



Tourette Syndrome Treatment Updates: a Review and Discussion of the Current and Upcoming Literature

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Abstract

Purpose of Review This study aims to examine the treatments currently available for Tourette syndrome (TS) and to discuss evolving therapies, spanning behavioral, pharmacologic, complementary and alternative medicine, and neuromodulation approaches.

Recent Findings Behavioral therapies have undergone several modifications to improve accessibility, including transitioning to a virtual format which is particularly important in the current pandemic. There are several recent or ongoing pharmacologic studies that have shown promise including the selective D1 receptor antagonist ecopipam and various cannabinoid compounds. Adaptive DBS may enable the physiologic markers of tics to determine stimulation parameters and improve tic outcomes related to neuromodulation.

Summary In recent years, there has been a wealth of research across multiple treatment domains in the TS field. This review highlights exciting and new potential options for the future treatment of patients with TS.

Keywords Tourette syndrome · Tics · CBIT · Pharmacotherapy · Neuromodulation · Deep brain stimulation

Introduction

Tourette syndrome (TS) is a childhood-onset disorder in which multiple motor tics and at least one phonic tic occur, lasting beyond a year and typically fluctuating over time. Although in many cases tics can be mild and non-bothersome, in others, tics can cause physical discomfort, academic and professional detriment, and social disability. Tics in TS may be associated with a number of comorbidities, including anxiety, attention deficit hyperactivity disorder (ADHD), and obsessive–compulsive disorder (OCD). Genetic factors drive some portion of risk, and hyperactivity in dopamine circuitry seems to play a pivotal role in the pathophysiology. Management begins with education about the nature of tics. When tics impair quality of life, there are many established and evolving treatment options that may

be considered. This review will discuss treatment updates for TS, including behavioral and other non-pharmacologic interventions, pharmacologic strategies, and neuromodulatory approaches.

Non-pharmacologic Interventions

Although pharmacotherapy plays a major role in the treatment of TS, medication side effects are common and may accumulate over time. For this reason, more conservative approaches are often considered first-line, including psychoeducation, behavioral interventions, and biofeedback.

Psychoeducation and Supportive Therapy (PST)

Psychoeducation and supportive therapy (PST) can help to mitigate misunderstandings of TS, reduce perceived stigmas, and provide age-appropriate explanations for TS and associated comorbidities [1]. One meta-analysis found that PST improves knowledge and misconceptions regarding TS [2]. However, a diagnostic label in isolation may lead to negative expectations of certain behaviors or even exacerbate symptoms [2]. Therefore, it is important that information is used

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to increase awareness and promote acceptance [2]. There is evidence for further reduction in tics when PST is added to pharmacotherapy, relative to pharmacotherapy alone [3]. PST has expanded to incorporate video footage [2] and telepsychoeducation strategies effectively [4].

Reliable information is critical to supporting well-being with tics. Virtual communication and social media use skyrocketed in the face of the COVID-19 pandemic, and individuals, particularly adolescents, increasingly turn to the Internet and social media for healthcare information [5, 6]. The increased consumption of information about TS from public sources with variable accuracy, combined with social isolation and need for connection, may have contributed to increased frequency of explosive onset functional tic-like behaviors [7]. Social media “influencers” have posted videos with very particular and extreme manifestations, and online communities have encouraged sharing tics and rating their severity. Although online support groups offer many positives with regard to acceptance, community, and information sharing, they may unintentionally propagate inaccurate ideas about tics and influence tic expression given the suggestibility of tics [8]. Therefore, it is equally important to educate patients about sources where reliable information about TS is available.

Multiple treatment guidelines recommend clinicians use psychoeducation to help educate patients, teachers, and peers about the natural history of TS [9••, 10••, 11]. Strategies to disseminate PST have recently been outlined in a guide by Wu and McGuire (2018) [12]. Combining education on an individual level with dissemination of resources that can aide educators or family members, such as those available through Tourette syndrome-focused national organizations, is advisable.

Behavioral Interventions

Behavioral interventions have the advantage of being effective at reducing tics without significant adverse effects and therefore are the first-line treatment according to several treatment guidelines [9••, 10, 11, 13••, 14••]. At least one study has demonstrated that behavioral interventions are comparable to pharmacotherapy at reducing tics [15]. Exposure and response prevention (ERP) exposes patients to the unpleasant sensation associated with a premonitory urge, simultaneously teaching habituation to the urge and how to prevent the tic from occurring [16]. Habit reversal therapy (HRT), which involves awareness training, competing response practice, and habit control motivation and generalization training, was one of the earliest behavioral interventions successfully used to reduce tics [17]. There is evidence that both of these interventions are effective at reducing tics [18–25]. Since then, HRT has been expanded into comprehensive behavioral intervention for tics (CBIT),

which includes psychoeducation, relaxation training, behavioral rewards, and function-based interventions [16]. Several critiques of CBIT, including that it is only useful for patients with mild tics, that it requires considerable effort for patients, that the tic improvements are modest and not sustained over time, and that CBIT may result in tic substitution or worsening, have been disproven [26, 27]. Although CBIT has not been shown to improve psychiatric comorbidities [24, 28], CBIT has repeatedly been shown to reduce tic frequency and severity with long-term improvement [29–32].

