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


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ABBREVIATIONS

1 TS Tourette syndrome

2 SMD Standardized mean difference

3 CBIT Comprehensive Behavioural Intervention for Tics

4
ABSTRACT

Objective: To systematically assess all high-quality randomized controlled trials that evaluate the efficacy of treatments for tics and the risks associated with their use, and to make recommendations on when clinicians and patients should pursue treatment for tics and how clinicians and patients should choose between evidence-based treatment options.

Methods: In May 2016, a multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives was recruited to develop this guideline. This guideline follows the methodologies outlined in the 2011 edition of the AAN’s guideline development process manual, as amended.

Results: There was high confidence that several interventions are more effective than placebo in reducing tic severity, including the Comprehensive Behavioural Intervention for Tics, haloperidol, risperidone, aripiprazole, tiapraide, clonidine and guanfacine. There was moderate confidence that pimozide, ziprasidone, metoclopramide, topiramate, botulinum toxin injections, tetrahydrocannabinol and deep brain stimulation of the globus pallidus were more effective than placebo in reducing tic severity. Evidence of harm associated with various treatments were also demonstrated.

Recommendations: Forty-nine recommendations were made regarding the assessment, evaluation, and management of tics in individuals with TS 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 re-assessment of the need for on-going therapy. Choosing between treatment options should be individualized, based on a
collaborative decision between patient, caregiver and clinician, and considering both the benefits and harms of individual treatment options, and the presence of comorbid disorders.
INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental condition characterised by the presence of multiple motor tics and at least one vocal tic which persist for at least one year\(^1\). Motor tics are defined as involuntary, sudden, rapid, recurrent, and nonrhythmic movements. Not all tics are “jerk-like” (clonic); some may be more sustained (dystonic), may consist of isometric contractions (tonic), are manifested by sudden and transient cessation of movement (blocking), or repetitive movements (stereotypic tics). Vocal tics are essentially motor tics that involve the nasal or respiratory muscles resulting in simple sounds such as sniffing, throat clearing or coughing, or complex vocalisations, including coprolalia, but also may manifest with speech blocking or stuttering-like symptoms. Tics are often accompanied by specific behavioral symptoms\(^2,3\). Tourette syndrome, in addition to other tic disorders, is included in both neurologic (Movement Disorders Society) and psychiatric (American Psychiatric Association) classification systems. Chronic motor tic disorder is characterized by the presence of motor tics only; a chronic vocal tic disorder by the presence of vocal tics only, which persist for more than one year.

In 1885, Georges Gilles de la Tourette described a case series of patients presenting with the clinical triad of tics, echolalia (repeating other people’s words), and coprolalia (repetitive use of obscene language or socially inappropriate remarks). Subsequently, Gilles de la Tourette (GTS), also known as TS, was long neglected and traditionally considered a rare medical curiosity\(^4\), but recent epidemiologic studies using current diagnostic criteria have consistently shown that the prevalence figures for TS in school children range from 0.4% to 1.5% across all cultures\(^5\). There
are few population-based estimates of the prevalence of TS in adults; one recent population- 
based study found a prevalence of diagnosed TS of approximately 1 per 1000\textsuperscript{6}.

Tics are the core symptoms of TS and present four times more frequently in males than females, 
with an average age at onset of 6 years. Across affected individuals, there are nearly limitless 
presentations of tics. Eye blinking is the most common initial tic, followed by a gradual 
spreading of motor tics (e.g., eye rolling, mouth opening, facial grimacing, neck jerking, 
shoulder shrugging, abdominal tensing, kicking) and appearance of vocal tics (e.g., grunting, 
sniffing, coughing, throat clearing). Complex motor tics involve multiple muscular components 
and can resemble purposeful voluntary actions (e.g., palipraxia, or repeating actions, usually a set 
number of times or until the movements feel “just right”; echopraxia, or copying other people’s 
actions; copropraxia, or rude or obscene gestures). In addition to echolalia and coprolalia, 
complex vocal tics include the production of entire words, animal sounds, or the repetition of 
one’s own words, usually a set number of times or until the sounds feel “just right”\textsuperscript{7,8}.

Interestingly, coprophenomena involving the production of obscene words or gestures have been 
reported in a minority of patients (10\% of patients in the community and up to 30\% of patients 
with more severe/complex presentation in specialist clinics) and are not included among current 
diagnostic criteria, despite their centrality in several media portrayals of TS\textsuperscript{9}.

Tics are preceded or accompanied by subjective feelings of tension or pressure, which are 
temporarily relieved by tic expression\textsuperscript{10}. A hallmark feature of tics, these physical sensations are 
sometimes referred to as premonitory urges and have often proved helpful in the differential 
diagnosis between TS and other hyperkinetic movement disorders. However, not all patients 
report about such premonitory urges, and some patients describe both tics with and without
premonitory sensations. Most patients with TS are able to voluntarily suppress their tics for short
periods of time (usually seconds to minutes), at the expense of mounting inner tension\textsuperscript{11,12}. Tics
are dynamic symptoms and tend to fluctuate in number, distribution, frequency, and severity
over time, exhibiting a characteristic waxing and waning course. In addition to spontaneous
fluctuations, both emotional and environmental factors have been shown to modulate tic
expression. Psychological stress, tiredness, and boredom are among commonly reported
exacerbating factors, whereas relaxation and mental and physical engagement in pleasant tasks
can alleviate tics. Tics improve by adulthood in a considerable proportion of individuals with TS;
however, the trajectory of the clinical course and the identification of prognostic factors are not
fully understood and require more research\textsuperscript{13,14}.

Little is known about the exact brain mechanisms underlying tic development and their
expression. Although evidence from neurochemical and neuroimaging investigations suggests
that dysfunction of the dopaminergic pathways within the cortico-striato-cortico-frontal circuitry
play a primary role, other neurotransmitter systems, including glutamatergic, GABAergic,
noradrenergic, and histaminergic pathways, have been proposed to be involved\textsuperscript{15,16}. Tics are
often present in different forms and with different severity in family members; however, it is
commonly reported that generations can be skipped. Recent research has highlighted the
complexity of possible heritability pathways, indicating that TS is a genetically heterogeneous
condition, with vulnerability loci scattered throughout the genome\textsuperscript{17}. Moreover, environmental
factors have been proposed to play a contributory role, as in most neuropsychiatric disorders.
Both epidemiologic and laboratory findings indicate that respiratory infections and autoimmune
dysfunction, and pre- and perinatal problems, can be involved in the etiologic mechanisms in at
least a subgroup of patients with TS\textsuperscript{18-20}. 
The majority of patients with TS, both in specialist clinics and in the community, report the presence of behavioral symptoms associated with their tics: the most common behavioral comorbidities are obsessive-compulsive disorder (or obsessive-compulsive behavior) and attention-deficit/hyperactivity disorder. Lifetime prevalence of comorbid behavioral disorders has been estimated to be nearly 90%. Interestingly, specific obsessive-compulsive symptoms, including counting (arithmomania), “just-right” perceptions, concerns of symmetry and “evening-up” behaviors, are more commonly reported by patients with tics than patients with obsessive-compulsive disorder without tics. Distinguishing hyperactivity and attentional lapses due to the presence of the tics (and the constant effort to suppress them) from comorbid attention-deficit/hyperactivity disorder can pose considerable challenges. Patients with TS also report higher rates of impulse control, anxiety, and affective disorders compared with people in the general population. A higher prevalence of both tics and stereotypic movement disorders, or stereotypies, has been reported in patients with autism spectrum disorders. It is worth noting that the associated behavioral comorbidities often compromise the overall well-being of patients with TS to a much greater extent than tic severity per se.

The purpose of this practice guideline is to systematically assess all high-quality randomized controlled trials that evaluate the efficacy of medical and behavioral treatments, including neurostimulation, for tics, and the risks associated with their use. A systematic review was performed to develop recommendations regarding the use of treatments for tics in children and adults with TS or chronic tic disorders. Antipsychotic medications have been commonly prescribed since the 1960s for the treatment of tics. 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 treatment options. In recent years, there has been a resurgence in the interest in
behavioral treatments and neuromodulation for tics and expanding evidence in this area.
Although individuals with TS and chronic tic disorders often have comorbid psychiatric
disorders, the focus of this practice guideline will be 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:

1. In children and adults with TS 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?

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

Based on evidence identified from the systematic review, general principles of care, and related
evidence, the practice guideline seeks to make recommendations 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 syndrome 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 of, or combine, these treatments?

DESCRIPTION OF THE ANALYTIC PROCESS

In May 2016, the Guideline Development, Dissemination and Implementation Subcommittee (GDDI) of the American Academy of Neurology (AAN) recruited the members of a multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives to develop this practice guideline. The physicians include content experts in TS with a background in child and adult neurology (TP, AC, JJ, MO, DM, KMV, MO, YH), child and adult psychiatry (VR, K MV) and pediatrics (MO, YH); the psychologists were both content experts in behavioral treatments for TS (JP, DW); the patient representatives (MR, EJ) are both volunteers with the Tourette Association of America. The panel also included a methodology expert (TP) and 2 GDDI members (YH, MO).

All panel members were required to submit online conflict of interest (COI) forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead author and AAN methodologist (TP), and an AAN staff person (SM), reviewed the COI forms and CVs for financial and intellectual COI. These documents were specifically screened to exclude individuals with a clear financial conflict as well as those whose professional and intellectual bias might diminish the perceived credibility of the review. In accordance with AAN policy, the lead author (TP) has no COI. Five of the 13 authors were determined to have COI, which were judged to be not significant enough to preclude them from authorship (JJ, VR, AC, JP, K MV).
All authors determined to have COI were not permitted to review or rate the evidence. These individuals served in an advisory capacity to help validate key questions, assess the scope of the literature search, and identify seminal articles to validate the literature search, and participated in the recommendation development process. AAN GDDI leadership provided final approval of the author panel. This panel was solely responsible for decisions concerning the design, analysis, and reporting of the proposed systematic review, which was then submitted for approval to the AAN GDDI.

This evidence-based practice guideline follows the methodologies described in the 2011 edition of the AAN’s guideline development process manual, as amended to include use of the revised scheme for classifying therapeutic articles, the GDDI Guideline Topic Nomination Process scoring tool, and the change in order of steps for external review. We summarize the process here and provide a detailed description in the appendices referenced below. This process is compliant with 2011 Institute of Medicine standards for systematic review and clinical practice guideline development. Over the course of guideline development, the public and experts had an opportunity to review the draft protocol during a 30-day public comment period, during which the document was posted on the AAN Web site. During this period, AAN staff sent invitations to review and comment on the guideline to key stakeholders, which included all AAN section members and pertinent external physician and patient organizations, including the Tourette Association of America. The guideline was reviewed by the GDDI before the public comment period and will be reviewed after public comment.

Study screening and selection criteria: inclusion criteria for article selection
We included systematic reviews and randomized controlled trials on the treatment of tics in individuals with TS or chronic tic disorders including at least 20 participants (10 participants if a crossover trial), except for neurostimulation trials, for which no minimum sample size was required. In order to obtain additional information on drug safety, we included cohort studies or case series that specifically evaluated adverse drug effects in individuals with TS.

**Types of participants**

We included individuals with TS or chronic tic disorders of any age or sex.

**Types of intervention**

We included any medical, behavioral, or neurostimulation (e.g., transcranial magnetic stimulation, deep brain stimulation) intervention for tics.

**Comparison group**

We included studies comparing medical, behavioral, or neurostimulation treatments with placebo or other active treatments.

**Types of outcome measures**

We assessed the effect of all treatments on measures of tic severity and tic-related impairment. The preferred instrument for evaluation of tic severity and tic-related impairment is the Yale Global Tic Severity Scale, and when outcome results with this instrument were reported, they were used to calculate effect size. Other acceptable instruments include the Shapiro TS Severity Scale; the Rush Video-Based Tic Rating Scale; Tourette’s Disorder Scale; Tourette Syndrome Clinical Global Impression; Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey; the Tourette Syndrome Global Scale; the Global Tic Rating Scale; and the Tourette Syndrome Symptom List. Weight gain was assessed through reported measurements in kilograms, or as the percentage of individuals gaining more than 7% of their body weight.
(commonly reported outcome in antipsychotic trials). Elevated prolactin was evaluated by assessing mean changes in prolactin between groups, or mean prolactin levels at endpoint between groups. Drug-induced movement disorders were based on assessments using validated scales, including the Extrapyramidal Symptoms Rating Scale, Barnes Akathisia Scale, Simpson Angus Scale, or the Abnormal Involuntary Movement Scale, or by clinician report. Sedation was evaluated based on patient/parent/clinician report and assessment. Hypotension and bradycardia were evaluated by assessment of reported changes in systolic and diastolic blood pressure and heart rate with treatment, and reported rates of presyncope and syncope. Reported electrocardiography changes were also included.

