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Practice Guideline: The Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders

Report by:

Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Presentation Objectives

- To present evidence on the efficacy of treatments for tics and the risks associated with their use
- To present practice recommendations for when clinicians and patients should treat tics and how clinicians and patients should choose between evidence-based treatment options

Overview

- Introduction
- Clinical questions
- American Academy of Neurology guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

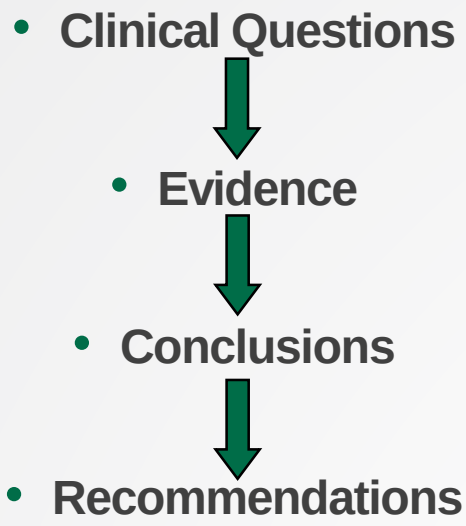
- This practice guideline reviews evidence for the efficacy of medical and behavioral treatments for tics, including neurostimulation, and the risks associated with their use.
- Antipsychotic medications have been commonly prescribed since the 1960s. The adverse effects associated with antipsychotic medications, including movement disorders such as acute and tardive dystonia, tardive dyskinesia, akathisia and drug-induced parkinsonism, and metabolic adverse effects, such as weight gain, hyperlipidemia, and hyperglycemia, have led clinicians to search for other effective treatments.
- In recent years, there has been a resurgence in the interest in behavioral treatments and neuromodulation for tics, yielding expanding evidence in this area.
- Although individuals with Tourette syndrome and chronic tic disorders often have comorbid psychiatric disorders, the focus of this practice guideline is on the management of tics, as treatment of comorbid conditions mainly follows recommendations given for the treatment of these disorders without tics.

Clinical Questions

The systematic review for this practice guideline addressed the following questions:

- In children and adults with Tourette syndrome or a chronic tic disorder, which medical, behavioral, and neurostimulation interventions, compared with placebo or other active interventions, improve tic severity and tic-related impairment?
- In children and adults with Tourette syndrome or a chronic tic disorder, what are the risks of harm, including weight gain, elevated prolactin levels, sedation, drug-induced movement disorders, hypotension, bradycardia, and electrocardiogram changes with medical treatments, compared with placebo or other active interventions?

AAN Guideline Process*



*Guideline developed using the 2011 *AAN Clinical Practice Guideline Process Manual*, as amended.

Literature Search/Review

Rigorous, Comprehensive, Transparent

2,407 abstracts

81 rated articles

Five databases (MEDLINE, Embase, PsychINFO, CENTRAL, and ClinicalTrials.gov) were searched through August 2016. An updated search was conducted to include studies published to September 2017.

Inclusion criteria:

- Randomized controlled trials on the treatment of tics in individuals with Tourette syndrome (TS) or chronic tic disorders
- Cohort studies or case series that specifically evaluated adverse drug effects in individuals with TS

Exclusion criteria:

- Randomized controlled trials that included fewer than 20 participants (fewer than 10 for crossover trials)

Class I

A clinical RCT of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:
a. Concealed allocation
b. No more than two primary outcomes specified
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following characteristics are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate.

* Note that numbers I to iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Class II
An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets items b–e (see Class I).
(Alternatively, a randomized crossover trial missing one of the following two characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.)
All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class III

- All other controlled trials (including studies with external controls such as well-defined natural history controls).
- (Alternatively, a crossover trial missing both of the following two criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.)
- A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

- Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Question 1

In children and adults with Tourette syndrome or a chronic tic disorder, which medical, behavioral, and neurostimulation interventions, compared with placebo or other active interventions, improve tic severity and tic-related impairment?

