REVIEW

Current Management of Tics and Tourette Syndrome: Behavioral, Pharmacologic, and Surgical Treatments

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Abstract

Tourette syndrome is a heterogeneous neurobehavioral disorder manifested by childhood-onset motor and phonic tics, often accompanied by a variety of behavioral comorbidities, including attention deficit and obsessive compulsive disorder. Treatment must be tailored to the needs and goals of the individual patients and their families. All patients should receive education on the condition and, if possible, engage behavioral therapy targeted towards tics and/or comorbidities. Pharmacological therapies, such as alpha agonists, topiramate, and vesicular monoamine transport type 2 inhibitors, are generally used as first-line therapies in patients with troublesome tics that are not controlled by behavioral therapy or when the latter is not available or accessible. Botulinum toxin injections can be used in patients with bothersome focal tics. Second-line therapy includes antipsychotics, such as fluphenazine, aripiprazole, risperidone, and ziprasidone. These medications are generally efficacious but carry the risk of metabolic syndrome, tardive dyskinesia, and other side effects. Much more research is needed before novel therapies such as cannabis-derived products or transcranial magnetic stimulation can be recommended. There is promise in ongoing clinical trials with D1 receptor antagonist ecopipam and other experimental therapeutics. Patients with tics that are refractory to conventional treatments may be candidates for deep brain stimulation, but further studies are needed to determine the optimal target selection.

Key Words Tourette syndrome (TS) · Tics · Deep brain stimulation (DBS) · Vesicular monoamine transport inhibitor (VMAT2) · Comprehensive behavioral therapy in tics (CBIT)

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder defined by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) by the presence of both motor and phonic tics prior to the age of 18 and persisting for a period of greater than 12 months without a secondary cause [1]. It is more common in males compared to females (3:1), with a reported prevalence ranging between 0.3 and 1% [2]. TS is often accompanied by a variety of behavioral comorbidities such as obsessive compulsive disorder (OCD) or attention deficit hyperactivity disorder (ADHD). The tics and behavioral comorbidities can lead to marked impairment in family and social interactions and school and job performance, and often seriously impact patients' quality of life. Treatment strategies must be individualized and tailored to the patient's specific needs, and should be accompanied by education to improve understanding of TS and the patient's specific goals and expectations (Fig. 1) [3].

## Nonpharmacological Treatments

Patient Education and Counseling

All newly diagnosed patients and their families should first be educated about TS and provided with reliable informational resources (e.g., the Tourette Association of America; https://tourette.org/) to facilitate better understanding of the condition. Topics to be discussed should include the neurological (brain) rather than the psychological origin of

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Fig. 1 Suggested treatment algorithm for the management of tics associated with Tourette syndrome
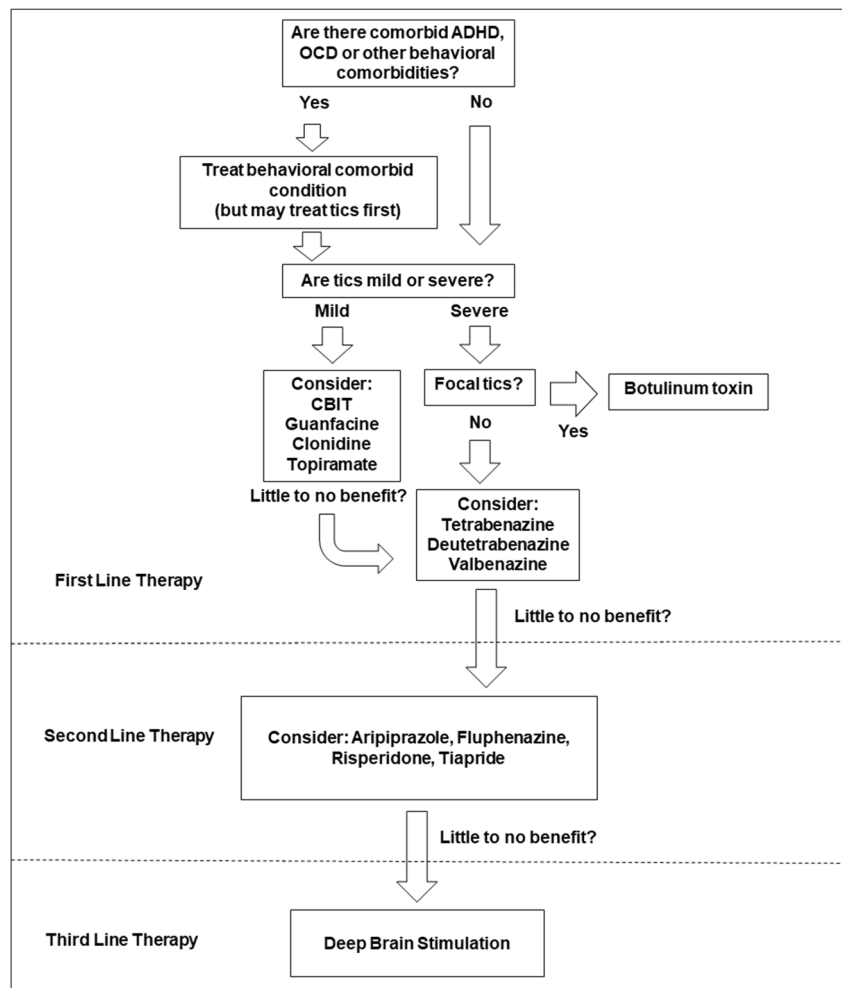
tics, the waxing and waning of the nature of symptoms, the natural history of progression, the potential for remission after age 18, and the various behavioral, medical, and surgical therapeutic options. The natural history of TS is quite variable, but generally, tic severity tends to peak just before puberty (i.e., age 10-12 years) and decline after adolescence. As such, watchful observation or behavioral therapy can be considered as acceptable alternatives to medications, particularly in early and mild cases [4].