The initial search was conducted in August of 2016 and included MEDLINE, EMBASE, PsychINFO, CENTRAL, and ClinicalTrials.gov (see appendix 1). The total number of references retrieved after duplicates were removed was 2196. After two reviewers working independently of each other reviewed the abstracts and titles of these 2196 references, the articles for 192 were selected and obtained for full text review. This included 16 systematic reviews, for which the references of all included studies were examined for missing studies. Four additional studies were identified using this method. In total, 66 randomized controlled trials and 12 studies evaluating drug safety were included in our analysis. Two nonconflicted panel members rated the class of evidence for each article according to the AAN scheme for classification of therapeutic articles (revised as denoted in a 2011 process manual amendment). Disagreements were resolved by a third panel member. Outcome data from included studies were extracted by the guideline methodologist and verified by a second panel member. A modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to develop conclusions. The confidence in the evidence (high,
moderate, low, or very low) is anchored to the error domain—class of evidence, indirectness of
evidence, and precision of effect estimate—with the highest risk of error.

Relative to the class of evidence (a measure of internal validity), the risk of error is determined
by the number and class of studies included in the synthesis. Evidence syntheses based solely on
multiple Class I studies are anchored to high confidence; those based solely on one Class I study
or multiple Class II studies are anchored to moderate confidence; those based solely on one Class
II study or multiple Class III studies are anchored to low confidence; and those based solely on
one Class III study or multiple Class IV studies are anchored to very low confidence. Confidence
in the evidence of syntheses including multiple studies of different risk-of-bias classes is
anchored to the study with the highest risk of bias. If the synthesis includes any Class IV study,
confidence is anchored to very low; any Class III study, low; or any Class II study, moderate.

Relative to the indirectness domain (a measure of external validity), confidence in the evidence
is anchored to the study included in the synthesis that has the most severe indirectness rating.
Only syntheses where all studies are judged to have minor degrees of indirectness can be
anchored to high confidence. Syntheses containing any study judged to have extreme
indirectness are anchored to very low confidence, those with any study judged to have severe
indirectness are anchored to low confidence; and those with any study judged to have moderate
indirectness are anchored to moderate confidence.

An effect size or standardized mean difference (SMD) of 0.20 was considered the minimal
clinically meaningful difference for reduction in tic severity; effect sizes smaller than 0.10 were
considered clinically unimportant. There were a number of studies that did not provide adequate
data to reliably calculate effect sizes. If multiple studies were available that evaluated the
same intervention/outcome pair, only those studies with the lowest risk of bias were used in
formulating the confidence in evidence statements. See the summary table later in this document for more information on the ratings for confidence in the evidence for each conclusion. For the complete evidence synthesis tables, see the evidence synthesis tables at AAN.com/practice-guidelines/home/public-comments.

Relative to precision (a measure of random error), the confidence in the evidence anchor depends upon whether the pooled effect size of the included studies includes no effect (i.e., the effect is “not significant”) and whether the summary confidence interval includes effect sizes judged to be clinically important, marginal (between important and unimportant thresholds), or unimportant. Important and unimportant effect size thresholds are determined by the author panel by consensus before the syntheses are performed.

If the pooled effect size is not significant and the 95% confidence interval includes only unimportant effect sizes, confidence of no effect is anchored to high; if the 95% confidence interval includes potentially marginal effect sizes, confidence is anchored to moderate; if the 95% confidence interval includes potentially marginal and important effect sizes, confidence is anchored to low; if the 95% confidence interval includes potentially important effect sizes, confidence is anchored to very low.

If the pooled effect is significant and the pooled 95% confidence interval includes only important effect sizes, confidence is anchored to high; if significant and the confidence interval includes potentially marginal effects, confidence is anchored to moderate; if significant and the confidence interval includes potentially unimportant effects, confidence is anchored to low. The confidence in the evidence determined by the lowest confidence from the major error domains (class of evidence, indirectness, and precision) serves as the anchor. This confidence level can be upgraded or downgraded by a maximum of one level based upon several other
domains: the magnitude of effect, direction of bias, and the presence of a dose response.

Confidence in the evidence is upgraded by one level if the magnitude of a significant effect point estimate is more than twice as large as that judged to be important. Conversely, confidence is downgraded by one level if the magnitude of a significant effect-size point estimate is less than the important threshold.

Confidence is also upgraded if the direction of bias in studies included in the synthesis are known (an unusual situation) and a significant effect is present that is in the opposite direction of the bias. Confidence is also upgraded if an expected dose response relationship is detected in the majority of the studies that tested for a dose response relationship and downgraded if an expected dose response relationship is not observed.

The panel formulated practice recommendations on the basis of the strength of evidence and other factors, including axiomatic principles of care, the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences. The panel assigned levels of obligation (A, B, C, U, R) to the recommendations using a modified Delphi process. Considerations for future research and recommendations were also developed during the development process of this practice guideline.

This practice guideline will be reassessed over time for currency and the need for updating according to the most current published AAN guideline development process manual.

**Pimozide and Haloperidol**
Our searches identified six trials that compared pimozide or haloperidol with placebo or with other medications (second-generation antipsychotics and traditional Chinese medicine) for the treatment of tics. One of the 6 studies was a parallel-group study, four were crossover studies, and one had both a parallel-group phase and a crossover phase. There were 162 patients in total participating in the included trials, with ages ranging from 7 to 53 years. Two of the six studies included in the review evaluated pimozide versus haloperidol versus placebo; a further two evaluated pimozide versus risperidone; one evaluated pimozide versus haloperidol, and one evaluated pimozide versus placebo. One additional study of haloperidol compared with placebo and the ningdong granule was found (study described in Ningdong granule section). The dosage of pimozide used in patients ranged from 1 to 12 mg per day. The dosage of haloperidol ranged from 1 to 12 mg, and the dosage of risperidone ranged from 0.5 to 6 mg. The length of each treatment phase ranged from 12 days to 8 weeks.

Outcome measures used for the assessment of tic severity varied considerably between studies. The scales used included the Yale Global Tic Severity Scale, the Tourette Syndrome Severity Scale, the Tourette Syndrome Global Scale, and the 5-minute videotape tic count. In general, a higher score for each of these outcome measures indicates greater tic severity (greater number of tics, more obvious tics, or more disability from tics).

Shapiro and Shapiro (Class II) compared pimozide with placebo in a crossover study of 20 patients. The mean dose of pimozide used was 6.9 mg per day, and there were two 6-week treatment phases. Mean tic severity, measured using the Tourette Syndrome Severity Scale, was 1.52 at the end of the pimozide phase, versus 4.42 at the end of the placebo phase (raw mean
difference, 2.90 [95% CI 1.63, 4.17, \( p < 0.0001 \)]. Mean videotape motor and vocal tic counts were also significantly lower after the pimozide phase, at 49.36 versus 102.42 in the placebo group (\( p = 0.0001 \)). More patients experienced akinesia (defined as sedation or lethargy), akathisia, or postural rigidity on pimozide. One person treated with pimozide reported weight gain as an adverse effect. One child developed an asymptomatic abnormal ECG (nonspecific T wave changes) during the pimozide phase, which resolved once the drug was stopped. There were no significant mean differences in heart rate or blood pressure between groups.

Sallee et al (Class II) compared pimozide, haloperidol, and placebo in a crossover study of 22 patients\(^\text{41}\). There were three 6-week treatment phases, with a 2-week washout period between each treatment phase. The mean pimozide dose was 3.4 mg, and the mean haloperidol dose was 3.5 mg. Tic severity, measured using the Tourette Syndrome Global Scale, was 17.1 after the pimozide phase, 20.7 after the haloperidol phase, and 26.8 after the placebo phase (\( p = 0.02 \) for pimozide versus placebo, nonsignificant for haloperidol versus placebo). Adverse events, measured using the Abnormal Involuntary Movements Scale, were not significantly different between treatment phases. The Extrapyramidal Symptoms Rating Scale showed that haloperidol had significantly more extrapyramidal side effects than pimozide (\( p < 0.05 \)) and placebo (\( p < 0.01 \)). Pimozide and haloperidol were indistinguishable from placebo in their effects on heart rate, rhythm, and waveform. Both pimozide and haloperidol were associated with a significant increase in prolactin levels compared with placebo (\( p < 0.01 \)).

Shapiro (Class II) compared pimozide, haloperidol, and placebo in a study of 57 patients using both a parallel-group and crossover study design\(^\text{44}\). All patients initially entered a 6-week parallel
study comparing pimozide, haloperidol, and placebo. After this parallel phase was completed, patients entered a 6-week crossover study of pimozide versus haloperidol. The mean pimozide dosage used in the study was 10.6 mg, while the mean haloperidol dosage was 4.5 mg. On completion of the parallel phase of the study, pimozide was seen to be significantly superior to placebo in controlling tics as measured by the Clinical Global Impressions Scale, 3.2 versus 1.9 ($p = 0.03$), but not as measured by the Tourette Syndrome Severity Scale, 2.5 versus 2.9.

Haloperidol was significantly superior to placebo on both measures. In the crossover phase of the study, haloperidol was superior to pimozide using the Tourette Syndrome Severity Scale, 1.4 versus 2.0 ($p = 0.011$), but with the Clinical Global Impressions Scale, there was no significant difference between pimozide and haloperidol, 3.4 versus 3.5. Benztropine for extrapyramidal symptoms was required by 6/20 patients treated with pimozide and 1/18 patients treated with haloperidol. There were no clinically meaningful ECG or cardiac adverse effects for patients treated with haloperidol or pimozide. The QTc interval was significantly prolonged by pimozide, but not by haloperidol or placebo. QTc changes were not associated with drug dosages or the age of patients.

Ross and Moldofsky (Class III) compared pimozide, haloperidol, and placebo in a crossover study of nine patients. This consisted of two 12-day treatment periods, with a 6-day placebo washout between periods. Pimozide and haloperidol dosages ranged from 10 to 12 mg. Tic severity, measured using the mean 5-minute videotape tic count, was not significantly different between pimozide and haloperidol, but both treatments were superior to placebo. Adverse events were not formally assessed in this study.
Gilbert (Class II) compared pimozide with risperidone in a crossover study of 13 patients. There were two 4-week treatment phases, with a 2-week placebo washout between treatments. The mean pimozide dosage used was 2.4 mg, while the mean risperidone dosage was 2.5 mg. Tic severity measured on the Yale Global Tic Severity Scale, was 34.2 at the end of the pimozide phase, versus 25.2 at the end of the risperidone phase ($p = 0.05$). The Extrapyramidal Symptoms Rating Scale showed that there was no difference between phases for adverse events nor for mean weight gain. There were no significant differences between treatments in changes in ECG parameters. In particular, increases in QTc were minimal and did not approach 450 ms.

Bruggeman (Class II) compared pimozide to risperidone in an 8-week parallel group study of 41 patients. The mean pimozide dose used was 2.9 mg compared with 3.8 mg of risperidone. The change in tic severity from baseline to endpoint was not significantly different between treatment groups, with the pimozide group improving by 2.3 points and the risperidone group improving by 2.4 points. There was no significant difference between treatment groups for adverse events, measured on the Extrapyramidal Symptoms Rating Scale, or mean weight gain. No clinically relevant differences in ECG parameters were detected between treatment groups.

In addition to these clinical trials, one study of the cardiovascular safety of pimozide found a significant increase in the QT and QTc interval from baseline at 6, 12, 18, and 24 months from treatment initiation. The mean QTc prolongation was 24.3 (SD 15.9) milliseconds.

Conclusion
For the treatment of tics in individuals with TS or other chronic tic disorders, pimozide is probably more effective than placebo in reducing tic severity (SMD, 0.66 [95% CI 0.06, 1.25]; moderate confidence; 3 Class II studies).

