Canadian Guidelines for the Evidence-Based Treatment of

Tourette Syndrome

Edited by Tamara Pringsheim

About This Book

Canadian Guidelines for the Evidence Based Treatment of Tourette Syndrome provides guidance on the treatment of Tourette Syndrome and it's most common co-morbid conditions: Attention Deficit Hyperactivity Disorder and Obsessive Compulsive Disorder. Based on a systematic review of the literature and expert consensus, evidence based recommendations on treatment are provided, in addition to information on the diagnosis of Tourette Syndrome, and deciding when individuals with Tourette Syndrome require treatment.

Tamara Pringsheim is a neurologist and movement disorder specialist at the University of Calgary. She is the director of the Calgary Tourette and Pediatric Movement Disorders Clinic at the Alberta Children's Hospital. Dr Pringsheim is a member of the professional advisory board of the Tourette Syndrome Foundation of Canada, and the American Academy of Neurology Guidelines Subcommittee.

The Tourette Syndrome Foundation of Canada is a national voluntary organization dedicated to improving the quality of life for those with or affected by Tourette Syndrome through programs of education, advocacy, self-help and the promotion of research.

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Edited by

Tamara Pringsheim MD MSC
Director, Calgary Tourette and Pediatric Movement Disorders Clinic
Assistant Professor, Department of Clinical Neurosciences, Psychiatry and Pediatrics,
University of Calgary, Calgary, Alberta, Canada

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Contributors

Lori Billinghurst MD MSc
Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

Alan Carroll MD
Clinical Professor, Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

Lundy Day BSc
Research Assistant, Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada

Yves Dion MD
Clinical Assistant Professor, Department of Psychiatry, University of Montreal, Montreal, Quebec, Canada

Asif Doja MD MEd
Assistant Professor, Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada

Daniel Gorman MD
Assistant Professor, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Sandra Luscombe MD
Assistant Professor, Department of Pediatrics, Memorial University, St John's, Newfoundland, Canada

Duncan McKinlay PhD
Brake Shop Clinic, Adjunct Clinical Professor, Department of Psychology, University of Western Ontario, London, Ontario, Canada

Tamara Pringsheim MD MSc
Director, Calgary Tourette and Pediatric Movement Disorders Clinic
Assistant Professor, Department of Clinical Neurosciences, Psychiatry and Pediatrics, University of Calgary, Calgary, Alberta, Canada

Paul Sandor MD
Director, Tourette Syndrome Neurodevelopmental Clinic
Professor, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Thomas Steeves MD MSc
Assistant Professor, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

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CHAPTER 1

The Diagnosis *of Tourette Syndrome*

Alan Carroll & Tamara Pringsheim

TICS – DESCRIPTION AND VARIATION

Tics are sudden, recurrent, meaningless motor movements or vocalizations. They can be simple or complex, often mimic some aspect or fragment of normal behavior, and vary in frequency and intensity. Simple motor tics are brief, meaningless movements such as eye blinking, eye movements, grimacing, head jerks or shoulder shrugs. Complex motor tics are slower, longer, more purposeful movements, and are rarely seen in the absence of simple motor tics. Examples include touching objects or oneself, dystonic postures, or obscene gestures (copropraxia). Simple vocal tics are sudden meaningless sounds or noises, such as throat clearing, coughing, sniffing, barking or grunting. Complex vocal tics include the utterance of syllables, words, phrases or statements, odd patterns of speech, echo phenomenon, or obscene, inappropriate and aggressive words or statements (coprolalia).

Tics usually start in childhood; characteristically, they wax and wane and manifest themselves differently at various times and ages. They can be temporarily suppressed, and can diminish when one is distracted or engaged in a task. There is a tendency for tics to worsen with stress or excitement.

Tics usually start at about 6 to 7 years of age and begin with simple tics of the face such as blinking. Vocal tics usually appear after motor tics. Tic severity tends to peak at 10 to 12 years of age. In adolescence and early adulthood, there is a decline in tic severity in the majority of people who tic.[1]

A significant sensory phenomenon is described by children over the age of 10 years as the "premonitory urge". This is a "sensation itch" or bodily discomfort that occurs before and is often relieved by the tic. The closest common sensation to the premonitory urge is the feeling experienced prior to a sneeze. Many patients report that their tics are partly or wholly voluntary in character, and are performed in response to an irresistible urge to make the movement.[2]

EPIDEMIOLOGY

The prevalence of Tourette Syndrome and chronic tics is much higher than previously recognized. Meta-analysis of 13 school-based studies in children revealed a prevalence of 7.7 per 1000, with more boys affected than girls by a ratio of 4 to 1. Transient tic disorder is the most common tic disorder, affecting 29.9 per 1000 children.[3] Tics occur in all races and cultures.[4]

DIAGNOSIS OF TICS AND TOURETTE SYNDROME

There are two main classification systems for Tourette Syndrome and tic disorders, the International Classification of Diseases-10 (ICD-10) and the Diagnostic and Statistical Manual for Mental Disorders (DSM).

International Classification of Diseases-10 Tic Disorder Categories

F 95.0 Transient tic disorder
F 95.1 Chronic motor or vocal tics
F 95.2 Combined multiple motor and vocal tics
F 95.3 Other tic disorders
F 95.9 Tic disorders unspecified

Diagnostic and Statistical Manual IV-Text Revision Tic Disorder Categories

307.21 Transient tic disorder
Multiple motor and/or phonic tics last at least 4 weeks but less than 1 year.

307.22 Chronic tic disorder
Single or multiple motor or phonic tics, but not both, lasting more than 1 year.

307.23 Tourette Syndrome
Both motor and phonic tics lasting more than 1 year

307.20 Tic disorder not otherwise specified

DSM-IV-TR Criteria for Tourette Syndrome [5]

- Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
- Tics occur many times a day (usually in bouts) nearly everyday or intermittently throughout a period of more then 1 year, and during this period there was never a tic free period of more than 3 months.
- Onset before 18 years
- Disturbance is not due to the direct physiological effects of a substance (e.g. stimulants, cocaine) or a general medical condition (e.g. Huntington's Chorea or post viral encephalitis).

HOW IS THE DIAGNOSIS MADE?

A diagnosis is based on a clinical interview and history, including a family history and collaborative history from the school. It is not uncommon for tics to be suppressed during the interview with the physician. There is no specific neurological abnormality on physical examination and there is no laboratory test for Tourette Syndrome.

Scales may be used to support diagnosis:

Self and Parent Report rating scales:

- MOVES (Motor tic, Obsessions and compulsions, Vocal tic, Evaluation Survey)[6]
- Tourette Symptom Self Report
- Parent Tic Questionnaire[7]
- Tourette Disorder Impairment Scale-Parent[8]

Clinical Rating Scales

- Yale Global Tic Severity Scale (YGTSS)[9]
- Tourette Syndrome Severity Scale (TSSS)[10]

Assessment should include a careful look for co-morbid conditions, such as Attention Deficit Hyperactivity Disorder, and Obsessive Compulsive Disorder. It is uncommon to diagnose 'pure' Tourette Syndrome, at least in tertiary care referral centers for the evaluation and treatment of tic disorders. In Freeman's database of 3500 individuals with Tourette Syndrome, only 12% had tics with no associated neuropsychiatric co-morbidity.[11]

The most common associated disorders are:

- Attention Deficit Hyperactivity Disorder
- Executive Dysfunction
- Obsessive Compulsive behaviours
- Mood dysregulation
- Behaviour problems
- Learning disability
- Speech and Language disorders
- Sleep disorders

It is important to complete a careful assessment and screen for these co-morbid conditions. Often it is the co-morbid symptoms that are the most challenging to treat as they cause the most dysfunction. Screening may be facilitated by the use of parent or patient rating scales to assess general pathology.

Self Reports:

- Child Behavior Check List (CBCL)[12]
- Strengths and Difficulties Questionnaire (SDQ)[13]

Structured Interview

- K-SADS[14]
- Mini International Neuropsychiatric Interview[15]

According to William Osler "it is much more important to know what sort of a patient has a disease than what sort of a disease a patient has".

DIFFERENTIAL DIAGNOSIS

From a phenomenological perspective, simple motor tics must be differentiated from myoclonus, chorea, seizures, dystonia and muscle spasms and cramps. Complex motor tics must be differentiated from motor stereotypies, restless leg syndrome, akathisia, and compulsions.

Tics can occur in other neurological conditions, as outlined in the following table:

Disorder	Shared Symptoms	Lab Tests
Huntington's Disease	Chorea, clonic, dystonic tics	DNA Analysis
Neuroacanthocytosis	Mouth movements, lip biting, motor & phonic tics	Acanthocytosis on blood smear, ↑ creatine kinase
Wilson's Disease	Dystonia & Dystonic tics	↓ ceruloplasmin, ↑ copper in urine Kayser Fleischer Rings
Sydenham's Chorea	Chorea, tic-like movements	Group A B haemolytic strep
Drug Induced	Motor and phonic tics	Stimulant drug use, cocaine, tardive tics secondary to antipsychotic medication exposure
Developmental Disorders	Stereotypic movements, mannerisms	Global developmental delay

PATHOPHYSIOLOGY OF TOURETTE SYNDROME

There is evidence to support subtle structural changes in the basal ganglia and corpus callosum in individuals with Tourette Syndrome, based on structural MRI[16] and pathological studies.[17] It is hypothesized that this leads to changes in brain function, specifically within corticostriatothalamocortical circuits. These changes appear to be genetically driven, though specific genetic abnormalities related to tic disorders have been found for only a small minority of patients. Tics are hypothesized to be associated with decreased inhibitory output from the basal ganglia, with resulting excessive activity in frontal cortical areas. Evidence supporting a dopaminergic abnormality in Tourette Syndrome comes mainly from therapeutic responses to antipsychotic medications which block dopamine receptors. The effect of dopamine on striatal neurons may be inhibitory or excitatory, depending on the membrane potential at the time of dopamine release. It is hypothesized that abnormalities in the regulation of the resting potential states of striatal neurons may cause an abnormal response to dopamine in individuals with tic disorders.[18]

CONCLUSION

Tourette Syndrome is a common, childhood onset neuropsychiatric disorder seen predominantly in boys. The diagnosis of Tourette Syndrome and tic disorders is made clinically, with reference to established diagnostic criteria. Individuals presenting with tic disorders should be screened for other neuropsychiatric disorders, given the high rate of co-morbidity. Rarely, tics are secondary to other neurological disorders, though a careful history and physical examination will reveal additional neurological abnormalities in such individuals.

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CHAPTER II

When do patients with Tourette Syndrome

Require Treatment?

Paul Sandor

The first reports of patients with Tourette syndrome (TS) focused on the most severe and persistent cases.[1] When Georges Gilles de la Tourette[2] described a series of nine cases it was considered to be a rare but fascinating disorder. However, considerable new data indicates that the prevalence of TS is approximately 1% of the general population.[3] This means that the average family practitioner with a caseload of 2000 patients will care for about 20 patients with this condition, although many of these may not have been diagnosed as such. Other specialists may encounter patients with TS even more often. For example, ophthalmologists are often consulted regarding the reason for frequent blinking or eye rolling, while allergists and ENT specialists will field questions about sniffing, snorting, throat clearing and coughing. Even in the 1980s, patients diagnosed with TS were mostly adults with persistent moderate to severe symptoms. Milder forms of TS are now recognized and diagnosed at an earlier age due to widespread knowledge of TS among physicians and in the general population. Similar trends exist with many other neurodevelopmental disorders. Large numbers of people who have been diagnosed in the last three decades form a cohort of parents who are rather vigilant and often bring their offspring for assessment within a few months of the onset of tics, before a formal diagnosis of TS can be made. It is therefore important to consider who should be treated and how a professional arrives at the conclusion that the treatment should be offered.

THE POTENTIAL IMPACT OF TS

Tourette syndrome begins in childhood and can have a negative effect on the child's functioning as well as psychological well-being.[4,5] Tics tend to be mild in preschool children and their peers tend to be quite accepting of differences, however starting around age 8 or 9 teasing, bullying and ostracism is not uncommon. This is more likely when a child has multiple challenges. Without timely intervention this can often lead to detrimental long-term effects on social adaptation, academic success, self-image and self-esteem. The long-term risks are particularly important for children who have not only TS but also one or more co-morbid conditions. Nevertheless the majority of patients with TS make a good adjustment in adult life[6] perhaps because the tic severity tends to decrease in the later teens and early 20s.[7]

DIAGNOSING TS

Accurate diagnosis must come before decisions about treatment. Our practice is currently informed by DSM IV diagnostic criteria that require the presence of 2 or more motor and 1 or more phonic tics that started before age 18. These may vary over time but tics must have been present for longer then a year. DSM IV also requires that tics must not be absent for longer then 3 months, although that is difficult to ascertain in practice, given that patients are usually aware of only some of their tics, but not all. There is also the customary exclusion of tics caused by other medical conditions – such cases however are rare.

In the differential diagnosis one has to consider Chronic motor or Chronic vocal tic disorder (the same criteria as for TS except that during the course of the disorder the affected person has experienced only motor, or only phonic tics, but not both), Transient tic disorder (the affected person must have tics that occur many times a day, nearly every day for at least 4 weeks, but for less than 12 months in a row) and Tic disorder not otherwise specified (similar to other tic disorders described above but having failed to meet a criterion e.g. onset after age 18).

DECISIONS ABOUT TREATMENT

The clinician must be sensitive to the great variability in the tolerance of tics among affected individuals and families. Consequently, the decision of whether and when to move on to more active intervention such as behavioural treatment or pharmacotherapy depends to a considerable extent on the attitude and needs of patients and their families, which have to be evaluated case by case. It is for this reason that one cannot specify a particular frequency or severity of tics as a threshold beyond which treatment is always necessary. Instead, the treatment should be offered when the symptoms interfere with academic, vocational, or social functioning, or cause physical pain or psychological distress. Moreover, it is important to keep in mind and to educate patients that for most individuals with TS, the tics subside on their own by the end of adolescence.[7] Awareness of this typical natural course of tics often leads to a more conservative approach to treatment, especially when considering medications that are associated with significant adverse effects. Furthermore, highly invasive treatment such as psychosurgery should be avoided in patients younger than 20 years.

TREATMENT OPTIONS

In general one can intervene at 3 levels:

- Educational
- Psychotherapeutic
- Pharmacological

EDUCATION

It is important to emphasize that individuals and their families often benefit from receiving the diagnosis and learning about the nature of the condition, including its natural course and prognosis. In the majority of mild cases, providing relevant information is sufficient to allow them to cope with the symptoms successfully.

Frequently, tics are less pronounced at school than at home because of the patient tendency to inhibit tics when in public, albeit at the cost of reduced attention and increased irritability. Nevertheless, tics are often experienced as disruptive and embarrassing in the school setting. There is room here for professional intervention in terms of recommending practical strategies, which often include informing teachers and classmates about the nature of tics in order to avoid unwarranted reprimands and teasing. Advising patients on how to handle questions about their tics is also useful and important. Individual psychotherapy can be helpful for those patients who are especially sensitive to mild tics not easily noticed by others. Many resources exist online, including the websites of the Tourette Syndrome Foundation of Canada (www.tourette.ca), the Tourette Syndrome Association (www.tsa-usa.org) and Life's a Twitch (www.lifesatwitch.com).

BEHAVIOURAL TREATMENT

It is noteworthy that comprehensive behavioural intervention for tics is supported by some of the strongest evidence for efficacy and safety. The use of this therapy however is limited by the lack of well-trained practitioners familiar with this approach and often the cost of the treatment. In addition, this treatment requires from the patient active participation and tolerance of distress, hence it is not suitable for everyone. Naturally such constraints influence the choice of this intervention.

PHARMACOLOGICAL TREATMENT

There has been no clear consensus about which one of the available treatments for tics should be employed first. Treatment becomes more complex yet when one considers that more than half of patients with TS present with concurrent disorders such as ADHD and/or OCD.[8] Clinical guidelines for the treatment of Tourette syndrome have been recently published in several countries,[9,10,11] including Canada.[12,13] Although there are variations in the availability of interventions and in clinical practices there is general consensus that the least intrusive effective intervention with the smallest risk of adverse effects should be chosen first. In practical terms this would mean alpha-2 agonists such as clonidine or guanfacine, followed by antipsychotics and tetrabenazine. As always, the physician needs to carefully balance potential benefits and risks of various courses of action, including the possibility of no active intervention.

WHEN TO CONSIDER TREATMENT

Tourette Syndrome is often mild and therefore no treatment is required. In general terms one needs to initiate treatment when the symptoms are distressing and/or when symptoms interfere with function. The tolerance for symptoms varies greatly among individuals and much depends on the underlying personality, the family attitude and social context. This very personal decision will be made by each patient/family, using the advice from his health professional after considering the specific factors in each situation at that given time. Since in the majority of patients TS symptoms improve substantially by the end of adolescence, providing a clear diagnosis and information about etiology, prognosis and treatment options is reassuring and may be the only intervention required. When treatment is necessary one should select an effective treatment with the least likelihood of inducing adverse effects following the appropriate evidence based treatment guidelines.

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CHAPTER III

Pharmacotherapy

for Tic Disorders & Tourette Syndrome

This chapter is a reproduction of Tamara Pringsheim, Asif Doja, Daniel Gorman, B Duncan McKinlay, Lundy Day, Lori Billinghurst, Alan Carroll, Yves Dion, Sandra Luscombe, Thomas Steeves, and Paul Sandor. Guidelines for the Evidence-Based Treatment of Tic Disorders: Pharmacotherapy. *Canadian Journal of Psychiatry* 2012; 57(3): 133–143.

Tic disorders, including Tourette syndrome, are common, childhood-onset, neuropsychiatric disorders of variable severity and favourable prognosis for improvement by adulthood. In many people, treatment, other than education, is not needed. If tics become severe or disabling, patients may choose medical or behavioural therapy.

Antipsychotics are the oldest and most effective medications for the treatment of tics, but they have many undesirable side effects, including EPS,[1,2] effects on prolactin,[1] metabolic effects, such as weight gain and elevation of cholesterol,[1] sedation, and prolongation of the QT interval on EKG.[3] These side effects have prompted clinicians to search for other treatments.

This article seeks to provide the practising clinician with guidance on the pharmacological management of tic disorders in children and adults. The primary clinical questions addressed in this guideline are: Which medications are effective in suppressing tics? What are the benefits and harms of these medications?

METHODS

SEARCH STRATEGY & DATA EXTRACTION

We performed a systematic review of the literature on the treatment of tic disorders. We included systematic reviews, RCTs and prospective open-label studies on the treatment of tics in children or adults. When this type of evidence was not available, we searched for retrospective case series. The primary outcome assessed for this review was the treatment effect on tics as measured using validated scales, such as the YGTSS. Secondary outcomes included EPS, sedation, metabolic side effects, and EKG changes.

To find relevant articles, we searched the MEDLINE (1950 to October 2010) and EMBASE (1980 to October 2010) databases using highly sensitive search strategies for clinical trials on the treatment of tics (Appendix 1 for MEDLINE search strategy). Abstracts retrieved from the searches were reviewed independently by 2 authors for relevant articles. Full text articles were then read in detail to determine whether inclusion criteria were fulfilled. Data were extracted independently by 2 authors from included studies and entered into pre-designed summary forms. These forms were developed to ensure completeness and consistency of the extracted data, and the 2 authors' forms were compared for accuracy. If studies reported common outcome measures, meta-analysis of study results was attempted. For prospective observational studies, we reported the difference in means and 95% confidence intervals between baseline and end point evaluations of tic severity.

PROCEDURES FOR EVALUATING THE EVIDENCE & DEVELOPING RECOMMENDATIONS

RCTs were evaluated for methodological quality using quality criteria developed by the USPSTF (Appendix 2).[4] Systematic reviews were evaluated for methodological quality using the AMSTAR tool.[5] Two authors independently assessed methodological quality for each included RCT and systematic review. Based on the fulfillment of USPSTF quality criteria, individual RCTs were rated as Good, Fair, or Poor. Systematic reviews were given an AMSTAR score of 0 to 11 points. We subsequently graded the body of evidence for each medication as High, Moderate, Low, or Very Low, based on the GRADE system[6] (Appendix 3).

A classification scheme based on the GRADE system was also used to make recommendations for the treatment of tics (Table 1). A strong recommendation is made when the benefits of treatment clearly outweigh the risks and burdens, and can apply to most patients in most circumstances without reservation. With a weak recommendation, the benefits, risks, and burdens are more closely balanced, and the best action may differ depending on circumstances. We created a third category, Category X, for medications where insufficient evidence exists to make a formal recommendation. A multi-institutional group of 14 experts in psychiatry, child psychiatry, neurology, pediatrics, and psychology engaged in a consensus meeting. The consensus group did not receive any industry sponsorship and developed this manuscript independently, with no restrictions of any kind. The evidence was presented and discussed, and nominal group techniques were employed to come to consensus on recommendations. The consensus group considered the evidence in both adults and youth, and, unless otherwise specified, recommendations apply to both age groups.

STAKEHOLDER INVOLVEMENT

The consensus group included 3 people from the Tourette Syndrome Foundation of Canada, whose role was to represent the interests of patients and families affected by tic disorders. Before the consensus group meeting, a needs assessment was performed through an anonymous survey of Canadian physicians. This needs assessments evaluated preferences on guideline content and dissemination materials, and was incorporated into the overall plan for the guideline project.

The combined MEDLINE and EMBASE searches yielded 1924 abstracts. Among these, 167 were chosen for full text review. Sixty-three studies met inclusion criteria. They comprised 52 studies and one systematic review on the pharmacological treatment of tics, 1 evidence-based review, 3 studies on behavioural interventions, 3 studies on deep brain stimulation, and 3 studies on transcranial magnetic stimulation (Appendix 4). The studies on nonpharmacological treatment modalities are described in the next chapter.[7]

Studies performed before 1990 used a wide variety of outcome measures for the measurement of tic severity, and frequently used crossover study designs, with poor reporting of results. Therefore, we were unable to perform a meta-analysis of study results for most medications. Most studies performed after 1990 used the YGTSS as the measure of tic severity. A decrease in the YGTSS total tic score of 8 points (out of 50) is considered clinically meaningful.

TABLE 1 GRADE RECOMMENDATIONS

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, low-quality or very low- quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation but may change when higher quality evidence becomes available
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Very weak recommendation; other alternatives may be equally reasonable
Category X1, no recommendation		Insufficient evidence to make a formal recommendation; requires further study.
Category X2, no recommendation		Insufficient evidence to make a formal recommendation; controversial, costly, or unavailable for clinical use

RESULTS

ANTIPSYCHOTICS FOR THE TREATMENT OF TICS

Appendix 5 lists all included trials of antipsychotics, and Table 2 summarizes recommendations and suggested dosage ranges.

Pimozide

Six RCTs have been conducted on the use of pimozide for tics.[8–13] These trials were included in a recent Cochrane systematic review[14] that received an AMSTAR score of 9 out of 11. Meta-analysis of study results was not possible because of methodological concerns and clinical heterogeneity.

The 6 RCTs included a total of 162 participants, aged 7 to 53 years. Mean dosages of pimozide ranged from 2.4 to 12.0 mg/day. Pimozide was compared to placebo alone,[8] haloperidol alone,[13] both placebo and haloperidol,[9,12] and risperidone.[10,11] The methodological quality of each of the 6 RCTs was fair. Pimozide was superior to placebo in all 3 RCTs. In comparison to haloperidol, pimozide showed similar efficacy in 2 RCTs (both treatments improved tics) and was inferior in 1. There was no significant difference between pimozide and risperidone in total tic scores in 2 RCTs, with both drugs showing benefit. The magnitude of improvement in tics in all studies was clinically important. Haloperidol was associated with more EPS than pimozide, while pimozide was associated with more EPS than placebo. QTc intervals were significantly prolonged by pimozide, but not by haloperidol or placebo.