Because therapy must be individualized, discussion should focus on the specific symptoms that are most troublesome to the particular patient. Although tics are often the presenting feature of TS, it is important to recognize and highlight the broad spectrum of motor and phonic tics from simple to complex, and the broad variety of comorbidities. For example, some complex motor tics may be accompanied by self-injurious behaviors, noted in at least a third of all patients with TS, particularly in the setting of underlying OCD [5].

Furthermore, complex phonic and motor tics may be characterized by inappropriate or obscene utterances (coprolalia) or gestures (copropraxia). Although coprophenomenon is relatively uncommon, occurring in less than 20% of all patients with TS,

this feature of TS could potentially have serious impact on social interactions, work performance, and academic activities. Encouraging patients and families to discuss potential behavioral and educational interventions with teachers and school administrators can be beneficial [6]. Accommodations afforded by section 504 of the U.S. Rehabilitation Act of 1973 should help students achieve their full academic potential. These include, but are not limited to, preferential seating; extended time on tests and assignments; reduced homework or classwork; verbal, visual, or technology aids; modified textbooks or audio–video materials; behavior management support; adjusted class schedules or grading; verbal testing; and pre-approved nurse's office visits.

Educational materials for students, parents, and teachers, such as those provided by the Tourette Association of America, should be made available from onset as they can lead to more positive impacts and attitudes among patients, peers, and teachers regarding TS [4]. A meta-analysis of 22 studies that evaluated the impact of providing educational information and programs on TS and ADHD to patients, peers, and educators found that providing educational materials can improve knowledge and attitudes towards TS in both adults and children [7].

Comprehensive Behavioral Intervention for Tics

Comprehensive behavioral intervention for tics (CBIT) is a program consisting of habit reversal training, relaxation training, and functional interventions designed to address situations which may worsen tics. It involves training patients to perform a competing behavior to avoid a tic whenever they feel a premonitory sensation [8]. The premonitory urge, a sensory phenomenon experienced by most TS patients just prior to execution of motor and phonic tics, has recently been linked to the dysfunction of the insula, particularly the anterior–dorsal region [9]. Sensory aspects of movement disorders, such as the premonitory sensory phenomenon in TS, have been increasingly recognized over the past few years [10].

CBIT has received a "high confidence" recommendation in clinical practice guidelines issued by the American Academy of Neurology (AAN) (Table 1) [4]. One trial recruited 126 children (ages 9-17) to participate in either CBIT or supportive counseling in 8 sessions over 10 weeks [11]. Compared to supportive counseling, the CBIT group showed significant improvement in tic scores with reduction of 4.1 points, 95% confidence interval (CI) 2.0, 6.2, as rated by the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) (range 0-50). Comparable improvement was seen in a trial involving an older population [12]. In this study, 122 patients, ages 16 to 69, were randomized to 8 sessions of CBIT or 8 sessions of supportive treatment over 6 weeks. CBIT was associated with a greater decrease in the YGTSS-TTS (from 24 ± 6.47 to 17.8 ± 7.32) compared with controls (from 21.8 ± 6.95 to 19.3 ± 7.40) with 38% of patients in the treatment group reporting much improvement in their symptoms compared to 6.4% in the control group. In both studies, the benefits of CBIT were sustained at 6 months. A meta-analysis of CBIT involving 8 randomized controlled trials involving 438 patients found that the treatment effect for CBIT (standardized mean difference (SMD) = 0.67; 95% CI 0.22, 1.12) was comparable to the treatment effect seen in randomized controlled trials of antipsychotic drugs for the treatment of tics [13]. A larger effect size was seen with older participants, in participants who had more therapeutic contact, and in participants who did not have comorbid ADHD.

Due to the nature of the therapy, potential barriers to CBIT include a lack of trained professionals, poor or no insurance coverage, and time and compliance demands on family and patients to adhere to the therapy. Other factors that may influence response to therapy include patients' age and self-motivation [3, 8]. Because the effect size for CBIT treatment is similar to that of most medications, it is recommended as first-line therapy to those patients who have access to this form of therapy, which unfortunately is a minority of those who would potentially benefit [3, 4, 8]. There is an ongoing clinical trial entitled "Internet-based CBIT for Children With Chronic Tics" (Clinical Trials ID NCT04087616) directed at evaluating the efficacy of CBIT when delivered via the internet in efforts to expand access [14].

Pharmacological Treatments for Tics

In cases in which CBIT is not feasible or not readily accessible, or of limited benefit, or the patient is unable to cooperate

Table 1 Currently available treatments in Tourette syndrome

Treatment	AAN recommendation (level of evidence) [4]	Potential side effects	Special considerations
CBIT	B	None	Dependent on patient motivation
Alpha agonist	B	Sedation, bradycardia	May be more effective with comorbid ADHD, requires tapering to avoid rebound hypertension
Topiramate	B	Cognitive language problems, somnolence, weight loss, nephrolithiasis	–
Antipsychotics	C	Weight gain, extrapyramidal side effects, tardive dyskinesia, QTC prolongation	Requires cardiac monitoring, requires tapering to avoid withdrawal dyskinesia, tardive syndrome
VMAT2 inhibitors	–	Drowsiness, depression, parkinsonism	Often costly and not covered by insurance, do not carry a risk of tardive dyskinesia
BoNT	C	Temporary weakness, hypophonia at the site of injection	Useful for bothersome focal tics or phonic tics
Cannabis-based medications	C	Dizziness, dry mouth, fatigue, impaired driving ability	Not recommended for children. Adult use only and where legislation allows
DBS	B	Hardware infection/removal, worsening of psychiatric conditions	For refractory cases, all patients should be screened by a multidisciplinary board before implantation

CBIT = comprehensive behavioral intervention in tics; VMAT2 = vesicular monamine transporter 2; BoNT = botulinum neurotoxin; DBS = deep brain stimulation