Clinical Question 1: *Conclusions*

High Confidence in the Evidence

People with tics receiving the **Comprehensive Behavioral Intervention for Tics** are more likely than those receiving **supportive psychotherapy** to have reduced tic severity (SMD 0.56; 95% confidence interval [CI], 0.31 to 0.82], high confidence, 2 Class I studies[22, 23]).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Moderate Confidence in the Evidence

People with tics receiving the following interventions are probably more likely than those receiving placebo to have reduced tic severity:

- **Haloperidol**, SMD 0.59 (95% CI, 0.11 to 1.06), 2 Class II studies[24, 25]
- **Risperidone**, SMD 0.79 (95% CI, 0.31 to 1.27), 2 Class II studies[26, 27]
- **Aripiprazole**, SMD 0.64 (95% CI, 0.31 to 0.97), 1 Class I study[28] and 1 Class II study[29] (children only)
- **Tiapride**, SMD 0.62 (95% CI, 0.36 to 0.88), 1 Class I study[30] (children only)
- **Clonidine**, SMD 0.45 (95% CI, 0.13 to 0.77), 1 Class I study[31] and 2 Class II studies[32, 33]
- **Onabotulinum toxin A injections**, SMD 1.27 (95% CI, 0.51to 2.03), 1 Class II study[34]; confidence in evidence upgraded due to magnitude of effect
- **Ningdong granule** (as formulated by Zhao), SMD 0.97 (95% CI, 0.45 to 1.49), 1 Class II study[35]; confidence in evidence upgraded due to magnitude of effect (children only)
- **5-Ling granule**, SMD 0.55 (95% CI, 0.33 to 0.76), 1 Class I study[30] (children only)

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Moderate Confidence in the Evidence (*continued*)

People with tics and a comorbid diagnosis of attention-deficit/hyperactivity disorder receiving the following interventions are probably more likely than those receiving placebo to have reduced tic severity:

- **Clonidine plus methylphenidate**, SMD 0.72 (95% CI, 0.22 to 1.22), 1 Class I study[31] (children only)
- **Methylphenidate**, SMD 0.61 (95% CI, 0.13 to 1.10), 1 Class I study[31] (children only)
- **Desipramine**, SMD 1.13 (95% CI, 0.47 to 1.79), 1 Class II study[36]; confidence in evidence upgraded due to magnitude of effect (children only). Desipramine is now rarely used in children after several case reports of sudden death associated with the use of this medication.[37]

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Moderate Confidence in the Evidence (*continued*)

People with tics receiving active **deep brain stimulation (DBS)** of the globus pallidus are probably more likely than those receiving sham DBS to have reduced tic severity (SMD 0.77 [95% CI, 0.14 to 1.40), 2 class II studies[38, 39] (adults only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Low Confidence in the Evidence

People with tics receiving the following interventions are possibly more likely than those receiving placebo to have reduced tic severity:

- **Pimozide**, SMD 0.66 (95% CI, 0.06 to 1.25), 3 Class II studies,[24, 40] confidence in evidence downgraded due to imprecision
- **Ziprasidone**, SMD 1.14 (95% CI, 0.32 to 1.97), 1 Class II study[41] (children only)
- **Metoclopramide**, SMD 1.14 (95% CI, 0.33 to 1.95), 1 Class II study[42] (children only)
- **Guanfacine**, SMD 0.45 (95% CI, 0.03 to 0.87)1 Class I study[43] and 2 Class II studies,[44, 45] confidence in evidence downgraded due to imprecision (children only)
- **Topiramate**, SMD 0.91 (95% CI, 0.11 to 1.71), 1 Class II study[46]
- **Tetrahydrocannabinol**, SMD 0.62 (95% CI, 0.01 to 1.22), 1 Class II[47] and 1 Class III study[48] (adults only)

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Low Confidence in the Evidence (*continued*)

For people with tics and a comorbid diagnosis of attention-deficit/hyperactivity disorder, **atomoxetine** does not worsen tics relative to placebo (1 Class II study[49]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Very Low Confidence in the Evidence

