

# Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders

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## Abstract

### Objective

To make recommendations on the assessment and management of tics in people with Tourette syndrome and chronic tic disorders.

### Methods

A multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives developed practice recommendations, integrating findings from a systematic review and following an Institute of Medicine–compliant process to ensure transparency and patient engagement. Recommendations were supported by structured rationales, integrating evidence from the systematic review, related evidence, principles of care, and inferences from evidence.

### Results

Forty-six recommendations were made regarding the assessment and management of tics in individuals with Tourette syndrome and chronic tic disorders. These include counseling recommendations on the natural history of tic disorders, psychoeducation for teachers and peers, assessment for comorbid disorders, and periodic reassessment of the need for ongoing therapy. Treatment options should be individualized, and the choice should be the result of a collaborative decision among patient, caregiver, and clinician, during which the benefits and harms of individual treatments as well as the presence of comorbid disorders are considered. Treatment options include watchful waiting, the Comprehensive Behavioral Intervention for Tics, and medication; recommendations are provided on how to offer and monitor these therapies. Recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics are provided as well as suggestions for future research.

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## Glossary

**AAN** = American Academy of Neurology; **ADHD** = attention-deficit/hyperactivity disorder; **CBD** = cannabidiol; **CBIT** = Comprehensive Behavioral Intervention for Tics; **CBT** = cognitive behavioral therapy; **DBS** = deep brain stimulation; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; **EVID** = evidence-based conclusions from the systematic review; **HRT** = habit reversal training; **INFER** = deductive inferences from other premises; **OCD** = obsessive-compulsive disorder; **PRIN** = generally accepted principles of care; **RELA** = strong evidence from related conditions; **THC** =  $\delta$ -9-tetrahydrocannabinol; **TS** = Tourette syndrome; **VMAT2** = vesicular monoamine transporter type 2.

This article presents the recommendations and suggestions for future research of an American Academy of Neurology (AAN) practice guideline on the treatment of tics in people with Tourette syndrome (TS) and chronic tic disorders. The complete and unabridged practice guideline is available as a data supplement at [links.lww.com/WNL/A882](https://links.lww.com/WNL/A882). A companion article summarizes the systematic review findings and conclusions.

The AAN guideline committee convened a multidisciplinary panel to perform a systematic review and develop guideline recommendations, founded on the systematic review, for the assessment and treatment of tics. This article focuses on the guideline's recommendations and does not include detailed analysis of the systematic review. Readers are urged to review the unabridged guideline for a full assessment.

The systematic review synthesizes the evidence supporting the efficacy and harms of medical, behavioral, and neurostimulation treatments for tics. The treatment of tics must be individualized and based on collaborative decisions among patients, caregivers, and clinicians. Many people with tic disorders have psychiatric comorbidities, requiring clinicians to establish treatment priorities with their patients. While neurologists are often consulted to diagnose and treat tics, the identification and management of comorbid disorders is of prime importance and must be factored into management decisions. Therefore, while the level of obligation and associated verbs (must, should, may) state that treatments may or should be used, these recommendations pertain only to the situation in which the patient and clinician have determined that treatment is necessary and collaboratively discussed treatment options and priorities.

The authors of the practice guideline seek to make recommendations, based on evidence identified from the systematic review, general principles of care, and related evidence, regarding the following questions:

1. In children and adults with TS or a chronic tic disorder, when should clinicians and patients pursue treatment for tics?
2. In children and adults with TS or a chronic tic disorder who require treatment for tics, how should clinicians and

patients choose between evidence-based treatment options and determine the sequence or combinations of these treatments?

## Practice recommendations

Much more than evidence must be considered when crafting practice recommendations. The evidence-based conclusions from our systematic review form the foundation of the AAN process, but other factors influence the structure of recommendations. The panel developed rationale statements that document, in a transparent manner, the deductive logic justifying each recommendation. These rationale statements precede each recommendation. Four types of premises can be used to support recommendations: (1) evidence-based conclusions from the systematic review (labeled EVID), (2) generally accepted principles of care (PRIN), (3) strong evidence from related conditions (RELA), and (4) deductive inferences from other premises (INFER). Recommendations must always be supported by at least one premise.