Table 2 Experimental therapeutics in Tourette syndrome

Class	Intervention	Trial ID	Trail design	Phase	Age group (years)	Treatment period	Primary outcome
2nd-generation antipsychotic	Aripiprazole	NCT03661983	Randomized placebo controlled	3b/4	6-17	12 weeks	YGTSS-TTS
Anti-serotonergic	Ondansetron	NCT03239210	Randomized placebo controlled	4	18-60	4 weeks	Sensory phenomena severity scale
D1 receptor antagonist	Ecopipam	NCT04007991	Randomized placebo controlled	2b	6-17	12 weeks	YGTSS-TTS
D1 receptor antagonist	Ecopipam	NCT04114539	Open label extension	2b	6-18	12 months	Incidence of AE
Cannabinoid	THC, CBD	NCT03247244	Placebo-controlled crossover study	2	18-65	–	Modified rush Video-based Tic rating Scale
Cannabinoid	Nabiximols	NCT03087201	Randomized placebo controlled	3	> 18	13 weeks	YGTSS-TTS
DBS	Thalamic stimulation	NCT01817517	Open label	N/A	> 15	1 year	YGTSS
DBS	CMT stimulation	NCT02056873	Open label	N/A	> 21	24 months	YGTSS-TTS
tDCS	Direct-current stimulation of SMA	NCT03401996	Randomized placebo controlled	N/A	> 16	1 week	YGTSS-TTS
rTMS	rTMS of the SMA	NCT04128397	Open label	N/A	6-65	5 days	YGTSS
rTMS	rTMS of the SMA	NCT03844919	Randomized placebo controlled	N/A	6-18	7 weeks	YGTSS
rTMS	rTMS of the SMA	NCT03642951	Randomized placebo controlled	N/A	8-20	2 months	YGTSS

THC = tetrahydrocannabinol; CBD = cannabidiol; YGTSS = Yale Global Tic Severity Scale; DBS = deep brain stimulation; CMT = centromedial thalamus; tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; SMA = supplemental motor area

with therapy (i.e., too young), pharmacological therapy is the next option. There is a remarkable paucity of well-designed, controlled, clinical trials that provide evidence supporting pharmacological treatment for tics. Indeed, there are only three Cochrane reviews of trials assessing three separate pharmacotherapies, pimozide, cannabis, and onabotulinum toxin, for which no firm conclusions could be drawn regarding treatment recommendations [15–17]. As such, guidelines for the pharmacological treatment of tics, such as those recently provided by the AAN, are based on expert consensus about initiation of pharmacological therapy [4]. Starting pharmacological treatments should include discussion of potential risks and benefits with the patients and their family and should align with their collective goals.

Alpha-2 Agonists

Multiple studies have shown that alpha-2 agonists, clonidine and guanfacine, have been effective in the treatment of TS, primarily in children [18–23]. Because of their relatively good safety profile, these drugs, usually prescribed by pediatricians or child psychiatrists, are often used as first-line therapy in patients with relatively mild tics. We also use them in patients with mild ADHD or impulse control disorder.

Clonidine has shown effectiveness in several randomized placebo control trials. In a multicenter 16-week, randomized,

double-blind, placebo-controlled trial (RDBPCT) of 136 children with ADHD and chronic tic disorder, patients were randomized to receive clonidine alone, methylphenidate alone, clonidine plus methylphenidate, or placebo [21]. Change in the YGTSS (range 0-100) was the primary outcome measure for tics. All treatment groups were superior when compared to placebo in reducing tic severity with the clonidine plus methylphenidate treatment group (reduction of 11.2; 98.3% CI − 0.1, 22.5) and the clonidine-alone treatment group (reduction of 10.9; 98.3% CI 2.1, 19.7) showing the greatest improvement. Furthermore, the study provided no evidence that methylphenidate worsened tics despite the common observation that central nervous system (CNS) stimulants trigger or exacerbate tics. The efficacy of clonidine in reducing tics was further supported by another RDBPCT involving 437 patients with tics or TS [23]. Patients who were randomized to receive a clonidine transdermal patch showed a significant reduction in tics as measured by the YGTSS when compared to placebo (reduction of 11.53 ± 8.22 vs 10.72 ± 7.50).

Guanfacine was found to be effective in reducing tics in a small open-label trial of 10 TS patients with ADHD. Duration of follow-up ranged from 4 to 20 weeks. At the end of the study, there was a 37.6% decrease in the mean YGTSS phonic tic score (range 0-25) (mean reduction 7.8 ± 4.6) [19]. In a RDBPCT, 34 patients (mean age 10.4 years) with tics and comorbid ADHD were assigned to receive guanfacine or

placebo for 8 weeks [18]. At the end of the trial, tic severity, measured by the YGTSS-TTS, was decreased by 31% in the treatment group compared to the placebo group, which showed no improvement. Another RDBPCT, however, failed to show similar efficacy [22]. In this trial, 34 patients with chronic tic disorder (age 6-17 years) were assigned to receive guanfacine extended release or placebo for 8 weeks. No significant difference was seen in the YGTSS between groups at the end of the study.

Based on existing published data, it appears that alpha agonists are more efficacious in TS patients with comorbid ADHD which may explain the results of the above negative trial. In a meta-analysis of 4 trials of clonidine and 2 trials of guanfacine, a significant benefit in reduction of tics was noted (SMD = 0.31; 95% CI 0.15, 0.48; $p < 0.001$ when alpha-2 agonist was compared to placebo) [24]. A greater effect was seen in trials that enrolled subjects with tics and ADHD (SMD = 0.68; 95% CI 0.36, 1.01) than in trials that excluded subjects with ADHD (SMD = 0.15; 95% CI − 0.06, 0.36). When this data was later stratified in subgroup analysis, the presence of comorbid ADHD led to a greater effect of alpha-2 agonist in reducing tics (α = 0.0053; 95% CI 0.0015, 0.0091). Neither clonidine nor guanfacine has been found to be superior to the other in the reduction of tics; however, guanfacine appears to be better tolerated and cause less sedation than clonidine [25].

