Practice Guideline: The treatment of tics in people with Tourette syndrome and chronic tic disorders

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

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AUTHOR CONTRIBUTIONS

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ABBREVIATIONS

AAN: American Academy of Neurology

ADHD: attention-deficit/hyperactivity disorder

CBD: cannabidiol

CBIT: the Comprehensive Behavioral Intervention for Tics

CBT: cognitive behavioral therapy

CI: confidence interval

COI: conflict of interest

DBS: deep brain stimulation

DSM-5: *Diagnostic and Statistical Manual of Mental Disorders (DSM–5),* Fifth Edition

GDDI: Guideline Development, Dissemination, and Implementation

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HRT: habit reversal training

OCD: obsessive-compulsive disorder

rTMS: repetitive transcranial magnetic stimulation

SMD: standardized mean difference

THC: delta-9-tetrahydrocannabinol

TS: Tourette syndrome

VMAT2: vesicular monoamine transporter type 2

ABSTRACT

Objective: To systematically evaluate the efficacy of treatments for tics and the risks associated with their use, and to make recommendations on when clinicians and patients should treat 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.

Results: There was high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinum toxin A injections, 5-ling granule, Ningdong granule and deep brain stimulation of the globus pallidus were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. Evidence of harm associated with various treatments was also demonstrated.

Recommendations: Forty-six recommendations were made regarding the assessment 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 reassessment of the need for ongoing therapy. Treatment options should be individualized, and the choice should be the result of a collaborative decision between patient, caregiver, and clinician, during which the benefits and harms of individual treatments as well as the presence of comorbid disorders are considered.

INTRODUCTION

Tourette syndrome (TS) is a neurodevelopmental condition that is characterised by the presence of multiple motor tics and at least one vocal tic that persist for at least one year.[1] Motor tics are defined as 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 they also may manifest with speech blocking or stuttering-like symptoms. Tics are often accompanied by specific behavioral symptoms.[2, 3] Tourette syndrome 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, which persist for more than one year. A chronic vocal tic disorder is characterized 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 TS was long neglected and traditionally considered a rare medical curiosity,[4] but recent epidemiologic studies that used 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 while the prevalence of chronic tic disorders range from 0.9 to 2.8%.[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 1,000.[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 may 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."[7, 8] Contrary to their centrality in media portrayals of TS, coprophenomena (the production of obscene words or gestures) are 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).[9]

Tics are often preceded or accompanied by subjective feelings of tension or pressure, which are temporarily relieved by tic expression[10] These physical sensations are sometimes referred to as premonitory urges and represent a hallmark feature of tics that may that may help to distinguish between TS and other hyperkinetic movement disorders. 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.[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.[13, 14]

Little is known concerning the neural pathways that underlie tic development and their expression. Tourette syndrome and chronic tic disorders are believed to share a common neurobiological origin, and we use the abbreviation TS throughout the manuscript to refer to all individuals with primary chronic tic disorders. 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 have been proposed to be involved, including glutamatergic, GABAergic, noradrenergic, and histaminergic pathways.[15, 16] Tics are often present in different forms and with different severity in family members; although generations may 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.[17] Moreover, environmental factors may play a contributory role, as in most neuropsychiatric disorders. Both epidemiologic and laboratory findings implicate respiratory infections and autoimmune dysfunction, and pre-

and perinatal problems, may be involved in the etiologic mechanisms in at least a subgroup of patients with TS.[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: most commonly obsessive-compulsive disorder (or obsessive-compulsive behavior) and attention-deficit/hyperactivity disorder(ADHD).[21] Lifetime prevalence of comorbid behavioral disorders is estimated to approach 90%.[22] 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.[23] 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.[24] Patients with TS also report higher rates of impulse control, anxiety, and affective disorders compared with people in the general population.[22, 25] A higher prevalence of both tics and stereotypic movement disorders, or stereotypies, has been reported in patients with autism spectrum disorders.[26] 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.[27, 28]

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 for tics, including neurostimulation, and the risks associated with their use. A systematic review was performed to develop recommendations pertaining to the treatments of tics in children and adults with TS or chronic tic disorders. Antipsychotic medications have been commonly prescribed for this purpose, since the 1960s. The adverse effects associated with antipsychotic medications,

including movement disorders such as acute and tardive dystonia, tardive dyskinesia, akathisia and drug-induced parkinsonism, and metabolic adverse effects, such as weight gain, hyperlipidemia, and hyperglycemia, have led clinicians to search for other effective treatments. In recent years, there has been a resurgence in the interest in behavioral treatments and neuromodulation for tics, yielding expanding evidence in this area. Although individuals with 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 TS or a chronic tic disorder, what are the risks of harm, including weight gain, elevated prolactin levels, sedation, drug-induced movement disorders, hypotension, bradycardia, and electrocardiogram changes with medical treatments, compared with placebo or other active interventions?

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 or combinations of these treatments?

DESCRIPTION OF THE ANALYTIC PROCESS

In May 2016, the Guideline Development, Dissemination and Implementation Subcommittee (GDDI) of the AAN (Appendices e-1-e2) recruited a multidisciplinary panel to develop this practice guideline, including 9 physicians, 2 psychologists, and 2 patient representatives. 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, KMV) and pediatrics (MO, YH). The psychologists were both content experts in behavioral treatments for TS (JP, DW). The patient representatives (MR, EJ) are both associated 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. 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, KMV). 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 (appendices e-3 through e-9). This process is compliant with 2011 Institute of Medicine standards for systematic review and clinical practice guideline development.[29] 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 was re-reviewed and edited 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 that included at least 20 participants (10 participants if a crossover trial), except for neurostimulation trials, for which no minimum sample size was required. 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 [DBS]) intervention for tics.

Comparison group

We included studies that compared, 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 was the Yale Global Tic Severity Scale, and when outcome results with this instrument were reported, they were used to calculate effect size. The YGTSS, the most extensively deployed rating scale for tics internationally, has displayed very good internal consistency, interrater reliability, and convergent and divergent validity[30]. 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 levels were 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 that used 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 by patient/parent/clinician report and assessment. Hypotension and bradycardia were evaluated by assessing 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 3). The total number of references retrieved after duplicates were removed was 2,196. After two reviewers working independently of each other reviewed the abstracts and titles of these 2,196 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 that evaluated 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 repeat search was conducted in September of 2017 to update our search results, with a total of 211 new abstracts retrieved after duplicate removal. Seven abstracts were selected for full-text review, and three articles met our inclusion criteria and were added to the analysis.

A modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to develop conclusions.[31] 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.

The effect size, or standardized mean difference (SMD) was calculated for each study intervention/outcome pair. The SMD expresses the size of the intervention effect relative to the variability observed in each study. The SMD is calculated by dividing the difference in the mean outcome between groups by the standard deviation of the outcome among participants. By convention, an SMD of 0.2 is considered a small effect size, an SMD of 0.5 is considered a medium effect size, and an SMD of 0.8 is considered a large effect size. For our analysis, an 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.[32-39] 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 table 1 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 (0.2 or greater), marginal (between important and unimportant thresholds, 0.1 and 0.2), or unimportant (0.10 or less). 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 (less than 0.1), confidence of no effect is anchored to high; if the 95% confidence interval includes potentially marginal effect sizes (between 0.1 and 0.2), confidence

of no effect is anchored to moderate; if the 95% confidence interval includes potentially unimportant and marginal effect sizes (up to 0.2), confidence of no effect is anchored to low; if the 95% confidence interval includes potentially unimportant and important effect sizes (greater than 0.2), confidence of no effect is anchored to very low.

If the pooled effect is significant and the pooled 95% confidence interval includes only important effect sizes (0.2 or greater), confidence is anchored to high; if significant and the confidence interval includes potentially marginal effects (0.1 or greater), confidence is anchored to moderate; if significant and the confidence interval includes potentially unimportant effects, confidence is anchored to low (less than 0.1).

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 lower limit of the 95% confidence interval for the magnitude of a significant effect point estimate is more than twice as large as that judged to be important (2*0.2 = 0.4 or greater). Conversely, confidence is downgraded by one level if the magnitude of a significant effect-size point estimate is less than the important threshold (less than 0.2).

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.[40]

Data Availability

All trials included in the evidence synthesis have been published and are available in the public domain. All analyses performed for the data synthesis as well as the outcome of the Delphi process are available as Appendices.

RESULTS

Pimozide and Haloperidol

Six trials 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,[41] four were crossover studies,[42-46] and one had both a parallel-group phase and a crossover phase.[47] 162 patients in total participated in the included trials, with ages from 7 to 53 years. Two of the six studies evaluated pimozide versus haloperidol

versus placebo[43, 44]; a further two evaluated pimozide versus risperidone[41, 42]; one evaluated pimozide versus haloperidol,[47] and one evaluated pimozide versus placebo.[46] One additional study of haloperidol compared with placebo and the Ningdong granule was found[36] (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.[46] 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 receiving pimozide experienced akinesia (defined as sedation or lethargy), akathisia, or postural rigidity. 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 enrolling 22 patients.[44] 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 (SD 14.1) after the pimozide phase, 20.7 (SD 17.3) after the haloperidol phase, and 26.8 (SD 15.9) 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.[47] 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 superior to placebo in controlling tics as measured by the Clinical Global Impressions Scale, 3.2 (SD 1.5) versus 1.9 (SD 2.1)

(P=0.03), but not as measured by the Tourette Syndrome Severity Scale, 2.5 (SD 3.0) versus 2.9 (SD 2.5). 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 (SD 1.5) versus 2.0 (SD 2.3) (P=0.011), but with the Clinical Global Impressions Scale, there was no significant difference between pimozide and haloperidol, 3.4 (SD 1.6) versus 3.5 (SD 1.5). Benztropine was required for extrapyramidal symptoms 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.[43] 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 (P<0.05). Adverse events were not formally assessed in this study.

Gilbert (Class II) compared pimozide with risperidone in a crossover study of 13 patients.[42] 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.[41] 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[48] found a significant increase in the QT and QT_c interval from baseline at 6, 12, 18, and 24 months from treatment initiation. The mean QT_c prolongation was 24.3 (SD 15.9) milliseconds.

Conclusion

People with tics receiving pimozide are possibly more likely than those receiving placebo to have reduced tic severity (SMD, 0.66 [95% CI 0.06, 1.25]; low confidence; 3 Class II studies, confidence in evidence downgraded due to imprecision).

People with tics receiving haloperidol are probably more likely than those receiving placebo to have reduced tic severity. (SMD, 0.59 [95% CI 0.11, 1.06]; moderate confidence; 2 Class II studies).

There is insufficient evidence to determine whether people with tics receiving haloperidol are more or less likely than those receiving pimozide to have reduced 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).

There is insufficient evidence to determine whether people with tics receiving risperidone are more or less likely than those receiving pimozide to have reduced 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).

People with tics receiving pimozide are probably more likely to have extrapyramidal symptoms than people receiving placebo (moderate confidence, 2 Class II studies).

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

People with tics receiving haloperidol are possibly more likely to have extrapyramidal symptoms than people receiving pimozide and placebo (low confidence, one Class II study).

People with tics receiving pimozide are possibly more likely to have increased prolactin than people receiving placebo (low confidence, 1 Class II study).

People with tics receiving haloperidol are possibly more likely to have increased prolactin than people receiving 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,[49, 50] two compared risperidone with pimozide,[41, 42] one compared risperidone with clonidine,[51] and one compared risperidone with aripiprazole.[52] 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 26 children and 8 adults.[50] 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.[49] 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.[51] 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 with a SMD of -0.19 (95% CI -1.06, 0.67). 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.[52] 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.

A prospective longitudinal study of antipsychotic safety was performed in 57 children with TS.[53] Children were monitored for drug-induced movement disorders, metabolic and hormonal adverse effects for a mean period of 10 months. Of 27 children treated with risperidone (mean dose 1.1 mg), there was a significant increase in prolactin and fasting insulin compared to baseline. Two children discontinued treatment due to persistent hyperprolactinemia. Eight of 27 children (30%) went from a healthy weight at baseline to an overweight or obese body mass index over the course of treatment, with six children ultimately discontinuing treatment secondary to this adverse effect. Seven children had abnormal scores on the Extrapyramidal Symptom Rating Scale examination over the course of treatment, with one child requiring a change in dose and one child discontinuing treatment.

Conclusion

People with tics receiving risperidone are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.79 [95% CI 0.31-1.27], moderate confidence, 2 Class II studies).

There is insufficient evidence to determine whether people with tics receiving risperidone are more or less likely than those receiving clonidine to have reduced tic severity (SMD, -0.19 [95% CI -1.06, 0.68]; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

There is insufficient evidence to determine whether people with tics receiving risperidone are more or less likely than those receiving pimozide to have reduced 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).

There is insufficient evidence to determine whether people with tics receiving aripiprazole are more or less likely than those receiving risperidone to have reduced 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).

People with tics receiving risperidone are probably more likely to gain weight than people receiving placebo (moderate confidence, 2 Class II studies).

People with tics receiving risperidone are possibly more likely to have higher parkinsonism scores on the Extrapyramidal Symptom Rating Scale Score than people receiving placebo (low confidence, 1 Class II study).

People with tics receiving risperidone are possibly more likely to require antiparkinsonian medication than people receiving placebo (low confidence, 1 Class II study).

People with tics receiving risperidone are possibly more likely to experience fatigue and somnolence than people receiving placebo (low confidence, 1 Class II study).

Aripiprazole

There are three randomized controlled trials of aripiprazole for tics, two versus placebo,[54, 55] and one versus risperidone.[52] 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.[54] 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 I) compared aripiprazole with placebo in an 8-week trial of 133 children and youth.[56] 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. Any extrapyramidal symptom-related adverse event (akathisia, dystonia, extrapyramidal disorder, parkinsonism, rest tremor and tremor) was reported in 1 of 44 children in the low dose group, 6 of 45 children in the high dose group, and in none of the 44 children in the placebo group. The mean change in weight from baseline to week 8 was 1.8 kg (SD 2.0) in the low dose group, 1.0 kg (SD 2.0) in the high dose group, and 0.6 kg (SD 2.1) in the placebo group. Potentially clinical relevant weight gain (>7%) occurred in 18.2% of the low dose group, 9.3% of the high dose group, and 9.1% of the placebo group.

One study of aripiprazole tolerability[57] found that sedation was the most commonly reported adverse effect of treatment. A prospective longitudinal study of antipsychotic safety was performed in 57 children with TS.[53] Children were monitored for drug-induced movement disorders, metabolic and hormonal adverse effects for a mean period of 10 months. Of the 30 children treated with aripiprazole (mean dose 6 mg), seven (24%) went from a healthy weight at baseline to an overweight or obese BMI over the course of treatment, with five discontinuing treatment due to this adverse effect. Thirteen children had abnormalities on the Extrapyramidal Symptom Rating Scale examination over the course of treatment, with two children requiring a change in dose and three children discontinuing treatment due to these symptoms.

Conclusion

People with tics receiving aripiprazole are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.64 [95% CI, 0.31-0.97], moderate confidence, 1 Class I study and 1 Class II study).

People with tics receiving aripiprazole are probably more likely to gain weight gain than those receiving placebo (moderate confidence, 1 Class I and I Class II study).

People with tics receiving aripiprazole are possibly more likely to have an increase in body mass index, and waist circumference than people receiving placebo (low confidence, I Class II study).

People with tics receiving aripiprazole are possibly more likely to experience sedation and somnolence than people receiving placebo (low confidence, 1 Class II study).

Ziprasidone

Sallee et al (Class II) evaluated ziprasidone for the treatment of tics.[58] 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.[59] This study demonstrated statistically significant increases from baseline to peak values in QT_c intervals, with a mean prolongation of 28 (SD 26) milliseconds.

Conclusion

People with tics receiving ziprasidone are possibly more likely than those receiving placebo to have reduced tic severity (SMD, 1.14 [95% CI, 0.32-1.97], low confidence, 1 Class II study).

Metoclopramide

Nicolson (Class II) compared metoclopramide with placebo for tics in a study of 28 children aged 7 to 18 years.[60] 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

People with tics receiving metoclopramide are possibly more likely than those receiving placebo to have reduced tic severity (SMD, 1.14 [95% CI, 0.33-1.95], low confidence, 1 Class II study).

People with tics receiving metoclopramide are possibly more likely to have a greater increase in prolactin levels than those receiving placebo (low confidence, 1 Class II study).

Tiapride (this medication is not available in the US)

There is one Class I study comparing tiapride with placebo and the 5-Ling granule in 603 children and youth with TS.[61] 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 than the other two treatment groups.

Conclusions

People with tics receiving tiapride are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.62 [95% CI, 0.36-0.88], moderate confidence, 1 Class I study).

People with tics receiving tiapride are probably more likely than those receiving placebo to have higher rates of physical tiredness and sleep disturbances (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[37, 62-65] and one comparing clonidine to levetiracetam.[66] Three trials were performed exclusively in children,[37, 62, 65] while the other three trials included both children and adults.[63, 64, 66] The oral form of clonidine was used in five trials, and the clonidine adhesive patch in one trial.[62] In total, 693 individuals participated in the six trials.

Du[62] 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[63] 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[64] 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[65] 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[37] 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[66] 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[67] in adults found that sedation was the most commonly reported adverse effect associated with treatment.

Conclusions

People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.45 [95% CI, 0.13, 0.77]; moderate confidence, 1 Class I and 2 Class II studies).

People with tics and a comorbid diagnosis of ADHD receiving clonidine plus methylphenidate are probably more likely than those receiving placebo to have reduced tic severity (SMD 0.72 [95% CI, 0.22, 1.22] moderate confidence, 1 Class I study).

There is insufficient evidence to determine whether people with tics receiving clonidine are more or less likely that those receiving levetiracetam to have reduced tic severity (SMD, 0.86 [95% CI, -0.03, 1.75]; very low confidence, 1 Class II study).

People with tics receiving clonidine are probably more likely to experience sedation than people receiving placebo (moderate confidence, 1 Class I and 1 Class II studies).

Guanfacine

There are three randomized controlled trials of guanfacine versus placebo for the treatment of tics in children and adolescents. In total, these three trials included 92 participants.

Scahill[68] 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[69] 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.

Murphy[70] compared guanfacine extended release 1 to 4 mg per day with placebo in an 8-week trial of 34 children with a chronic tic disorder (Class I). There was no difference between guanfacine extended release and placebo in the Yale Global Tic Severity Scale Total Tic Score, with an SMD of 0.13 (-0.54, 0.81). Fatigue, drowsiness, dry mouth, headache, irritability and stomachache were more frequent in children treated with guanfacine extended release compared to placebo ($P<0.05$).

Conclusion

People with tics receiving guanfacine are possibly more likely than those receiving placebo to have reduced tic severity (SMD, 0.45 [95% CI, 0.03-0.87], low confidence, 1 Class I and 2 Class II studies, confidence in evidence downgraded due to imprecision).

People with tics receiving guanfacine are probably more likely than those receiving placebo to have drowsiness, dry mouth, headache, irritability and stomachache than placebo (moderate confidence, 1 Class I study).

Onabotulinum Toxin A Injections

There is one Class II randomized crossover trial of onabotulinum toxin A injection versus placebo for the treatment of simple motor tics in 20 adolescents and adults.[71] Patients were treated with onabotulinum toxin A 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 onabotulinum toxin A 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 onabotulinum toxin A than with placebo. Two patients experienced motor restlessness or developed new tics after treatment with onabotulinum toxin A.

Conclusion

People with tics receiving onabotulinum toxin A injections are probably more likely than those receiving placebo to have reduced 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.[72] 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 nephrolithiasis. 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

People with tics receiving topiramate are possibly more likely than those receiving placebo to have reduced tic severity (SMD 0.91 [95%CI 0.11-1.71]; low confidence, 1 Class II study).

Baclofen

There is one Class II study comparing baclofen with placebo in a 10-week crossover trial of 10 children.[73] 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

*There is insufficient evidence to determine whether people with tics receiving baclofen are more or less likely than those receiving placebo to have reduced tic severity (*SMD, 0.55 [95% CI, -0.39, 1.49] *very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).*

Levetiracetam

There are two studies comparing levetiracetam with placebo for the treatment of tics.[74, 75] 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.[74]

One Class II trial compared levetiracetam with placebo in a crossover trial of 22 children with TS.[75] 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

There is insufficient evidence to determine whether people with tics receiving levetiracetam are more or less likely than those receiving placebo to have reduced tic severity (SMD 0.22 [95% CI, -0.38, 0.82]; *very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).*

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 disorder.[76] 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

*There is insufficient evidence to determine whether people with tics receiving N-acetylcysteine are more or less likely than those receiving placebo to have reduced tic severity (*SMD 0.45 [95% CI, -0.27-1.17]; *very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision)*

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.[77] 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

There is insufficient evidence to determine whether people with tics receiving omega-3 fatty acids are more or less likely than those receiving placebo to have reduced tic severity (SMD 0.69 [95% CI, 0-1.39]; *very low confidence, one Class II study; confidence in evidence downgraded due to imprecision).*

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.[78] 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

People with tics receiving the Ningdong granule (as formulated by Zhao[78]) are probably more likely than those receiving placebo to have reduced tic severity (SMD 0.97 [95% CI 0.45-1.49]; 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.[36] 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

There is insufficient evidence to determine whether people with tics receiving the Ningdong granule (as formulated by Wang) are more or less likely than those receiving placebo to have reduced tic severity (very low confidence, 1 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.[61] 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 schisandrae 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

People with tics receiving the 5-Ling granule are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.55 [95% CI, 0.33-0.76], moderate confidence, 1 Class I study).

Tetrahydrocannabinol (THC)

There are two trials comparing delta-9 tetrahydrocannabinol (THC) with placebo in adults with TS, including a total of 36 participants.[79, 80] One study compared a single dose of THC (5-10 mg) to placebo in a Class II crossover study of 12 adults.[79] 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.[80] 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

People with tics receiving THC are possibly more likely than those receiving placebo to have reduced tic severity (SMD, 0.62 [95% CI, 0.01, 1.22]; low confidence, 1 Class II and 1 Class III study).

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[81] 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.[82] 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

*There is insufficient evidence to determine whether people with tics receiving nicotine are more or less likely than those receiving placebo to have reduced tic severity (*SMD, 0.38 [95% CI, -0.14, 0.90] *very low confidence, 1 Class III study).*

There is insufficient evidence to determine whether people with tics receiving the nicotine patch added to haloperidol are more or less likely than those receiving placebo added to haloperidol to have reduced tic severity (SMD 0.71 [95% CI, 0.17, 1.25] *very low confidence, 1 Class III study).*

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.[35] 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

There is insufficient evidence to determine whether people with tics receiving mecamylamine are more or less likely than those receiving placebo to have reduced 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.[33] 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

There is insufficient evidence to determine whether people with tics receiving flutamide are more or less likely than those receiving placebo to have reduced 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.[83] 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

There is insufficient evidence to determine whether people with tics receiving riluzole are more or less likely than those receiving placebo to have reduced tic severity (SMD 0.17 [95% CI -0.91, 1.25]; very low confidence, 1 Class I study; confidence in evidence downgraded due to imprecision).

There is insufficient evidence to determine whether people with tics receiving D-serine are more or less likely than those receiving placebo to have reduced tic severity (SMD -0.04 [95% CI -

1.13, 1.05]; 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.[84] 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

*There is insufficient evidence to determine whether people with tics receiving ondansetron are more or less likely than those receiving placebo to have reduced tic severity (*SMD 0.53 [95% CI, -0.20, 1.25]; *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.[85] 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

There is insufficient evidence to determine whether people with tics receiving pramipexole are more or less likely than those receiving placebo to have reduced tic severity (SMD 0.0 [95%CI -0.53, 0.53]; 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.[86] 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

There is insufficient evidence to determine whether people with tics receiving IVIG are more or less likely than those receiving placebo to have reduced tic severity (SMD 0.50 [95%CI -0.24, 1.24]; very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).

Methylphenidate and Dextroamphetamine

There are three studies (1 Class I,[65] 2 Class III [38,87]) 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.[65]

One Class III study compared 3 doses of methylphenidate with placebo in a crossover study of 71 children with TS and ADHD.[87] 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.[38] The children received low, medium, and high doses of each drug for 1 week each (methylphenidate 15 mg, 25 mg and 45 mg twice daily; dextroamphetamine 7.5 mg, 15 mg and 22.5 mg twice daily). 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

People with tics and a comorbid diagnosis of ADHD receiving methylphenidate are probably more likely than those receiving placebo to have reduced tic severity (SMD, 0.61 [95% CI, 0.13, 1.10]; moderate confidence, 1 Class I study).

Deprenyl

There is one Class II crossover study comparing deprenyl with placebo in 24 children with TS and ADHD.[88] 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

There is insufficient evidence to determine whether people with tics receiving deprenyl are more or less likely than those receiving placebo to have reduced tic severity (SMD, 0.47 [95% CI, -0.05, 0.99]; very low confidence, 1 Class II study; confidence in evidence downgraded due to imprecision).

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.[45] 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 people with tics and a comorbid diagnosis of ADHD, atomoxetine does not worsen tics relative to placebo (low confidence, 1 Class II study).

People with tics and a comorbid diagnosis of ADHD receiving atomoxetine are possibly more likely to have a decrease in body weight than people receiving placebo (low confidence, 1 Class II study).

People with tics and a comorbid diagnosis of ADHD receiving atomoxetine are possibly more likely to have an increase in heart rate than people receiving placebo (low confidence, 1 Class II study).

Desipramine

There is one Class II[89] and one Class III study[37] 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.[37]

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.[89] 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.[90]

Conclusion

People with tics and a comorbid diagnosis of ADHD receiving desipramine are probably more likely than those receiving placebo to have reduced tic severity (SMD 1.13 [95% CI 0.47, 1.79];

moderate confidence, 1 Class II study; confidence in evidence upgraded due to magnitude of effect).

People with tics and a comorbid diagnosis of ADHD receiving desipramine are possibly more likely to have an increase in diastolic blood pressure and increased heart rate than people receiving 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.[91] Comorbid conditions within this sample were frequent, 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 over a period of 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 available CBIT responders 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.[92] 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.[93] 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 discussed in the manuscript.

Wilhelm conducted a Class III randomized unblinded study of habit reversal therapy compared with supportive psychotherapy in 32 adults with TS.[94] 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 discussed in the manuscript.

There is one Class II study comparing exposure and response prevention (ERP) to habit reversal therapy in 43 children and adults with TS.[95] 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 discussed in the manuscript.

There is one Class II study comparing psychoeducation with habit reversal training in 33 children with TS.[96] 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 discussed in the manuscript. .

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.[97] 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 discussed in the manuscript.

There is one Class II study comparing CBIT delivered face to face with CBIT delivered through telehealth in 20 children with TS.[98] 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 discussed in the manuscript.

Conclusion

People with tics receiving CBIT are more likely than those receiving supportive psychotherapy to have reduced tic severity (SMD, 0.56 [95% CI, 0.31-0.82], high confidence, 2 Class I studies).

There is insufficient evidence to determine whether people with tics receiving habit reversal therapy are more or less likely than those receiving exposure and response prevention to have reduced tic severity (SMD 0.25 [95% CI -0.40, 0.90]; very low confidence, 1 class II study, confidence in evidence downgraded due to imprecision).

There is insufficient evidence to determine whether people with tics receiving habit reversal therapy are more or less likely than those receiving educational group treatments to have reduced tic severity (SMD 0.55 [95% CI -0.17, 1.27]; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

There is insufficient evidence to determine whether people with tics receiving face-to-face habit reversal therapy are more or less likely than those receiving habit reversal therapy through video conferencing to have reduced tic severity (SMD 0.24 [95%CI 0.24, -0.70, 1.18]; very low confidence, 1 Class II study, confidence in evidence downgraded due to imprecision).

There is insufficient evidence to determine whether people with tics receiving habit reversal therapy by video conferencing are more or less likely than those on a wait list control to have reduced tic severity (SMD 0.24 [95% CI -0.66, 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.[39] 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

There is insufficient evidence to determine whether people with tics receiving relaxation therapy are more or less likely than those receiving minimal therapy to have reduced 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.[34] 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

There is insufficient evidence to determine whether people with tics receiving biofeedback are more or less likely than those receiving sham to have reduced tic severity (very low confidence, 1 Class III study).

Deep Brain Stimulation

Globus Pallidus

There are two Class II studies of deep brain stimulation (DBS) of the globus pallidus. The first study was performed in 15 adults with severe, medically refractory TS.[99] 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 the 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 (SD 22.6). 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.

The second study included 19 adults with severe and medically refractory TS and compared active stimulation of the anterior globus pallidus with sham stimulation. After 3 months of treatment, the Yale Global Tic Severity Scale Total Tic Score decreased by a median of 4.5 points (interquartile range -12.5 to 0.5) in adults receiving active stimulation, compared to a median increase of 5.0 points (interquartile range -2.5 to 17.5) in adults receiving sham stimulation, with a SMD of 0.74 (95% CI -0.28, 1.76). Fifteen serious adverse events occurred in 13 patients. Seven events were related to surgery and included infections leading to removal or the stimulator and electrodes in four patients. Seventeen adverse events were related to stimulation- increased tic severity and anxiety, depressive symptoms, dysarthria, sleep disorder, imbalance and abnormal movements resembling dyskinesia that resolved rapidly after stimulator adjustment.

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.[100] 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

People with tics receiving active DBS of the globus pallidus are possibly more likely than those receiving sham DBS of the globus pallidus to have reduced tic severity (SMD 0.77 [95% CI 0.14, 1.40]; moderate confidence, two class II studies).

Thalamus

There is one Class III study of DBS of the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus cross point in the thalamus in 6 adults with severe refractory TS.[101] 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.[102] 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[103] 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,[104] 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

There is insufficient evidence to determine whether people with tics receiving active DBS of the thalamus are more or less likely than those receiving sham DBS of the thalamus to have reduced tic severity (SMD 1.58 [95% CI -0.12, 3.28]; very low confidence, 1 Class III study).

There is insufficient evidence to determine whether people with tics receiving active DBS of the centromedian-parafascicular complex are more or less likely than those receiving sham DBS of the centromedian-parafascicular complex to have reduced tic severity (SMD 0.99 [95% CI -0.28, 2.26]; 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.[105] 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

There is insufficient evidence to determine whether people with tics receiving cTBS of the supplementary motor area are more or less likely than those receiving sham stimulation to have reduced tic severity (SMD -0.15 [95% CI -1.29, 0.99]; 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.[106] 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

There is insufficient evidence to determine whether people with tics receiving rTMS of the supplementary motor area are more or less likely than those receiving sham stimulation to have reduced tic severity (SMD 0.19 [95% CI -0.69, 1.07]; 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 TS[32]. 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

There is insufficient evidence to determine whether people with tics receiving rTMS of the left motor or prefrontal cortex are more or less likely than those receiving sham stimulation to have reduced 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, requiring clinicians 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 management decisions. Therefore, while the level of obligation and associated verbs (see below) state that treatments **may** or **should** be used, these recommendations pertain only to the situation in which the patient, caregivers and clinician have

determined that treatment is necessary, and a collaborative discussion of treatment choices and priorities has occurred.

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 were 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].[107] 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].[108] 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 Behavioral 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].[109] Improving peers' attitudes about and teachers' knowledge of TS may positively affect people with TS [INFER].

Recommendation 2: Clinicians should refer people with TS to resources for psychoeducation for teachers and peers, such as the Tourette Association of America or Tourette Canada (Level B).

Assessment and Treatment of ADHD in children with tics

Comorbid attention-deficit/hyperactivity disorder (ADHD) is common in people with TS, with prevalence ranging from 30% to 50% depending on the population studied [RELA].[22, 110] 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 likely than placebo to reduce tic severity [EVID] and reduce ADHD symptoms. In children with tics and ADHD, atomoxetine does not worsen tics relative to placebo [EVID] and reduces ADHD symptoms. Comorbid ADHD is strongly associated with functional impairment in children with TS [RELA].[111] While ADHD symptoms may improve in adolescence [RELA],[108] adults with TS may require ongoing care for this comorbidity.

Recommendation 3a: Clinicians should ensure an assessment for comorbid ADHD is performed in people with tics (Level B).

Recommendation 3b: Clinicians should evaluate the burden of ADHD symptoms in people with tics (Level B).

Recommendation 3c: In people with tics and functionally impairing ADHD, clinicians should ensure appropriate ADHD treatment is provided (Level B).

Assessment and Treatment of 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, 110]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].[112, 113] 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, 110] Comorbid mood disorders appear more prevalent in adolescents and adults than children and in those with greater tic severity [RELA].[22, 114] 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].[115]

Recommendation 5a: Clinicians must ensure appropriate screening for anxiety, mood, and disruptive behavior disorders is performed in people with tics (Level A).

Recommendation 5b: Clinicians must inquire about suicidal thoughts and suicide attempts in people with TS and refer to appropriate resources if present (Level A).

Assessment of Tic Severity and Treatment Expectations

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].[30] Evaluation of the effect 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 result in complete cessation of tics (Level A).

Psychosocial Treatments

Rationale. Children and adults with tics receiving the Comprehensive Behavioral Intervention for Tics (CBIT) are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. [EVID]. CBIT is a manualized treatment program consisting of habit reversal training, relaxation training, and a functional intervention to address situations that sustain or worsen tics [RELA].[116] 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 substantial clinical comorbidity may benefit from a longer course of therapy. Most children (aged 9 years or older) and adults showing an initial positive response to CBIT, will maintain their treatment gains for at least 6 months [EVID]. CBIT can be effective for children under age 9 years, though there is little evidence available to determine efficacy in

children of this age group [RELA].[117] 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 medication[118] [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

People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity, and people with tics receiving guanfacine are possibly more likely than those receivng placebo to have reduced tic severity, with the majority of trials conducted in children [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 and guanfacine is probably associated with higher rates of drowsiness, dry mouth, headache, irritability and stomachache [EVID]. A systematic review of alpha-2 adrenergic agonists for ADHD in children and adolescents demonstrated hypotension, bradycardia, and sedation with both agents, and QTc prolongation with guanfacine extended release [RELA].[119] Abrupt withdrawal of alpha-2 adrenergic agonists may cause rebound hypertension [RELA].[120]

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 probably more likely than placebo to reduce tic severity [EVID], and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity [EVID]. There is insufficient evidence to determine the relative efficacy of these 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 (including tardive dyskinesia, drug-induced parkinsonism, akathisia, acute dystonia and tardive dystonia), weight gain, adverse metabolic side effects, prolactin increase, and QT prolongation with both first- and second-generation antipsychotics in both children and adults across psychiatric and neurologic conditions [RELA].[121, 122] 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.[123] 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], and evidence-based monitoring protocols are available for reference.[124] Abrupt discontinuation of antipsychotic medications can cause withdrawal dyskinesias[125, 126] [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 electrocardiography and measure the QT_c interval before and after starting pimozide or

ziprasidone, or if antipsychotics are co-administered 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 toxin injections for tics

Botulinum neurotoxin injections with onabotulinum toxin A are probably more likely than placebo to reduce tic severity in adolescents and adults [EVID]. Premonitory urges may also be improved by botulinum toxin injections in a proportion of patients [RELA].[127] There is no evidence on the efficacy of other botulinum toxins for tics [EVID]. Relative to placebo, onabotulinum toxin A is associated with higher rates of weakness [EVID]. Hypophonia is a common side effect of botulinum toxin injections in the laryngeal muscles for vocal tics [RELA].[128] The effect of botulinum toxin 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 toxin 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 toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks (Level C).

Recommendation 10c: Physicians must counsel individuals with tics that botulinum toxin injections may cause weakness and hypophonia, and that all effects are temporary (Level A).

Topiramate for the treatment of tics

Topiramate is possibly more likely than placebo to reduce 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].[129-131]

Recommendation 11a: Physicians should prescribe topiramate for the treatment of tics when the benefits of treatment outweigh the risks (Level B).

Recommendation 11b: Physicians must counsel patients regarding common adverse effects of topiramate, including cognitive and language problems, somnolence, weight loss, and an increased risk of renal stones (Level A).

Cannabis-based medications for the treatment of patients with TS

A large number of patients with TS use cannabis as a self-medication for the treatment of both tics and different comorbidities [RELA].[132] There is limited evidence that the most psychoactive ingredient of cannabis, delta-9-tetrahydrocannabinol (THC, dronabinol), is possibly more likely than placebo to reduce tic severity in adults with TS [EVID]. There is insufficient evidence to determine whether 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].[133] 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].[134] Acute withdrawal of cannabinoids is generally safe and well tolerated without significant adverse events [RELA].[133, 135] 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]. Prescription of and access to medical marijuana varies by region; practitioners must abide by regional legislation on the use of medical marijuana [PRIN].

Recommendation 12a: Due to the risks associated with cannabis use and widespread self-medication with cannabis for tics, where regional legislation and resources allow, physicians must offer to direct patients to appropriate medical supervision when cannabis is used as self-medication for tics (Level A). Appropriate medical supervision would entail education and monitoring for efficacy and adverse effects.

Recommendation 12b: Where regional legislation allows, physicians may consider treatment with cannabis-based medication in otherwise treatment resistant adult patients with TS suffering from clinically relevant tics (Level C).