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the development panel assigns one of 3 recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the verb *must*. These recommendations are rare because they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the verb *should*. Such recommendations tend to be more common because the requirements are less stringent but still based on the evidence and benefit–risk profile. Level C corresponds to the verb *may*. These recommendations represent the lowest allowable recommendation level that the AAN considers useful within the scope of clinical practice and accommodates the highest degree of practice variation.

Non–evidence-based factors that need to be transparently and systematically considered when formulating recommendations include (1) the relative value of the benefit compared with the risk, (2) the feasibility of complying with the intervention (e.g., the intervention's availability), (3) the cost of the intervention, and (4) the expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention. The panel

### Supplemental Data

Full measurement set

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assigned levels of obligation (A, B, C, U, or R) to each recommendation by using a modified Delphi process that synthesizes all previously listed factors. The opinions of the guideline panel, with regard to the importance of each factor, were elicited through an online questionnaire, with statistical analysis of responses. The panel voted anonymously and independently on each recommendation in 3 rounds of online voting. Using precisely defined rules for consensus for each recommendation, the panel achieved consensus, revised the recommendation, or did not carry the recommendation forward. In some cases, the panel reviewed, revised, and revoted on recommendations on the basis of public commentary and other input during the guideline development process, reflecting the dynamic nature of this process. Suggestions for future research were created during guideline development.

## Counseling recommendation: Natural history of TS

### Rationale

Providing information to families about the natural history of a disorder can help inform treatment decisions (PRIN). Tics begin in childhood and demonstrate a waxing and waning course. Peak tic severity usually occurs between the ages of 10 and 12 years, with many children experiencing an improvement in tics in adolescence (RELA).<sup>1</sup> A longitudinal study demonstrated that tic severity declined yearly during adolescence, with 18% of adolescents older than 16 years having no tics and 60% having minimal or mild tics 6 years after initial examination (RELA).<sup>2</sup> There is no evidence that treatment is more effective the earlier it is started. As tics may improve with time, watchful waiting is an acceptable approach in individuals who do not experience any functional impairment from their tics (INFER). However, even in such cases, the Comprehensive Behavioral Intervention for Tics (CBIT) could be employed if the patient is motivated to attempt treatment (INFER). As a result of partial or complete remission during the natural course of the disorder, medication prescribed for tics in childhood may no longer be required over time (INFER).

### Recommendation 1a

Clinicians must inform patients and their caregivers about the natural history of tic disorders (Level A).

### Recommendation 1b

Clinicians must evaluate functional impairment related to tics from the perspective of the patient and, if applicable, the caregiver (Level A).

### Recommendation 1c

Clinicians should inform patients and caregivers that watchful waiting is an acceptable approach in people who do not experience functional impairment from their tics (Level B).

### Recommendation 1d

Clinicians may prescribe CBIT as an initial treatment option relative to watchful waiting, for people with tics who do not

experience functional impairment if they are motivated to attempt treatment (Level C).

### Recommendation 1e

Physicians prescribing medications for tics must periodically re-evaluate the need for ongoing medical treatment (Level A).

## Psychoeducation, teacher and classroom

### Rationale

TS is common, affecting approximately 1% of schoolchildren (RELA).<sup>3</sup> Psychoeducation about TS with peers can result in more positive attitudes toward a person with TS, while psychoeducation about TS with teachers can improve knowledge about the condition (RELA).<sup>4</sup> Improving peers' attitudes about and teachers' knowledge of TS may positively affect people with TS (INFER).

### Recommendation 2

Clinicians should refer people with TS to resources for psychoeducation for teachers and peers, such as the Tourette Association of America (Level B).