The most common side effects of alpha-2 agonists include sedation and drowsiness [3]. Other potential side effects include headache, dry mouth, irritability, bradycardia, and hypotension as well as prolonged QTC, particularly with the use of guanfacine XR [3, 4].

Topiramate

There have been several studies that have found topiramate to be a viable treatment option for tics in TS [26, 27]. In a pilot RDBPCT, 29 patients with TS, age 7 to 65 years, were randomized to receive either topiramate or placebo for 10 weeks [27]. Compared to the placebo group, there was a significant reduction of the YGTSS-TTS by 14.29 ± 10.47 points from baseline compared to only a 5.0 ± 9.88 point improvement in the placebo group. Additionally, patients in the topiramate group showed improvement in premonitory urge, but this effect was not quantified.

A meta-analysis evaluating 14 trials involving 1003 patients, age 7 to 17 years, evaluated the use of topiramate for treatment of tics compared to conventional treatment [28]. All trials included a drug comparator; 12 used haloperidol and 2 used tiapride as comparators. In 3 trials that used the YGTSS as an outcome measure, there was a significant improvement of tics (reduction of mean 7.74 points in the total YGTSS score; 95% CI 10.49, 4.99) favoring topiramate compared to a control group. In the remainder of the studies, no superiority

was seen when comparing topiramate to either haloperidol or tiapride [28].

Topiramate is currently recommended for use in relatively mild cases of TS or when other therapy cannot be tolerated. The typical dose is 25 to 150 mg daily. Side effects include cognitive and language problems, weight loss, renal stones, and somnolence [4].

Antipsychotics

The use of antipsychotic medications, which act primarily by blocking dopamine receptors, for treatment of tics dates back to the late 1960s when haloperidol was first approved by the US Food and Drug Administration (FDA) for treatment of TS [8]. After haloperidol, pimozide was the second antipsychotic approved by the FDA for the treatment of TS, and in 2014, the FDA approved aripiprazole as the third drug for TS. Several studies have evaluated second- and third-generation antipsychotics such as ziprasidone, risperidone, and aripiprazole and found them to be effective in reducing the frequency and intensity of tics when compared to placebo [29–33].

Aripiprazole was FDA approved for the treatment of TS following a 2013 RDBPCT involving 61 subjects (ages 6-18) [30]. Patients in the treatment group had a reduction in the YGTSS-TTS of 15.0 ± 8.4 compared to a 9.6 ± 8.8 reduction in the placebo group. In 2017, Sallee et al. reported the results of phase 3 RDBPCT of aripiprazole involving 133 patients with TS [31]. At week 8 of the trial, the treatment difference in YGTSS-TTS *vs* placebo was − 6.3 (95% CI 10.2, − 2.3) in the low-dose group (5-10 mg/day) and − 9.9 (95% CI 13.8, − 5.9) in the high-dose group (10-20 mg/day). The most common adverse events were sedation and fatigue. Although no tardive dyskinesia was reported in these trials, it is now well recognized that patients treated with aripiprazole and other antipsychotics, with possible exception of clozapine, may develop tardive dyskinesia as a result of their dopamine receptor blocking action [34].

Risperidone, although not FDA approved, has also been shown to be efficacious in the treatment of tics. In one RDBPCT, 48 adolescent and adult TS patients were randomized to risperidone or placebo for 8 weeks [32]. At the end of the study, 60.8% of patients in the treatment group showed at least one point improvement in the Global Severity Rating of the Tourette Syndrome Severity Scale, compared to 26.1% in the placebo group, significantly favoring risperidone. In another RDBPCT, 34 patients with TS (age 6-62 years) were randomized to risperidone or placebo for 8 weeks [33]. At the end of this study, there was a 36% mean reduction in the YGTSS-TTS in the treatment group (mean change from 26.0 ± 5.06 to 17.6 ± 4.75) compared to a 7% reduction in the placebo group (mean change from 27. 4 ± 8.51 to 25.4 ± 8.75). Notably, a mean increase in body weight of 2.8 kg was noted in the risperidone group. In a 6-week open label trial, 14

TS patients (age 7-14 years) were administered ziprasidone with a 30% reduction in YGTSS-TTS by the end of the study (mean change from 31.92 ± 7.32 to 22.50 ± 9.37) [35]. Side effects included drowsiness, sedation, and a mean weight gain of 4.1 kg.

A meta-analysis of 10 studies evaluated the use of antipsychotic medications for the treatment of tics in TS [24]. Trials compared haloperidol, pimozide, risperidone, and ziprasidone to placebo. The meta-analysis demonstrated that there was a medium to large treatment effect of the antipsychotic agent improving tic symptoms when compared to placebo (SMD = 0.58; 95% CI 0.36, 0.80). A stratification analysis comparing efficacy in between antipsychotic agents did not find significant differences between the various antipsychotics.

Before the advent of the class of drugs that act as dopamine depleters by inhibiting presynaptic vesicular membrane transport type 2 (VMAT2) (discussed below), we have used fluphenazine as the main dopamine receptor blocking drug in the treatment of TS [36]. In a retrospective chart review, 268 TS patients (age 4-70) were initiated on fluphenazine for management of their tics; 211 (80.5%) reported moderate to marked improvement in their symptoms based on a 5-point rating scale comparing reduction in tics to the baseline visit (1 = marked reduction, 5 = worsening of tics). The most common side effects were drowsiness or fatigue. Although no cases of tardive dyskinesia were noted in this study (average duration of treatment of 2.6 ± 3.2 years), fluphenazine, like other antipsychotics, can cause this iatrogenic complication.