For the treatment of tics in individuals with TS or other chronic tic disorders, haloperidol is more effective than placebo in reducing tic severity (SMD, 0.59 [95% CI 0.11, 1.06]; high confidence; 2 Class II studies, confidence in evidence upgraded due to magnitude of effect).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of haloperidol compared with pimozide in reducing tic severity (SMD, 0.11 [95% CI -0.41, 0.62]; very low confidence, 2 Class II studies, confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of risperidone compared with pimozide in reducing tic severity (SMD, 0.24 [95% CI -0.51, 0.99]; very low confidence; 2 Class II studies, confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, pimozide probably has a higher risk of extrapyramidal symptoms than placebo (moderate confidence, 2 Class II studies).
For the treatment of tics in individuals with TS or other chronic tic disorders, pimozide possibly prolongs the QT interval compared to placebo and haloperidol (low confidence, 1 Class II study).

For the treatment of tics in individuals with TS or other chronic tic disorders, haloperidol possibly has a higher risk of extrapyramidal symptoms than pimozide and placebo (low confidence, one Class II study).

For the treatment of tics in individuals with TS or other chronic tic disorders, pimozide possibly increases prolactin compared with placebo (low confidence, 1 Class II study).

For the treatment of tics in individuals with TS or other chronic tic disorders, haloperidol possibly increases prolactin compared with placebo (low confidence, 1 Class II study).

Risperidone

Six randomized controlled trials have assessed risperidone for the treatment of tics; two compared risperidone with placebo \(^{47,48}\), two compared risperidone with pimozide \(^{42,43}\), one compared risperidone with clonidine \(^{49}\), and one compared risperidone with aripiprazole \(^{50}\). These six studies included a total of 235 patients, aged 6 to 62 years, with mean dosages of 0.7 to 3.8 mg/d. In all trials an improvement in tics with risperidone was reported. Trials comparing
risperidone with pimozide, risperidone with aripiprazole, and risperidone with clonidine found
similar benefits with each treatment.

Scahill et al (Class II) compared risperidone with placebo in a trial of 8 weeks in 34 children and
adults. Participants treated with risperidone experienced a 32% (8.4-point) decrease in their
YGTSS total tic scores, while the placebo group’s scores decreased by 7% ($p = 0.002$).
Subanalysis of study results including only pediatric participants revealed a significant
improvement in tic severity with risperidone compared with placebo. Weight gain was
significantly higher with risperidone (2.8 kg, compared with no change, $p < 0.001$).
Extrapyramidal symptoms were not reported or observed. Two children on risperidone
developed acute social phobia, and two adult males developed erectile dysfunction.

Dion et al (Class II) compared risperidone with placebo in a trial of 8 weeks in 48 participants.
Among risperidone-treated participants, 60.8% improved by at least 1 point on the 7-point
Global Severity Rating of the Tourette Syndrome Severity Scale, compared with 26.1% of
placebo-treated participants ($p = 0.04$). Participants taking risperidone had a significantly higher
total score for parkinsonism on the Extrapyramidal Symptom Rating Scale and significantly
higher rates of fatigue and somnolence. There was also a trend for a higher rate of depression in
the risperidone group (26.1%, compared with 4.4%; $p = 0.10$).

Gaffney et al (Class II) compared risperidone with clonidine in an 8-week trial in 21 children.
Children treated with risperidone and clonidine had significant improvement in the Yale Global
Tic Severity Scale Global Severity Scores from baseline to endpoint, but there was no significant
difference in the amount of improvement between groups. Sedation was the most common adverse effect reported in children treated with clonidine, and stiffness was the most common adverse effect reported in children treated with risperidone. There was no significant difference between groups in extrapyramidal symptoms based on the Simpson Angus Scale. Mean weight gain was higher in risperidone-treated children (2.1 kg) compared with clonidine-treated children (0.1 kg), but this difference was not statistically significant. There were no significant ECG changes in either group.

Ghanizadeh (Class III) compared risperidone with aripiprazole in an 8-week trial of 60 children. Significant baseline to endpoint improvement in the Yale Global Tic Severity Scale Total Tic Scores were seen in both groups, with no significant difference between groups in the amount of improvement. Both groups also had significant improvements in health-related quality of life, as measured by the Pediatric Quality of Life Inventory, with the risperidone group demonstrating significantly greater improvement in the social functioning subscale than the aripiprazole group. Increased appetite and drowsiness were the most common adverse effects in both groups.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, risperidone is more effective than placebo in reducing tic severity (SMD, 0.79 [95% CI 0.31-1.27], high confidence, 2 Class II studies; confidence in evidence upgraded due to magnitude of effect).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of risperidone compared with clonidine in reducing tic
For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of risperidone compared with pimozide in reducing tic severity (SMD, 0.24 [95% CI -0.51, 0.99]; very low confidence; 2 Class II studies; confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of risperidone compared with aripiprazole in reducing tic severity (SMD, 0.17 [95% CI -0.34, 0.68]; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, risperidone is probably associated with greater weight gain compared with placebo (moderate confidence, 2 Class II studies).

For the treatment of tics in individuals with TS or other chronic tic disorders, risperidone is possibly associated with higher parkinsonism scores on the Extrapyramidal Symptom Rating Scale Score compared with placebo (low confidence, 1 Class II study).
For the treatment of tics in individuals with TS or other chronic tic disorders, risperidone is possibly associated with a higher risk of requiring antiparkinsonian medication compared with placebo (low confidence, 1 Class II study).

For the treatment of tics in individuals with TS or other chronic tic disorders, risperidone is possibly associated with higher rates of fatigue and somnolence compared with placebo (low confidence, 1 Class II study).

Aripiprazole

There are three randomized controlled trials of aripiprazole for tics, two versus placebo and one versus risperidone. These three trials included a total of 254 youth 6 to 18 years of age, with dosages of aripiprazole ranging from 2 to 20 mg daily. All three trials reported benefit with aripiprazole, with superiority over placebo, and similar improvement compared with risperidone.

Yoo et al (Class II) compared aripiprazole with placebo in a 10-week trial in 61 children and adolescents. There was a significant difference in the Yale Global Tic Severity Scale Total Tic Score at endpoint between children treated with aripiprazole versus placebo, with a mean difference of 5.35 points (95% CI, 0.89-9.81), favoring aripiprazole. There was no difference between groups in extrapyramidal disorders or symptoms as measured with the Simpson Angus Scale, Abnormal Involuntary Movement Scale, or the Barnes Akathisia Scale. Weight gain, increase in body mass index, and increase in waist circumference were all significantly higher in
children treated with aripiprazole. There were no significant or clinically relevant changes in
blood pressure, heart rate, or ECG over the course of the study.

Sallee et al (Class II) compared aripiprazole with placebo in an 8-week trial of 133 children and
youth. Children were randomized to low-dose aripiprazole (5 mg if less than 50 kg, 10 mg if
more than 50 kg), high-dose aripiprazole (10 mg if less than 50 kg, 20 mg if more than 50 kg), or
placebo. Both low-dose and high-dose aripiprazole were associated with significant
improvement in the Yale Global Tic Severity Scale Total Tic Score, with a mean difference of
6.3 points (95% CI, 2.3-10.2) with low-dose treatment versus placebo, and a mean difference of
9.9 points (95% CI 5.9, 13.8) with high-dose treatment versus placebo. Sedation was the most
common adverse effect and occurred more frequently in children treated with aripiprazole.
Treatment discontinuation occurred in 22.5% of the high-dose group, compared with 4.5% in the
low-dose group, and 4.5% of the placebo group. Akathisia was reported in 3 of 45 children in the
high-dose group and was not reported in the low-dose or placebo groups.

One study of aripiprazole tolerability found that sedation was the most commonly reported
adverse effect of treatment.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, aripiprazole is
more effective than placebo in reducing tic severity (SMD, 0.64 [95% CI, 0.31-0.97], high
confidence, 2 Class II studies; confidence in evidence upgraded due to magnitude of effect).
For the treatment of tics in individuals with TS or other chronic tic disorders, aripiprazole is possibly associated with a greater weight gain, greater increase in body mass index, and greater increase in waist circumference compared with placebo (low confidence, 1 Class II study).

For the treatment of tics in individuals with TS or other chronic tic disorders, aripiprazole is possibly associated with higher rates of sedation and somnolence compared with placebo (low confidence, 1 Class II study).

**Ziprasidone**

Sallee et al (Class II) evaluated ziprasidone for the treatment of tics. Twenty-eight youths, aged 7 to 17 years, were randomized to ziprasidone or placebo for 8 weeks at a mean dose of 28.2 mg/d. Total tic severity on the Yale Global Tic Severity Scale Total Tic Score decreased from 27.7 to 16.8 with ziprasidone and from 24.6 to 22.9 with placebo ($p = 0.008$). The most common adverse event with ziprasidone was sedation, and one participant developed akathisia. Scores on the Simpson Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale were similar between groups, as was change in body weight over the study. Prolactin levels increased transiently to above the upper limit of normal in five children treated with ziprasidone, and one boy developed mild gynecomastia. There were no clinically significant changes in heart rate, blood pressure, or ECG parameters.

There is one study of ECG changes in 20 children with TS, obsessive-compulsive disorder, or pervasive development disorder. This study demonstrated statistically significant increases
from baseline to peak values in QTc intervals, with a mean prolongation of 28 (SD 26) milliseconds.

Conclusion

For people with tics, ziprasidone is probably more effective than placebo in reducing tic severity (SMD, 1.14 [95% CI, 0.32-1.97], moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

Metoclopramide

Nicolson (Class II) compared metoclopramide with placebo for tics in a study of 28 children aged 7 to 18 years. Children received metoclopramide (mean dose 32.9 mg/d) or placebo for 8 weeks. The study reported a 38.7% decrease in the Yale Global Tic Severity Scale Total Tic Score with metoclopramide, compared with a 12.6% decrease with placebo (p = 0.001). Weight gain was not different between groups, and there was no difference between groups in extrapyramidal symptoms. Three of 14 metoclopramide-treated participants reported increased sedation. Prolactin was significantly increased in the metoclopramide group compared with placebo. There were no statistically significant or clinically relevant changes in cardiac conduction parameters in either group.

Conclusion
For people with tics, metoclopramide is probably more effective than placebo in reducing tic severity (SMD, 1.14 [95% CI, 0.33-1.95], moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

For people with tics, metoclopramide is possibly associated with greater increases in prolactin levels compared with placebo (low confidence, 1 Class II study).

Tiapride

There is one Class I study comparing tiapride with placebo and the 5-Ling granule in 603 children and youth with TS. While the primary purpose of this trial was to evaluate the efficacy of a traditional Chinese medicine, the 5-Ling granule, for tics, it also provides placebo-controlled evidence for the efficacy of tiapride. Children in the study not only had a diagnosis of TS as per DSM-IV criteria, but they also had a condition fitting the excessive subtype in traditional Chinese medicine-based diagnosis. Patients with the excessive subtype disorder must have at least three of the following signs and symptoms: (a) hard or dry stools; (b) yellow or burning urination; (c) bloodshot eyes; (d) bitter taste with or without bad odor in the mouth; (e) fever sensation of palm or sole or both; (f) yellow or greasy coated tongue with red body of the tongue; and (g) wiry, slippery, or rapid pulse. Patients with a principal diagnosis of ADHD or OCD were excluded from the study. Children were randomized to receive tiapride (200 to 400 mg/d), placebo, or 5-Ling granule for 8 weeks. In comparison with placebo, tiapride was significantly more effective in decreasing tics on the Yale Global Tic Severity Scale Total Tic
Score (SMD, 0.62 [95% CI, 0.36-0.88]) and tic-related impairment (SMD, 0.69 [95% CI, 0.43-0.96]). The 5-Ling granule was also more effective than placebo in decreasing tics on the Yale Global Tic Severity Scale Total Tic Score (SMD, 0.55 [95% CI, 0.33-0.76]), and tic-related impairment (SMD, 0.58 [95% CI, 0.37-0.80]). Physical tiredness and sleep disturbances were significantly more frequent in those treated with tiapride.

Conclusions

For the treatment of tics in individuals with TS or other chronic tic disorders, tiapride is more effective than placebo in reducing tic severity (SMD, 0.62 [95% CI, 0.36-0.88], high confidence, 1 Class I study; confidence in evidence upgraded due to magnitude of effect).