## Assessment and treatment of attention-deficit/hyperactivity disorder (ADHD) in children with tics

### Rationale

Comorbid ADHD is common in people with TS, with prevalence ranging from 30% to 50% (RELA).<sup>5,6</sup> Several trials have specifically addressed the medical treatment of both ADHD and tics in children with both disorders. This includes trials of psychostimulants and atomoxetine, in which the aim was to demonstrate efficacy of these treatments for ADHD symptoms without concomitant worsening of tics. In children with tics and ADHD, clonidine, clonidine plus methylphenidate, methylphenidate, and guanfacine are probably more likely than placebo to reduce tic severity (EVID) and reduce ADHD symptoms. In children with tics and ADHD, atomoxetine does not worsen tics relative to placebo (EVID) and reduces ADHD symptoms. Comorbid ADHD is strongly associated with functional impairment in children with TS (RELA).<sup>7</sup> While ADHD symptoms may improve in adolescence (RELA),<sup>2</sup> adults with TS may require ongoing care for this comorbidity.

### Recommendation 3a

Clinicians should ensure an assessment for comorbid ADHD is performed in people with tics (Level B).

### Recommendation 3b

Clinicians should evaluate the burden of ADHD symptoms in people with tics (Level B).

### Recommendation 3c

In people with tics and functionally impairing ADHD, clinicians should ensure appropriate ADHD treatment is provided (Level B).

## Assessment and treatment of obsessive-compulsive disorder (OCD) in children with tics

### Rationale

Obsessive-compulsive behaviors are common in people with TS, with a comorbid diagnosis of OCD made in 10%–50% (RELA).<sup>5,6</sup> Subanalyses of trials of interventions for OCD in children suggest that individuals with tics may not respond as well as those without tics to selective serotonin reuptake inhibitors but respond equally well to cognitive behavioral therapy (CBT) for OCD symptoms (RELA).<sup>8,9</sup> For this reason, CBT is considered first-line treatment of OCD in individuals with tic disorders (INFER).

### Recommendation 4a

Clinicians should ensure an assessment for comorbid OCD is performed in people with tics (Level B).

### Recommendation 4b

In people with tics and OCD, clinicians should ensure appropriate OCD treatment is provided (Level B).

## Other psychiatric comorbidities

### Rationale

Population-based and clinic-based studies have shown that people with TS are at high risk of other psychiatric comorbidities, including anxiety disorders, oppositional defiant disorder, and mood disorders (RELA).<sup>5,6</sup> Comorbid mood disorders appear more prevalent in adolescents and adults than children and in those with greater tic severity (RELA).<sup>6,10</sup> A matched case-cohort study using a national registry has shown an increased risk of dying by suicide and attempting suicide in people with TS compared with controls, which persisted after adjusting for psychiatric comorbidity. Persistence of tics beyond young adulthood, previous suicide attempts, and comorbid personality disorders increased the risk of death by suicide (RELA).<sup>11</sup>

### Recommendation 5a

Clinicians must ensure appropriate screening for anxiety, mood, and disruptive behavior disorders is performed in people with tics (Level A).

### Recommendation 5b

Clinicians must inquire about suicidal thoughts and suicide attempts in people with TS and refer to appropriate resources if present (Level A).

## Assessment of tic severity and treatment expectations

### Rationale

There are several rating scales available for measuring tic severity, with the Yale Global Tic Severity Scale the most extensively deployed and validated (RELA).<sup>12</sup> Evaluation of the effect of treatment on tic severity in trials is measured using such scales (EVID). The use of validated scales to measure tic severity can aid the evaluation of treatment response in the clinical setting (INFER). While medications, behavioral

therapy, and neurostimulation can result in meaningful reduction in tics (EVID), these interventions rarely result in complete cessation of tics.

### Recommendation 6a

Clinicians may measure tic severity using a valid scale to assess treatment effects (Level C).