Recommendation 12c: Where regional legislation allows, 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 likely than sham stimulation to reduce tic severity [EVID]. There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region in reducing tic severity [EVID]. Complications of treatment, including infection and removal of hardware, appear more common with TS [EVID] than with other neurological conditions.

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].[136] Appropriate patient selection is one of the most important predictors of success or failure of DBS treatment, making multidisciplinary evaluation essential [RELA].[137] 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].[138] 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-2-agonists) and behavioral therapy have been administered (or are contraindicated) 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. 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" program.[139] As the evidence is insufficient at present to conclude that CBIT delivered by teleconference is as effective as face-to-face treatment, further well-designed studies with adequate sample sizes are needed to establish non-inferiority. Additional work to more accurately characterize the 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 algorithms.[140]

2. Future research on medications for tics should include non-inferiority 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, non-inferiority 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 haloperidol.[141-143] Clinical trials are currently underway with the selective D1 antagonist ecopipam versus placebo for the treatment of tics in children and adolescents and evidence on the efficacy of this drug is expected in the near future. Ecopipam is not currently available for clinical use.
3. The dopamine depleters, such as tetrabenazine, deutetrabenazine, and valbenazine, act by blocking vesicular monoamine transporter type 2 (VMAT2). Although no randomized, double-blind, placebo-controlled trials have been published 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 deutetrabenazine for the treatment of tics.[144-146]

4. Our systematic review included three different traditional Chinese medicine products, the 5-Ling granule,[61] the Ning Dong granule as formulated by Zhao,[78] and the Ning Dong granule as formulated by Wang.[36] We did not make any formal recommendations for or against the use of these compounds, all of which reported superiority over placebo. Our guideline panel had concerns about the criteria for inclusion in the 5-Ling granule study, as children in this study not only had a diagnosis of TS as per DSM-IV criteria, but also had a condition fitting the excessive subtype in traditional Chinese medicine-based diagnosis. There is no equivalent diagnosis in Western medicine or clear understanding of pathophysiology. Furthermore, this study excluded children with the two most common comorbidities seen with TS - ADHD and OCD. There are therefore some issues with respect to the generalizability of these findings. Furthermore, the availability of these three compounds outside of the trial centers is unknown and safety concerns remain regarding the ingredients used - the Ning dong granule as formulated by Wang contains human dried placenta. Further research and information on the safety and reliability of mass production of these agents is required before formal recommendations on use can be made.
5. There is a need for more long-term studies of drug efficacy and adverse effects, as well as the efficacy and safety of medication combinations for severe tics resistant to monotherapy.
6. Few studies have been performed investigating the efficacy and safety of cannabis-based medicine in children with various diseases. However, only recently could it be

demonstrated that the cannabinoid cannabidiol (CBD) may significantly reduce convulsive-seizure frequency in children with Dravet syndrome.[147] There is preliminary evidence that cannabinoids such as tetrahydrocannabinol (THC, dronabinol) might also be effective in children in preventing vomiting due to antineoplastic treatment[148, 149] and in treatment resistant spasticity.[150] 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.[148, 150] There is increasing evidence that cannabis-based medicine might be effective in the treatment of adults with TS with improvement of both tics and different psychiatric comorbidities.[151] A recent press release for a single dose study of a first-in-class small molecule inhibitor of monoacylglycerol lipase (MGLL), ABX-143, which regulates one of the key natural activators of the cannabinoid receptor, suggests efficacy for the treatment of tics.[152]

7. 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,[153] 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 non-standardized 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.

8. Future research on the effect of special diets, nutritional supplements and exercise on tic severity is needed. There is a great deal of patient interest in the use of non-medical therapies for tics, and very few controlled studies have been performed in this area.

Table 1: Confidence in Evidence

High confidence: more likely than	CBIT vs psychoeducation and supportive therapy
Moderate confidence: probably more likely than	Haloperidol vs placebo Risperidone vs placebo Aripiprazole vs placebo Tiapride vs placebo Clonidine vs placebo Clonidine plus methylphenidate vs placebo* Methylphenidate vs placebo* 5-Ling Granule vs placebo Onabotulinum toxin A injections vs placebo Ningdong granule (formulated by Zhao) vs placebo Active vs sham deep brain stimulation of the globus pallidus Desipramine vs placebo*
Low confidence: possibly more likely than	Pimozide vs placebo Ziprasidone vs placebo Metoclopramide vs placebo Guanfacine vs placebo Topiramate vs placebo THC vs placebo
Very low confidence: insufficient evidence to determine	Haloperidol vs pimozide Pimozide vs risperidone Risperidone vs clonidine Risperidone vs aripiprazole Baclofen vs placebo Levetiracetam vs placebo IVIG vs placebo

	N-acetylcysteine vs placebo Nicotine vs placebo Nicotine added to haloperidol vs placebo added to haloperidol Ningdong granule (formulated by Wang) vs placebo Riluzole vs placebo D-serine vs placebo Ondansetron vs placebo Pramipexole vs placebo HRT vs ERP HRT vs education Internet HRT vs waitlist Face-to-face HRT vs internet HRT Continuous theta burst stimulation of SMA vs sham rTMS of SMA vs sham DBS of the thalamus ON vs OFF DBS of the centromedian-parafascicular complex ON vs OFF

*in children with tics and ADHD

DISCLAIMER

Practice guidelines, practice advisories, comprehensive systematic reviews, focused systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

CONFLICT OF INTEREST

The AAN is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs

and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual, as amended.[154]

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix 3: Complete search strategy

MEDLINE 1946 to Present

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

#	Searches
1	tic disorders/dh, dt, th, pc, px, su or tourette syndrome/dh, dt, th, pc, px, su
2	((tic or tics or tourette*) adj3 (syndrome or disease or disorder)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	exp Antipsychotic Agents/
4	exp Adrenergic alpha-Agonists/
5	exp Anticonvulsants/
6	exp Botulinum Toxins/
7	exp Behavior Therapy/
8	habit reversal training.mp.
9	exp Electric Stimulation Therapy/ or exp Deep Brain Stimulation/
10	exp Transcranial Magnetic Stimulation/ or exp Electric Stimulation/

11	or/3-10
12	2 and 11
13	1 or 12
14	2 and (treat* or therap* or pharmacol* or drug*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15	13 or 14
16	limit 15 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial)
17	randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/
18	exp clinical trials/ or placebos/ or research design/
19	(clinic* adj25 trial*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	(placebo* or random* or (latin adj square)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22	comparative study/ or exp evaluation studies/ or follow-up studies/ or prospective studies/ or cross-over studies/ or cohort*.mp. [mp=title, abstract, original title, name of

	substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23	(control* or prospective* or volunteer*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24	or/17-23
25	16 and 24
26	16 or 25
27	2 and 24
28	27 and stimulat*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
29	27 and outcome*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
30	26 or 28 or 29
31	(shapiro* or scale* or global* or symptom* or severity).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
32	27 and 31
33	30 or 32
34	remove duplicates from 33

CENTRAL

Same strategy as for MEDLINE - 268

PsychINFO 1967 to July Week 4 2016

#	Searches
1	tics/ or tourette syndrome/
2	drug therapy/ or exp drugs/ or exp "side effects (drug)"/
3	exp Neuroleptic Drugs/ or exp "Side Effects (Drug)"/ or exp Treatment Effectiveness Evaluation/
4	exp behavior therapy/ or exp cognitive behavior therapy/
5	neuromodulation/
6	exp Anticonvulsive Drugs/
7	exp Adrenergic Drugs/
8	exp Botulinum Toxin/
9	exp Deep Brain Stimulation/ or exp Electrical Brain Stimulation/
10	exp Transcranial Magnetic Stimulation/
11	1 and 2
12	or/3-10
13	1 and 12
14	11 or 13
15	14 and (trial* or cohort*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16	limit 14 to ("0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or "0830 systematic review" or 1200 meta analysis)
17	15 or 16

EMBASE 1988 to 2016 Week 32

#	Searches
1	tic/ or gilles de la tourette syndrome/
2	tic/dt, dm, pc, th, su or gilles de la tourette syndrome/dt, dm, pc, th, su
3	exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/
4	2 and 3
5	4 not conference abstract.pt.
6	limit 5 to human

ClinicalTrials.gov

Acronym: Short Title

Age Groups: Notes

Completion Date: Notes

Conditions: Keywords

Enrollment: Notes

First Received: Notes

Funded Bys: Notes

Gender: Notes

Interventions: Notes

Last Updated: Notes

Last Verified: Notes

NCT Number: Accession Number

Other IDs: Notes

Outcome Measures: Notes

Phases: Notes

Start Date: Date| Year

Start Date: Year

Recruitment: Notes

Results First Received: Notes

Sponsor/Collaborators: Author

Start Date: Notes

Study Designs: Notes

Study Results: Notes

Study Types: Notes

Title: Title

URL: Publisher

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

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

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

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

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

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

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

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

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

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

Appendix e-5 Evidence tables

Antipsychotics

Bruggeman 2001 Risperidone versus **pimozide** in Tourette's disorder: a comparative double-blind parallel group study.	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Primary outcome not defined	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Participants meeting DSM-IIIR criteria for Tourette Age 10 to 65 years N=50 8 weeks	Pimozide up to 6 mg/day (n=24) Risperidone up to 6 mg/day (n=26)	*Tourette Syndrome Severity Scale (TSSS)* *Global impression score* *Difference in mean shifts -0.1 (-0.9, 0.7)* *SMD -0.07 95% CI -0.62, 0.49* *Total score* *Difference in mean shifts -0.2 (-1.1, 0.8)* *SMD -0.12 95% CI -0.68, 0.43*			*Number of patients reporting extrapyramidal symptoms:* 4/26 risperidone 8/24 pimozide RR 0.46 (0.16, 1.33) p=0.13 *Extrapyramidal Symptom Rating Scale* Baseline: Risperidone 3.5 Pimozide 4.0 Endpoint: Risperidone 3.5 Pimozide 4.0 *Somnolence* Risperidone 12/26 Pimozide 10/24 *Depression* Risperidone 8/26 Pimozide 6/24	

				Mean weight gain Risperidone 3.9 kg Pimozide 2.9 kg Significant increase in weight in both groups but was not different between groups. When stratified by age, patients under 18 had significantly greater weight gain with risperidone than participants over 18. *ECG* – no clinically relevant differences detected *BP and HR* – no clinically significant changes

Gilbert 2004 Tic reduction with **risperidone** versus **pimozide** in a randomized, double blind, crossover trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study; baselines for entire group presented but not across treatment order groups. Statistics	Yes	Yes	Yes	No	II

		describing period and carryover effects.					
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 7-17 years meeting DSM-IV-TR criteria for Tourette or CMTD N=19 12 weeks	Pimozide up to 4 mg/day Risperidone up to 4 mg/day	*Yale Global Tic Severity Scale (total)* 13 patients analyzed Baseline 43.3 (SD 17.5) Pimozide 34.2 (SD 14.2) Risperidone 25.2 (SD 13.6) "There was a significantly lower YGTSS score after risperidone versus after pimozide ($F_{1,11}$=4.7; p=0.05)." SMD 0.65 (0.0-1.35)		*Extrapyramidal symptom rating scale* Baseline 0.1 (SD 0.3) Pimozide 0.2 (SD 0.6) Risperidone 0.2 (SD 0.6) p=0.89 *Mean weight increase* Pimozide 1.0 kg Risperidone 1.9 kg *ECG* – no significant differences between treatments in changes in ECG parameters. QT_c increases were minimal and did not approach 450 ms.	

Ross 1978 Comparison of **pimozide** with **haloperidol** in Gilles de la Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover trial; baselines for entire group presented but not across treatment order groups. Statistics describing	Unclear	No primary outcome defined	No	Yes	III

		period and carryover effects not present.					
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Individuals with Tourette Syndrome, 8 to 28 years old. N=9 33 days	Pimozide 10-12 mg Haloperidol 10-12 mg Placebo	*Mean 5 minute tic counts for last 4 days of each treatment:* Both pimozide ($p<0.04$) and haloperidol ($p<0.02$) significantly decreased tic frequency compared to baseline and placebo. Tic severity was not significantly different between treatment groups. Pimozide 29.4 SD 30.9 Haloperidol 21.9 SD 18.8 Placebo 44.6 SD 37.2 SMD Pimozide vs Placebo 0.65 (0.18, 1.11) SMD Haloperidol vs Placebo 0.77 (0.03,1.51) SMD Haloperidol vs Pimozide 0.30 (-0.13, 0.720			Not formally discussed. Pimozide led to significantly fewer complaints of adverse effects, particularly tiredness ($p<0.03$).	

Sallee 1997 Relative efficacy of **haloperidol** and **pimozide** in children and adolescents with Tourette's Disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes; crossover. Analysis for carryover effects performed; comparison of baseline	Unclear	Yes	Yes	Yes	II

		characteristics across treatment order groups performed and equivalent.					
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Children and adolescents meeting DSM-III-R criteria for Tourette N=24 24 weeks	Pimozide 1-6 mg/day Haloperidol 1-8 mg/day Placebo	*Tourette Syndrome Global Scale* *Total Score* Baseline 28.5 (SD 14.5) Placebo 26.8 (SD 15.9) Pimozide 17.1 (SD 14.1) p=0.02 vs placebo Haloperidol 20.7 (SD 17.3) SMD pimozide vs placebo 0.65 (0, 1.3) SMD haloperidol vs placebo 0.37 (-0.22, 0.95) SMD haloperidol vs pimozide -0.23 (-0.80, 0.35)			*Extrapyramidal symptoms rating scale* The number of EPS in the haloperidol group (mean 4.1, SD 6.9) was higher in comparison with both the placebo group (mean 1.4, SD 3.0, p<0.01) and the pimozide group (mean 2.0, SD 3.0, p<0.05). Pimozide was not significantly different than placebo. Individuals receiving 2 mg of pimozide or more had a higher rate of EPS than those receiving 1-2 mg; 11/16 vs 1/10. *Abnormal involuntary movements scale* AIMS ratings did not differ among the treatments. Placebo mean 0.2 SD 0.7 Pimozide mean 0.4 SD 1.1 Haloperidol Mean 0.3 SD 1.1 3 patients treated with haloperidol developed treatment emergent depression or anxiety, 2 developed academic failure.	

				ECG effects of pimozide and haloperidol were not evident; both treatments were indistinguishable from placebo in their effects on HR, rhythm, and waveform. *Prolactin* Placebo 6.8 SD 2.5 Pimozide 21.6 SD 19.5 ($p<0.01$) Haloperidol 12.9 SD 8.4 ($p<0.01$)

Shapiro 1984 Controlled study of **pimozide** vs **placebo** in Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study. Baseline characteristics presented for entire sample. Data analyzed for period and carryover effects.	Unclear	No primary outcome specified	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Individuals meeting DSM-III criteria for Tourette Mean age 24.7 years;	Pimozide 6.88 mg/day (mean dose) Placebo	*Tourette Syndrome Severity Scale (TSSS)* Pimozide mean 1.52 Placebo mean 4.42 Mean Difference Pimozide Placebo -2.90 Standard error of the difference 0.65		*Akinesia (sedation, lethargy)* Pimozide 18/20 Placebo 11/20 *Akathisia* Pimozide 8/20 Placebo 2/20 *Postural rigidity*		

	range 11-53. N=24 14 weeks		SMD 1.22 (0.51, 1.93)	Pimozide 4/20 Placebo 0/20 *Weight gain* Pimozide 1/20 Placebo 0/20 *Abnormal ECG* Pimozide 1/20 – nonspecific T wave change Placebo 0/20 *No significant mean difference in HR or BP.*

Shapiro 1989 Controlled study of **haloperidol, pimozide**, and **placebo** for the treatment of Gilles de la Tourette's Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes. For crossover phase, period and carryover effects analyzed.	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	DSM III criteria for Tourette Age 8 to 65 years Average age 21 years N=68	Parallel group phase and cross-over phase. Haloperidol and pimozide compared to placebo in parallel phase. Pimozide compared to	*Parallel group phase* *Tourette Syndrome Severity Scale* Placebo 2.9 (SD 2.5) n=19 Haloperidol 1.2 (SD 1.2) n=18 Pimozide 2.5 (SD 3.0) n=20 SMD Haloperidol vs Placebo: 0.86 (0.19, 1.53)		*Parallel group phase* *Extrapyramidal Symptoms* *Use of benztropine* Haloperidol 1/18 Pimozide 6/20 *Acute dystonia* Haloperidol 1/18 Pimozide and Placebo 0 *Akathisia* Haloperidol 1/18 Pimozide 2/20 Placebo 2/19		

	15 to 21 weeks (depending if allocated to placebo in initial phase of study)	haloperidol in cross-over phase. Pimozide up to 20 mg/day (mean dose 10.6 mg) Haloperidol up to 10 mg day (mean dose 4.5 mg) Placebo	SMD Pimozide vs Placebo: 0.15 (-0.48, 0.77) *Videotape counts (no/min)* Total motor tics Placebo 9.5 (SD 5.8) Haloperidol 6.8 (SD 8.0) Pimozide 5.7 (SD 7.9) SMD Haloperidol vs Placebo: 0.39 (-0.26, 1.04) SMD Pimozide vs Placebo: 0.55 (-0.09, 1.19) Total vocal tics Placebo 0.7 (SD 1.2) Haloperidol 0.2 (SD 0.3) Pimozide 0.5 (SD 1.1) SMD Haloperidol vs Placebo: 0.57 (-0.09, 1.22) SMD Pimozide vs Placebo: 0.17 (-0.46, 0.80) *Cross-over phase* *Tourette Syndrome Severity Scale at endpoint* (n=55) Haloperidol 1.4 (SD 1.5) Pimozide 2.0 (SD 2.3) SMD 0.31 (0.06, 0.55) p=0.011 *Videotape counts (no/min)* *Total motor tics* Haloperidol 5.6 (SD 6.3) Pimozide 5.2 (SD 6.4) *Total vocal tics* Haloperidol 0.3 (SD 0.7) Pimozide 0.4 (SD 0.8)	*Tremor* Pimozide 1/20 Haloperidol and Placebo 0 *Weight gain* Haloperidol 2/18 Pimozide 1/20 Placebo 2/19 No clinically meaningful ECG or cardiac adverse effects. QTc interval was significantly prolonged by pimozide, but not by haloperidol or placebo.

Dion 2002 **Risperidone** in the treatment of Tourette Syndrome: a double blind, **placebo** controlled trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Patients 14 to 65 years meeting DSM-III-R criteria for Tourette N=46 8 weeks	Risperidone 0.5 to 6.0 mg/day Placebo	*Proportion of patients who improved at endpoint by at least one point on the seven point global severity rating of the Tourette Syndrome Severity Scale* Risperidone 60.8% Placebo 26.1% p=0.04 *Tourette Syndrome Severity Scale Total Score* Raw mean difference at endpoint between risperidone and placebo 1.07 (0.048, 2.092, p=0.04) SMD 0.59 (0.01, 1.17) *Tourette Syndrome Severity Scale Global Severity* Raw mean difference at endpoint between risperidone and placebo 0.65 (0.056, 1.244, p=0.03) SMD 0.62 (0.04, 1.20)		*Extrapyramidal symptoms rating scale* Patients treated with risperidone had significantly (p=0.004) greater total score for the parkinsonism examination than those treated with placebo. Risperidone 5.56 (SD 5.11) Placebo 2.88 (SD 3.03) *Antiparkinsonian medication* was prescribed to a greater proportion of individuals receiving risperidone (9/23) than placebo (2/23), p=0.04. *Fatigue* 13/23 risperidone, 4/23 placebo, p=0.01 *Somnolence* 8/23 risperidone, 1/23 placebo, p=0.02 *Depression* 6/23 risperidone, 1/23 placebo, p=0.1 *Weight increase* 5/23 risperidone, 1/23 placebo, p=0.19		

Scahill 2003 A **placebo**-controlled trial of **risperidone** in Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adults with DSM-IV diagnosis of Tourette Age range 6-62 years N=34 8 weeks	Risperidone 1 to 4 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Scores* *All participants (n=34)* Risperidone (n=16) Baseline 26.0 (SD 5.07) Endpoint 17.6 (SD 4.75) Change score 8.64 (4.9-12.0) Placebo (n=18) Baseline 27.4 (SD 8.75) Endpoint 25.4 (SD 8.75) SMD 1.09 (0.37, 1.81) *Pediatric sample (n=26)* Risperidone (n=12) Baseline 27.0 (SD 5.02) Endpoint 17.3 (SD 4.75) Change score 9.8 (6.0-13.6) Placebo (n=14) Baseline 28.6 (SD 8.00) Endpoint 26.0 (SD 8.66) SMD 1.22 (0.38, 2.06)		*Weight gain* Risperidone 2.8 kg Placebo no change p = 0.0001 *Increased appetite* 7/16 risperidone, 1/18 placebo *EPS* not reported or observed in children or adults No abnormalities or clinically significant changes observed in any laboratory values, cardiovascular indices as measured by the *ECG*, or *vital signs* during the study 2 children in the risperidone group developed *acute social phobia* 2 adult males developed *sexual side effects*-erectile dysfunction, decreased libido *Sedation* 3/16 risperidone, 1/18 placebo *Fatigue* 6/16 risperidone, 1/18 placebo	

Gaffney 2002 Risperidone versus **clonidine** in the treatment of children and adolescents with Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 7 to 17 years who met DSM-III-R criteria for Tourette N=21 8 weeks	Risperidone, up to 0.06 mg/kg/day Clonidine, up to 0.005 mg/kg/day	*Yale Global Tic Severity Scale Global Severity Score* Risperidone (n=9) Baseline 51.8 (SD 13.8) Change -10.9 (SD 11.7) Clonidine (n=12) Baseline 52.3 (SD 17.0) Change -13.8 (SD 16.9) Significant effect by time (p=0.003) but not by group (p=0.728). SMD -0.19 (-1.06, 0.67)		*Sedation* Clonidine 5/12 Risperidone 1/9 *Stiffness* Clonidine 1/12 Risperidone 2/9 *No significant differences between groups in EPS based on the Simpson Angus Scale* *Mean weight change* Clonidine 0.1 kg (SD 5.9) Risperidone 2.1 kg (SD 2.3) *No significant ECG changes in either group.*		

Ghanizadeh 2014 Aripiprazole versus **risperidone** for treating children and adolescents with tic disorder: a randomized double	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	No	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

blind clinical trial	Children and adolescents meeting DSM IV criteria for a tic disorder Age 6-18 N=60 8 weeks	Aripiprazole, up to 10 mg/day for children less than 40 kg, up to 15 mg/day for children over 40 kg Risperidone, up to 2mg/day in children less than 40 kg, up to 3mg/day in children over 40 kg	*Yale Global Tic Severity Scale Total Tic Score* Aripiprazole (n=31) Baseline 16.5 (SD 6.4) 8 weeks 5.7 (SD 6.2) Risperidone (n=29) Baseline 19.0 (SD 7.3) 8 weeks 9.9 (SD 7.7) SMD 0.17 (-0.33, 0.68) Both groups significantly improved with time. There was no difference in the amount of improvement between groups. Both risperidone and aripiprazole significantly increased all quality of life subscale scores during the trial. There was a significant difference between aripiprazole and risperidone in the social functioning subscale.	*Increased appetite* Aripiprazole 8/31 Risperidone 8/29 *Drowsiness* Aripiprazole 8/31 Risperidone 5/29 *Diurnal urinary incontinence* Aripiprazole 0/31 Risperidone 4/29

Yoo 2013 A multicenter, randomized, double-blind **placebo** controlled study of **aripiprazole** in children and adolescents with Tourette's disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes; some differences at baseline	Yes	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 6-18	Aripiprazole, mean dose 11 mg/day	*Yale Global Tic Severity Scale Total Tic Score* Mean Difference between Aripiprazole (n=32) and		*Extrapyramidal disorder* Aripiprazole 3/32 Placebo 2/28		

	years with DSM-IV diagnosis of Tourette N=61 10 weeks	Placebo	Placebo (n=29): 5.35 (0.89-9.81) SMD 0.60 (0.09, 1.12)	No difference between aripiprazole and placebo groups in scores on the Simpson Angus Rating Scale, Abnormal Involuntary Movements Scale, or Barnes Akathisia Rating Scale *Weight gain* Aripiprazole 1.6 kg (SD 2.0) Placebo 0.2 kg (SD 1.7) p=0.0055 *BMI increase* Aripiprazole 0.5 (SD 0.8) Placebo -0.1 (SD 0.8) p=0.01 *Waist circumference increase* Aripiprazole 1.7 cm (SD 3.7) Placebo 0.1 (SD 2.7) p=0.03 There were no significant or clinically relevant changes in *blood pressure, heart rate, or ECG* over the course of the study.

Sallee 2017 Once daily oral **aripiprazole** for the treatment of tics in children and adolescents with Tourette's	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	

disorder: a randomized, double-blind, **placebo-controlled** trial	Trial Length Children and adolescents 7-17 years meeting DSM-IV-TR criteria for Tourette N=133 8 weeks	Aripiprazole Low dose group: 5 mg if less than 50 kg, 10 mg if more than 50 kg High dose group: 10 mg if less than 50 kg, 20 mg if more than 50 kg Placebo	*Yale Global Tic Severity Scale Total Tic Score* Change from baseline to week 8 Low dose aripiprazole (n=44) -13.4 (SE 1.6) High dose aripiprazole (n=45) -16.9 (SE 1.6) Placebo (n=44) -7.1(SE 1.6) Mean difference, low dose and placebo -6.3 (-10.2, -2.3) p=0.002 SMD: 0.66 (0.23, 1.09) Mean difference, high dose and placebo -9.9 (-13.8, -5.9) p<0.0001 SMD: 1.03 (0.59, 1.48)	*Treatment discontinuation rate* Low dose 4.5% High dose 22.5% Placebo 4.5% *Increased appetite* Low dose 4/44 High dose 3/45 Placebo 1/44 *Akathisia* Low dose 0/44 High dose 3/45 Placebo 0/44 *Sedation* Low dose 8/44 High dose 4/45 Placebo 1/44 Any extrapyramidal symptom-related adverse event (akathisia, dystonia, extrapyramidal disorder, parkinsonism rest tremor, and tremor) Low dose 1/44 High dose 6/45 Placebo 0/44 Mean change in weight from baseline to week 8 Low dose 1.8 kg (SD 2.0) High dose 1.0 kg (SD 2.0) Placebo 0.6 kg (SD 2.1) Potentially clinical relevant weight gain (>7%) Low dose 18.2% High dose 9.3% Placebo 9.1%

Sallee 2000 Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study.	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No (3 primary efficacy variables)	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 7 to 17 years with DSM-IV diagnosis of Tourette or CMTD N= 28 8 weeks	Ziprasidone up to 40 mg/day Placebo	*Yale Global Tic Severity Scale Global Severity Score* Placebo (n=11) Baseline 46.9 (SD 17.7) Endpoint 39.3 (SD 21.3) Change 7.6 (SD 10.6) Ziprasidone (n=16) Baseline 46.9 (SD 13.8) Endpoint 28.6 (SD 17.3) Change 18.3 (SD 9.9) p=0.016 SMD 1.05 (0.233, 1.87) *Yale Global Tic Severity Scale Total Tic Score* Placebo Baseline 24.6 (SD 9.6) Endpoint 22.9 (SD 10.8) Change 1.7 (SD 5.0) Ziprasidone Baseline 24.7 (SD 6.8) Endpoint 16.1 (SD 7.4) Change 8.6 (SD 6.7) p=0.008 SMD 1.14 (0.31, 1.96)		*Two severe side effects in ziprasidone group-sedation and akathisia.* Most common adverse effect of ziprasidone was *sedation*, in 11/16 patients, compared to 5/11 patients with placebo. No clinically significant effects were observed in specific assessments for movement disorders. *Mean Simpson Angus, Barnes Akathisia and Abnormal Involuntary Movement Scales* scores in the ziprasidone group were similar to those in the placebo group (data not shown). *Change in body weight* Ziprasidone +0.7 kg (SD 1.5) Placebo +0.8 (SD 2.3) *Prolactin*		

				Ziprasidone 5/16 experienced increases in serum prolactin greater than 1.1 times the upper limit of normal. Elevations were transient and returned to normal by the end of the study. One boy experienced mild gynecomastia. *No clinically significant changes in HR, BP or ECG parameters.*

Zheng 2016 A proprietary herbal medicine (**5-Ling Granule**) for Tourette syndrome (includes **tiapride** and **placebo** controls)	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents meeting DSM-IV criteria for Tourette AND had a condition fitting the excessive subtype in traditional Chinese medicine based	5-Ling Granule 15-22.5 g/day Tiapride 200-400 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Placebo n=116 Baseline 22.7 SD 6.7 Week 8 14.4 SD 7.5 Tiapride n=123 Baseline 23.1 SD 6.9 Week 8 10.1 SD 6.4 SMD tiapride vs placebo: 0.62 (0.36-0.88) 5-Ling granule n=362 Baseline 23.7 SD 6.8 Week 8 10.6 SD 6.8 SMD 5-ling vs placebo: 0.55 (0.33-0.76) *Yale Global Tic Severity Scale Impairment Score*		Physical tiredness and sleep disturbances were significantly more frequent in those treated with tiapride.		

	diagnosis (see text) N=603 8 weeks		Placebo Baseline 27.3 SD 8.0 Week 8 17.2 SD 9.2 Tiapride Baseline 28.3 SD 8.3 Week 8 11.2 SD 8.1 SMD tiapride vs placebo: 0.69 (0.43-0.96) 5-Ling granule Baseline 28.3 SD 8.3 SD 11.6 SD 9.7 SMD 5-ling vs placebo 0.58 (0.37-0.80)	

Nicolson 2005 A randomized double-blind, **placebo**-controlled trial of **metoclopramide** for the treatment of Tourette's disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No primary outcome specified	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 7-18 years with DSM-IV-TR diagnosis of	Metoclopramide, up to 40 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Metoclopramide (n=14) Baseline 22.6 (SD 5.3) Endpoint 13.9 (SD 3.7) Placebo (n=13) Baseline 22.2 (SD 6.8) Endpoint 19.4 (SD 5.8) p=0.001		*Weight gain* Metoclopramide 1.0 kg (SD 1.9) Placebo 0.5 kg (SD 1.4) *Sedation* Metoclopramide 3/14 Placebo 1/13 *Extrapyramidal Symptoms*		

	Tourette or a chronic tic disorder N= 27 8 weeks		SMD 1.14 (0.33, 1.95)	No subjects in either group showed any evidence of EPS. The scores in both groups on the Simpson Angus Rating Scale did not change from baseline, while the changes in score on the Abnormal Involuntary Movement Scale were almost identical and did not differ significantly between the groups (no raw data given). *ECG* No statistically significant group differences in the change in any cardiac conduction parameters (PR, QRS, QTc) *Prolactin* Significant increase seen in metoclopramide treated group compared to baseline.

Other Medications

Du 2008 Randomized double-blind multicenter **placebo**-controlled clinical trial of the **clonidine**	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II

adhesive patch for the treatment of tic disorders	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics	Adverse Effects
	Children and adolescents 6-18 years of age who met Chinese Classification of Mental Disorders 3rd edition criteria for Transient Tic Disorder, Chronic motor or vocal tic disorder, or Tourette disorder N=437 4 weeks	Clonidine adhesive patch, 1.0, 1.5 or 2.0 mg per week depending on body weight Placebo adhesive patch	*Yale Global Tic Severity Scale Total Tic Score* Clonidine (n=326) Baseline 21.35 SD 8.67 Endpoint 9.83 SD 7.77 Difference -11.53 SD 8.22 Placebo (n=111) Baseline 22.56 SD 8.79 Endpoint 11.84 SD 8.01 Difference -10.72 SD 7.50 SMD 0.26 (0.04, 0.47)	Clonidine *Abnormal ECG* in 2/326 *HR* increased from baseline 80.80 to 81.84 on treatment *Systolic BP* decreased from 98.87 to 97.60 *Diastolic BP* decreased from 64.97 to 64.01

Leckman 1991 Clonidine treatment of Gilles de la Tourette's Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No primary outcome specified	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Children and adults with Tourette according to DSM III criteria N=47 12 weeks	Clonidine, 4 to 5 micrograms per kg, up to maximum of 0.25 mg/day Placebo	*Tourette Syndrome Global Scale, Motor tics* Clonidine (n=21) Baseline 18.9 SD 5.4 Endpoint 12.3 SD 7.8 Difference 6.6 SD 9.49 Placebo (n=19) Baseline 17.9 SD 4.0 Endpoint 16.4 SD 4.6 Difference 1.5 SD 6.1 SMD 0.63 (0.00, 1.27) *Tourette Syndrome Global Scale, Vocal tics* Clonidine (n=21) Baseline 13.5 SD 6.9 Endpoint 9.4 SD 7.1 Difference 4.1 SD 9.90 Placebo (n=19) Baseline 12.6 SD 6.0 Endpoint 9.0 SD 5.1 Difference 3.6 SD 7.88 SMD 0.06 (-0.57, 0.68)	*Clonidine* Sedation or fatigue 90% Dry mouth 57% Faintness or dizziness 43% Irritability 33% *Placebo* Sedation or fatigue 37% Dry mouth 26% Faintness or dizziness 21% Irritability 5% *Vital signs* were unchanged during the course of the study

Goetz 1987 Clonidine and Gilles de la Tourette syndrome: double-blind study using objective rating methods	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	No; crossover study. No description of period or carryover effects.	Unclear	No primary outcome specified	Yes	Unclear	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adults meeting DSM III	Clonidine, 0.0075 or 0.015 mg/kg/day	*Tic Scores-Motor tics Number* Placebo 46.3 SD 28.2 Clonidine 41.8 SD 23.6		Clonidine Sedation 57% Dry mouth 37% Restlessness 27%		

	criteria for Tourette N= 30 6 months	Placebo	SMD 0.17 (-0.27, 0.61) *Tic Scores-Vocal tics Number* Placebo 4.3 SD 4.4 Clonidine 5.6 SD 8.7 SMD -0.19 (-0.63, 0.25)	No clinically significant changes were observed in the supine or standing blood pressure or pulse.

Hedderick 2009 Double-blind, crossover study of **clonidine** and **levetiracetam** in Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study. Baseline characteristics presented but not across treatment order groups. Statistics describing period and carryover effects.	Yes	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adults with Tourette defined according to Tourette Syndrome Classificati	Clonidine, up to 0.4 mg/day Levetiracetam, up to 2500 mg/day	*Yale Global Tic Severity Scale Total Tic Score* Clonidine Baseline 25.2 SD 4.3 Endpoint 21.8 SD 4.4 Change score -3.4 (-5.55, -1.25) SD 3.47 p=0.013 Levetiracetam		*Irritability* Levetiracetam 4/10 Clonidine 3/10 *Tired/sleepy* Levetiracetam 2/10 Clonidine 5/10		

	on Study Group N=10 15 weeks		Baseline 22.7 SD 5.7 Endpoint 23.6 SD 10.6 Change score 0.9 (-2.91, 4.71) SD 6.15 p=0.655 SMD Clonidine vs Levetiracetam 0.86 (-0.03, 1.75)	

Tourette Syndrome Study Group 2002 Treatment of ADHD in children with tics	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Children meeting DSM IV criteria for Tourette disorder, chronic motor or vocal tic disorder and ADHD N= 136 16 weeks	Clonidine, up to 0.6 mg/day Methylphenidate up to 60 mg/day Combined clonidine and methylphenidate Placebo	*Yale Global Tic Severity Scale Total Score* Clonidine versus placebo Treatment effect 10.9, 98.3% CI 2.1-19.7, p=0.003 SMD 0.72 (0.22, 1.22) Methylphenidate versus placebo Treatment effect 9.4, 98.3% CI 0.7-18.1, p=0.01 SMD 0.61 (0.13, 1.10) Combination versus placebo Treatment effect 11.0, 98.3% CI 2.1-19.8, p=0.003 SMD 0.72 (0.22, 1.22)			Sedation Clonidine 48% Methylphenidate 14% Placebo 6%	

Singer 1995 The treatment of Attention Deficit Hyperactivity Disorder in Tourette's Syndrome: A Double Blind Placebo Controlled Study with **Clonidine** and **Desipramine**	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study. Baseline provided for entire group but not across treatment order groups. Statistics describing period effects.	Unclear	Primary outcome not specified	No	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children with Tourette and ADHD N=34 18 weeks	Clonidine 0.05 mg QID Desipramine 25 mg QID Placebo	*Parent linear analogue scale, tics* End of treatment values Clonidine 41.1 SD 1.1 Desipramine 30.0 SD 0.7 Placebo 47.4 SD 1.8 Unable to calculate SMDs due to inconsistencies in data.		Not described in manuscript		

Scahill 2001 A **placebo**-controlled study of **guanfacine**	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating

in the treatment of children with tic disorders and attention deficit hyperactivity disorder				specified			
	Yes	Yes	Unclear	Primary outcome not specified	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents with DSM IV criteria for ADHD (any type) and tic disorder (any type) N=34 8 weeks	Guanfacine, up to 4 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Guanfacine (n=15) Baseline 15.2 SD 6.6 Endpoint 10.7 SD 7.0 Placebo (n=17) Baseline 15.4 SD 7.0 Endpoint 15.4 SD 5.5 SMD 0.75 (0.03, 1.47)		No serious side effects. Sedation in 7 subjects treated with guanfacine, causing treatment withdrawal in one subject. No difference in lying and standing blood pressure or heart rate across treatment groups or time.		