For people with tics, tiapride is probably associated with higher rates of physical tiredness and sleep disturbances compared with placebo (moderate confidence, 1 Class I study).

Clonidine

There are six randomized controlled trials of clonidine for the treatment of tics, five including a placebo control and one comparing clonidine to levetiracetam. Three trials were performed exclusively in children, while the other three trials included both children and adults. The oral form of clonidine was used in five trials, and the clonidine adhesive patch in one trial. In total, 693 individuals participated in the six trials.
Du\textsuperscript{58} compared the clonidine adhesive patch with placebo in a 4-week trial (Class II) of 437 children with tic disorders. The dose of clonidine was 1.0, 1.5, or 2.0 mg per week, depending on body weight. At endpoint, children treated with the clonidine adhesive patch had significantly lower scores on the Yale Global Tic Severity Scale Total Tic Score than children treated with placebo, with an SMD of 0.26 (95% CI, 0.04-0.47). There were non-clinically significant decreases in blood pressure and heart rate associated with clonidine use. Abnormal ECGs occurred in two patients that returned to normal at the next visit and did not lead to withdrawal from the study.

Leckman\textsuperscript{59} compared clonidine with placebo in a 12-week trial (Class II) of 47 children and adults with tics. Clonidine treatment (4 to 5 micrograms per kilogram, up to a maximum of 0.25 mg per day) resulted in a significant improvement in motor tics on the Tourette Syndrome Global Scale, with a SMD of 0.63 (95% CI, 0.01, 1.27) versus placebo. There was no difference between clonidine and placebo in vocal tics. Sedation/fatigue, dry mouth, faintness/dizziness, and irritability were more common in those treated with clonidine than with placebo. Vital signs were unchanged over the course of the study.

Goetz\textsuperscript{60} compared clonidine with placebo in a 6-month trial (Class III) of 30 children and adults with TS. Participants were treated with clonidine 0.0075 or 0.015 mg/kg/d or placebo for 3 months then crossed over to the alternate treatment. No difference between clonidine and placebo was found in motor or vocal tic number or severity. Sedation and dry mouth were the most common adverse effects associated with clonidine use. There were no clinically significant changes in supine or standing blood pressure or pulse.
The Tourette Syndrome Study Group\textsuperscript{61} compared clonidine (up to 0.6 mg/d), methylphenidate (up to 60 mg/d), combined clonidine and methylphenidate, and placebo in a 16-week trial of 136 children meeting diagnostic criteria for both TS/chronic motor or vocal tic disorder and attention-deficit/hyperactivity disorder (Class I). Children in all three active treatment groups had a significant improvement in the Yale Global Tic Severity Scale Total Tic Score versus placebo, with an SMD of 0.72 (95\% CI, 0.22, 1.22) in those receiving clonidine, an SMD of 0.61 (95\% CI, 0.13, 1.10) in those receiving methylphenidate, and an SMD of 0.72 (95\% CI, 0.22, 1.22) in those receiving combined clonidine and methylphenidate. Sedation occurred in 48\% of children receiving clonidine, 14\% of children receiving methylphenidate, and 6\% of children receiving placebo.

Singer\textsuperscript{36} compared clonidine (0.05 mg four times a day), desipramine (25 mg four times a day), and placebo in an 18-week crossover study (Class III) of 34 children with TS and Attention Deficit/Hyperactivity Disorder. With use of a parent linear analogue scale to measure tic severity at the end of each treatment period, children treated with desipramine had significant improvement compared with placebo, while clonidine did not have a significant effect. Due to inconsistencies in the reported data, we were unable to calculate SMDs between clonidine, desipramine, and placebo. Adverse effects of treatment were not reported in the manuscript.

Hedderick\textsuperscript{62} compared clonidine (up to 0.4 mg/d) with levetiracetam (up to 2500 mg/d) in a 15-week crossover trial (Class II) of 10 children and adults with TS. Those treated with clonidine had a significant improvement in the Yale Global Tic Severity Scale Total Tic Score from
baseline to endpoint, with a change score of -3.4 points (95% CI, -5.55, -1.25), while those treated with levetiracetam did not (0.9 points [95% CI, -2.91, 4.71]). The difference between the two treatments favors clonidine, but the 95% CI for the SMD just crosses zero (SMD, 0.86 [95% CI, -0.03, 1.75]). The most common adverse effect associated with clonidine treatment was tiredness, occurring in 5 of 10 participants.

One study of tolerability of clonidine\textsuperscript{63} in adults found that sedation was the most commonly reported adverse effect associated with treatment.

\section*{Conclusion}

\textit{For the treatment of tics in individuals with TS or other chronic tic disorders, clonidine is more effective than placebo in reducing tic severity (SMD, 0.45 [95% CI, 0.13, 0.77]; high confidence, 1 Class I and 2 Class II studies; confidence in evidence upgraded due to magnitude of effect).}

\textit{For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD, clonidine plus methylphenidate is more effective than placebo in reducing tic severity (high confidence, 1 Class I study, confidence in evidence upgraded due to magnitude of effect).}

\textit{For the treatment of tics in individuals with TS or other chronic tic disorders, clonidine is possibly no more effective than levetiracetam in reducing tic severity (SMD, 0.86 [95% CI, -0.03, 1.75]; low confidence, 1 Class II study).}
For the treatment of tics in individuals with TS or other chronic tic disorders, clonidine is probably associated with higher rates of sedation compared with placebo (moderate confidence, 1 Class I and 1 Class II studies).

**Guanfacine**

There are two randomized controlled trials of guanfacine versus placebo for the treatment of tics in children and adolescents. In total, these two trials included 58 participants.

Scanhill compared guanfacine (up to 4 mg/d) with placebo in an 8-week trial of 34 children diagnosed with both a tic disorder and Attention Deficit Hyperactivity Disorder (Class II). A significant improvement in the Yale Global Tic Severity Scale Total Tic Score occurred from baseline to endpoint, with an SMD of 0.75 (95% CI, 0.03-1.47). There were no serious side effects. Sedation occurred in seven participants treated with guanfacine, leading one participant to withdraw from treatment. There was no difference in blood pressure or heart rate across treatment groups or time.

Cummings compared guanfacine (up to 2 mg/d) with placebo in a 4-week trial of 24 children with a chronic tic disorder (Class II). While a greater change from baseline to endpoint was noted in the Yale Global Tic Severity Scale Total Tic Score with guanfacine than with placebo, this difference was not statistically significant, with an SMD of 0.53 (95% CI, -0.29, 1.34). Fatigue/sleepiness prevented dose escalation in 2 of 12 children treated with guanfacine.
Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, guanfacine is more effective than placebo in reducing tic severity (SMD, 0.65 [95% CI, 0.11-1.19], high confidence, 2 Class II studies; confidence in evidence upgraded due to magnitude of effect).

Botulinum Neurotoxin Injections

There is one Class II randomized crossover trial of botulinum neurotoxin injection versus placebo for the treatment of simple motor tics in 20 adolescents and adults. Patients were treated with botulinum neurotoxin or placebo for up to two simple motor tics as determined by the patient, and crossed over to the other treatment after at least 12 weeks. The primary outcome was the number of treated tics per minute as observed on a 12-minute videotape protocol. The unweighted median proportional change in treated tics per minute was -39% during the botulinum neurotoxin phase and +5.8% during the placebo phase, with a median net effect of -37% (interquartile range, -77, -15%; \( p=0.0007 \)). Weakness subjectively or on examination occurred more commonly with botulinum neurotoxin than with placebo. Two patients experienced motor restlessness or developed new tics after treatment with botulinum neurotoxin.

Conclusion

For the treatment of specific simple motor tics in individuals with TS or other chronic tic disorders, botulinum neurotoxin injections are probably more effective than placebo in reducing...
tic severity (SMD, 1.27 [95% CI, 0.51, 2.03]; moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

**Topiramate**

There is one 12-week Class II randomized controlled trial of topiramate (50 to 100 mg/d) versus placebo in 29 children and adults with TS\(^6^7\). Topiramate was superior to placebo in the Yale Global Tic Severity Scale Total Tic Score at endpoint compared with placebo, with an SMD of 0.91 (95% CI, 0.11-1.71). Rates of drowsiness were similar in participants treated with topiramate and those treated with placebo (2 patients each). One individual treated with topiramate had a kidney stone. Those treated with topiramate had a mean decrease in weight of 2.1 kg, compared with a mean increase of 1.9 kg with placebo.

**Conclusion**

For the treatment of tics in individuals with TS or other chronic tic disorders, topiramate is probably more effective than placebo in reducing tic severity (moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

**Baclofen**

There is one Class II study comparing baclofen with placebo in a 10-week crossover trial of 10 children\(^6^8\). Children were randomized to 4 weeks of treatment with baclofen 60 mg per day, followed by a 2-week washout phase and 4 weeks of placebo, or the reverse treatment order.
While there was no difference in the Yale Global Tic Severity Scale Total Tic Score (SMD, 0.55 [95% CI, -0.39, 1.49]) or Global Score (SMD, 0.75 [95% CI, -0.13, 1.63]) between baclofen and placebo after 4 weeks, there was a significant difference in the Yale Global Tic Severity Scale Impairment Score (SMD, 0.84 [95% CI, 0.10, 1.58]). No major adverse effects were reported.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of baclofen compared with placebo in reducing tic severity (very low confidence, 1 Class II study).

Levetiracetam

There are two studies comparing levetiracetam with placebo for the treatment of tics. One Class III trial was only able to collect baseline and endpoint data on tic severity in less than half of trial participants, and the presentation of results does not allow meaningful interpretation of study findings.

One Class II trial compared levetiracetam with placebo in a crossover trial of 22 children with TS. Children were treated with up to 30 mg/kg/d of levetiracetam or placebo for 4 weeks, and crossed over to 4 weeks of the alternate treatment after a washout period. No significant differences were noted in any of the tic outcome measures with levetiracetam versus placebo, with an SMD of 0.22 (95% CI, -0.38, 0.82) on the Yale Global Tic Severity Scale Total Tic Score.
Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of levetiracetam compared with placebo in reducing tic severity (very low confidence, 1 Class II study).

N-Acetylcysteine

There is one Class II study comparing N-acetylcysteine with placebo as an add-on therapy in 31 children with TS or another chronic tic disorder71. Children were treated with up to 2400 mg/d of N-acetylcysteine or placebo for 12 weeks. There was no difference between treatment groups in tic severity as measured by the Yale Global Tic Severity Scale Total Tic Score (SMD, 0.45 [95% CI, -0.27-1.17]). There were no significant differences in adverse effect rates between groups.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of N-acetylcysteine compared with placebo in reducing tic severity (very low confidence, 1 Class II study)

Omega-3 Fatty Acids
There is one Class II study comparing omega-3 fatty acids with placebo for 20 weeks for the
treatment of tics in 33 children with TS\textsuperscript{72}. Children received up to 6000 mg per day of omega-3
fatty acids (combined EPA+DHA, ratio 2:1) or olive oil as a placebo. While there was a greater
decrease in both the Yale Global Tic Severity Scale Total Tic Score and Impairment Score from
baseline to endpoint with omega-3 fatty acids compared with placebo, the difference was not
statistically significant. The difference in the decrease from baseline to endpoint in the Yale
Global Tic Severity Scale Global Score (Total Tic Score + Impairment Score) was marginally
significant between groups, with an SMD of 0.69 (95% CI, 0-1.39). No significant treatment
differences were found in adverse events. The most frequently reported adverse events in the
omega-3 fatty acid group were headache, nausea/stomachache, and diarrhea/loose stool.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, omega-3 fatty
acids are possibly no more effective than placebo in reducing tic severity (low confidence, one
Class II study).