Recommendation Grade for Pimozide: Weak Recommendation, High-Quality Evidence

While there is high-quality evidence that pimozide is effective in the treatment of tics, our consensus group has made a weak recommendation based on the risk-benefit profile of this medication. Treatment with pimozide requires monitoring for EPS and of EKGs for QT interval prolongation. Clinicians within our consensus group use lower dosages of pimozide than used in the RCTs, and do not recommend using more than 6 mg/day.

Haloperidol

Five studies have assessed haloperidol for tics; 2 fair-quality RCTs compared haloperidol to pimozide and placebo,[9,12] and 1 fair-quality RCT compared haloperidol to pimozide.[13] In addition, 2 single-blind, placebo-controlled, crossover studies compared haloperidol to other medications; 1 compared haloperidol to clonidine and placebo,[15] and the other compared haloperidol to trifluoperazine, fluphenazine, and placebo.[15]

The 5 studies included a total of 113 patients, aged 7 to 46 years. Dosages of haloperidol ranged from 2.5 to 20 mg/day. All studies reported clinically meaningful improvement in tics with haloperidol, relative to baseline and compared with placebo. Conversely, all studies reported higher rates of sedation, lethargy, and EPS with haloperidol than with other medications and placebo.

Recommendation Grade for Haloperidol: Weak Recommendation, High-Quality Evidence

While there is high-quality evidence that haloperidol is effective in the treatment of tics, our consensus group has made a weak recommendation based on the risk-benefit profile of this medication. Treatment with haloperidol requires monitoring for EPS. The consensus group recommends keeping dosages of haloperidol to less than 3 mg/day to minimize side effects.

Fluphenazine

One single-blind, placebo-controlled crossover study comparing fluphenazine to haloperidol, trifluoperazine, and placebo has been performed.[15] This study included 10 patients, aged 12 to 43 years, and used dosages of fluphenazine of 8 to 24 mg/day. The study authors reported that in comparison to placebo, all 3 drugs produced statistically significant improvements in tics (numerical data not provided), and none of the 3 proved to be more efficacious than any other. They reported that fluphenazine was the least likely to produce side effects, and that haloperidol was associated with significantly higher rates of sedation and EPS than fluphenazine and trifluoperazine.

There is 1 open-label study of fluphenazine in 21 patients, aged 7 to 47 years, during a 5-year period.[16] All patients had been intolerant to previous haloperidol treatment. Dosages of fluphenazine ranged from 2 to 15 mg/day. Sixteen of the 21 patients reported fewer side effects with fluphenazine, compared with haloperidol, and they experienced greater or similar improvement in their tics.

Recommendation Grade for Fluphenazine: Weak Recommendation, Low-Quality Evidence

Treatment with fluphenazine requires monitoring for EPS. The evidence and clinical experience suggest that fluphenazine has fewer adverse effects than haloperidol.

Metoclopramide

One fair-quality RCT of metoclopramide for tics has been conducted.[17] This study randomized 28 children, aged 7 to 18 years, to placebo or metoclopramide at a dose of 5 to 40 mg/day for 8 weeks. The study reported a 38.7% decrease in the YGTSS 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 were no EPS. Three of 14 metoclopramide-treated subjects reported increased appetite and sedation.

Recommendation Grade for Metoclopramide in Children and Adolescents: Weak Recommendation, Low-Quality Evidence. Recommendation Grade for Metoclopramide in Adults: Category X1, No Specific Recommendation.

As none of the members of the consensus group had clinical experience using metoclopramide for the treatment of tics in children or adults, the recommendations are based on the one research study presented. We are unable to make a recommendation on the use of metoclopramide in adults, as there are no data on adult treatment. Members of the consensus group

expressed concerns about the use of this medication for tic suppression, as chronic use of metoclopramide for the treatment of gastrointestinal disorders, in both children and adults, has been associated with severe, treatment refractory tardive dyskinesia,[18–20] as well as parkinsonism.[21]

Risperidone

Five RCTs of fair quality have assessed risperidone for the treatment of tics; 2 compared risperidone to pimozide,[10,11] 2 compared risperidone to placebo,[22,23] and 1 compared risperidone to clonidine.[24] These five studies included a total of 175 patients, aged 6 to 62 years, with mean dosages of 1.5 to 3.8 mg/day. All trials reported an improvement in tics with risperidone. Trials comparing risperidone to pimozide and risperidone to clonidine found similar benefits with each treatment.

Scahill et al[22] compared risperidone to placebo in an RCT of 8 weeks in 34 participants. Subjects 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). Weight gain was significantly higher with risperidone (2.8 kg, compared with no change, P < 0.001). EPS were not reported or observed. Two children on risperidone developed acute social phobia, and 2 adult males developed erectile dysfunction. Dion et al[23] compared risperidone to placebo in an RCT of 8 weeks in 48 participants. Among risperidone-treated participants , 60.8% improved by at least 1 point on the 7-point Global Severity Rating of the Tourette Syndrome Severity Scale, compared with 26.1% of placebo-treated participants (P = 0.04). Subjects taking risperidone had a significantly higher total score for parkinsonism on the Extrapyramidal Symptom Rating Scale, as well as 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).

Recommendation Grade for Risperidone: Weak Recommendation, High-Quality Evidence

While there is high-quality evidence that risperidone is efficacious in suppressing tics, we have made a weak recommendation based on the risk-benefit profile of this medication. Risperidone treatment requires monitoring for EPS and metabolic side effects.[1]

Aripiprazole

There are 5 prospective, open-label studies on the use of aripiprazole for tics in youth.[25–29] These studies include a total of 138 patients, aged 6 to 19 years, taking a mean daily dosage of 3.3 to 9.8 mg/day. Each study reported a significant improvement in total tic severity on the YGTSS from baseline to end point, and meta-analysis of all 5 studies revealed a mean decrease of 14.9 points (95% CI –16.4 to –13.3, P < 0.001). Significant improvements were usually seen by the second or third week of treatment. The most common adverse effects reported were nausea, sedation, and EPS. No significant changes in BMI or lipids were reported, though weight gain was reported in some studies. There are 2 case series of aripiprazole for tics in adults,[30,31] both reporting benefit.

Recommendation Grade for Aripiprazole: Weak Recommendation, Low-Quality Evidence

Currently, there is consistent evidence from open-label studies that aripiprazole is efficacious for the treatment of tics. An RCT is under way on the pediatric use of aripiprazole for tics, so we expect higher-quality evidence will soon be available. Aripiprazole was given a weak recommendation based on its adverse effect profile. Aripiprazole treatment requires monitoring for metabolic abnormalities and EPS.

Olanzapine

The use of olanzapine for tics is supported by 3 prospective open-label studies,[32–34] 1 nonrandomized single-blind study with a 2-week placebo run-in,[35] and 1 nonrandomized crossover study comparing olanzapine to pimozide.[36] These 5 studies included a total of 50 participants, aged 7 to 54 years. Mean daily dosages ranged from 10 to 15 mg/day. All studies reported a significant decrease in tic severity with olanzapine. Meta-analysis of the 3 studies reporting a change in the YGTSS total tic score, from baseline to end point, revealed a mean decrease of 10.9 points (95% CI −14.2 to −7.6, $P < 0.001$). All studies reported sedation as a side effect of treatment. Weight gain and increased appetite were also frequently reported, with mean increases of 4 to 5 kg during the 6- to 8-week study periods.

Recommendation Grade for Olanzapine: Weak Recommendation, Low-Quality Evidence

While there is consistent evidence from open-label studies that olanzapine is effective in suppressing tics, a weak recommendation has been made because of the concerns about significant metabolic side effects associated with this medication. Olanzapine causes the most weight gain among second-generation antipsychotics, and has been associated with increases in BMI and waist circumference, lipids, liver enzymes, and blood sugar.[1] The use of olanzapine requires monitoring for metabolic abnormalities and EPS.

Quetiapine

There are 2 open-label studies of quetiapine for the treatment of tics, one in youth and one in adults. DeJonge et al[37] treated 12 adults with quetiapine at a mean dose of 205.8 mg/day for 12 weeks. The YGTSS total tic score was not significantly different between baseline and end point, and all study participants complained of sedation. Mukaddes and Abali[38] treated 12 children and adolescents with quetiapine at a mean dose of 72.9 mg/day for 8 weeks. They reported a decrease in the YGTSS tic plus impairment score from 61.17 points at baseline to 24.17 points at end point ($P < 0.001$). Sedation was reported as a side effect in 3 of the 12 patients during the first week. There was no significant change in weight from baseline to end point.

TABLE 2 GRADE RECOMMENDATIONS FOR ANTIPSYCHOTIC MEDICATIONS FOR THE TREATMENT OF TICS

Medication	GRADE	Suggestions for Medication Dosing
Pimozide	Weak Recommendation High Quality Evidence	Children: 1 to 4 mg Adult: 1 to 6 mg per day
Haloperidol	Weak Recommendation High Quality Evidence	Children: 0.5 to 3 mg Adult: 0.5 to 3 mg per day
Fluphenazine	Weak Recommendation Low Quality Evidence	Children: 0.25 to 3 mg per day Adult: 2.5 to 10 mg per day
Metoclopramide	CHILDREN Weak Recommendation Low Quality Evidence ADULTS Category X1. No specific recommendation	Children: 0.5 mg/kg per day, up to 40 mg (children over 6 years of age)
Risperidone	Weak Recommendation High Quality Evidence	Children: 0.25 mg to 3 mg per day Adult: 0.25 to 6 mg per day
Aripiprazole	Weak Recommendation Low Quality Evidence	Children: 2 to 15 mg per day Adult: 2 to 20 mg per day
Olanzapine	Weak Recommendation Low Quality Evidence	Children: 2.5 to 10 mg per day Adult: 2.5 to 20 mg per day
Quetiapine	Weak Recommendation Very Low Quality Evidence	Children: 25 to 400 mg per day Adult: 25 to 400 mg per day
Ziprasidone	CHILDREN Weak Recommendation Low Quality Evidence ADULTS Category X1. No specific recommendation	Children: 20 to 40 mg per day

Recommendation Grade for Quetiapine: Weak Recommendation, Very Low-Quality Evidence

The evidence for the use of quetiapine is limited and mixed, with one small negative study in adults, and one small positive study in youth. It is the experience of the consensus group that tic suppression with quetiapine is generally achieved at higher doses, which are not tolerable for many patients. Despite the report of no weight gain in the pediatric trial, multiple pediatric and adult studies of quetiapine for other indications indicate that it carries a significant risk of metabolic side effects, including weight gain and increases in BMI, waist circumference, and lipids.[1] The use of quetiapine requires monitoring for metabolic side effects.

Ziprasidone

One RCT of fair quality has evaluated ziprasidone for the treatment of tics.[39] Twenty-eight youths, aged 7 to 17, were randomized to ziprasidone or placebo for 8 weeks at a mean dose of 28.2 mg/day. Total tic severity on the YGTSS 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 was sedation and one subject developed akathisia.

Recommendation Grade for Ziprasidone in Children and Adolescents: Weak Recommendation, Low-Quality Evidence. Recommendation Grade for Ziprasidone in Adults: Category X1, No Specific Recommendation.

Currently, there are no data on the use of ziprasidone in adults for tics, preventing formal recommendations. The use of ziprasidone requires monitoring for EPS as well as QT interval prolongation on EKG.[40]

NONANTIPSYCHOTICS FOR THE TREATMENT OF TICS

Appendix 6 lists all included trials of nonantipsychotics and Table 3 summarizes recommendations and suggested dosage ranges.

Clonidine

Six RCTs have evaluated the use of clonidine for tics. Significant improvement in tics with clonidine was found in 1 good-quality study[41] comparing oral clonidine to levetiracetam and 2 poor studies comparing oral clonidine to placebo.[42,43] These 3 studies examined a total of 72 patients, aged 7 to 48 years. Dosages of clonidine ranged from 3.0 to 5.5 μg/kg/day. One fair study[44] comparing the clonidine patch to placebo in 437 patients (aged between 6 and 18 years) found benefit for tics using 1 to 2 mg clonidine patches administered on a weekly basis. Two additional poor-quality studies[45,46] failed to show any effect of clonidine on tics. Side effects commonly seen with clonidine include sedation, bradycardia, orthostatic hypotension, and dry mouth, as well as localized skin irritation with the clonidine patch.

The use of clonidine for the treatment of ADHD in children with tics has also been studied, with both tic and ADHD outcomes assessed. Kurlan et al[47] randomized 136 children to clonidine, methylphenidate, clonidine plus methylphenidate, or placebo for 16 weeks. In comparison to placebo, children treated with clonidine had a significant decrease in the YGTSS score (–10.9 points, P = 0.003), and in their ADHD symptoms.

Recommendation Grade for Clonidine: Strong Recommendation, Moderate-Quality Evidence

There is evidence of moderate quality for the efficacy of clonidine for tics, and our consensus group believes that it has a preferable side effect profile, compared with antipsychotics. Therefore, the recommendation for its use can be applied to most patients in most circumstances without reservation. Patients on clonidine should be monitored for sedation and vital sign abnormalities, including postural changes. Clonidine should not be abruptly discontinued, owing to a risk of rebound hypertension.

Guanfacine

Two RCTs and 2 open-label studies have evaluated the use of guanfacine for tics. One fair-quality RCT [48] compared guanfacine to placebo in 34 children, aged 7–14 years. Doses ranged from 1.5 to 3.0 mg/day. After 8 weeks, the YGTSS total tic score decreased from 15.2 to 10.7 points in the guanfacine group, with no change in the placebo group (P = 0.05). An improvement in ADHD symptoms was also demonstrated. There were no differences in side effects. The only other RCT [49] of guanfacine, which was of poor quality, failed to show a difference between guanfacine and placebo.

Two open-label studies have shown a positive effect of guanfacine on tics. Chappell et al[50] studied 10 youths, aged 8 to 16 years, on a daily guanfacine dose of 1.5 mg. There was a significant decrease in the phonic tic score on the YGTSS (12.5 to 7.7, P < 0.02), but no significant change in motor tics. The most common side effects were fatigue, headache, and insomnia. Boon-yashidi et al[51] studied 25 youths, aged 7 to 16 years, taking a mean dose of guanfacine of 2 mg/day. Significant decreases from baseline were noted in the YGTSS total motor score (10.26 to 6.68 points) and total phonic score (8.84 to 4.95 points) (P < 0.001). Side effects included fatigue, insomnia, irritability, lightheadedness, stomachache, and sleep disturbance.

Recommendation Grade for Guanfacine in Children and Adolescents: Strong Recommendation, Moderate-Quality Evidence. Recommendation Grade for Guanfacine in Adults: Category X1, No Specific Recommendation.

There is evidence of moderate quality that guanfacine is efficacious for tics in youth. Currently, there are no data on the use of guanfacine in adults for tics, preventing formal recommendations. The side effect profile of guanfacine is more favourable than that of antipsychotics. Monitoring of sedation and postural vital signs should occur for patients on guanfacine. Approval from the Health Canada Special Access Program is required to prescribe guanfacine.

Topiramate

One fair-quality RCT examined the effect of topiramate on tics.[52] Twenty-nine patients, aged 7 to 65 years, were studied. The mean daily dose of topiramate was 118 mg. The YGTSS total tic score improved by 14.3 points at study end point with topiramate, compared with 5.0 points with placebo (P = 0.03). No differences were observed in adverse events between groups.

Recommendation Grade for Topiramate: Weak Recommendation, Low-Quality Evidence

Evidence from one small, fair-quality RCT supports the treatment of tics with topiramate. Despite no differences noted in adverse events between the topiramate and placebo groups in this study, experience with topiramate in the treatment of other conditions such as epilepsy suggests that patients should be monitored for cognitive side effects, mood changes, and weight loss.[53] Additionally, patients should be warned about the possibility of glaucoma[54] and nephrolithiasis.[53]

Baclofen

There is 1 poor-quality RCT [55] of 10 children, aged 8 to 14 years, treated for 4 weeks with baclofen 60 mg/day for tics. The mean Clinical Global Impression Severity score improved modestly with baclofen (–0.5) and worsened modestly with placebo (+0.4), resulting in a significant difference between groups (–0.9; 95% CI –1.7 to –0.1, P = 0.04). While the YGTSS total score decreased 14.7 points with baclofen relative to placebo, this was not statistically significant (P = 0.06). Transient side effects reported during baclofen treatment included constipation, nausea, anxiety, and headache.

One open-label study [56] of 264 youths, aged 6 to 18 years, evaluated baclofen for tics. Patients were treated with a mean dose of 30 mg/day for 4 weeks. Significant decreases were noted in motor (P < 0.02) and vocal (P < 0.02) tics as measured by the YGTSS, although further data were not provided. Six patients experienced sedation and drowsiness.

Recommendation Grade for Baclofen in Children and Adolescents: Weak Recommendation, Very Low-Quality Evidence. Recommendation Grade for Baclofen in Adults: Category X1, No Specific Recommendation.

There is very limited, poor quality data to support the efficacy of baclofen in the treatment of tics in youth. Furthermore, there are no data on the use of baclofen in adults for tics, preventing formal recommendations.

Botulinum Toxin Injections

One poor-quality RCT compared botulinum toxin injections to placebo injections for tics in 20 patients, aged 15 to 55 years.[57] The dosage of botulinum toxin used was not stated. The median proportional change in tics, as recorded by blinded observers of 12-minute patient videos, was –39% in the botulinum toxin group and +5.8% in the placebo group. The median

net effect was –37% (interquartile range –77, –15%). Twelve patients in the botulinum toxin group noted weakness of injected muscles, 2 had motor restlessness, 2 had swallowing difficulty, 2 developed new tics that replaced the treated tic, and 1 had increased urge to tic.

Four open-label studies also examined the effect of botulinum toxin injections on tics.[58–61] These studies had a total of 90 patients, aged 8 to 84 years. Doses of botulinum toxin ranged from 2.5 to 300.0 units. Most studies used a 0 to 4 response rating of peak effect, with 65% to 100% of patients showing improvement in motor tics, phonic tics, or both. Forty-five patients experienced side effects, including ptosis, weakness, dysphagia, hypophonia (associated with injections for vocal tics), loss of facial expression, and development of a new tic.

Recommendation Grade for Botulinum Toxin Injections: Weak Recommendation, Low-Quality Evidence

While the consensus group believes that botulinum toxin injections are generally safe and without systemic side effects, we recommend using this treatment in only very specific situations. Botulinum toxin injections should be considered for the treatment of severely disabling vocal tics, such as coprolalia, or very distressing motor tics involving the upper face or neck. Further, only an experienced clinician should administer botulinum toxin injections.

Tetrabenazine

One open-label study examined tetrabenazine for the treatment of tics.[62] Nine patients, aged 10 to 48 years, were treated with tetrabenazine 25 to 150 mg/day, and outcomes included the Jankovic hyperkinesia rating scale and family member report. Four patients had sustained improvement on tetrabenazine, with benefits lasting for more than 6 months, while 3 had improvement for less than 6 months. Eight patients experienced side effects, including drowsiness, nervousness, oculogyric crises, depression, nausea, tremulousness, parkinsonism, and insomnia.

Recommendation Grade for Tetrabenazine: Weak Recommendation, Very Low-Quality Evidence

Data regarding the efficacy of tetrabenazine are limited to 1 small open-label trial. If tetrabenazine is to be used, care should be made to monitor for side effects, including EPS, depression, anxiety, and hypotension. Death due to pneumonia has been described with the use of this medication.[63,64]

Cannabinoids

Two poor-quality RCTs[65,66] examined the effect of cannabinoids on tics. Both studies were included in a Cochrane review[67] that received an AMSTAR score of 8 out of 11. A total of 28 patients, aged 18 to 69 years, were studied. The dosage range of delta-9-THC was 5 to 10 mg/day. Both trials reported a positive effect from THC, although the improvements in tic frequency and severity were small and were detected only by some outcome measures. No serious adverse events were reported. Five patients in the THC group reported tiredness, dry mouth, and dizziness.

TABLE 3 GRADE RECOMMENDATIONS FOR ANTIPSYCHOTIC MEDICATIONS FOR THE TREATMENT OF TICS

Medication	GRADE	Suggestions for Medication Dosing
Clonidine	Strong Recommendation Moderate Quality Evidence	Dosing should be titrated according to blood pressure and heart rate Children: 0.025 mg to 0.3 mg/day Adult: 0.025 to 0.6 mg/day
Guanfacine	CHILDREN Strong Recommendation Moderate Quality Evidence ADULTS Category X1. No specific recommendation.	Dosing should be titrated according to blood pressure and heart rate Children: 0.5 to 3mg/day
Topiramate	Weak Recommendation Low Quality Evidence	Children: 1 mg/kg to 9 mg/kg per day; doses over 200 mg are poorly tolerated Adult: 50 to 200 mg per day
Baclofen	CHILDREN Weak Recommendation Very Low Quality Evidence ADULTS Category X1. No specific recommendation.	Children: 10 to 40 mg/day (children less than 8 years), to 60 mg (children older than 8 years)
Botulinum toxin injections	Weak Recommendation Low Quality Evidence	Therapy must be individualized depending on target muscles injected
Tetrabenazine	Weak Recommendation Very Low Quality Evidence	Children: 12.5 to 50 mg/day Adult: 12.5 to 100 mg/day
Cannabinoids	CHILDREN Not recommended ADULTS Weak Recommendation Low Quality Evidence	Adults: Nabilone 1 to 6 mg per day

Recommendation Grade for Cannabinoids in Children and Adolescents: Category X, Level 2, Not Recommended. Recommendation Grade for Cannabinoids in Adults: Weak Recommendation, Low-Quality Evidence.

There is no evidence to support the use of cannabinoids for the treatment of tics in children or adolescents. Given this lack of evidence, as well as concerns about potential misuse, we do not recommend that cannabinoids be used for treating tics in youth. However, there is low-quality evidence that cannabinoids have modest benefits in the treatment of tics in adults.

The consensus group recommends against the use of levetiracetam,[68,69] intravenous immune globulin,[70] mecamylamine,[71] fluoxetine,[72] and ondansetron[73] for the treatment of tics, as evidence suggests that these treatments are ineffective.

There was insufficient evidence to make formal recommendations on the use of ropinirole,[74] naloxone,[75] naltrexone,[76] adjunctive nicotine,[77,78] ningdong granule,[79,80] nifedipine,[81] flunarizine,[81] and nicardipine[82] for the treatment of tics. While there is some literature evaluating the use of these agents to treat tics, the judgment of the consensus group was that further study is required to enable formal recommendations.

There was insufficient evidence to make formal recommendations on the use of flutamide,[83] lecithin,[84] physostigmine,[85] citalopram,[86] fluvoxamine,[86] and propranolol[87] for the treatment of tics. While limited studies of these agents exist, the judgment of the consensus group was that further research on their use for treating tics is not warranted because of concerns about potential worsening of tics, unacceptable adverse events, or poor scientific rationale to support further study.

DISCUSSION

While evidence supports the efficacy of numerous medications for treating tics, most available agents have the potential to cause significant adverse events, causing us to downgrade recommendations to the weak category. With a weak recommendation, the benefits are closely balanced with the risks and side effects. In situations where tics are not severe or disabling, the use of a medication with only a weak recommendation is not warranted. However, when tics are more distressing and interfering, the need for tic suppression to improve quality of life is stronger, and patients and clinicians may be more willing to accept the risks of pharmacotherapy.

Among the available treatment options, our consensus group determined that behavioural therapy (see next chapter[7]) clonidine, and guanfacine should be considered first-line therapies for tics. Botulinum toxin injection was also considered a first-line therapy in adult patients to target severe motor tics affecting the eyes or face, or severe vocal tics, such as coprolalia. Risperidone and aripiprazole are second-line therapies. Pimozide, fluphenazine, haloperidol, and ziprasidone are considered third-line therapies. In children with a co-morbid diagnosis of ADHD, the use of clonidine or guanfacine for tics is favoured, as evidence supports their efficacy for treating ADHD symptoms as well.[47,48]

For people who are overweight at baseline, we recommend avoiding olanzapine, quetiapine, and risperidone because of the risk of further weight gain with these medications.[1] Before starting therapy, patients should be informed that medications only suppress tics in the present, and do not alter the natural history of the disorder. Tic severity typically decreases during adolescence, with nearly three-quarters of patients reporting that their tics are greatly diminished by adulthood.[88] Given this natural history of tic disorders, medications should be tapered periodically to determine if the treatment is still required.