### Recommendation 6b

Clinicians must counsel patients that treatments for tics infrequently result in complete cessation of tics (Level A).

## Behavioral treatments

### Rationale

People with tics receiving CBIT are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity (EVID). CBIT is a manualized treatment program consisting of habit reversal training (HRT), relaxation training, and a functional intervention to address situations that sustain or worsen tics (RELA).<sup>13</sup> The child and adult CBIT trials demonstrated the efficacy of an 8-session protocol, though cases complicated by poor tic awareness, treatment motivation, more severe tics, or substantial clinical comorbidity may benefit from a longer course of therapy. Most children (aged 9 years or older) and adults showing an initial positive response to CBIT will maintain their treatment gains for at least 6 months (EVID). CBIT can be effective for children younger than 9 years, though there is little evidence to determine efficacy in children of this age group (RELA).<sup>14</sup> There is some evidence that the efficacy of CBIT for reducing tics is greater for patients not concurrently taking anti-tic medication (RELA).<sup>15</sup> There is insufficient evidence to determine the relative efficacy of HRT compared with exposure and response prevention or educational group treatment in reducing tic severity (EVID). There is insufficient evidence to determine the relative efficacy of HRT by video conferencing compared with either face-to-face HRT or wait-list control for reducing tic severity (EVID). There is insufficient evidence to determine the efficacy of relaxation training for reducing tic severity (EVID). The evidence demonstrates no increased risk of adverse effects for people treated with CBIT compared with those treated with psychoeducation plus supportive therapy (EVID). The effect size for CBIT appears similar to effect sizes for medications (EVID). In light of clinician responsibility to optimally balance safety and effectiveness in treatment decisions (PRIN), CBIT should be considered as an initial treatment choice for tics (INFER). Given the effort required from patients or their families, along with its benign safety profile, CBIT is an acceptable intervention for people with tics that lead to psychosocial or physical impairment and who are motivated to participate in treatment (INFER).

### Recommendation 7a

For people with tics who have access to CBIT, clinicians should prescribe CBIT as an initial treatment option relative to other psychosocial/behavioral interventions (Level B).



### Recommendation 7b

For people with tics who have access to CBIT, clinicians should offer CBIT as an initial treatment option relative to medication (Level B).

### Recommendation 7c

Clinicians may prescribe CBIT delivered over teleconference or secure voice over Internet protocol delivery systems if face-to-face options are unavailable in a patient care center. If CBIT is unavailable, other behavioral interventions for tics may be acceptable, such as exposure and response prevention (Level C).

## **α-Agonists for the treatment of tics**

### Rationale

People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity, and people with tics receiving guanfacine are possibly more likely than those receiving placebo to have reduced tic severity, with the majority of trials conducted in children (EVID). In children with tics and comorbid ADHD, clonidine and guanfacine have demonstrated beneficial effects on both tics and ADHD symptoms (EVID). The effect size of clonidine and guanfacine on tics appears larger in children with tics and ADHD compared with individuals with tics without a comorbid diagnosis of ADHD (EVID). Relative to placebo, clonidine is probably associated with higher rates of sedation, and guanfacine is probably associated with higher rates of drowsiness (EVID). A systematic review of α<sub>2</sub> adrenergic agonists for ADHD in children and adolescents demonstrated hypotension, bradycardia, and sedation with both agents, and QTc prolongation with guanfacine extended release (RELA).<sup>16</sup> Abrupt withdrawal of α<sub>2</sub> adrenergic agonists may cause rebound hypertension (RELA).<sup>17</sup>

### Recommendation 8a

Physicians should counsel individuals with tics and comorbid ADHD that α<sub>2</sub> adrenergic agonists may provide benefit for both conditions (Level B).

### Recommendation 8b

Physicians should prescribe α<sub>2</sub> adrenergic agonists for the treatment of tics when the benefits of treatment outweigh the risks (Level B).