Modifications of Existing Behavioral Interventions

The original CBIT study was geared toward pediatric TS patients aged 9–17 years [30]. Since then, CBIT has undergone a variety of modifications (Table 1). CBIT has been adapted via “The Opposite Game” for children as young as 5–8 years of age [33]. An educational HRT-training DVD has been incorporated for families at home in parallel to in-person CBIT [34]. CBIT has been expanded to group settings [35–38]. Cognitive psychophysiological approaches to address both tics and cognitive issues have been created [39, 40]. The typical 8 sessions delivered over 10 weeks has been reduced to 4 sessions delivered over 3 months [41] and, in some cases, condensed into a single week [42, 43]. These CBIT modifications have all been shown to reduce tics as effectively as traditional CBIT and improve accessibility, especially in communities in which there is a shortage of CBIT-trained providers.

Virtual or Tele-behavioral Interventions

Flexible methods of CBIT delivery have become especially important during the COVID-19 pandemic, which fueled rapid widespread implementation of telehealth. When delivered virtually, there are similar reductions in tic severity comparable to in-person behavioral interventions [44–46], and subjects found telehealth delivery to be an acceptable format [44]. A virtual, self-guided format provided by the website TicHelper.com is available for independent patient use [47]. An alternative virtual platform called TicTrainer incorporates ERP-like strategies via a self-guided website [48], and additional virtual CBIT programs have recently been proposed [49, 50]. However, further work is needed to establish the comparative efficacy of these modalities.

Biofeedback

Based on the observation that autonomic changes impact tic expression and frequency [51], biofeedback has been attempted to exert voluntary control over symptoms by providing feedback through psychological or physiological means [52]. Studies using electrodermal biofeedback have

Table 1 Summary of the major behavioral intervention studies evaluating tic improvement for patients with TS or chronic tic disorder

Study	Study design	Main findings
O'Connor 2001 [21]	N = 47 CTD and 43 HD; 4-month cognitive behavioral treatment program, compared to 38 waitlist control participants	Significant improvement in tic control compared to baseline, with more than 50% of participants reporting sustained improvement at 2-year follow-up
Wilhelm 2003 [20]	N = 32 TS; randomized to HRT or supportive psychotherapy	Significant reduction in tic severity in the HRT group compared to the supportive psychotherapy group, maintained at 10-month follow-up
Verdellen 2004 [18]	N = 43 TS; randomized to HRT or ERP treatment	Significant reduction in YGTSS compared to baseline; no significant difference between ERP or HRT groups
Deckersbach 2006 [19]	N = 30 adult TS; randomized to HRT or PST	Significant reduction in YGTSS in the HRT group compared to the supportive psychotherapy group, maintained at 6-month follow-up
Piacentini 2010 [30]	N = 126 pediatric TS (ages 9–17); randomized to PST or CBIT (8 sessions for 10 weeks)	YGTSS significantly improved in the CBIT group compared to the PST group, maintained at 6-month follow-up
Woods 2011 [28]	N = 126 pediatric TS; randomized to PST or CBIT (8 sessions for 10 weeks)	No significant difference or worsening in secondary neuropsychiatric measures including ADHD Rating Scale, Disruptive Behavior Rating Scale, CY-BOCS in the acute or long-term follow-up setting
Wilhelm 2012 [29]	N = 122 TS; randomized to PST or CBIT (8 sessions for 10 weeks)	YGTSS significantly improved in the CBIT group compared to the PST group, maintained at 6-month follow-up
Himle 2012 [44]	N = 20 pediatric TS or CTD; randomized to CBIT delivered either face-to-face or via videoconference	Significant reduction in YGTSS compared to baseline, maintained at 4-month follow-up; no differences between groups
McGuire 2015 [24]	N = 34 pediatric CTD (ages 7–17); waitlist-controlled study using Living with Tics psychosocial intervention	Significant improvement in tics compared to the waitlist-controlled group
Ricketts 2016 [45]	N = 20 pediatric CTD (ages 8–17); randomized, waitlist-controlled study using voice-over-Internet-delivered CBIT	Significant reduction in YGTSS following voice-over-Internet-delivered CBIT compared to the waitlist control
O'Connor 2016 [40]	N = 49 TS and 36 CTD open-label study evaluating psychophysiological intervention	Significant reduction in YGTSS following intervention compared to baseline, maintained at 6-month follow-up
Leclerc 2016 [39]	N = 13 pediatric TS (ages 8–12 years); open-label study in which patients participated in a manualized treatment for tics called <i>Facotik</i>	Significant reduction in YGTSS compared to baseline
Yates 2016 [35]	N = 39 pediatric TS or CTD (ages 9–13); randomized to group HRT sessions or group education sessions	Significant tic reduction in both groups compared to baseline; significant reduction in motor tic score in the HRT group compared to the education group
Rizzo 2018 [15]	N = 110 pediatric TS or CTD (ages 8–17); randomized to behavioral therapy (either ERP or HRT), pharmacotherapy, or PST	Significant improvement in tic severity in the behavioral and pharmacotherapy groups compared to PST group
Nissen 2018 [37]	N = 59 pediatric TS; randomized to individual or group setting for HRT + ERP	Significant reduction in YGTSS compared to baseline, no significant difference between individual or group setting
Dabrowski 2018 [36]	N = 28 pediatric TS; randomized to group-based HRT or group-based PST	Significant reduction in YGTSS compared to baseline, maintained at 12-month follow-up; no significant difference between groups but trend toward HRT group having further reduction compared to PST group
Seragni 2018 [22]	N = 21 TS; randomized to HRT or standard of care	Reduction in tics in the HRT group compared to the standard of care group
Andren 2019 [46]	N = 23 pediatric TS or CTD (ages 8–16); randomized to ERP or HRT, both delivered via an online self-help format with parent and therapist support	Significant reduction in YGTSS compared to baseline in both online treatment groups
Chen 2020 [41]	N = 46 pediatric TS or CTD (ages 6–18); randomized to PST or CBIT (4 sessions for 3 months)	Significant reduction in YGTSS in the modified CBIT group as compared to the PST group, maintained at 3-month follow-up