Cummings 2002 Neuropsychiatric effects of **guanfacine** in children with mild Tourette syndrome: a pilot study	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Primary outcome not specified	Yes	Yes	II
	Population N	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Trial Length			
	Children and adolescents with a chronic tic disorder according to DSM IV or TS based on TS Classification Group criteria N= 24 4 weeks	Guanfacine up to 2 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Guanfacine (n=12) Baseline 17.92 SD 7.8 Endpoint 11.25 SD 7.0 Difference 6.67 SD 10.48 Placebo (n=12) Baseline 15.67 SD 5.6 Endpoint 14.62 SD 9.4 Difference 1.05 SD 10.94 SMD 0.525 (-0.289, 1.338)	Fatigue/sleepiness prevented dose escalation in 2/12 subjects treated with guanfacine

Murphy 2017 Extended release guanfacine does not show a large effect on tic severity in children with chronic tic disorders	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Children 6-17 years with a chronic tic disorder N=34 8 weeks	Extended release guanfacine, 1 to 4 mg per day Placebo	Yale Global Tic Severity Scale Total Tic Score Guanfacine XR (n=16) Baseline 26.25 (SD 6.61) Endpoint 23.56 (SD 6.42) Placebo (n=18) Baseline 27.67 (SD 8.7) Endpoint 24.72 (SD 10.54) SMD 0.13 (-0.54, 0.81)			Fatigue/tiredness Guanfacine 14/16, Placebo 3/18 Drowsiness Guanfacine 12/16, Placebo 3/18 Dry mouth Guanfacine 10/16, Placebo 4/18 Headache Guanfacine 10/16, Placebo 2/18 Irritability	

				Guanfacine 9/16, Placebo 1/18 Stomachache Guanfacine 8/16, Placebo 2/18

Marras 2001 Botulinum toxin for simple motor tics	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study. Baseline characteristics presented but not across treatment order groups. Statistics describing period effects presented.	Yes	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Tic disorder, with at least one simple motor tic performed by a muscle amenable to	Botulinum toxin Placebo	*Number of treated tics per minute as observed on the 12 minute videotape protocol* Unweighted median proportional change in treated tics per minute was -39% during the botulinum toxin phase and +5.8% during the placebo phase		*Subjective weakness* Botulinum toxin 9 Placebo 2 *Weakness on examination* Botulinum toxin 12 Placebo 2 *Neck discomfort* Botulinum toxin 3 Placebo 1 *Swallowing difficulty* Botulinum toxin 2		

	injection, age 15-55 N=20 24 weeks		Median net effect was -37% (interquartile range -77, -15%) p=0.0007 Using data provided from Figure 2 Raw mean difference, Change Botox- Change Placebo = -46.17 SD 44.42 SMD 1.27 (0.51, 2.03)	Placebo 0 *Motor restlessness* Botulinum toxin 2 Placebo 0 *New tics* Botulinum toxin 2 Placebo 0

Jankovic 2010 A randomized double-blind **placebo** controlled study of **topiramate** in the treatment of Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Children and adults meeting DSM-IV criteria for Tourette N= 29 12 weeks	Topiramate 50 to 200 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Mean score at baseline Topiramate 26.64 SD 8.78 Placebo 28.77 SD 7.53 Mean score at 12 weeks Topiramate 12.36 SD 12.04 Placebo 23.1 SD 8.99 Mean change from baseline Topiramate -14.29 SD 10.47 Placebo -5.0 SD 9.88 p=0.026 SMD 0.91 SD 0.11-1.71			*Kidney stone* Topiramate 1/15 *Mean weight change* Topiramate -2.1 kg Placebo +1.9 kg *Drowsiness* Topiramate 2/15 Placebo 2/14	

Singer 2001 Baclofen treatment in Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes; crossover. Baseline characteristics described across treatment order and statistics describing period effects.	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children with Tourette syndrome N=10 10 weeks	Baclofen 60 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Raw mean difference (baclofen – placebo) -5.8 (-17.1, 5.6) p=0.27 SMD 0.55 (-0.39, 1.49) *Yale Global Tic Severity Scale Impairment Score* Raw mean difference (baclofen – placebo) -8.9 (14.9, -2.9) p=0.01 SMD 0.84 (0.10, 1.58) *Yale Global Tic Severity Scale Global Score* Raw mean difference (baclofen-placebo) -14.7 (-30.3, 0.9) p=0.06 SMD 0.75 (-0.13, 1.63)		Baclofen was well tolerated.		

Awaad 2009 Levetiracetam in	Masked or objective	Baseline characteristics presented	Concealed allocation	No more than two	Inclusion exclusion	Minimum 80% completion rate	Class Rating

Tourette syndrome	outcome rating	and equivalent		primary outcomes specified	criteria defined		
	Yes	No	Unclear	Primary outcome not specified	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 6-18 years with Tourette syndrome. 14/24 had comorbid epilepsy. N=24 8 weeks	Levetiracetam, 1000 to 2000 mg daily Placebo	Outcome data incomplete; no raw data provided.		Outcome data incomplete; no raw data provided.		

Smith-Hicks 2007 A double blind randomized **placebo** controlled trial of **levetiracetam** in Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Baseline characteristics presented but not across treatment	Unclear	Yes	Yes	Yes	II

		order groups. Carryover effects analyzed.					
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Children meeting TS study group criteria for Tourette N=22 10 weeks	Levetiracetam, up to 30 mg/kg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Levetiracetam Baseline 18.95 SD 7.35 Post treatment 16.8 SD 6.25 Placebo Baseline 20.4 SD 5.32 Post treatment 18.95 SD 7.28) Raw mean difference -1.49 (-5.51, 2.53) p=0.47 SMD 0.22 (-0.38, 0.82)			Side effects reported during the levetiracetam phase included irritability, insomnia, sadness, tiredness, verbal aggression, reduced school participation, anxiousness and headache. Side effects reported during the placebo phase included headache, irritability, aggression, low frustration tolerance, insomnia, tiredness, sadness, worry, anxiousness and dry mouth	

Bloch 2016 N-Acetylcysteine in the treatment of pediatric Tourette Syndrome: Randomized, double-blind, **placebo controlled add-on** trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Presented but differences present between groups	Unclear	Yes	Yes	Yes	II

	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics	Adverse Effects
	Children and adolescents with a primary diagnosis of Tourette or chronic tic disorder N=31 12 weeks	N-Acetylcysteine up to 2400 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* N-Acetylcysteine Baseline 27.1 SD 7.2 Week 12 24.3 SD 7.9 Placebo Baseline 26.3 SD 7.7 Week 12 21.3 SD 4.6 SMD 0.45 (-0.26, 1.17)	No significant differences in side effect rates between NAC and placebo. No severe side effects reported.

Gabbay 2012 A double-blind, **placebo-**controlled trial of **omega-3 fatty acids** in Tourette's Disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Presented; some differences noted between groups at baseline; adjustment for differences made in analysis	Unclear	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents meeting	Omega-3 fatty acids up to 6000 mg/day	Yale Global Tic Severity Scale Total Tic Score Decrease from baseline to endpoint		No significant treatment differences were found in adverse events. Most frequently reported		

	DSM-IV-TR criteria for Tourette N=33 20 weeks	(combined EPA+DHA ratio of 2:1) Placebo (olive oil)	Omega-3 fatty acids (n=17) 5.2 SD 7.3 Placebo (n=16) 3.6 SD 5.6 p>0.1 SMD 0.25 (-0.44, 0.93) Yale Global Tic Severity Scale Impairment Score Omega-3 fatty acids 9.7 SD 8.6 Placebo 3.1 SD 8.3 p=0.06 SMD 0.78 (0.07, 1.49) Yale Global Tic Severity Scale Global Score Omega-3 fatty acids 14.9 SD 12.1 Placebo 6.7 SD 11.6 p<0.05 SMD 0.69 (0, 1.39)	adverse events in the omega-3 fatty acid group were headache, nausea/stomachache, and diarrhea/loose stool.

Zhao 2010 Traditional Chinese medicine **Ningdong granule**: the beneficial effects in Tourette's Disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents meeting DSM-IV – TR criteria for Tourette N=33	Ningdong granule 1 g/kg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Ningdong Granule Baseline 23.00 SD 7.34 Week 8 13.48 SD 7.25 Placebo Baseline 22.42 SD 6.42 Week 8 20.00 SD 6.12 SMD 0.97 (0.45-1.49)		No serious adverse effects reported during the study. 2 subjects reported loss of appetite and 1 subject reported constipation in the Ningdong granule group versus no subjects in the placebo group.		

	8 weeks			

Wang 2012 Effects of Chinese herbal medicine **Ningdong granule** on regulating dopamine, serotonin and GABA in patients with Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Minimal baseline characteristics provided	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents meeting DSM-IV criteria for Tourette N=120 8 weeks	Ningdong granule 5 mg/kg/day Haloperidol Ningdong granule + haloperidol Placebo	*Yale Global Tic Severity Scale* No raw data provided-only graph given, and unable to precisely determine values from graph. Unable to calculate SMDs. According to text: patients in the control group had no significant change in YGTSS motor, vocal or total tic scores. From the 2-week assessment onward, patients in the Ningdong granule group, haloperidol group, and Ningdong granule + haloperidol group had significantly reduced motor, vocal and total tic scores ($p<0.05$)		*Sedation* Control 1/28 Ningdong granule 3/29 Haldol 10/30 Ningdong granule + Haldol 12/30 *Weight gain* Control 2/28 Ningdong granule 2/29 Haldol 4/30 Ningdong granule + Haldol 5/30 *Extrapyramidal symptoms* Control 0/28 Ningdong granule 0/29 Haldol 5/30 Ningdong granule + Haldol 5/30 *QT prolongation* Control 0/28 Ningdong granule 0/29 Haldol 5/30 Ningdong granule + Haldol 5/30 *Anxiety* Control 1/28 Ningdong granule 0/29 Haldol 6/30		

				Ningdong granule + Haldol 4/30

Muller-Vahl 2002 Treatment of Tourette's Syndrome with Delta-9 **Tetrahydro-cannabinol**	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Baseline characteristics presented but not across treatment order groups. Period and carryover effects described.	Yes	No	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults meeting DSM-IIIR criteria for Tourette N=12 Patients received a single dose of THC or placebo, and crossed	Single dose of THC 5 to 10 mg Placebo	*Yale Global Tic Severity Scale Total Score* Change from baseline THC -10.25 SD 12.95 Placebo -3.75 SD 9.12 p=0.132 SMD 0.58 (-0.24, 1.40) *Tourette Syndrome Symptom List* Change from baseline THC -14.0 SD 10.97 Placebo -4.92 SD 6.69 p=0.015 SMD 1.00 (0.02, 1.98)		No serious adverse reactions Blood pressure and pulse did not change significantly. Transient adverse events with THC including dizziness, tiredness.		

	over to the other treatment 4 weeks later				

Muller-Vahl 2003 Delta-9 Tetrahydro-cannabinol is effective in the treatment of tics in Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults meeting DSM-IIR criteria for Tourette N=24 6 weeks	THC, up to 10 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Change from baseline THC (n=9) -4.44 SD 7.62 Placebo (n=11) -0.45 SD 4.48 SMD 0.66 (-0.25, 1.56)		Blood pressure and pulse did not change. 5 patients in the THC group reported mild side effects like tiredness, dry mouth, dizziness.		

Howson 2004 Clinical and attentional effects of acute **nicotine** treatment in Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes; crossover study	Unclear	No	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Children and adolescents meeting DSM-IV criteria for Tourette, on antipsychotic medications N=23 1 week	Single transdermal 7 mg dose of nicotine Placebo	Acute effect of nicotine on tics Total tic frequency (videotaped counts) (n=14) Placebo Baseline 18.4 SE 3.0 Post treatment 16.0 SE 2.3 SD 8.6 Nicotine Baseline 23.3 SE 3.7 Post treatment 21.1 SE 4.6 SD 17.2 SMD 0.38 (-0.14, 0.89) No significant difference between treatments on clinical assessment 1 week after treatment received.	Most common adverse effects associated with nicotine were itching at the site of patch application, dizziness, headache and vomiting.

Silver 2001 Transdermal nicotine and haloperidol in Tourette's disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 8+ meeting DSM-IV criteria for Tourette. All subjects were treated with haloperidol until they reached a	Transdermal nicotine patch 7 mg Placebo	*Yale Global Tic Severity Scale Global Severity Total* On day 5 (optimal haloperidol dose plus transdermal patch: Nicotine (n=27) Change from baseline: -17.4 (SEM 2.5 SD 13.0) Placebo (n=29)		*Nausea* Nicotine 25/35 Placebo 6/35 *Vomiting* Nicotine 14/35 Placebo 3/35		

	plateau in therapeutic effectiveness for at least two weeks, then were randomized to add-on nicotine or placebo. Five days after randomization, dose of haloperidol was decreased by 50%. N=70 33 days		Change from baseline: -8.2 (SEM2.4 SD 12.92) p=0.01 SMD 0.71 (0.17, 1.25) On day 19 (50% haloperidol dose plus transdermal patch): Nicotine (n=27) Change from baseline: -12.7 (SEM3.1 SD 16.1) Placebo (n=29) Change from baseline: -5.6 (SEM3.0 SD 16.2) p=0.1 SMD 0.44 (-0.09, 0.97) On day 33 (50% haloperidol dose alone) Nicotine (n=27) Change from baseline: -7.5 (SEM2.7 SD 14.0) Placebo (n=29) Change from baseline: -0.4 (SEM2.6 SD 14.0) p=0.04 SMD (-0.03, 1.04)	

Silver 2001 Multicentre, double-blind, **placebo**-controlled study of **mecamylamine** monotherapy for Tourette's disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Children and adolescents 8 to 17 years meeting DSM-IV criteria for Tourette N=61 8 weeks	Mecamylamine 7.5 mg/day Placebo	*Tourette's Disorder Scale-Clinician Rated* Mecamylamine (n=25) Baseline 76.8 Endpoint 65.6 (ns) Placebo (n=25) Baseline 65.9 Endpoint 50.1 (ns) *Tourette's Disorder Scale-Parent Rated* Mecamylamine Baseline 83.3 Endpoint 61 (ns) Placebo Baseline 66.5 Endpoint 46.7 (ns) Baseline imbalance, no SDs, CIs, or p values given. Unable to calculate SMD.	No group differences in blood pressure. Significant group difference in heart rate with a higher mean standing heart rate at week 1 in the mecamylamine group.

Peterson 1998 A double blind placebo controlled crossover trial of an antiandrogen in the treatment of Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover study. Examined baseline characteristics across treatment order. Treatment by period assessed in model.	Yes	Yes	Yes	Yes	I
	Population N	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Trial Length			
	Adults 18 to 55 years with Tourette syndrome N=13 8 weeks-treatment for 3 weeks with flutamide and placebo with 2 week washout period in between	Flutamide 250 mg three times a day Placebo	*Yale Global Tic Severity Scale Motor Tic Severity* Minimal data provided. From manuscript text: The backward stepwise elimination of variables from the mixed-effects repeated measures ANOVA produced for motor tic severity a mode that included only treatment ($F1, 61=7.0$, $p<0.01$) and phase ($F1, 61=5.1$, $p<0.03$) main effects, with parameter estimates of 0.96 (SE=0.36) and 0.77 (SE 0.34) respectively. Motor tics improved during flutamide treatment and during phase 2 of the study. Although the therapeutic effect on motor symptoms was statistically highly significant, the percentage decrease in motor tic symptom severity (7%) was relatively small from the standpoint of clinical significance. Unable to calculate SMD due to inadequate data.	Free and total testosterone increased, LH increase, estradiol unchanged.

Lemmon 2015 Efficacy of glutamate modulators in tic suppression: a double blind randomize	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I

d controlled trial of D-serine and riluzole in Tourette Syndrome	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics	Adverse Effects
	Children and adolescents 8-17 yeas meeting criteria for Tourette as defined by the TS Classification Study group N=24 8 weeks	Riluzole, up to 200 mg/day D-serine, up to 30 mg/kg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Placebo (n=5) Baseline 31.4 SD 7.1 Endpoint 21.2 SD 8.4 Riluzole (n=10) Baseline 29.9 SD 19.4 Endpoint 19.4 SD 11.5 SMD vs placebo 0.17 (-0.91, 1.24) D-serine (n=9) Baseline 27.8 SD 4.6 Endpoint 21.6 SD 10.6 SMD vs placebo -0.04 (-1.13, 1.05)	No serious adverse effects. No adverse effect related discontinuation.

Toren 2005 Ondansetron treatment in Tourette's Disorder: a 3-week randomized double blind placebo-controlled study	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	No- placebo group had significantly higher tic severity as baseline	Unclear	Primary outcome not specified	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Individuals age 12+ who met DSM-IV criteria for Tourette	Ondansetron up to 24 mg/day Placebo	*Yale Global Tic Severity Scale Total Tic Score* Ondansetron Baseline 24.04 SD 9.44 Week 3 17.50 SD 9.48 Placebo Baseline 31.82 SD 7.15 Week 3 27.28 SD 12.12		One patients in the ondansetron group dropped out because of mild and transient abdominal pain.		

	N=30 3 weeks		SMD 0.53 (-0.20, 1.25)	

Kurlan 2012 A multicenter randomized **placebo-**controlled clinical trial of **pramipexole** for Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Not presented but stated equivalent	Unclear	Yes	Yes	No drop outs reported	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 6-17 years with Tourette N= 63 6 weeks	Pramipexole, up to 0.25 mg twice daily Placebo	Yale Global Tic Severity Scale Total Tic Score Mean change from baseline to endpoint Placebo -7.17 SD 8.94 (n=20) Pramipexole -7.16 SD 9.07 (n=42) p=0.996 SMD 0.0 (-0.53, 0.53)		Pramipexole generally well tolerated. No serious adverse effects. Most frequent adverse effects in the pramipexole group were headache (27.9%), nausea (18.6%). Vomiting (11.6%).		

Hoekstra 2004 Lack of effect of intravenous **immunoglobulins** on tics: a double-blind **placebo-**controlled study	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Trial Length			
	Patients age 14 + with DSM-IV tic disorders N=30 14 weeks	IVIG 1 g/kg daily for 2 consecutive days Placebo	*Yale Global Tic Severity Scale Total Tic Score* Baseline IVIG (n=14) 25.0 Placebo (n=15) 25.5 Week 14 IVIG 20.1 Placebo 24.3 p=0.18 RMD 4.2 (-1.94, 10.34) SMD 0.50 (-0.24, 1.24)	*Headache* IVIG 11/14 Placebo 4/15 *Fever* IVIG 5/14 Placebo 0/15 *Nausea* IVIG 7/14 Placebo 1/15

Gadow 2007 Immediate release **methylphenidate** for ADHD in children with comorbid chronic multiple tic disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	No; crossover study. Did not present statistics describing period and carryover effects.	Unclear	Yes	Yes	No discussion of drop-outs	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 6-12 years old meeting DSM-IIR or DSM-IV criteria for ADHD	Methylphenidate at three different doses: 0.1, 0.3 and 0.5 mg/kg Placebo	*Yale Global Tic Severity Scale Global Severity* Placebo 31.8 SD 16.3 MPH 0.1 mg/kg 30.3 SD 14.7 SMD vs placebo: 0.10 (-0.19, 0.38) MPH 0.3 mg/kg 32.2 SD 14.8		There were significant dose related effects of MPH on heart rate, diastolic blood pressure and weight loss.		

	and either Tourette disorder or Chronic Motor Tic Disorder N=71 8 weeks	Each treatment was given for 2 weeks	SMD vs placebo: 0.02 (-0.26, 0.30) MPH 0.5 mg/kg 30.5 SD 14.2 SMD vs placebo: 0.09 (-0.20, 0.38)	

Castellanos 1997 Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment group order or describe period and carryover effects.	Unclear	Yes	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Boys with Tourette syndrome as defined by the Tourette Syndrome	Subjects randomly assigned to crossover trial of 3 weeks each of MPH,	Group 1 Tic severity was significantly greater during the 2nd and 3rd weeks of DEX and during the 2nd week of MPH than during any of the placebo weeks, or during the 3rd week of MPH.			Appetite suppression and weight loss with psychostimulants.	

	Classification Study Group, and ADHD N=20 9 weeks	DEX or placebo. Group 1 12 boys underwent weekly increases in stimulant dose: low-medium-high. MPH 15, 25 and 45 mg BID. DEX 7.5, 15 and 22.5 mg BID. Group 2 6 boys underwent: low-medium-medium dose titration. MPH 15, 25, and 25 mg BID. DEX 7.5, 15, and 15 mg BID. Group 3 4 boys underwent: low-high-high dose titration. MPH 15, 45, and 45 mg BID. DEX 7.5, 22.5, 22.5 mg BID	Group 2 No significant main effect of drug on tic severity in this group. Tic severity was less severe during the 3rd week of MPH than during the first week for 4/6 subjects; same pattern observed for 3/6 subjects on DEX. Group 3 Statistical trend for tic severity to be greater on DEX although this did not reach significance. Interaction between drug and dose was not statistically significant. When ratings on the lowest dose were compared across the entire subject group (n=20), there was no significant effect of either stimulant on tic severity rating. When the data from subjects who received medium stimulant doses were combined (n=16), the overall effect of drug on tics was not significant. When the data from subjects who received high doses were combined (n=14), the overall effect of drug on tics was significant. DEX resulted in significantly greater tic severity than placebo, while tic severity on MPH was indistinguishable from placebo. Unable to calculate SMDs due to inadequate data.	

Feigin 1996 A controlled trial of **deprenyl** in children with Tourette syndrome and ADHD	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes, some differences between groups; crossover. Did not present baseline characteristics across treatment order groups. Statistics describing period and carryover effects.	Unclear	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents with Tourette and ADHD meeting DSM-IIIR criteria N=24 Two 8 week treatment periods separated	Deprenyl 5 mg BID Placebo	*Yale Global Tic Severity Scale Total Score* Mean improvement with deprenyl relative to placebo: 9.3 (-0.4, 19.0) SD 24.25 p=0.06 SMD 0.47 (-0.05, 0.99)		Rash, nausea, agitation, irritability, drowsiness, headache.		

	by a 6 week washout				

Allen 2005 Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and youth 7 to 17 years old meeting DSM-IV criteria for Tourette syndrome and ADHD n=148 18 weeks	Atomoxetine 0.5 to 1.5 mg/kg/day Placebo	Yale Global Tic Severity Scale Total Tic Score Atomoxetine (n=74) Baseline 21.7 SD 7.8 Change -5.5 SD 6.9 Placebo (n=71) Baseline 22.2 SD 8.3 Change -3.0 SD 8.7 Difference 95% CI -0.13, 4.88, p=0.06 SMD 0.32 (-0.01, 0.65) The lower bound of the one-sided 95% CI 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 non-inferiority of atomoxetine relative to placebo.		2 discontinuations due to adverse events in atomoxetine group- headache and vomiting. Decreased appetite and nausea occurred at higher rates in the atomoxetine group. Atomoxetine group showed a mean decrease of body weight at endpoint (-0.9 kg) that was different from the increase seen in the placebo group (+1.6 kg). Atomoxetine group had an increase in HR by +8.3 bpm.		

Spencer 2002 A double-blind	Masked or objective	Baseline characteristics presented	Concealed allocation	No more than two primary	Inclusion exclusio	Minimum 80% completion rate	Class Rating

comparison of **desipramine** and **placebo** in children and adolescents with chronic tic disorder and comorbid ADHD	outcome rating	and equivalent		outcomes specified	n criteria defined		
	Yes	Yes	Unclear	Primary outcome not specified	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 5 to 17 years of age with a DSM-IV diagnosis of ADHD and a chronic tic disorder n=41 6 weeks	Desipramine up to 3.5 mg/kg Placebo	*Yale Global Tic Severity Scale Total Score* Desipramine (n=21) Baseline 63 SD 18 Week 6 43 SD 23 p<0.001 Placebo (n=20) Baseline 61 SD 15 Week 6 65 SD 15 P=0.08 SMD desipramine vs placebo 1.13 (0.47-1.79)		No serious adverse effects. *Decreased appetite* Desipramine 24% Placebo 0% p=0.02 *Increased DBP* Desipramine 70 mmHg Placebo 65 mmHg p=0.03 *Increased HR* Desipramine 97 bpm Placebo 84 bpm p<0.005		

Piacentini 2010 Behaviour therapy for children with Tourette Disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

	Children 9 to 17 with Tourette or chronic tic disorder n=126 10 weeks	Comprehensive behavioral intervention for tics (CBIT) Supportive therapy and education	*Yale Global Tic Severity Scale Total Tic Score* Baseline Behavioural intervention (n=61) 24.7 (23.1-26.3) Control (n=65) 24.6 (23.2-26.0) Week 10 Behavioural intervention 17.1 (15.1-19.1) Control 21.1 (19.2-23.0) SMD 0.51 (0.15-0.86)	No serious adverse events Tic worsening reported in 1 participant receiving behavioral intervention, and 4 participants in the control group.

Wilhelm 2012 Randomized trial of **behaviour therapy** for adults with Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Individuals 16+ with Tourette syndrome or a chronic tic disorder N=122 10 weeks	Comprehensive behavioral intervention for tics (CBIT) Supportive therapy and education	*Yale Global Tic Severity Scale Total Tic Score* CBIT (n=63) Baseline 24.0 SD 6.5 Week 10 17.8 SD 7.3 Supportive therapy/Psychoeducation (n=59) Baseline 21.8 SD 6.6 Week 10 19.3 SD 7.4 SMD 0.62 (0.25-0.98)		Tic worsening was reported by 4 patients in the CBIT group and 4 patients in the control group.		

Deckersbach 2006 Habit reversal	Masked or objective	Baseline characteristics presented	Concealed allocation	No more than two	Inclusion exclusion	Minimum 80% completion rate	Class Rating

versus supportive psychotherapy in Tourette's disorder	outcome rating	and equivalent		primary outcomes specified	criteria defined		
	No	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Adults who met DSM-IV criteria for Tourette N=35 5 months	Habit reversal, consisting of self-monitoring, competing responses, relaxation training, and contingency management Supportive psychotherapy	*Yale Global Tic Severity Scale Total Tic Score* Habit reversal (n=15) Baseline 29.3 SD 5.8 Post treatment 18.3 SD 5.2 Supportive psychotherapy (n=15) Baseline 27.7 SD 6.3 Post treatment 26.8 SD 6.7 SMD 1.41 (0.62-2.22)			None reported	

Wilhelm 2003 Habit reversal versus supportive psychotherapy for Tourette's disorder	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	No	Yes	Unclear	Yes	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Adults meeting DSM-IV criteria	Habit reversal therapy-consisting of	*Yale Global Tic Severity Scale Total Tic Score* Score at endpoint			Not reported	

	for Tourette N=32 5 months	awareness training, self monitoring, relaxation training, competing response training, contingency management, and inconvenience review Supportive psychotherapy	Habit reversal (n=16) 19.81 SD 7.58 Supportive psychotherapy (n=13) 26.88 SD 9.19 SMD 0.85 (0.09-1.61) Yale Global Tic Severity Scale Impairment Score Score at endpoint Habit reversal 9.44 SD 10.33 Supportive psychotherapy 22.69 SD 12.35 SMD 1.18 (0.38-1.97)	

Verdellen 2004 Exposure with response prevention versus habit reversal in Tourette's syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	No	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	7-55 years DSM-IV criteria for Tourette N=43	Exposure and response prevention, 12 weekly treatment sessions Habit reversal therapy, 10 weekly treatment sessions	*Yale Global Tic Severity Scale Total Tic Score* ERP (n=19) Baseline 26.2 SD 7.6 Post Rx 17.6 SD 7.6 HRT (n=18) Baseline 24.1 SD 7.2 Post Rx 19.7 SD 9.3 SMD ERP vs HRT: 0.25 (-0.40-0.90)		Adverse effects not reported.		

Yates 2016 Habit reversal training and educational group treatments for children with Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 9-13 years with a diagnosis of Tourette syndrome or chronic tic disorder N=33 8 sessions	Habit reversal therapy (CBIT) Psychoeducation	*Yale Global Tic Severity Scale Motor Tic Severity* Mean difference (Education-HRT) 2.1 SMD 0.55 (-0.16, 1.27) *Yale Global Tic Severity Scale Phonic Tic Severity* Mean difference (Education-HRT) -1.5 SMD -0.26 (-0.97, 0.44)		Adverse effects not reported		

Ricketts 2016 A randomized waitlist-controlled pilot trial of voice over Internet protocol-delivered behaviour	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		

therapy for youth with chronic tic disorders	Children and youth 8-17 years with a DSM-IV TR diagnosis of Tourette's disorder or chronic tic disorder N=20 8 sessions over 10 weeks	CBIT using voice over internet protocol Waiting list	*Yale Global Tic Severity Scale Total Tic Score* CBIT-VoIP (n=12) 18.5 SD 7.75 Waitlist (n=8) 20.25 SD 6.21 SMD 0.24 (-0.65, 1.14)	Adverse effects not reported

Himle 2012 A randomized pilot trial comparing videoconference versus face to face delivery of behaviour therapy for childhood tic disorders							
	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children 8-17 years who met DSM-IV-TR criteria for Tourette	CBIT – face to face CBIT – via telehealth	*Yale Global Tic Severity Scale Total Tic Score* Telehealth (n=10) Pre 23.4 SD 7.5 Post 15.6 SD 9.8 Effect size 0.54 Face-to-face (n=8) Pre 24.1 SD 3.9 Post 17.6 SD 6.5		Adverse effects not reported		

	syndrome or chronic tic disorder N=20 8 sessions of CBIT delivered over 10 weeks		Effect size 0.75 SMD Telehealth vs Face-to-face 0.24 (-0.70, 1.17)	

Bergin 1998 Relaxation therapy in Tourette Syndrome: a pilot study	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Yes	No	No	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Children and adolescents 7-18 years with diagnosis of Tourette syndrome according to Tourette Syndrome Classification Study Group N=23	Relaxation therapy- awareness training, diaphragmatic breathing, behavioral relaxation training, applied relaxation techniques, electromyographic feedback Minimal therapy	No difference between treatments noted on any of the tic rating scales used- Yale Global Tic Severity Scale, Hopkins Motor and Vocal Tic Scale, Tourette Syndrome Severity Scale, Parent Linear Analogue Scale, Goetz Videotape scale. No raw data provided.		Adverse effects not described.		

	6 weekly one hour training sessions			

Nagai 2014 Biofeedback treatment for Tourette syndrome: a preliminary randomized controlled trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	No	Unclear	Yes	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Adults with DSMIV-TR criteria for Tourette syndrome N=21 4 week treatment, during which individuals attended 30 minute biofeedback sessions 3 times a week	Active biofeedback Sham control	Change in 10-minute tic count from baseline to endpoint- severe baseline imbalance, no change score or p value provided for between group difference. Unable to calculate SMD. Biofeedback group Baseline 143.17 SD 97.55 Endpoint 110.25 SD 77.69 Sham control Baseline 43.00 SD 33.52 Endpoint 21.22 SD 19.65 Significant improvement from baseline to endpoint in both group, but no difference between groups in effect.			Adverse effects not reported.	

Kefalopoulou 2015 Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double blind, randomized crossover trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment order groups. Statistics describing period effects.	Yes	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Severe medically refractory Tourette, age >20 years n=15 6 months	DBS GPi stimulation on first DBS GPi stimulation off first Switch to opposite condition after 3 months	*Yale Global Tic Severity Scale Global Score* Off-stimulation 80.7 SD 12.0 On-stimulation 68.3 SD 18.6 RMD -12.4 SD 15.9 p=0.048 95% CI for RMD (-24.7, -0.1) SMD 0.79 (0, 1.61) Open label stimulation (last follow-up) 51.5 SD 18.5 Comparison to baseline 87.9 SD 9.2 RMD -36.3 SD 22.6		2 patients developed infection of the hardware for DBS, necessitating the removal of leads, extension cables, and implantable pulse generators and administration of antibiotics. 1 patient developed worsened tics and hypomania during the on-stimulation period. Hospital admission was necessary.		

Welter 2017 Anterior pallidal deep brain stimulation for Tourette syndrome: a randomized, double-blind, controlled trial	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Not presented	Yes	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Adults 18-60 years with severe and medically refractory Tourette syndrome N=19 3 months	DBS of the anterior globus pallidus – active stimulation versus sham	Yale Global Tic Severity Scale Total Score Active stimulation -4.5 (median) (-12.5, 0.5) (interquartile range) Sham Stimulation 5.0 (median) (-2.5, 17.5) (interquartile range) SMD 0.74 (-0.28, 1.76)			15 serious adverse events occurred in 13 patients 7 events related to surgery – infections leading to removal or the stimulator and electrodes in 4 patients 17 adverse events were related to stimulation-increased tic severity and anxiety, depressive symptoms, dysarthria, sleep disorder, imbalance and abnormal movements resembling dyskinesia that resolved rapidly after stimulator adjustment.	

Ackermans 2011 Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment order groups, but only one patient randomized to OFF-ON. No statistics describing period effects.	Yes	Yes	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Severe refractory patients with Tourette >25 years n=6 6 months	DBS thalamus stimulation on first DBS thalamus stimulation off first Switch to opposite condition after 3 months	Yale Global Tic Severity Scale Total Tic Score Stimulation on 25.6 SD 12.8 Stimulation off 41.1 SD 5.4 p=0.046 SMD 1.58 (-0.12, 3.28) Open label stimulation (at one year) 21.5 SD 11.1 Comparison to baseline 42.3 SD 3.1		1. Small parenchymal hemorrhage in one patient, resulting in vertical gaze palsy. Persistent subjective slowing of vertical fixation and pursuit on stimulation led the patient to switch off the stimulator after the study. 2.Infection requiring 6 weeks of IV antibiotics. 3. Motor and psychiatric symptoms including lethargy, binge eating, dysarthria, gait disturbance, falls.	

				CT showed cerebral atrophy. All patients reported substantial restriction in ADLs due to lack of energy. Subjective oculomotor abnormalities in all patients.

Welter 2008 Internal pallidal and thalamic stimulation in patients with Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment order groups. No statistics describing period effects.	Unclear	Yes	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults with severe TS and medically refractory to treatment n=3	Crossover study of 4 conditions: 1) bilateral thalamic stimulation 2) bilateral pallidal stimulation 3) bilateral thalamic and	Yale Global Tic Severity Scale Results only presented graphically and individually for each of the 3 subjects. No means or standard deviations provided for group. Unable to determine effect sizes. Largest responses		Thalamic stimulation-cheiro-oral or arm paresthesias, decreased libido Pallidal stimulation-lethargy, nausea, vertigo, anxiety		

	8 months	pallidal stimulation 4)sham stimulation Each stimulation condition was maintained for two months	seen with pallidal stimulation.	

Maciunas 2007 Prospective randomized double blind trial of **bilateral thalamic deep brain stimulation** in adults with Tourette Syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment order groups. No statistics describing period effects.	Unclear	Yes	Yes	Yes	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults with Tourette syndrome who are medically refractory to treatment	Target: centromedian-parafascicular complex Stimulators were independentl	Yale Global Tic Severity Scale Total Tic Score off-off 40.6 SD 5.2 on-on 34.8 SD 6.4 p=0.06, Friedman test, comparison of 4 stimulator states. SMD 0.99 (-0.28, 2.26)		One patient had excellent initial response that waned substantially after 3 months, requiring re-programming of stimulator.		

	n=5 28 days	y enabled on or disabled off on the right and left sides in 4 combinations: 1) off-off 2) off-on 3) on-off 4) on-on Participants randomized to each condition for 7 days		

Okun 2013 A trial of scheduled deep brain stimulation for Tourette syndrome Centromedian region	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present baseline characteristics across treatment order groups. No statistics describing period effects.	Yes	Yes	Yes	No	III
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults with medicatio	DBS of the centromedia	Yale Global Tic Severity Scale		No significant adverse events. Transient and reversible program		

	n refractory and severely disabling Tourette syndrome n=5	n thalamic region Participants randomized to received immediate DBS activation at postoperative day 30 or delayed-start DBS activation at postoperative day 60	The results of the delayed start design comparing the 2 participants who were randomized to on stimulation at day 30 vs the 3 participants who were randomized to on stimulation at day 60 were not statistically different. Baseline versus 6 month YGTSS score (open label stimulation) YGTSS Global Score Baseline 91.6 SD 8.8 6 months 73.8 SD 11.5	related adverse effects, including dizziness, paraesthesia, dizziness, nausea, gait and balance problems, eye movement abnormalities.

Wu 2014 Functional MRI navigated rTMS on SMA in chronic tic disorders	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	No	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Individuals >10 years old with chronic tic disorders or Tourette according to DSM-IV-TR N=12	30 Hz Continuous theta burst stimulation (cTBS) at 90% resting motor threshold over the supplementary motor area, 8 trains over 2 consecutive days	Yale Global Tic Severity Score Total Tic Score Active cTBS (n=6) Day 1 27.5 SD 7.4 Day 9 23.2 SD 9.8 Sham cTBS (n=6) Day 1 26.8 SD 4.8 Day 9 21.9 SD 7.7 SMD -0.15 (-1.28, 0.99)			3 participants complained of mild adverse effects (abdominal pain, headache, dry eyes) which resolved without medical intervention.	