This guideline synthesizes the current evidence on the treatment of tics, and provides recommendations based on the evidence while incorporating clinical expertise. We are limited by the strength of the available evidence; many of the trials are small, and include clinically heterogeneous samples. The ability of clinicians to predict which treatment has the greatest chance of success for a given patient is limited. Further large-scale clinical trials comparing the effectiveness of different treatment regimens are likely to be helpful in improving the care of people with tic disorders.

ABBREVIATIONS

ADHD	Attention-Deficit Hyperactivity Disorder
AMSTAR	Assessment of Multiple Systematic Reviews
BMI	Body Mass Index
EKG	Electrocardiogram
EPS	Extrapyramidal Symptom
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
QTC	Corrected QT Interval
RCT	Randomized Controlled Trial
THC	Tetrahydrocannabinol
USPSTF	US Preventive Services Task Force
YGTSS	Yale Global Tic Severity Scale

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APPENDIX 1 MEDLINE SEARCH STRATEGY

1	exp Tourette Syndrome/
2	exp Tic Disorders/
3	exp Tics/
4	1 or 2 or 3
5	(randomized controlled trial or controlled clinical trial).pt.
6	randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/
7	5 or 6
8	clinical trial.pt.
9	exp clinical trials/ or placebos/ or research design/
10	(clinic$ adj25 trial$).mp.
11	((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).mp.
12	(placebo$ or random$).mp.
13	(latin adj square).mp.
14	or/8-13
15	comparative study/ or exp evaluation studies/ or follow-up studies/ or perspective studies/ or cross-over studies/
16	(control$ or perspective$ or volunteer$).mp.
17	15 or (control$/ or perspective$/ or volunteer$/)
18	7 or 14 or 17
19	4 and 18

Studies are graded good only if *all* of the following are met:

YES	NO	UNCLEAR	
_____	_____	_____	Comparable groups assembled
_____	_____	_____	Follow-up at least 80%
_____	_____	_____	Interventions are clearly stated
_____	_____	_____	All important outcomes are considered
_____	_____	_____	Measurement instruments acceptable and applied equally
_____	_____	_____	Outcome assessment is blinded
_____	_____	_____	Appropriate attention to confounders in analysis
_____	_____	_____	Intention to treat is used
_____	_____	_____	Concealment: Adequate measures to conceal allocation to study groups from those responsible for assessing patients for entry in the trial

Studies are graded fair if *any* of the following problems occur, without the fatal flaws listed in the "poor" category:

YES	NO	UNCLEAR	
_____	_____	_____	Generally comparable groups, or some minor problems with follow-up
_____	_____	_____	Some but not all important outcomes are considered
_____	_____	_____	Some but not all important confounders are accounted for
_____	_____	_____	Method of randomization not stated in methods

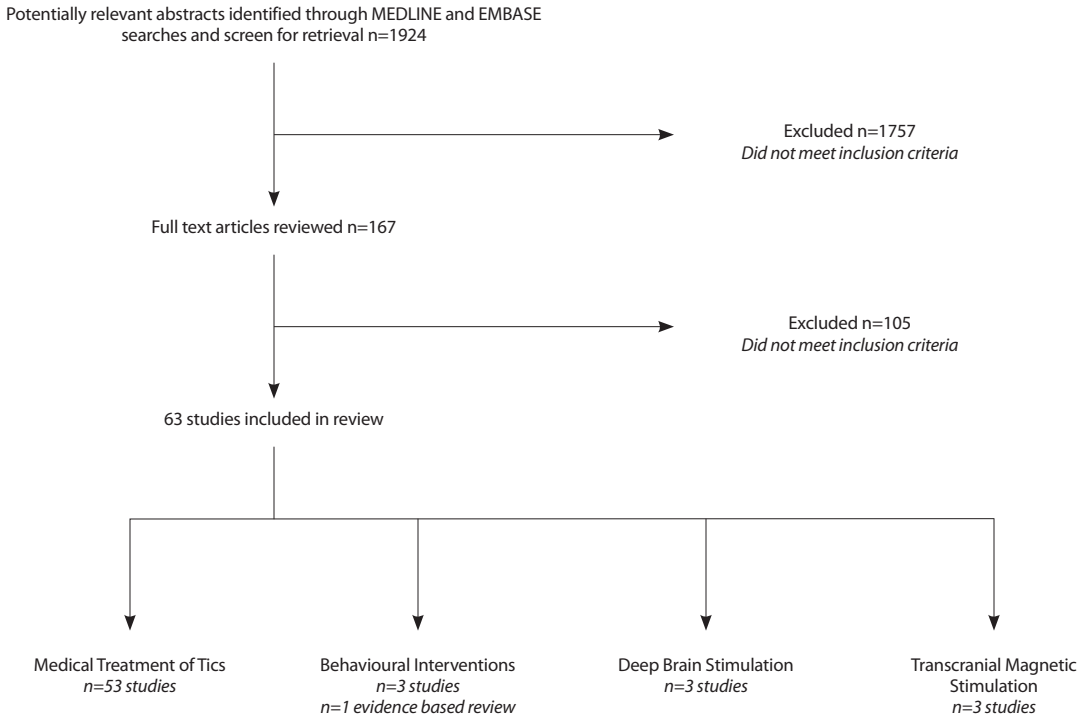
Studies are graded poor if *any* of the following fatal flaws exist:

YES	NO	UNCLEAR	
_____	_____	_____	Groups assembled are not comparable
_____	_____	_____	Unreliable or invalid measurements are used, or are not applied equally
_____	_____	_____	Lack of blinding to outcome assessment
_____	_____	_____	Key confounders are not addressed
_____	_____	_____	Intention to treat analysis is lacking
_____	_____	_____	Inadequate power of study

APPENDIX 3 GRADE SYSTEM, QUALITY OF A BODY OF EVIDENCE

HIGH QUALITY	MODERATE QUALITY	LOW QUALITY	VERY LOW QUALITY
We are very confident that the true effect lies close to that of the estimate of the effect.	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

APPENDIX 4 FLOW DIAGRAM OF INCLUDED STUDIES



APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS

AUTHOR, YEAR	Cui, 2010	Lyon, 2009	Murphy, 2009	Seo, 2008
METHODOLOGICAL QUALITY	Open label	Open label	Open label	Open label
DRUG	Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole
MEAN DOSE	8.17±2.41mg/day	4.5± 3.0 mg/day	3.3±2.1mg/day	8.17±4.06 mg/day
LENGTH OF TREATMENT	8 weeks	10 weeks	6 weeks	12 weeks
# OF INDIVIDUALS	72	11	16	15
MEAN AGE	10.23 years	13.3 years	12 years	12.2 years
AGE RANGE	6 –18 years	9 –19 years	8 –17 years	7–19 years
OUTCOMES ASSESSED	· YGTSS · CGI-Tics · CBCL	· YGTSS · CGI-tics · CGAS · ADHD-RS · CDRS · CGI-OCD · CYBOCS · CGI-ADHD · MASC · AIMS · SMURF	· YGTSS · CYBOCS · CGI-I · CGI-S · ESRS	· YGTSS
TREATMENT EFFECT ON TICS	**YGTSS TOTAL TIC SCORE** 30.13± 7.08 → 14.98±4.57 p<0.0001 **YGTSS IMPAIRMENT** 29.58±13.58 → 12.86±4.83 p<0.0001 **CGI-TIC SEVERITY** 4.77±1.69 → 2.20±1.39 p=0.000	**YGTSS TOTAL TIC SCORE** 28.18±7.74 → 16.73±7.54 p=0.003 **GLOBAL SEVERITY** 61.82±13.49 → 33.73 ±15.18 p=0.003 **CGI-TIC SEVERITY** 4.45±0.52 → 3.18±0.60 p=0.004	**YGTSS TOTAL TIC SCORE** 32.0±7.8 → 14.7±7.6 p<0.0001 **CGI-S** 4.9±0.7 → 3.2±0.5 p<0.0001 **CGI-I** 3.0±0 → 5.5±0.5 p<0.0001	**TOTAL TICS** 24.53±11.12 → 10.87±7.54 **MOTOR TICS** 15.07±6.53 → 7.53±5.26 **VOCAL TICS** 9.47±8.48 → 3.33±5.34 **GLOBAL IMPAIRMENT** 30.0±10.0 → 15.0±10.52 p<0.001
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Nausea 21/72 (29%) · Sedation 19/72 (26%) · BMI 20.71 → 21.57 p=0.35	· 4 received Benztropine & 1 received Lorazepam for EPS during the study · Weight gain 7/11 · EPS 10/11 · Mean Weight gain: 2.16±8.63lbs	· Weight: 43.7 → 46.0 kg p<0.003 · Mean change 2.3kg · 1 subject exhibited mild parkinsonism	· 7/15 nausea · 5/15 sedation · BMI: 20.53-20.61 · P=0.749

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (2)

AUTHOR, YEAR	Yoo, 2007	Borison, 1983a	Borison, 1983b	Saccomani, 2000
METHODOLOGICAL QUALITY	Open label	RCT: Poor	RCT: Poor	Open label
DRUG	Aripiprazole	Haloperidol Clonidine Placebo	Haloperidol Fluphenazine Trifluoperazine Placebo	Haloperidol Trazodone
MEAN DOSE	9.8±4.8 mg/day	2.5–8.5mg 0.25–0.9mg	5–20mg 8–24mg 10–25mg	0.044 mg/kg/day 1.4 mg/kg/day
LENGTH OF TREATMENT	8 weeks	6 weeks	Undefined	3 months
# OF INDIVIDUALS	24	22	10	10
MEAN AGE	11.8 years	16 years	20.5 years	10.5 years
AGE RANGE	7–18 years	8–44 years	12–43 years	7.3–13.7 years
OUTCOMES ASSESSED	· YGTSS · CGI-I · CGI-S · ESRS	15 Item scale measured frequency & intensity of tics	15 Item scale measured frequency & intensity of tics	· YGTSS
TREATMENT EFFECT ON TICS	**YGTSS TOTAL TIC SCORE** 26.7±5.5 → 12.6 ± 7.6 (58% decrease) p<0.001 **CGI-I** 19/24 improved or very much improved **CGI-S** 5.5± 0.5 → 3.0±1.4 p<0.001	No raw data Haloperidol & Clonidine both produced greater therapeutic effect than placebo p<0.005 No significant difference comparing Clonidine to Haloperidol Haloperidol worked faster than Clonidine	No raw data All 3 drugs produced significant therapeutic tic suppression compared to placebo p<0.01 No significant difference between groups	**YGTSS TOTAL TIC SCORE** 21.2 → 9.3 p<0.001 **YGTSS OVERALL IMPAIRMENT** 31 → 12
IMPORTANT SIDE EFFECTS ENCOUNTERED	· 6 Discontinued due to side effects · Hypersomnia 37.5% · Nausea 20.8% · Headache 16.6% · EPS 8.3% · Akathisia 8.3%	**HALOPERIDOL** · Sedation 15/22 · Lethargy 12/22 · Depression 5/22 · Akathisia 9/22 · Parkinsonism 6/22 · Dystonic Reactions 3/22 **CLONIDINE** · Dry mouth 5/22 · Sedation 4/22 · Dizziness/ Palpitations 2/22 · Insomnia 1/22 **PLACEBO** · Dry mouth 2/22 · Insomnia 2/22	Haloperidol produced higher incidence of sedation & EPS Fluphenazine was least likely to produce side effects	Absence of AEs

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (3)

AUTHOR, YEAR	Nicolson, 2005	Budman, 2001	McCracken, 2008	Onofrj, 2000
METHODOLOGICAL QUALITY	RCT: Fair	Open label	Open label	RCT: Poor
DRUG	Metoclopramide Placebo	Olanzapine	Olanzapine	Olanzapine Pimozide
MEAN DOSE	32.9± 5.1 mg/day	10.9±6.0mg/day	11.3±5.6 mg/day	5 & 10 mg/day 2 & 4 mg/day
LENGTH OF TREATMENT	8 weeks	8 weeks	6 weeks	4 months each drug
# OF INDIVIDUALS	27	10	12	4
MEAN AGE	11.9 years	28.4 years	11.3 years	28.5 years
AGE RANGE	7–18 years	20–44 years	7–14 years	19–40 years
OUTCOMES ASSESSED	· YGTSS · CGI-I · CGI-S · YBOCS · CPRS- hyperactivity · SAS · AIMS	· YGTSS · YBOCS · ADHD behaviour checklist for adults	· YGTSS · CGI-I · CGI-S · OAS · SNAP IV · MASC	· TSSE · TSGS · RVT · UKU
TREATMENT EFFECT ON TICS	**YGTSS TOTAL TIC SCORE** · Metoclopramide 22.6±5.3 → 13.9±3.7 · Placebo: 22.2±6.8 → 19.4±5.8 p=0.001 **CGI-S** · Metoclopramide 4.9±0.9 → 3.7±1.1 · Placebo 4.7±0.6 → 4.5±0.7 p=0.01	**YGTSS TOTAL TIC SCORE** 26.6±5.0 → 18.6±7.3 p=0.04 **YGTSS SEVERITY** 65.5±6.5 → 44.9±14.5 p=0.004	**YGTSS TOTAL TIC SEVERITY** 31.92±7.39 → 22.5±9.37 p=0.01 **YGTSS IMPAIRMENT** 33.33±10.73 → 20.50±13.73 p<0.001	**TSGS** · Baseline 23.6±4.88 · Pimozide 2mg 19.6±3.75 · Pimozide 4mg 16.72±3.8 · Olanzapine 5mg 14.15±4.8 · Olanzapine 10mg 6.97±2.59 **RVT** · Baseline 14.75±1.7 · Pimozide 2mg 13.0±2.1 p=0.06 · Pimozide 4mg 11.75±2.0 p=0.06 · Olanzapine 5mg 10.5±1.2 p<0.05 · Olanzapine 10mg 7.0±0.8 p<0.005
IMPORTANT SIDE EFFECTS ENCOUNTERED	**METOCLOPRAMIDE** · Increased appetite 3/14 · Sedation 3/14 · 1 subject very high prolactin · Weight gain: 1.0±1.9kg **PLACEBO** · Weight gain 0.5±1.4kg · Not significant	· 2/10 dropped out due to sedation · Mean weight gain: 4.5±3.2kg · 8/8 weight gain · 8/8 sedation · 6/8 increased appetite · 5/8 dry mouth	· Mean weight gain: 4.1±2kg · Drowsiness · Increased appetite · Sedation · Increase in ALT, AST & cholesterol but not clinically significant	**PIMOZIDE** · Sedation · Sleepiness · Mild Hypokinesia · Reduced Salivation · Akathisia **OLANZAPINE** · Drowsiness

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (4)

AUTHOR, YEAR	Stamenkovic, 2000	Stephens, 2004	Bruggeman, 2001	Gilbert, 2004
METHODOLOGICAL QUALITY	Open label	Open label	RCT: Fair	RCT: Fair
DRUG	Olanzapine	Olanzapine	Pimozide Risperidone	Pimozide Risperidone
MEAN DOSE	15±3.3mg/day	14.5mg/day	2.9mg 3.8mg	2.4mg 2.5mg
LENGTH OF TREATMENT	6 weeks	8 weeks	12 weeks	4 weeks each
# OF INDIVIDUALS	14	10	50	19
MEAN AGE	32.6 years	9.9 years	N/A	11 years
AGE RANGE	19–54 years	7–13 years	11–50 years	7–17 years
OUTCOMES ASSESSED	· YGTSS · CGI-S · FSCL-NL	· CBCL-Agg · TRF-Agg · CGI · YGTSS · AIMS · SAAS · MASC · CY-BOCS · CDI-T	· TSSS · CGI · PGI · HAM-A · GAF · Y-BOCS · ESRS · Weight gain	· YGTSS · CGI-I · TSSR · ESRS · Weight gain
TREATMENT EFFECT ON TICS	**YGTSS** 68.79±12.39 → 34.0± 22.78 p<0.005 **CGI-S** 5.93±0.62 → 4.08±1.24 p<0.005	**YGTSS TOTAL TIC SCORE** 20.3 → 6.0 p<0.007 **CGI-TIC SEVERITY** 1.9±0.73 → 1.0±0.47 p<0.04	**TSSS TOTAL SCORE** Pimozide improvement 2.3 points Risperidone improvement 2.4 points No difference between groups	**YGTSS** 34.2 at the end of Pimozide phase 25.2 at the end of Risperidone phase p=0.05
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Mild Sedation · Mean Weight: 70.6±8.3kg → 71.0±7.8kg	· Weight Gain: 12±5.71 lbs p<0.005 · ALP: 213.3±18.19 → 240.1±21.04 p<0.02 · Daytime fatigue	No difference between groups for AE's or weight gain	No difference between groups for AE's or weight gain

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (5)

AUTHOR, YEAR	Ross, 1978	Sallee, 1997	Shapiro, 1984	Shapiro, 1989
METHODOLOGICAL QUALITY	RCT: Fair	RCT: Fair	RCT: Fair	RCT: Fair
DRUG	Pimozide Haloperidol Placebo	Pimozide Haloperidol Placebo	Pimozide Placebo	Pimozide Haloperidol
MEAN DOSE	10–12mg 10–12mg	3.4mg 3.5mg	6.88mg/day	10.6mg 4.5mg
LENGTH OF TREATMENT	12 days each	6 weeks each	6 weeks each	6 week parallel group study 6 week cross-over study
# OF INDIVIDUALS	9	22	20	68
MEAN AGE	18.7 years	10.2 years	24.65 years	21 years
AGE RANGE	8–28 years	7–16 years	11–53 years	8–46 years
OUTCOMES ASSESSED	Mean daily 5 minute tic count for last 4 days of each study condition	· TSGS · CGI- Tic Severity · TSSL · AIMS · ESRS	· TSSS · CGI-Therapeutic effect & Adverse events · Physician Global Evaluation · Patient Global Evaluation · Videotape Tic Counts · Adverse Events Record	· TSSS · CGI- Physician & Patient, effect of medication, adverse events · Videotape counts of tics per minute · Adverse reaction record
TREATMENT EFFECT ON TICS	Both Pimozide and Haloperidol significantly decreased tic frequency compared to baseline and placebo Tic severity was not significantly different between treatment groups Pimozide 29.4 Haloperidol 21.9	**TSGS TIC SEVERITY** · 17.1 after Pimozide phase · 20.7 after Haloperidol phase · 26.8 after the placebo phase · p=0.02 for Pimozide vs placebo · p=NS for Haloperidol vs placebo	**TSSS TIC SEVERITY** 1.52 at the end of the Pimozide phase 4.42 at the end of the placebo phase p=0.0001 Videotape motor and vocal tic counts were significantly lower after the Pimozide phase Pimozide 49.36, Placebo 102.42 p=0.0001	**PARALLEL GROUP STUDY** Pimozide was significantly superior to placebo in controlling tics as measured by CGI, 3.2 versus 1.9 p= 0.03 No significant difference in TSSS between Pimozide and placebo, 2.5 versus 2.9 Haloperidol was significantly superior to placebo on both measures **CROSS-OVER PHASE** Haloperidol was superior to Pimozide on the TSSS, 1.4 versus 2.0 p=0.011 No significant difference between Pimozide and Haloperidol on the CGI scale, 3.4 versus 3.5
IMPORTANT SIDE EFFECTS ENCOUNTERED	Adverse events were not formally assessed	**ESRS** Haloperidol had significantly more extrapyramidal side effects than Pimozide ($p<0.05$) and placebo($p<0.01$)	CGI- Adverse Events Scale showed significantly higher adverse events after the Pimozide phase p=0.0089 One child developed an asymptomatic abnormal ECG (nonspecific T wave change) during the Pimozide phase which resolved once the drug was stopped	CGI Adverse events scale showed significantly higher adverse events in the Haloperidol group compared to placebo, but not the Pimozide group during parallel group phase No difference in adverse events between Pimozide and Haloperidol during cross-over The QTc interval was significantly prolonged by Pimozide, but not Haloperidol or placebo

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (6)

AUTHOR, YEAR	de Jonge, 2007	Mukaddes, 2003	Dion, 2002	Gaffney, 2002
METHODOLOGICAL QUALITY	Open label	Open label	RCT: Fair	RCT: Fair
DRUG	Quetiapine	Quetiapine	Risperidone Placebo	Risperidone Clonidine
MEAN DOSE	205.8mg/day	72.9±22.5mg/day	2.5mg/day (median)	1.5±0.9 mg/day 0.175±0.075 mg/day
LENGTH OF TREATMENT	12 weeks	8 weeks	8 weeks	8 weeks
# OF INDIVIDUALS	12	12	48	21
MEAN AGE	38 years	11.4 years	32 years	11.37 years
AGE RANGE	20–52 years	8–16 years	14–49 years	7–17 years
OUTCOMES ASSESSED	· YGTSS	· YGTSS	· TSSS · CGI · YBOCS · ESRS · GAF	·YGTSS ·YBOCS ·ADHD RS ·CGI-S ·SAS
TREATMENT EFFECT ON TICS	**YGTSS TIC SEVERITY** 23.6±11.8 → 18.0±8.3 not significant **YGTSS IMPAIRMENT** 4.4±1.8 → 2.0±1.2 p=0.003	**YGTSS** 61.17±15.24 → 24.17±14.04 p<0.001 Significant decrease at weeks 4 & 8	60.8% of Risperidone group compared to 26.1% of placebo group improved by at least one point on the 7 point TSSS severity rating p=0.04 **TSSS TOTAL SCORE** · Risperidone 5.24±1.30 → 3.39±2.18 · Placebo 5.37±1.35 → 4.59±2.17 p=0.05	**YGTSS CHANGE FROM BASELINE** · Risperidone -10.9±11.7 · Clonidine -13.8±16.9 *Both were significant from baseline but not significant between groups*
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Somnolence 8/8 · Tiredness 5/8 · Headaches 3/8 · Anxiety 3/8 · Akathisia 3/8 · Dizziness 3/8	· 3/12 sedation · Weight: 42.75±10.34-43.16±10.14 p>0.05	Risperidone associated with greater incidence of fatigue, 56% vs 17.4% p=0.01 and somnolence, 34.8% versus 4.4% p=0.02 than placebo	**CLONIDINE** · Sedation 5/12 · Dizziness 2/12 · Risperidone: · Sedation 1/9 · Dizziness 1/9 · Stiffness 2/9 **WEIGHT GAIN** · Risperidone: 2.1± 2.3kg · Clonidine: 0.1±5.9 kg *Not significant*

APPENDIX 5 INCLUDED STUDIES OF ANTIPSYCHOTIC MEDICATIONS (7)

AUTHOR, YEAR	Scahill, 2003	Sallee, 2000
METHODOLOGICAL QUALITY	RCT: Fair	RCT: Fair
DRUG	Risperidone Placebo	Ziprasidone Placebo
MEAN DOSE	2.5±0.85mg	28.2±9.6 mg/day
LENGTH OF TREATMENT	8 weeks	56 days
# OF INDIVIDUALS	34	28
MEAN AGE	19.7 years	11 years
AGE RANGE	6–62 years	7–17 years
OUTCOMES ASSESSED	· YGTSS · CGI-I · TSSR · YBOCS · SAFTEE · AIMS · Height · Weight · HR/BP · ECGs	· YGTSS · CGI-TS · Goetz Videotape Rating Scale · CY-BOCS · BAS · SAS · AIMS
TREATMENT EFFECT ON TICS	**YGTSS TOTAL TIC SCORE** · Risperidone: 26.0±5.06 → 17.6±4.75 · Placebo: 27.4±8.51 → 25.4±8.75 p=0.002 **TSSR** · Risperidone 22.3 → 14.5 · Placebo 21.4 → 20.9 p=0.03 **CGI-I** · Risperidone 10/16 · Placebo 1/18 *much/very much improved p=0.0005*	**YGTSS TOTAL TIC SCORE** · Placebo 24.6±9.6 → 22.9±10.8 · Ziprasidone 24.7±6.8 → 16.1±7.4 p=0.008 **YGTSS GLOBAL SEVERITY** · Placebo 46.9±17.7 → 39.3± 21.3 · Ziprasidone 46.9±13.8 → 28.6±17.3 p=0.016 **CGI-TS NOT SIGNIFICANT** Mean change Goetz Videotape Rating · Ziprasidone 49.8% · Placebo 3.5% p=0.039
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Mean weight gain with Risperidone 2.8kg, None with Placebo · 2 children with acute social phobia · 2 adult males with ED	**ZIPRASIDONE** · Somnolence 1/16 · Akathisia 1/16 · Most common AE was transient mild sedation · Prolactin elevation 5/16 · 1 mild gynecomastia