Ningdong Granule

There are two studies on the use of the ningdong granule, a traditional Chinese medicine, as a
treatment for tics. The list of active ingredients contained in the ningdong granule differed
between these two studies and therefore should not be considered the same treatment.
Zhao studied the use of the ningdong granule as a treatment for tics in a Class II study of 33 children and adolescents with TS for 8 weeks. The ningdong granule used in this study consisted of eight active ingredients—rhizome gastrodiae, codonopsis pilosula, dwarf lilyturf tuber, white peony alba, keel, oyster shell, pheretima asiatica, and liquorice—in a ratio of 2:3:2:4:5:5:2:2. A significantly greater improvement in the Yale Global Tic Severity Scale Total Tic Score was found with the ningdong granule compared with placebo, with an SMD of 0.97 (95% CI, 0.45-1.49). There were no serious adverse effects associated with treatment.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, the ningdong granule (as formulated by Zhao) is probably more effective than placebo in reducing tic severity (moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

Wang studied the use of the ningdong granule as a treatment for tics in a Class II study of 120 children and adolescents with TS. The ningdong granule was compared with placebo, haloperidol, and the combination of the ningdong granule and haloperidol for 8 weeks. The ningdong granule used in this study consisted of eight active ingredients: uncaria rhynchophylla jacks, gastrodia elate blume, ligusticum chuanxiong hort, buthus martensii kirsch, scolopendra subspinipes mutilans l. Koch, haliotis diversicolor reeve, dried human placenta, and glycyrrhiza uralensis fisch. The results section did not provide means, SDs, or effect sizes for outcome data, and thus SMDs could not be calculated. The text states that the Yale Global Tic Severity Scale motor, vocal, and total tic scores were significantly reduced ($p<0.05$) in the ningdong granule,
haloperidol, and ningdong granule-plus-haloperidol groups, but not the placebo group. Sedation, extrapyramidal symptoms, QT prolongation, and anxiety occurred more frequently in those treated with haloperidol.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of the ningdong granule (as formulated by Wang) compared with placebo in reducing tic severity (very low confidence, I Class II study).

5-Ling Granule

There is one Class I study comparing the 5-Ling granule with tiapride and placebo in 603 children and youth with TS. The 5-Ling Granule is a patented polyherbal product manufactured from 11 herbal products: radix paeoniea alba, rhizoma gastrodiae, fructus tribuli, ramulus uncariae cum uncis, lucid ganoderma, caulis polygoni multiflora, semen zizphi spinosae, fructus schisandracea chinensis, fructus gardeniae, rhizoma arisaematis cum bile, and radix scutellariae. Children in the study not only had a diagnosis of TS as per DSM-IV criteria, but they also had a condition fitting the excessive subtype in traditional Chinese medicine-based diagnosis. Patients with the excessive subtype disorder must have at least three of the following signs and symptoms: (a) hard or dry stools; (b) yellow or burning urination; (c) bloodshot eyes; (d) bitter taste with or without bad odor in the mouth; (e) fever sensation of palm or sole or both; (f) yellow or greasy-coated tongue with red body of the tongue; and (g) wiry, slippery, or rapid pulse. Patients with a principal diagnosis of ADHD or OCD were excluded from the study.
Children were randomized to receive 5-Ling granule, tiapride (200 to 400 mg/d), or placebo for 8 weeks. The 5-Ling granule was also more effective than placebo in decreasing tics on the Yale Global Tic Severity Scale Total Tic Score (SMD, 0.55 [95% CI, 0.33-0.76]), and tic-related impairment (SMD, 0.58 [95% CI, 0.37-0.80]).

Conclusions

For the treatment of tics in individuals with TS or other chronic tic disorders, 5-Ling Granule is more effective than placebo in reducing tic severity (SMD, 0.55 [95% CI, 0.33-0.76], high confidence, 1 Class I study; confidence in evidence upgraded due to magnitude of effect).

Tetrahydrocannabinol (THC)

There are two trials comparing delta-9 tetrahydrocannabinol (THC) with placebo in adults with TS, including a total of 36 participants. One study compared a single dose of THC (5-10 mg) to placebo in a Class II crossover study of 12 adults. Tic severity was rated over the period of a single day, and crossover to the alternate treatment occurred 4 weeks later. While there were no significant differences between treatments on the clinician-rated measure of tic severity, the Yale Global Tic Severity Scale (SMD, 0.58 [95% CI, -0.24,1.40]) a significant difference was found on the patient-rated measure of tic severity, the Tourette Syndrome Symptom List, with an SMD of 1.00 (95% CI, 0.02, 1.98). No serious adverse reactions were reported during the trial. Blood pressure and pulse did not change significantly. Transient adverse events with THC included dizziness and tiredness.
One Class III study compared THC (up to 10 mg/d) with placebo in a 6-week trial of 24 adults. A significant improvement in both the Tourette Syndrome Clinical Global Impression Scale and the Shapiro Tourette Syndrome Severity Scale ($p<0.05$) were reported with THC, but there was no significant difference between THC and placebo on the Yale Global Tic Severity Scale (SMD, 0.66 [95% CI, -0.25, 1.56]).

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, THC is probably more effective than placebo in reducing tic severity (SMD, 0.62 [95% CI, 0.01, 1.22]; moderate confidence, 1 Class II and 1 Class III study; confidence in evidence upgraded due to magnitude of effect).

Nicotine

There are two Class III studies evaluating the effect of nicotine on tics in children and adolescents with TS. One study evaluated a single transdermal 7-mg dose of nicotine for the acute effect on tics by measuring videotaped counts in 23 individuals. There was no difference between transdermal nicotine and placebo patches between baseline and posttreatment tic counts (SMD, 0.38 [95% CI, -0.14, 0.90]). The nicotine patch was associated with itching at the site of application, dizziness, headache, and vomiting.

The second study evaluated the effect of nicotine added to haloperidol treatment in 70 individuals with TS. All participants were first treated with haloperidol until they reached a
plateau in therapeutic effectiveness for at least 2 weeks. They were then randomized to add-on
transdermal nicotine 7 mg or placebo. Five days after randomization (days 5 to 19), the dose of
haloperidol was decreased by 50%. From days 19 to 33, the patches were discontinued, and the
participants remained on the 50% dose of haloperidol only. Compared with baseline, there was a
significantly greater decrease in the Yale Global Tic Severity Scale Global Severity with the
nicotine patch than placebo on day 5 (optimal haloperidol dose), with an SMD of 0.71 (95% CI,
0.17, 1.25), but not on day 19 (50% haloperidol dose). There was a significantly greater
decrease in the Global Severity on day 33 (50% haloperidol dose alone) in those who had
received the nicotine patch compared with those who had received placebo. Nausea and
vomiting were significantly more common in those receiving nicotine than placebo.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient
evidence to determine the efficacy of the nicotine patch compared with placebo in reducing tic
severity (very low confidence, 1 Class III study).

For the treatment of tics in individuals with TS or other chronic tic disorders, the nicotine patch
added to haloperidol is possibly more effective than placebo added to haloperidol in reducing tic
severity (low confidence, 1 Class III study; confidence in evidence upgraded due to magnitude of
effect).

Mecamylamine
There is one Class II study comparing mecamylamine 7.5 mg per day with placebo in 61 children and adolescents with TS for 8 weeks. Mecamylamine was not superior to placebo in measures of tic severity. There were inadequate data presented in the manuscript to allow the calculation of SMDs between mecamylamine and placebo.

**Conclusion**

*For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of the mecamylamine compared with placebo in reducing tic severity (very low confidence, 1 Class II study).*

**Flutamide**

There is one Class I study comparing flutamide with placebo in an 8-week crossover study of 13 adults with TS. Participants received 3 weeks of treatment with flutamide 250 mg three times a day or placebo, with a 2-week washout interval between treatments. The primary outcome was the effect on motor tic severity on the Yale Global Tic Severity Scale. Motor tics improved during flutamide treatment and during phase 2 of the study. According to the manuscript, the therapeutic effect on motor symptoms was statistically highly significant, but the percentage decrease in motor tic symptom severity (7%) was relatively small from the standpoint of clinical significance. Free and total testosterone and luteinizing hormone levels increased with treatment. The treatment was not recommended by the study authors due to the small effect size and the risk of fulminant hepatic failure associated with flutamide use. An SMD between
flutamide and placebo could not be calculated, as inadequate data were presented in the manuscript.

Conclusion

_For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of flutamide compared with placebo in reducing tic severity (very low confidence, 1 Class I study)._"}

**Glutamate modulators**

There is one Class I study comparing riluzole (up to 200 mg/d), D-serine (30 mg/kg/d) and placebo in an 8-week study of 24 children and adolescents with TS. There was no difference between riluzole and placebo (SMD, 0.17 [95% CI, -0.91, 1.25]) or D-serine and placebo (SMD, -0.04 [95% CI, -1.13, 1.05]) in tic severity as measured on the Yale Global Tic Severity Scale.

Conclusion

_For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of riluzole compared with placebo in reducing tic severity (very low confidence, 1 Class I study; confidence in evidence downgraded due to imprecision)._"}

_For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of D-serine compared with placebo in reducing tic severity (very low confidence, 1 Class I study; confidence in evidence downgraded due to imprecision)._"}
**Ondansetron**

There is one Class III study comparing ondansetron with placebo in 30 people aged 12 years and older with TS\textsuperscript{78}. Participants were randomized to ondansetron (up to 24 mg/d) or placebo for 3 weeks. The difference between ondansetron and placebo in the Yale Global Tic Severity Scale Total Tic Score was not statistically significant, with an SMD of 0.53 (95% CI, -0.20, 1.25).

**Conclusion**

*For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of ondansetron compared with placebo in reducing tic severity (very low confidence, 1 Class III study).*

**Pramipexole**

There is one Class II study comparing pramipexole (up to 0.25 mg twice daily) with placebo in a 6-week study of 63 children and adolescents with TS\textsuperscript{79}. There was no difference between pramipexole and placebo in measures of tic severity, including the primary outcome, the Yale Global Tic Severity Scale Total Tic Score, with an SMD of 0.0 (95% CI, -0.53, 0.53).

**Conclusion**
For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of pramipexole compared with placebo in reducing tic severity (very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).

**Intravenous Immunoglobulins**

There is one Class II study comparing intravenous immunoglobulin infusion with placebo in a 14-week study of 30 adolescents and adults meeting DSM-IV criteria for a tic disorder\(^{80}\). None of the included patients met PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) criteria. Intravenous immunoglobulin 1 g/kg/d or placebo was infused over 2 consecutive days, and patients followed every 2 to 4 weeks for 14 weeks. There was no difference in tic severity between intravenous immunoglobulin and placebo as measured by the Yale Global Tic Severity Scale Total Tic Score at any time point, with an SMD at week 14 of 0.50 (95% CI, -0.24, 1.24).

**Conclusion**

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of intravenous immunoglobulin compared with placebo in reducing tic severity.

**Methylphenidate and Dextroamphetamine**

There are three studies (1 Class I\(^{61}\), 2 Class III \(^{37,81}\)) evaluating the effect of psychostimulants on tics in children with TS and comorbid ADHD. The purpose of these studies was to establish if
treatment of ADHD symptoms with psychostimulants worsened tics in children with both
disorders. The results of the Class I study are presented in the section on clonidine, as this study
included a treatment arm with clonidine.61

One Class III study compared 3 doses of methylphenidate with placebo in a crossover study of
71 children with TS and ADHD. Children received 2 weeks of treatment with methylphenidate
at 0.1 mg/kg/d, 0.3 mg/kg, 0.5 mg/kg/d, and placebo. On the primary outcome for tic severity,
the Yale Global Tic Severity Scale Global Severity score, there was no difference between each
dose of methylphenidate and placebo. On the Teacher Global Tic Rating Scale, Total Tic
Severity, treatment with methylphenidate 0.5 mg/kg/d was superior to placebo for the treatment
of tics, with an SMD of 0.41 (95% CI, 0.07-0.74).

The other Class III study compared three doses of methylphenidate, three doses of
dextroamphetamine, and placebo in a 9-week crossover study of 22 boys with TS and ADHD.37
The children received low, medium, and high doses of each drug for 1 week each. When ratings
on the lowest doses of methylphenidate, dextroamphetamine, and placebo were compared, there
was no significant effect of either stimulant on tic severity ratings. Similarly, when the data on
medium stimulant doses were compared, the overall effect of drug on tics was not significant.
When the data on high doses of stimulants were compared, the overall effect of drug on tics was
significant. Dexamphetamine resulted in significantly greater tic severity than placebo, while tic
severity on methylphenidate was indistinguishable from placebo.

Conclusion
For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD, methylphenidate is more effective than placebo in reducing tic severity (SMD, 0.61 [95% CI, 0.13, 1.10]; high confidence, 1 Class I study; confidence in evidence upgraded due to magnitude of effect).