Besides tardive dyskinesia, there are many other risks associated with prescribing antipsychotic medications, including weight gain and metabolic syndrome, prolactin increase, and QTC prolongation [4]. In one retrospective study that evaluated siblings with discordant TS or chronic tic disorder, 7804 patients were found to have a higher risk of metabolic or cardiovascular disorders compared to sibling controls (hazard ratio 1.37; 95% CI 1.24, 1.51) and the general population (HR 1.99; 95% CI 1.90, 2.09) [37]. Although this was apparently not related to long-term (> 1 year) use of antipsychotics, it is important to keep in mind that these drugs can cause weight gain and metabolic syndrome.

If antipsychotics are ineffective or associated with adverse effects, they should be gradually discontinued to avoid withdrawal and tardive dyskinesia [4, 38, 39]. Given the associated risk of metabolic syndrome and tardive dyskinesia, and the need for periodic cardiac monitoring, antipsychotic agents should be considered second-line therapy after first-line agents have failed (Fig. 1).

VMAT2 Inhibitors

VMAT2 inhibitors block the vesicular monoamine transporter type 2 which is normally necessary for packing monoamines, such as dopamine, into presynaptic vesicles for release into the synaptic cleft [40]. The result of VMAT2 inhibitors is presynaptic striatal dopamine depletion and a reduction of dopamine release. Medications in this class include tetrabenazine, deutetrabenazine, and valbenazine. Deutetrabenazine has been approved by the FDA to treat Huntington's chorea and tardive dyskinesia, and valbenazine has been approved to treat tardive dyskinesia. However, VMAT2 inhibitors have been also used successfully off label for treatment of a broad variety of hyperkinetic movement disorders, including tics [40, 41].

In an open-label, pilot, study of 23 patients (age 12-18 years) with TS, up to 36 mg daily of deutetrabenazine (mean daily dose 32.1 mg) was administered over an 8-week period [42]. Following treatment, patients had a 37% reduction in tic severity measured by the YGTSS-TTS (reduction of 11.6 ± 8.2). In one retrospective chart review, 77 TS patients (mean age 77) were prescribed tetrabenazine off label for treatment [43]. Among those prescribed the medication, 80% reported improvement in their symptoms as measured by a 5-point rating scale (1 = marked reduction, 5 = worsening of tics). In another retrospective chart review of 135 patients, 67 of whom had TS, treated with tetrabenazine, deutetrabenazine, or valbenazine for tics, when surveyed about severity of symptoms before and after treatment, the majority of respondents reported improvement as measured by a 4-point Likert scale (1 = normal or mildly ill, 4 = severely ill) [41].

Despite the improvement observed in open-label studies and "real-world" experience, 2 recent RDBPCTs, 30,046 ARTISTS 1 (flexible-dose titration), and 30,060 ARTISTS 2 (fixed dose) were negative [44]. In the ARTIST 1 trial, 119 patients were enrolled and, after initial dose titration, were followed for a total of 12 weeks, whereas in the ARTIST 2 trial, 158 patients were enrolled in a fixed-dose design and followed for 8 weeks. Although reduction in the YGTSS-TTS and responder analyses favored deutetratrabenazine over placebo, the primary endpoint was not met in either study. Although the full reports have not yet been published, this unfortunately parallels the findings from similar, yet unpublished, studies with valbenazine in pediatric and adult TS populations. There are many possible explanations for the unexpected results, including difficulties in assessing a highly variable disorder and subtherapeutic dosing. The latter explanation is supported by the observation of a very low frequency of adverse effects, specifically no evidence of depression or suicidal ideation.

Side effects of VMAT2 inhibitors, noted in long-term observational studies and real-world experience, include depressive symptoms, akathisia, weight gain, insomnia, and parkinsonism [41]. However, unlike D2 receptor antagonists, VMAT2 inhibitors do not carry a risk of developing tardive dyskinesia [40]. There is also supportive evidence that they cause less weight gain, especially in the pediatric population, than antipsychotic therapy [45].

The off-label use of VMAT2 inhibitors in TS and other hyperkinetic movement disorders is associated with many hurdles to prescribers and patients that limit potential widespread utilization of the drugs. Such barriers include high out-of-pocket cost, insurance denials, lengthy appeals, and requiring trials of older medications that may be less efficacious or carry more side effects before the VMAT2 inhibitor is approved [41]. Given the efficacy observed by many clinicians around the world in a large number of TS patients, good tolerability, minimal side effect profile, and low or no risk of tardive dyskinesia, VMAT2 inhibitors should be considered viable alternative therapy to antipsychotic medications as first-line therapy in patients with troublesome tics, although, given the recent negative trials, FDA approval in the near future is unlikely.

New and Emerging Therapies

D1 Receptor Antagonist

Although all available dopamine receptor blocking drugs act primarily by antagonizing D2 receptors, there is a possibility that inhibition of D1 receptors may also have beneficial effects. The D1 receptor antagonist ecopipam was initially developed in the 1980s as a potential antipsychotic therapy, but it failed in trials for schizophrenia [46, 47]. It has, however, shown promise in treatment of tics. In one open-label trial, 18 adults (mean age 36.2 years) were administered 100 mg ecopipam for 8 weeks [48]. At the end of the study, there was a significant reduction in YGTSS-TTS when compared to baseline (from 30.6 ± 8.8 to 25.3 ± 9.2; $p = 0.0004$). There was also an improvement of the YGTSS impairment score (from 29.7 ± 10.9 to 22.8 ± 13.7; $p = 0.04$). Most common adverse events were sedation and fatigue, insomnia, anxiety, headache, and muscle twitching.

In a phase 2b RDBPCT, 40 adolescents (aged 7-17) were administered ecopipam for 30 days [49]. When compared to placebo, ecopipam was associated with a reduction in YGTSS-TTS of 3.2 points (95% CI 6.1 to 0.3) which was considered clinically meaningful. No weight gain or drug-induced movement disorders were seen, and the medication was otherwise well tolerated. In the current, larger, phase 2b, multicenter RDBPCT (D1AMOND), ecopipam is being evaluated for the efficacy and safety in children and adolescents with TS (Clinical Trials ID NCT04007991) (Table 2) [50]. If ecopipam is found to carry low risk of weight gain or metabolic syndrome and is otherwise well tolerated, it may be considered in the future as an early line therapy in TS.