There is insufficient evidence to determine whether people with tics receiving the following interventions are more or less likely than those receiving placebo to have reduced tic severity:

- **Baclofen**, SMD 0.55 (95% CI, -0.39 to 1.49) 1 Class II study[50]; confidence in evidence downgraded due to imprecision (children only)
- **Levetiracetam**, SMD 0.22 (95% CI, -0.38 to 0.82), 1 Class II study[51]; confidence in evidence downgraded due to imprecision (children only)
- **N-acetylcysteine**, SMD 0.45 (95% CI, -0.27 to 1.17), 1 Class II study[52]; confidence in evidence downgraded due to imprecision (children only)
- **Omega-3 fatty acids**, SMD 0.69 (95% CI, 0.00 to 1.39), 1 Class II study[53]; confidence in evidence downgraded due to imprecision (children only)
- **Ningdong granule** (as formulated by Wang), 1 Class II study[17] (children only)
- **Nicotine**, SMD 0.38 (95% CI, -0.14 to 0.90), 1 Class III study[54] (children only)
- **Nicotine patch added to haloperidol**, SMD 0.71 (95% CI, 0.17 to 1.25), 1 Class III study[55] (children only)
- **Mecamylamine**, 1 Class II study[16] (children only)
- **Flutamide**, 1 Class I study[14] (adults only)
- **Riluzole**, SMD 0.17 (95% CI, -0.91 to 1.25), 1 Class I study[56]; confidence in evidence downgraded due to imprecision (children only)
- **D-serine**, SMD -0.04 (95% CI, -1.13 to 1.05), 1 Class I study[56]; confidence in evidence downgraded due to imprecision (children only)
- **Ondansetron**, SMD 0.53 (95% CI, -0.20 to 1.25), 1 Class III study[57]
- **Pramipexole**, SMD 0.00 (95% CI, -0.53 to 0.53), 1 Class II study[58]; confidence in evidence downgraded due to imprecision (children only)
- **Intravenous immunoglobulin**, SMD 0.50 (95% CI, -0.24 to 1.24), 1 Class II study[59]; confidence in evidence downgraded due to imprecision
- **Deprenyl,** SMD 0.47 (95% CI, -0.05 to 0.99), 1 Class II study[60]; confidence in evidence downgraded due to imprecision (children only)

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 1: *Conclusions*

Very Low Confidence in the Evidence (*continued*)

There is insufficient evidence to determine whether people with tics receiving the following interventions are more or less likely than those receiving an alternate intervention to have reduced tic severity:

- **Haloperidol versus pimozide**, SMD 0.11 (95% CI, -0.41 to 0.62), 2 Class II studies,[24, 25] confidence in evidence downgraded due to imprecision
- **Risperidone versus pimozide**, SMD 0.24 (95% CI, -0.51 to 0.99), 2 Class II studies, confidence in evidence downgraded due to imprecision
- **Risperidone versus clonidine**, SMD -0.19 (95% CI, -1.06 to 0.68), 1 Class II study,[e1] confidence in evidence downgraded due to imprecision (children only)
- **Aripiprazole versus risperidone**, SMD 0.17 (95% CI, -0.34 to 0.68), 1 Class II study,[e2] confidence in evidence downgraded due to imprecision (children only)
- **Clonidine versus levetiracetam**, SMD 0.86 (95% CI, -0.03 to 1.75), 1 Class II study[e3] (children only)
- **Habit reversal therapy versus exposure and response prevention**, SMD 0.25 (95% CI, -0.40 to 0.90), 1 class II study,[e4] confidence in evidence downgraded due to imprecision
- **Habit reversal therapy versus educational group treatments**, SMD 0.55 (95% CI, -0.17 to 1.27), 1 Class II study,[e5] confidence in evidence downgraded due to imprecision (children only)
- **Face-to-face habit reversal therapy versus habit reversal therapy through video conferencing**, SMD 0.24 (95% CI, -0.70 to 1.18), 1 Class II study,[e6] confidence in evidence downgraded due to imprecision (children only)
- **Habit reversal therapy by video conferencing versus wait list control**, SMD 0.24 (95% CI, -0.65 to 1.14), 1 Class II study,[e7] confidence in evidence downgraded due to imprecision (children only)
- **Relaxation therapy versus minimal therapy**, 1 Class III study[20] (children only)
- **Biofeedback versus sham**, 1 Class III study[15] (adults only)
- **Active DBS of the thalamus versus sham DBS of the thalamus**, SMD 1.58 (95% CI, -0.12 to 3.28), 1 Class III study[e8] (adults only)
- **Active DBS of the centromedian-parafascicular complex versus sham DBS of the centromedian-parafascicular complex**, SMD 0.99 (95% CI, -0.28 to 2.26), 1 Class III study[e9] (adults only)
- **Continuous theta burst transcranial magnetic stimulation of the supplementary motor area versus sham transcranial magnetic stimulation**, SMD -0.15 (95% CI, -1.29 to 0.99), 1 Class II study[e10]; confidence in evidence downgraded due to imprecision
- **Repetitive transcranial magnetic stimulation (rTMS) of the supplementary motor area versus sham stimulation**, SMD 0.19 (95% CI, -0.69 to 1.07), 1 Class II study,[e11] confidence in evidence downgraded due to imprecision (adults only)
- **rTMS of the left motor or prefrontal cortex versus sham stimulation**, 1 Class III study[13]