LEGEND

YGTSS	Yale Global Tic Severity Scale
CGI	Clinical Global Impression
CBCL	Child Behavior Checklist
CGAS	Children's Global Assessment Scale
ADHD-RS	Attention Deficit Hyperactivity Disorder Rating Scale
CDRS	Children's Depression Rating Scale Revised
CGI- OCD	Clinical Global Impression-Obsessive Compulsive Disorder
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
CGI- ADHD	Clinical Global Impression – Attention Deficit Hyperactivity Disorder
MASC	Multidimensional Anxiety Scale for Children
AIMS	Abnormal Involuntary Movement Scale
SMURF	Safety Monitoring Uniform Report Form
CGI-I	Clinical Global Impression – Improvement
CGI- S	Clinical Global Impression – Severity
ESRS	Extrapyramidal Symptom Rating Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
CPRS	Conners' Parent Rating Scale
SAS	Simpson-Angus Scale
OAS	Overt aggression scale
SNAP IV	Swanson, Nolan and Pelham Questionnaire revision, Parent
TSSE	Tourette Syndrome Symptomatology Evaluation
TSGS	Tourette Syndrome Global Scale
RVT	Rush Video Based Tic Rating Scale
UKU	Udvalg for Kliniske Undersogelser Psycholeptic Drugs Side Effect Rating Scale
FSCL	Fischer Symptom Check List
TRF	Teacher Report – Long Form
SAAS	Simpson Angus Akathisia Scale
CDI- T	Children Depression Inventory
TSSS	Tourette Syndrome Severity Scale
PGI	Patient Global Impressions Scale
HAM-A	Hamilton Rating Scale for Anxiety
GAF	Global Assessment of Functioning
TSSR	Tic Symptom Self Report
TSSL	Tourette Syndrome Symptom List
SAFTEE	Systematic Assessment for Treatment Emergent Effects
BAS	Barnes Akathisia Scale

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS

AUTHOR, YEAR	Awaad, 1999	Singer, 2001	Jankovic, 1994	Kwak, 1990
METHODOLOGICAL QUALITY	Open label	RCT: Poor	Open label	Open label
DRUG	Baclofen Botulinum Toxin	Baclofen Placebo	Botulinum Toxin	Botulinum Toxin
MEAN DOSE	30mg/day 5–200 units	60mg/day	30–300 units	119.9 units/Visit
LENGTH OF TREATMENT	4 weeks	4 weeks each	Length undefined	Mean # treatments = 3.3
# OF INDIVIDUALS	450	10	10	35
MEAN AGE	12 years	11.7 years	24.2 years	23.3 years
AGE RANGE	6–18 years	8–14 years	13–53 years	8–69 years
OUTCOMES ASSESSED	· YGTSS · Quantified videotaped microstructured analysis of tics	· YGTSS · CGI · TIS · TTS	· 0–3 Premonitory sensory rating · 0–4 "peak effect" rating	· 0–4 "peak effect" rating · 0–4 Global rating · Latency · Duration of response · Premonitory sensory rating
TREATMENT EFFECT ON TICS	**BACLOFEN** · 250/264 had a decrease in motor and vocal tic severity ($p<0.02$) within 1 to 2 weeks. · 8/264 showed no change in symptoms · 6/264 experienced side effects	**YGTSS MEAN IMPROVEMENT** · Baclofen -15.1 · Placebo -0.4 p=0.06 **TIS MEAN IMPROVEMENT** · Baclofen -11.1 · Placebo -2.2 p=0.01 **CGI MEAN IMPROVEMENT** · Baclofen -0.5 · Placebo 0.4 p=0.04	All patients experienced moderate to marked improvement in tics 2/29 sessions failed to reduce the amplitude and frequency of tics Premonitory symptoms were markedly relieved or abolished in all patients Benefit Lasted 2-20 weeks	**MEAN PEAK EFFECT RESPONSE** 2.8±1.5 **MEAN GLOBAL RESPONSE RATING** 2.7±1.5 **MEAN DURATION OF BENEFIT** 14.4± 10.3 weeks **MEAN LATENCY TO ONSET OF BENEFIT** 3.8±2.9 days 84% of patients with premonitory sensations had marked relief of symptoms Mean premonitory relief benefit 70.6%
IMPORTANT SIDE EFFECTS ENCOUNTERED	**BACLOFEN** · Sedation & drowsiness n=6 **BOTULINUM TOXIN** · Soreness n=5 · Transient neck weakness n=4 · Ptosis n=3	**BACLOFEN TREATMENT** · Stomach pains or nausea 2/9 · Anxiety 1/9 · Constipation 1/9 · Headache 1/9	· Transient ptosis 2/10 · Neck pain 2/10 · Neck weakness 2/10 · Neck stiffness 1/10	· Neck weakness n=4 · Ptosis n=2 · Dysphagia n=2 · Nausea n=1 · Generalized weakness n=1 · Fatigue n=1 · Hypophonia n=1

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (2)

AUTHOR, YEAR	Marras, 2001	Porta, 2003	Rath, 2010	Caine, 1979
METHODOLOGICAL QUALITY	RCT: Poor	Open label	Open label	RCT: Poor
DRUG	Botulinum Toxin Placebo	Botulinum Toxin	Botulinum Toxin	Chlorimipramine Desipramine Placebo
MEAN DOSE	Variable dose	2.5 IU	2.5–75 IU	150mg/day
LENGTH OF TREATMENT	2 weeks each	Mean # treatments = 1.9	Mean # treatments =11	4 weeks each
# OF INDIVIDUALS	20	30	15	6
MEAN AGE	31.5 years (median)	26 years	43 years	19.2 years
AGE RANGE	15–55 years	10–65 years	18–84 years	13–31 years
OUTCOMES ASSESSED	· Videotape counts of tics · TSGS · YGTSS · UTRS · STSSS	· Phenomenology of tics · Global impression of change · Time to response · Duration of response · Premonitory Sensory · Interference with social life, work, or school	· Efficacy 4 point rating scale · Duration of Effect · Latency of Response · Changes in premonitory urges	· Tic count (5 min period) · Global rating
TREATMENT EFFECT ON TICS	CHANGE IN TICS PER MINUTE · Botulinum toxin -39% · Placebo +5.8% YGTSS – INTENSITY · Botulinum toxin -0.59 · Placebo -0.09 p=.01 No significant difference between botulinum toxin and placebo on STSSS, TSGS, UTRS and YGTSS – Frequency, Interference	93% showed improvement in vocal tics 50% of patients showed no phonic tics after treatment MEAN RESPONSE 5.8 days MEAN DURATION OF RESPONSE 102 days Interference with social life decreased from 50% of patients severely impacted to 13% Interference with work and school activities decreased from 47% of patients severely impacted to 10% Premonitory experienced dropped from 53% of patients to 20%	89% reported short-term efficacy as good or moderate 11/12 tics reported similar or increased benefit long term All patients with premonitory urges reported urges lessened or disappeared after treatment 5 tics responded within 2 days, 9 tics within 1 week	CHLORIMIPRAMINE +15.1 tics/5 min DESIPRAMINE +1.2 tics/5 min No significant or clinical improvement
IMPORTANT SIDE EFFECTS ENCOUNTERED	BOTULINUM TOXIN · Subjective weakness n=9 · Weakness on examination n=12 · Neck discomfort lasting 1-2 weeks n=3 · Blurred vision n=1 · Swallowing difficulty n=2 · Motor restlessness n=2 · Increased urge to tic n=1 · New tics "to replace treated tic" n=2	80% of subjects experienced hypophonia	· Developed a new tic 1/15 · Flu-like Symptoms 1/15 · Congestion 1/15 · Muscle Weakness 1/15 · Loss of facial Expression 1/15	CHLORIMIPRAMINE · Symptom exacerbation 1/6 · Racing thoughts, nervous feelings 1/6 · Blurred vision, GI distress, difficulty sleeping 1/6 · Orthostatic hypotension 1/6 · Mild increase in tics, dry mouth 1/6 · Shortness of breath after exercise 1/6 Desipramine: · Somnolence 2/5 · Dry mouth 1/5 · Blurred vision 1/5

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (3)

AUTHOR, YEAR	Du, 2008	Gancher, 1990	Goetz, 1987	Hedderick, 2009
METHODOLOGICAL QUALITY	RCT: Fair	RCT: Poor	RCT: Poor	RCT: Good
DRUG	Clonidine Patch Placebo	Clonidine Placebo	Clonidine Placebo	Clonidine Levetiracetam
MEAN DOSE	1.0–2.0mg/week	Child: 8.1±2.5ug/kg/day Adult: 4.5±1.6ug/kg/day	0.0075 or 0.015mg/kg/day	0.2 mg/day 1,150mg/day
LENGTH OF TREATMENT	4 weeks	2 months each	12 weeks each	6 weeks each
# OF INDIVIDUALS	437	10	30	12
MEAN AGE	10 years	Adult: 28 years Child:12 years	19.2 years	14.9 years
AGE RANGE	6–18 years	N/A	8–62 years	8–27 years
OUTCOMES ASSESSED	· YGTSS · CGI	· TSGS · TSSL	Video and audio recordings (1 min segments)	· YGTSS (TTS) · YGTSS total · CGI · CY-BOCS · MASC · CDI-S
TREATMENT EFFECT ON TICS	**YGTSS TOTAL SCORE** CLONIDINE · 11.53 Placebo · 10.72 (test group had significantly lower rate of decreased total YGTSS score than control) TEST GROUP · 62/321 clinically recovered · 153/321 obviously improved · 36/321 improved · 64/321 ineffective CONTROL GROUP · 13/111 clinically recovered · 39/111 obviously improved · 39/111 improved · 20/111 ineffective	TSSL scores were lower with Clonidine than placebo, but not significantly different. TSGS scores were not significantly different between groups.	**TIC SCORES** MOTOR BODY AREAS · Clonidine 5.3 · Placebo 5.6 NUMBER · Clonidine 41.8 · Placebo 46.3 SEVERITY · Clonidine: 3.0 · Placebo 3.1 VOCALIZATIONS NUMBER · Clonidine 5.6 · Placebo 4.3 SEVERITY · Clonidine 1.0 · Placebo 1.2 Differences between clonidine and placebo were not significant	YGTSS total tic score: · Clonidine: 25.2±4.3 → 21.8±4.4 (-3.4) p=.013 · Levetiracetam: 22.7±5.7 → 23.6±10.6 (+0.9) p=NS Mean total YGTSS scores demonstrated no improvement with either medication
IMPORTANT SIDE EFFECTS ENCOUNTERED	TEST GROUP · Rashes on skin 3/326 · Abnormal ECG 2/326 · Somnolence 1/326 · Light headedness 1/326 · Insomnia 1/326 · Heart rate: +1.04 beats/min · Blood pressure: -1.27/-0.96 (sys/dia) Control group: · Rashes on skin 6/111 · Nausea 1/111 · Dry mouth 1/111 · Light headedness 1/111 · Dizziness 1/111 · Somnolence 1/111	CLONIDINE · Transient heart burn 5/9 · Dose dependent drowsiness 7/9 · Dry mouth 5/9 · Localized erythema and dry skin 4/9 PLACEBO · Transient heart burn 4/9 · Dry mouth 3/9 · Localized erythema and dry skin 2/9	CLONIDINE · Sedation 57% · Dry mouth 37% · Restlessness 27% PLACEBO Sedation and dry mouth (not same degree as clonidine)	CLONIDINE/LEVETIRACETAM · Tired/sleepy (5,2) · Irritability (3,4) · Sad/depressed (1,2) · Hyperactive (0,2) · Anxious (4,3) · Lethargic (2,1) · Fatigue (3,1) · Dizzy (1,1) · Aggression (3,2) · Stomach ache (2,0)

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (4)

AUTHOR, YEAR	Leckman, 1985	Leckman, 1991	Cubo, 2008	Micheli, 1990
METHODOLOGICAL QUALITY	RCT: Poor	RCT: Poor	Open label	RCT: Poor
DRUG	Clonidine Placebo	Clonidine Placebo	Donepezil	Flunarizine Nifedipine Placebo
MEAN DOSE	5.5u/kg/d po	4.4±0.7ug/kg/day	10mg	13mg Single 10mg dose
LENGTH OF TREATMENT	20 weeks	12 weeks	14 weeks	Length undefined
# OF INDIVIDUALS	13	47	20	7
MEAN AGE	11.99 years	15.6 years	11.3 years	21.1 years
AGE RANGE	9–16 years	7–48 years	8–14 years	12–31 years
OUTCOMES ASSESSED	· TSGS · C-GAS · TSSL · CPQ · CBCL	· TSGS · STSSS · TS-CGI · Videotape tic counts · TSSL	· C-GAS · YGTSS · CY-BOCS · CPRS	· Videotape recordings · Goetz et al. rating scale (tic severity and frequency)
TREATMENT EFFECT ON TICS	**TSGS** Reduction in 28% and 33% for the first and second 8-week trials **PHONIC TICS** Reduction in 36% and 40% for the first and second 8-week trials **MOTOR TICS** Reduction in 10% and 24% for the first and second 8-week trials	**TSGS** · Clonidine -9.4 · Placebo -3.9 p=.05 **STSSS** · Clonidine: -1.6 · Placebo -0.5 p=.06 **MOTOR VIDEOTAPE TIC COUNTS** · Clonidine -4.4 · Placebo +3.4 p=.03 **TSSL** Motor tics: · Clonidine -3.4 · Placebo -1.0 p=.10 Phonic tics: · Clonidine –0.1 · Placebo -1.7 p=.09	**YGTSS** · Baseline: 18.6±9.3 · Week 14: 12.3±9.7 · Washout: 12.2±11.0 · P=.006	**FREQUENCY - TICS/MIN** *Baseline → Placebo → Flunarizine* · Motor tics: 34.5±2.6 → 32.2±3.1 → 16.7±3.1 · Phonic tics: 4.0±0.5 → 3.8±0.5 → 0.5±0.3 **TIC SEVERITY (GOETZ RATING)** · Motor tics: 3.4 → 3.2 → 1.7 · Phonic tics: 2.0 → 2.3 → 0.3 *Patients (n=3) receiving Nifedipine did not improve*
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Sedation 6/13 · Postural hypotension 1/13 · Early morning awakening 3/13 · Headache 3/13 · Abdominal pain 1/13 · Nosebleeds 1/13 · Developed insulin dependent diabetes 1/13	**CLONIDINE** · Sedation/fatigue 90% · Dry mouth 57% · Faintness/dizziness 43% · Irritability 33% **PLACEBO** · Sedation/fatigue 37% · Dry mouth 26% · Faintness/dizziness 21% · Irritability 5%	· Irritability 4/20 · GI symptoms 4/20 · Headache, sedation, nightmares, urinary incontinence, dizziness 1/20	**FLUNARIZINE** · Motor slowness and mild depression 1/7 · Transient headaches 1/7 · Bradykinesia 2/7

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (5)

AUTHOR, YEAR	Scahill, 1997	Peterson, 1998	Boon-yasidhi, 2005	Chappell, 1995
METHODOLOGICAL QUALITY	RCT: Fair	RCT: Good	Open label	Open label
DRUG	Fluoxetine Placebo	Flutamide Placebo	Guanfacine	Guanfacine
MEAN DOSE	20mg/day	750 mg/day	2.0±0.6mg/day	1.5 mg/day
LENGTH OF TREATMENT	8 or 12 weeks each	3 weeks each	8 weeks	4–20 weeks
# OF INDIVIDUALS	14	13	25	10
MEAN AGE	19.0 years	31.7 years	10.6 years	10.7 years
AGE RANGE	8.9–33.5 years	19–53 years	7–16 years	8–16 years
OUTCOMES ASSESSED	· YGTSS · Y-BOCS · SAFTEE	· YGTSS · Y-BOCS · HAM-A · HAM-D · SAFTEE	· YGTSS · CPRS-Hyperactivity · Teacher rated ADHD scale	· CPRS · YGTSS · TSSR
TREATMENT EFFECT ON TICS	**YGTSS** *Baseline → Week 8* · Fluoxetine: 27.6±3.92 → 26.9±10.65 · Placebo: 23.1±6.81 → 21.6±9.06 *No significant difference* **YGTSS** *Baseline → Endpoint* · Fluoxetine: 24.0±8.68 → 24.4±7.96 · Placebo: 25.5±7.15 → 24.8±9.55 *No significant difference*	No raw data Flutamide provided significant reduction in motor tic severity but not phonic	Mean improvement of 38.95% on the total tic severity scale **YGTSS TOTAL TIC SCORE** 19.05±7.98 → 11.63±7.48 p<0.001	**SS** · Motor tic: 15.6±3.7 → 14.5±2.8 NS · Phonic tic: 12.5±2.7 → 7.8±4.6 p<0.02 **TSSR** · Motor Tic: 22.6±9.9 → 13.5±7.1 p<0.02 · Phonic Tic: 14.01±8.1 → 11.1±5.0 NS
IMPORTANT SIDE EFFECTS ENCOUNTERED	**(FLUOXETINE, PLACEBO)** · Insomnia (5,2) · Fatigue (2,0) · Motor restless (7,2)* · Increased motor tics (2,1) · Dizziness (1,0) · Tremor (1,0) · Blurred vision (1,0) · Decreased appetite (3,0) · Diarrhea (3,1) · Nose Bleeds (2,1) **p=.04*	Rates of reported side effects did not differ between groups One woman developed major depressive disorder	· Headache 4/25 · Stomachache 4/25 · Tiredness 3/25 · Irritability 3/25 · Sleep disturbances 3/25 · Dizziness 3/25	· Fatigue 6/10 · Headaches 4/10 · Insomnia 3/10 · Sedation 2/10 · Dizziness/lightheadedness 2/10 · Transitory slurred speech 1/10 · Irritability 1/10

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (6)

AUTHOR, YEAR	Cummings, 2002	Scahill, 2001	Hoekstra, 2004	Polinsky, 1980
METHODOLOGICAL QUALITY	RCT: Poor	RCT: Fair	RCT: Fair	RCT: Good
DRUG	Guanfacine Placebo	Guanfacine Placebo	IVIG Placebo	Lecithin Placebo
MEAN DOSE	1.0mg bid	2.5mg/day	1g/kg/day	Max 45g/day
LENGTH OF TREATMENT	4 weeks	8 weeks	2 days	4 weeks each
# OF INDIVIDUALS	24	34	30	6
MEAN AGE	10.4 years	10.4 years	29.75 years	26 years
AGE RANGE	6–16 years	7–14 years	14–63 years	12–69 years
OUTCOMES ASSESSED	· YGTSS · BRIEF · CPRS-R · ADHD RS IV · BASC · Digit Span · SOPT · TOL · LWF · TOVA	· ADHD rating scale · YGTSS · CPRS · Continuous · Performance Test	· YGTSS · Y-BOCS · CGI	Count of tics
TREATMENT EFFECT ON TICS	**YGTSS** No significant improvement with Guanfacine **TOTAL TIC SCORE** · Guanfacine: 17.92±7.8 → 11.25±7.0 · Placebo 15.67±5.6 → 14.62±9.4 **IMPAIRMENT** · Guanfacine: 14.17±11.6 → 12.50±10.6 · Placebo: 17.50±10.6 → 12.50±12.2 **TOTAL SCORE** · Guanfacine: 32.08±14.1 → 23.25±15.7 · Placebo: 32.33±12.7 → 28.92±19.9	**YGTSS** · Guanfacine: 15.2±6.6 → 10.7±7.0 · Placebo: 15.4±7.0 → 15.4±5.5 p=.05	**YGTSS** IVIG: 25.0 → 20.1 Placebo: 25.5 → 24.3 *Not significant*	**MOTOR TIC COUNT (/5MIN)** · Lecithin: 58.8 (*Continuous tic activity was too rapid to quantify in two patients*) · Placebo: 76.1 **VOCAL TIC COUNT (/5MIN)** · Lecithin: 46.02 · Placebo: 53.12 *No significant difference between groups*
IMPORTANT SIDE EFFECTS ENCOUNTERED	**GUANFACINE** · Headache, flu-like symptoms, fatigue n=1 · Fatigue/sleepiness n=1 · Bad dreams n=1 · Reduced dose because of mild fatigue n=2	1 patient on Guanfacine withdrew due to sedation · Mild sedation n=6 · Sleep awakening n=3 · Dry mouth n=4 · Constipation n=2 · Loss of morning appetite n=2 *No significant differences between placebo and Guanfacine*	**(IVIG/PLACEBO)** · Any side effects (13,4) · Chills (6,1) · Headache (11,4) · Fever (5,0) · Vomiting (4,0) · Nausea (7,1) · Dizziness (3,0)	None

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (7)

AUTHOR, YEAR	Smith-Hicks, 2007	Silver, 2001	Van Wattum, 2000	Howson, 2004
METHODOLOGICAL QUALITY	RCT: Poor	RCT: Poor	RCT: Poor	RCT: Poor
DRUG	Levetiracetam Placebo	Mecamylamine Placebo	Naloxone Placebo	Nicotine Placebo
MEAN DOSE	1,563 mg/day	2.5–7.5mg/day	30 or 300ug/kg/day	7 or 5mg
LENGTH OF TREATMENT	4 weeks each	8 weeks	3 separate days	4 hr treatment each separated by 1 week
# OF INDIVIDUALS	22	61	15	23
MEAN AGE	12.2 years	11.3 years	29.2 years	12.0 years
AGE RANGE	8–16 years	8–17 years	18–49 years	8–17 years
OUTCOMES ASSESSED	· YGTSS · CGI-I · DuPaul ADHD scale · CY-BOCS · MASC	· TODS-CR · CGI · YGTSS · RAScal	Total # of tics	· Videotape tic count · YGTSS · TSSL-P · TSSL-C · CBCL · CPRS
TREATMENT EFFECT ON TICS	**YGTSS TOTAL TIC SCORE** · Levetiracetam: 18.95±7.35 → 16.8±6.25 · Placebo: 20.4±5.32 → 18.95±7.28 **YGTSS TOTAL SCORE** · Levetiracetam: 43.7±21.18 → 37.15±20.36 · Placebo: 41.65±17.03 → 35.05±14.5 *No significant treatment effect*	No significant improvement with Mecamylamine **TODS-CR** · Mecamylamine: 76.8 → 65.6 · Placebo: 65.9 → 50.1 **YGTSS TOTAL MOTOR TIC** · Mecamylamine: 14.6 → 12.6 · Placebo: 12.1 → 8.4 **YGTSS TOTAL PHONIC TIC** · Mecamylamine: 10.7 → 9.4 · Placebo: 8.8 → 4.9	**TOTAL # OF TICS** · Placebo 64.8±12.3 · 30 ug: 56.4±9.7 · 300 ug: 85.2±21.0 p<.0001	**TIC FREQUENCIES** · Total: Nicotine 23.3±3.7 → 21.1±4.6 · Placebo: 18.4±3.0 → 16.0±2.3 *No significant differences* **TSSL-C TOTAL** · Nicotine 25.7±4.1 → 19.5±3.7 · Placebo 23.3±4.3 → 15.7±2.6
IMPORTANT SIDE EFFECTS ENCOUNTERED	**LEVETIRACETAM** · Irritability · Tiredness · Sadness · Worry · Hyperkinesia · Anxiousness · Dry mouth	Headache affected more than 30% of subjects in each group **(MECAMYLAMINE, PLACEBO)** · Asthenial/weakness (27%/9%) · Aggressive (24%/9%) · Vomiting (17%/6%) · Muscle twitching (17%/6%) · Hypersomnia (17%/6%) · Dysphoria (17%/6%) · Mouth ulcer (10%/3%) · Constipation (10%/3%) · Fine tremor (10%/3%)	Not reported	**(NICOTINE, PLACEBO)** · Dizziness (28.6%, 14.3%) · Weakness/fainting (7.1%, 0%) · Headache (14.3%, 14.3%) · Nausea (7.1%, 7.1%) · Numbness (7.1%, 0%) · Vomiting (14.3%, 0%) · Itching (57.1%, 14.3%)