Cannabis-Based Medications

Cannabis-based therapy has been explored in the past as a potential treatment option for TS. In a RDBPCT of 12 adult patients with TS, patients given delta 9-tetrahydrocannabinol reported significant improvement in their tics and obsessive compulsive behavior 3 to 4 h after treatment when compared to placebo based in the Tourette syndrome symptom list (-14 ± 10.97 change from baseline in the treatment group $vs -4.69 \pm 6.69$ in the placebo group) [51]. There was also a nonsignificant trend towards improvement in tics in the treatment group seen on the Shapiro Tourette syndrome severity scale, the Tourette syndrome global scale, and the YGTSS. Serum tetrahydrocannabinol (THC) concentrations were also measured during the study and correlated with improvement in tics as measured by the examiner [51]. In a follow up RDBPCT over 6 weeks, involving an additional 24 patients, there was again a trend towards improvement in the THC treatment group compared to the placebo group at the end of the study, though this was not found to be statistically significant [52].

As the legislative landscape has changed, there has been more interest in exploring cannabis-based medications as a potential therapy; however, there is a paucity of well-designed and well-conducted studies. In one cross-sectional survey of 42 patients with TS who were already undergoing treatment with medical cannabis, all patients interviewed reported some improvement with tics while taking medical cannabis when asked about the efficacy of medical cannabis in treating their symptoms (mean response = 3.85 ± 1.41 out of a 5-point Likert scale, 1 = worsening symptoms, 5 = favorable response) [53]. Adverse effects led to discontinuation of treatment in 10 patients, including one patient because of an episode of psychosis. Other patients who discontinued treatment had side effects that included hallucinations (4 patients), irritability and confusion (6 patients), and subjective cognitive decline (7 patients).

A recent 12-week RDBPCT evaluating the use of THX-10 (dronabinol, tetrahydrocannabinol, palmitoylethanolamide) in adult TS patients has apparently met its primary endpoint and led to significant improvement in symptoms, but further information is needed [54].

In the setting of renewed interests, there are several ongoing RDBPCTs evaluating cannabis and its derivative products. The CANNAbinoids in the Treatment of TICS (CANNA-TICS) study is evaluating the use of nabiximols to treat chronic tic disorders (Clinical Trials ID NCT03087201) [55]. The Safety and Efficacy of Cannabis in Tourette Syndrome trial is evaluating medical cannabis in adults with TS (Clinical Trials ID NCT03247244) (Table 2) [56].

ABX-1431 is a monoacylglycerol lipase inhibitor that regulates endocannabinoid and eicosanoid signaling pathways. It has recently been shown to be well tolerated in phase 1 clinical studies, and data from an exploratory phase 1b study suggest

that it has potential for treatment of symptoms of TS in adult patients [57]. It is currently undergoing phase 2 trials in TS (clinical trial ID NCT03625453) (Table 2) [58].

As of now, there is limited evidence that dronabinol reduces tic severity when compared to placebo. There is insufficient evidence on the use of cannabis-based compounds nabiximol, nabilone, and cannabidiol for treatment of tics. The most common side effects seen with these medications include dry mouth, dizziness, and fatigue. For patients who are interested, physicians should direct them to appropriate medical and legal information [4]. Much more evidence is needed before cannabis-based medications can be safely recommended to patients for management of TS.

Alternative Medications

Given concerns over treatment side effects, more patients and their families have pursued complementary and alternative medicine (CAM) with the perception that such practices are "natural" and therefore safe [59]. In a survey of 110 TS patients (< 18 years old) and caregivers, 69.1% reported using CAM therapy [59]. The most commonly reported CAM therapies were stress management (44.6%), herbal medicine (18.2%), homeopathy (18.2%), and meditation (9.1%). Of those patients participating in CAM therapy, 93% reported improvement in tics.

Several clinical trials have evaluated the benefit of the herbal medicines Qufeng Zhidong Recipe (QZR) and Ningdong granules. In a meta-analysis of 4 randomized control trials (2 trials involving QZR and 2 involving Ningdong granules), QZR had significant effects across 2 trials in reducing YGTSS-TTS score when compared to a combination of haloperidol and trihexyphenidyl ($n = 142$; weighted mean difference $= -18.34$; 95% CI -23.07, -13.60) [60]. When compared to placebo, Ningdon granules were found to lead to a significant reduction in YGTSS-TTS compared to placebo (-6.52; 95% CI -9.80, -3.24); however, no such difference was found when compared to treatment with haloperidol. Notably all 4 studies evaluated in the meta-analysis were noted to be at high risk of bias, with only 1 of the 4 studies being a blinded study.

One multisite RDBPCT evaluated the herbal medicine 5-Ling granule in 608 TS patients (aged 5-18) [61]. Patients were randomized to receive 5-Ling granule, tiapride, or placebo for 8 weeks. At 8 weeks, patients in the 5-Ling granule group showed significant improvement in the YGTSS compared to placebo (effect size $= 0.608$), but no difference was observed when compared to tiapride (effect size $= 0.075$). Notably, patients in this study that met inclusion criteria needed to have a condition known in traditional Chinese medicine as "excessive subtype disorder," a condition for which there does not exist a western medicine equivalent.

Patients with common TS comorbidities, ADHD and OCD were also excluded.

Due to concerns about the generalizability of the 5-Ling granule study and multiple unknowns regarding the safety of ingredients used in these herbal compounds, the AAN guidelines do not offer formal recommendations on the use of Chinese medicine products [4]. They, however, assigned "moderate confidence" to 5-Ling granule and Ningdong granule, and concluded that these treatments "were probably more likely than placebo to reduce tics" [4].