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2

In children and adults with Tourette syndrome or a chronic tic disorder, what are the risks of harm, including weight gain, elevated prolactin levels, sedation, drug-induced movement disorders, hypotension, bradycardia, and electrocardiogram changes with medical treatments compared with placebo or other active interventions?

Clinical Question 2: *Conclusions*

Weight Gain

- People with tics receiving risperidone are probably more likely to gain weight than people receiving placebo (moderate confidence, 2 Class II studies[27, e1]).
- People with tics receiving aripiprazole are probably more likely to gain weight than those receiving placebo (moderate confidence, 1 Class I study[28] and I Class II study[29]) (children only).
- People with tics receiving aripiprazole are possibly more likely to have an increase in body mass index and waist circumference than people receiving placebo (low confidence, I Class II study[29]) (children only).
- People with tics and a comorbid diagnosis of ADHD who are receiving atomoxetine are possibly more likely to have a decrease in body weight than people receiving placebo (low confidence, 1 Class II study[49]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Elevated Prolactin Levels

- People with tics receiving pimozide are possibly more likely to have increased prolactin levels than people receiving placebo (low confidence, 1 Class II study[24]).
- People with tics receiving haloperidol are possibly more likely to have increased prolactin levels than people receiving placebo (low confidence, 1 Class II study[24]).
- People with tics receiving metoclopramide are possibly more likely to have greater increases in prolactin levels than people receiving placebo (low confidence, 1 Class II study[42]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Sedation

- People with tics receiving risperidone are possibly more likely to experience fatigue and somnolence than people receiving placebo (low confidence, 1 Class II study[26]).
- People with tics receiving aripiprazole are possibly more likely to experience sedation and somnolence than people receiving placebo (low confidence, 1 Class II study[29]) (children only).
- People with tics receiving tiapride are probably more likely to experience higher rates of physical tiredness and sleep disturbances compared with people receiving placebo (moderate confidence, 1 Class I study[30]) (children only).
- People with tics receiving clonidine are probably more likely to experience sedation than people receiving placebo (moderate confidence, 1 Class I[31] and 1 Class II studies[33]).
- People with tics receiving guanfacine are probably more likely than those receiving placebo to have drowsiness (moderate confidence, 1 Class I study[43]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Drug Induced Movement Disorders

- People with tics receiving pimozide are probably more likely to have extrapyramidal symptoms than people receiving placebo (moderate confidence, 2 Class II studies[40]).
- People with tics receiving haloperidol are possibly more likely to have extrapyramidal symptoms than people receiving pimozide and placebo (low confidence, 1 Class II study[24, 25]).
- People with tics receiving risperidone are possibly more likely to have higher parkinsonism scores on the Extrapyramidal Symptom Rating Scale Score than people receiving placebo (low confidence, 1 Class II study[26]).
- People with tics receiving risperidone are possibly more likely to require antiparkinsonian medication than people receiving placebo (low confidence, 1 Class II study[26]).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Blood Pressure