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (8)

AUTHOR, YEAR	Silver, 2001	Li, 2009	Zhao, 2010	Toren, 2005
METHODOLOGICAL QUALITY	RCT: Poor	RCT: Poor	RCT: Poor	RCT: Poor
DRUG	Transdermal Nicotine Haloperidol Placebo	Ningdong granule Haloperidol	Ningdong granule Placebo	Ondansetron Placebo
MEAN DOSE	7mg/24hrs Undefined	3–9g bid +Haloperidol 2–6mg/day	1g/kg/day	24mg/day
LENGTH OF TREATMENT	33 days	6 months	8 weeks	3 weeks
# OF INDIVIDUALS	70	90	68	30
MEAN AGE	11.1 years	9.59 years	12.2 years	21.7 years
AGE RANGE	≥8 years	≤18 years	7–18 years	12–46 years
OUTCOMES ASSESSED	· CGI · PGI · YGTSS	YGTSS	YGTSS	· TSGS · YGTSS · Y-BOCS · CGI-I
TREATMENT EFFECT ON TICS	**YGTSS** There was a significant difference in motor tic score between the treatment group and placebo on day 5, but no difference on days 19 and 33. The overall impairment score showed a significant reduction difference between placebo and the treatment group on day 33. There was no significant difference between global severity, or phonic tic scores.	**YGTSS OVERALL SEVERITY SCORE** · ND granule + haloperidol: 21.18±6.45 → 7.15±6.29 · Haloperidol: 21.27±7.22 → 11.5±7.08 p<0.01 **TOTAL TIC SCORE** · ND granule + haloperidol: 21.18±6.45 → 7.15±6.29 · Haloperidol: 21.27±7.22 → 11.50±7.08 p<0.01	**YGTSS TOTAL TIC SCORE** · ND granule: 23.0±7.34 → 13.48±7.25 · Placebo: 22.42±6.4 → 20.0±6.21 p<.001	**TSGS** · Ondansetron: 29.62±20.33 → 20.58±12.82 · Placebo: 47.14±17.59 → 40.78±23.72 p=.002 **YGTSS** · Ondansetron: 24.04±9.44 → 17.50±9.48 · Placebo: 31.82±7.15 → 27.28±12.12 *Not significant* **CGI-I** Ondansetron: 7/13 improved 6/13 non-improved **PLACEBO** 3/14 improved 11/14 non-improved
IMPORTANT SIDE EFFECTS ENCOUNTERED	**NICOTINE** · Nausea 25/35 · Vomiting 14/35 **PLACEBO** · Nausea 6/35 · Vomiting 3/35	**ND GRANULE + HALOPERIDOL** · Drowsiness 3/60 · Lassitude 2/60 · Poor appetite 3/60 **HALOPERIDOL** · Drowsiness 4/30 · Lassitude 3/30 · Poor appetitive 1/30 · Constipation 1/30 · Akathisia 2/30	**NINGDONG GRANULE GROUP** · Loss of appetite 2/33 · Constipation 1/33	One patient in ondansetron group dropped out due to GI complaints Mild and transient abdominal pain reported by one patient in each group

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (9)

AUTHOR, YEAR	Stahl, 1981	Kurlan, 1991	Sverd, 1983	Anca, 2004
METHODOLOGICAL QUALITY	RCT: Poor	RCT: Poor	RCT: Poor	Open label
DRUG	Physostigmine Placebo	Propoxyphene Naltrexone Placebo	Propranolol Placebo	Ropinirole
MEAN DOSE	0.05mg/kg	260mg/day 50mg/day	30–120 mg/day	0.25–0.5 mg bid
LENGTH OF TREATMENT	4.5hrs	6 weeks each	43 days	8 weeks
# OF INDIVIDUALS	6	10	5	15
MEAN AGE	22.6 years	33 years	22 years	28.1 years
AGE RANGE	8–54 years	≥18 years	12–36 years	15–49 years
OUTCOMES ASSESSED	Tic count from 10-minute video segments	· Goetz Rating Scale · TSGS · TSSL · LOI	Rating scale (1–7) for severity of symptoms	· TSGS · CGIC · STSS
TREATMENT EFFECT ON TICS	**NUMBER OF TICS/MINUTE** *Baseline → 30 minutes after infusion* 8.98 → 1.85 (every patient had significant results)	Mean Change in Goetz rating scores and TSGS were not significant. **TSSL MEAN CHANGE** · Placebo 7.0±4.1 · Propoxyphene -3.8±4.1 · Naltrexone -4.9±3.1* **Significant vs. placebo p<.04*	Mean Ratings of Overall Disorder at Each Dosage Level per Day of Propranolol: · Baseline: 5.9 · Placebo: 4.9 · 30 mg: 5.0 · 60 mg: 5.0 · 90 mg: 4.5 · 120 mg 4.3 · 90 mg: 4.2 · 60 mg: 4.1 · 30 mg: 4.5 · Placebo: 4.3 *No significant effect*	*Baseline → Week 4 → Week 8 → Week 10* **TSGS** 12.3±6.2 → 9.5±5.0 → 6.7±4.2 → 9.4±4.0 p=.02 **MOTOR SHAPIRO SEVERITY SCALE** 3.8±1.0 → 3.0±1.0 → 2.9±0.9 → 3.3±1.0 p=.03 **VOCAL SHAPIRO SEVERITY SCALE** 2.8±1.2 → 2.5±0.9 → 2.2±0.8 → 2.5±0.8 p=.05 *Week 4 → Week 8 → Week 10* **CGIC** 0.5±0.8 → 1.1±1.0 → -0.3±1.3
IMPORTANT SIDE EFFECTS ENCOUNTERED	**PROPANTHELINE** · Dry mouth · Tachycardia **PHYSOSTIGMINE** · Nausea · Vomiting · GI distress	1 patient was unable to complete Naltrexone due to palpitations 1 patient did not tolerate Propoxyphene due to a skin rash	Not reported	None

APPENDIX 6 INCLUDED STUDIES OF NON-ANTIPSYCHOTIC MEDICATIONS (10)

AUTHOR, YEAR	Jankovic, 1984	Muller-Vahl, 2003	Muller-Vahl, 2002	Jankovic, 2009
METHODOLOGICAL QUALITY	Open label	RCT: Poor	RCT: Fair	RCT: Fair
DRUG	Tetrabenazine	Tetrahydrocannabinol	Tetrahydrocannabinol Placebo	Topiramate Placebo
MEAN DOSE	82mg/day	2.5–10mg	5–10mg	118mg
LENGTH OF TREATMENT	1–20 months	6 weeks	Single dose	70 days
# OF INDIVIDUALS	9	24	12	29
MEAN AGE	21 years	33 years	34 years	16.5 years
AGE RANGE	10–48 years	18–68 years	18–66 years	7–65 years
OUTCOMES ASSESSED	· Global assessment based on hyperkinesia scale · Films · Sleep studies · Patients · Parents or spouse assessments · Number of tics/recording	· TS-CGI · STSSS · YGTSS · TSSL · Videotape-based rating scale	· TSSL · STSSS · YGTSS · TSGS	· YGTSS · CGI · Y-BOCS/CY-BOCS · CPRS-R:L · CAARS-S:L
TREATMENT EFFECT ON TICS	**IMPROVEMENT** · Marked & Lasting: 4/9 patients · Mild or Transient: 3/9 patients · No response or worsening: 2/9 patients	**TS-CGI** Significant difference between THC and placebo at visit 3 (p=.05) and visit 4 (p=.008) **STSS** Significant difference between THC and placebo at visit 4 (p=.033) **YGTSS** Not significant **TSSL** At 10 treatment days, there was a significant difference between THC and placebo (p<.05) Videotape: "motor tic intensity" significant difference at visit 4 (p=.03)	**TSSL** Significant improvement in tic score after treatment (p=.015) compared to placebo; significant improvement in subscores: SMT, CMT, MT, and CVT **TSGS** No significant difference (only CMT was significant [p=.015]) **STSSS** Not significant **YGTSS** Not significant	**YGTSS MEAN TOTAL TIC SCORE** · Topiramate: 26.64±8.78 → 12.36±12.04 · Placebo: 28.77±7.53 → 23.10±8.99 p = .0259 **YGTSS GLOBAL SEVERITY SCORE** · Topiramate: 57.36±20.04 → 20.21±24.96 · Placebo: 58.00±18.86 → 50.10±18.08 p = .0030 *Mean Change in Goetz rating scores and TSGS were not significant.*
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Drowsiness 6/9 · Nervousness 2/9 · Depression 2/9 · Parkinsonism 1/9 · Oculogyric crisis 1/9	**THC** · 1 dropped out at day 4 due to anxiety and restlessness · Mild side effects including tiredness, dry mouth, dizziness, and muzziness (n=5) **PLACEBO** Tiredness, dizziness, anxiety and depression (n=3)	**THC** 5 experienced mild transient adverse reactions lasting between 1–6 hours (headache, nausea, dizziness, hot flush, anxiety, tremble, sensitivity, dry mouth, ataxia, poor concentration, cheerfulness) **PLACEBO** 2 reported mild side effects	**TOPIRAMATE** · Headache 3/15 · Diarrhea 3/15 · Abdominal pain 2/15 · Drowsiness/hypersomnia 2/15 · Cognitive slowing 1/15 · Kidney stone 1/15 · Mean weight change from baseline to day 70: -2.1 kg **PLACEBO** · Headache 3/14 · Diarrhea 1/14 · Abdominal pain 2/14 · Drowsiness/hypersomnia 2/14 · Mean weight change from baseline to day 70: 1.9 kg

LEGEND

YGTSS	Yale Global Tic Severity Scale
CGI	Clinical Global Impression
TIS	Tic Impairment Scale
TTS	Total Tic Score
TSGS	Tourette Syndrome Global Scale
UTRS	Unified Tic Rating Scale
STSSS	Shapiro Tourette Syndrome Severity Scale
TSSL	Tourette Syndrome Symptom List
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
MASC	Multidimensional Anxiety Scale for Children
CDI-S	Children's Depression Inventory-Short Version
CGAS	Children's Global Assessment Scale
CPQ	Conners Parent Questionnaire
CBCL	Children's Behavior Checklist
SAFTEE	Systematic Assessment for Treatment Emergent Effects
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
CPRS-R	Conners' Parent Rating Scale-Revised
TSSR	Tic Symptom Self Report
BRIEF	Behavioral Rating Inventory of Executive Function
BASC	Behavior Assessment System for Children
SOPT	Self-Ordered Pointing Test
TOL	Tower of London
LWF	Letter-Word Fluency
TOVA	Tests of Variables of Attention
TODS-CR	Tourette's Disorder Scale-Clinician Rated
RAScal	Rage Attack Scale
PGI	Parental Global Improvement Scale
LOI	The Leyton Obsessional Inventory
CGIC	Clinical Global Impression of Change
CAARS-S:L	Conners; Adult A-D/HD Rating Scale – Self Report: Long Version

CHAPTER IV

Behavioural Therapy, Deep Brain Stimulation, & Transcranial Magnetic Stimulation

for Tic Disorders & Tourette Syndrome

This chapter is a reproduction of Thomas Steeves, B Duncan McKinlay, Daniel Gorman, Lori Billinghurst, Lundy Day, Alan Carroll, Yves Dion, Asif Doja, Sandra Luscombe, Paul Sandor & Tamara Pringsheim. Behavioural Therapy, Deep Brain Stimulation and Transcranial Magnetic Stimulation for Tic Disorders. *Canadian Journal of Psychiatry* 2012; 57(3): 144–151.

The tic disorders constitute a spectrum of heritable neuropsychiatric conditions characterized by the presence of tics that begin in childhood, typically peak in severity just before adolescence, and improve by adulthood.[1] Education is the only treatment needed for most patients with tics; however, for patients with more severe or disabling tics, medical or behavioural interventions may be offered. Historically, the mainstay of treatment for severe tics has been antipsychotics. While the clinical efficacy of these agents is established, they often have undesirable side effects. An attractive alternative to pharmacotherapy are behavioural interventions, which require an investment of time but are generally free of side effects. Behavioural interventions to treat tics have a long history, but during the last decade a growing interest in this approach has led to the completion of several RCTs in this area. During a similar period, DBS has been evaluated to treat people with the most severe and medically intractable tics. More recently still, the efficacy of rTMS has been studied as another alternative to pharmacotherapy for tics.

Here, we review the evidence for the efficacy of the nonpharmacological treatments for tics and provide evidence-based recommendations for their use. This guideline attempts to address the essential questions: Which nonpharmacological interventions are effective in the treatment of tics? What are the benefits and harms of these therapies?

METHODS

The methodology for the systematic review, consensus group meeting, and generation of treatment recommendations are described in detail in the previous chapter on the pharmacotherapy of tic disorders.[2]

RESULTS

BEHAVIOURAL INTERVENTIONS FOR TICS

Cook and Blacher[3] published an evidence-based review of behavioural interventions for tic disorders, applying evidence-based criteria to synthesize results from research studies performed between 1970 and 2005. Included in their review were 6 different types of behavioural interventions: HRT, massed negative practice, self-monitoring, contingency management, ERP, and generic cognitive-behavioural treatment. As Cook and Blacher[3] have summarized most studies conducted until 2005, we chose to review their work in detail and then provide an analysis of studies published on behavioural interventions for TS from 2005 onwards.

Cook and Blacher[3] included in their review only randomized studies with a control group and adequate outcome measures. Based on the APA criteria, they classified behavioural interventions as either well established or probably efficacious. To be classified as well established, treatments needed to be explicitly detailed or manualized and to have been shown in multiple, adequately powered studies conducted by different teams of researchers to be superior to alternative treatments or placebo. Probably efficacious treatments were defined as treatments with results that were promising and met certain thresholds of empirical support, but that still needed independent replication with a larger sample size or with a sufficient control group.

In total, 30 studies were included in Cook and Blacher's analysis,[3] representing a total of 221 participants, aged 7 to 66 years. Only studies evaluating HRT and ERP met criteria for well-established or probably efficacious treatments for tics. The remaining 4 types of psychological treatments did not fulfill criteria for consideration as well established or probably efficacious.

HRT attempts to break a postulated cycle of negative reinforcement that occurs when the performance of a tic reduces the unpleasant urge to make it. The protocol for HRT first emphasizes awareness of premonitory sensations or urges, and then trains the person to perform a competing voluntary movement that is physically incompatible with the performance of the tic, typically until the urge to perform the tic goes away.

Twenty HRT studies were included in Cook and Blacher's review,[3] including 6 RCTs, and 14 rigorous single-case experimental designs. In all but one study, most participants demonstrated significant improvement in tics. Based on APA criteria, Cook and Blacher[3] concluded that HRT was a well-established treatment.

The rationale for ERP is similarly based on learning theory, which proposes that tics occur as a conditioned response to the unpleasant internal stimuli (urge). When such stimuli recur over time, the simple association between the sensation and the tic is strengthened. Instead of using competing responses, ERP attempts to break this association by asking the patient to suppress tics for prolonged periods through the use of various cognitive tools. In theory, this teaches the patient to habituate to the sensation, that is, learn to tolerate the unpleasant sensation without responding to it, which may lessen the urge to perform the tic.

Only a single study of ERP was included in the review. Verdellen et al[4] compared ERP to HRT in 43 participants, aged from 7 to 55 years. Participants were randomized to 12 weekly sessions of ERP or 10 weekly sessions of HRT. Total tic severity on the YGTSS improved significantly between baseline and end point in both treatment groups, with no significant differences demonstrated between treatments. Based on APA criteria, Cook and Blacher[3] concluded that ERP satisfied the requirements necessary for a probably efficacious treatment.

Since Cook and Blacher's 2005 evidence-based review,[3] three additional studies on HRT for tics have been published (Table 1). Piacentini et al[5] performed a good-quality RCT on HRT, compared with supportive therapy, for the treatment of tics in 126 youth with tic disorders. Co-morbid conditions within this sample were considerable, and 36.5% of the sample were

already on a stable dose of medication for their tics. Subjects were randomized to 8 sessions of therapy during 10 weeks. Total tic severity on the YGTSS decreased from 24.7 points at baseline to 17.1 points at week 10 with HRT, in comparison to a decrease from 24.6 points to 21.1 points with supportive therapy (P < 0.001). Among children receiving HRT, 52.5% were rated as very much improved or much improved on the Clinical Global Impressions – Improvement Scale, compared with 18.5% of children receiving supportive therapy (P < 0.001). One participant receiving HRT and 4 participants receiving supportive therapy reported worsening of tics. No adverse events related to the study were encountered. Notably, 86.9% of participants receiving HRT remained treatment responders even at 6 months follow-up.

Deckersbach et al[6] conducted an unblinded RCT of HRT, compared with supportive psychotherapy, in 30 adults with TS. Subjects received 14 sessions of therapy during a 5-month period. HRT decreased YGTSS total tic scores from 29.3 points at baseline to 18.3 points post treatment, in comparison to supportive psychotherapy, which decreased YGTSS total tic scores from 27.7 points to 26.6 points (P = 0.001). Ten of 15 subjects receiving HRT were classified as much improved or very much improved at the end of treatment, in contrast to 2 of 15 subjects in the supportive psychotherapy group (P = 0.008).

Himle et al[7] conducted an open, pilot study of 3 children receiving HRT for tics delivered via video conference. Improvements in 2 of the 3 children were comparable to results obtained in previous RCTs of face-to-face HRT, leading the authors to suggest that video conference delivery may be a promising method for disseminating HRT to areas where regional expertise or services are lacking.

Recommendation Grade for HRT: Strong Recommendation, High-Quality Evidence.
Recommendation Grade for ERP: Strong Recommendation, Low-Quality Evidence.

Based on current evidence, we recommend both HRT and ERP as first-line behavioural treatments both for children and for adults. It should be noted that past concerns of tic suppression resulting in a so-called rebound effect have been more recently debunked.[8,9] Other behavioural treatments identified in the literature have insufficient evidence to recommend their use. Relaxation training in isolation lacks a sufficient evidence base to be considered a stand-alone efficacious treatment,[10,11] but is often incorporated into HRT protocols.[12]

If both HRT and ERP are available, HRT would be the preferred mode of therapy, as a substantially larger base of evidence supports its use. However, HRT requires a skilled therapist, who may not be available at all centres. Conversely, as ERP is an established technique for the treatment of obsessive-compulsive disorder, it is possible that in centres where HRT is not available, therapists with expertise in ERP may more easily be able to provide treatment using this alternative modality. One important caveat is that behavioural therapies are unlikely to be helpful in very young children (aged 9 years and younger), or in children with severe, untreated attention-deficit hyperactivity disorder who may have difficulties sustaining engagement in therapy. Clinicians interested in learning more about HRT may consult Leaky Brakes[13] on the Child and Parent Resource Institute website, which contains written information and instructional videos.

TABLE 1 COGNITIVE BEHAVIORAL THERAPY STUDIES

AUTHOR, YEAR	Deckersbach, 2006	Himle, 2010	Piacentini, 2010
TREATMENT	Habit reversal therapy (HR) Supportive psychotherapy (SP)	Habit reversal training (HRT) via video conference	Comprehensive Behavioral Intervention Therapy Control: supportive therapy and education
LENGTH OF TREATMENT	14 individual sessions (50 min each) over 5 months	8 x 1hr sessions	8 sessions over 10 weeks
# OF INDIVIDUALS	30	3	126
MEAN AGE	35.1 years	13.7 years	11.7 years
AGE RANGE	Undefined age range	11–17 years	9–17 years
OUTCOMES ASSESSED	YGTSS, CGI-I, BDI, YBOCS, ADHD Symptom Checklist, Sheehan Disability Inventory, SOS-10, VSP	Frequency of tics in 15-30 min videos	YGTSS, CGI-I, Parent Tic Questionnaire
TREATMENT EFFECT ON TICS	**YGTSS** HR *Pretreatment → Post-Treatment → Follow-Up* 29.3±5.8 → 18.3±5.2 → 18.4±7.1 SP *Pretreatment → Post-Treatment → Follow-Up* 27.7±6.3 → 26.8±6.7 → 26.6±8.6	% INTERVALS WITH TICS *Baseline → Introduction To Treatment → Post-Treatment → Follow-Up* · Dan: 62% → 37% → 20% → 22% · Earl: 84% → 74% → 55% → Not reported FREQUENCY OF TICS (TICS/OBSERVATION) Thomas: 28 → 4.5 → 1/3 → 0	**YGTSS** TOTAL TIC *Baseline → Week 5 → Week 10* · CBIT: 24.7 → 19.7 → 17.1 · Control: 24.6 → 22.8 → 21.1 · Group difference at week 10: 4.1 TOTAL MOTOR *Baseline → Week 5 → Week 10* · CBIT: 14.6 → 12.2 → 10.7 · Control: 14.6 → 13.6 → 12.5 · Group difference at week 10: 1.9 TOTAL VOCAL *Baseline → Week 5 → Week 10* · CBIT: 10.1 → 7.4 → 6.5 · Control: 10.0 → 9.3 → 8.6 · Group difference at week 10: 2.2 IMPAIRMENT *Baseline → Week 5 → Week 10* · CBIT: 25.0 → 16.8 → 12.2 · Control: 23.4 → 20.1 → 16.4 · Group difference at week 10: 4.7 PARENT TIC QUESTIONNAIRE TOTAL SCORE *Baseline → Week 5 → Week 10* · CBIT: 34.2 → 25.8 → 20.0 · Control: 35.7 → 33.7 → 27.6 · Group difference at week 10: 7.8
IMPORTANT SIDE EFFECTS ENCOUNTERED	Not reported	Not reported	TIC WORSENING · CBIT (n=1) · Control (n=4)
METHODOLOGICAL QUALITY	Poor	Open study	Good

BDI Beck Depression Inventory
CGI-I Clinical Global Impression-Improvement
SOS-10 Schwartz Outcome Scale
VSP Visuospatial priming
YBOCS Yale-Brown Obsessive Compulsive Scale
AIMS Abnormal Involuntary Movement Scale
CGI-TS Clinical Global Impression-Tourette's Syndrome
MOVES Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey
PANAS Positive and Negative Affect Schedule

To date, 25 published studies, representing data from 69 patients, have reported on the efficacy of DBS in the treatment of TS refractory to medical and behavioural treatments. With the exception of one large-scale case series from Italy,[14] most of these studies have reported results of stimulation in individual patients. RCTs with large numbers of patients are lacking. Among the 69 patients reported to date, improvement in tics have been reported in 65 (93.7%), and in some instances associated co-morbidities have improved as well. DBS has almost certainly been performed in many more patients than the numbers reported to date, leaving open the possibility of a substantial reporting bias. Attempts to interpret the existing results are further complicated by the large number of different structures that have been targeted with DBS, which, depending on the specific stereotactic coordinates and terminology reported, may extend to ten. The rational for the choice of all targeted structures to date is that all belong to the ventro striatal-thalamo-cortical circuits that are thought dysfunctional in TS. The 2 areas most frequently stimulated have been regions of the CM nucleus of the thalamus and the GPi of the striatum.

For our evidence-based analysis, only 3 studies met inclusion criteria (Table 2). Ackermans et al[15] performed a poor-quality crossover RCT to evaluate 6 adults with TS. The specific target for stimulation was the intersection of CM nucleus – substantia periventricularis – nucleus ventro-oralis internus. The authors randomly assigned patients to Stimulation *on* for 3 months followed by stimulation *off* for 3 months (group A) or vice versa (group B). No medication changes were allowed while patients were in the blind. This blinded period was then followed by 6 months of open-label evaluation. Cognitive evaluations were performed with stimulation *on* at 1 year, postoperatively.