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) delivers a repetitive magnetic pulse to a targeted area of the cortex. Various parameters of the magnetic stimulation (frequency, intensity, duration) have been found to modulate cortical excitability and induce sustained changes beyond the stimulation period [62]. TMS has been used in the treatment of depression but more recently has been explored as a potential treatment for tics in TS. In 1 meta-analysis of 8 studies in the literature, there was noted to be a significant reduction in tics (Hedges' $g = -0.61$; 95% CI -0.94, -0.29) and OCD symptoms ($g = -0.48$; CI -0.83, -0.14) when all studies were assessed as a whole [63]. However, in a second analysis within the same publication, which accounted for a placebo arm, there was no significant reduction in tics seen between the 2 groups.

There are currently several ongoing placebo controlled trials evaluating the effects of TMS on tics and related conditions such as OCD (Table 2) [64]. In the Transcranial Magnetic Stimulation for Intervening in Children With Tourette's Syndrome study (TICS-CIHR), children (age 6-18 years) will be randomized to either repetitive TMS (rTMS) and CBIT or sham rTMS and CBIT over 3 weeks (Clinical Trials ID NCT03844919) [65]. The Multi-site Transcranial Magnetic Stimulation Therapy of the Supplementary Motor Area in Children With Tourette Syndrome trial will randomize TS patients (age 8-20) to rTMS or sham stimulation for 2 weeks (Clinical Trials ID NCT03642951) [66]. If found effective, TMS has potential as an adjunctive therapy in TS, because it seems to be generally well tolerated, with the most commonly reported side effect being headache. Further research, however, is still needed to support its safety and efficacy, especially in children with TS.

Botulinum Toxin Injections

For localized bothersome motor or phonic (vocal) tics, botulinum toxin injections can be a very useful alternative to other medical therapies. In one study, 35 patients were treated with onabotulinumtoxin A injections at a site determined by their most problematic tic [67]. Patients reported improvement in

severity of tics based on a peak effect rating scale (2.8 ± 1.5, range 0-4, 0 = no effect, 4 = marked improvement). The mean latency of onset was 3.8 days with a mean duration of benefit of 14 weeks. Furthermore, 84% of patients reported improvement in the premonitory sensation with treatment based on a subjective percentage scale (mean reported benefit = 70.6% improvement). Complications were mild and transient and included weakness at the site of injection.

These results have been replicated in a RDBPCT of 18 patients who received botulinum toxin injections for simple motor tics [68]. Patients who received botulinum toxin injections had a 39% reduction in tics counted per minute compared to placebo which showed a 5.8% increase in tics. There was also nonsignificant improvement in the sensation of premonitory urge in this study when compared to placebo based on a patient-administered scale on premonitory urge severity (reduction of -0.25; 95% CI -0.091, 0.41, range 0-4, in which a higher number correlates with severity).

Besides motor tics, onabotulinumtoxin A has been also used successfully in the treatment of simple and complex phonic tics. In an open-label trial, 30 TS patients received bilateral vocal cord injections for phonic tics [69]. After treatment, 93% of participants showed improvement in vocal tics as determined by clinical exam, with 50% of patients being tic free. The mean duration of response was about 102 days (range 20-300). As with the other trials, there was further data to support treatment of premonitory urge (52% of patients reported premonitory sensations before treatment, compared to 20% after treatment). Transient hypophonia was noted in 80% of patients receiving treatment.

The duration of response to botulinum injections is typically 12 to 16 weeks and requires repeated injections for optimal long-term management. The main side effect is weakness at the site of injection [4]. Botulinum injections carry several advantages over systemic medical therapy. Botulinum toxin only acts in the site of injection, and therefore, any side effects of weakness are typically localized to the injected muscles and typically resolve in a few weeks. Botulinum toxin treatment can be used safely in combination with drug therapy as it does not cause sedation or any other systemic side effects except for occasional transient flu-like symptoms [70]. Importantly, botulinum toxin appears to have some effect in treating the premonitory sensation preceding most tics, suggesting that it is not merely just masking tics by inducing local muscle weakness, but may be leading to relief via more complex peripheral mechanisms. This treatment is most suitable in cases with bothersome focal or segmental tics such as blinking or dystonic tics involving the neck (the "whiplash" tics) and shoulders or disabling phonic tics (such as loud screams or coprolalia), especially in patients who are unable to tolerate other medications or have not had a satisfactory improvement in their tics (Fig. 1) [3, 4, 71].

Deep Brain Stimulation

Deep brain stimulation (DBS) is a potential treatment reserved for patients with severe TS that has been refractory to medical treatment (Fig. 1). Although the pathophysiology of tics is not fully understood, it is thought that tics are due to dysfunction in the basal ganglia–thalamo–cortical circuits, which can be favorably modified by DBS [72]. As it is not currently FDA approved for the treatment of tics, proposed indications for DBS in the treatment of TS include the presence of high tic severity and poor symptomatic relief despite the use of at least three different classes of pharmaceutical treatments: alpha agonist, antipsychotic, and an additional class of medication such as a VMAT2 inhibitor or topiramate [73].

Multiple targets for DBS have been studied over the past 2 decades including the centromedian parafascicular complex of the thalamus, the anterior and posterior globus pallidus internus (GPi), and the anterior limb of the internal capsule (ALIC) [73, 74]. In a review of 185 TS patients from the international DBS registry, patients were found to have 40.1% improvement on average from baseline YGTSS scores at 1 year following implantation (from 75.01 ± 18.36 to 41.19 ± 20.00) [75]. Four targets were evaluated in this retrospective study: the anterior GPi, the posterior GPi, the centromedian thalamic region, and the ALIC. There were no statistically significant differences seen between target groups; however, the anterior GPi showed greatest improvement with a 50.5% reduction in the YGTSS score (from 84.33 ± 11.32 to 41.78 ± 15.75), followed by a 46.3% reduction in the central thalamic region (from 74.49 ± 2.28 to 40.02 ± 2.70) and a 27.7% reduction in the posterior GPi (from 65.12 ± 3.96 to 45.65 ± 4.68); no significant change was seen with the ALIC group; however, the number of participants in this group was small (4 patients) [75].