Table 1 (continued)

Study	Study design	Main findings
McGuire 2020[32]	N = 122 CTD; randomized to PST or CBIT (8 sessions for 10 weeks)	YGTSS significantly improved in the CBIT group compared to the PST group, maintained at 6-month follow-up; improvement in obsessions in the acute phase, but not maintained at 6-month follow-up
Bennett 2020[33]	N = 15 pediatric TS (ages 5–8); open-label study using a modified version of CBIT more accessible for younger participants	Significant reduction in tics as measured by YGTSS and Parent Tic Questionnaire compared to baseline, maintained at 1-year follow-up
Singer 2020 [34]	N = 44 pediatric TS (ages 7–13) and their families; randomized to home-based therapy groups or in-person HRT	Significant reduction in YGTSS compared to baseline but no significant difference between the two groups
Viefhaus 2020[23]	N = 27 pediatric TS or CTD (ages 8–19); waitlist-controlled design in which patients participated in a modified version of HRT	Significant reduction in YGTSS compared to baseline and improvement in sense of controllability of tics
Heijerman-Holtgreve 2021[38]	N = 14 pediatric CTD (ages 9–14); enrollment in an ERP-based group program called <i>Tackle your Tics</i>	Significant reduction in YGTSS compared to baseline, maintained at 2-month follow-up

been mixed [52, 53], but a recent fMRI neurofeedback study was able to demonstrate significant reduction in tics compared to sham neurofeedback [54].

In summary, behavioral therapies are generally low-risk. When accessible, they are recommended as first-line or adjunctive treatment components when tic severity does not call for urgent pharmacologic intervention or when individual preference or characteristics do not make them unsuitable.

Pharmacologic Interventions

In spite of the widespread use of pharmacotherapy for the treatment of TS, there is a surprising lack of large, well-controlled studies for medication efficacy in TS [55]. Medications should be considered in patients if more conservative treatments such as behavioral interventions are ineffective or if the tics are severe [56•]. Although there are a wide variety of medication options for TS, only 3 medications are currently FDA-approved for use in TS: haloperidol (> 3 years old), pimozide (> 12 years old), and aripiprazole (ages 6–18 years old) [55]. In clinical practice, choosing which medication to use depends on tic severity, comorbidities, and potential adverse effects.

Alpha-2-adrenergic Agonists

Due to their relatively safer side effect profile, the medications that are most often recommended as first-line pharmacotherapy are alpha-2-adrenergic agonists, which may work to suppress the sympathetic nervous system [57•]. Although early studies of the effectiveness of clonidine were mixed [58], clonidine has been shown to be more effective than placebo at reducing tics [59] and additionally helps improve tics in patients with comorbid TS and ADHD [60]. The clonidine adhesive patch has additionally been shown to be safe and effective for TS management [61–63] and is comparable to haloperidol [64–66]. Guanfacine has had mixed results with some studies demonstrating safety and efficacy [67, 68], but others not demonstrating significant tic reduction [69, 70]. Therefore, clonidine is recommended with moderate confidence in the evidence, whereas guanfacine is recommended with low confidence [9••]. However, guanfacine may be less sedating because of selectivity for alpha-2 receptors and therefore is often chosen over clonidine in clinical practice [56•]. To date, guanfacine and clonidine have not been directly compared.

GABAergic Medications and Anticonvulsants

Given that dysfunctional GABA pathways may contribute to the underlying etiology of TS, medications that act on

GABA receptors or influence GABA concentrations have been explored for use in the treatment of TS [71]. Topiramate, a broad-spectrum antiepileptic, has been studied in a double-blind, placebo-controlled study with significantly reduced tics compared to placebo [72], and a retrospective study found similar results [73]. Side effects include paresthesias, cognitive slowing, and decrease in appetite leading to weight loss, as well as increased risk of glaucoma and kidney stones [57•]. Levetiracetam had mixed results in placebo-controlled trials: one small study with improvement [74] and two others without [75, 76]. Clonazepam and baclofen have been reported in case reports and case series or open-label reports but are without RCTs demonstrating tic reduction [57•, 77•]. Baclofen showed improvement in impairment scores but not tics in one small RCT [78]. Based on a meta-analysis of treatments for TS, topiramate was found to possibly have some benefit compared to placebo, whereas there is insufficient evidence to determine if levetiracetam, clonazepam, or baclofen would have any more benefit compared to placebo [9••]. In practice, topiramate can be useful when weight gain from neuroleptics has occurred or is undesirable. Benzodiazepines may have a limited role when comorbid anxiety is prominent, weighing benefit against risk of dependence, and baclofen may be considered if severe muscle pain or tension is present.

Dopamine Receptor Blocking Agents (Neuroleptics)

Due to potential significant side effects, dopamine receptor blocking agents are generally used as second-line agents [79]. A recent meta-analysis summarized most common side effects: increased risk of weight gain with risperidone and aripiprazole; elevated prolactin levels with pimozide, haloperidol, and metoclopramide; increased risk of sedation with risperidone, aripiprazole, tiapride, clonidine, and guanfacine; and increased risk of extrapyramidal symptoms or parkinsonism with pimozide, haloperidol, and risperidone [13••]. In addition, serious cardiac side effects such as QTC prolongation can occur, especially in pimozide and ziprasidone [56•, 80]. In practice, these potential side effects may occur with any of the medications in this class.