People with tics and a comorbid diagnosis of ADHD receiving desipramine are possibly more likely to have an increase in diastolic blood pressure than people receiving placebo (low confidence, 1 Class II study[36]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Heart Rate

- People with tics and a comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD) receiving atomoxetine are possibly more likely to have an increase in heart rate than people receiving placebo (low confidence, 1 Class II study[49]) (children only).
- People with tics and a comorbid diagnosis of ADHD receiving desipramine possibly more likely to have an increased heart rate than people receiving placebo (low confidence, 1 Class II study[36]) (children only).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Clinical Question 2: *Conclusions*

Electrocardiogram changes

People with tics receiving pimozide are possibly more likely to have a prolonged QT interval than people receiving placebo and haloperidol (low confidence, 1 Class II study[25]).

Note: Unless otherwise specified, trial participants included both children (individuals aged 18 years and younger) and adults (individuals older than 18 years).

Practice Recommendations

Recommendation 1:
Natural History of Tourette syndrome
Rationale

Providing information to families about the natural history of a disorder can help inform treatment decisions. Tics begin in childhood and demonstrate a waxing and waning course. Peak tic severity usually occurs between the ages of 10 years and 12 years, with many children experiencing an improvement in tics in adolescence.[1] 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.[2] 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. However, even in such cases, the Comprehensive Behavioral Intervention for Tics (CBIT) could be employed if the patient is motivated to attempt treatment. 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.

Practice Recommendations

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Recommendation Statements 1a–1e:

- **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 Comprehensive Behavioral Intervention for Tics (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**).

Practice Recommendations

Recommendation 2: Psychoeducation—Teacher and Classroom

Rationale

Tourette syndrome is common, affecting approximately 1% of schoolchildren.[3] 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.[4] Improving peers' attitudes about and teachers' knowledge of TS may positively affect people with TS.

Practice Recommendations

Recommendation Statement 2:

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

Practice Recommendations

Recommendation 3:
Assessment and Treatment of attention-deficit/hyperactivity disorder (ADHD)
Rationale

Comorbid ADHD is common in people with Tourette syndrome (TS), with prevalence ranging from 30% to 50%.[5, 6] 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 and reduce ADHD symptoms. In children with tics and ADHD, atomoxetine does not worsen tics relative to placebo and reduces ADHD symptoms. Comorbid ADHD is strongly associated with functional impairment in children with TS.[7] While ADHD symptoms may improve in adolescence,[2] adults with TS may require ongoing care for this comorbidity.

Practice Recommendations

Recommendation Statements 3a–3c:

- **Recommendation 3a**: Clinicians should ensure an assessment for comorbid attention-deficit/hyperactivity disorder (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**).

Practice Recommendations

Recommendation 4:
Assessment and Treatment of Obsessive-Compulsive (OCD) in Children with Tics

Rationale

Obsessive-compulsive behaviors are common in people with Tourette syndrome, with a comorbid diagnosis of OCD made in 10% to 50%.[5, 6] Sub-analyses 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.[8, 9] For this reason, CBT is considered first-line treatment of OCD in individuals with tic disorders.

Practice Recommendations

Recommendation Statements 4a–4b:

- **Recommendation 4a:** Clinicians should ensure an assessment for comorbid obsessive-compulsive disorder (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**).

Practice Recommendations

Recommendation 5:
Other Psychiatric Comorbidities
Rationale

Population-based and clinic-based studies have shown that people with Tourette syndrome (TS) are at high risk of other psychiatric comorbidities, including anxiety disorders, oppositional defiant disorder, and mood disorders.[5, 6] Comorbid mood disorders appear more prevalent in adolescents and adults than children and in those with greater tic severity.[6, 10] 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.[11]

Practice Recommendations

Recommendation Statements 5a–5b:

- **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**).