	9 days	Sham stimulation		

Landeros 2015 Randomized sham controlled double-blind trial of rTMS for adults with severe Tourette syndrome	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics		Adverse Effects		
	Adults with severe TS according to DSM-IV-TR criteria n=20 3 weeks	Active rTMS at 110% motor threshold over the SMA, 15 sessions, 1-Hz; 30 minutes, 1,800 pulses per day. Once a day, 5 days per week, for 3 weeks Sham rTMS	*Yale Global Tic Severity Scale Total Tic Score* Active rTMS (n=9) Baseline 35.8 SD 9.2 Week 3 29.6 SD 11.9 Sham rTMS (n=11) Baseline 36.3 SD 8.2 Week 3 31.5 SD 8.1 SMD 0.19 (-0.69, 1.07)		Headache, neck pain and muscle sprain were the only severe side effects reported during active treatment.		

Chae 2004 A pilot safety study of rTMS in Tourette's	Masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than two primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class Rating
	Yes	Crossover. Did not present	Unclear	Not stated	Yes	Yes	III

syndrome		baseline characteristics across treatment order groups. No statistics describing period effects.					
	Population N Trial Length	Intervention and Comparator	Primary Outcome Tics			Adverse Effects	
	Individuals 13 to 60 with DSM-IV diagnosis of Tourette syndrome n=8 5 days; effect of treatment on tic severity measured at the end of each day of stimulation	rTMS at 110% motor threshold over left motor cortex (twice) or left prefrontal cortex (twice) , using either 1 Hz or 15 Hz TMS, or sham TMS (once); each treatment paradigm was received for one day with effects assessed same day	Yale Global Tic Severity Scale Total Tic Score There were no statistically significant specific effects of rTMS by site or frequency. Data presented in graphical form- no raw scores given. Unable to calculate SMD.			3 reports of headache following treatment (40 treatment sessions total).	

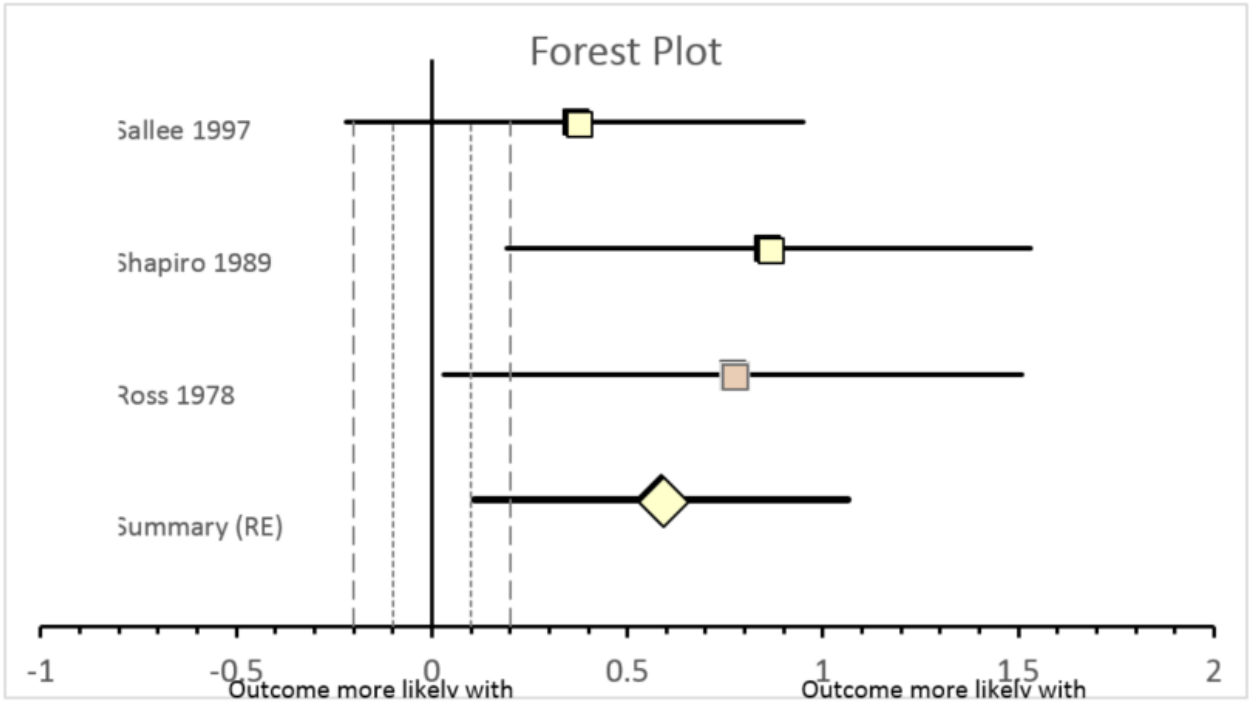
Appendix e-6. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
    - High confidence: highly likely or highly probable
    - Moderate confidence: likely or probable
    - Low confidence: possibly
    - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
    - High: requires 2 or more Class I studies
    - Moderate: requires 1 Class I study or 2 or more Class II studies
    - Low: requires 1 Class II study or 2 or more Class III studies
    - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
    - Consistency
    - Precision
    - Directness
    - Publication bias
    - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
    - Magnitude of effect
    - Dose response relationship
    - Direction of bias

Appendix e-7. Evidence synthesis tables

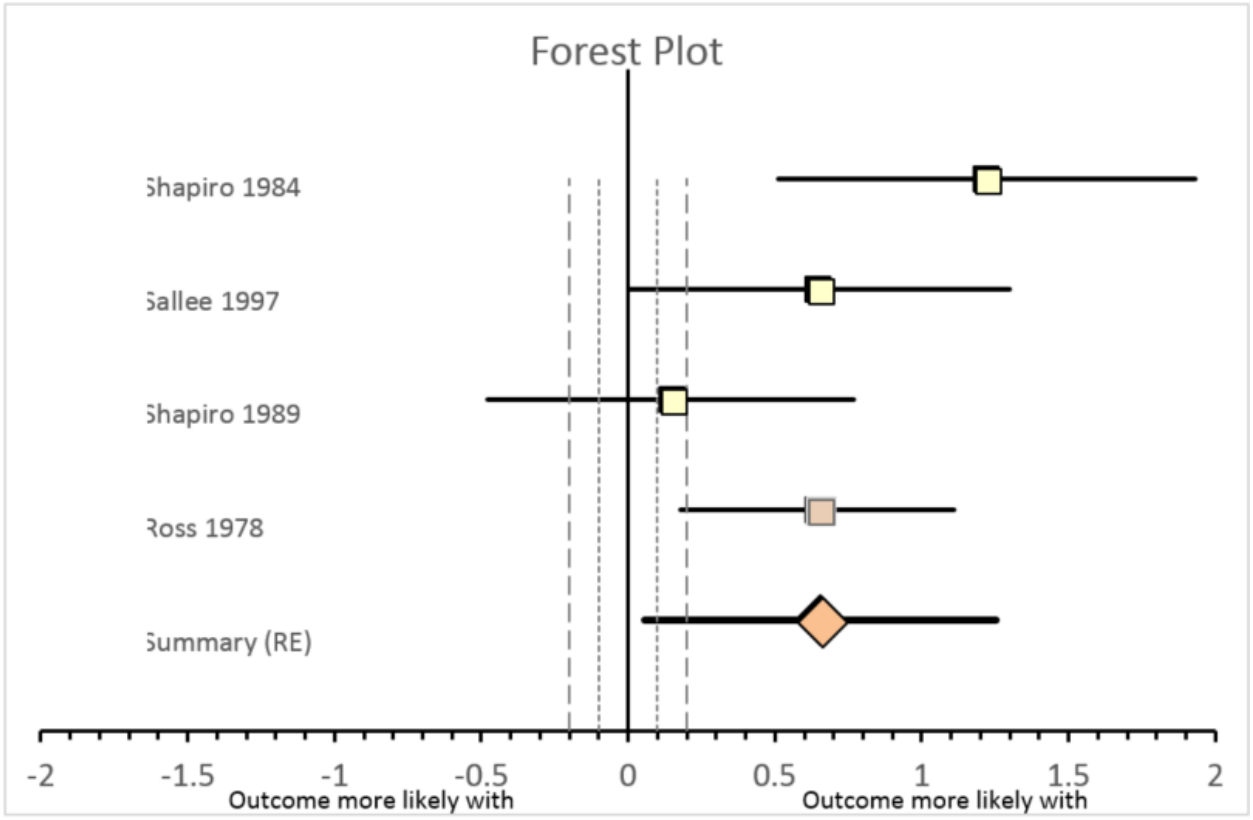
Haloperidol vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving haloperidol								
-1	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Sallee 1997	II	Minor	0.370	-0.220	0.950			2.000	
1	Shapiro 1989	II	Minor	0.860	0.190	1.530			2.000	
0	~~Ross 1978~~	III	Minor	0.770	0.030	1.510			3.000	
	Summary (RE)	2; II	Minor	0.587	0.110	1.064	NC	NC	Isq: 14	NA
	Conclusion (moderate confidence)	People with tics receiving haloperidol are probably more likely than those receiving placebo to have reduced tic severity								



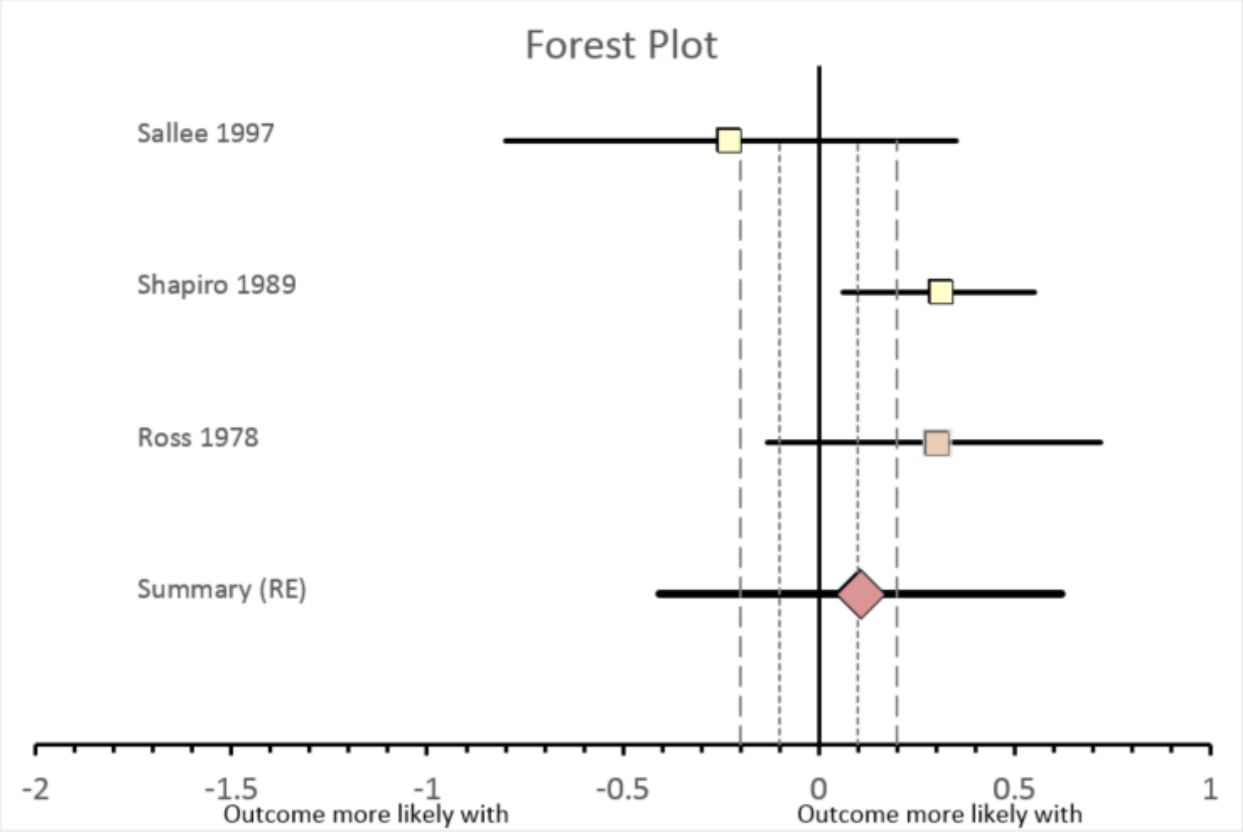
Pimozide vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
0	Population	People with tics							
	Intervention	receiving pimozide							
-1	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
0	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Shapiro 1984	II	Minor	1.220	0.510	1.930			2.000	
1	Sallee 1997	II	Minor	0.650	0.000	1.300			2.000	
1	Shapiro 1989	II	Minor	0.150	-0.480	0.770			2.000	
0	~~Ross 1978~~	III	Minor	0.650	0.180	1.110			3.000	
	Summary (RE)	3; II	Minor	0.655	0.056	1.253	NC	NC	Isq: 59	NA
	Conclusion (low confidence)	People with tics receiving pimozide are possibly more likely than those receiving placebo to have reduced tic severity								



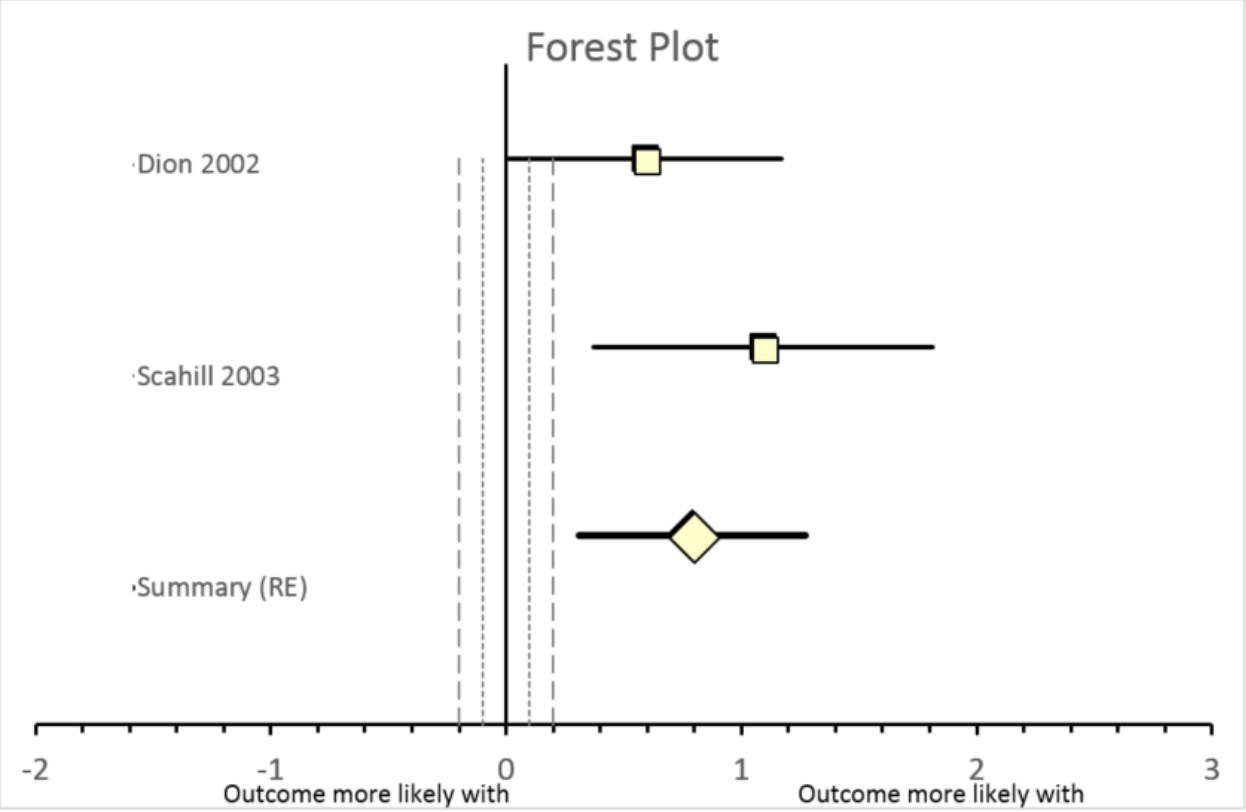
Haloperidol vs Pimozide

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
0	Population	People with tics							
	Intervention	receiving haloperidol							
-1	Comparator	those receiving pimozide							
	Outcome	have reduced tic severity							
0	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Sallee 1997	II	Minor	-0.230	-0.800	0.350			2.000	
1	Shapiro 1989	II	Minor	0.310	0.060	0.550			2.000	
0	~~Ross 1978~~	III	Minor	0.300	-0.130	0.720			3.000	
	Summary (RE)	2; II	Minor	0.105	-0.408	0.619	NC	NC	Isq: 65	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving haloperidol are more or less likely than those receiving pimozide to have reduced tic severity								



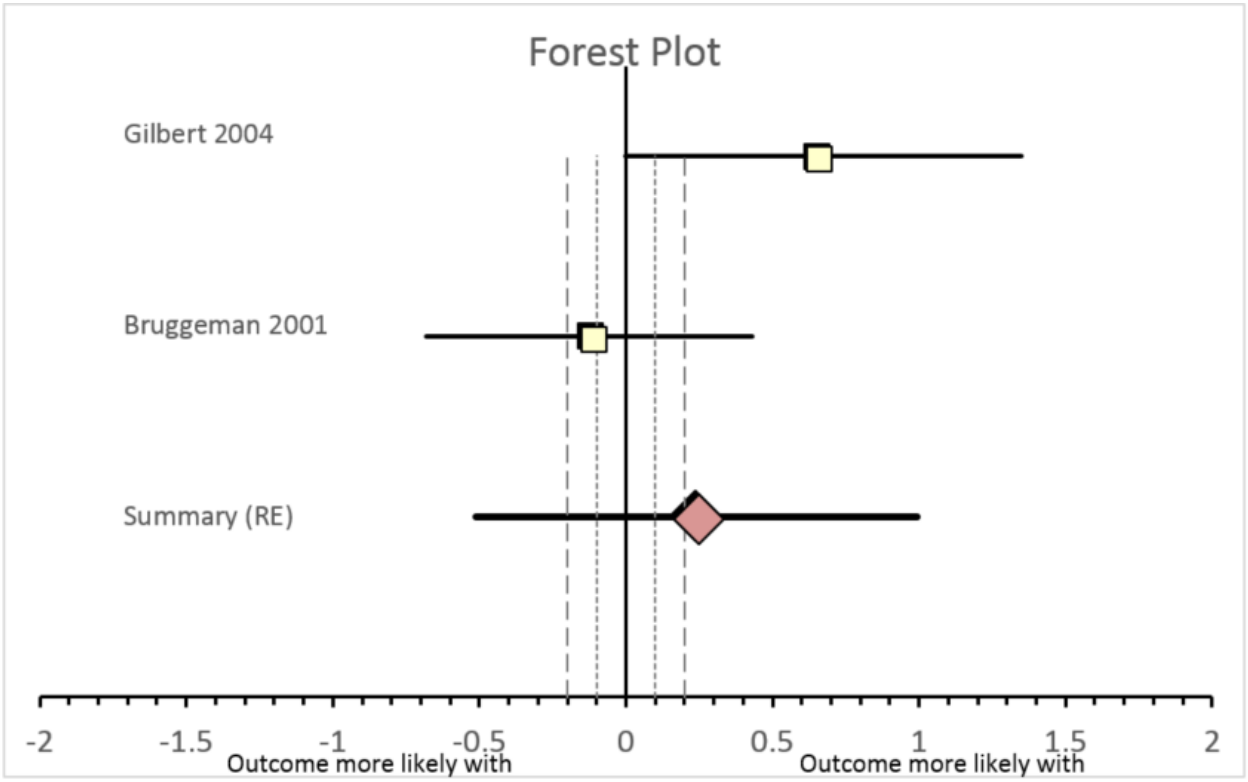
Risperidone vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving risperidone								
-1	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Dion 2002	II	Minor	0.590	0.010	1.170			2.000	
1	Scahill 2003	II	Minor	1.090	0.370	1.810			2.000	
	Summary (RE)	2; II	Minor	0.793	0.312	1.274	NC	NC	Isq: 11	NA
	Conclusion (moderate confidence)	People with tics receiving risperidone are probably more likely than those receiving placebo to have reduced tic severity								



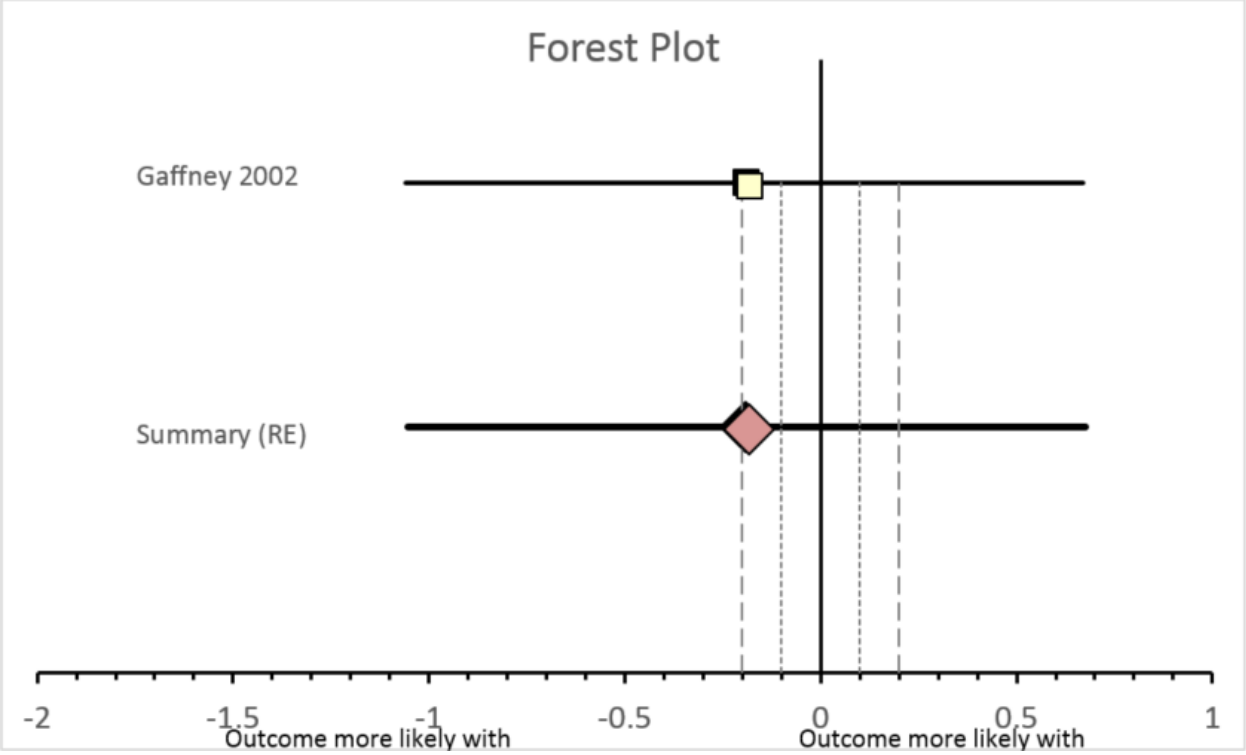
Pimozide vs Risperidone

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving risperidone								
-1	Comparator	those receiving pimozide								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Gilbert 2004	II	Minor	0.650	0.000	1.350			2.000	
1	Bruggeman 2001	II	Minor	-0.120	-0.680	0.430			2.000	
	Summary (RE)	2; II	Minor	0.240	-0.513	0.993	NC	NC	Isq: 66	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving risperidone are more or less likely than those receiving pimozide to have reduced tic severity								



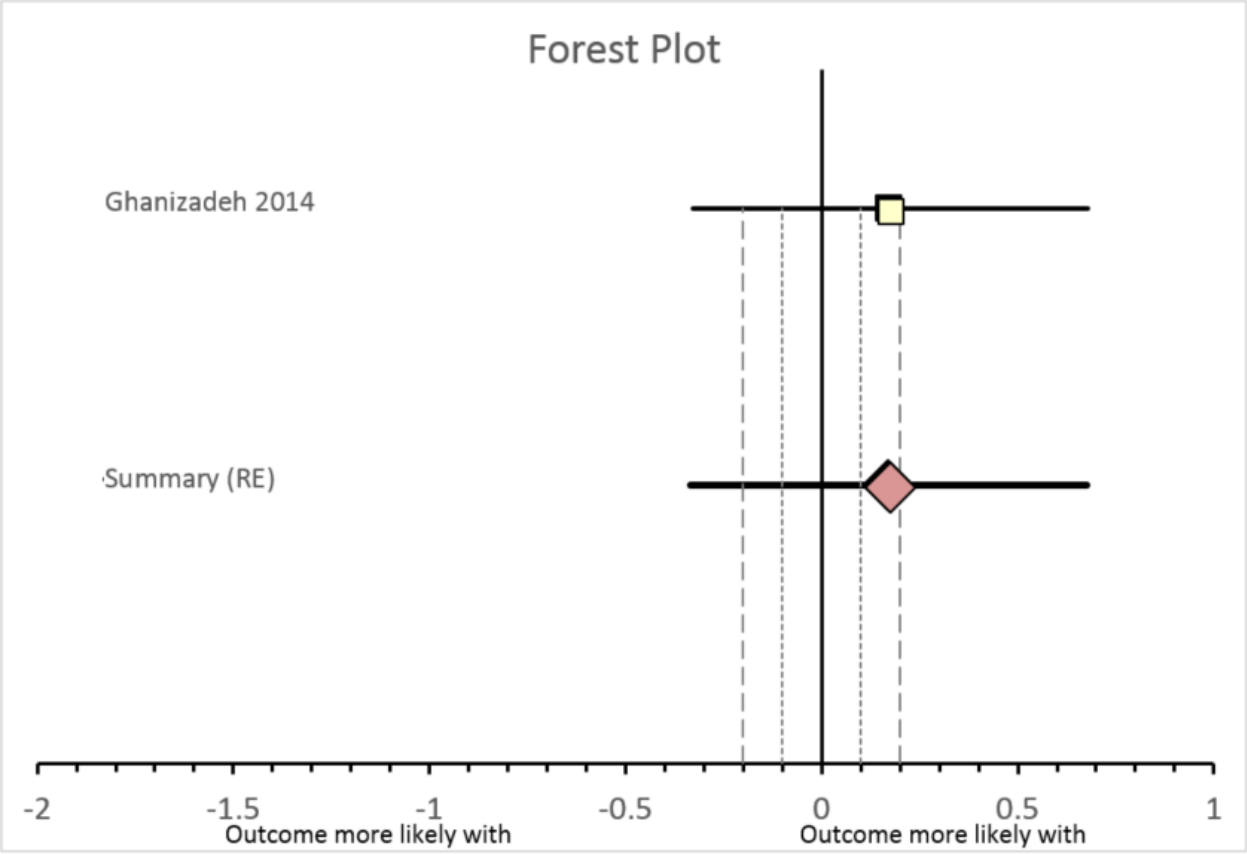
Risperidone vs Clonidine

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving risperidone								
-1	Comparator	those receiving clonidine								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Gaffney 2002	II	Minor	-0.190	-1.060	0.670			2.000	
	Summary (RE)	1; II	Minor	-0.190	-1.055	0.675	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving risperidone are more or less likely than those receiving clonidine to have reduced tic severity								



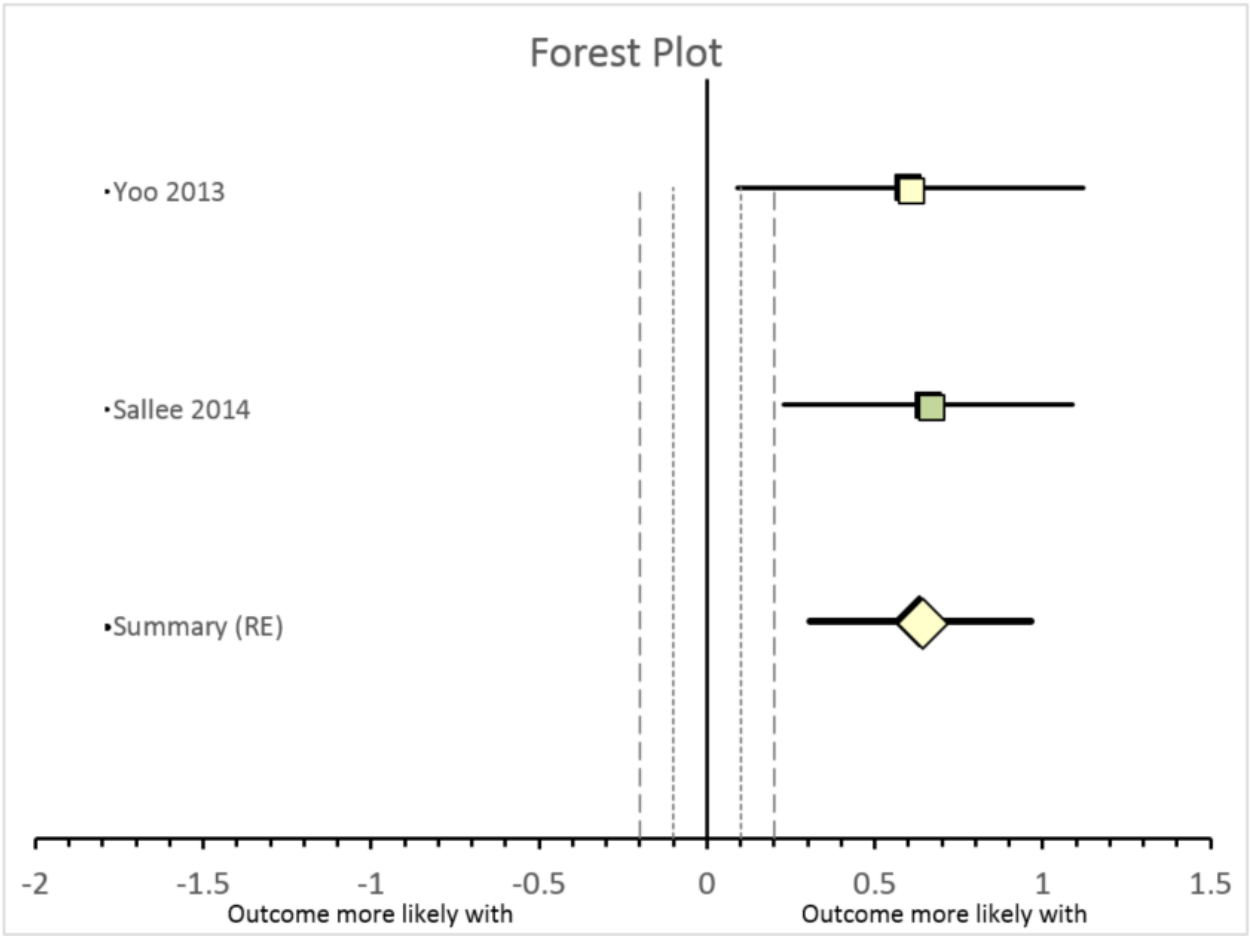
Risperidone vs Aripiprazole

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving aripiprazole								
-1	Comparator	those receiving risperidone								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Ghanizadeh 2014	II	Minor	0.170	-0.330	0.680			2.000	
	Summary (RE)	1; II	Minor	0.170	-0.335	0.675	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving aripiprazole are more or less likely than those receiving risperidone to have reduced tic severity								



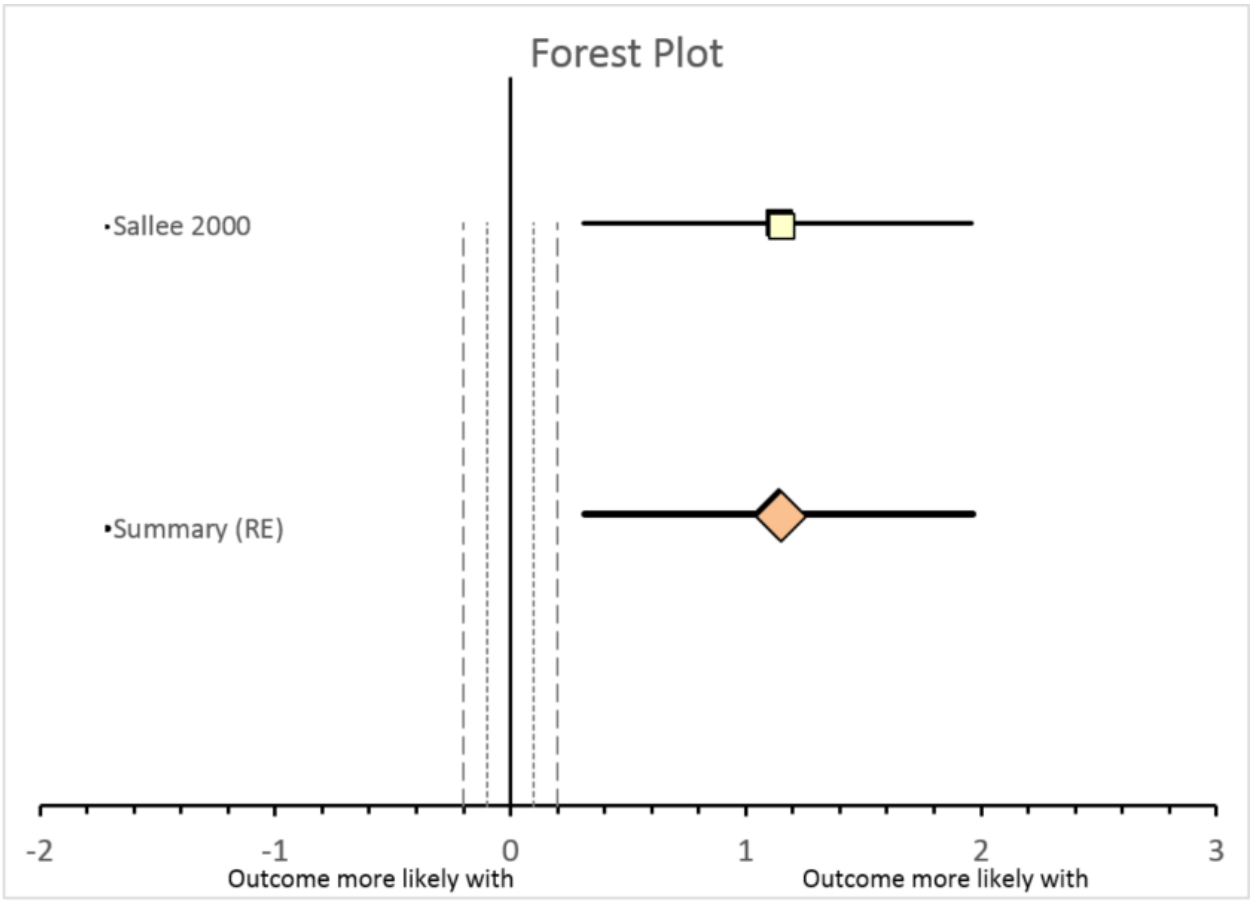
Aripiprazole vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving aripiprazole								
-1	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Yoo 2013	II	Minor	0.600	0.090	1.120			2.000	
1	Sallee 2014	I	Minor	0.660	0.230	1.090			1.000	
	Summary (RE)	2; II	Minor	0.635	0.305	0.965	NC	NC	Isq: 0	NA
	Conclusion (moderate confidence)	People with tics receiving aripiprazole are probably more likely than those receiving placebo to have reduced tic severity								