At the end of the blinded *on* period, the authors reported a 37% mean reduction in YGTSS (P = 0.05) and a significant reduction in total video tic counts (P = 0.05), compared to the end of the blinded *off* period, but no significant difference in the MRVBRS. At 1-year follow-up, unblinded, a 49% reduction in the YGTSS (P = 0.03) and a 35% reduction in the MRVBRS (P = 0.05) was documented, compared with the preoperative assessment. No significant effects on behavioral or mood symptoms were observed at the group level. At 1 year, patients took significantly more time to complete the Stroop colour-word test, a measure of selective attention and response inhibition.

The authors reported numerous significant adverse events. All patients reported subjective downgaze impairments and reduced energy sufficient to restrict daily activity. Notably, one patient, during the year following electrode implantation, suffered an unexplained syndrome of apathy, gait disturbance, and progressive cerebral atrophy. One patient suffered a small hemorrhage ventral to the tip of one of the stimulating electrodes and another, a skin infection at the site of the pulse generator.

Welter et al[16] performed a fair-quality crossover RCT of 3 patients treated with bilateral DBS of the CM-Pf complex and GPi. They evaluated patients 1 month before surgery and 2 months after surgery, all without stimulation. Patients were then stimulated with identical parameters (60 usecs and 130Hz) and evaluated monthly during 5-day hospitalization

periods, with the following double-blinded, randomized protocols: bilateral thalamic stimulation for 2 months; bilateral GPi stimulation for 2 months; bilateral thalamic plus GPi stimulation for 2 months; and sham stimulation (no current) for 2 months. This period of blinded evaluation was then followed by an open-label follow-up performed at postoperative months 60, 33, and 20 for patients 1 to 3, respectively.

The authors reported the best improvements with ventromedial GPi stimulation: 65%, 96%, and 74% reductions in total YGTSS for patients 1 to 3, respectively. This is compared with the best effects of CM-Pf thalamic stimulation, which produced reductions of 64%, 30%, and 40%. Combined thalamic-GPi stimulation did not improve tic reduction further.

The authors also commented on the stability of treatment effects. For patients 1 and 3, the effects remained stable or improved during 2 months. For patient 2, the effect decreased or disappeared at 2 months. At long-term follow-up, patient 2 required monthly adjustments in stimulation parameters to maintain efficacy. The authors noted that psychiatric symptoms tended to improve with stimulation and cognition remained stable.

Numerous adverse effects were noted. With thalamic stimulation, all 3 patients reported decreased libido as well as transient paresthesias, particularly in arms and around the mouth. For GPi stimulation, 2 patients reported transient lethargy, nausea, and vertigo, and 1 patient reported anxiety.

Maciunas et al[17] performed a fair-quality crossover RCT evaluating bilateral DBS of the CM-Pf of the thalamus in 5 adult patients with TS. Patients were implanted and their stimulation parameters were then optimized in a single session. Patients were then randomized into 4 combinations of stimulations (*off/off; on/off; off/on; on/on*) for 7 days each, with the response to treatment evaluated in a double-blinded manner at the end of each 7-day period. This period of blinded assessment was then followed by 3 months of open-label *on/on* stimulation.

The authors reported in the *on/on* state a significant 4.2 point reduction (P = 0.03) in the MRVBRS and a significant raw tic count reduction of 53% (P = 0.02). The authors also noted at the start of the open-label phase a reduction of 5.4 points in the MRVBRS and a 67% reduction in raw tic counts. At 3 months in the open-label phase, the authors reported a reduction of 2.6 points in the MRVBRS and a 40% reduction in raw tic counts, compared with the preoperative state. Phonic tics were likewise reduced by 70% at the start of the open-label phase, reduced by 31% at 3 months, but then increased by 21% at the end of the open-label phase. The authors reported no effect with unilateral stimulation. By 3 months in open-label stimulation, there was a trend for measures of neuropsychological performance to decline, and a trend for mood, anxiety, and OCD symptoms to improve.

Recommendation Grade for DBS, Adults: Category X1, Insufficient Evidence to Make a Formal Recommendation. Recommendation Grade for DBS, Children: Not Recommended.

TABLE 2 DEEP BRAIN STIMULATION STUDIES

AUTHOR, YEAR	Ackermans, 2011	Maciunas, 2007	Welter, 2008
TREATMENT	Sequential monopolar stimulation Pulse width: 60 µsec Frequency: 100 Hz Voltage: progressively increased until unwanted side effects occurred	Bilateral placement of stimulating electrodes Pulse width: 90–210µsec Frequency: 130–185 Hz Amplitude: 3.5-3.6 V	Bilateral placement of stimulating electrodes in the CM-Pf and the GPi Pulse: 60 µsec Frequency: 130 Hz
LENGTH OF TREATMENT	N/A	4 weeks (28 days)	N/A
# OF INDIVIDUALS	6	5	3
MEAN AGE	40.33 years	28.2 years	32 years
AGE RANGE	35–48 years	18–34 years	30–36 years
OUTCOMES ASSESSED	YGTSS, Behavioral disorders and mood	mRVRS, YGTSS, TSSL, BDI-2, HAM-D, HAM-A, Y-BOCS	YGTSS, RVRS
TREATMENT EFFECT ON TICS	**YGTSS TOTAL** · Before surgery: 42.3±3.1 · OFF: 41.1±5.4 · ON: 25.6±12.8 · 1 year: 21.5±11.1 · p=.046* (ON vs. OFF); p=.028* (before surgery vs. 1 year) **VIDEO-TICS** · Before surgery: 233.3±82.1 · OFF: 195.3±98.6 · ON: 85.3±72.3 · 1 year: 65.3±81.6 · p=.046* (ON vs. OFF); p=.028* (before surgery versus 1 year) **MRVRS** · Before surgery: 12.1±1.1 · OFF: 10.8±1.5 · ON: 6.3±3.6 · 1 year: 7.8±3.2 · p=.580 (ON vs. OFF); p=.046* (before surgery vs. 1 year) * denotes a significant value	**MRVRS** Preop 17.0±2.6; Prestim 16.4±2.8; Lf off/Rt off 15.4±4.6; Lt off/Rt on 15.8±4.8; Lt on/Rt off 14.4±4.0; Lf on/Rt on 12.8±4.5; Endpoint 11.6±5.1; 3 month follow-up 14.4±4.0 mRVRS was reduced by 4.2 points in the randomized on-on state, by 5.4 points at the start of the open-label phase, and by 2.6 points 3 months after the start of the open-label phase. Randomized phase showed a significant (p<.03) reduction in mRVRS score. Significant reduction in motor tic counts (p=.02) **YGTSS** Compared with the preop state, the mean YGTSS scores were reduced by 2.4 points in the randomized on-on state and by 9.0 points at the 3-month follow up. The mean complete-scale YGTSS score was reduced 38.8 points at 3 months compared with the preop score. **TSSL** Mean scores were reduced by 30.1 points in the randomized on-on state and by 23.1 points at 3 months. No significant differences in either the YGTSS or TSSL scores.	**TOTAL YGTSS** *Reduction For Patients 1, 2 & 3, Respectively* · GPi: 65%, 96%, 74% · Combined GPi and CM-Pf stimulation: 50%, 43%, 76% **GLOBAL TIC SEVERITY** *Reduction For Patients 1, 2 & 3, Respectively* CM-Pf: 64%, 30%, 40% **YGTSS MOTOR AND PHONIC SUBSCORE %** *Reduction For Patients 1, 2 & 3, Respectively* · GPi: 80%, 90%, 67% · CM-Pf: 41%, 37%, 41% · Combined: 59%, 16%, 70%
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Small parenchymal haemorrhage resulting in vertical gaze (n=1) · Staphylococcus aureus infection in the infracalvicularreigion (n=1) · Varying motor and psychiatric symptoms (n=1) · One year after surgery, all the patients reported a substantial restriction in their daily activities due to lack of energy. · Multidirectional nystagmus (n=1) · On direct questioning, all patients reported visual disturbances varying from blurred vision to fixation problems	· Acute psychosis 1/5 · Spontaneous recurrence of tics during open phase 2/5 · Symptom control waned by 3 month follow-up 1/5	· Nausea and vertigo with GPi (n=3) · Anxiety with GPi (n=1) · Libido decrease with CM-Pf (n=1)
METHODOLOGICAL QUALITY	Poor	Fair	Fair

The current evidence suggests that DBS should remain an experimental treatment for severe, medically refractory tics that have imposed significant limitations on quality of life. Some evidence exists for its efficacy, but, to date, no RCTs have included large numbers of patients, and some of the reported beneficial effects following DBS may still be due to the natural waxing and waning of tics, or to placebo effects, particularly in a population known to be suggestible.[18] Our recommendation is that the procedure should be reserved for treatment within research protocols and performed by physicians expert in DBS programming and in the management of TS. Stimulation of the thalamus (CM-Pf) and the GPi have also been associated with significant adverse events, and patients should be counselled carefully about complications before proceeding with surgery.

TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF TICS

The effects of TMS have also been evaluated for TS. The intervention is based on the principal of electromagnetic induction, whereby a brief magnetic field delivered at the surface of the scalp induces a current along the surface of the cortex that can alter the activation of cortical neurons and interneurons. Studies using paired pulses of TMS to examine intrinsic inhibition or excitation of the cortex have found a general deficiency of inhibition in the motor cortices of patients with TS.[19] Simultaneously, rTMS has been shown to have varying effects on the function underlying the motor cortex, possibly as a function of the frequency of application, with long slow trains of rTMS temporarily reducing corticospinal excitability[20] and faster trains increasing it.[21,22] Therefore, numerous studies have applied rTMS protocols to patients with TS, attempting to normalize the presumed cortical hyperexcitability with the goal of reducing tics.

We identified a total of 3 studies evaluating the effects of rTMS in adults with TS that satisfied our inclusion criteria (Table 3).[23–25] None of these studies found a significant change in tic symptoms with rTMS.

Recommendation Grade for rTMS in Adults: Category X1, Insufficient Evidence to Make a Formal Recommendation. Recommendation Grade for rTMS in Children: Not Recommended.

On review of the existing studies, our recommendation is that there is no good evidence to support the use of rTMS in the treatment of TS. However the procedure is associated with a low rate of known complications, and should continue to be reserved for evaluation within research protocols.

TABLE 3 TRANSCRANIAL MAGNETIC STIMULATION STUDIES

AUTHOR, YEAR	Chae, 2004	Munchau, 2002	Orth, 2005
TREATMENT	Repetitive Transcranial Magnetic Stimulation Five 4-hour sessions Frequency: Low (1 Hz); High (15 Hz) 9600 active stimuli and 2400 sham stimuli	Repetitive Transcranial Magnetic Stimulation Two 20-minute sessions per treatment block (6 sessions in total) Frequency: 1 Hz	Repetitive Transcranial Magnetic Stimulation 1800 stimuli of 1 Hz pre-motor cortex @ 80% MT
# OF INDIVIDUALS	8	16	5
MEAN AGE	34.9 years	38 years	29 years
AGE RANGE	19–60 years	Undefined range	19–52 years
OUTCOMES ASSESSED	YGTSS, CGI-TS, Mood/pain ratings, YBOCS, AIMS, PANASP	MOVES	YGTSS, MOVES, Video analysis (MRVS)
TREATMENT EFFECT ON TICS	No statistically significant effects of rTMS by site or frequency. TOTAL YGTSS 70.3±22.4 → 55.8 ±20.7 TOTAL TIC TGTSS 48.5±29.8 ± 39.0±22.6 Not significant HIGH FREQUENCY PFC YGTSS 28.9±28.2% improvement LOW FREQUENCY PFC YGTSS 17.4±24.1% improvement SHAM 22.4±25.1% improvement HIGH FREQUENCY MC YGTSS 20.7±24.2% improvement LOW FREQUENCY MC YGTSS 15.2±17.5% improvement Not significant CGI-TS 5.2±1.2 → 3.7±1.0 (p=.041) TIC SYMPTOM SELF REPORT Motor: 17.4±12.8 → 8.5±6.3 Vocal: 7.7±7.8 → 4.0±4.0 BLINDED TIC COUNT (YGTSS) 20.8±8.9 → 19.4±5.2	No significant effects for any MOVES scores	LEFT AND RIGHT PREMOTOR · MOVES Total: 11.8±5.0 → 11.2±4.7 · MOVES Tic: 7.4±2.3 → 7.8±2.6 · YGTSS Total: 46.2±1 → 45±8.3 · YGTSS Motor: 14.4±2.7 → 13.4±1.9 · YGTSS Vocal: 7.8±3.2 → 7.4±2.6 LEFT PRE-MOTOR · MOVES Total: 13.4±4.7 → 11±5.1 · MOVES Tic: 8.2±1.3 → 7.2±2.6 · YGTSS Total: 51±27.3 → 51.2±27.4 · YGTSS Motor: 15.2±4.5 → 15.2±4.9 · YGTSS Vocal: 9.8±4.8 → 10±4.7 SHAM · MOVES Total: 11.8±4.1 → 9.2±3.1 · MOVES Tic: 7.2±1.3 → 6.2±1.5 · YGTSS Total: 48.2±8.0 → 49.4±8.8 · YGTSS Motor: 13.8±2.6 → 14.4±3.5 · YGTSS Vocal: 8.4±6.0 → 9±5.5 None significant
IMPORTANT SIDE EFFECTS ENCOUNTERED	· Headache (n=3) · High-frequency of MC resulted in increased excitability manifested by increase in evoked twitch and motor evoked potential amplitude (n=1)	· Mild headache after premotor rTMS (n=1) · Excessive tiredness after premotor and motor rTMS lasting for 1 day (n=2)	None reported
METHODOLOGICAL QUALITY	Fair	Poor	Poor

DISCUSSION

Based on the current available evidence, we have made strong recommendations for HRT and ERP, preferably embedded within a supportive, psycho-educational program, and with the option of combining either of these approaches with drug treatment. The quality of the evidence for the use of DBS in the treatment of tics is poor, and the risks and burdens of the procedure are finely balanced with the perceived benefits. Our recommendation is that this intervention should continue to be considered as an experimental treatment in adults for severe, medically refractory tics that have imposed severe limitations on quality of life. We feel that the procedure should only be performed within the context of research studies and by physicians expert in DBS programming and in the management of TS. There is no good-quality evidence to support the use of rTMS in the treatment of TS. However, the treatment is associated with a low rate of known complications and should continue to be evaluated within research protocols. These recommendations are based on current knowledge, and further studies may result in their revision in future.

ABBREVIATIONS

APA	American Psychological Association
CM	Centromedian
DBS	Deep Brain Stimulation
ERP	Exposure and Response Prevention
GPi	Globus Pallidus interna
HRT	Habit Reversal Therapy
MRVBRS	Modified Rush Video-Based Rating Scale
Pf	Parafascicular
RCT	Randomized Controlled Trial
rTMS	repetitive TMS
TMS	Transcranial Magnetic Stimulation
TS	Tourette Syndrome
YGTSS	Yale Global Tic Severity Scale

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CHAPTER V

Pharmacological Treatment of Attention Deficit Hyperactivity Disorder *in Children with Co-Morbid Tic Disorders*

Tamara Pringsheim, Thomas Steeves & Daniel Gorman

BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) is a common co-morbidity in individuals with chronic tic disorders. The clinical implications of a diagnosis of co-morbid ADHD are significant. The risk of aggressive and delinquent behaviour in children with tic disorders is largely due to the presence of ADHD,[1] and the greatest independent predictor of psychosocial quality of life is ADHD symptom severity.[2] In contrast, the presence of a co-morbid tic disorder has limited impact on outcome in patients with ADHD.[3]

Rates of association between tic disorders and ADHD are much higher than would be expected based on chance alone. Kurlan[4] used direct interviews in a community-based study of school children to determine the prevalence of tic disorders and any co-morbid psychopathology. They included 1596 children aged 9 to 17 years from 10 New York State school districts over a four-year period. In this study, 38% of children with tics had a diagnosis of co-morbid ADHD. Clinic-based studies yield even higher rates of co-morbid ADHD. In a review of a multi-site, international database of 3500 individuals with tic disorders, Freeman[5] reported that 60% of children with tic disorders also had ADHD, with a range of 33% to 91% among sites reporting more than 50 cases.

The association between tic disorders and ADHD is a compelling one, and a number of investigators have proposed that the disorders share a common pathophysiology. Specifically, both conditions are thought to involve alterations in noradrenergic and dopaminergic transmission, resulting in inadequate modulation of corticostriatal circuits and thus failure to inhibit intrusive thoughts, sensory input, and motor responses.[6] Neurochemical models based on dopaminergic and noradrenergic dysfunction have likewise guided treatment approaches.

Medications most commonly used to treat ADHD symptoms include the stimulants methylphenidate and amphetamine, followed by nonstimulants such as atomoxetine, alpha agonists, and tricyclic antidepressants.[7] Given the impairment associated with co-morbid ADHD in many children with a tic disorder, treatment for ADHD symptoms is often a greater priority than treatment for tics. For decades, however, clinicians were reluctant to use stimulants to treat symptoms of ADHD in children with tics for fear of worsening the tics. In the 1970s and early 1980s, several case reports and small case series were published of children who experienced the onset or worsening of tics after the initiation of stimulants for the treatment of ADHD.[8,9] Despite new evidence that suggests that this temporal relationship was not causal,[10] product monographs for stimulants approved for the treatment of ADHD by Health Canada and the US Food and Drug Administration continue to include warnings against the use of these medications in children with co-morbid tic disorders or a family history of Tourette syndrome.

The mechanisms of action of medications used for ADHD generally involve either direct or indirect modulation of dopamine and norepinephrine neurotransmission. Stimulants block the re-uptake of dopamine and norepinephrine into the presynaptic neuron (methylphenidate), or increase the release of these monoamines into the extraneuronal space (amphetamines).[11] Atomoxetine selectively inhibits presynaptic re-uptake of norepinephrine, resulting in increased norepinephrine levels in the synapse.[12] The efficacy of tricyclic antidepressants in the treatment of ADHD is likewise thought to be mediated by their action on re-uptake of catecholamines, especially norephinephrine. The alpha agonists appear to alter basal adrenergic tone.[13]

Given how commonly chronic tic disorders and ADHD co-occur, the impact of ADHD on psychosocial quality of life in individuals with tics, and the concern among clinicians about potential worsening of tics with stimulants, an up-to-date systematic review of pharmacological treatments for ADHD in children with tics is needed. We synthesized the evidence on the efficacy of these agents for tic-related ADHD, as well as their effects on tics. While physicians specializing in this area of practice may already be aware of this literature, it may be less familiar to non-specialists. Furthermore, children and families affected by tic disorders and co-morbid ADHD frequently have concerns about the use of ADHD medications, including potential worsening of tic symptoms, and they routinely seek information and advice on this issue.

Our objectives were (1) to conduct a systematic review of the effects of ADHD medications on ADHD and tic symptoms in children with both conditions, and (2) to make evidence based recommendations on the treatment of ADHD in this population.

METHODS

The evidence review for this guideline was based on a Cochrane systematic review published by two of the authors.[14] Methods for the systematic review followed standard Cochrane review procedures. We included randomized, double-blind, controlled trials of any pharmacological treatment for ADHD used specifically in children with co-morbid tic disorders. We included both parallel group and cross-over study designs. Our population of interest was children aged 18 years or younger with a clinical diagnosis of ADHD and a chronic tic disorder (Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder). The primary outcomes we evaluated were ADHD and tic symptom severity as measured by validated clinician, teacher, or parent report scales. Specifically, we evaluated:

- ADHD symptom-related behaviour in the home setting
- ADHD symptom-related behaviour in the school setting
- Tic severity

Secondary outcomes evaluated were treatment side effects, including:

- Cardiovascular effects, such as changes in heart rate, blood pressure, or the electrocardiogram
- Weight changes.

A search strategy was devised for MEDLINE and modified as necessary for other databases. Search filters were used to find randomized studies. No date or language restrictions were applied.

We searched the following databases:

- *The Cochrane Library* (2009, Issue 4)
- MEDLINE (1950 to October 2010)
- EMBASE (1980 to October 2010)
- CINAHL (1982 to July 2009)
- PSYCINFO (1806 to July Week 4 2009)
- BIOSIS Previews (1985 to July 2009)
- Dissertation abstracts were searched via Dissertation Express
- MetaRegister of Controlled Trials

Two authors (TP and TS) independently reviewed titles and abstracts of references retrieved from the searches and selected all potentially relevant studies. Copies of these articles were obtained and read in detail for fulfillment of inclusion criteria. The authors resolved any dispute regarding the fulfillment of inclusion criteria by discussion. Authors were not blinded to the names of the trial authors, institutions, or journals of publication.

Both authors (TP and TS) extracted data independently from each included study and entered the data into pre-designed summary forms. The following data were extracted:

1 Study procedures
2 Study design
3 Randomization method
4 Method of allocation concealment
5 Method of blinding
6 Inclusion and exclusion criteria
7 Number of participants
8 Age distribution
9 Gender
10 Loss of follow-up
11 Premature discontinuation of study and reasons for discontinuation
12 Outcome measures
13 Method of analysis
14 Comparability of groups at baseline

Extracted data were compared to ensure accuracy. Data were entered into Review Manager 5 by one author (TP) and then checked by the second author (TS). Discrepancies were resolved by consensus.

Risk of bias was assessed independently by both review authors according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Review authors independently assessed the risk of bias within each included study based on the following six domains, with ratings of 'Yes' (low risk of bias), 'No' (high risk of bias), and 'Unclear' (uncertain risk of bias).

- Sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

Possible sources included:

- Design-specific risk of bias, e.g., washout adequacy in cross-over trials
- Early stopping
- Baseline imbalance
- Inappropriate administration of a co-intervention
- An insensitive instrument used to measure outcomes

As a result of significant clinical heterogeneity among studies and incomplete reporting of the results from cross-over trials, meta-analysis of the study data was not possible. Results are therefore presented for studies individually.

Unit of analysis issues occurred in this review, as none of the included cross-over studies presented paired data for analysis but rather provided the means and standard deviations for each treatment type.

We assessed clinical heterogeneity by comparing the distribution of important participant factors among trials and by comparing trial design.

As there was an insufficient number of studies found for each treatment type, we did not create funnel plots to assess for publication bias.

A classification scheme based on the GRADE system[16] was used to make recommendations for the treatment of ADHD in children with tics (Table 1). A strong recommendation is made when the benefits of treatment clearly outweigh the risks and burdens, and can apply to most patients in most circumstances without reservation. With a weak recommendation, the benefits, risks, and burdens are more closely balanced, and the best action may differ depending on circumstances. We created a third category, Category X, for medications where insufficient evidence exists to make a formal recommendation. A multi-institutional

TABLE 1 GRADE RECOMMENDATIONS

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, low-quality or very low- quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation but may change when higher quality evidence becomes available
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Very weak recommendation; other alternatives may be equally reasonable
Category X1, no recommendation		Insufficient evidence to make a formal recommendation; requires further study.
Category X2, no recommendation		Insufficient evidence to make a formal recommendation; controversial, costly, or unavailable for clinical use

group of 14 experts in the fields of psychiatry, child psychiatry, neurology, pediatrics, and psychology engaged in a consensus meeting. The consensus group did not receive any industry sponsorship and developed this manuscript independently with no restrictions of any kind. The evidence was presented and discussed, and nominal group techniques were employed to come to consensus on recommendations.

RESULTS

We found 548 citations using the search strategy run in October 2008, of which 21 qualified for further review. The searches were re-executed in October 2010 and 51 additional citations were found, of which none qualified for further review. Of the 21 manuscripts reviewed, eight were randomized controlled trials of pharmacological treatments for ADHD in children with co-morbid tic disorders, and were therefore included in the review. Eight of the 21 manuscripts were re-publications of data already presented in the eight studies included in the review (see Appendices 1–8 for study details). The remaining five manuscripts were excluded for other reasons.