A meta-analysis of 57 studies comprising 156 TS cases showed that DBS led to a significant improvement in YGTSS scores (52.68% reduction; interquartile range (IQR) = 40.83) [76]. Improvement in symptoms was seen across all targets, including the posterior ventral lateral GPi, anteromedial GPi, and the ALIC. Comparable improvement was seen with both the anteromedial GPi and posterior ventral lateral GPi (58.03%; IQR = 61.09 and 55.32%; IQR = 38.13 reduction in YGTSS score respectively). Stimulation in the ALIC region showed improvement to a lesser extent (44%; IQR = 24.58). A lower YGTSS score on initial evaluation was a favorable predictor of improvement (correlation coefficient = 0.337). There was also suggestion that younger patients may benefit more than older patients; however, this correlation was not found to be significant [76]. Other case series and meta-analyses have demonstrated similar findings [77–79].

Few randomized control trials have evaluated the efficacy of DBS in TS. One RDBPCT assessing DBS in adults (ages

18-60 years) did not replicate what had previously been reported in the literature [80]. In this study, 16 patients underwent DBS placement with lead placement in the anterior GPi. They were then randomized to receive stimulation or sham stimulation for 3 months. No significant difference was seen in YGTSS scores between groups at 3 months (1.1% reduction in the treatment group, IQR = − 23.9 to 38.1, compared to 0.0% change in the placebo group, IQR = − 10.6 to 4.8). Furthermore, 4 patients experienced complications because of hardware infections, and 1 had electrode misplacement. In the treatment group, 1 patient reported an episode of depression and another reported increased anxiety and worsening of tics. Notably, the treatment group patients were exposed to intensity set below side effect thresholds to maintain blinding so it was possible they were not receiving adequate stimulation. In another randomized double-blind crossover study, 15 TS patients (mean age 34.7) received GPi-targeted DBS and were also randomized to receive stimulation or sham stimulation for 3 months and then switch treatment arms for an additional 3 months [81]. Compared to sham stimulation, treatment led to an average of 15.3% reduction in YGTSS scores (95% CI 5.3, 25.3). In one of the only prospective studies evaluating DBS for the treatment of TS, 16 patients received anterior GPi DBS and were then followed by longitudinal observation for 48 months [82]. Ultimately, 12 patients completed the study, with 4 lost to follow-up. A mean 49.3% ± 38.2% reduction in YGTSS was found at 48 months. The authors noted that 25% of their patients appeared to be "nonresponders"; however, those who did respond (remaining 9 patients) had a 69.5% reduction in the YGTSS suggesting that more research is needed to determine which patients are most suitable for this form of therapeutic intervention.

Typical exclusion criteria for DBS implantation include the presence of cognitive impairment, an unstable or untreated psychiatric disorder, suicidal ideation, or psychiatric inpatient hospitalization in the preceding 6 months. The decision for DBS placement and potential target should be made collectively by a multidisciplinary team composed of neurologist, neurosurgeons, psychiatrist, and neuropsychologist. Potential complications from DBS may include infection, dysarthria, paresthesia, fatigue, apathy, lethargy, and manic symptoms. Compared with other populations receiving DBS, there does appear to be a need for more frequent hardware revisions in TS patients [4, 73, 75]. The reasons for this are not clear, but some patients, particularly those with severe comorbid OCD, may repeatedly touch, scratch, or strike the impulse generator or its leads requiring revisions.

Treatment of Comorbid Conditions

Comorbid psychiatric conditions often accompany TS. The lifetime prevalence psychiatric comorbidities in TS patients is as high as 86%; 72.1% of patients meet criteria for OCD or ADHD [83]. TS patients have also been found to have a higher incidence of comorbid psychopathology such as depression or anxiety, heightened stress, and poor global functioning [84].

A subanalysis of a trial pertaining to OCD has shown that patients afflicted with OCD and tics do not respond as robustly to the selective serotonin reuptake inhibitor sertraline when compared to patients with OCD without tics (posttreatment Children's Yale-Brown Obsessive Compulsive Scale score 15.5 ± 5.3 in the OCD-only group compared to 17.0 ± 5.6 in the OCD-plus-tics group) [85]. Both groups, however, did respond equally well to cognitive behavioral therapy. Patients with comorbid ADHD experience greater psychosocial stress and poorer global functioning compared to TS patients without OCD and are also more likely to carry a diagnosis of oppositional defiant disorder [84]. Although there has been concern that stimulant medications may worsen tics, studies suggest this is not always the case [18]. Although it has been shown that methylphenidate does not adversely affect tics, many parents report that initiation of central nervous system (CNS) stimulants triggers or exacerbates tics in their children. We, therefore, often prescribe anti-tic medications as first-line treatments, and when the tics are relatively well controlled, we add CNS stimulants in patients who require treatment of both tics and ADHD (Fig. 1).

Conclusion

TS is a heterogeneous and variable disorder with no 2 patients experiencing the same symptoms. Tics, the most characteristic feature of TS, can be mild or moderately troublesome, and in some cases may be associated with self-injurious behavior or become otherwise disabling. The cornerstone of any treatment is patient education and a therapeutic approach that is individualized and tailored to address those symptoms that are most troublesome or disabling to the patient. Comorbid behavioral and psychiatric conditions may worsen overall disability and adversely impact quality of life. Therefore, a holistic approach to treatment is required, targeting not only motor but also behavioral and psychiatric symptoms associated with TS. DBS should be reserved for the most refractory cases as it carries with it its own risks. Currently, there are several new and emerging treatments that are promising but require additional research (Table 2).

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