### Recommendation 8c

Physicians must counsel patients regarding common side effects of α<sub>2</sub> adrenergic agonists, including sedation (Level A).

### Recommendation 8d

Physicians must monitor heart rate and blood pressure in patients with tics treated with α<sub>2</sub> adrenergic agonists (Level A).

### Recommendation 8e

Physicians prescribing guanfacine extended release must monitor the QTc interval in patients with a history of cardiac conditions, patients taking other QT-prolonging agents, or patients with a family history of long QT syndrome (Level A).

### Recommendation 8f

Physicians discontinuing α<sub>2</sub> adrenergic agonists must gradually taper them to avoid rebound hypertension (Level A).

## **Antipsychotic treatment for tics**

### Rationale

Haloperidol, risperidone, aripiprazole, and tiapride are probably more likely than placebo to reduce tic severity (EVID), and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity (EVID). There is insufficient evidence to determine the relative efficacy of these drugs (EVID). Relative to placebo, the evidence demonstrates a higher risk of drug-induced movement disorders with haloperidol, pimozide, and risperidone (EVID), a higher risk of weight gain with risperidone and aripiprazole (EVID), a higher risk of somnolence with risperidone, aripiprazole, and tiapride (EVID), a higher risk of QT prolongation with pimozide (EVID), and a higher risk of elevated prolactin with haloperidol, pimozide, and metoclopramide (EVID). Systematic reviews of trials and cohort studies demonstrate a higher risk of drug-induced movement disorders (including tardive dyskinesia, drug-induced parkinsonism, akathisia, acute dystonia, and tardive dystonia), weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation antipsychotics across psychiatric and neurologic conditions (RELA).<sup>18,19</sup> The long-term use of metoclopramide is associated with tardive dyskinesia, resulting in a black box warning from the US Food and Drug Administration.<sup>20</sup> The relative propensity for these adverse effects varies by agent and is often dose-dependent (RELA). Physicians have a duty to monitor the effectiveness and safety of prescribed medications (PRIN), and evidence-based monitoring protocols are available.<sup>21</sup> Abrupt discontinuation of antipsychotic medications can cause withdrawal dyskinesias (RELA).<sup>22,23</sup>

### Recommendation 9a

Physicians may prescribe antipsychotics for the treatment of tics when the benefits of treatment outweigh the risks (Level C).

### Recommendation 9b

Physicians must counsel patients on the relative propensity of antipsychotics for extrapyramidal, hormonal, and metabolic adverse effects to inform decision-making on which antipsychotic should be prescribed (Level A).

### Recommendation 9c

Physicians prescribing antipsychotics for tics must prescribe the lowest effective dose to decrease the risk of adverse effects (Level A).

### Recommendation 9d

Physicians prescribing antipsychotics for tics should monitor for drug-induced movement disorders and for metabolic and hormonal adverse effects of antipsychotics, using evidence-based monitoring protocols (Level B).

### Recommendation 9e

Physicians prescribing antipsychotics for tics must perform electrocardiography and measure the QT<sub>c</sub> interval before and after starting pimozide or ziprasidone, or if antipsychotics are coadministered with other drugs that can prolong the QT interval (Level A).

### Recommendation 9f

When attempting to discontinue antipsychotics for tics, physicians should gradually taper medications over weeks to months to avoid withdrawal dyskinesias (Level B).

### Botulinum toxin injections for tics

Botulinum toxin injections with onabotulinumtoxinA are probably more likely than placebo to reduce tic severity in adolescents and adults (EVID). Premonitory urges may also be improved by botulinum toxin injections (RELA).<sup>24</sup> Relative to placebo, onabotulinumtoxinA is associated with higher rates of weakness (EVID). Hypophonia is a common side effect of botulinum toxin injections in the laryngeal muscles for vocal tics (RELA).<sup>25</sup> The effects of botulinum toxin injections last 12–16 weeks, after which treatment needs to be repeated (PRIN).