Practice Recommendations

Recommendation 6:
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.[12] Evaluation of the effect of treatment on tic severity in trials is measured using such scales. The use of validated scales to measure tic severity can aid the evaluation of treatment response in the clinical setting. While medications, behavioral therapy, and neurostimulation can result in meaningful reduction in, these interventions rarely result in complete cessation of tics.

Practice Recommendations

Recommendation Statements 6a–6b:

- **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**).

Practice Recommendations

Recommendation 7:
Behavioral Treatments
Rationale

People with tics receiving Comprehensive Behavioral Intervention for Tics (CBIT) are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. 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.[13] 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. CBIT can be effective for children younger than 9 years, though there is little evidence to determine efficacy in children of this age group.[14] There is some evidence that the efficacy of CBIT for reducing tics is greater for patients not concurrently taking anti-tic medication.[15] 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. 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. There is insufficient evidence to determine the efficacy of relaxation training for reducing tic severity. The evidence demonstrates no increased risk of adverse effects for people treated with CBIT compared with those treated with psychoeducation plus supportive therapy. The effect size for CBIT appears similar to effect sizes for medications. In light of clinician responsibility to optimally balance safety and effectiveness in treatment decisions, CBIT should be considered as an initial treatment choice for tics. 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.

Practice Recommendations

Recommendation Statements 7a–7c:

- **Recommendation 7a**: For people with tics who have access to Comprehensive Behavioral Intervention for Tics (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**).

Practice Recommendations

Recommendation 8:
Alpha 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 receivng placebo to have reduced tic severity, with the majority of trials conducted in children. In children with tics and comorbid attention-deficit/hyperactivity disorder (ADHD), clonidine and guanfacine have demonstrated beneficial effects on both tics and ADHD symptoms. 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. Relative to placebo, clonidine is probably associated with higher rates of sedation, and guanfacine is probably associated with higher rates of drowsiness. A systematic review of alpha-2 adrenergic agonists for ADHD in children and adolescents demonstrated hypotension, bradycardia, and sedation with both agents, and QTc prolongation with guanfacine extended release.[16] Abrupt withdrawal of alpha-2 adrenergic agonists may cause rebound hypertension.[17]

Practice Recommendations

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Recommendation Statements 8a–8f:

- **Recommendation 8a**: Physicians should counsel individuals with tics and comorbid ADHD that alpha-2 adrenergic agonists may provide benefit for both conditions (**Level B**).
- **Recommendation 8b**: Physicians should prescribe alpha-2 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 alpha-2 adrenergic agonists, including sedation (**Level A**).
- **Recommendation 8d**: Physicians must monitor heart rate and blood pressure in patients with tics treated with alpha-2 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 alpha-2 adrenergic agonists must gradually taper them to avoid rebound hypertension (**Level A**).

Practice Recommendations

Recommendation 9:
Antipsychotic Treatment for Tics
Rationale

Haloperidol, risperidone, aripiprazole, and tiapride are probably more likely than placebo to reduce tic severity, and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity. There is insufficient evidence to determine the relative efficacy of these drugs. Relative to placebo, the evidence demonstrates a higher risk of drug-induced movement disorders with haloperidol, pimozide, and risperidone, a higher risk of weight gain with risperidone and aripiprazole, a higher risk of somnolence with risperidone, aripiprazole, and tiapride, a higher risk of QT prolongation with pimozide, and a higher risk of elevated prolactin with haloperidol, pimozide, and metoclopramide. 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.[18, 19] The long-term use of metoclopramide is associated with tardive dyskinesia, resulting in a black box warning from the US Food and Drug Administration.[20] The relative propensity for these adverse effects varies by agent and are often dose dependent. Physicians have a duty to monitor the effectiveness and safety of prescribed medications, and evidence-based monitoring protocols are available.[21] Abrupt discontinuation of antipsychotic medications can cause withdrawal dyskinesias.[22, 23]

Practice Recommendations

AMERICAN ACADEMY OF NEUROLOGY®

Recommendation Statements 9a–9f:

- **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_c 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**).