Deprenyl

There is one Class II crossover study comparing deprenyl with placebo in 24 children with TS and ADHD. Children were treated with either deprenyl 5 mg twice daily or placebo for 8 weeks and then crossed over to the alternate treatment for 8 weeks after a 6-week washout period. The mean improvement in the Yale Global Tic Severity Scale Total Score with deprenyl relative to placebo was 9.3 points (95% CI, -0.4 to 19.0; p=0.06).

Conclusion

For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD, deprenyl is possibly no more effective than placebo in reducing tic severity (SMD, 0.47 [95% CI, -0.05, 0.99]; low confidence, 1 Class II study).

Atomoxetine

There is one Class II study comparing atomoxetine with placebo for the treatment of ADHD symptoms in children and youth with TS and ADHD. This study was carried out to test the hypothesis that atomoxetine does not significantly worsen tics relative to placebo in children.
with TS and comorbid ADHD. One hundred and forty-eight children were treated for 18 weeks
with atomoxetine or placebo. Both atomoxetine- and placebo-treated children showed
improvements in tic severity on the Yale Global Tic Severity Scale Total Tic Score, with
atomoxetine almost reaching statistical significance for a greater reduction in tics compared with
placebo (SMD, 0.32 [95% CI, -0.01, 0.65]). The lower bound of the one-sided 95% confidence
interval for the difference in mean change between the two treatment groups was 0.27, which,
being greater than the prespecified lower limit of -3.7, indicated noninferiority of atomoxetine
relative to placebo for the effect on tics. Atomoxetine use was associated with nausea, decreased
appetite, weight loss, and increased heart rate.

Conclusion

For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD,
atomoxetine does not worsen tics relative to placebo (low confidence, 1 Class II study).

For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD,
atomoxetine is possibly associated with a decrease in body weight compared with placebo (low
confidence, 1 Class II study).

For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD,
atomoxetine is possibly associated with a greater increase in heart rate compared with placebo
(low confidence, 1 Class II study).

Desipramine
There is one Class II \(^{36}\) and one Class III study \(^{36}\) evaluating desipramine for the treatment of tics and ADHD symptoms in children and adolescents with both disorders. The Class III study is described in the clonidine section, as this trial included a clonidine arm\(^{36}\).

The Class II study compared desipramine (up to 3.5 mg/kg/d) to placebo in a 6-week trial of 41 children and adolescents with ADHD and a chronic tic disorder \(^{34}\). Desipramine treatment resulted in a significant improvement in the Yale Global Tic Severity Scale Total Score, with an SMD relative to placebo of 1.13 (95% CI, 0.47-1.79). The use of desipramine was associated with significantly greater rates of decreased appetite, increased diastolic blood pressure, and increased heart rate.

Desipramine is now rarely used in children after several case reports of sudden death associated with the use of this medication in children\(^{85}\).

**Conclusion**

*For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD, desipramine is probably more effective than placebo in reducing tic severity (moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).*

*For individuals with TS or other chronic tic disorders and a comorbid diagnosis of ADHD, desipramine is possibly associated with an increased diastolic blood pressure and increased heart rate compared with placebo (low confidence, 1 Class II study).*
Behavioral Therapy

Comprehensive behavioral intervention for tics/Habit Reversal Therapy

The comprehensive behavioral intervention for tics (CBIT) is a behavioral approach to the management of tics, with its primary component consisting of habit reversal training. Habit reversal training involves the development of tic awareness, which is self-monitoring of tics and the premonitory urges associated with them, and competing response training, which is engaging in a voluntary behavior that is physically incompatible with the tic when the urge to perform the tic occurs. CBIT also includes relaxation training and the identification of situational factors influencing tic severity, with the development of behavioral strategies to reduce the influence of these factors.

Piacentini performed a Class I study on CBIT, compared with supportive therapy, for the treatment of tics in 126 youth with tic disorders. Comorbid conditions within this sample were considerable, and 36.5% of the sample were already on a stable dose of medication for their tics. Participants were randomized to 8 sessions of therapy during 10 weeks. Total tic severity on the Yale Global Tic Severity Scale Total Tic Score decreased from 24.7 points at baseline to 17.1 points at week 10 with CBIT, in comparison with a decrease from 24.6 points to 21.1 points with supportive therapy (SMD, 0.51 [95% CI, 0.15-0.86]). One participant receiving CBIT and four participants receiving supportive therapy reported worsening of tics. No serious adverse events related to the study were encountered. Notably, 86.9% of participants receiving CBIT remained treatment responders even at 6 months of follow-up.
Wilhelm performed a Class I study on CBIT versus supportive therapy and psychoeducation for the treatment of tics in 122 individuals aged 16 and older. Participants were randomized to eight sessions of therapy over 10 weeks. CBIT was superior to supportive therapy and psychoeducation for the treatment of tics, as measured on the Yale Global Tic Severity Scale Total Tic Score, with an SMD of 0.62 (95% CI, 0.25-0.98). Four participants receiving CBIT and four participants receiving supportive therapy reported worsening of tics over the course of the study.

Deckersbach conducted a Class III randomized, unblinded study of habit reversal therapy, compared with supportive psychotherapy, in 30 adults with TS. Participants received 14 sessions of therapy during a 5-month period. Habit reversal therapy decreased Yale Global Tic Severity Scale Total Tic Scores from 29.3 points at baseline to 18.3 points post treatment, in comparison with supportive psychotherapy, which decreased scores from 27.7 points to 26.6 points (SMD, 1.41 [95% CI, 0.62-2.22]). Ten of 15 participants receiving habit reversal training were classified as much improved or very much improved at the end of treatment, in contrast to 2 of 15 participants in the supportive psychotherapy group (p = 0.008). Side effects of treatment were not reported.

Wilhelm conducted a Class III randomized unblinded study of habit reversal therapy compared with supportive psychotherapy in 32 adults with TS. Participants received 14 sessions of therapy over a 5-month period. Habit reversal therapy was more effective than supportive psychotherapy in improving tics, with an SMD of 0.85 (95% CI, 0.09-1.61) on the Yale Global
Tic Severity Scale Total Tic Score, and an SMD of 1.18 (95% CI, 0.38-1.97) on the Impairment Score. Side effects of treatment were not reported.

There is one Class II study comparing exposure and response prevention (ERP) to habit reversal therapy in 43 children and adults with TS\textsuperscript{90}. Individuals randomized to ERP received 12 weekly 2-hour sessions, while those randomized to habit reversal therapy received 10 weekly 1-hour sessions with a psychologist trained in the use of these techniques. Both treatment groups had significant improvement in tic severity from baseline to endpoint, as measured by the Yale Global Tic Severity Scale Total Tic Score, with no difference between treatments in efficacy (SMD, 0.25 [95% CI, -0.40, 0.90]). Adverse effects of therapy were not reported.

There is one Class II study comparing psychoeducation with habit reversal training in 33 children with TS\textsuperscript{91}. Children received eight sessions of habit reversal therapy or psychoeducation over a 2-month period. There was no difference between treatments in the two primary outcome measures, the Yale Global Tic Severity Scale Motor Tic Severity (SMD, 0.55 [95% CI, -0.16, 1.27]) or Vocal Tic Severity (SMD, -0.26 [95% CI, -0.97, 0.44]). There was a significant improvement over time in motor tic severity when the whole sample was analyzed together, suggesting that both treatments may have been beneficial in decreasing motor tics. Adverse effects of therapy were not reported.

There is one Class II study comparing CBIT using a voiceover Internet protocol (VoIP) to wait list controls for the treatment of 20 children and youth with TS or another chronic tic disorder\textsuperscript{92}. Children randomized to CBIT VoIP received eight sessions of CBIT delivered remotely to their
home over the Internet over 10 weeks. While children receiving CBIT VoIP had a significant
decrease in the Yale Global Tic Severity Scale Total Tic Score from baseline to endpoint, there
was no significant difference between the CBIT VoIP and wait list control groups at endpoint
(SMD, 0.24 [95% CI, -0.65, 1.14]). Adverse effects of therapy were not reported.

There is one Class II study comparing CBIT delivered face to face with CBIT delivered through
telehealth in 20 children with TS. Children were randomized to receive eight sessions of CBIT
over 10 weeks either in person or by video conference. Both groups had significant
improvement in tic severity, as measured with the Yale Global Tic Severity Scale Total Tic
Score from baseline to endpoint, but there was no difference between the methods of treatment
administration at endpoint on tic severity (SMD, 0.24 [95% CI, -0.70, 1.17]). Adverse effects of
treatment were not reported.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, CBIT is more
effective than supportive psychotherapy in reducing tic severity (SMD, 0.56 [95% CI, 0.31-0.82],
high confidence, 2 Class I studies).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient
evidence to determine the efficacy of habit reversal therapy compared with exposure and
response prevention in reducing tic severity (very low confidence, 1 class II study, confidence in
evidence downgraded due to imprecision).
For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of habit reversal therapy compared to educational group treatments in reducing tic severity (very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of face-to-face habit reversal therapy compared with habit reversal therapy through video conferencing in reducing tic severity (very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of habit reversal therapy by video conferencing compared with wait list control in reducing tic severity (very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

**Relaxation Therapy**

There is one Class III study comparing relaxation therapy with minimal therapy in 23 children and adolescents with TS. Relaxation therapy consisted of awareness training, diaphragmatic breathing, behavioral relaxation training, applied relaxation techniques, and electromyographic feedback, and minimal therapy comprised awareness training and quiet time training, in which participants listened quietly to music or environmental sounds. All participants received six weekly 1-hour training sessions. No difference between treatments was noted on any of the tic
rating scales used, including the Yale Global Tic Severity Scale, Hopkins Motor and Vocal Tic Scale, Tourette Syndrome Severity Scale, Parent Linear Analogue Scale, and the Goetz Videotape scale. No raw data were provided, so an SMD between relaxation therapy and minimal therapy could not be calculated. Adverse effects of treatment were not discussed.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of relaxation therapy compared with minimal therapy in reducing tic severity (very low confidence, 1 Class III study).

Biofeedback

There is one Class III trial of active versus sham biofeedback in 21 adults with TS. In this 4-week treatment trial, individuals attended 30-minute biofeedback sessions 3 times a week. For the primary endpoint, the change in the 10-minute tic count from baseline to endpoint, there was no difference between active biofeedback and sham treatment. Both active and sham groups demonstrated a significant decrease in tics from baseline to endpoint. An SMD between biofeedback and sham could not be calculated because of inadequate data provided in the manuscript. Adverse effects of treatment were not discussed.

Conclusion
For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of biofeedback compared with sham in reducing tic severity (very low confidence, 1 Class III study).

Deep Brain Stimulation

Globus Pallidus

There is one Class II study of deep brain stimulation (DBS) of the globus pallidus in 15 adults with severe, medically refractory TS. In this crossover study, adults were randomized to stimulation on or off for 3 months, then crossed over to the opposite condition. Compared with off-stimulation, stimulation resulted in a significant decrease in Yale Global Tic Severity Scale Global Score, with a raw mean difference of -12.4 points (95% CI, -24.43, -0.37), and an SMD of 0.79 (95% CI, 0.0-1.61). Open-label stimulation at last follow-up examination of participants compared with baseline revealed a greater improvement over time, with a raw mean difference of -36.3 points. Adverse effects of treatment included internal infection from the DBS hardware in 2 patients, which necessitated the removal of leads, extension cables, and implantable pulse generators and administration of antibiotics to these patients. One patient developed worsened tics and hypomania during the on-stimulation period, requiring hospital admission.
There is one Class III study of 3 adults with severe and medically refractory TS, each treated with 4 modalities: DBS of the globus pallidus, DBS of the thalamus, DBS of the globus pallidus and thalamus, and sham stimulation. This was a crossover study, in which participants were randomized to each stimulation condition for 2 months. The primary outcome was the Yale Global Tic Severity Scale Total Tic Score; however, results are only presented graphically and individually for each of the three participants. No means or SDs were provided, so we are unable to calculate SMDs. The best response was seen in all three participants with pallidal stimulation. Adverse effects seen with thalamic stimulation included paresthesia near the mouth or arms and decreased libido. Adverse effects seen with pallidal stimulation included lethargy, nausea, vertigo, and anxiety.