### Recommendation 10a

Physicians may prescribe botulinum toxin injections for the treatment of adolescents and adults with localized and bothersome simple motor tics when the benefits of treatment outweigh the risks (Level C).

### Recommendation 10b

Physicians may prescribe botulinum toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks (Level C).

### Recommendation 10c

Physicians must counsel individuals with tics that botulinum toxin injections may cause weakness and hypophonia, and that all effects are temporary (Level A).

### Topiramate for the treatment of tics

#### Rationale

Topiramate is possibly more likely than placebo to reduce tic severity (EVID). In patients with mild but troublesome tics who are not obtaining a satisfactory response or experience adverse effects from other treatments, topiramate may be a useful alternative. While generally well-tolerated at low doses (25–150 mg/day) it may cause adverse effects, including cognitive and language problems, somnolence, and weight loss, and may increase the risk of renal stones (RELA).<sup>26–28</sup>

### Recommendation 11a

Physicians should prescribe topiramate for the treatment of tics when the benefits of treatment outweigh the risks (Level B).

### Recommendation 11b

Physicians must counsel patients regarding common adverse effects of topiramate, including cognitive and language problems,

somnolence, weight loss, and an increased risk of renal stones (Level A).

### Cannabis-based medications for the treatment of patients with TS

#### Rationale

Some patients with TS use cannabis as a self-medication for tics and comorbidities (RELA).<sup>29</sup> There is limited evidence that  $\delta$ -9-tetrahydrocannabinol (THC), dronabinol, is possibly more likely than placebo to reduce tic severity in adults with TS (EVID). There is insufficient evidence to determine whether the efficacy of nabiximols, nabilone, and cannabidiol (CBD), as well as different strains of medicinal cannabis—standardized for different levels of THC and CBD—is similar to THC. Compared with placebo, cannabis-based medications are associated with increased risk of short-term adverse events, most commonly dizziness, dry mouth, and fatigue (RELA).<sup>30</sup> There is no evidence that controlled treatment with cannabis-based medication may induce addiction to cannabinoids. Acute withdrawal of cannabinoids is generally safe and well-tolerated without significant adverse events (RELA).<sup>30,31</sup> Cannabis-based medications should be avoided in children and adolescents, not only due to a paucity of evidence but due to the association between cannabis exposure in adolescence and potentially harmful cognitive and affective outcomes in adulthood (RELA, PRIN).<sup>32</sup> Cannabis-based medication should not be used in women who are pregnant or breastfeeding or in patients with psychosis (PRIN). Prescription of and access to medical marijuana varies by region; practitioners must abide by regional legislation on the use of medical marijuana (PRIN).

### Recommendation 12a

Due to the risks associated with cannabis use and widespread self-medication with cannabis for tics, where regional legislation and resources allow, physicians must offer to direct patients to appropriate medical supervision when cannabis is used as self-medication for tics (Level A). Appropriate medical supervision would entail education and monitoring for efficacy and adverse effects.

### Recommendation 12b

Where regional legislation allows, physicians may consider treatment with cannabis-based medication in otherwise treatment-resistant adults with clinically relevant tics (Level C).

### Recommendation 12c

Where regional legislation allows, physicians may consider treatment with cannabis-based medication in adults with TS who already use cannabis efficiently as a self-medication in order to better control and improve quality of treatment (Level C).

### Recommendation 12d

Where regional legislation allows, physicians prescribing cannabis-based medication must prescribe the lowest effective dose to decrease the risk of adverse effects (Level A).

### Recommendation 12e

Physicians prescribing cannabis-based medication must inform patients that medication may impair driving ability (Level A).

### Recommendation 12f

Physicians prescribing cannabis-based medication to patients with TS must periodically reevaluate the need for ongoing treatment (Level A).