Although haloperidol was one of the earliest dopamine blocking agents to demonstrate efficacy for the treatment of TS, follow-up studies have shown that it has more serious side effects and is inferior to other agents [57•]. Thus, haloperidol is typically used only after other medications have failed. Ziprasidone, fluphenazine, olanzapine, and quetiapine are antipsychotics that are sometimes recommended by experts in the field; however, evidence to support their use in TS is limited [77•]. Studies have demonstrated that both pimozide and risperidone lead to significant tic reduction in comparison to placebo as well as in comparison to several alternative dopamine blocking agents [57•, 77•].

Aripiprazole is an atypical neuroleptic with partial agonist activity on D2 dopamine receptors, as well as serotonergic effects. Two meta-analyses found that across 17 RCTs, aripiprazole was well-tolerated, with significantly less side effects and similar efficacy compared to placebo or other agents [81, 82]. A recent RCT compared aripiprazole to intravenous valproic acid and determined that both treatments led to similar significant reduction in tics, though the intravenous valproic acid group responded to treatment faster [83].

Benzamides such as tiapride, sulpiride, and amisulpiride are D2-blocking agents that are commonly used to treat TS outside of the USA [77•]. In contrast to other dopamine receptor blocking agents, benzamides have fewer extrapyramidal side effects [77•, 84]. Most evidence for benzamides comes from remote open-label studies or case reports [77•]. There have been no recent studies assessing the efficacy of these medications.

A recent meta-analysis found that there is moderate confidence that haloperidol, risperidone, aripiprazole, and tiapride would lead to tic reduction compared to placebo, whereas pimozide and ziprasidone were only possibly more likely to receive benefit in tic severity compared to placebo [13••].

Ecopipam is a first-in-class drug that has selective D1 receptor antagonism. An open-label study demonstrated that ecopipam was safe and led to significant tic reduction [85], and a follow-up placebo-controlled trial demonstrated similar results [86]. A phase IIb trial called the DIAMOND study is currently underway to test ecopipam further (NCT04007991) with a corresponding open-label extension following the randomization period (NCT04114539).

VMAT2 Inhibitors

Biogenic amines including dopamine are transported by vesicular monoamine transporter-2 (VMAT-2). VMAT2 inhibitors work by depleting dopamine pre-synaptically [56•]. In open-label studies, tetrabenazine has reduced tics [87, 88]. Deutetrabenazine is an isomer of tetrabenazine with a longer half-life and less risk of side effects [77•]. Open-label studies have demonstrated that deutetrabenazine is safe and effective for tic disorders [89]. However, the phase 2/3 ARTIST1 and phase 3 ARTIST2 trials failed to reach the primary end point of tic reduction (NCT03567291, NCT03571256). The safety and tolerability of valbenazine for tics were established in the T-Force study but placebo-controlled trials in adults (T-Forward), pediatrics at fixed doses (T-Force green), and pediatrics at optimized doses (T-Force gold), as well as open-label extension studies (T-Fusion and T-Force gold+) failed to meet the primary endpoint [90]. As a result, this class of medications is often reserved for cases that have been refractory to other classes or in whom potential side effect profiles favor avoiding other classes.

Cannabinoids

The two main types of cannabinoids are tetrahydrocannabinol (THC) (psychoactive) and cannabidiol (CBD) (non-psychoactive) [55]. Dronabinol is a synthetic version of THC and nabiximol is part THC and part CBD [55]. Patients self-reporting tic improvement following use of cannabinoids have led to interest in studying them systematically [91]. A placebo-controlled trial of a single dose of THC led to significant reduction in tics [92] and when administered for 6 weeks led to significant improvement in subjects' perceived tic severity and quality of life as well as trends toward reduction in tic scores [93]. A Cochrane review determined that there was not enough evidence to support whether or not cannabinoids are an effective treatment for TS [94]. Side effects include dry mouth, nausea/vomiting, headache, fatigue, disorientation, and anxiety [95]. Risks that may be specific to the developing brain have not been fully explored.

A recent survey revealed that in patients who have independently used cannabinoids for TS treatment, patients tend to favor THC-rich cannabis over dronabinol or nabiximols [96]. There are currently several ongoing trials. An RCT was planned with different ratios of THC and CBD versus placebo to determine if a specific composition would have better safety and efficacy; however, the study was terminated due to slow enrollment (NCT03247244). A study comparing a THC and CBD compound in a 1:1 ratio versus an inert oil has been registered, but results are not yet available (ACTRN12618000545268). Similarly, the CANNA-TICS protocol plans to test nabiximol in comparison to placebo [97].

There have also been attempts to modify the endogenous endocannabinoid system in the treatment of TS. Lu-AG06466 (previously referred to as ABX-1431) is a selective inhibitor of monoacylglycerol lipase (MAGL), which prevents the breakdown of an endogenous ligand of the endocannabinoid system [95]. In a single-dose placebo-controlled crossover study evaluating Lu-AG06466 in 20 adult patients with TS, there was significant improvement in tic scores [98]. However, a follow-up multicenter, double-blind, randomized, placebo-controlled trial found no significant differences in tic severity between Lu-AG06466 and placebo at 8-week follow-up [99]. In addition to these studies, there are active trials evaluating palmitoylethanolamide (PEA), which is an endogenous fatty acid amide that mimics the properties of cannabinoids [95]. Furthermore, PEA may reduce the side effects associated with cannabinoids, making it an appealing compound to study in combination with traditional cannabinoids [95]. A phase 2 open-label study evaluating dronabinol in combination with PEA (THX-110) found an averaged YGTSS reduction of 20% compared to baseline [100]. A larger, placebo-controlled trial is currently under development (NCT03651726). In

addition, the psychoactive properties of cannabinoids need to be accounted for when designing placebo-controlled trials in the future.