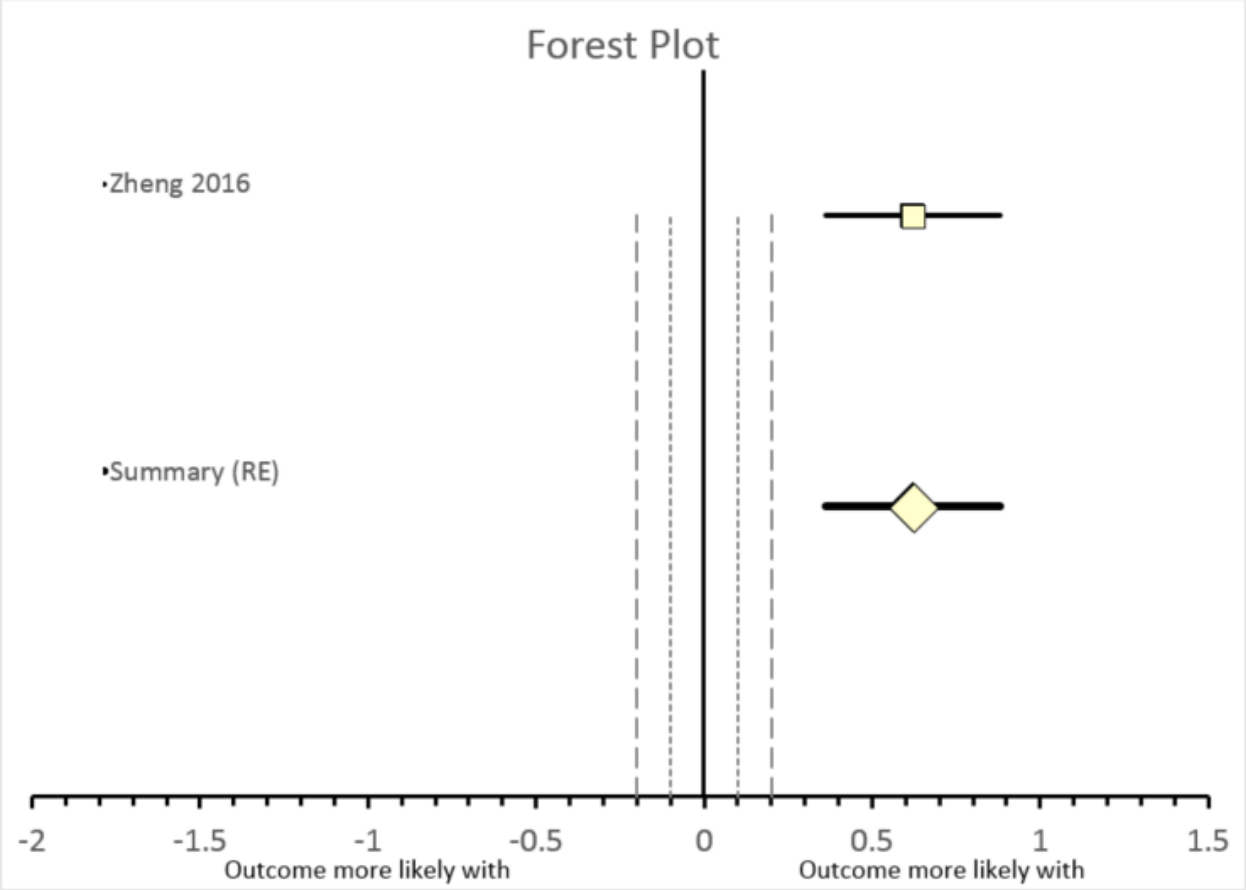
Ziprasidone vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
0	Population	People with tics								
	Intervention	receiving ziprasidone								
-1	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
0	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Sallee 2000	II	Minor	1.140	0.310	1.960			2.000	
	Summary (RE)	1; II	Minor	1.140	0.315	1.965	NC	NC	Isq: NA	NA
	Conclusion (low confidence)	People with tics receiving ziprasidone are possibly more likely than those receiving placebo to have reduced tic severity								



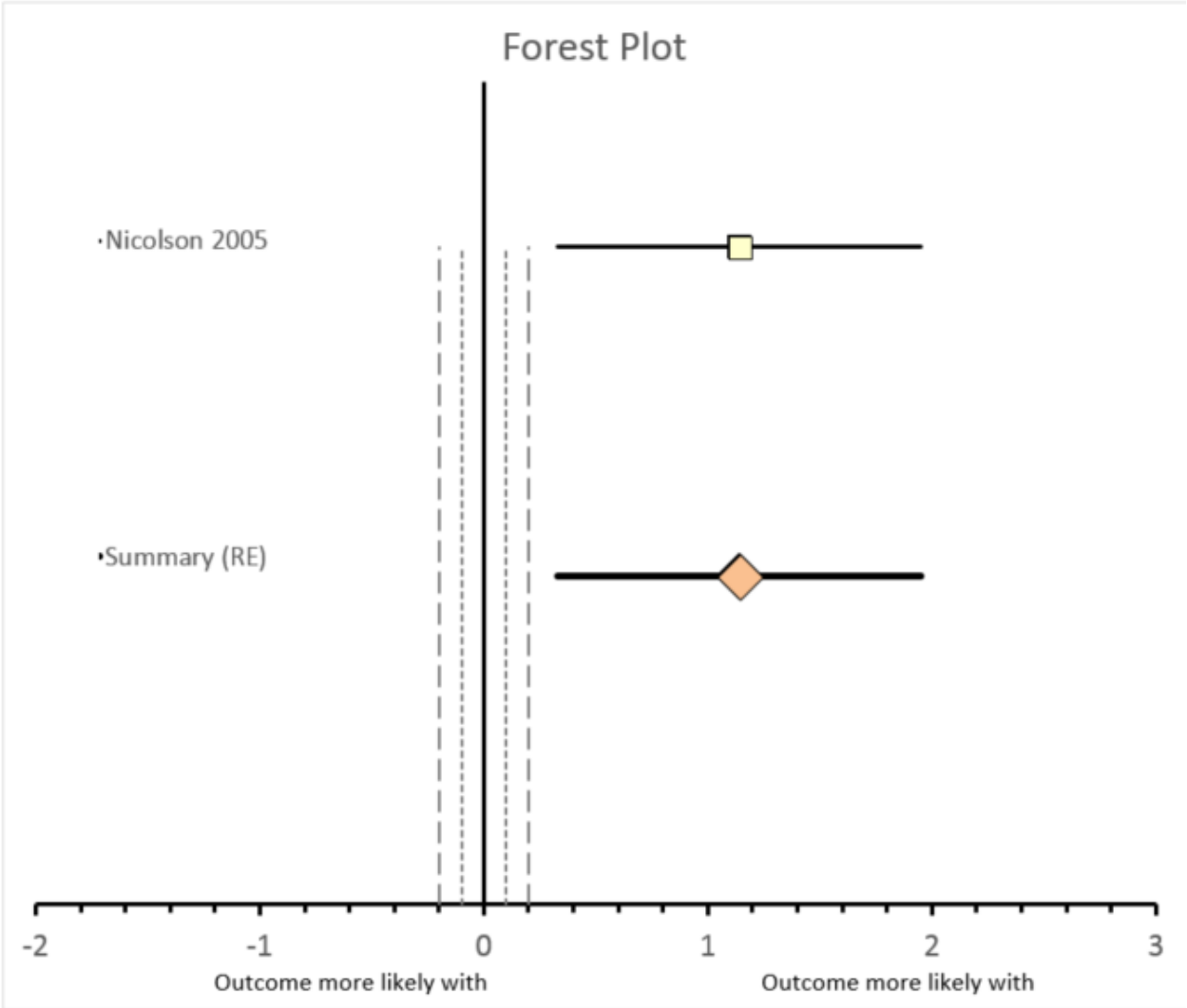
Tiapride vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving tiapride								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Zheng 2016	I	Moderate	0.620	0.360	0.880			2.000	
	Summary (RE)	1; I	Moderate	0.620	0.360	0.880	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving tiapride are probably more likely than those receiving placebo to have reduced tic severity								



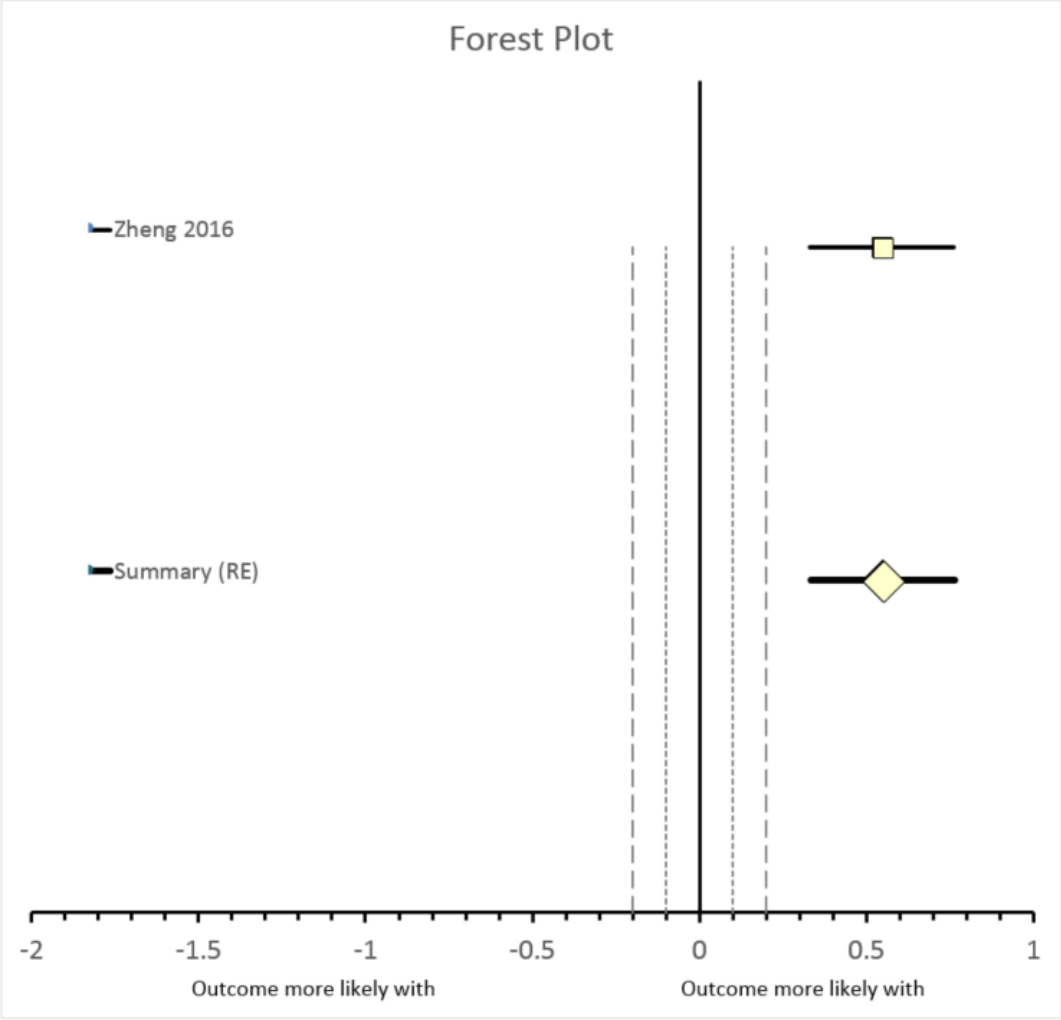
Metoclopramide vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving metoclopramide								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Nicolson 2005	II	Minor	1.140	0.330	1.950			2.000	
	Summary (RE)	1; II	Minor	1.140	0.330	1.950	NC	NC	Isq: NA	NA
	Conclusion (low confidence)	People with tics receiving metoclopramide are possibly more likely than those receiving placebo to have reduced tic severity								



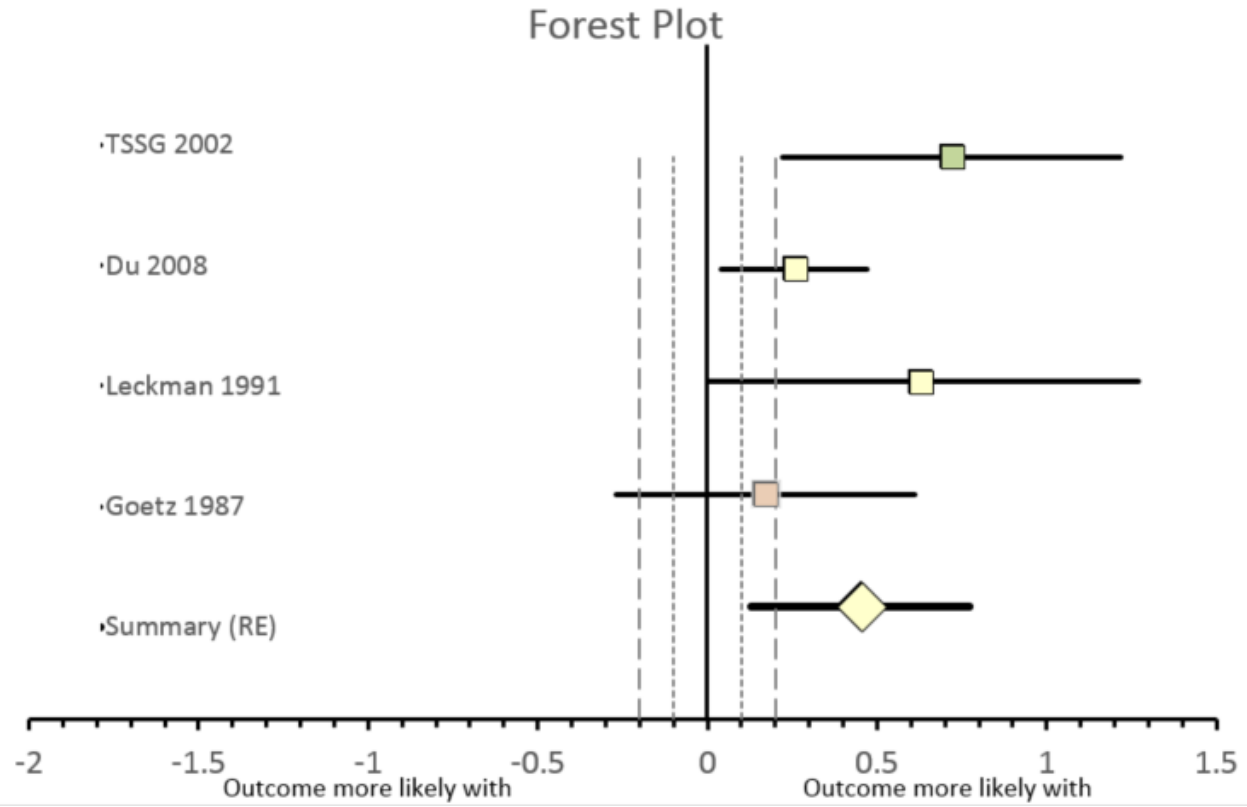
5-Ling Granule vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving 5-Ling granule							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Zheng 2016	I	Moderate	0.550	0.330	0.760			2.000	
	Summary (RE)	1; I	Moderate	0.550	0.335	0.765	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving 5-Ling granule are probably more likely than those receiving placebo to have reduced tic severity								



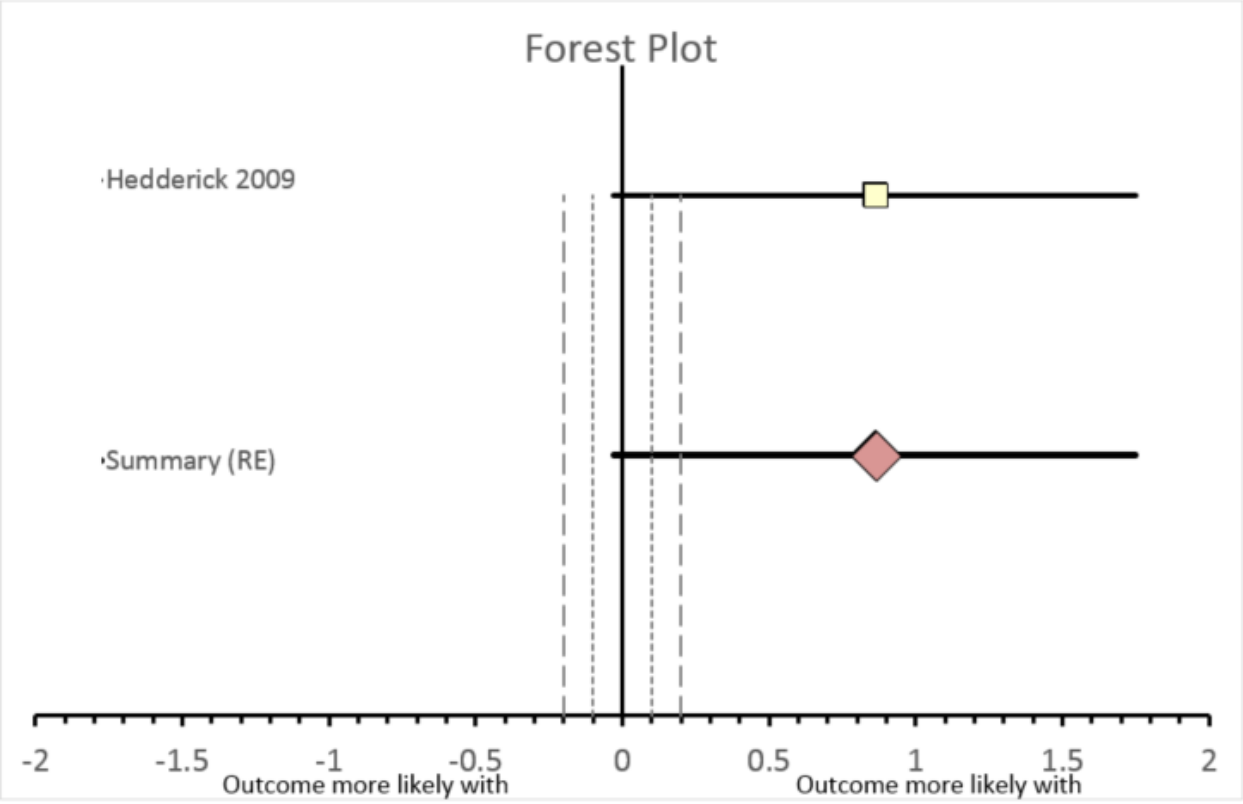
Clonidine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving clonidine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	TSSG 2002	I	Minor	0.720	0.220	1.220			1.000	
1	Du 2008	II	Minor	0.260	0.040	0.470			2.000	
1	Leckman 1991	II	Minor	0.630	0.000	1.270			2.000	
0	~~Goetz 1987~~	III	Minor	0.170	-0.270	0.610			3.000	
	Summary (RE)	3; II	Minor	0.451	0.130	0.772	NC	NC	Isq: 43	NA
	Conclusion (moderate confidence)	People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity								



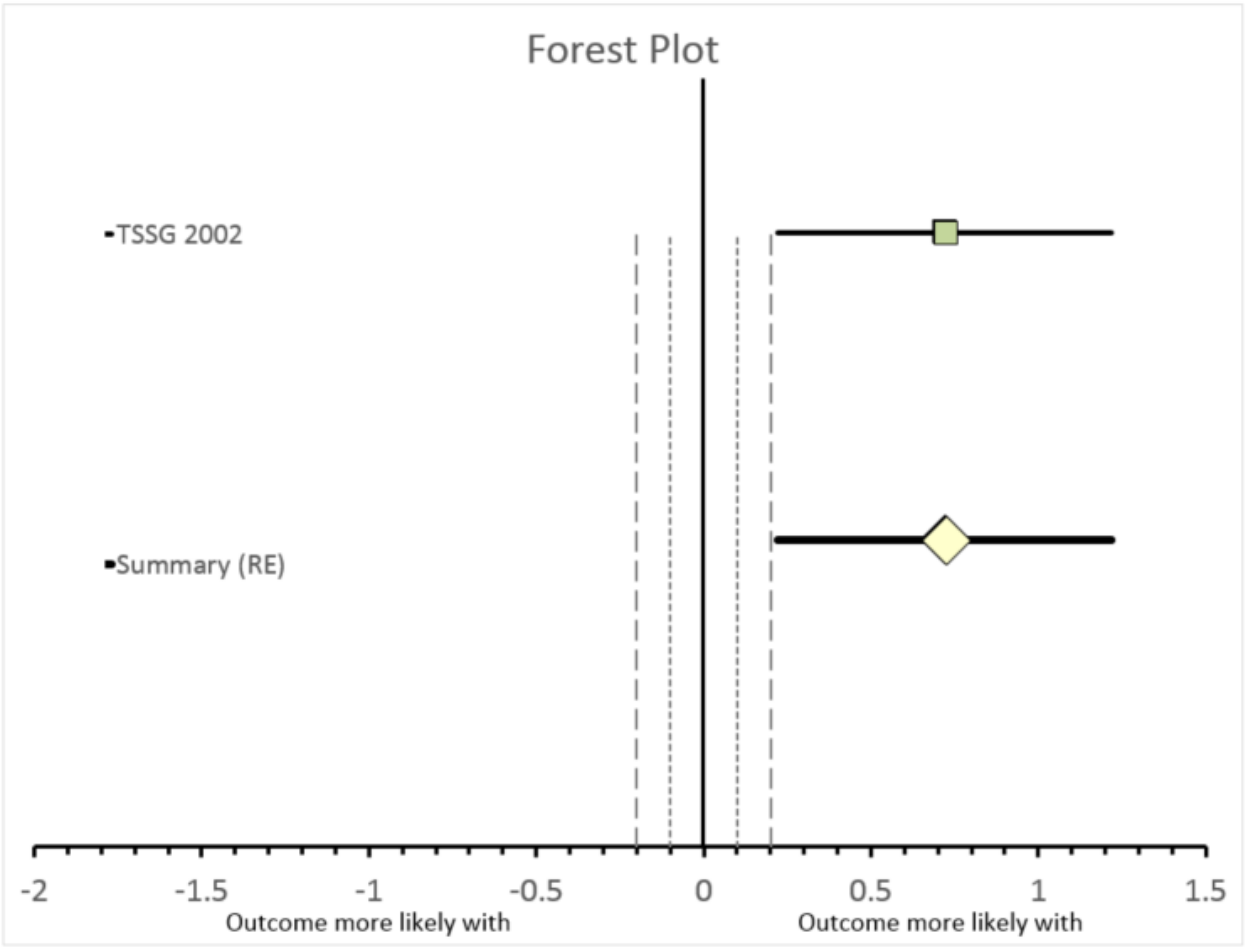
Clonidine vs Levetiracetam

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving clonidine those receiving levetiracetam have reduced tic severity							
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Hedderick 2009	II	Minor	0.860	-0.030	1.750			2.000	
	Summary (RE)	1; II	Minor	0.860	-0.030	1.750	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving clonidine are more or less likely than those receiving levetiracetam to have reduced tic severity								



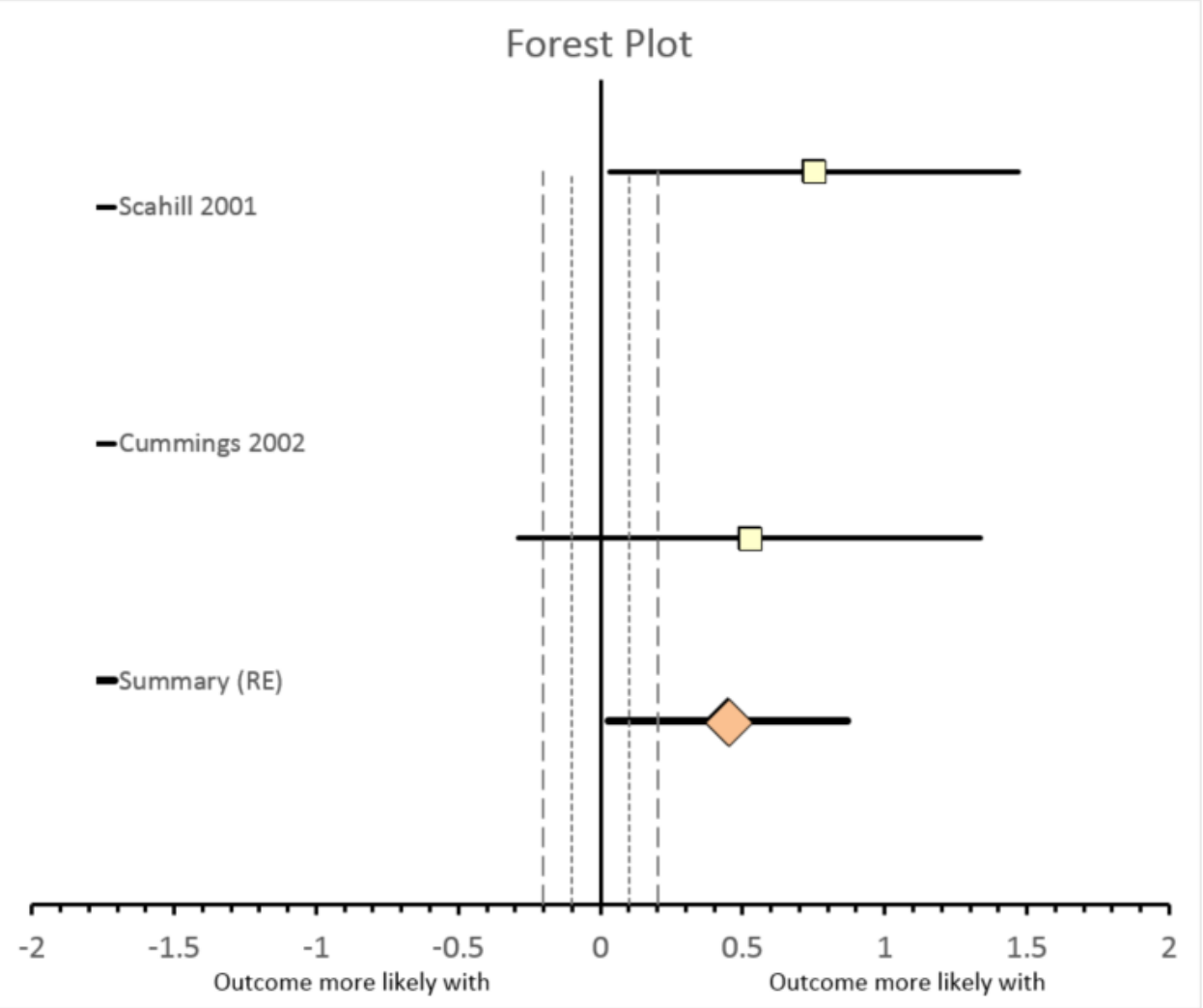
Clonidine + MPH vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receivingclonidine + MPH							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	TSSG 2002	I	Minor	0.720	0.220	1.220			1.000	
	Summary (RE)	1; I	Minor	0.720	0.220	1.220	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receivingclonidine + MPH are probably more likely than those receiving placebo to have reduced tic severity								



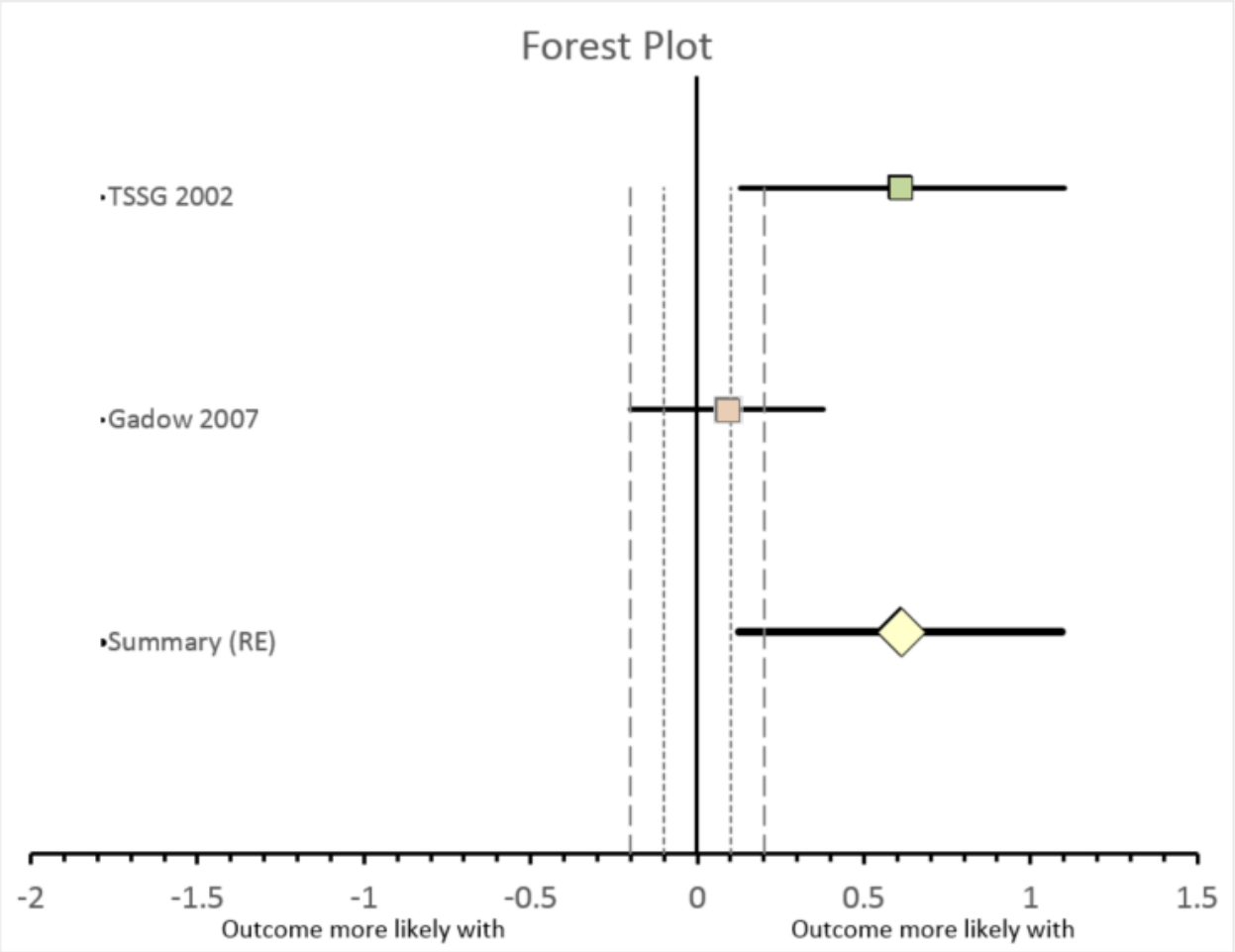
Guanfacine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving guanfacine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Scahill 2001	II	Minor	0.750	0.030	1.470			2.000	
1	Murphy 2017	I	Minor	0.130	-0.540	0.810				
1	Cummings 2002	II	Minor	0.525	-0.289	1.338			2.000	
	Summary (RE)	3; II	Minor	0.448	0.027	0.869	NC	NC	Isq: 0	NA
	Conclusion (low confidence)	People with tics receiving guanfacine are possibly more likely than those receiving placebo to have reduced tic severity								



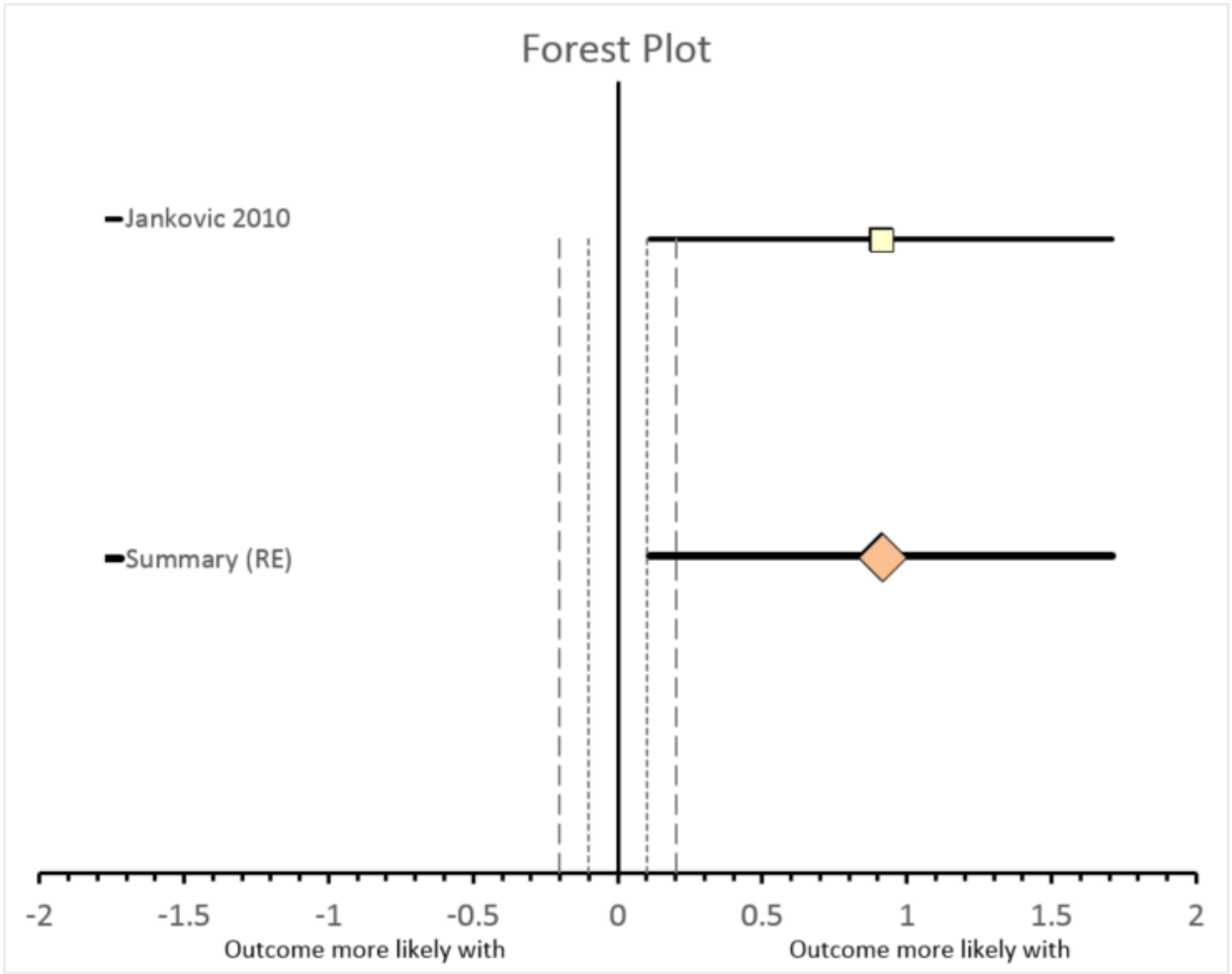
MPH vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving MPH those receiving placebo have reduced tic severity								
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	TSSG 2002	I	Minor	0.610	0.130	1.100			1.000	
0	~~Gadow 2007~~	III	Minor	0.090	-0.200	0.380			3.000	
	Summary (RE)	1; I	Minor	0.610	0.125	1.095	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving MPH are probably more likely than those receiving placebo to have reduced tic severity								



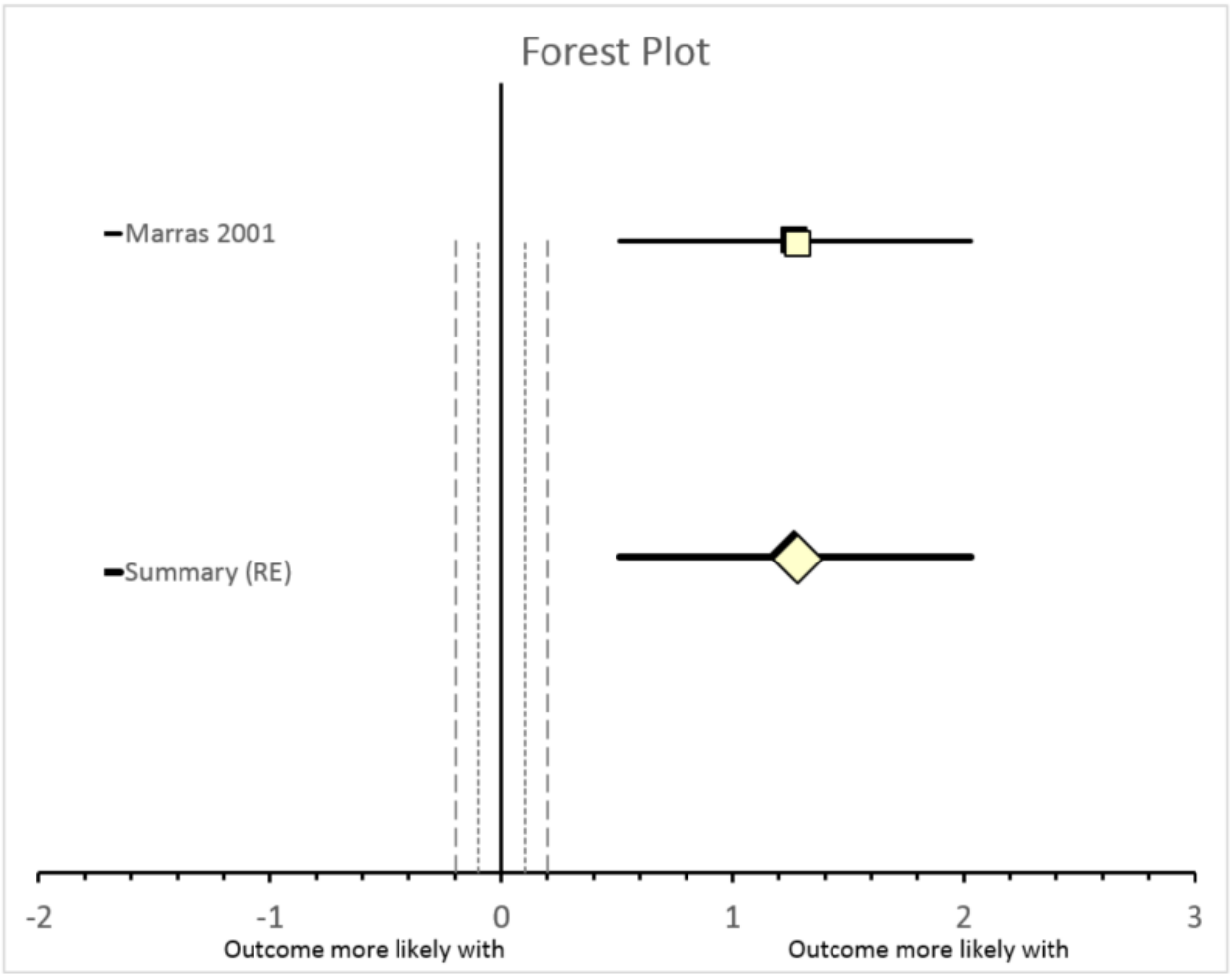
Topiramate vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving topiramate							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Jankovic 2010	II	Minor	0.910	0.110	1.710			2.000	
	Summary (RE)	1; II	Minor	0.910	0.110	1.710	NC	NC	Isq: NA	NA
	Conclusion (low confidence)	People with tics receiving topiramate are possibly more likely than those receiving placebo to have reduced tic severity								