## Deep brain stimulation (DBS) for tics in the setting of TS

### Rationale

Patients with severe TS, resistant to medical and behavioral therapy, may benefit from the application of DBS. An important challenge and limitation in the evaluation of the evidence around DBS in TS is that, even in expert DBS centers, few operations per year are performed. Furthermore, there is limited information from randomized clinical trials for analysis and interpretation. There is no consensus on the optimal brain target for the treatment of tics, but the following regions have been stimulated in patients with TS: the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. DBS of the anteromedial globus pallidus is probably more likely than sham stimulation to reduce tic severity (EVID). There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region of the thalamus in reducing tic severity (EVID). Complications of treatment, including infection and removal of hardware, appear more common with TS (EVID) than with other neurologic conditions.

Recommendations from the Movement Disorders Society suggest that, when DBS is used in TS, best practices used for other DBS applications are followed, including confirmation of diagnosis, use of multidisciplinary screening, and stabilization of psychiatric comorbidities inclusive of active suicidality (RELA).<sup>33</sup> Appropriate patient selection is one of the most important predictors of success of DBS treatment, making multidisciplinary evaluation essential (RELA).<sup>34</sup> Because of the complexity of the patient population, centers performing DBS have been encouraged to screen candidates preoperatively and to follow them postoperatively. There has been concern about high risk of suicide and other negative psychiatric sequelae in patients with TS not screened and monitored for depression, anxiety, and bipolar tendencies. The largest available randomized trials of DBS have revealed benefits on motor and phonic tics for the ventral globus pallidus internus and the centromedian thalamic region target; however, these studies have raised methodologic concerns that need to be addressed in future trials (RELA).<sup>35</sup> There is little information on the effects of DBS on psychiatric comorbidities and on the efficacy of DBS in children with TS.

### Recommendation 13a

Physicians must use a multidisciplinary evaluation (psychiatrist or neurologist, neurosurgeon, and neuropsychologist) to

establish when the benefits of treatment outweigh the risks of prescribing DBS for medication-resistant motor and phonic tics (Level A).

### Recommendation 13b

Physicians should confirm the DSM-5 diagnosis of TS and exclude secondary and functional tic-like movements when considering DBS for medication-resistant tics (Level B).

### Recommendation 13c

A mental health professional must screen patients preoperatively and follow patients postoperatively for psychiatric disorders that may impede the long-term success of the therapy (Level A).

### Recommendation 13d

Physicians must confirm that multiple classes of medication (antipsychotics, dopamine depleters,  $\alpha 2$  agonists) and behavioral therapy have been administered (or are contraindicated) before prescribing DBS for tics (Level A).

### Recommendation 13e

Physicians may consider DBS for severe, self-injurious tics, such as severe cervical tics that result in spinal injury (Level C).

## Suggestions for future research

1. Future research on behavioral interventions for tics should include comparisons of the relative efficacy of CBIT vs pharmacotherapy. Additional research should be conducted on treatment sequencing and decision-making and for whom particular sequences of treatment are most effective. Further research should continue to test the efficacy of other behavioral treatments, including exposure and response prevention, mindfulness-based treatments, or more global tic-related interventions.<sup>36</sup> As the evidence is insufficient at present to conclude that CBIT delivered by teleconference is as effective as face-to-face treatment, further well-designed studies with adequate sample sizes are needed to establish non-inferiority. Additional work to more accurately characterize the neurocognitive and behavioral mechanism of action underlying CBIT will be necessary to enhance the overall effectiveness and inform patient-treatment matching algorithms.<sup>37</sup>
2. Future research on medications for tics should include noninferiority trials of agents commonly used for the treatment of tics for which limited evidence from randomized controlled trials is available. Agents for which evidence is promising but limited include the first-generation antipsychotic fluphenazine.<sup>38-40</sup> Trials are currently underway with the selective D1 antagonist ecopipam and evidence on the efficacy of this drug is expected soon.
3. The dopamine depleters, tetrabenazine, deutetabenazine, and valbenazine, act by blocking vesicular monoamine transporter type 2 (VMAT2). Although no randomized controlled trials have been published with the VMAT2



inhibitors in the treatment of tics, these drugs are increasingly used off-label. When appropriately dosed, these drugs are generally well-tolerated but may be associated with drowsiness, depression, and parkinsonism. Although an initial phase II trial of valbenazine did not reach the primary endpoint in adults and children with TS, this was thought to be due to underdosing. Further and better-designed trials are currently underway with valbenazine and deutetrabenazine for the treatment of tics.<sup>41–43</sup>