Conclusion

For adult people with severe, medically refractory TS, deep brain stimulation ON of the globus pallidus is probably more effective than deep brain stimulation OFF of the globus pallidus in reducing tic severity (moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

Thalamus

There is one Class III study of DBS of the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus crosspoint in the thalamus in 6 adults with severe refractory TS. Adults were randomized to stimulation-on first or stimulation-off first for 3 months and then crossed over to the opposite condition. Compared with off stimulation, stimulation produced a
significant decrease in the Yale Global Tic Severity Scale Total Tic Score, with a raw mean difference of -15.5 points (95% CI, -26.62, -4.38) and an SMD of 1.58 (95% CI, -0.12, 3.28). Further benefits were noted with open-label stimulation at one year compared with baseline, with a raw mean difference of -20.8 points (95% CI, -30.0, -11.58). Adverse effects included a small parenchymal hemorrhage in one patient, resulting in vertical gaze palsy, with persistent subjective slowing of vertical fixation, and pursuit on stimulation led the patient to switch off the stimulator after the study. One patient developed an infection requiring 6 weeks of intravenous antibiotics. One patient developed motor and psychiatric symptoms, including lethargy, binge eating, dysarthria, gait disturbance, and falls; CT brain imaging showed cerebral atrophy. All patients reported subjective oculomotor abnormalities and substantial restriction in activities of daily living due to lack of energy.

There is one Class III study of DBS of the centromedian-parafascicular complex in five adults with TS who were medically refractory to treatment. Participants were randomized to 7 days of treatment with each of four different conditions. The stimulators were independently enabled on or disabled off on the right and left sides to give the combination of each of the following: (1) off-off, (2) off-on, (3) on-off, (4) on-on. The Yale Global Tic Severity Scale Total Tic Score was 40.6 SD 5.2 in the off-off state, compared with 34.8 SD 6.4 in the on-on state (SMD, 0.99 [95% CI, -0.28, 2.26]).

There is one Class III study of DBS of the centromedian thalamic region in five adults with medically refractory and severely disabling TS. Participants were randomized to receive immediate DBS activation at postoperative day 30 or delayed-start DBS activation at day 60.
There was no significant difference in tic severity between participants randomized to immediate versus delayed-start DBS activation (data not provided in publication). The authors reported a significant decrease in Yale Global Tic Severity Scale Global Scores at 6 months (open-label stimulation) versus baseline measurement (91.6, SD 8.8, vs 73.8, SD 11.5).

In addition to these trials, there is one cohort study of 48 patients undergoing DBS for TS at a single center, in which adverse effects of treatment were described. Eleven of the 48 patients had to have the device removed, either for inflammatory complications (n=8) or poor compliance of the patients or caregivers or both (n=3).

**Conclusion**

*For adults with severe, medically refractory TS, there is insufficient evidence to determine the efficacy of DBS ON of the thalamus compared with DBS OFF of the thalamus in reducing tic severity (very low confidence, 1 Class III study).*

*For adults with severe, medically refractory TS, there is insufficient evidence to determine the efficacy of DBS ON of the centromedian-parafascicular complex compared with DBS OFF of the centromedian-parafascicular complex (very low confidence, 1 Class III study).*

**Transcranial Magnetic Stimulation**

There is one Class II study of 30-Hz continuous theta burst stimulation (cTBS) at 90% resting motor threshold over the supplementary motor area for the treatment of tics in nine children and...
adults with TS\textsuperscript{100}. Participants received eight trains of active or sham stimulation over 2 consecutive days, with the effect on tic severity measured 1 week after treatment. The Yale Global Tic Severity Scale Total Tic Score was not significantly different between active and sham stimulation, with an SMD of -0.15 (95% CI, -1.28, 0.99). Three participants complained of mild adverse effects (abdominal pain, headache, dry eyes) which resolved without medical intervention.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of cTBS of the supplementary motor area compared with sham stimulation in reducing tic severity (very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).

There is one Class II study of repetitive TMS (rTMS) in 20 adults with severe TS\textsuperscript{101}. Participants received active vs sham 1-Hz rTMS at 110% motor threshold over the SMA once daily for 30 minutes, 5 days per week, for 3 weeks. The Yale Global Tic Severity Scale Total Tic Score was not significantly different between active and sham stimulation, with an SMD of 0.19 (95% CI, -0.69, 1.07). Headache, neck pain, and muscle sprain were the only severe side effects reported during active treatment.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of rTMS of the supplementary motor area compared with
sham stimulation in reducing tic severity (very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).

There is one Class III crossover study of rTMS at 110% motor threshold over the left motor cortex (twice) or left prefrontal cortex (twice) using active TMS (either 1 Hz or 15 Hz) or sham TMS (once) for the treatment of 8 children and adults with TS31. Each treatment paradigm was received for one day, with effects on tic severity assessed the same day. There were no statistically significant specific effects of rTMS by site or frequency. As data were presented in the publication in graphical form, SMDs between rTMS and placebo could not be calculated.

The main adverse effect was headache, reported after 3 of 40 rTMS sessions.

Conclusion

For the treatment of tics in individuals with TS or other chronic tic disorders, there is insufficient evidence to determine the efficacy of rTMS of the left motor or prefrontal cortex compared with sham stimulation in reducing tic severity (very low confidence, 1 Class III study).

Putting the Evidence into a Clinical Context

The systematic review synthesizes the available evidence supporting the efficacy and harms demonstrated through randomized controlled trials of medical, behavioral, and neurostimulation treatments for tics. The treatment of tics in individuals with TS and other chronic tic disorders must be individualized and based on collaborative decisions between patients, caregivers, and clinicians. Many children and adults with tic disorders have psychiatric comorbidities, and clinicians must endeavor to establish treatment priorities with their patients. While neurologists
are often consulted to address the motor and phonic manifestations of the disorder, the
identification and management of comorbid disorders is of prime importance for individuals with
tic disorders and must be factored into decision making for the management of tics.

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. Working in teams, 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
three 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 helping verb must. These
recommendations are rare, as 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 helping verb should. Such
recommendations tend to be more common, as the requirements are less stringent but still based
on the evidence and benefit-risk profile. Finally, Level C corresponds to the helping verb *may*.

These recommendations represent the lowest allowable recommendation level the AAN considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Other, 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 assigned levels of obligation (A, B, C, U, or R) to each recommendation, using a modified Delphi process which synthesizes all the factors listed above. The opinions of the guideline panel with regard to the importance of each factor is elicited through an online questionnaire, with statistical analysis of responses. The panel voted anonymously and independently on each recommendation in three rounds of voting. Voting was done by all panelists online. Using precisely defined rules for consensus for each recommendation, the panel either achieved consensus for the recommendation, 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. Considerations for future research and suggestions for future studies were also developed during the guideline development process.

**Counseling Recommendation: Natural history of TS**
Providing information to families about the natural history of a disorder can help inform treatment decisions [PRIN]. Tics begin in early childhood and demonstrate a waxing and waning course over time. Peak tic severity usually occurs between the ages of 10 and 12 years, with many children experiencing an improvement in tics in adolescence [RELA]\textsuperscript{102}. A recent longitudinal study demonstrated that tic severity declined yearly during adolescence, with 18% of adolescents older than age 16 years having no tics and 60% having minimal or mild tics 6 years after initial examination [RELA]\textsuperscript{103}. There is no evidence to suggest that treatment is more effective the earlier it is started. As tics may improve with time, watchful waiting is an acceptable treatment approach in individuals who do not experience any functional impairment from their tics [INFER]. However, even in such cases, Comprehensive Behavioural Intervention for Tics (CBIT) could be employed if the patient is motivated to attempt treatment [INFER]. As a result of partial or complete spontaneous remission during the natural course of the disease, medication prescribed for treatment of 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 their caregivers that watchful waiting is an acceptable treatment approach in individuals 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

Tourette syndrome is a common disorder, affecting approximately 1% of schoolchildren [RELA]⁵. 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]¹⁰⁴. Improving the attitudes of peers’ 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 or Tourette Canada.

Assessment and Treatment of ADHD in children with tics

Attention-deficit/hyperactivity disorder (ADHD) is a common diagnosis in people with TS, with comorbidity rates in the range of 30% to 50% depending on the population studied [RELA]²²,¹⁰⁵. Several randomized controlled trials have specifically addressed the medical treatment of both ADHD and tics in children diagnosed 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 more
effective than placebo in reducing 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]^{106}. While ADHD symptoms may improve in adolescence [RELA]^{103},
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 impact 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 OCD in children with tics**

Obsessive compulsive behaviours are common in people with TS, with a comorbid diagnosis of
obsessive-compulsive disorder (OCD) made in 10% to 50% of people with tics depending on the
population studied [RELA]^{22, 105}. Subanalyses of randomized controlled 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 behavioural
therapy for OCD symptoms [RELA]^{107, 108}. For this reason, cognitive behavioural therapy 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

Population-based and clinic-based studies have shown that people with TS are at high risk for other psychiatric comorbidities, including anxiety disorders, oppositional defiant disorder, and mood disorders [RELA]22, 105. Comorbid mood disorders appear more prevalent in adolescents and adults than children and in those with greater tic severity [RELA]22, 109. A matched case-cohort study using a national registry has shown that there is an increased risk of dying by suicide and attempting suicide in people with TS compared with control participants, which persisted after controlling for the presence of psychiatric comorbidity. Persistence of tics beyond young adulthood, previous suicide attempts, and comorbid personality disorders increased the risk of death by suicide [RELA]110.

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 necessary resources if present (Level A).

Assessment of Tic Severity and Treatment Expectations

There are several clinician-administered rating scales available for measuring tic severity, with the Yale Global Tic Severity Scale the most extensively deployed and validated [RELA]111.
Evaluation of the impact of treatment on tic severity in clinical 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 tic severity [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 abolish tics entirely (Level A).

### Psychosocial Treatments

**Rationale.** Comprehensive Behavioral Intervention for Tics (CBIT) is more effective than psychoeducation plus supportive therapy in reducing tic severity in children and adults [EVID]. CBIT is a manualized treatment program consisting of habit reversal training, relaxation training, and a functional intervention to address situations that sustain or worsen tics [RELA]112. The child and adult CBIT trials demonstrated the efficacy of an eight-session protocol, though cases complicated by poor tic awareness, treatment motivation, more severe tics, or significant 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 under age 9 years, though there is little evidence available to determine efficacy below this age [RELA]113. There is some evidence that the efficacy of CBIT for reducing tics is greater for patients not on concurrent anti-tic medication than for those on anti-tic medication114 [RELA]. There is insufficient evidence to
determine the relative efficacy of habit reversal therapy (HRT) compared with exposure and response prevention (ERP), or educational group treatment in reducing tic severity [EVID].

There is insufficient evidence to determine the relative efficacy of habit reversal training by video conferencing compared with either face-to-face habit reversal therapy 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 children and adults treated with CBIT compared with those treated with psychoeducation plus supportive therapy [EVID]. In addition, comparing the effect size of CBIT with those of certain medications, it appears the efficacy of the two treatment options may be similar [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 reducing tics [INFER]. Given the effort required from patients or their families, along with its benign safety profile, CBIT is an acceptable intervention for children and adults with tics that lead to psychosocial or physical impairment or both and who are motivated to participate in the 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, secondary forms of psychosocial interventions for tics may be acceptable, such as exposure and response prevention (Level C).

**Alpha agonists for the treatment of tics**

Clonidine and guanfacine are more effective than placebo in reducing tics, 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]. There is no evidence regarding the relative efficacy of clonidine and guanfacine for tics [EVID]. Relative to placebo, clonidine is probably associated with higher rates of sedation [EVID]. A systematic review of alpha-2 adrenergic agonists for ADHD in youth demonstrated hypotension, bradycardia, and sedation with both agents, and QTc prolongation with guanfacine extended release [RELA]¹¹⁵. Abrupt withdrawal of alpha-2 adrenergic agonists may cause rebound hypertension [RELA]¹¹⁶.

**Recommendation 8a**: Physicians should counsel individuals with tics and comorbid ADHD that alpha-2 adrenergic agonists may provide therapeutic benefit for both conditions (Level B).

**Recommendation 8b**: Physicians should prescribe alpha-2 adrenergic agonists for the treatment of people with 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 all 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 QTc-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).