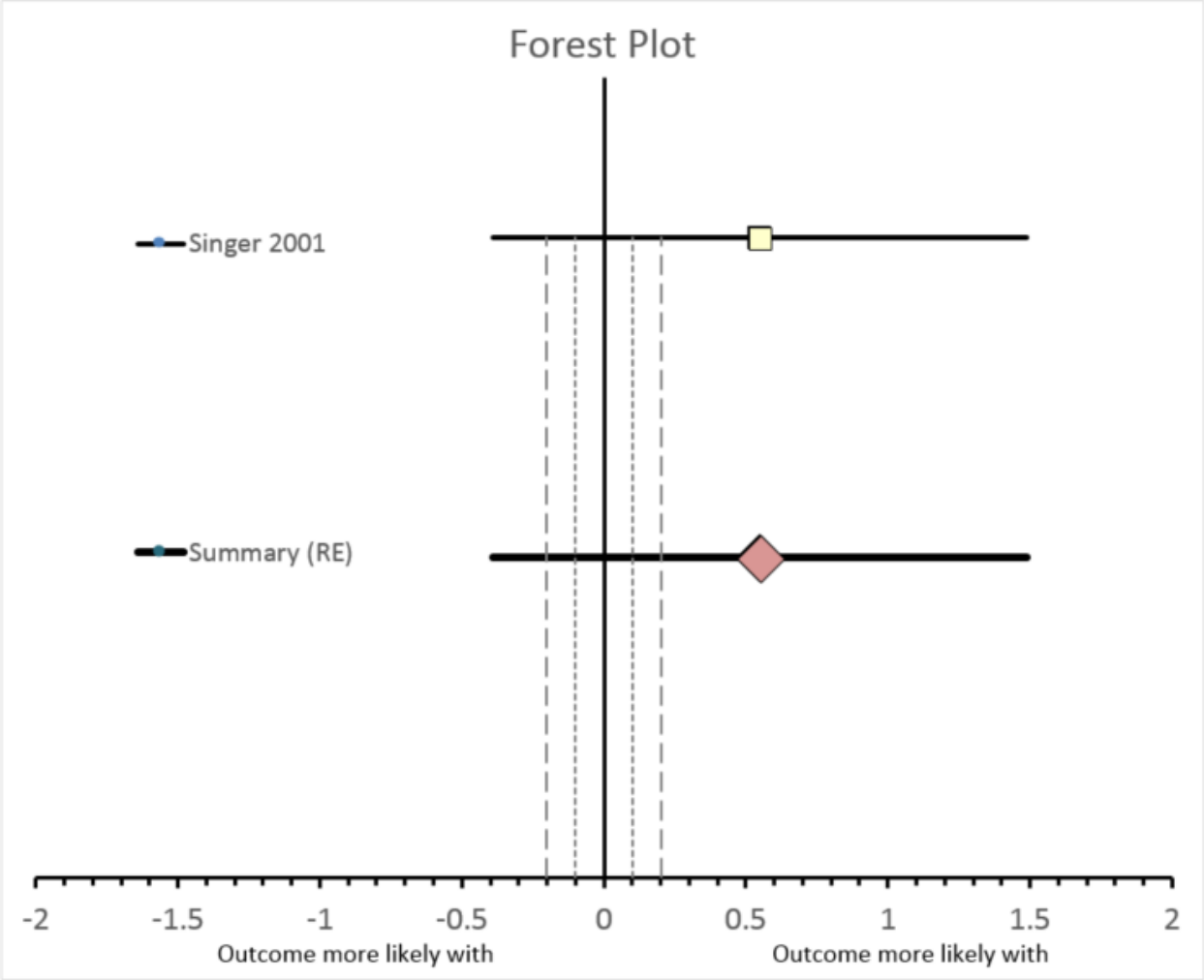
Botox vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving botox							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Marras 2001	II	Minor	1.270	0.510	2.030			2.000	
	Summary (RE)	1; II	Minor	1.270	0.510	2.030	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving botox are probably more likely than those receiving placebo to have reduced tic severity								



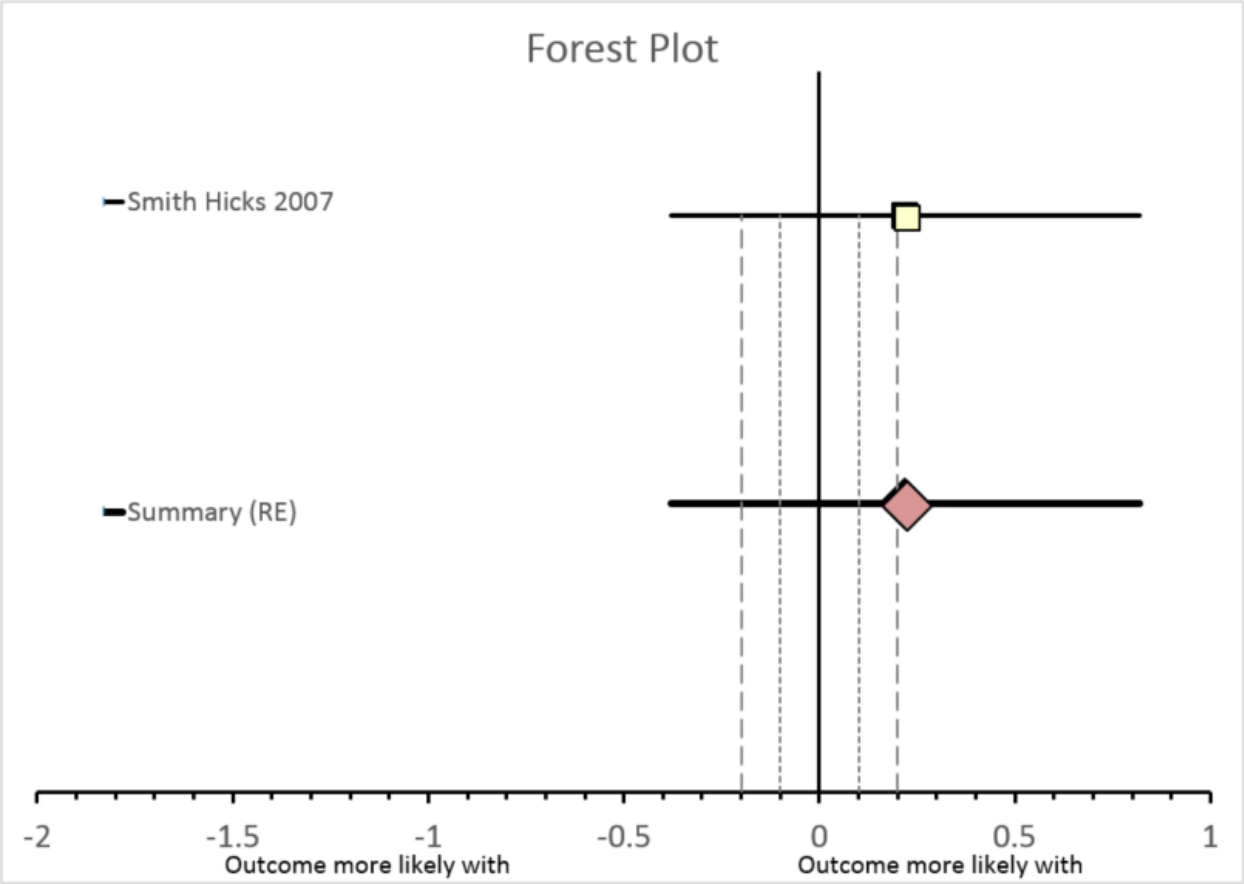
Baclofen vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving baclofen							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Singer 2001	II	Minor	0.550	-0.390	1.490			2.000	
	Summary (RE)	1; II	Minor	0.550	-0.390	1.490	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving baclofen are more or less likely than those receiving placebo to have reduced tic severity								



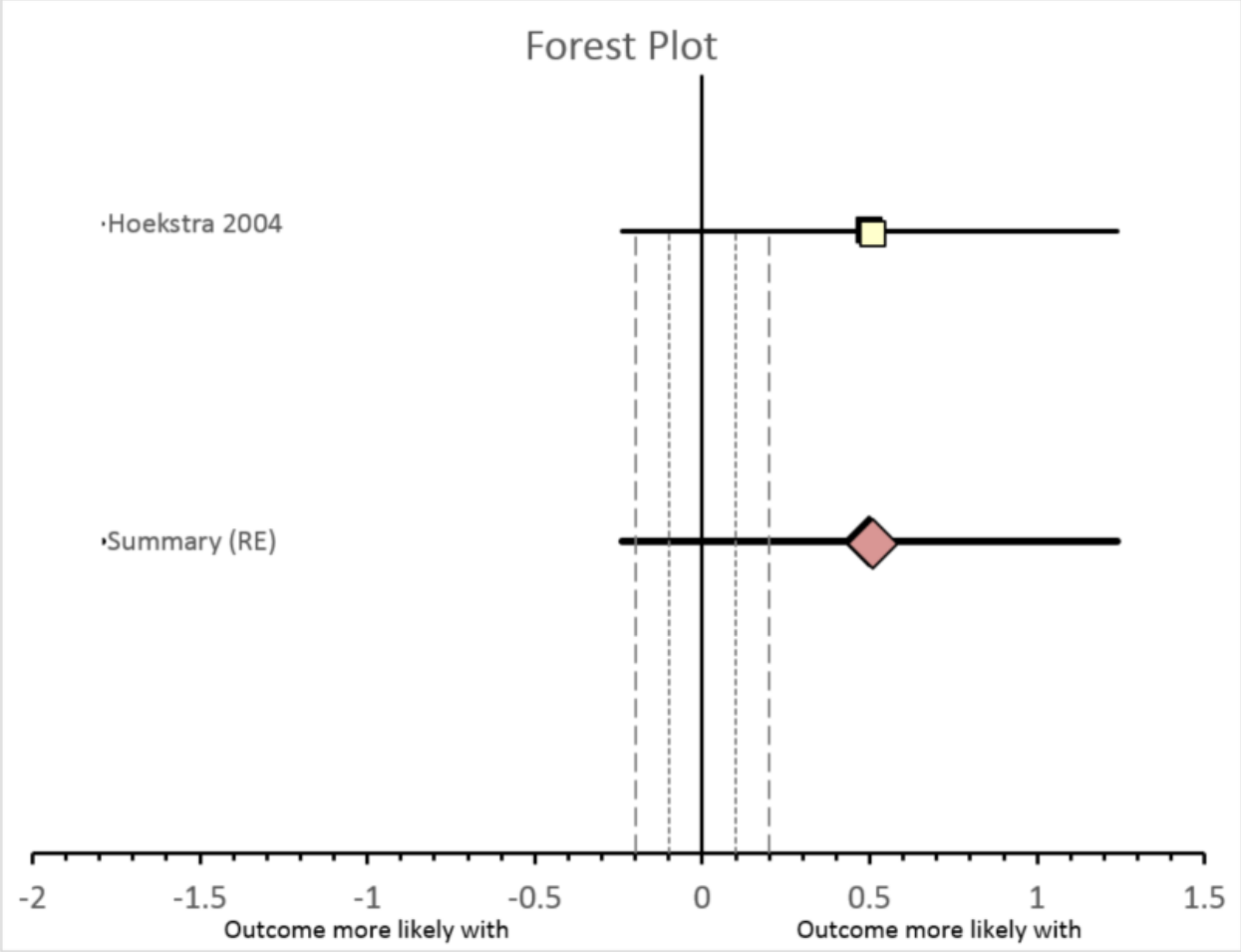
Levetiracetam vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving levetiracetam								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Smith Hicks 2007	II	Minor	0.220	-0.380	0.820			2.000	
	Summary (RE)	1; II	Minor	0.220	-0.380	0.820	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving levetiracetam are more or less likely than those receiving placebo to have reduced tic severity								



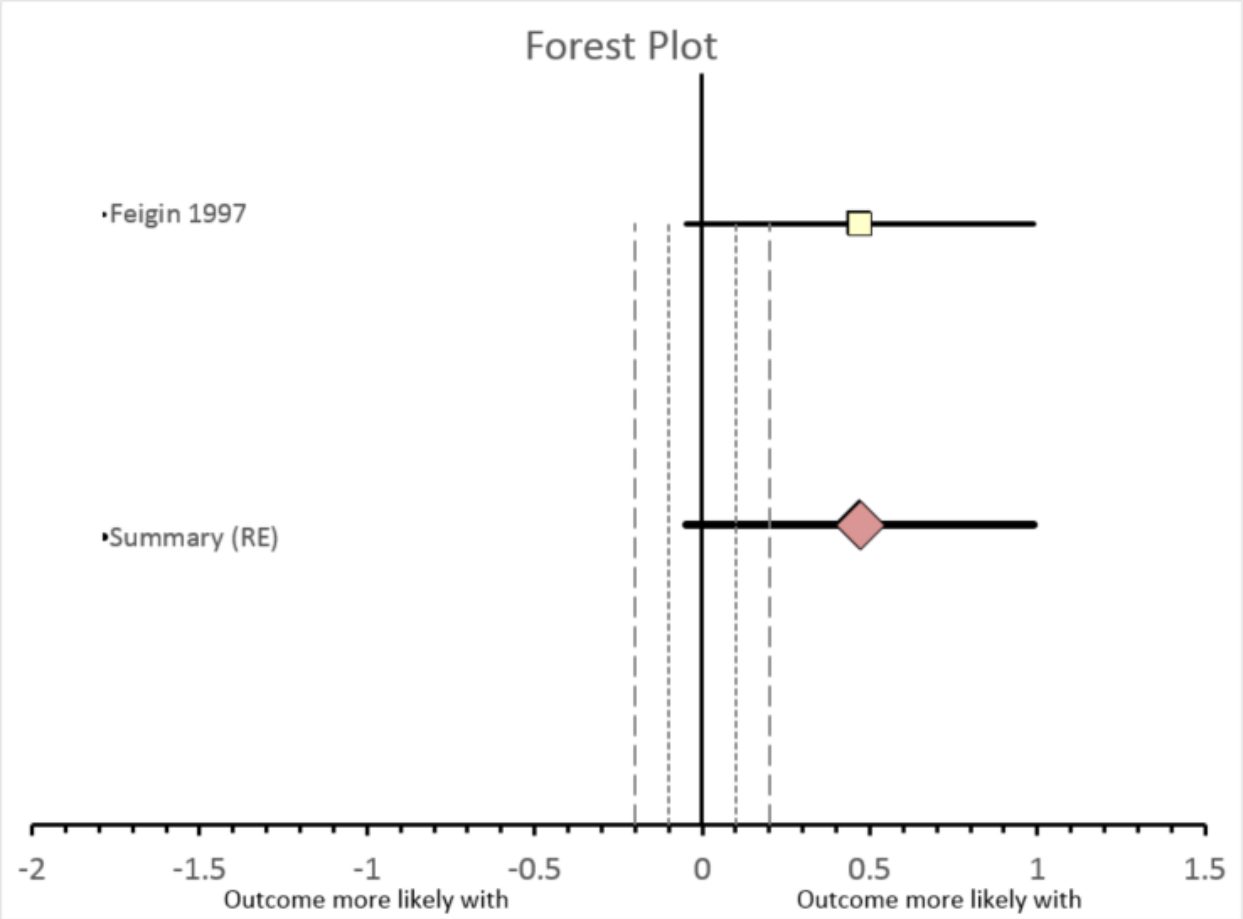
IVIG vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving IVIG								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Hoekstra 2004	II	Minor	0.500	-0.240	1.240			2.000	
	Summary (RE)	1; II	Minor	0.500	-0.240	1.240	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving IVIG are more or less likely than those receiving placebo to have reduced tic severity								



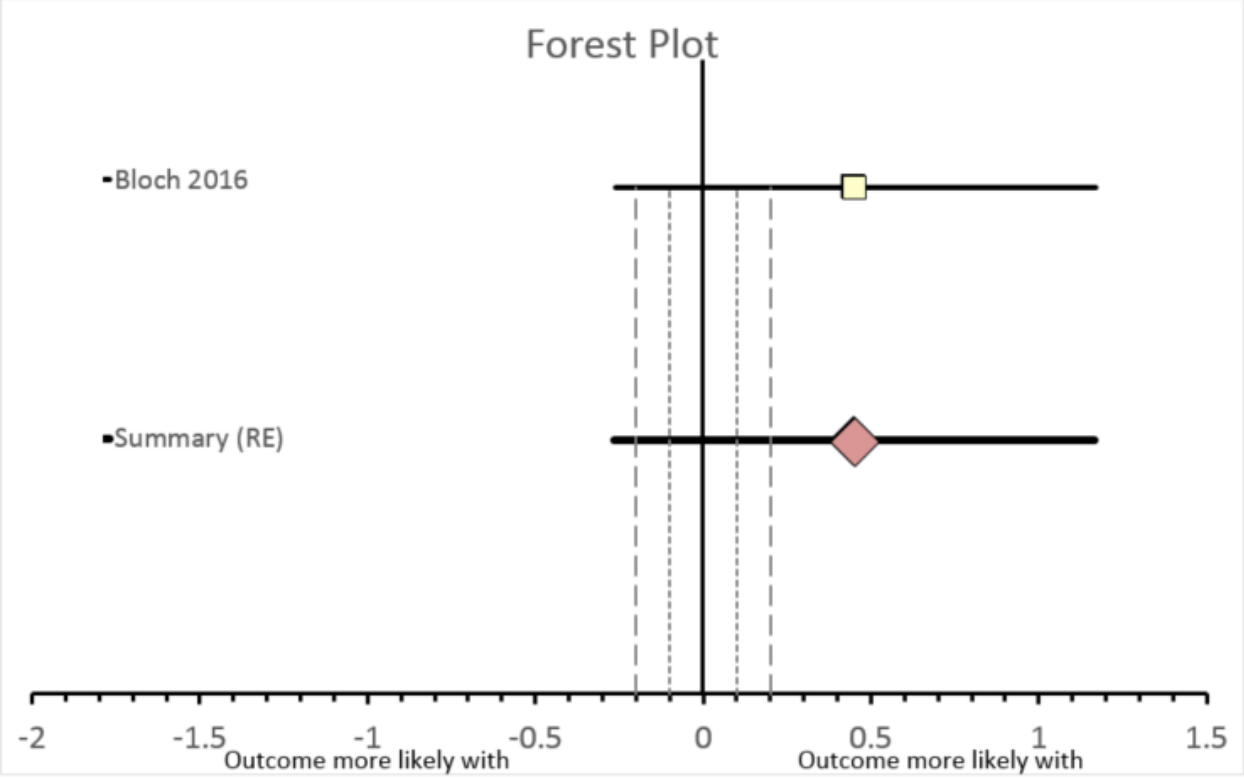
Deprenyl vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving deprenyl								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Feigin 1997	II	Minor	0.470	-0.050	0.990			2.000	
	Summary (RE)	1; II	Minor	0.470	-0.050	0.990	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving deprenyl are more or less likely than those receiving placebo to have reduced tic severity								



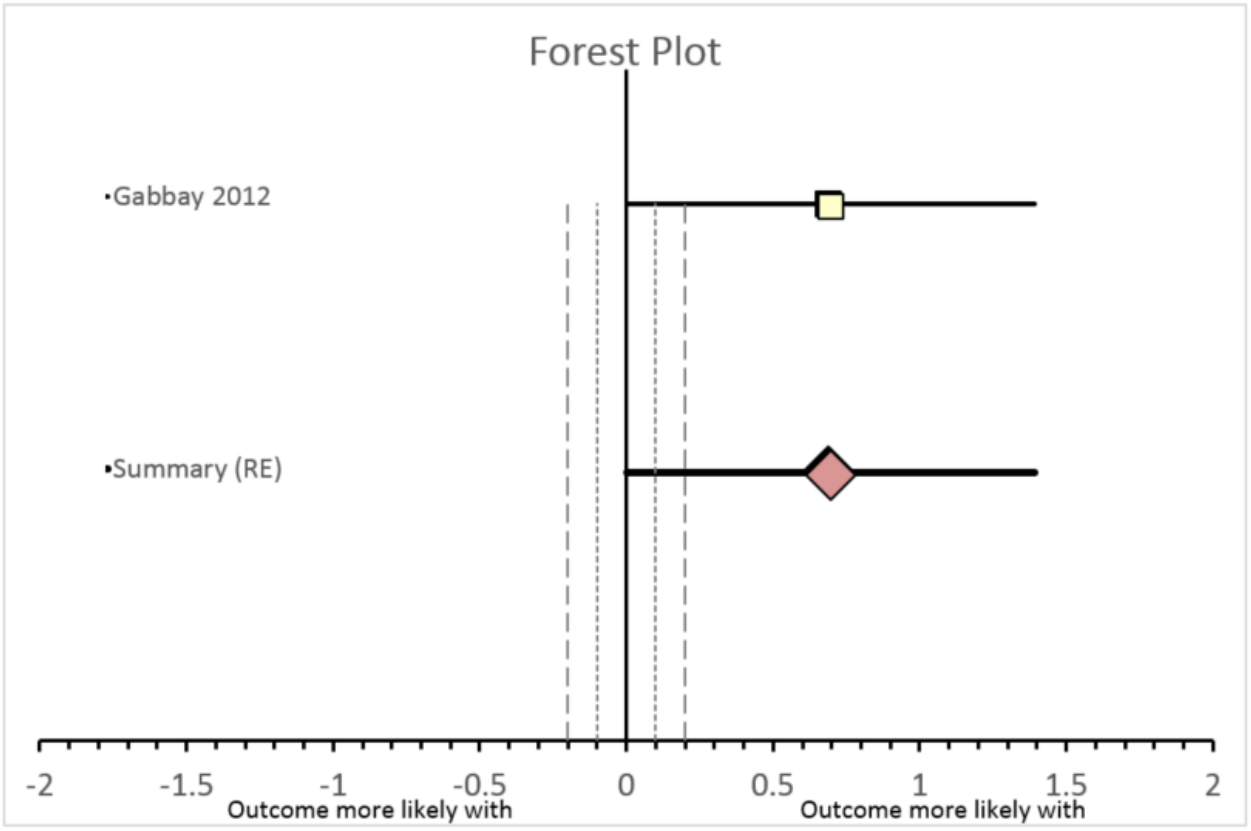
N-acetylcysteine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving N-acetylcysteine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Bloch 2016	II	Minor	0.450	-0.260	1.170			2.000	
	Summary (RE)	1; II	Minor	0.450	-0.265	1.165	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving N-acetylcysteine are more or less likely than those receiving placebo to have reduced tic severity								



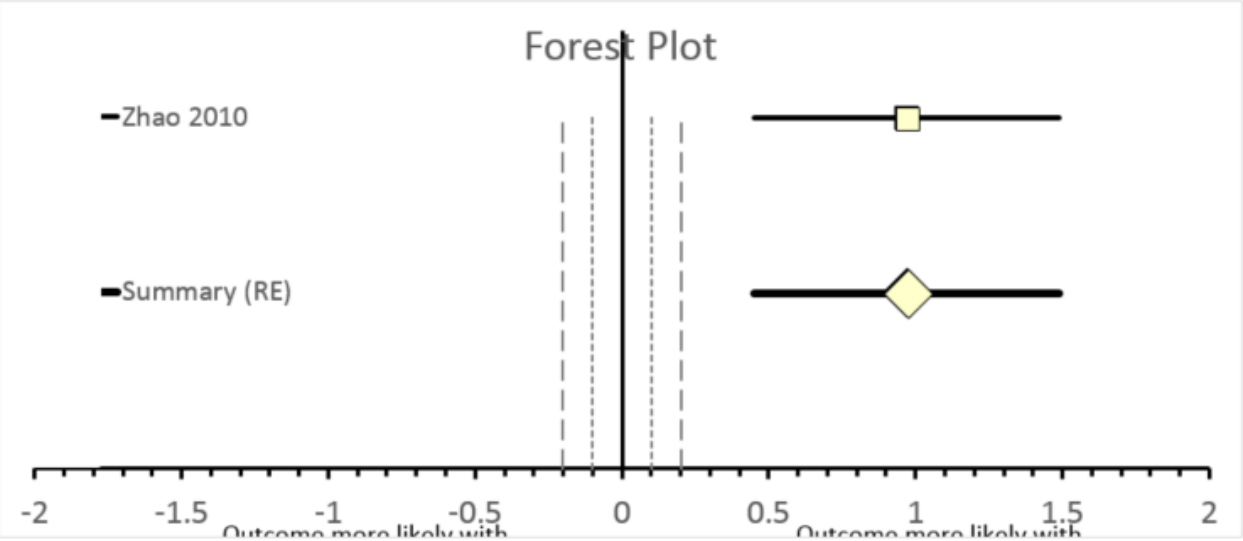
Omega 3 vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving omega 3								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Gabbay 2012	II	Minor	0.690	0.000	1.390			2.000	
	Summary (RE)	1; II	Minor	0.690	0.000	1.390	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving omega 3 are more or less likely than those receiving placebo to have reduced tic severity								



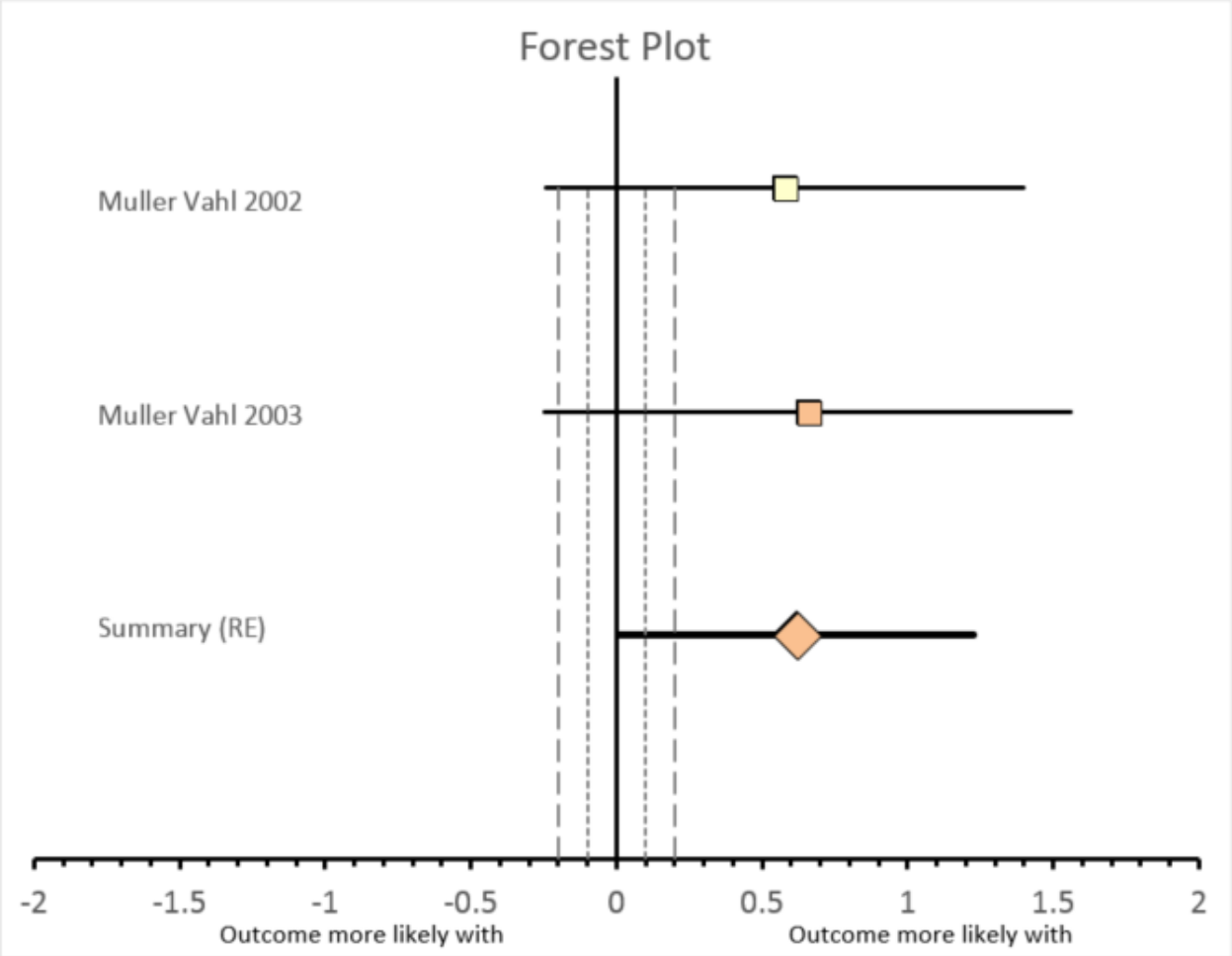
Ningdong Granule vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving Ningdong granule							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Zhao 2010	II	Minor	0.970	0.450	1.490			2.000	
	Summary (RE)	1; II	Minor	0.970	0.450	1.490	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving Ningdong granule are probably more likely than those receiving placebo to have reduced tic severity								



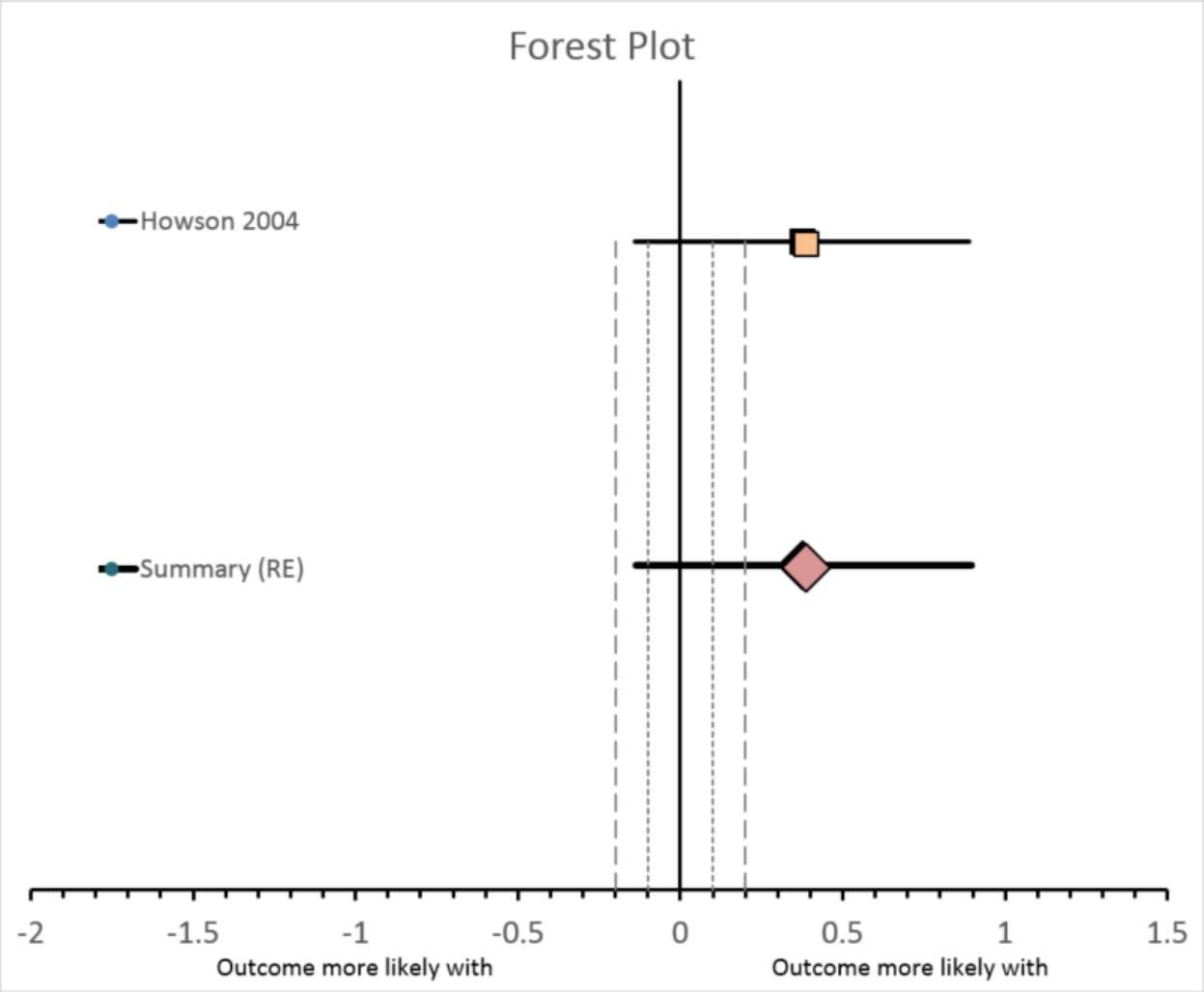
THC vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving THC							
	Comparator	those receiving placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Muller Vahl 2002	II	Minor	0.580	-0.240	1.400			2.000	
1	Muller Vahl 2003	III	Minor	0.660	-0.250	1.560			3.000	
	Summary (RE)	2; III	Minor	0.616	0.008	1.224	NC	NC	Isq: 0	NA
	Conclusion (low confidence)	People with tics receiving THC are possibly more likely than those receiving placebo to have reduced tic severity								



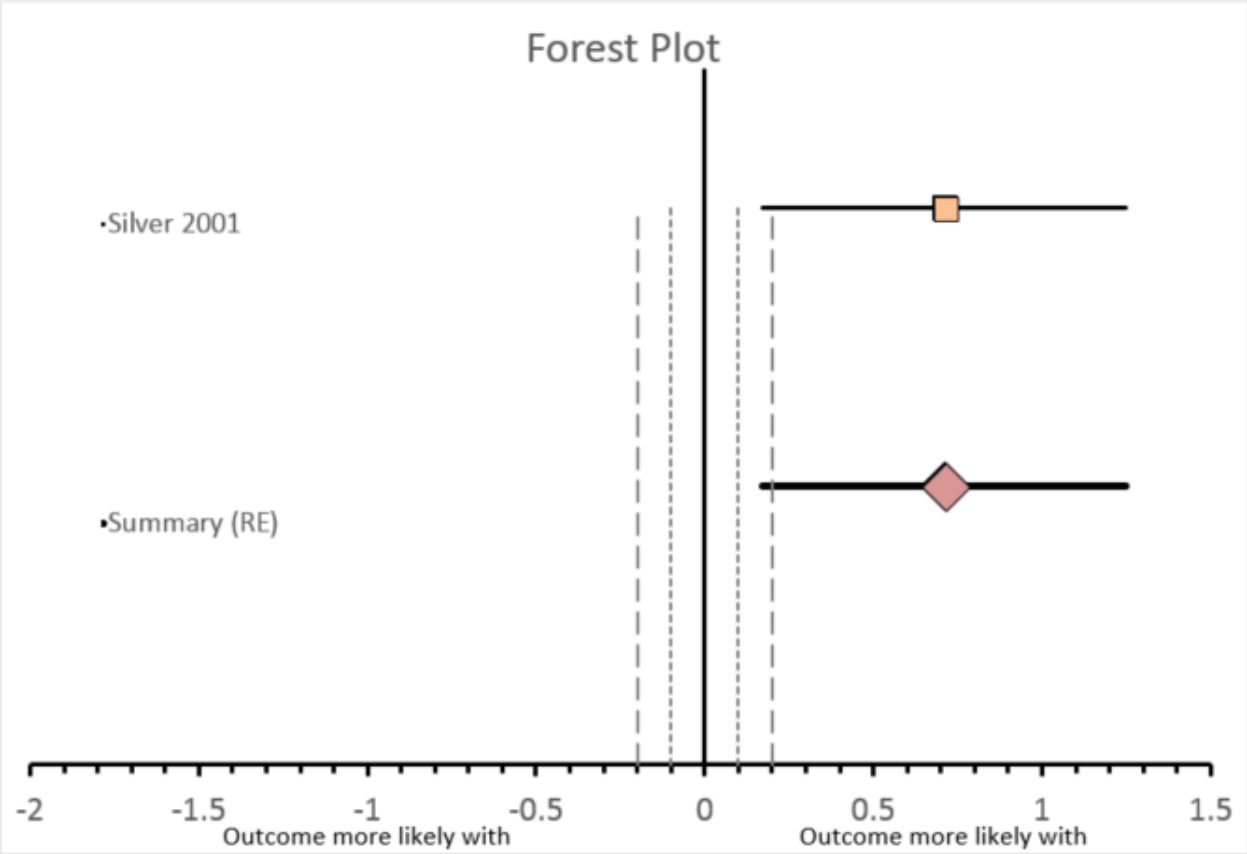
Nicotine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving nicotine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Howson 2004	III	Minor	0.380	-0.140	0.890			3.000	
	Summary (RE)	1; III	Minor	0.380	-0.135	0.895	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving nicotine are more or less likely than those receiving placebo to have reduced tic severity								



