharmacotherapy, there are a significant number of TD patients who do not tolerate or benefit from these interventions and for which other modalities need to be explored.

Repetitive Transcranial Magnetic Stimulation (rTMS) A non-invasive technique thought to correct abnormal cortical excitability in patients with TD through repetitive generation of a brief, powerful magnetic field by a coil placed over the scalp that induces small electric currents. The exact mechanism of treatment is unclear. This therapy is thought to correct abnormal cortical excitability in patients with TD and is affected by the intensity, frequency, pulse number, and duration. High frequencies (> 5 Hz) are thought to promote cortical excitability while a low frequency (< 1 Hz) is thought to inhibit cortical excitability. The targets for therapy involve the orbitofrontal cortex (OFC) and supplementary motor area (SMA). This treatment has been shown to be safe in children with minimal side effects such as headache and sleepiness [24]. The earliest childhood study examining male children (between ages 9 and 14 years) showed symptom relief for 12 weeks after a 10-day course of rTMS. Treatment protocols for rTMS studies varied from 10 days to 4 weeks [24, 25]. The downside to this therapy is that it requires extensive training and is a non-portable therapy, requiring that the patient would need to come to the treating centers several times a week for several weeks per treatment course, depending on the center protocol. One paper that used a meta-regression analysis examining rTMS suggested that a younger age was associated with a better outcome, likely due to the easier plasticity. Improvements in symptoms of OCD were also noted [26•].

Transcranial Direct Current Stimulation (tDCS) It is a form of neuromodulation that uses a constant, low current delivered to the area of interest—the supplementary motor area—via electrodes that are placed on the scalp. The current is thought to modulate the neuronal excitability. This therapy is more affordable, portable, non-invasive, flexible, and simple to operate and has shown some benefit in TD in preliminary studies [27•]. This therapy has been demonstrated to have efficacy in major depressive disorder, obsessive compulsive disorder, and ADHD which are often comorbid with TD [28].

Deep Brain Stimulation (DBS) This is a therapy approved for use in Parkinson's disease and essential tremor and becoming increasingly popular in intractable cases of TD. This therapy was first published for TD in 1999, where a target of the medial thalamus was treated in a refractory case [29]. Several other targets have been described in the literature with specific structures including the subthalamic nucleus, medial thalamus (most common), internal globus pallidus, nucleus accumbens, and the anterior limb of the internal capsule. This is an invasive therapy with side effects that may include dysarthria, paresthesias, reduced energy, and visual disturbance, sleep disorders, erectile dysfunction, anxiety, agitation, mutism, infection, and anorexia. Some of the behavioral comorbidities may be improved with this therapy [30]. This is a more complex intervention requiring a tertiary center with a multidisciplinary team [31]. This therapy is therefore reserved for the most disabling cases that have severe disruption of interpersonal relationships, for example when coupled with refractory OCD or is life threatening (due to whiplash tics causing vertebral artery dissection or myelopathy) [32, 33]. A prospective international registry to assess efficacy and safety of DBS demonstrated symptomatic improvement but highlighted important adverse events, the most common being dysarthria (6.3%) and paresthesias (8.2%) in the cohort of 158 patients [34•].

Electroconvulsive Therapy (ECT) Also known as electroshock therapy, in this approach, seizures are induced by means of a strong electrical current in order to treat specific psychiatric disorders. There have been some studies and case reports in adult TD populations suggesting some effectiveness of ECT for disabling TD that has been unresponsive to other treatments; however, ECT does not currently have an indication for treatment of TD in pediatric populations. ECT was first invented in Italy in 1937 and became widespread in the 1940s and 1950s. It is widely accepted that ECT is a safe therapeutic modality that has a strong evidence base for effectiveness in certain psychiatric conditions; however, concerns exist regarding adverse effects to memory. ECT is most often used as a treatment for refractory and severe major depression and for schizophrenia in adults. Small case reports and case series have reported some benefits in TD [34•, 35, 36].

Conclusion

Tourette disorder is a developmental disorder limited to children and adolescents in the majority of cases but it can persist into adulthood. Many individuals are so mildly affected that

they never get referred for medical evaluation; this is fortunate because approximately 1 out of every 5 elementary school-aged children will have an occasional tic (and even more in the special education population). It is reasonable to identify all children with tic disorders, but only a relatively small percentage have symptoms severe enough due to pain, distraction, or social discomfort that they would benefit from any interventions. Another reason for identification is the high incidence of comorbidities including ADHD, OCD, and anxiety disorders as well as other frequent association with conditions such as headaches, sleep disorders, and autism. Treatment of complex cases needs to individualized, and it is always preferable to address the most disabling symptoms in ways that do not adversely affect other aspects. Most patients respond to a combination of behavioral and/or pharmacologic interventions. Even when tics are severe, they tend to improve over time, and the majority will outgrow motor and verbal tics by mid-adolescence even if comorbidities persist. It is a rare child or adolescent who is so disabled by tics that it would be appropriate to consider invasive technology such as deep brain stimulation which is becoming increasingly utilized in adults. Surgical intervention remains as a therapy of last resort given the potentially high morbidity. With the growing body of knowledge suggesting efficacy and safety using some of the non-invasive stimulation modalities such as rTMS, this may one day become a consideration as an initial therapy, especially in young children with comorbid OCD. Studies comparing the efficacy between these stimulation modalities and behavioral and pharmacologic therapies ought to be done. Further studies are needed to evaluate the long-term effects of some of the newer therapies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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