Botulinum Toxin Injections

Botulinum toxin inhibits acetylcholine release at the neuromuscular junction, leading to temporary relaxation of the muscle injected [77•]. There have been several case reports [101–104] and open-label studies [105–108] that demonstrated botulinum toxin led to significant reduction in tics. However, only one randomized, placebo-controlled trial has been conducted with botulinum toxin in the TS population [109], which was the only study which met the criteria for a recent Cochrane review, classifying the evidence for botulinum toxin in TS as low-quality [110]. A meta-analysis of treatments for TS has determined that onabotulinumtoxin A injections are probably more likely to reduce tic severity compared to placebo [13••]. In practice, botulinum toxin injections may be most helpful for specific focal tics such as blinking, facial movements, neck jerking, and disabling coprolalia or loud vocal tics (vocal cord injections). Risks generally relate to excessive weakness of injected or surrounding muscles, so careful dosing and expert injection are critical.

Complementary Alternative Medicine (CAM) and Supplementation

Due to the side effects associated with pharmacologic treatments, there is increasing interest in using complementary alternative medicine (CAM). A wide range of CAM modalities including meditation, vitamins, prayer, and other homeopathic regimens have been implemented, though not well-studied systematically [111].

Two recent meta-analyses reported that traditional Chinese medicine (TCM) had the potential to reduce tics relative to placebo or western medicine [112, 113•]. Ningdong granule (NDG) is a combination of plant, animal, and placental products thought to modulate the D2 receptor pathway and has been shown to be well-tolerated and effective at reducing tics compared to placebo [77•]. Choudongning (CDN) capsule has shown promise in several double-blind, placebo-controlled studies [113•, 114, 115]. 5-Ling granule (5-LGr) contains 11 different herbs and has shown comparable efficacy to tiapride with better tolerability [116]. Another proprietary polyherbal product called Changma Xifeng was reported to have similar efficacy as western medicine [117, 118]. In addition, a placebo-controlled trial is ongoing for tic reduction from Yi-Gan San, a traditional herbal remedy that has been used to reduce restlessness and agitation in children (NCT03564132). The underlying mechanism for potential tic reduction by these herbal supplements is unknown.

Acupuncture for TS was the subject of a recent systematic review which found that across 22 RCTs, acupuncture was identified as superior in the overall effectiveness rate, YGTSS score, number of adverse events, and recurrence rates during follow-up [119]. This review had similar conclusions to other systematic reviews on the topic [120, 121]. According to a recent meta-analysis, NDG (formulated by Zhao) and 5-LGr were found to be probably more likely than placebo to reduce tic severity [9••]. Generalizability of the findings of these studies in other tic populations still needs to be established.

Other forms of supplementation also show promise. Taurine, a GABA-receptor agonist, when added to tiapride significantly improved tics compared to placebo, without significantly more adverse events [122]. Whether vitamin D levels correlate with tic severity is unclear [123, 124], but at least one study has demonstrated that vitamin D supplementation led to significant improvement in tic symptoms [125]. Further investigation is needed to confirm benefit and determine if deficiency is needed in order to have potential benefit. In addition to supplementation, a small open-label study described an oral splint (typically used to treat temporomandibular joint disorders) as being helpful for tics. The authors hypothesized that proprioceptive input to the insular cortex might have a modulating effect on tics but acknowledged that a placebo effect may be contributory [126].

Ongoing Clinical Trials.

There are several active or recent studies regarding novel compounds or innovative treatments for TS. There is an ongoing trial investigating atomoxetine, a noradrenaline reuptake inhibitor, which is hypothesized to improve response inhibition in individuals with TS (NCT04354103). AZD5213 is an H3-receptor antagonist that has been assessed for safety and tolerability in the TS population (NCT01904773) but unfortunately has not shown any significant difference compared to placebo. Pimavanserin is a serotonin receptor inverse agonist currently being investigated in an open-label phase 1 pilot study (NCT04794413). Since serotonin is low in co-occurring conditions such as depression, anxiety, and OCD, this medication may be an appropriate treatment choice for patients with TS.

There have also been studies investigating the gut–brain axis. *Lactobacillus plantarum* PS128 is a probiotic that can modulate neurotransmitter levels in the brain [127]. At least one study has demonstrated improvement in oppositional defiant behaviors in individuals with autism [127], and a trial is currently underway to investigate whether PS128 can reduce tic severity in patients with TS (NCT04805385). Similarly, a case report and an open-label study found that 4/5 patients had significant reduction in YGTSS scores following fecal microbiota transplantation [128, 129].

Studies have also evaluated whether medication can augment behavioral therapies. D-cycloserine is an

antibiotic which has been shown to enhance learning. A recent study demonstrated significant tic reduction with D-cycloserine + HRT compared to placebo + HRT [130]. A follow-up study is underway to determine if there are long-lasting effects when D-cycloserine is provided prior to the start of each HRT session (NCT04357951).