### Antipsychotic Treatment for Tics

**Rationale:** Haloperidol, risperidone, aripiprazole, and tiapride are more effective than placebo in reducing tics [EVID], and pimozide, ziprasidone, and metoclopramide are probably more effective than placebo in reducing tics [EVID]. There is insufficient evidence to determine the relative efficacy of these dopamine receptor blocking 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 randomized controlled trials and cohort studies demonstrate a higher risk of drug-induced movement disorders, weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation antipsychotics in both children and adults across psychiatric and neurologic conditions [RELA]^{117,118}. The chronic use of metoclopramide is associated with the development of tardive dyskinesia, resulting in a black box warning from the US Food and Drug Administration^{119}. The relative propensity for these adverse effects varies by agent. These adverse effects are often dose dependent [RELA]. Physicians have a duty to
monitor the effectiveness and safety of prescribed medications [PRIN]. Abrupt discontinuation of antipsychotic medications can cause withdrawal dyskinesias\textsuperscript{120,121} [RELA].

**Recommendation 9a**: Physicians may prescribe antipsychotic medications for the treatment of people with tics when the benefits of treatment outweigh the risks (Level C).

**Recommendation 9b**: Physicians must counsel patients on the relative propensity of antipsychotic medications for extrapyramidal, hormonal, and metabolic adverse effects to inform decision making on which antipsychotic should be prescribed (Level A).

**Recommendation 9c**: Physicians prescribing antipsychotic medications for tics must prescribe the lowest effective dose of medication to decrease the risk of adverse effects (Level A).

**Recommendation 9d**: Physicians prescribing antipsychotic medications 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 antipsychotic medications for tics must perform electrocardiograms and measure the QT\textsubscript{c} interval before and after starting antipsychotics, especially when prescribing 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 antipsychotic medications for tics, physicians should gradually taper medications over weeks to months to avoid withdrawal dyskinesias (Level B).

**Botulinum neurotoxin injections for tics**

Botulinum neurotoxin injections with onabotulinumtoxinA are probably more effective than placebo in reducing tics in adolescents and adults [EVID]. Premonitory urges may also be
improved by botulinum neurotoxin injections in a proportion of patients [RELA]^{122}. There is no
evidence on the efficacy of other botulinum neurotoxins for tics [EVID]. Relative to placebo,
onabotulinumtoxinA is associated with higher rates of weakness [EVID]. Hypophonia is a
common side effect of botulinum neurotoxin injections in the laryngeal muscles for vocal tics
[RELA]^{123}. The effect of botulinum neurotoxin injections last between 12 and 16 weeks in the
majority of patients, after which treatment needs to be repeated [PRIN].

**Recommendation 10a:** Physicians may prescribe botulinum neurotoxin injections for the
treatment of older 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 neurotoxin 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 neurotoxin
injections may cause weakness and hypophonia, and that all effects are temporary (Level A).

**Topiramate for the treatment of tics**

Topiramate is probably more effective than placebo in reducing tic severity in people with tics
[EVID]. In patients with mild but troublesome tics who are not obtaining a satisfactory response
or experience adverse effects from other medical or behavioral treatments, topiramate may be a
useful alternative. While generally well tolerated at low doses (25 to 150 mg/d) it may cause a
variety of adverse effects, including cognitive and language problems, somnolence, and weight
loss, and it may increase the risk of renal stones, particularly in poorly hydrated individuals
[RELA]^{124-126}.
Recommendation 11a: Physicians should prescribe topiramate for the treatment of tics when the benefits of treatment outweigh the risks.

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.

Cannabis-based medications for the treatment of patients with TS

A large number of patients with TS use cannabis as a self-medication for the treatment of both tics and different comorbidities [RELA]127. There is limited evidence that the most psychoactive ingredient of cannabis, delta-9-tetrahydrocannabinol (THC, dronabinol), is more effective than placebo in reducing tics in adults with TS [EVID]. There is insufficient evidence to determine whether efficacy of other cannabinoids such as 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]128. There is no evidence suggesting that controlled treatment with cannabis-based medication may induce addiction to cannabinoids. There is limited evidence that in patients with TS, THC does not cause cognitive deficits [RELA]129. Acute withdrawal of cannabinoids is generally safe and well tolerated without significant adverse events [RELA]128,130. 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] (Levine 2017).
Cannabis-based medication should not be used in women who are pregnant or breastfeeding, and in patients suffering from psychosis [PRIN].

**Recommendation 12a:** Due to the risks associated with cannabis use and widespread self-medication with cannabis for tics, where regional legislation allows, physicians must offer to direct patients to appropriate medical supervision when cannabis is used for the treatment of tics (Level A).

**Recommendation 12b:** Physicians may consider treatment with cannabis-based medication in otherwise treatment resistant adult patients with TS suffering from clinically relevant tics (Level C).

**Recommendation 12c:** Physicians may consider treatment with cannabis-based medication in adult patients 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 for Tics in the Setting of TS**

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, only a handful of operations per year are performed. Furthermore, there is a paucity of information from large randomized clinical trials available 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 effective than sham stimulation in reducing tic severity [EVID]. There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region in reducing tic severity [EVID].

Recommendations from the Movement Disorders Society suggest that, when DBS is used as therapy in TS, best practices used for other DBS targets are followed, including confirmation of diagnosis, use of multidisciplinary screening, and stabilization of psychiatric comorbidities inclusive of active suicidality [RELA]^{131}. Appropriate patient selection is one of the most important predictors of success or failure of DBS treatment, making multidisciplinary evaluation essential [RELA]^{132}. 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 in the DBS community about high risk for suicide and other negative psychiatric sequelae in patients with TS not screened and monitored for depression, anxiety, and bipolar tendencies. The largest available randomized clinical studies 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 clinical trials [RELA]^{133}. There is a paucity of
information available 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, a neurosurgeon, and a neuropsychologist) to establish when the benefits of treatment
outweigh the risks for prescribing DBS as an option for medication resistant motor and phonic
tics in the setting of TS (Level A).

**Recommendation 13b**: Physicians should confirm the DSM-5 diagnosis of TS and exclude
secondary and functional tic-like movements when considering DBS as an option for medication
resistant tics in the setting of TS (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 before prescribing DBS for tics in the setting of TS (Level A).

**Recommendation 13e**: Physicians may consider DBS for severe, self-injurious tics in the setting
of TS, such as severe cervical tics that may result in spinal injury (Level C).

**Suggestions for Future Research**

1. The dopamine depleters, such as tetrabenazine, deutetрабеназин, and valbenazine, act by
blocking vesicular monoamine transporter type 2 (VMAT2). Although no randomized,
double-blind, placebo-controlled trials have been conducted with the VMAT2 inhibitors
in the treatment of tics, these drugs are increasingly used off label, and some experts
prescribe these as the first-line treatment in patients with troublesome tics in the setting of TS. When appropriately dosed, these drugs are generally well tolerated but may be associated with drowsiness, depression, and parkinsonism; no tardive dyskinesia has been documented with any of the VMAT2 inhibitors. Although an initial phase II trial of valbenazine, already approved by the FDA for the treatment of tardive dyskinesia, did not reach the primary endpoint in adults and children with TS, this was thought to be due to underdosing. Further and better-designed double-blind, placebo-controlled trials are currently under way with valbenazine and deutetrafenazine.

2. Over the last 2 decades, case reports and small case series have comprised the majority of the outcomes data available for review on the efficacy of DBS for TS. An international DBS registry and database, sponsored by the Tourette Association of America, has been developed to collect data on DBS outcomes in patients with TS implanted in various centers around the world. The outcomes database 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 in DBS in patients with TS should be to improve outcomes and quality of life by conducting well-designed multicenter studies, share data across many 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 this group of patients. Even at expert DBS centers, there are only a handful of cases appropriate for surgery each year, making recruitment difficult in single-center studies. In addition, the uncertainty in optimal target and the individual variability in
programming and management between participants make clinical trials challenging.

Finally, there has been reluctance from device manufacturers to endorse an FDA Humanitarian Exemption due to the cost and liability in small disease populations. 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.

3. Future research on psychosocial interventions for tics should include head-to-head comparisons of the relative efficacy of CBIT versus pharmacotherapy. Additional research should be conducted on treatment sequencing and decision making; in particular, efforts should be made to determine the order in which treatments should be implemented, and for whom particular sequences of treatment are most effective. Further research should continue to test the efficacy of other psychosocial treatments, including exposure and response prevention, mindfulness-based treatments, or more global tic-related interventions such as the “Living with Tics” program¹³⁷. 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 neural, neurocognitive, and behavioral mechanism of action underlying CBIT and other psychosocial interventions will be necessary to enhance the overall effectiveness of these treatments and inform patient-treatment matching algorithms¹³⁸.
4. Future research on medications for tics should include noninferiority trials of agents commonly used for the treatment of tics but for which limited evidence from randomized controlled trials is available. As the use of aripiprazole for tics is supported with high-quality evidence, and this drug has been FDA approved for the treatment of tics, noninferiority trials could be conducted against aripiprazole. Agents for which evidence is promising but limited include the first-generation antipsychotic fluphenazine. Existing evidence on fluphenazine suggests superior tolerability compared with other first-generation antipsychotics, such as haloperidol139-141.

5. Until recently, only very few studies have been performed investigating the efficacy and safety of cannabis-based medicine in children with various diseases. However, only recently could it be demonstrated that the cannabinoid cannabidiol (CBD) significantly reduces convulsive-seizure frequency in children with Dravet syndrome\textsuperscript{142}. There is preliminary evidence that cannabinoids such as tetrahydrocannabinol (THC, dronabinol) might also be effective in children in preventing vomiting due to antineoplastic treatment\textsuperscript{143, 144} and in treatment resistant spasticity\textsuperscript{145}. From these studies it is even suggested that children may tolerate higher doses than adults that and side effects seem to be in most cases rare and only mild\textsuperscript{143, 145}. In minors with TS, in one case study beneficial effects of THC have been reported in a 15-year-old boy with improvement of tics and comorbid ADHD\textsuperscript{146}. In another case report of an 8-year-old boy with TS, significant improvement of tics, ADHD, depression, and quality of life has been described after treatment with THC\textsuperscript{147}. In both cases, no relevant side effects occurred. There is increasing evidence that cannabis-based medicine such as cannabis, nabiximols,
and THC$^{73, 74, 148-156}$ might be effective in the treatment of adults with TS with improvement of both tics and different psychiatric comorbidities.
## Summary Table: Confidence in Evidence

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<td>Desipramine vs placebo*</td>
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<td>DBS of the GPI ON vs OFF</td>
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| Low confidence: possibly more effective than | Nicotine added to haloperidol vs placebo added to haloperidol |
| Low confidence: possibly no more effective than | Clonidine vs levetiracetam |
|                                                   | Deprenyl vs placebo |
|                                                   | Omega-3 fatty acids vs placebo |

<p>| Very low confidence: insufficient evidence to determine efficacy | Haloperidol vs pimozide |
|                                                               | Pimozide vs risperidone |
|                                                               | Risperidone vs clonidine |
|                                                               | Risperidone vs aripiprazole |</p>
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<td>N-acetylcysteine vs placebo</td>
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<td>Nicotine vs placebo</td>
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<td>Riluzole vs placebo</td>
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<td>D-serine vs placebo</td>
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<td>DBS of the centromedian-parafascicular complex ON vs OFF</td>
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* in children with tics and ADHD
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Clinical Practice Guideline Development Manual, available at
Appendix 1: Complete search strategy

MEDLINE 1946 to Present

Ovid MEDLINE(R)
In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

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1 Central
2 Same strategy as for MEDLINE - 268
3
4 PsychINFO 1967 to July Week 4 2016

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**EMBASE 1988 to 2016 Week 32**

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**ClinicalTrials.gov**

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REFERENCES


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and adolescents treated with ziprasidone: a prospective study. *Journal of the American
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randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment
of Tourette's disorder. *Journal of the American Academy of Child & Adolescent
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controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders.
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the treatment of children with tic disorders and attention deficit hyperactivity disorder.
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Neuropsychiatric effects of guanfacine in children with mild tourette syndrome: a pilot
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placebo-controlled study of topiramate in the treatment of Tourette syndrome. *Journal of


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