STUDY DESIGNS

We included a total of eight randomized controlled studies. Three of these trials assessed multiple agents. Agents assessed were methylphenidate, dextroamphetamine, clonidine, guanfacine, atomoxetine, desipramine, and deprenyl.

The three studies that assessed multiple agents included a parallel group study by the Tourette Syndrome Study Group,[10] which randomized 136 children (age range 7 to 14 years) to a flexible dose of methylphenidate (mean dose 25.7 mg per day), clonidine (mean dose 0.25 mg/day), clonidine plus methylphenidate (mean doses 0.28 and 26.1 mg/day, respectively), or placebo for 16 weeks each. The second study was a complex placebo-controlled cross-over study by Castellanos[17] that randomized 20 participants (mean age 9.4 years) into three cohorts of children, each sequentially receiving for three weeks placebo, one of three different dosage titrations of methylphenidate (maximum dose 45 mg twice daily), and one of three different dosage titrations of dextroamphetamine (maximum dose 22.5 mg twice daily). The third multiple agent study[18] was a three-phase cross-over study in 34 children (age range 7 to 14 years) of clonidine 0.05 mg four times daily, desipramine 25 mg four times daily, and placebo. Each treatment was taken for six weeks, separated by a one week washout period.

Methylphenidate was studied in a single agent cross-over trial with placebo.[19] Seventy-one children (age range 6 to 12 years) were randomized to three sequential doses of methylphenidate (0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg) twice daily for two weeks each.

Desipramine was evaluated versus placebo in 41 children (age range 5 to 17 years) in a parallel group study in which desipramine was titrated weekly up to 3.5 mg/kg per day for six weeks.[20]

Guanfacine, an alpha-2 receptor agonist, was studied versus placebo in a parallel group trial of eight weeks duration.[21] Thirty-four children (age range 7 to 15 years) were randomized to placebo or guanfacine 1.5 to 3.0 mg/day.

Atomoxetine, a highly selective noradrenergic re-uptake inhibitor, was evaluated at doses of 0.5 to 1.5 mg/kg/day versus placebo in a parallel group study of 18 weeks duration in 148 children (age range 7 to 17 years).[22] Participants considered to be clinical nonresponders at week 12 of the study were allowed to withdraw early from the double-blind study and enter an open label study of the drug.

Deprenyl, a type B monoamine oxidase inhibitor, was evaluated in 24 children (age range 7 to 16 years).[23] Participants were randomized to treatment with deprenyl 5 mg twice daily or placebo for eight weeks, and then crossed over to the alternate treatment after a six-week washout period.

Participants in all included studies were children between 5 and 17 years of age with diagnoses of ADHD and Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder based on DSM-III-R or DSM-IV-TR criteria. Participant numbers ranged from 22 to 148 children, with all studies having a predominance of male participants.

All trials included both ADHD and tic outcomes. A primary outcome was not specified for the majority of trials. The scales chosen to measure ADHD severity varied considerably among studies. Three studies used the ADHD Rating Scale;[20–22] three studies used the Conners Teacher Rating Scale with or without the Conners Parent Rating Scale;[10,17,19] one study used the DuPaul ADHD Scale,[23] and one study used various subscales of the Child Behavior Checklist to measure ADHD symptoms.[18] All studies used the Yale Global Tic Severity Scale for one measure of tic severity.

RISK OF BIAS IN INCLUDED STUDIES

ALLOCATION (SELECTION BIAS)

Sequence generation was judged to be at low risk of bias for three of the eight studies.[10,20,23] In the remaining five studies it was not described, and therefore the risk of bias was judged to be 'unclear'.

Allocation concealment was adequately described in five of the eight studies.[10,18–20,22] It was inadequately described in the remaining three studies, preventing us from make a judgment on whether it was appropriate or not.

BLINDING (PERFORMANCE BIAS AND DETECTION BIAS)

Blinding of participants, clinicians, and outcome assessors was a requirement for inclusion. All included studies were therefore judged as being at low risk of bias in relation to blinding.

INCOMPLETE OUTCOME DATA (ATTRITION BIAS)

Incomplete outcome data were not adequately addressed in four of the eight studies. Feigin[23] had a very high drop-out of study participants after the first period of the study, especially in the treatment group, and it was unclear if data from those who dropped out

of the study were included in the analysis. Gadow[19] did not explain how incomplete data sets were handled in the analysis. Castellanos[17] provided little raw data from study results; only F scores and P values for analysis of variance tests were reported. In addition, all of the above studies, which were cross-over studies, did not provide paired data for analysis. Rather, all studies provided only means and standard deviations for each treatment type, and with the exception of Castellanos[17] they did not provide original data.

selective reporting (reporting bias)

Singer[18] did not provide outcome data for many variables described as collected in the Methods section, only presenting data for those scales showing significant changes. They often reported 'male only' results.

other potential sources of bias

Allen had a high rate of early treatment termination at 12 weeks in both treatment groups. None of the other studies appeared to have other potential sources of bias.

effects of interventions

All treatments, with the exception of deprenyl, were efficacious in treating the symptoms of ADHD. Tic symptoms improved in children treated with methylphenidate, clonidine, the combination of methylphenidate and clonidine, guanfacine, and desipramine. Fear of worsening tics limited dose increases of methylphenidate in one study.[10] High dose dextroamphetamine appeared to worsen tics in one study,[17] although the duration of treatment was only three weeks (please see Table 2 for Summary of Recommendations).

methylphenidate

In the parallel group study,[10] children were randomized to: (1) clonidine, (2) a flexible dose of methylphenidate, (3) clonidine plus methylphenidate, or (4) placebo, for 16 weeks each. The primary outcome was the change from baseline to week 16 in the ADHD Conners Abbreviated Symptoms Questionnaire for Teachers (ASQ); the main secondary outcome was the change from baseline in the YGTSS. A statistically significant treatment effect in comparison to placebo was observed with methylphenidate alone (3.3 points, 98.3% confidence interval (CI) -0.2 to 6.8, P = 0.02) and with clonidine plus methylphenidate (6.3 points, 98.3% CI 2.8 to 9.8, P < 0.0001) on the ASQ. YGTSS scores also significantly improved compared to placebo, with a statistically significant treatment effect observed for methylphenidate alone (11.0 points, 98.3% CI 2.1 to 19.8, P = 0.003) and for methylphenidate plus clonidine (11.0 points, 98.3% CI 2.1 to 19.8, P = 0.003).

In participants treated with methylphenidate (alone or with clonidine), worsening of tics occurred in 20%, which was no more frequent than in participants who received placebo (22%) or clonidine alone (26%). Nonetheless, tics limited dosage increases more often in participants assigned to methylphenidate alone (35%) than in those assigned to methylphenidate plus clonidine (15%), clonidine alone (18%), or placebo (19%).

In Gadow's cross-over trial[19] that randomized children to three different doses of methylphenidate and placebo for two weeks each, the primary outcome was the YGTSS score. Several secondary outcomes were measured, including ADHD symptoms using the ASQ. Regarding ADHD symptoms, all three doses of methylphenidate were superior to placebo on all rating scales, including the ASQ. Furthermore, a dose-response relationship was observed, with the 0.5 mg/kg dose of methylphenidate showing superiority over the lower doses on the ASQ. Mean scores on the ASQ were: 11.6 ± 6.9 during placebo treatment; 8.0 ± 6.0 with the 0.1 mg/kg dose of methylphenidate; 7.3 ± 5.8 with the 0.3 mg/kg dose; and 5.7 ± 5.1 with the 0.5 mg/kg dose (F = 24.7, P = 0.0001).

On the YGTSS, Gadow[19] found no difference in tic severity among treatments with respect to mean total motor tic, total phonic tic, tic-related impairment, or global severity scores. The teacher ratings on the Global Tic Rating Scale, however, indicated an improvement in tic severity with methylphenidate treatment at all doses compared to placebo (F ratio 5.33, P = 0.0015). On the other hand, the two-minute tic/habit count showed an increase in simple motor tics during treatment with the 0.3 mg/kg and 0.5 mg/kg doses of methylphenidate compared to placebo (F = 3.96, P = 0.0091).

With respect to other adverse drug reactions, there were higher levels of somatic symptoms (sleep and appetite problems, headache, stomach upset, dizziness) on the Stimulant Side Effects Checklist during methylphenidate treatment compared to placebo (F = 8.1, P = 0.0001). Diastolic blood pressure was higher during treatment with the 0.5 mg/kg dose of methylphenidate compared to both placebo and the 0.1 mg/kg dose, and heart rate was higher with the 0.3 mg/kg and 0.5 mg/kg doses compared to placebo.

In the Castellanos cross-over trial,[17] in which children were randomized to three weeks each of methylphenidate, dextroamphetamine, and placebo, methylphenidate significantly decreased hyperactivity at all doses. In the first cohort of 10 participants, analysis of variance of total tic severity showed that tic severity was significantly greater during the second week of methylphenidate treatment (20–25 mg twice daily) than during any of the placebo weeks or during the third week of methylphenidate treatment (35–45 mg twice daily) (P < 0.01). In the second and third cohorts of participants, there was no significant main effect of drug on tic severity.

With respect to other adverse events, appetite suppression with transient weight loss occurred in three children during methylphenidate treatment, and initial insomnia occurred in two children.

Methylphenidate Recommendation Grade: Strong, High Quality Evidence. Despite this recommendation, clinicians should warn patients that tics may worsen on initiation of methylphenidate therapy and with dosage increases. Randomized controlled trial data are available only for short acting methylphenidate, but clinical experience suggests that results with long acting formulations are similar.

DEXTROAMPHETAMINE

Castellanos' study[17] was a placebo-controlled cross-over study of dextroamphetamine that randomized 20 children into three cohorts. Each child received one of three different dosage titrations of dextroamphetamine over three weeks, including dosages of 5–7.5 mg, 12.5–15 mg, and 20–22.5 mg twice daily. In all cohorts, dextroamphetamine significantly decreased hyperactivity, as measured by teachers, but there was no significant interaction between drug and dose, indicating that additional improvements in hyperactivity were not observed for higher doses.

In the first cohort of 10 participants, tic severity was significantly greater during weeks two (12.5–15 mg twice daily) and three (20–22.5 mg twice daily) of dextroamphetamine treatment compared to the weeks on placebo (F = 3.50, 98.3% CI 4 to 36, P = 0.03). In the second cohort of six participants, there was no significant main effect of the drug on tic severity. In the third cohort of four participants, there was a trend that did not reach statistical significance for tic severity to be greater with dextroamphetamine.

Appetite suppression with transient weight loss occurred in four children on dextroamphetamine. Initial insomnia occurred in 10 children on dextroamphetamine.

Dextroamphetamine Recommendation Grade: Strong, Low Quality Evidence. Despite this recommendation, clinicians should warn patients that worsening of tics may occur, especially with higher doses (≥25 mg per day). Randomized controlled trial data are available only for short acting dextroamphetamine, but clinical experience with the long acting formulation suggests similar results.

CLONIDINE

In the Tourette Syndrome Study Group parallel group study of children randomized to clonidine, methylphenidate, clonidine plus methylphenidate, or placebo, the primary outcome was the change from baseline to week 16 in the ASQ, and the main secondary outcome was the change from baseline in the YGTSS.[10]

In comparison to placebo, a statistically significant treatment effect on the ASQ was observed with clonidine alone (3.3 points, 98.3% CI -0.2 to 6.8, P = 0.02) and with clonidine plus methylphenidate (6.3 points, 98.3% CI 2.8 to 9.8, P < 0.0001). YGTSS scores also significantly improved compared to placebo, with a statistically significant treatment effect observed for clonidine alone (10.9 points, 98.3% CI 2.1 to 19.7, P = 0.003) and for clonidine plus methylphenidate (11.0 points, 98.3% CI 2.1 to 19.8, P = 0.003).

Sedation was common in children receiving clonidine, with 48% of the clonidine-treated participants reporting this side effect compared to 14% of those treated with methylphenidate and 6% with placebo.

Singer's study was a three-arm cross-over study[18] comparing clonidine 0.05 mg four times daily to placebo and desipramine 25 mg four times daily. The authors did not define a primary outcome and presented data for only those scales showing significant changes. Clonidine did not show a significant difference compared to either placebo or desipramine on any of the outcome measures of ADHD and tic severity, with the exception of the nervous/overactive subscale of the Child Behaviour Checklist in a subgroup of boys aged 6 to 11 years, in which clonidine was superior to placebo. Specific side effects of treatment were not reported, but the authors did indicate that 28 of 34 children experienced at least one drug-related problem while taking clonidine, compared to 26 of 34 children during desipramine treatment and 15 of 34 children during the placebo phase.

Clonidine Recommendation Grade: Strong, Moderate Quality Evidence. Clinicians should be aware that based on clinical experience, clonidine appears to have less of an effect on ADHD symptoms compared to stimulants. Clonidine is unlikely, however, to worsen tics.

GUANFACINE

Scahill's study[21] was an eight-week parallel group trial of guanfacine versus placebo in 34 children; no primary outcome was defined. After eight weeks of treatment, guanfacine significantly reduced symptoms of ADHD and tics based on the total score of the ADHD Rating Scale completed by the teacher ($p < 0.01$)) and the YGTSS total tic ($p < 0.05$)).

There was no significant difference between the guanfacine and placebo groups in any side effects, including laboratory test results, weight, or cardiovascular parameters. One participant in the guanfacine group withdrew at week four of the study because of sedation.

Guanfacine Recommendation Grade: Strong, Moderate Quality Evidence. Clinical experience suggests that as with clonidine, guanfacine has less of an effect than stimulants on ADHD symptoms but is unlikely to worsen tics.

ATOMOXETINE

In Allen's parallel group study of atomoxetine[22] in 148 children (0.5 to 1.5 mg/kg/day), the primary stated objective was to test the hypothesis that atomoxetine does not worsen tics in participants with ADHD and a co-morbid tic disorder (non-inferiority trial). On the primary outcome of tic severity based on the YGTSS total tic score, atomoxetine was non-inferior to placebo after 18 weeks of treatment. The atomoxetine group showed a greater mean improvement in the YGTSS at endpoint (-5.5 ± 6.9) compared to placebo (-3.0 ± 8.7), but this difference was not statistically significant ($P = 0.06$). With respect to the secondary outcome of ADHD severity, children in the atomoxetine group had a mean decrease of 10.9 ± 10.9 points in their ADHD Rating Scale (parent version) total score, compared to a decrease of 4.9 ± 10.3 points in the placebo group ($P = 0.002$).

Rates of decreased appetite (16% versus 3%, P = 0.01) and nausea (16% versus 1%, P = 0.002) were significantly higher in participants treated with atomoxetine compared to placebo. The atomoxetine group showed a mean decrease of body weight at endpoint (-0.9 ± 1.9 kg) that was significantly different from the 1.6 ± 2.3 kg weight gain seen in the placebo group. Participants receiving atomoxetine also had a significant increase in heart rate (+8.3 ± 12.0 beats per minute) compared to the decrease in heart rate seen in the placebo group (-1.2 ± 12.7 beats per minute). Electrocardiography revealed a decrease in QT interval in the atomoxetine group versus a slight increase in the placebo group.

The proportion of children completing the entire 18-week study was low in both treatment groups: 34.2% in the atomoxetine group and 26.4% in the placebo group. Rates of discontinuation due to reported lack of efficacy were high in both groups, but higher with placebo (62.5%) than with atomoxetine (50%). The majority of discontinuations occurred at week 12 of the study, when self-reported clinical nonresponders were allowed to withdraw from the double-blind phase and enter an open label phase. Therefore, the high discontinuation rates may be a reflection not so much of patient satisfaction with treatment, but of a design flaw which created an incentive to discontinue blinded participation in order to ensure treatment with active drug.

Atomoxetine Recommendation Grade: Strong, Moderate Quality Evidence. Clinical experience suggests that atomoxetine has less of an effect than stimulants for ADHD symptoms; however, atomoxetine is unlikely to worsen tics.

DESIPRAMINE

Two studies evaluated desipramine in children with ADHD and a chronic tic disorder: Spencer's parallel group study of 41 children, comparing placebo to desipramine titrated weekly up to 3.5 mg/kg/day for six weeks,[20] and Singer's crossover study comparing desipramine to both placebo and clonidine.[18]

In Spencer's study[20] a primary outcome was not specified, although ADHD and tic severity were assessed using the ADHD Rating Scale and the YGTSS. Both ADHD and tic severity were significantly improved at week 6 compared to baseline in children treated with desipramine, but not in children who received placebo. The ADHD Rating Scale score decreased from 46 ± 5.9 points at baseline to 24 ± 12 points at week 6 (P < 0.001), and the YGTSS score decreased from 63 ± 18 at baseline to 43 ± 23 at week 6 (P < 0.001). There were no changes noted in measures of anxiety, obsessive-compulsive behaviours, or depression between the desipramine and placebo groups.

No serious adverse events were reported. Children treated with desipramine had significantly higher rates of appetite suppression compared to placebo (24% versus 0%, P < 0.02). Mild but statistically significant increases in diastolic blood pressure and heart rate also occurred in the desipramine treated participants.

Likewise in Singer's study[18] no primary outcome was defined, and the authors presented data only for those scales that showed significant changes. With respect to ADHD symptoms, desipramine was found to be superior to placebo (and clonidine) in the parent linear analogue scale for hyperactivity ($P < 0.05$), with a mean score of 32.8 ± 1.3 during desipramine treatment compared to 64.4 ± 0.6 during placebo treatment (and 51.6 ± 2.2 during clonidine treatment). The hyperactivity subscale of the Child Behaviour Checklist demonstrated a statistically significant drug effect only for male children aged 6 to 11 years with desipriamine compared to both clonidine and placebo ($P < 0.05$). Hyperactivity subscale scores were 68.6 ± 1.4 during desipramine treatment compared to 75.8 ± 1.0 during placebo treatment (and 70.7 ± 1.2 during clonidine treatment).

With respect to its effect on tic severity, desipramine was superior to both placebo and clonidine ($P < 0.05$) on the parent linear analogue scale. Mean scores were 30.0 ± 0.7 during desipramine treatment compared to 47.4 ± 1.8 during placebo treatment (and 41.4 ± 1.1 during clonidine treatment). Other measures of tic severity, including the Tourette Syndrome Severity Scale and the YGTSS, did not demonstrate significant differences between treatment groups.

Specific side effects of treatment were not reported. The authors stated that 26 of 34 children reported at least one drug-related problem during desipramine treatment, compared to 15 of 34 during placebo treatment and 28 of 34 during clonidine treatment.

Desipramine Recommendation Grade: Category X, Level 2. Although moderate quality evidence supports the benefits of desipramine for both ADHD and tics, concerns about its cardiac toxicity, including cases of sudden death, has led to its very limited use in children.

DEPRENYL

In Feigin's cross-over trial of deprenyl versus placebo,[23] the primary outcome measure for ADHD was the total score on the DuPaul ADHD scale, and the primary outcome measure for tics was the total score on the YGTSS. The primary analysis revealed no significant improvement on the DuPaul ADHD scale with deprenyl relative to placebo (mean improvement 1.3, 95% CI -2.7 to 5.3, $P = 0.50$). The YGTSS total score improved by a mean of 9.3 points with deprenyl relative to placebo, but this was significant at only a trend level (95% CI -0.4 to 19.0, $P = 0.06$). Nine of the 24 participants dropped out of the study before entering the second treatment period (six who had received deprenyl and three who had received placebo). Adverse events were not reported to have occurred more frequently with deprenyl than with placebo; however, the authors did not include a description of adverse events by treatment group.

Deprenyl Recommendation Grade: Strong Recommendation Against its Use, Moderate Quality Evidence. Available evidence suggests that deprenyl is not effective for the treatment of ADHD in children with tics.

TABLE 2 SUMMARY OF RECOMMENDATIONS

Medication	Recommendation Grade
Methylphenidate	Strong Recommendation, High Quality Evidence
Dextroamphetamine	Strong Recommendation, Low Quality Evidence
Clonidine	Strong Recommendation, Moderate Quality Evidence
Guanfacine	Strong Recommendation, Moderate Quality Evidence
Atomoxetine	Strong Recommendation, Moderate Quality Evidence
Desipramine	Category X Level 2
Deprenyl	Strong Recommendation Against Use, Moderate Quality Evidence

DISCUSSION

While data are still limited, the findings of this review suggest that a number of treatment options are available to treat children with tic disorders and co-morbid ADHD. All agents discussed in this review, with the exception of deprenyl, were effective in treating symptoms of ADHD in children with tic disorders. The results of Kurlan's study[10] suggest that methylphenidate and clonidine have similar efficacy in treating symptoms of ADHD, and their combination is superior to either treatment alone. This finding may be seen as contrary to clinical experience, which has traditionally proposed that stimulants are more effective than alpha agonists in treating ADHD symptoms.[24] One explanation for the unexpected finding may be that the methylphenidate doses used in the study were relatively low. In Singer's study,[18] desipramine was superior to clonidine for the treatment of ADHD symptoms. This trial, however, has limited applicability for two reasons. First, given that it can take a few months for the effects of clonidine to become apparent, a six week trial of this medication may not have been adequate to evaluate its efficacy. Second, desipramine is now used only rarely in children because of concerns about cardiac toxicity, including the risk of sudden death.[25]

Tics do not appear to worsen with alpha agonists, and the majority of studies reported an improvement in tic severity with these agents. The effect of atomoxetine on tic severity was non-inferior to placebo.[22] The three studies of methylphenidate suggest that this drug does not worsen tics in the majority of children when moderate doses are used. The only study of dextroamphetamine on tic symptoms[17] found worsening of tics during the second (12.5–15 mg twice daily) and third weeks (20–22.5 mg twice daily) of dextroamphetamine treatment compared to the weeks on placebo. As treatment with dextroamphetamine was for only three weeks, however, it is unknown if worsening of tic symptoms would have resolved over time. Furthermore, the higher doses used in this study are on the high end of what is used in clinical practice, and no additional benefit for ADHD symptoms was

observed with the higher doses compared to the lower dose (5–7.5 mg twice daily), which did not worsen tics. Taken together, the results from this single study suggest that lower doses of dextroamphetamine could be considered when treating children with co-morbid ADHD and tics.

Despite the clinical relevance of the findings described, it should be kept in mind that only a moderate number of randomized controlled trials have assessed pharmacological treatments for ADHD in children with tic disorders, and the number of trials for each individual agent is small. Furthermore, no trials have been conducted with long-acting stimulants, long-acting alpha agonists, or other ADHD medications such as bupropion or modafinil. The evidence is also limited by the short duration of all trials reviewed, as well as other important methodological concerns. Many of the trials were small, selective outcome reporting was occasionally an issue, and reporting of results from cross-over trials was generally poor (no study presented paired data for analysis).

Given the methodological difficulties inherent in comparing effect sizes across studies with divergent inclusion criteria, efficacy measures, and designs, this review cannot provide evidence based recommendations for choosing among pharmacological treatment options. Stimulants have generally been found to provide the most reliable and robust response for ADHD symptoms, but their use in patients with tic disorders has been controversial because of concern, based on decades old case reports and case series, that they might exacerbate tics. This review of randomized controlled trials supports the efficacy of stimulants for ADHD symptoms in patients with tic disorders. Furthermore, short-term use of stimulants at moderate doses has not been found to worsen tics on average. Little information is available, however, regarding the long-term effects of stimulants on tics, and in fact no long-term trial qualified for this review. It should also be kept in mind that stimulants may cause tic exacerbation in individual patients, and this risk appears to be greater at higher doses. In these instances, atomoxetine or an alpha agonist may be used instead, or adding an alpha agonist to the stimulant may be considered. Although desipramine has been found to have benefits for tics as well as ADHD symptoms, safety concerns will likely continue to limit its use.

APPENDIX 1 ALLEN 2005

Methods	Subject received atomoxetine 0.5 to 1.5 mg/kg per day or placebo for 18 weeks under double blind conditions. Parallel group study.
Participants	Children 7 to 17 years meeting DSM-IV criteria for ADHD and TS or chronic motor tic disorder • Mean age 11.2 years • N = 148 • 131 boys, 17 girls
Interventions	Atomoxetine 0.5 to 1.5 mg/kg per day or placebo, administered in a divided dose, once in the morning and once in the late afternoon.