There is a great deal of potential to continue improving the pharmacologic treatments available for TS. Although results for VMAT2 inhibitor studies have been disappointing, studies of ecopipam, cannabinoids, intravenous valproic acid, adjunctive taurine, vitamin D, and D-cycloserine have all demonstrated potential therapeutic benefit [131]. Larger, placebo-controlled studies are needed to confirm these findings.

Non-invasive Brain Stimulation (NIBS)

Though not yet having a role in routine clinical care of TS, the following NIBS have been studied: transcranial magnetic stimulation, transcranial direct current stimulation, and peripheral nerve stimulation.

Transcranial Magnetic Stimulation (TMS)

Repetitive transcranial magnetic stimulation (rTMS) at frequencies of 5 Hz and higher leads to excitatory modulation, whereas rTMS at low frequencies of 1 Hz leads to inhibitory modulation. Many case reports and open-label studies using inhibitory stimulation targeted at the supplementary motor area (SMA) demonstrate very promising results [132–138], while other studies have shown no significant differences following rTMS [139, 140], and RCTs have shown trends toward improvement in tics without significant differences between active and sham stimulation (Table 2) [135, 141]. A more recent randomized rTMS study which targeted the bilateral parietal cortex showed significant improvements in tic scores compared to sham stimulation [142]. One meta-analysis concluded that rTMS appears to be an appropriate option for treatment-resistant tic [143]. rTMS may also be a tool to address comorbid symptoms, including OCD [144–146]. Other innovative approaches include combining rTMS with CBIT, of which three trials are actively recruiting (NCT04578912, NCT04795908, NCT03844919). rTMS appears to be safe in adult and pediatric populations [133, 134, 136, 141]. However, heterogeneity between stimulation targets, number of pulses, and sample size may account for variability in outcomes, and further work is needed to determine optimal stimulation parameters.

Table 2 Summary of rTMS stimulation parameters and results for patients with TS

Study	Number of patients	Brain target	Frequency	Intensity	Total daily pulses	Number of days	Number of sessions per day	Total pulses	Main findings
Munchau 2002[139]	<i>N</i> = 12; crossover design to 2 different active and 1 sham condition	PMC or MC	1 Hz	80% AMT	1,200	2 per condition	1	4,800 active stimuli; 2,400 sham stimuli	No significant improvement in MOVES score
Chae 2004[132]	<i>N</i> = 8; crossover design to four different active and 1 sham condition	PFC or MC	1 Hz or 15 Hz at each target site	110% RMT	2,400	5	1	9,600 active stimuli; 2,400 sham stimuli	YGTSS decreased by 24% over the 5 days of stimulation; no difference between target site or frequency; larger improvement in active conditions compared to sham, but this was not statistically significant
Orth 2005[140]	<i>N</i> = 5; crossover design to three different stimulation conditions	L PMC followed by R PMC; L PMC followed by sham; sham followed by sham	1 Hz	80% AMT	1,800	2	2	5,400 active stimuli; 5,400 sham stimuli	No significant difference in YGTSS, MOVES, or video-rated tic scores following active or sham stimulation
Mantovani 2006[137]	<i>N</i> = 10; open-label study	SMA	1 Hz	100% RMT	1,200	10	1	12,000	Significant improvement in YGTSS, Y-BOCS, HDRS, HARS scores following active stimulation, maintained at 3-month follow-up
Mantovani 2007[138]	<i>N</i> = 2; open-label study	SMA	1 Hz	110% RMT	1,200	10	1	12,000	Significant improvement in YGTSS scores following active stimulation; one patient required booster treatment sessions due to relapse in symptoms

Table 2 (continued)

Study	Number of patients	Brain target	Frequency	Intensity	Total daily pulses	Number of days	Number of sessions per day	Total pulses	Main findings
Lim 2009[16]	N=8; open-label study	SMA	1 Hz	100% RMT	1,200	5	1	6,000	Significant reduction in YGTSS following active stimulation, maintained at 8-week follow-up
Kwon 2011[134]	N=10; open-label study	SMA	1 Hz	100% RMT	1,200	10	1	12,000	Significant improvement in YGTSS following active stimulation, maintained at 12-week follow-up
Le 2013[136]	N=25; open-label study	SMA	1 Hz	110% RMT	1,200	20	1	24,000	Significant improvement in YGTSS, ADHD scores, and anxiety following active stimulation, maintained at 6-month follow-up
Wu 2014[141]	N=12; randomized to active vs. sham	SMA	30 Hz cTBS	90% RMT	4,800	2	8	9,600	Significant reduction in YGTSS scores following stimulation but no significant difference between active and sham stimulation
Landeros-Weisenberger 2015[135]	N=20; randomized to active vs. sham	SMA	1 Hz	110% RMT	1,800	15	1	27,000	Significant reduction in YGTSS score during the 3-week open-label phase; however, no significant difference in YGTSS score between active and sham stimulation

Table 2 (continued)

Study	Number of patients	Brain target	Frequency	Intensity	Total daily pulses	Number of days	Number of sessions per day	Total pulses	Main findings
Bloch 2016[145]	N=12; open-label study	SMA	1 Hz using H-coil	110%	2,400	20	1	24,000	No significant improvement in tic severity as a whole, but in patients with TS-OCD there was tic improvement following stimulation
Singh 2018[146]	N=3; open-label study	SMA	1 Hz	110% RMT	900	20	1	18,000	Significant improvement in YGTSS and Y-BOCS scores in patients with TS-OCD phenotype; however no significant improvement in patient with TS only
Fu 2021[142]	N=30; randomized to active vs. sham stimulation	Bilateral parietal cortex	0.5 Hz	90% RMT	2,400 divided equally to each side	10	1	24,000	Significant improvement in YGTSS, MRVBTS, and PUTS scores in the active treatment group compared to sham, which was maintained at 1-month follow-up
Kahl 2021[133]	N=10; open-label study	SMA	1 Hz	100% RMT	1,200	15	1	18,000	Significant improvement in YGTSS following stimulation; maintained at 4-week follow-up