Practice Recommendations

Recommendation 10:
Botulinum Toxin Injections for Tics
Rationale

Botulinum toxin injections with onabotulinum toxin A are probably more likely than placebo to reduce tic severity in adolescents and adults. Premonitory urges may also be improved by botulinum toxin injections.[24] Relative to placebo, onabotulinum toxin A is associated with higher rates of weakness. Hypophonia is a common side effect of botulinum toxin injections in the laryngeal muscles for vocal tics.[25] The effect of botulinum toxin injections last 12 to 16 weeks, after which treatment needs to be repeated.

Practice Recommendations

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Recommendation Statements 10a–10c:

- **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**).

Practice Recommendations

Recommendation 11:
Topiramate for the Treatment of Tics
Rationale

Topiramate is possibly more likely than placebo to reduce tic severity. 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 to 150 mg/d) it may cause adverse effects, including cognitive and language problems, somnolence, and weight loss, and may increase the risk of renal stones.[26-28]

Practice Recommendations

Recommendation Statements 11a–11b:

- **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**).

Practice Recommendations

Recommendation 12:
Cannabis-Based Medications for the Treatment of Patients with Tourette Syndrome (TS)
Rationale

Some patients with TS use cannabis as a self-medication for tics and comorbidities.[29] There is limited evidence that delta-9-tetrahydrocannabinol (THC), dronabinol, is possibly more likely than placebo to reduce tic severity in adults with TS. 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.[30] 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.[30, 31] 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.[32] Cannabis-based medication should not be used in women who are pregnant or breastfeeding or in patients suffering from psychosis. Prescription of and access to medical marijuana varies by region; practitioners must abide by regional legislation on the use of medical marijuana.

Practice Recommendations

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Recommendation Statements 12a–12f:

- **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 suffering from 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**).

Practice Recommendations

Recommendation 13:
Deep Brain Stimulation for Tics in the Setting of Tourette Syndrome (TS)
Rationale

Patients with severe TS, resistant to medical and behavioral therapy, may benefit from the application of deep brain stimulation (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. 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. Complications of treatment, including infection and removal of hardware, appear more common with TS 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.[33] Appropriate patient selection is one of the most important predictors of success of DBS treatment, making multidisciplinary evaluation essential.[34] 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.[35] There is little information on the effects of DBS on psychiatric comorbidities and on the efficacy of DBS in children with TS.

Practice Recommendations

Recommendation Statements 13a–11b:

- **Recommendation 13a**: Physicians must use a multidisciplinary evaluation (psychiatrist or neurologist, neurosurgeon, and neuropsychologist) to establish when the benefits of treatment outweigh the risks for 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-1 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 Comprehensive Behavioral Intervention for Tics (CBIT) versus 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.[36] 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 noninferiority. 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.[37]

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.[38-40] 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, deutetrabenazine, 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 Tourette syndrome (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.[41-43]

Suggestions for Future Research (*continued*)

4. Our systematic review included 3 different traditional Chinese medicine products, the 5-Ling granule,[44] the Ningdong granule formulated by Zhao,[45] and the Ningdong granule formulated by Wang.[46] 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—attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. 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.

Suggestions for Future Research (*continued*)

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 cannabidiol may significantly reduce convulsive seizure frequency in children with Dravet syndrome.[47] There is preliminary evidence that delta-9-tetrahydrocannabinol might also be effective in children for vomiting due to antineoplastic treatment[48, 49] and in treatment-resistant spasticity.[50] There is increasing evidence that cannabis-based medicine might be effective in adults with TS.[51] 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.[52]

7. Case reports and case series have comprised the majority of the outcomes data on the efficacy of deep brain stimulation (DBS) for TS. An international DBS registry[53] 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.

References

References cited here can be found in the recommendations summary article and systematic review summary article. To locate these materials, please visit AAN.com/guidelines.

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Thank You.

Questions?