4. Our systematic review included 3 different traditional Chinese medicine products: the 5-Ling granule,<sup>44</sup> the Ningdong granule formulated by Zhao,<sup>45</sup> and the Ningdong granule formulated by Wang.<sup>46</sup> We did not make formal recommendations for or against the use of these compounds, all of which reported superiority over placebo. Our panel had concerns about the inclusion criteria for the 5-Ling granule study, as participants also had a condition fitting the “excessive subtype” in traditional Chinese medicine–based diagnosis (see full and unabridged practice guideline for full details), with no equivalent diagnosis in Western medicine or clear understanding of pathophysiology. Furthermore, this study excluded children with the 2 most common comorbidities seen with TS: ADHD and OCD. There are therefore concerns with respect to the generalizability of these findings. Finally, the availability of these compounds outside of the trials is unknown and safety concerns remain regarding the ingredients—the Ningdong granule formulated by Wang contains human dried placenta. Further research and information on the safety and reliability of production of these agents is required before formal recommendations can be made.
5. There is a need for more long-term studies of drug efficacy and adverse effects as well as the efficacy and safety of medication combinations for severe tics resistant to monotherapy.
6. Few studies have been performed investigating the efficacy and safety of cannabis-based medicine in children with various diseases. Recently it was reported that CBD may significantly reduce convulsive seizure frequency in children with Dravet syndrome.<sup>47</sup> There is preliminary evidence that THC might also be effective in children for vomiting due to antineoplastic treatment<sup>48,49</sup> and in treatment-resistant spasticity.<sup>50</sup> There is increasing evidence that cannabis-based medicine might be effective in adults with TS.<sup>51</sup> A recent press release for a single-dose study of a first-in-class small molecule inhibitor of monoacylglycerol lipase, ABX-1431, which regulates one of the key natural activators of the central cannabinoid CB1 receptor, suggests efficacy for the treatment of tics.<sup>52</sup>
7. Case reports and case series have comprised the majority of the outcomes data on the efficacy of DBS for TS. An international DBS registry<sup>53</sup> has been developed to collect data on DBS outcomes in patients with TS implanted in various centers. The registry also collects

information about response to nonstandardized selection criteria, various brain targets, differences in hardware, and variability in the programming parameters used. The goal of future research on DBS in TS should be to improve outcomes and quality of life by conducting well-designed multicenter studies, share data across centers, uncover best practices, and provide critical information to regulatory agencies that will lead to approval of DBS in TS. There are important limitations to the currently available trials using DBS in TS. The uncertainty in optimal target and the individual variability in programming and management between participants make trials challenging. Recent research on DBS in TS has revealed the intriguing possibility that it may not be necessary to have the devices activated continuously as has been the standard for other movement disorders. Moreover, adaptive closed-loop DBS is being explored in an ongoing clinical trial.

8. Future research on the effect of special diets, nutritional supplements, and exercise on tic severity is needed.

### Author contributions

Dr. Pringsheim: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Okun: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Müller-Vahl: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Martino: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Jankovic: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Cavanna: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Woods: study concept and design, critical revision of the manuscript for important intellectual content. M. Robinson: study concept and design, critical revision of the manuscript for important intellectual content. E. Jarvie: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Roessler: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Oskoui: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Holler-Managan: study concept and design, acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Piacentini: study concept and design, critical revision of the manuscript for important intellectual content.

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