Key: AMT, active motor threshold; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MC, motor cortex; MOVES, Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey; PMC, premotor cortex; RMT, resting motor threshold; SMA, supplementary motor area; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; YGTSS, Yale Global Tic Severity Score

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) uses constant, low current delivered via electrodes attached directly to the scalp. Anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases cortical excitability [147]. As opposed to rTMS, which is expensive, requires specialized training to administer, and travels to a center which has a TMS machine, tDCS is cheap, portable, and easy to administer [147]. Thus far, results have been heterogeneous, with many studies demonstrating significant improvement in tic severity following active stimulation [147–152], but only a few demonstrate a significant difference between active and sham stimulation (Table 3) [148, 149]. In addition, many studies were of open-label study design, so it is unclear how much a placebo response led to the improvement in tic severity [151–153]. Currently, one trial is actively recruiting to assess efficacy of 1 mA tDCS to the SMA (NCT03401996).

Peripheral Nerve Stimulation

Case reports of patients who were treated with vagal nerve stimulation (VNS) for unrelated causes found that tics also improved when the VNS was turned on [154, 155]. More recently, a case report used transcutaneous VNS combined with breathing exercises to reduce tics [156]. It is currently unclear how VNS influences tics but may be through reduction of the “signal-to-noise ratio” hypothesized to help decipher appropriate motor signals from background noise [157].

It is also known that certain frequency bands, in particular alpha or mu (8–14 Hz) and beta (15–30 Hz), are associated with suppression of movement, and entraining these cortical oscillations could theoretically lead to the suppression of tics [158]. In a recent study, rhythmic pulses delivered at 12 Hz to the median nerve led to entrainment of mu-band oscillations in the brain and significant reduction in tic frequency and severity as well as the urge to tic [159]. A follow-up, sham-controlled study is currently recruiting in an attempt to replicate these results (NCT04731714).

Cranial Electrotherapy Stimulation (CES)

Cranial electrotherapy stimulation is a technique which uses a small handheld device to stimulate the brain with a small amount of current. At least one study has combined CES with functional MRI to demonstrate stronger functional connectivity in the anterior cingulate cortex and weaker activity in the SMA, suggesting that CES may suppress disinhibited brain activity associated with TS [160]. A randomized, double-blind, sham-controlled trial known as the Study of CES

as an Add-on Treatment for Tic Disorders (SCATT study) is currently underway to determine if CES is a therapeutically meaningful tool to reduce tic severity (NCT03705988).

Deep Brain Stimulation (DBS)

Approximately 5% of patients with TS are refractory to more conservative therapies, and DBS may therefore be a valuable treatment option [161]. However, it is important to be aware of patient selection, target selection, and surgical complications before proceeding with surgical intervention for TS.

Candidate Selection

Guidelines for DBS candidate selection for TS were published in 2015 and include 5 main components: (1) a diagnosis of TS which fulfills DSM V criteria made by a clinician with expertise in tic disorders; (2) tics cause significant disability in daily life; (3) YGTSS severity is ≥ 35 for at least 1 year; (4) patients have tried and failed conservative treatment in at least three different medication classes and behavioral therapy; and (5) comorbid symptoms such as ADHD and OCD are stable for at least 6 months [162].

These recommendations were refined further recently. First, the presence of malignant tics may not be captured by a YGTSS score, and therefore, tics leading to ≥ 2 emergency department visits or 1 hospitalization may also fulfill the tic severity requirement [163••]. Second, using quality of life scales to determine if the tics or comorbid symptoms are the primary cause of disability is relevant [163••]. Third, due to known fluctuations of tics, duration of treatment attempt should be at least 4–12 weeks [163••].

Although the natural history of TS suggests tics may improve with age and without surgical intervention, there is growing evidence that DBS is safe and efficacious in the pediatric TS population [164, 165, 166•]. DBS has been used to successfully treat patients as young as 12 years of age [165]. Early intervention with DBS may reduce the risk of tic-induced social isolation, minimize harm from malignant tics, and minimize the impact of tics in the academic and professional setting during crucial developmental years [164]. Although there are no strict age cutoffs for DBS in the TS population, the decision to surgically intervene in the pediatric population remains a topic of controversy, and it is recommended that a local ethics committee review cases for patients 18 years old or younger [162, 166•, 167].

International TS DBS Registry

In collaboration with the Tourette Association of America (TAA), several centers joined together in 2012 to create the International TS DBS Registry [168]. There are currently