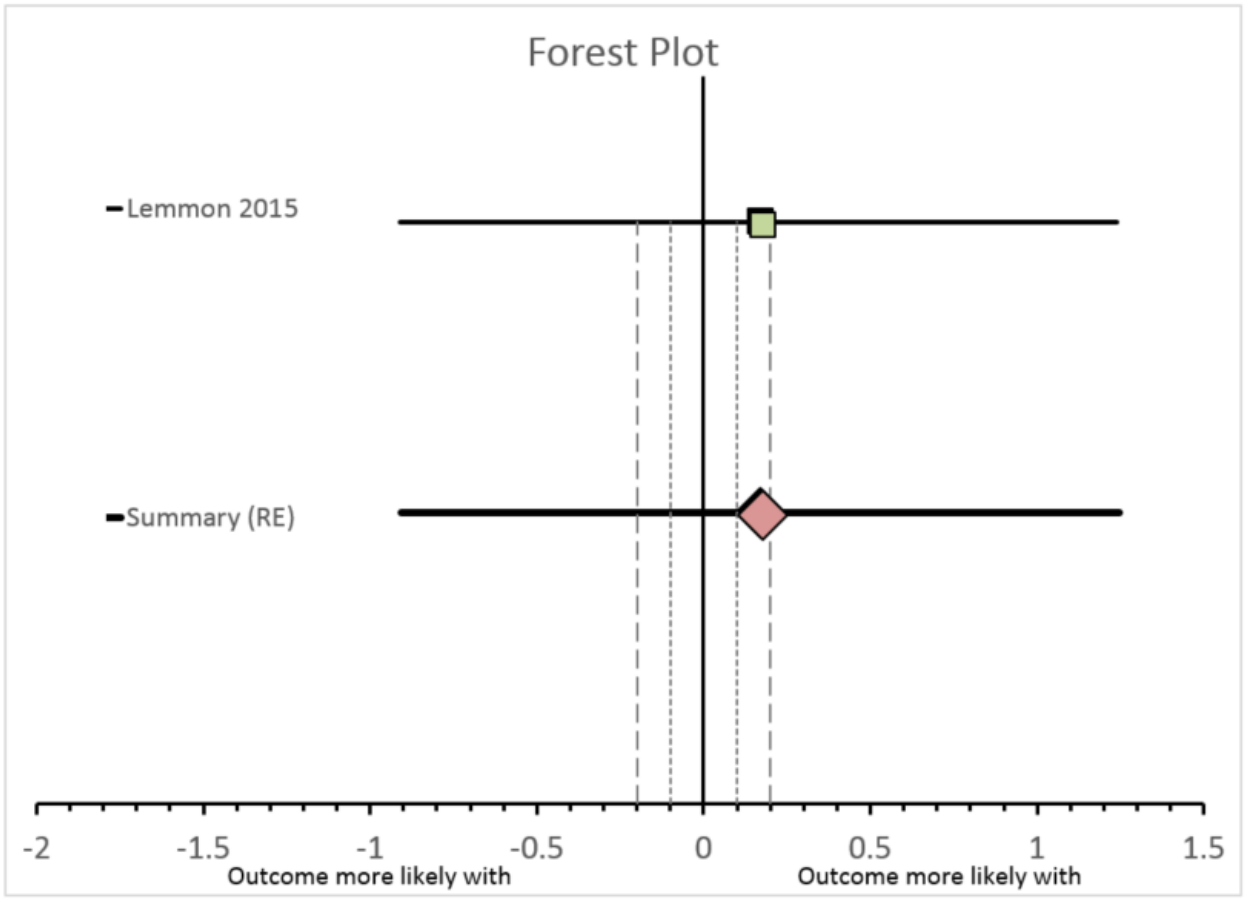
Nicotine vs Placebo + Haldol

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving nicotine							
	Comparator	those receiving haldol + placebo							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Silver 2001	III	Minor	0.710	0.170	1.250			3.000	
	Summary (RE)	1; III	Minor	0.710	0.170	1.250	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving nicotine are more or less likely than those receiving haldol + placebo to have reduced tic severity								



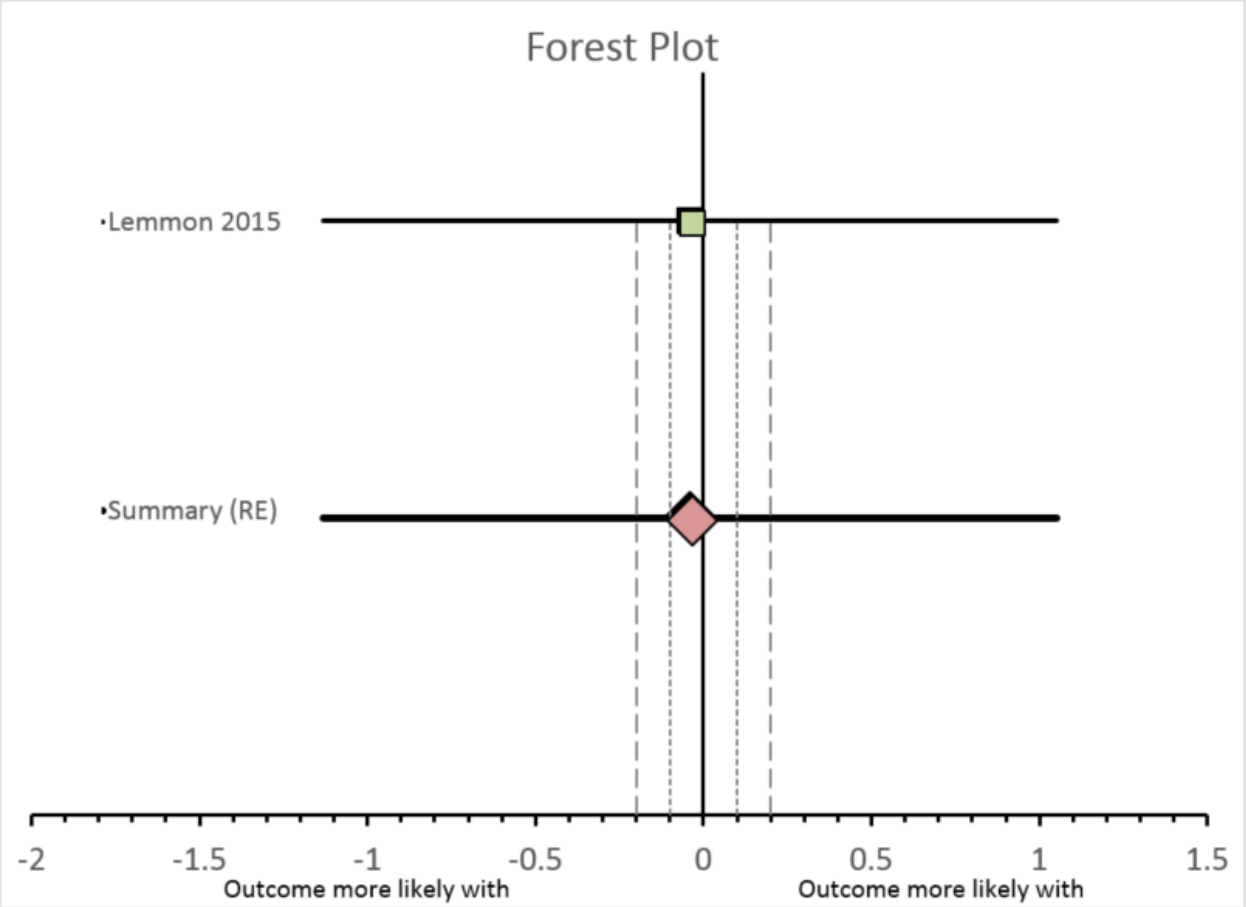
Riluzole vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving riluzole								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Lemmon 2015	I	Minor	0.170	-0.910	1.240			1.000	
	Summary (RE)	1; I	Minor	0.170	-0.905	1.245	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving riluzole are more or less likely than those receiving placebo to have reduced tic severity								



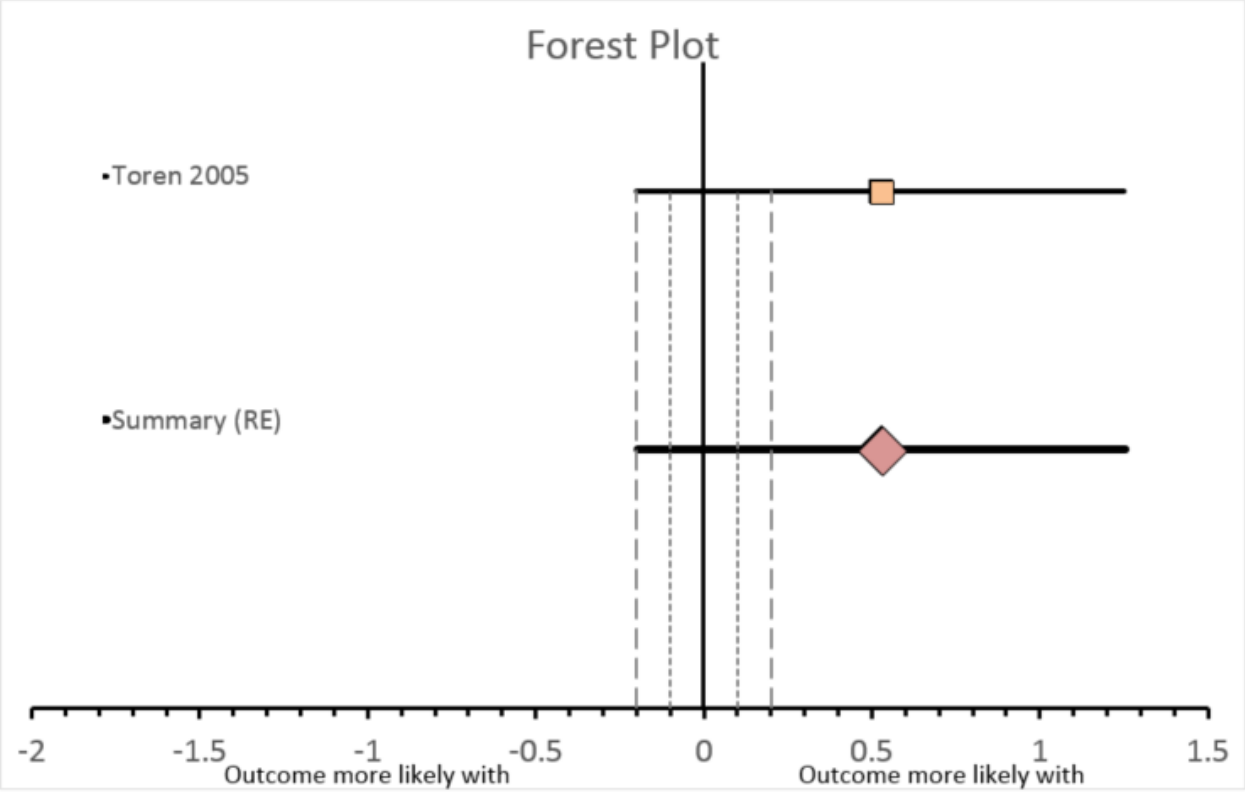
D-serine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving D-serine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Lemmon 2015	I	Minor	-0.040	-1.130	1.050			1.000	
	Summary (RE)	1; I	Minor	-0.040	-1.130	1.050	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving D-serine are more or less likely than those receiving placebo to have reduced tic severity								



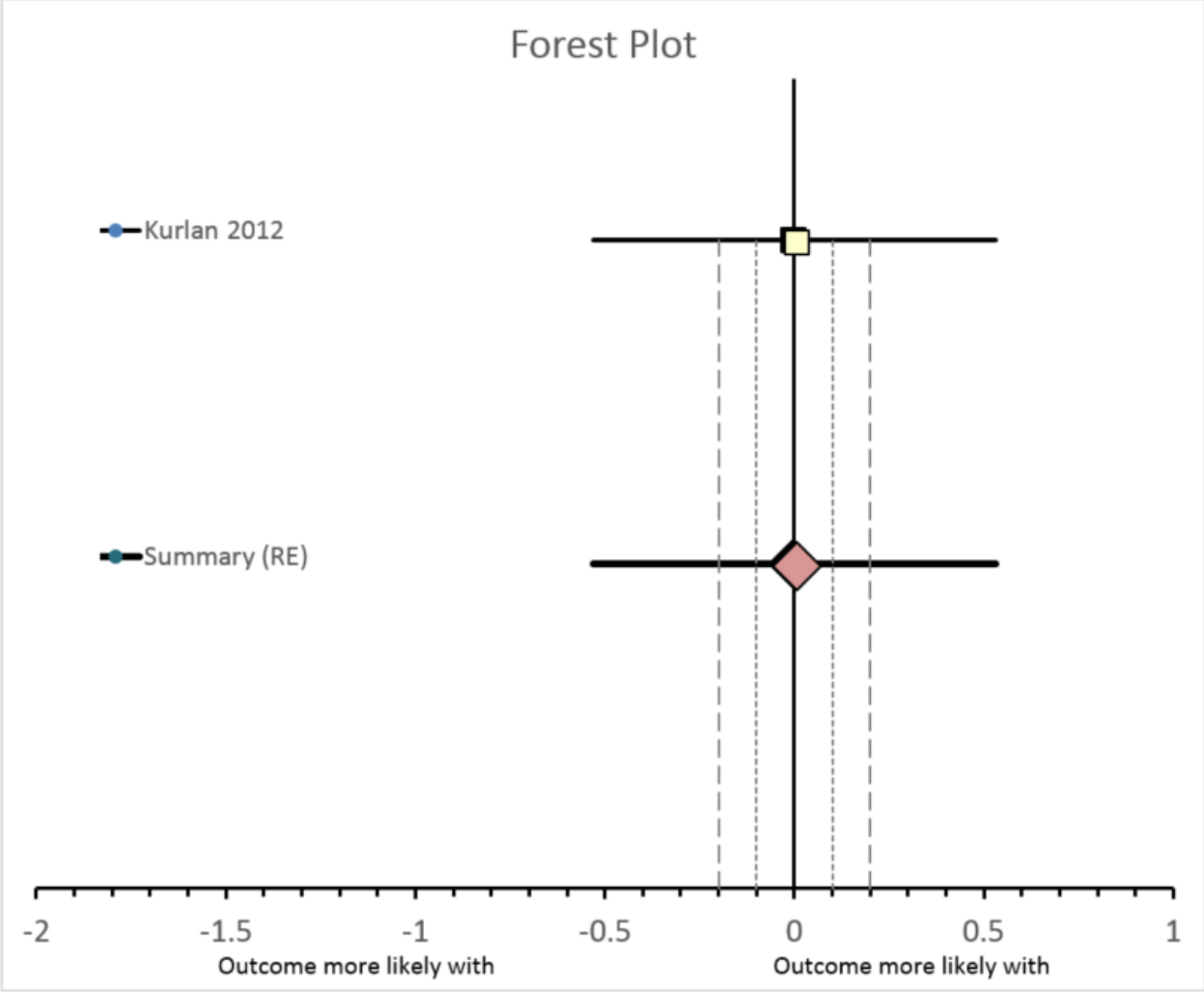
Ondansetron vs Placebo

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving Ondansetron those receiving placebo have reduced tic severity							
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Toren 2005	III	Minor	0.530	-0.200	1.250			3.000	
	Summary (RE)	1; III	Minor	0.530	-0.195	1.255	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving Ondansetron are more or less likely than those receiving placebo to have reduced tic severity								



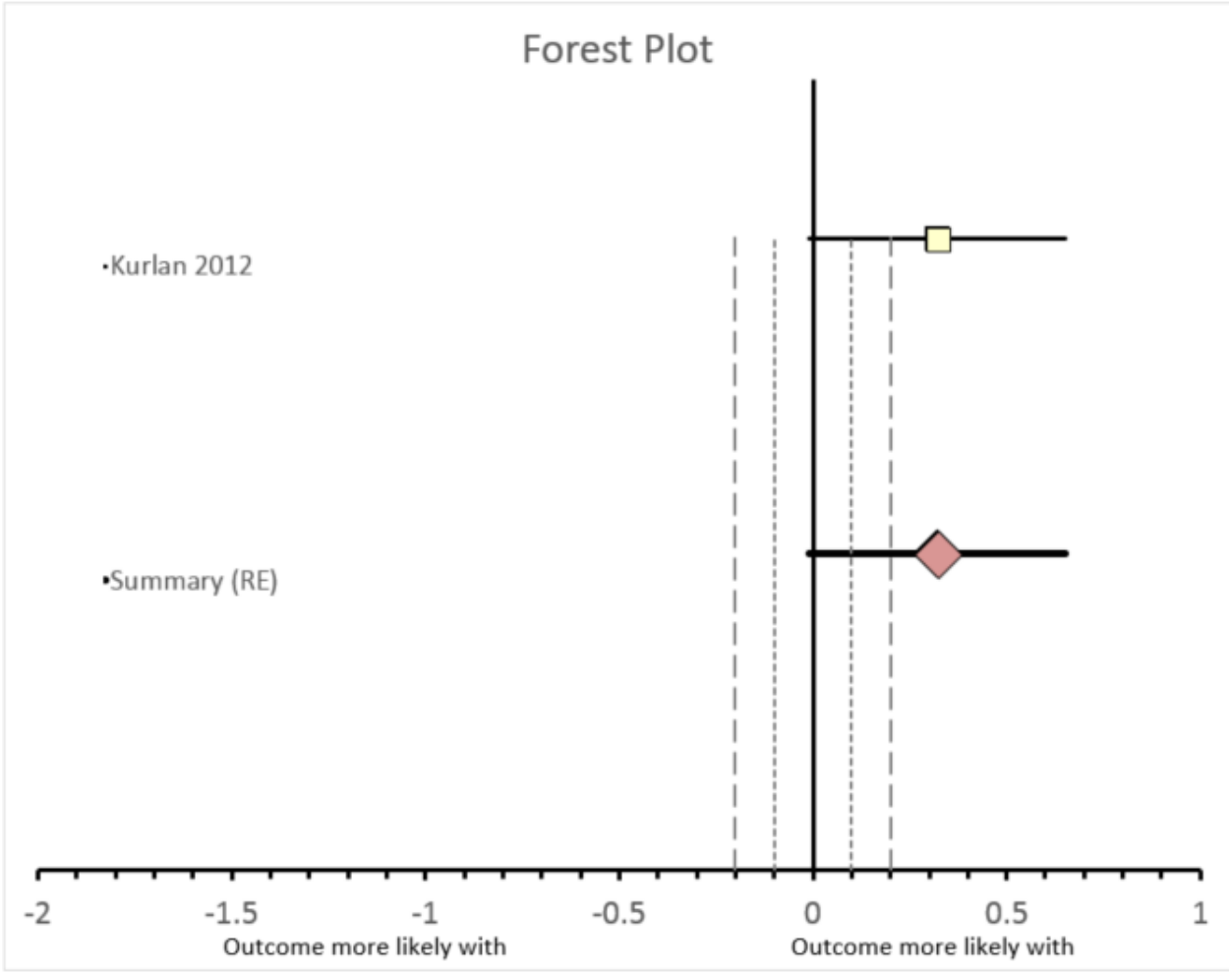
Pramipexole vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving Pramipexole								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Kurlan 2012	II	Minor	0.000	-0.530	0.530			2.000	
	Summary (RE)	1; II	Minor	0.000	-0.530	0.530	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving Pramipexole are more or less likely than those receiving placebo to have reduced tic severity								



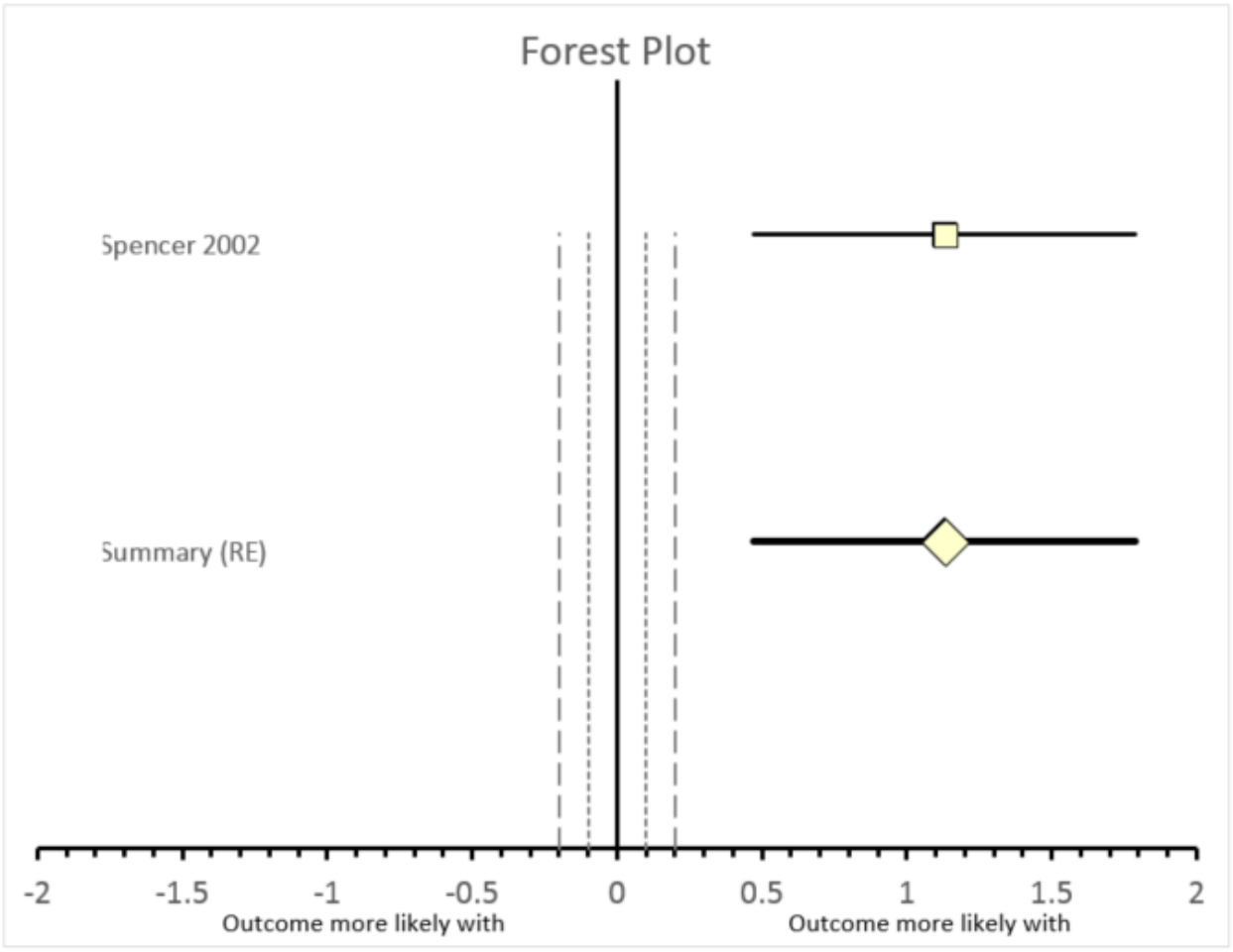
Atomoxetine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving Atomoxetine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Kurlan 2012	II	Minor	0.320	-0.010	0.650			2.000	
	Summary (RE)	1; II	Minor	0.320	-0.010	0.650	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving Atomoxetine are more or less likely than those receiving placebo to have reduced tic severity								



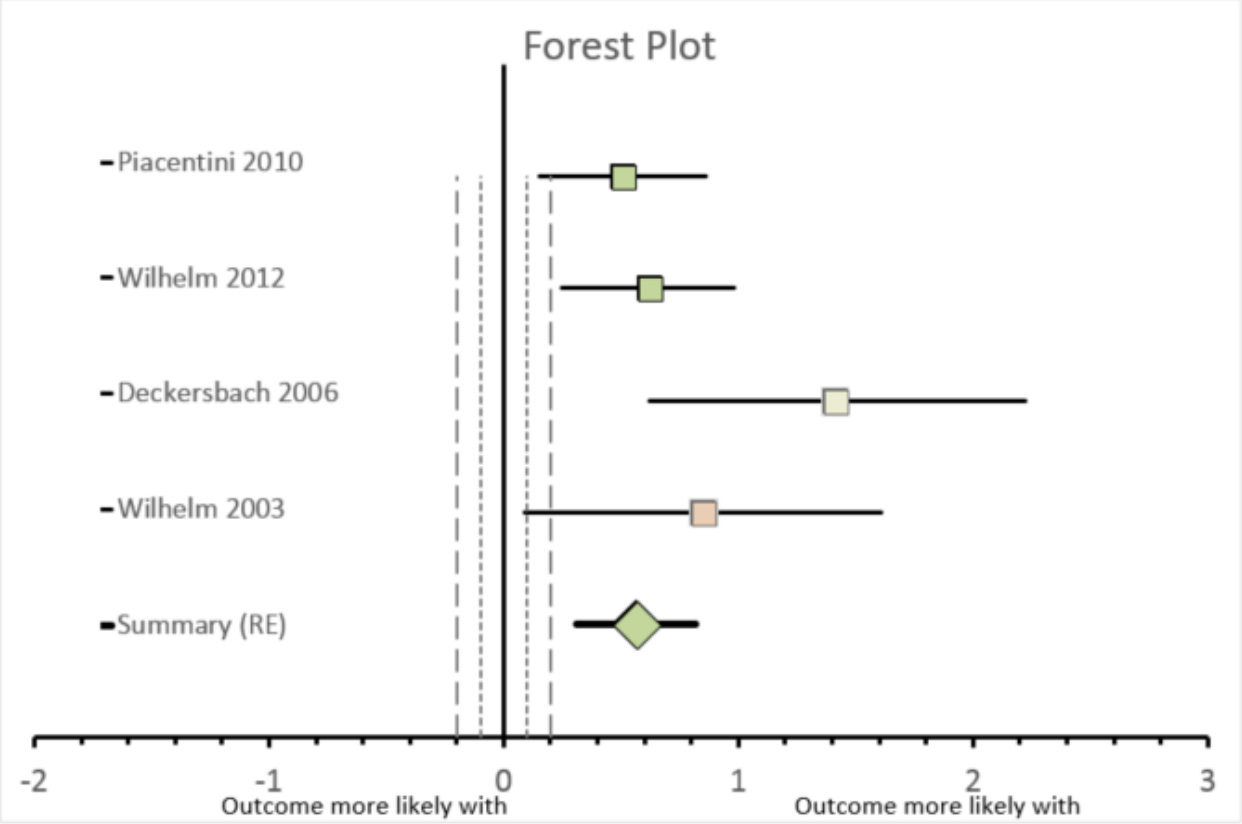
Desipramine vs Placebo

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving Desipramine								
	Comparator	those receiving placebo								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Spencer 2002	II	Minor	1.130	0.470	1.790			2.000	
	Summary (RE)	1; II	Minor	1.130	0.470	1.790	NC	NC	Isq: NA	NA
	Conclusion (moderate confidence)	People with tics receiving Desipramine are probably more likely than those receiving placebo to have reduced tic severity								



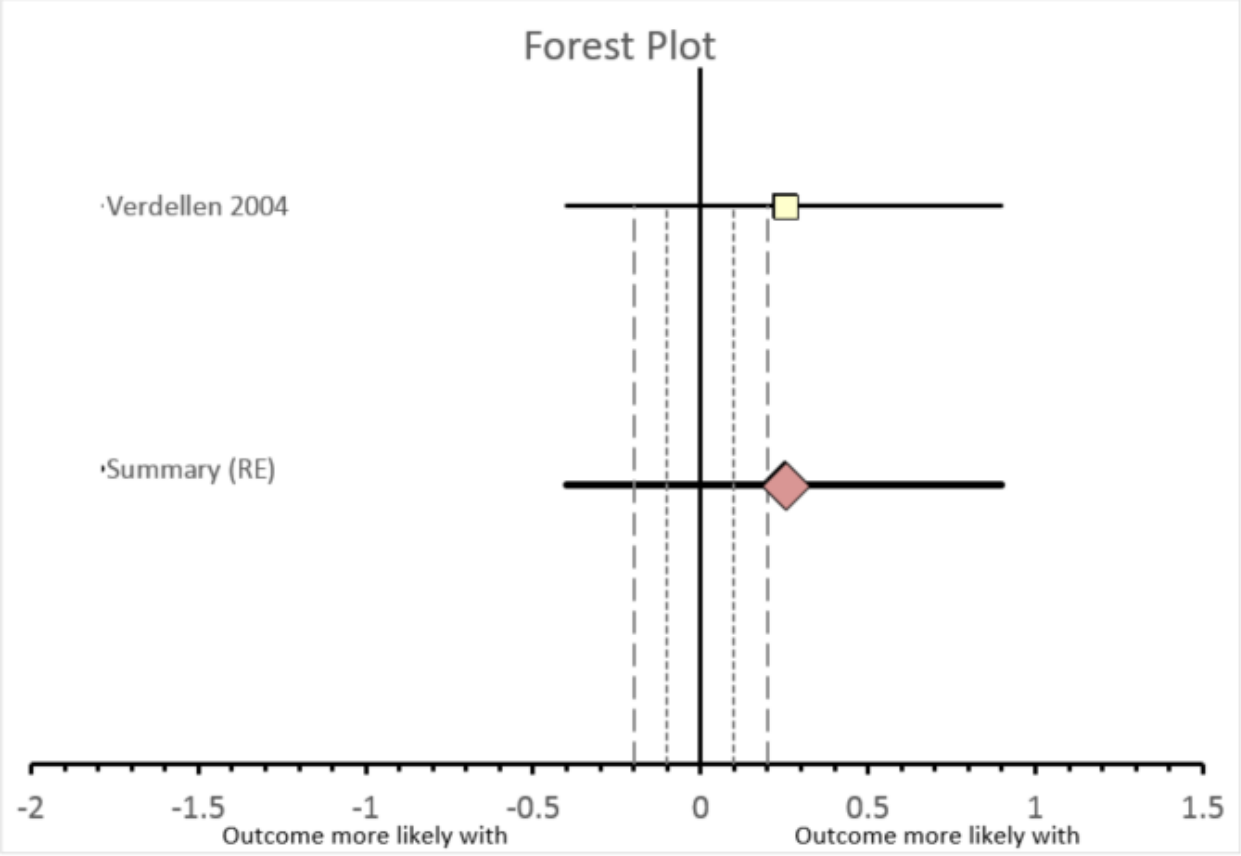
HRT vs Supportive Therapy

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving habit reversal therapy							
	Comparator	those receiving supportive therapy							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Piacentini 2010	I	Minor	0.510	0.150	0.860			1.000	
1	Wilhelm 2012	I	Minor	0.620	0.250	0.980			1.000	
0	~~Deckersbach 2006~~	II	Minor	1.410	0.620	2.220			2.000	
0	~~Wilhelm 2003~~	III	Minor	0.850	0.090	1.610			3.000	
	Summary (RE)	2; I	Minor	0.563	0.309	0.818	NC	NC	Isq: 0	NA
	Conclusion (high confidence)	People with tics receiving habit reversal therapy are more likely than those receiving supportive therapy to have reduced tic severity								



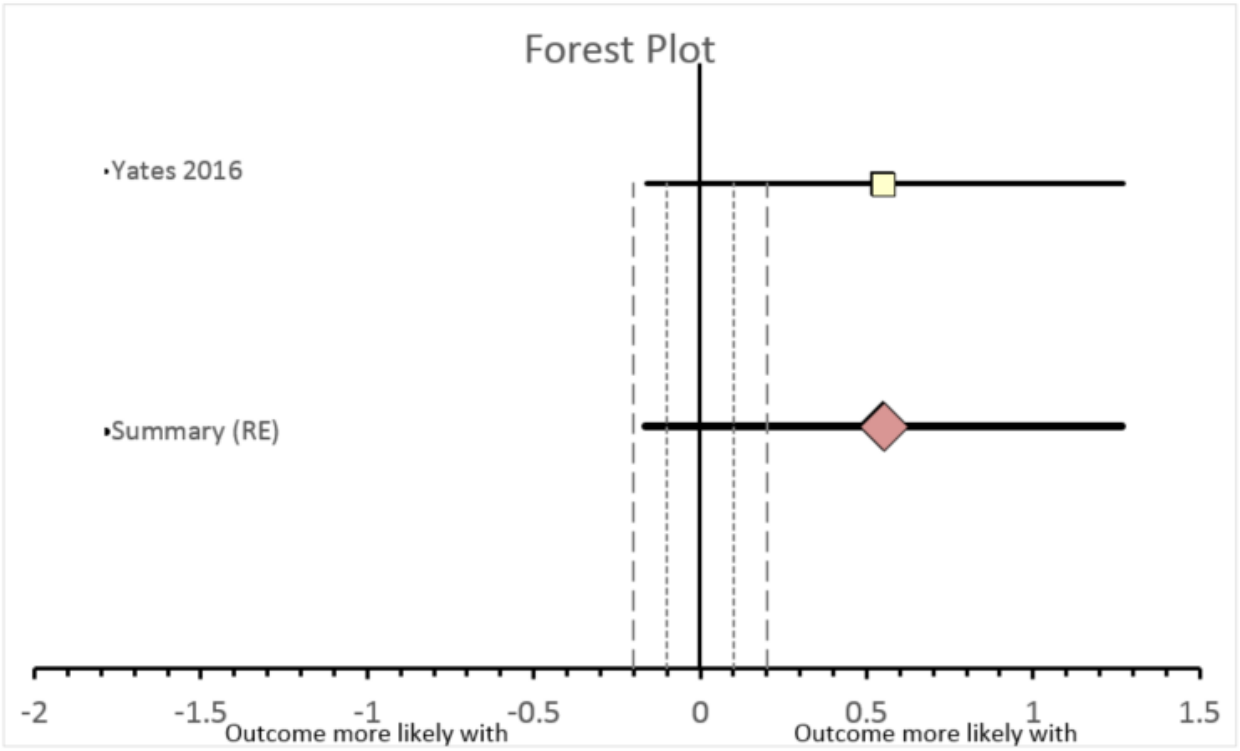
HRT vs ERP

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving habit reversal therapy							
	Comparator	those receiving exposure and response prevention							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Verdellen 2004	II	Minor	0.250	-0.400	0.900			2.000	
	Summary (RE)	1; II	Minor	0.250	-0.400	0.900	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving habit reversal therapy are more or less likely than those receiving exposure and response prevention to have reduced tic severity								



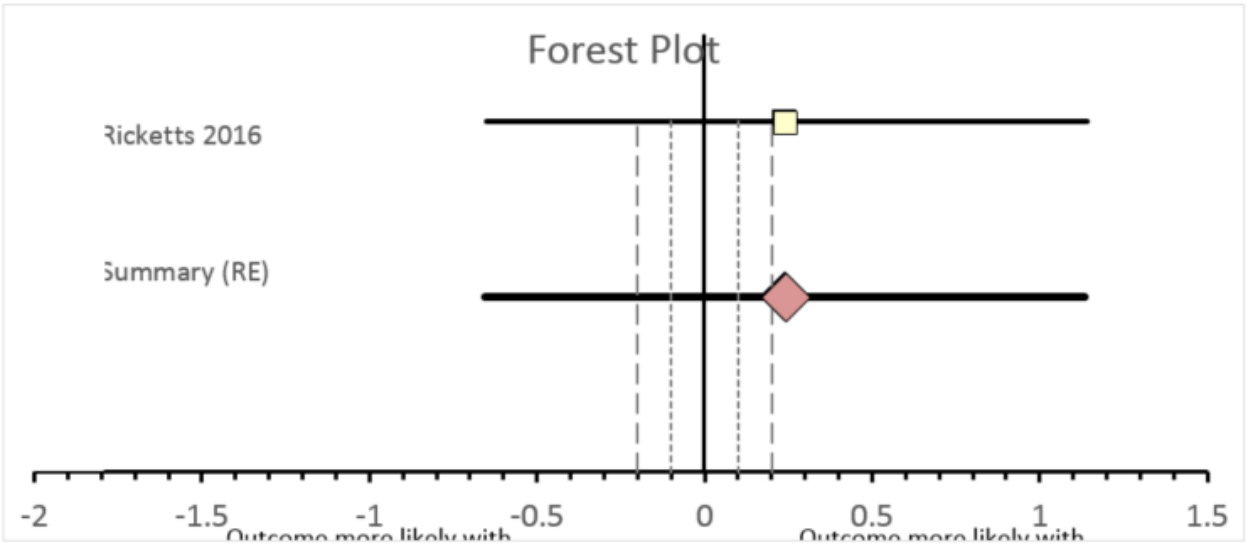
HRT vs Education

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	habit reversal therapy								
	Comparator	those receiving educational group treatments								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Yates 2016	II	Minor	0.550	-0.160	1.270			2.000	
	Summary (RE)	1; II	Minor	0.550	-0.165	1.265	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics habit reversal therapy are more or less likely than those receiving educational group treatments to have reduced tic severity								