Table 3 Summary of tDCS study design and clinical findings in patients with TS

Study name	Study design	Stimulation parameters	Main findings
Mrakic-Sposta 2008[150]	N = 2; crossover design with active and sham stimulation	5 days of 2 mA cathodal tDCS for 15 min over the left motor cortex	Significant improvement in YGTSS following active but not sham stimulation
Carvalho 2015[152]	N = 1; open-label study	10 days of 1.425 mA cathodal tDCS over the pre-SMA for 30 min	Significant improvement in the YGTSS following stimulation, which was maintained at 6-month follow-up
Eapen 2017[147]	N = 2; crossover design between active and sham stimulation	18 days of 1.4 mA cathodal tDCS over the SMA for 20 min	Significant improvement in ATQ and PUTS scores following active stimulation but no difference compared to sham
Behler 2018[153]	N = 3; open-label study	5 days of 2 mA cathodal tDCS over the pre-SMA for two 15-min sessions	One patient had a reduction in tic severity, but the other two had increased tics severity
Dyke 2019[148]	N = 10; crossover design between active and sham stimulation	1 day of 4.5 mA cathodal tDCS over the SMA for 20 min	Significant improvement in YGTSS and MRVS following active stimulation compared to sham stimulation
Tajadini 2019[151]	N = 1; open-label study	5 days of 2 mA cathodal tDCS of the left motor cortex and left inferior frontal brain regions for two 30-min sessions	Significant improvement in tic severity following active stimulation, maintained at 1-year follow-up
Martino 2020[149]	N = 12; randomized, sham-controlled study	5 days of 1 mA cathodal tDCS of the SMA for two 20-min sessions	Significant improvement in YGTSS following active but not sham stimulation at day 7

Key: *ATQ*, adult tic questionnaire; *MRVS*, modified Rush video scale; *PUTS*, Premonitory Urge for Tics Scale; *SMA*, supplementary motor area; *tDCS*, transcranial direct current stimulation; *YGTSS*, Yale Global Tic Severity Score.

34 different centers contributing data, with 340 registered patients representing 700 DBS leads. The majority of patients have been implanted with bilateral leads, and collectively, a 44% decrease in total YGTSS score across all targets 1 year following DBS surgery compared to baseline has been recorded (<https://tourettedeepbrainstimulationregistry.ese.uflhealth.org/>, accessed 11/4/2021). Both motor and vocal tics demonstrate improvement. The strengths of the TS registry are that it pools cases from across the globe to generate meaningful comparisons between patients, with the goal of providing recommendations for optimal patient and target selection, sharing effective stimulation paradigms, and facilitating regulatory approval [168].

Target Selection

At least 9 different target sites have been reported in the literature, with the thalamus, anterior globus pallidus internus (aGPi), and nucleus accumbens and anterior internal capsule (ALIC-NAc) as some of the most common targets [167]. Given the complexity and heterogeneity amongst patients with TS, identifying one specific target site for all patients with TS may not be feasible or productive. In fact, understanding individual differences in patients with TS may lead to individualizing the DBS target locations for each patient. For example, tic-predominant TS may be more effectively modulated by thalamic targets, whereas TS with predominant comorbid symptoms may be more effectively modulated by pallidal or ALIC-NAc targets, although further studies are needed to support these observations [167, 169–171].

DBS Outcomes

Overall, there is a 30–50% improvement in tics following DBS, regardless of target [161, 172]. There have been a number of small studies targeting the thalamus [173–178] and GPi [176, 179, 180] that have demonstrated significant improvement in tic severity. A recent study comparing active and sham stimulation in 8 adult TS patients demonstrated significantly more tic reduction in the active stimulation phase compared to the sham stimulation phase [181]. Combining thalamic and pallidal stimulation did not significantly reduce tics more compared to either type of stimulation alone [182]. In addition, younger age, lower baseline YGTSS, and more severe baseline impairment scores have been shown to predict better DBS outcomes [166, 169, 181]. Complications from DBS in the TS population occur at similar rates to DBS for other indications [167].

Adaptive Stimulation

Local field potentials (LFPs) have specific characteristics that correlate with tics and can theoretically be analyzed

by the DBS system in a “closed-loop” paradigm to adjust stimulation parameters independently [183]. Bursts of oscillations in the theta range have been associated with worse motor tic severity [184]. Adaptive stimulation minimizes the amount of unwanted stimulation when patients are in a tic-free state and also reduces the power requirements of the IPG [170]. At least one case report demonstrated significant tic reduction with adaptive neurostimulation in response to a 5–15 Hz oscillatory band, which was comparable to the tic reduction seen with scheduled stimulation, as well as a 63% improvement in the estimated battery life [185].

Conclusions

Treatment options have greatly evolved over the past several decades, enabling more opportunities to improve the quality of life for patients with TS. Modifications to existing therapies have enabled behavioral interventions to be more accessible through virtual CBIT platforms, condensing the number of CBIT sessions to occur over a shorter timeframe and providing behavioral therapy in a group setting. These modifications are especially relevant during the COVID-19 pandemic, in which resource allocation and adaptation to telemedicine are paramount. There are several potentially promising pharmacologic options on the horizon which may expand the ability to reduce tics, hopefully with less adverse effects. In addition, there are many CAM options via TCM or vitamin supplementation that are low-risk and may expand the options for primary or adjuvant therapy. Finally, the future of the neuromodulation realm carries many exciting developments, including the use of NIBS to ameliorate tics as well as closed-loop DBS which can tailor stimulation to a patient’s unique physiology. While the most effective treatment for TS still depends on the individual symptoms and needs of the patient, these behavioral, pharmacologic, and neuromodulatory developments will continue to pave the way for the future treatment of TS.

Key: *ADHD*, attention deficit hyperactivity disorder; *CBIT*, Comprehensive Behavioral Intervention for Tics; *COSA*, Child Occupational Self-Assessment; *CTD*, chronic tic disorder; *ERP*, exposure response prevention; *HRT*, habit reversal training; *PST*, psychoeducation and supportive therapy; *TS*, Tourette syndrome; *YGTSS*, Yale Global Tic Severity Scale.

Compliance with Ethical Standards

Conflict of Interest The authors have no disclosures to report relevant to the content of this paper.

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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