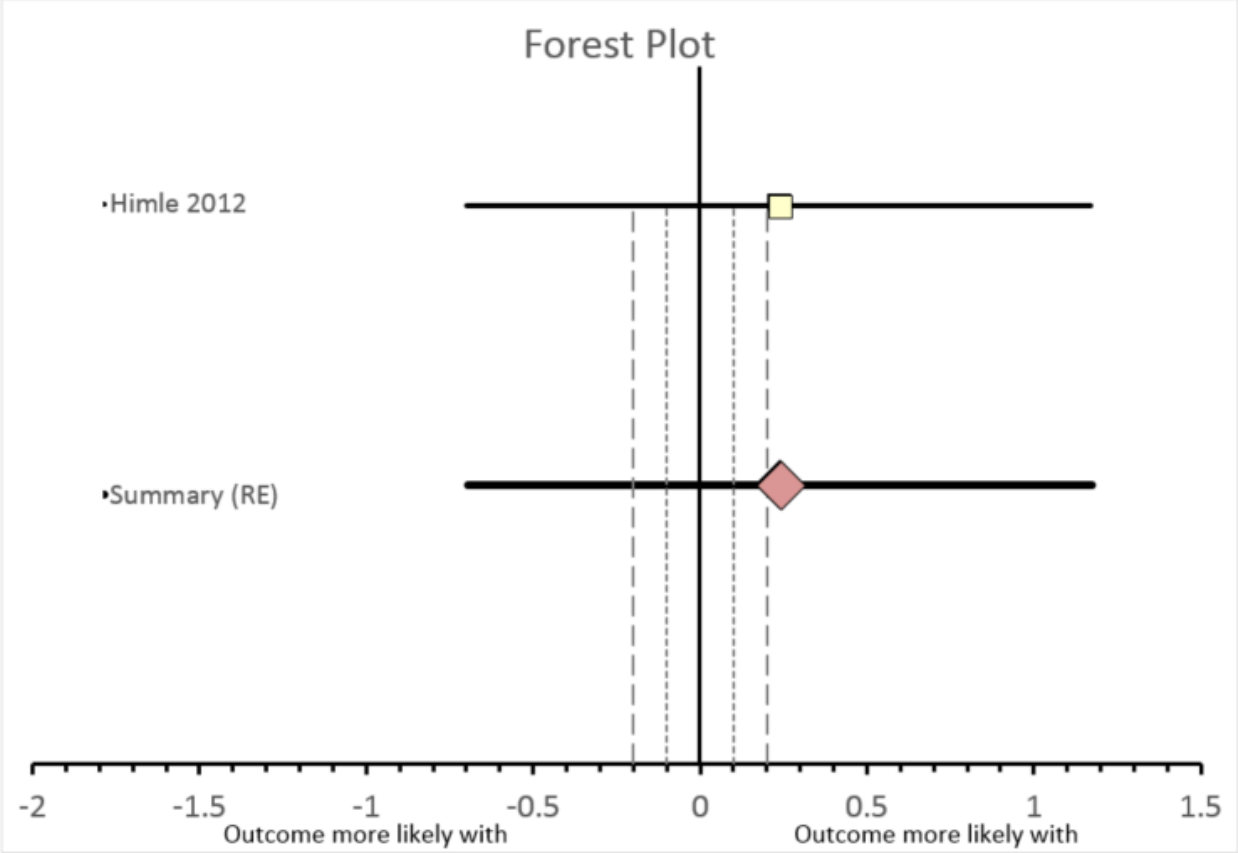
Internet HRT vs Wait List

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving habit reversal therapy over internet							
	Comparator	those on a wait list							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Ricketts 2016	II	Minor	0.240	-0.650	1.140			2.000	
	Summary (RE)	1; II	Minor	0.240	-0.655	1.135	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving habit reversal therapy over internet are more or less likely than those on a wait list to have reduced tic severity								



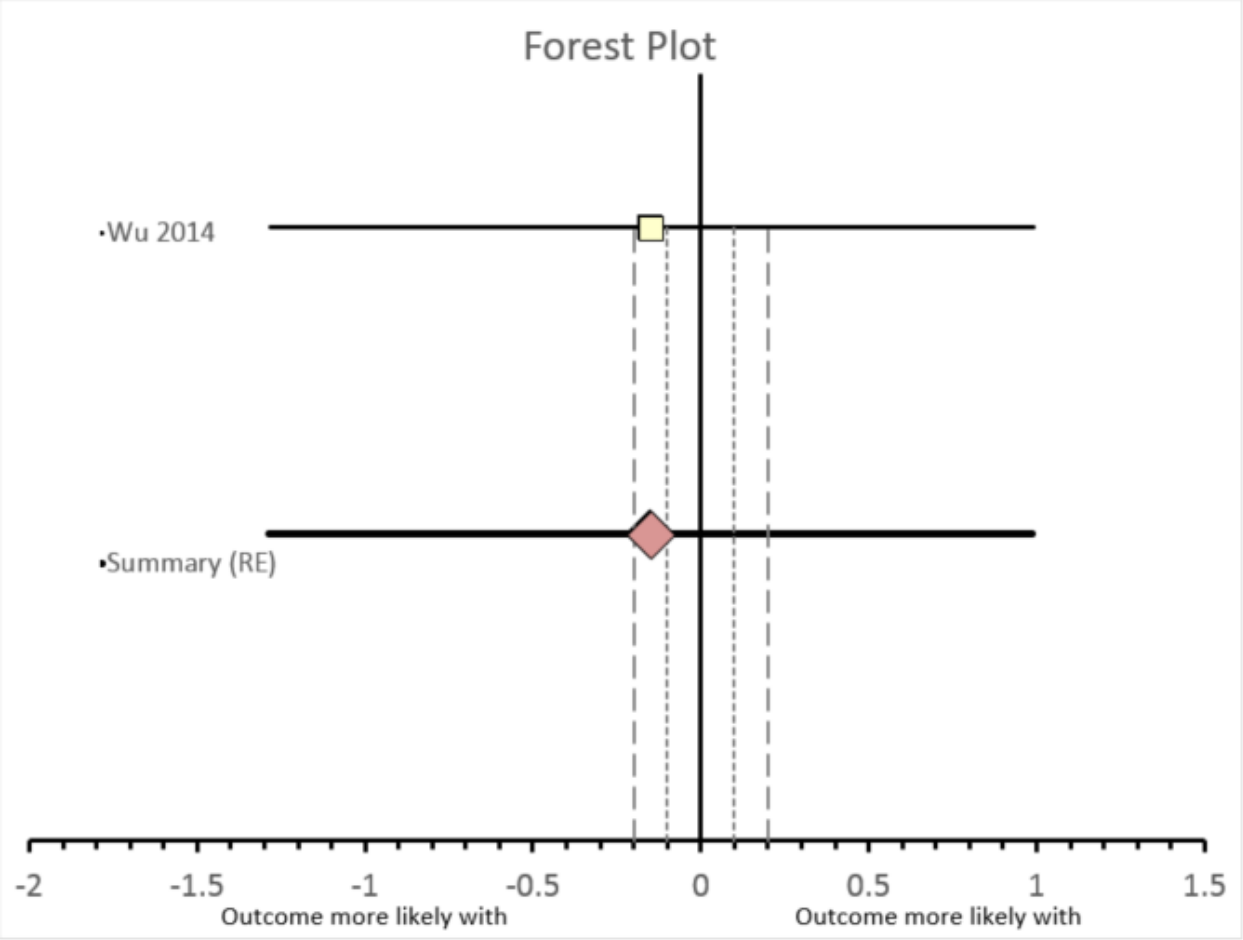
Face to Face vs Internet HRT

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving face to face habit reversal therapy those receiving habit reversal therapy via videoconferencing have reduced tic severity							
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Himle 2012	II	Minor	0.240	-0.700	1.170			2.000	
	Summary (RE)	1; II	Minor	0.240	-0.695	1.175	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving face to face habit reversal therapy are more or less likely than those receiving habit reversal therapy via videoconferencing to have								



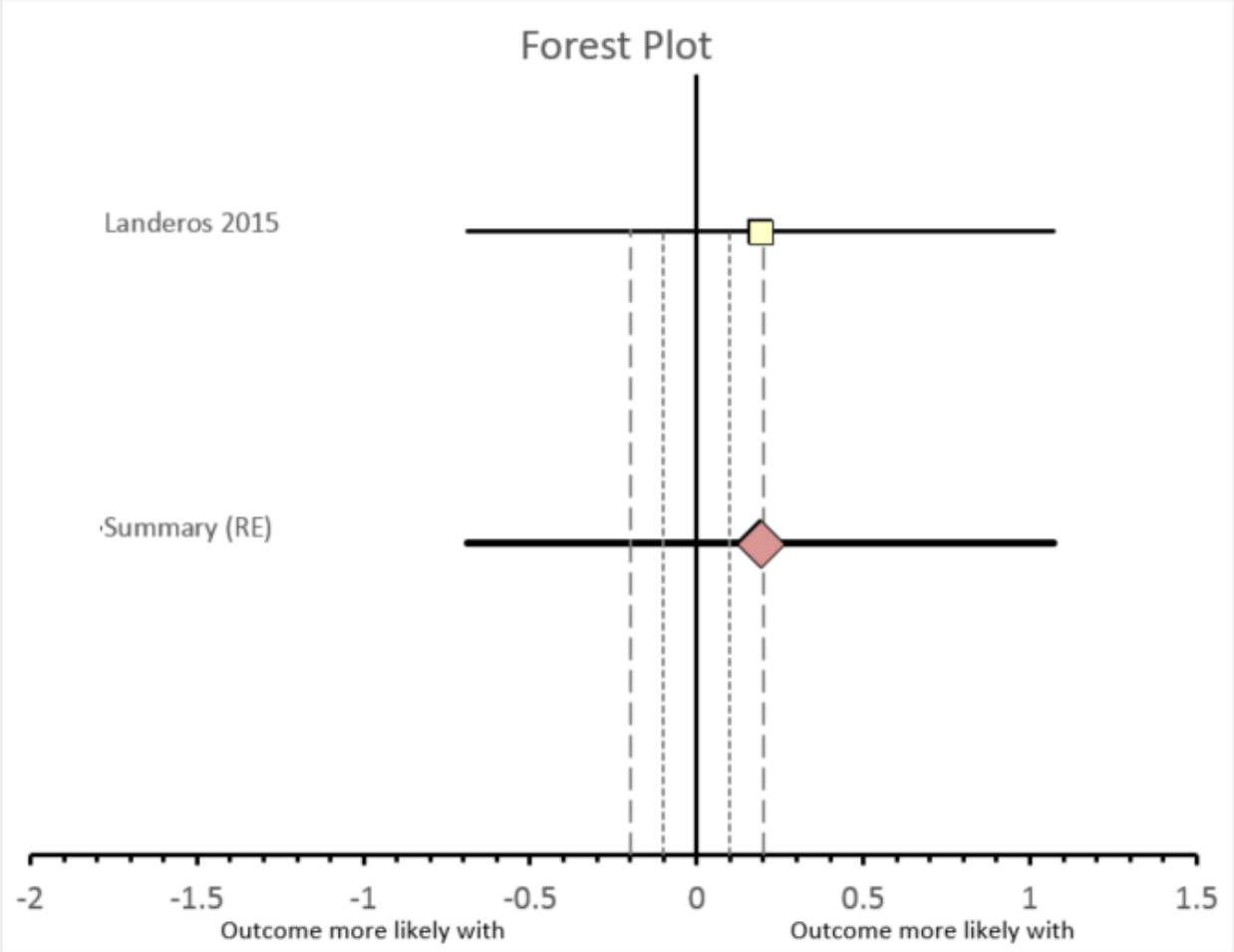
Cont Theta Burst St SMA vs Sham

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population	People with tics								
	Intervention	receiving continuous theta burst stimulation of SMA								
	Comparator	those receiving sham stimulation								
	Outcome	have reduced tic severity								
	Important effect size	0.200	Effect values less than 0 indicate:							
	Unimportant effect size	0.100	Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Wu 2014	II	Minor	-0.150	-1.280	0.990			2.000	
	Summary (RE)	1; II	Minor	-0.150	-1.285	0.985	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving continuous theta burst stimulation of SMA are more or less likely than those receiving sham stimulation to have reduced tic severity								



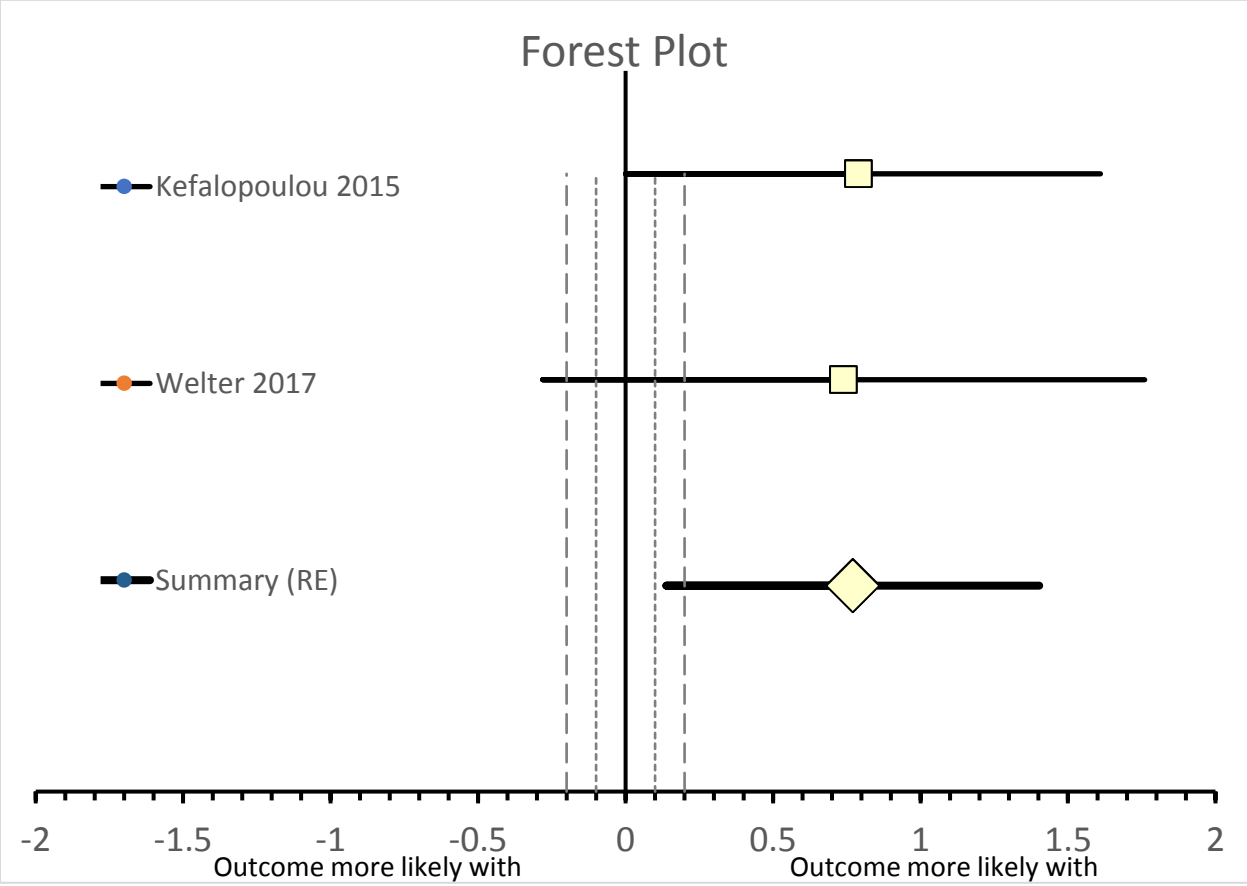
rTMS SMA vs Sham

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving rTMS of SMA							
	Comparator	those receiving sham stimulation							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Landeros 2015	II	Minor	0.190	-0.690	1.070			2.000	
	Summary (RE)	1; II	Minor	0.190	-0.690	1.070	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving rTMS of SMA are more or less likely than those receiving sham stimulation to have reduced tic severity								



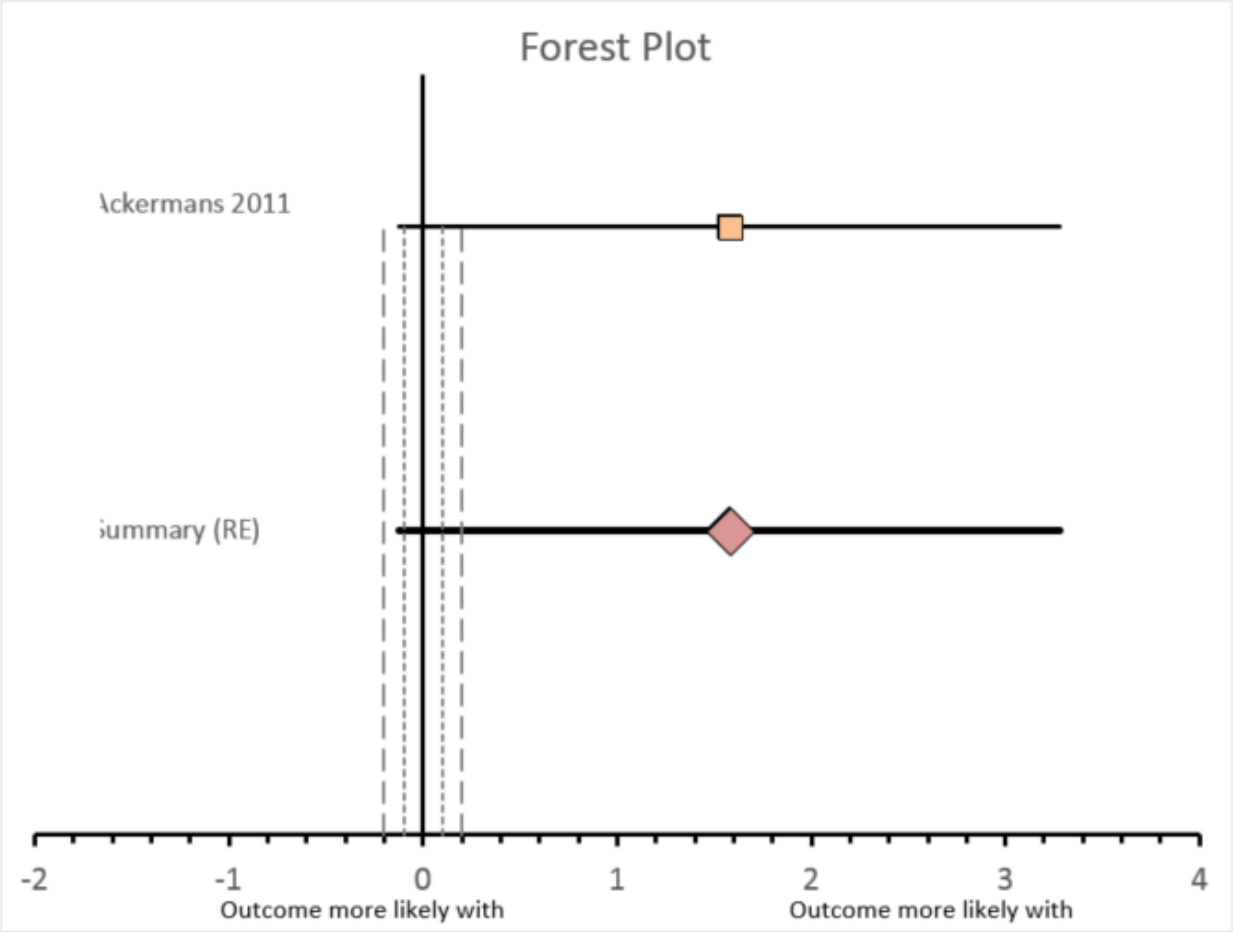
DBS GPi on vs off

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population	People with tics							
	Intervention	receiving DBS Gpi stimulation							
	Comparator	those receiving sham stimulation							
	Outcome	have reduced tic severity							
	Important effect size	0.200	Effect values less than 0 indicate:						
	Unimportant effect size	0.100	Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Kefalopoulou 2015	II	Minor	0.790	0.000	1.610			2.000	
1	Welter 2017	II	Minor	0.739	-0.281	1.760			2.000	
	Summary (RE)	2; II	Minor	0.770	0.138	1.402	NC	NC	Isq: 0	NA
	Conclusion (moderate confidence)	People with tics receiving DBS Gpi stimulation are probably more likely than those receiving sham stimulation to have reduced tic severity								



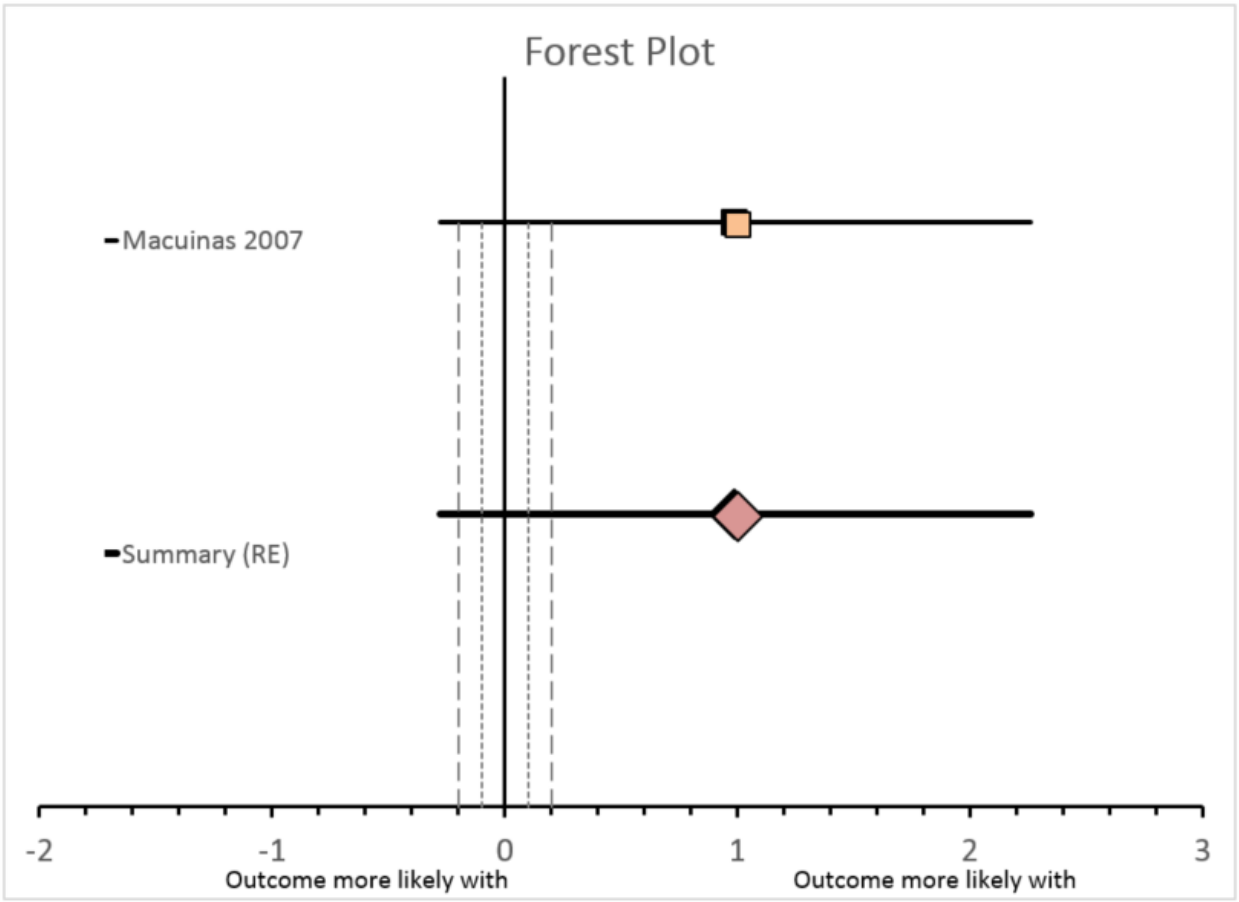
DBS Thalamus on vs off

	Therapeutic	Random effects		Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving DBS thalamus stimulation on those receiving DBS thalamus stimulation off have reduced tic severity								
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1							
1	Biological Plausibility (prior)	Yes		0	-1000	1000				
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Ackermans 2011	III	Minor	1.580	-0.120	3.280			3.000	
	Summary (RE)	1; III	Minor	1.580	-0.120	3.280	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving DBS thalamus stimulation on are more or less likely than those receiving DBS thalamus stimulation off to have reduced tic severity								



DBS CM-PFC on vs Off

	Therapeutic	Random effects	Narrative conclusion: Yes			Comments:			
	Population Intervention Comparator Outcome	People with tics receiving DBS centromedian-parafascicular complex stimulation on those receiving DBS centromedian-parafascicular complex stimulation off have reduced tic severity							
	Important effect size Unimportant effect size	0.200 0.100	Effect values less than 0 indicate: Outcome more likely with comparator -1						
1	Biological Plausibility (prior)	Yes		0	-1000	1000			
Include	Study (Author Year)	Class	Indirectness	Std mean diff	LCL	UCL	Sig. Dose Response	Bias favors	Regress Heterog.	Pub. Bias (p)
1	Macuinas 2007	III	Minor	0.990	-0.280	2.260			3.000	
	Summary (RE)	1; III	Minor	0.990	-0.280	2.260	NC	NC	Isq: NA	NA
	Conclusion (very low confidence)	There is insufficient evidence to determine whether people with tics receiving DBS centromedian-parafascicular complex stimulation on are more or less likely than those receiving DBS centromedian-parafascicular complex stimulation off to								



Appendix e-8. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- $\geq$ 80% agreement on dichotomous judgments
- $\geq$80% agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10^{th} percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
    - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
        - Level A: High confidence
        - Level B: Moderate confidence
        - Level C: Low confidence

        - Level U: Very low confidence
    - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
        - Level A: 100%
        - Level B: ≥ 80% to < 100%
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%
    - Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
        - Level B: ≥ 80% to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
        - Level C: ≥ 50% to < 80%
        - Level U or R: < 50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
    - Magnitude relative to harm rated on 4-point ordinal scale
        - Large benefit relative to harm: benefit judged large, harm judged none
        - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
        - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
        - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
    - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
        - Level A: large benefit relative to harm
        - Level B: moderate benefit relative to harm
        - Level C: small benefit relative to harm
        - Level U: too close to call
    - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains

- Importance of the outcome: critical, important, mildly important, not important
- Expected variation in patient preferences: none, minimal, moderate, large
- Financial burden relative to benefit expected: none, minimal, moderate, large
- Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-9 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-9. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based. Please see appendix e-8 for the steps and rules for formulating recommendation strength.

PRACTICE RECOMMENDATIONS

Counseling recommendation: Natural history of TS: recommendation 1

Rationale

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][107]. 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][108]. 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 Behavioral 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].

Statement 1a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 2	Usually 1	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	#NAME?

Statement 1b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 3	Modest 2	Minimal 8	No
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because variation in preferences. Recommendation downgraded to Level B.

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 4	Very important 6	Critically important 3	No
Variation in preferences	Large 0	Moderate 3	Modest 9	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 10	Usually 3	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 10	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1e

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 1	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Psychoeducation, teacher and classroom: recommendation 2

Rationale

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][109]. Improving peers' attitudes about and teachers' knowledge of TS may positively affect people with TS [INFER].

Statement 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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 3	Modest 4	Minimal 6	No
Feasible	Rarely 0	Occasionally 1	Usually 7	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Assessment and treatment of ADHD in children with tics: recommendation 3

Rationale

Comorbid attention-deficit/hyperactivity disorder (ADHD) is common in people with TS, with prevalence ranging from 30% to 50% depending on the population studied [RELA][22, 110]. 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 likely than placebo to reduce tic severity [EVID] and reduce ADHD symptoms. In children with tics and ADHD, atomoxetine does not worsen tics relative to placebo [EVID] and reduces ADHD symptoms. Comorbid ADHD is strongly associated with functional impairment in children with TS [RELA][111]. While ADHD symptoms may improve in adolescence [RELA][108], adults with TS may require ongoing care for this comorbidity.

Statement 3a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 1	Moderate 1	Modest 4	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 3b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 6	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 3c

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 10	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Assessment and treatment of OCD in children with tics: recommendation 4

Rationale

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, 110]. 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][112, 113]. For this reason, cognitive behavioural therapy is considered first-line treatment of OCD in individuals with tic disorders [INFER].

Statement 4a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 3	Usually 6	Always 4	No
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 4b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 2	Usually 6	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

Other psychiatric comorbidities: recommendation 5

Rationale

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, 110]. Comorbid mood disorders appear more prevalent in adolescents and adults than children and in those with greater tic severity [RELA][22, 114]. 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][115].

Statement 5a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Statement 5b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Assessment of tic severity and treatment expectations: recommendation 6

Rationale

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][30]. 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.

Statement 6a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 3	Benefit >> harm 6	Benefit >>> harm 4	No
Importance of outcomes	Not important or unknown 1	Mildly Important 1	Very important 7	Critically important 4	Yes
Variation in preferences	Large 3	Moderate 1	Modest 5	Minimal 4	No
Feasible	Rarely 0	Occasionally 4	Usually 5	Always 4	No
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because benefit relative to harm, variation in preferences, and feasible. Recommendation downgraded to Level C.

Statement 6b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 0	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 3	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Psychosocial treatments: recommendation 7

Rationale

Children and adults with tics receiving the Comprehensive Behavioral Intervention for Tics (CBIT) are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. [EVID]. CBIT is a manualized treatment program consisting of habit reversal training, relaxation training, and a functional intervention to address situations that sustain or worsen tics [RELA][116]. 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 substantial clinical comorbidity may benefit from a longer course of therapy. Most children (aged 9 years or older) and adults showing an initial positive response to

CBIT, will maintain their treatment gains for at least 6 months [EVID]. CBIT can be effective for children under age 9 years, though there is little evidence available to determine efficacy in children of this age group [RELA][117]. 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 medication[118] [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].

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Statement 7b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 8	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 3	Very important 6	Critically important 3	No
Variation in preferences	Large 2	Moderate 5	Modest 5	Minimal 1	No
Feasible	Rarely 1	Occasionally 8	Usually 4	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 10	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Alpha agonists for the treatment of tics: recommendation 8

Rationale

People with tics receiving clonidine are probably more likely than those receiving placebo to have reduced tic severity, and people with tics receiving guanfacine are possibly more likely than those receivng placebo to have reduced tic severity, with the majority of trials conducted in children [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 and guanfacine is probably associated with higher rates of drowsiness, dry mouth, headache, irritability and stomachache [EVID]. A systematic review of alpha-2 adrenergic agonists for ADHD in children and adolescents demonstrated hypotension, bradycardia, and sedation with both agents, and QTc prolongation with guanfacine extended release [RELA][119]. Abrupt withdrawal of alpha-2 adrenergic agonists may cause rebound hypertension [RELA][120].

Statement 8a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 8	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 10	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 12	Benefit >>> harm 1	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 10	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 1	Modest 11	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 8c

Physicians must counsel patients regarding common side effects of alpha-2 adrenergic agonists, including sedation (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 8d

Physicians must monitor heart rate and blood pressure in all patients with tics treated with alpha-2 adrenergic agonists (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 3	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 5	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 8f

Physicians discontinuing alpha-2 adrenergic agonists must gradually taper them to avoid rebound hypertension (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 0	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Antipsychotic treatment for tics: recommendation 9

Rationale

Haloperidol, risperidone, aripiprazole, and tiapride are probably more likely than placebo to reduce tic severity [EVID], and pimozide, ziprasidone, and metoclopramide are possibly more likely than placebo to reduce tic severity [EVID]. There is insufficient evidence to determine the relative efficacy of these 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][121, 122]. 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[123]. 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], and evidence-based monitoring protocols are available for reference[124]. Abrupt discontinuation of antipsychotic medications can cause withdrawal dyskinesias[125, 126] [RELA].

Statement 9a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 4	Benefit >> harm 5	Benefit >>> harm 3	No
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 6	Critically important 5	Yes
Variation in preferences	Large 3	Moderate 3	Modest 5	Minimal 2	No
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 4	Moderate 6	Small 3	No
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because benefit relative to harm, variation in preferences, and cost relative to net benefit. Recommendation downgraded to Level C.

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Statement 9c

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 0	Very important 4	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 8	Yes
Feasible	Rarely 1	Occasionally 1	Usually 2	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 9e

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 3	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 5	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 9f

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Botulinum toxin injections for tics: recommendation 10

Rationale

Botulinum neurotoxin injections with onabotulinum toxin A are probably more likely than placebo to reduce tic severity in adolescents and adults [EVID]. Premonitory urges may also be improved by botulinum toxin injections in a proportion of patients [RELA][127]. There is no evidence on the efficacy of other botulinum toxins for tics [EVID]. Relative to placebo, onabotulinum toxin A is associated with higher rates of weakness [EVID]. Hypophonia is a common side effect of botulinum toxin injections in the laryngeal muscles for vocal tics [RELA][128]. The effect of botulinum toxin injections last between 12 and 16 weeks in the majority of patients, after which treatment needs to be repeated [PRIN].

Statement 10a

Physicians may prescribe botulinum toxin 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 8	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 5	Modest 8	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 8	Usually 5	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 12	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Statement 10b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 8	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 5	Modest 6	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 7	Usually 6	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 12	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 10c

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 2	Usually 1	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 1	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Topiramate for the treatment of tics: recommendation 11

Rationale

Topiramate is possibly more likely than placebo to reduce 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][129-131].

Statement 11a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 4	Benefit >> harm 8	Benefit >>> harm 1	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 7	Critically important 4	Yes
Variation in preferences	Large 1	Moderate 4	Modest 7	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 1	Usually 7	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 11b

Physicians must counsel patients regarding common adverse effects of topiramate, including cognitive and language problems, somnolence, weight loss, and an increased risk of renal stones (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 1	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 1	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Cannabis-based medications for the treatment of patients with TS: recommendation 12

Rationale

A large number of patients with TS use cannabis as a self-medication for the treatment of both tics and different comorbidities [RELA][132]. There is limited evidence that the most psychoactive ingredient of cannabis, delta-9-tetrahydrocannabinol (THC, dronabinol), is possibly more likely than placebo to reduce tic severity in adults with TS [EVID]. There is insufficient evidence to determine whether 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][133]. 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][134]. Acute withdrawal of cannabinoids is generally safe and well tolerated without significant adverse events [RELA][133, 135]. 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]. Prescription of and access to medical marijuana varies by region; practitioners must abide by regional legislation on the use of medical marijuana [PRIN].

Statement 12a

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Statement 12b

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 6	Benefit >> harm 5	Benefit >>> harm 1	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 3	Very important 7	Critically important 3	No
Variation in preferences	Large 4	Moderate 8	Modest 0	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 9	Usually 4	Always 0	Yes
Cost relative to net benefit	Very large 1	Large 2	Moderate 9	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 12c

Where regional legislation allows, 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 2	Benefit >> harm 5	Benefit >>> harm 5	No
Importance of outcomes	Not important or unknown 0	Mildly important 3	Very important 6	Critically important 4	No
Variation in preferences	Large 1	Moderate 5	Modest 3	Minimal 4	No
Feasible	Rarely 0	Occasionally 7	Usually 3	Always 3	No
Cost relative to net benefit	Very large 1	Large 1	Moderate 7	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 1	Moderate 0	Modest 1	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 2	Usually 0	Always 11	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 0	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 12e

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 12f

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 0	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 4	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 2	Usually 0	Always 11	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 2	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Deep brain stimulation for tics in the setting of TS: recommendation 13

Rationale

Patients with severe TS, resistant to medical and behavioral therapy, may benefit from the application of DBS. An important challenge and limitation in the evaluation of the evidence around DBS in TS is that, even in expert DBS centers, 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 possibly more likely than sham stimulation to reduce tic severity [EVID]. There is insufficient evidence to determine the efficacy of DBS of the thalamus or the centromedian-parafascicular complex region in reducing tic severity [EVID]. Complications of treatment, including infection and removal of hardware, appear more common with TS [EVID] than with other neurological conditions.

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][136]. Appropriate patient selection is one of the most important predictors of success or failure of DBS treatment, making multidisciplinary evaluation essential [RELA][137]. 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][138] . 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.

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 1	Critically important 12	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 3	Usually 2	Always 8	No
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

*Failed to meet consensus because feasible. Recommendation downgraded to Level B.

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 0	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 1	Critically important 12	Yes
Variation in preferences	Large 0	Moderate 0	Modest 3	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Statement 13d

Physicians must confirm that multiple classes of medication (antipsychotics, dopamine depleters, alpha-1-agonists) and behavioral therapy have been administered (or are contraindicated) before prescribing DBS for tics in the setting of TS (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 2	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 4	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 2	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 1	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very Important 5	Critically Important 8	Yes
Variation in preferences	Large 0	Moderate 4	Modest 6	Minimal 3	No
Feasible	Rarely 0	Occasionally 7	Usually 4	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 3	Moderate 7	Small 3	No
Strength of recommendation	R/U	C	B	A	

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