APPENDIX 2 CASTELLANOS 1997

Methods	Double blind, placebo-controlled cross-over study of methylphenidate and dextroamphetamine for 3 weeks each.
Participants	Children meeting DSM-IIIR criteria for ADHD and Tourette Syndrome • Mean age 9.4 years • N=22, all boys
Interventions	Methylphenidate 15 mg (low), 25 mg (medium) and 45 mg (high), dextroamphetamine 7.5 mg (low), 15 mg (medium) and 22.5 mg (high) and placebo. Doses were given twice daily at breakfast and lunch for a one week period. One group of 12 boys was given drug dosages in a low, medium, high sequence for one week each. One group of 6 boys was given drug dosages in a low, medium, medium sequence for one week each. One group of 4 boys was given drug dosages in a low, high, high sequence for one week each.

APPENDIX 3 FEIGIN 1996

Methods	Randomized, double blind, placebo-controlled crossover study. Two 8-week treatment periods separated by 6 week washout period.
Participants	Children 7 to 16 years meeting DSM-IIIR criteria for Tourette Syndrome and ADHD • Mean age 12 years • N=24 • 21 boys, 3 girls
Interventions	Deprenyl 5 mg twice daily or placebo for 8 weeks, followed by cross-over to the alternate treatment after a washout period of 6 weeks.

APPENDIX 4 GADOW 2007

Methods	Participants received placebo and three doses of methylphenidate (0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg) for 2 weeks each under double-blind conditions. Cross-over study.
Participants	Children 6 to 12 years meeting DSM-IIIR or DSM-IV criteria for ADHD and chronic motor tic disorder or TS • Mean age 8.9 years • N = 71 • 57 boys, 14 girls
Interventions	Methylphenidate 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg and placebo for two weeks each. Medication was administered twice daily, 3.5 hours apart, 7 days per week.

APPENDIX 5 SCAHILL 2001

Methods	Randomized, placebo-controlled study of guanfacine versus placebo for 8 weeks. Parallel group.
Participants	Children 7 to 15 years meeting DSM-IV criteria for ADHD and a chronic tic disorder. • Mean age 10.4 years • N = 34 • 31 boys, 3 girls
Interventions	Guanfacine 1.5 to 3 mg day or placebo, divided into 3 daily doses, for 8 weeks

APPENDIX 6 SINGER 1995

Methods	Randomized, placebo-controlled cross-over study of clonidine and desipramine.
Participants	Children 7 to 14 years meeting DSM III-R criteria for Tourette Syndrome and ADHD • Mean age 10.6 years • N = 34 • 31 boys and 3 girls
Interventions	Clonidine 0.05 mg four times daily for six weeks Desipramine 25 mg four times daily for six weeks Placebo four times daily for six weeks One week washout period between treatments

APPENDIX 7 SPENCER 2002

Methods	Double-blind parallel-group trial of desipramine versus placebo.
Participants	Children 5 to 17 years with DSM-IV diagnosis of ADHD and Tourette Syndrome or chronic motor tic disorder Mean age of overall sample not provided; 10.6 years for desipramine treated children, 11.3 for placebo treated children • N = 41 • 34 boys, 7 girls
Interventions	Desipramine 3.5 mg/kg or placebo given twice daily for six weeks.

APPENDIX 8 TS STUDY GROUP 2002

Methods	Randomized, controlled, parallel-group study of clonidine, methylphenidate, clonidine plus methylphenidate or placebo.
Participants	Children 7 to 14 years meeting DSM-IV criteria for ADHD and a chronic tic disorder • N = 136 • Mean age not provided for entire sample; 9.7 years placebo, 10.7 methylphenidate, 9.7 years clonidine, 10.6 years clonidine plus methylphenidate • 85% male
Interventions	Flexible dose, administered two to three times per day for 16 weeks Mean dose clonidine 0.25 mg per day (alone) 0.28 mg per day (with methylphenidate) Mean dose methylphenidate 25.7 mg per day (alone) 26.1 mg per day (with clonidine)

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CHAPTER VI

Pharmacotherapy of Obsessive-Compulsive Disorder *in Individuals with Co-Morbid Tic Disorders*

Lundy Day, Daniel Gorman, & Tamara Pringsheim

BACKGROUND

High rates of psychiatric co-morbidities exist in individuals with Tourette syndrome (TS) and tic disorders. In a large Swedish school population, Khalifa reported that one or more co-morbid conditions were present in 92% of children with TS.[1] Two of the most common are obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) with several studies reporting a higher frequency of these disorders in children and adolescents with tics compared to those without.[2–5] With respect to OCD in particular, prevalence estimates in individuals with tics or TS have ranged from 11 to 42%.[1–4,6] These rates were higher in individuals with TS compared to other tic disorders, and in one study they were higher in children compared to adults.[6] Clinically, it is often challenging to distinguish compulsions from complex tics, as they can appear similar and certain behaviours may have aspects of both. In general, however, compulsions are more elaborate and often serve to relieve anxiety associated with an obsession, whereas tics tend to be performed in response to a feeling of physical tension or "premonitory urge."

Given that OCD is highly co-morbid with tics and often causes considerable distress and psychosocial impairment,[7] we performed a systematic review on the treatment of OCD in individuals with co-morbid tic disorders. This chapter focuses specifically on pharmacotherapy.

METHODS

We performed a systematic review on the pharmacological treatment of obsessive-compulsive disorder in individuals with tics. Using highly sensitive search strategies, we searched MEDLINE (1950 to October 2010) and EMBASE (1980 to October 2010) for all systematic reviews, randomized controlled trials, and prospective open-label studies on the treatment of OCD in children and adults. Abstracts were independently reviewed by two reviewers for all relevant articles on the treatment of OCD. Reviewers also searched for abstracts of relevant articles on the treatment of OCD in individuals with co-morbid tic disorders.

Where possible, we used existing published systematic reviews and treatment guidelines on the treatment of OCD in children and adults to evaluate treatment effects. These systematic reviews on the treatment of OCD were also reviewed and their references searched for any studies pertaining specifically to individuals with OCD and a co-morbid tic disorder. All studies included in the systematic reviews were read in detail by two reviewers to assess whether subjects with co-morbid tics were included, and if so, the proportion of these subjects in the sample. We also assessed whether an analysis was performed to evaluate the influence of co-morbid tics on OCD treatment outcomes. We focused on randomized controlled trials (RCTs) and prospective open-label studies, but because such data were limited, we also searched for retrospective open-label studies and case series.

All identified RCTs, systematic reviews, and meta-analyses, as well as a clinical practice guideline, were independently graded for quality. Using pre-designed, standardized forms, two reviewers abstracted data from the prospective open-label studies and RCTs pertaining to the treatment of tic-related OCD. The primary outcome evaluated was the treatment effect for obsessive-compulsive behaviors. Secondary outcomes included the treatment effect for tics as well as adverse events. Criteria developed by the USPSTF were used to evaluate the methodological quality of the RCTs, with studies rated as good, fair, or poor.[8] The AMSTAR tool,[9] which includes an 11-point rating scale, was used to rate the quality of the systematic reviews and meta-analyses. The AGREE appraisal instrument[10] was used to evaluate the methodological quality of the clinical practice guideline. AGREE requires ratings in six individual categories (scope and purpose, stakeholder involvement, rigour and development, clarity and presentation, applicability, and editorial independence), and based on these ratings an overall rating is provided: strongly recommend, recommend (with provisos or alterations), would not recommend, or unsure. In all instances, the two reviewers compared their completed data abstraction and quality/rating forms and reached agreement by discussion.

The systematic review of the literature was presented at a consensus group meeting attended by 14 experts in psychiatry, child psychiatry, neurology, pediatrics, and psychology. Based on this review and using the GRADE system,[11] pharmacotherapy recommendations for tic-related OCD were proposed separately for adults and children, and consensus was reached through group discussion. In accordance with GRADE, the quality of evidence supporting the use of a given medication was graded as high, moderate, low, or very low. In addition, the strength with which the medication can be recommended was graded as weak, strong, or category X. A weak recommendation was given if the benefits were thought to be closely balanced with the risks and burdens, and the best action may differ depending on the circumstances. A strong recommendation was given if the benefits clearly outweigh the risks and burdens and apply to most patients in most circumstances without reservation. Although category X is not part of the original GRADE system, we created it for situations where evidence was insufficient to make a formal recommendation. Please see Table 1 for a description of the GRADE categories.

RESULTS

Our search strategy for articles on the treatment of obsessive compulsive disorder yielded 6983 abstracts. Two reviewers independently searched the abstracts for any guidelines, systematic reviews, or RCTs on the treatment of OCD, yielding 277. They also searched the abstracts for any article mentioning co-morbid tic disorders, yielding 27. References of reviews and RCTs were searched for any studies mentioning OCD with co-morbid tics. We identified eight systematic reviews and meta-analyses on the treatment of obsessive-compulsive disorder in adults and children. Three of these reviews are not included in this chapter, as they address treatment with cognitive behavioural therapy (CBT) exclusively. The five remaining systematic reviews included 47 studies, each of which was searched for the proportion of individuals with tics. Twenty-one of these articles did not mention tics or excluded all individuals with tics, leaving 26 studies that addressed pharmacotherapy for tic-related OCD.

TABLE 1 GRADE RECOMMENDATIONS

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation, can apply to most patients in most circumstances without reservation
Strong recommendation, low-quality or very low- quality evidence	Benefits clearly outweigh risk and burdens	Strong recommendation but may change when higher quality evidence becomes available
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Very weak recommendation; other alternatives may be equally reasonable
Category X1, no recommendation		Insufficient evidence to make a formal recommendation; requires further study.
Category X2, no recommendation		Insufficient evidence to make a formal recommendation; controversial, costly, or unavailable for clinical use

TREATMENT OF ADULT OCD

We included one guideline on the treatment of OCD in adults[12] and a more recent systematic review evaluating the use of antipsychotic medications in this population.[13] In addition, we included two earlier systematic reviews on antipsychotics for adult OCD[14,15] because they specifically address the issue of whether co-morbid tics influence treatment outcomes.

An American Psychiatric Association clinical practice guideline was published in 2007 to outline treatment recommendations for adult patients with obsessive-compulsive disorder.[12] This guideline provided little information specific to the treatment of tic-related OCD. With respect to pharmacotherapy, their general recommendation was to treat OCD symptoms with serotonin re-uptake inhibitors (SRIs). They also noted that patients with co-morbid chronic motor tics or TS who do not respond to an SRI might benefit from the addition of a first- or second-generation antipsychotic (SGA). Two authors evaluated this guideline separately using the AGREE tool, and they resolved any discrepancies through discussion. Overall, the guideline received a rating of "recommend".

The most recent systematic review of the treatment of adult OCD with SGAs was performed by Komossa.[13] This review received an AMSTAR rating of 10 points (out of 11). The authors included 11 short-term RCTs with a total of 396 patients, aged 18 years and older, who had mostly treatment-resistant OCD. The duration of the trials ranged from 6 to 16 weeks. RCTs with only 3 SGAs were identified: olanzapine (2 trials), quetiapine (5 trials), and risperidone (4 trials). All trials examined the effects of an SGA as an adjunct to an antidepressant (AD); no trial of an SGA versus an AD as monotherapy was found. The primary outcome assessed was failure to respond to treatment, defined as <25% reduction in OCD symptom severity.

Komossa included two trials with a total of 70 patients evaluating olanzapine plus AD versus placebo plus AD.[16,17] Doses of olanzapine ranged from 5 to 20 mg/day. No significant differences in efficacy outcomes were found between adjunctive olanzapine and placebo. The authors indicated that insufficient data exists to make any judgment regarding adjunctive treatment with olanzapine in adults with OCD.

Five trials including 219 patients treated with adjunctive quetiapine and AD versus placebo and AD were also included in the review.[18–22] Doses of quetiapine ranged from 200 to 600 mg/day. There was no significant difference between quetiapine and placebo on the primary outcome, but very limited data suggested some benefits. These benefits must be weighed against worse overall tolerability (especially sedation and weight gain) with adjunctive quetiapine compared to AD monotherapy.

Finally, four trials of 103 patients treated with risperidone plus AD versus placebo plus AD were included in the review.[23–26] Doses of risperidone ranged from 0.5 mg/day to 2.25 mg/day. Although no benefits from risperidone were found based on the mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, risperidone was superior to placebo based on the primary outcome measure (defined as failure to demonstrate a reduction in OCD symptom severity of at least 25% as measured by a validated scale). Risperidone may have also provided some benefit

for anxiety and depressive symptoms. These studies were limited in that side effects were insufficiently reported, especially regarding weight gain. Overall, limited data suggest that risperidone augmentation may be efficacious, but it is associated with decreased tolerability.

Komossa concludes that the quality of evidence for adjunctive SGAs in the treatment of adult OCD is low, and that while limited evidence supports the efficacy of quetiapine or risperidone, this must be weighed against the adverse effects associated with these medications. A limitation of this review, however, is that it does not address whether the presence of tics influences treatment outcome. This possibility is plausible given that antipsychotics are efficacious for treating tics, and compulsions often overlap with tics in individuals with tic disorders.

Following publication of Komossa's systematic review, two RCTs of aripiprazole augmentation for adults with treatment-resistant OCD were published.[27,28] Two reviewers independently assessed these for quality as well. Muscatello examined aripiprazole augmentation of a selective serotonin re-uptake inhibitor (SSRI) or clomipramine in a RCT of 40 patients aged 20 to 70 years.[27] Individuals were randomized to a daily dose of aripiprazole 15 mg or placebo for 16 weeks. Aripiprazole augmentation of SRIs was well tolerated and resulted in a significant reduction in obsessive-compulsive symptoms compared to placebo based on the Y-BOCS total score (p=0.001). This RCT was given a quality rating of fair given the large proportion of drop-outs from the study (25%). Selvi performed an 8-week single-blind active comparator trial of SGA augmentation in OCD patients who were non-responders to 12 weeks of SSRI monotherapy.[28] Forty-one patients aged 18 to 65 were randomized to risperidone (3 mg/day) or aripiprazole (15 mg/day). Both groups showed a significant reduction in obsessive-compulsive symptoms after antipsychotic augmentation compared to baseline ($p<0.05$). Patients treated with risperidone, however, showed significant improvement compared to aripiprazole in the Y-BOCS obsessions score and total score ($p<0.05$). This study was limited in that it did not address adverse effects, and it was rated as poor because outcome assessment was not blinded and it was unclear if an intention to treat analysis was performed.

ANTIPSYCHOTIC AUGMENTATION FOR OCD: DOES THE PRESENCE OF TICS MATTER?

Two systematic reviews of antipsychotic augmentation in adults address the influence of co-morbid tics on OCD outcomes.[15,29] Although these reviews are less recent than that performed by Komossa, we feel they are worth discussing because of their attention to this issue.

Bloch performed a systematic review and meta-analysis of antipsychotic augmentation in adults with treatment-resistant OCD,[29] and it received an AMSTAR rating of 11 out of 11. Five out of nine double-blind, randomized, placebo-controlled, high quality trials included OCD patients with co-morbid tic disorders.[17,18,24,26,30] Overall, 46 of the 278 participants that contributed to the meta-analysis had tics. Only one of the included trials[30] had an adequate sample size (n=34) to evaluate the influence of co-morbid tics on treatment response for OCD. In this trial, McDougle reported a significantly greater response rate to haloperidol in patients with OCD and co-morbid tics compared to those without tics. The meta-analysis supported this result despite the limited data, finding that the number needed to treat in

patients with OCD and co-morbid tics was 2.3 versus 5.9 in OCD patients without tics. This evidence suggests that antipsychotic augmentation may be especially beneficial in treatment-resistant OCD patients with co-morbid tic disorders, although the meta-analysis is limited in that the adverse effects of antipsychotics are not addressed. Furthermore, a meaningful treatment response to antipsychotic augmentation was observed in only 1/3 of patients, and a comparable response rate (26%) was found with continued SRI monotherapy. Taken together, these findings suggest that patients should be treated with at least three months of SRI therapy at the maximum tolerated dose before an antipsychotic is added.

Skapinakis also conducted a meta-analysis of antipsychotic augmentation of SRIs for treatment-resistant OCD in adults.[15] This meta-analysis was given an AMSTAR rating of 7 out of 11. Studies were stratified according to whether they included patients with co-morbid tic disorders, and five out of 10 RCTs did.[17,18,20,26,30] These five studies included a total of 176 participants treated with haloperidol (mean dose 6.2 mg/day), risperidone (mean dose 2.2 mg/d), olanzapine (mean dose 6.1 mg/day), and quetiapine (mean dose 168.7 in one study and 215 mg /day in another). Responder status was the primary outcome assessed. In the overall meta-analysis, antipsychotic augmentation was associated with a higher response rate than placebo. In contrast with the findings of Bloch, however, studies that included patients with co-morbid tics had a smaller and non-significant response rate ratio. On the other hand, higher antipsychotic doses were associated with higher response rates in general, and the association was more pronounced in studies that included patients with tics. Indeed, in the three studies that included patients with tics and used a low dose of antipsychotic, the combined response rate did not differ significantly from placebo. While the data are very limited, these results suggest that patients with co-morbid tics may require higher antipsychotic doses to achieve response for OCD symptoms.

PEDIATRIC OCD

We reviewed 4 meta-analyses of pharmacological treatment of pediatric OCD.[31–34] All of these analyses were evaluated by two independent reviewers using the AMSTAR tool.

Geller performed a meta-analysis on 12 RCTs that included a total of 1044 children and adolescents, aged 6 to 19 years, who had OCD and were treated with an SSRI or clomipramine.[31] The analysis received an AMSTAR rating of 5 points out of 11. Fluoxetine was evaluated in three studies,[35–37] paroxetine in two studies,[38,39] fluvoxamine[40] and sertaline[41] in one study each, and clomipramine in five studies.[42–46] The duration of the trials ranged from 8 to 16 weeks. Pooled effect results showed that each medication was significantly better than placebo or comparator treatments ($p<0.001$), and the pooled standardized mean difference for all studies was 0.46. While all SSRIs were comparably effective, clomipramine was significantly superior to each SSRI ($p=0.002$). Adverse effects were not addressed in the analysis.

Bridge performed a meta-analysis to assess both the efficacy of antidepressants and their risk of inducing suicidal ideation or behaviour in the treatment of pediatric major depressive disorder, obsessive-compulsive disorder, and non-OCD anxiety disorders.[32] This analysis received an AMSTAR rating of 9 out of 11. Six RCTs studied SSRIs for OCD in a total

of 718 children and adolescents aged 6 to 18 years. The specific SSRIs investigated were sertraline (two studies),[41,47] fluoxetine (two studies),[35,37] fluvoxamine (one study)[40] and paroxetine (one study).[48] Study duration ranged from 8 to 13 weeks. With respect to treatment response, the authors reported a significant risk difference of 20% favouring SSRIs (52%) over placebo (32%). Furthermore, a medium effect size of 0.48 was found for SSRIs. The rate of suicidal ideation or suicide attempt did not differ significantly between SSRIs and placebo in the OCD trials; however, when all trials were pooled across all indications (including major depression and non-OCD anxiety disorders), a significant risk difference of 0.7% with SSRIs was found, yielding a number needed to harm of 143. No other adverse effects were evaluated in the meta-analysis.

Watson performed a meta-analysis on 13 RCTs for the treatment of pediatric OCD, including studies of both pharmacotherapy and CBT.[33] This analysis received an AMSTAR rating of 5 out of 11 points. Ten of the trials in the analysis involved antidepressants, specifically sertraline (two studies),[41,47] paroxetine (two studies),[39,48] fluoxetine (three studies),[35–37] fluvoxamine (one study),[40] and clomipramine (two studies).[42,45] The duration of these trials ranged from 8 to 16 weeks, and the mean age of the participants ranged from 11.3 to 14.5 years. Compared to placebo, the overall effect size of antidepressant treatment for OCD symptoms was 0.48. The effect sizes for the individual medications ranged from 0.31 (fluvoxamine) to 0.85 (clomipramine), and the effect was statistically significant for each one except fluvoxamine (p=0.09). The analysis did not address adverse effects.

Ipser performed a systematic review and meta-analysis on 22 RCTs of pharmacotherapy for a range of pediatric anxiety disorders.[34] This review received an AMSTAR rating of 11 out of 11. Eleven trials included children or adolescents with a primary diagnosis of OCD, and a post-hoc analysis of seven of these trials compared the effect of medication versus placebo on OCD symptom severity based on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). The analysis included 765 youths aged 6 to 17 years who were treated with an SSRI or clomipramine for 8 to 13 weeks. Pharmacotherapy resulted in an overall decrease of 4.5 points on the CY-BOCS. Results for each agent were as follows: two trials in a total of 146 patients treated with fluoxetine 20-80 mg/day resulted in a 5.5 point reduction;[35,37] one trial in 120 patients treated with fluvoxamine 50-200 mg/day resulted in a 2.7 point reduction;[40] one trial in 196 patients treated with a mean dose of paroxetine 30.1 mg/day resulted in a 3.4 point reduction;[48] two trials in a total of 243 patients treated with a mean dose of sertraline 167-170 mg/day resulted in a 3.8 point reduction;[41,47] and one trial in 60 patients treated with clomipramine 25-200 mg/day resulted in an 8.9 point reduction.[42] These results replicate the finding by Geller and Watson that clomipramine has a greater effect than SSRIs for pediatric OCD symptoms; however, in the Ipser analysis, the result for clomipramine is based on a single small trial.[42] Four clomipramine studies included in Geller[43–46] and one clomipramine study included in Watson[45] were deemed ineligible for inclusion by Ipser. Overall, results of this meta-analysis suggest that short-term therapy with an SSRI or clomipramine can help reduce OCD symptoms in children and adolescents, and the medications are generally well tolerated. Nevertheless, evidence for long-term efficacy is lacking and the value of treatment should be weighed against possible side effects and risks.

The four meta-analyses described are limited in that they provide very little information about the influence of co-morbid TS or tics on OCD treatment outcomes. We searched all studies included in the meta-analyses for the proportion of children or adolescents with a co-morbid tic disorder. One of the following limitations was found, however, for each study: TS could not be the primary diagnosis; patients with TS or other tic disorders were excluded; the proportion of patients with co-morbid tics was small; information about co-morbid tics was not reported.

PHARMACOTHERAPY DATA FOR TIC-RELATED OCD

Our search for pharmacotherapy studies specific to tic-related OCD yielded a handful of case reports,[49–52] two retrospective studies,[53,54] five prospective open-label trials,[39,55–58] and three RCTs. [4,59,60]

Overall, the case reports and retrospective studies suggest that SSRIs and clomipramine may be beneficial for OCD symptoms in patients with co-morbid tics, although the benefits may not be as great as in patients without tics. Eapen performed an open retrospective study of fluoxetine 20-60 mg/day in 30 children and adults with TS and obsessive-compulsive behaviours.[54] After 12 weeks, 76% of individuals showed an overall improvement based on the Clinical Global Impression scale for obsessive-compulsive symptomatology. In a retrospective case-control analysis, McDougle compared treatment with fluvoxamine in 33 adults with OCD and a co-morbid chronic tic disorder versus 33 adults with OCD but no tics.[53] Patients were treated with fluvoxamine at a mean dose of 284.1mg/day for eight weeks. Both groups showed a significant improvement in obsessive-compulsive symptoms, but the mean reduction in Y-BOCS score was significantly greater in patients without co-morbid tics (32%) compared to those with tics (17%) ($p<0.03$). Similarly, the proportion of patients who met response criteria was significantly greater in the group without tics (52%) than in the group with tics (21%) ($p<0.02$).

Five prospective open-label trials also support the efficacy of SSRIs or clomipramine for tic-related OCD. Como evaluated fluoxetine 20 or 40 mg/day in 32 individuals aged 6 to 42 years with TS and OCD.[55] After approximately four months of treatment, both children ($p=0.001$) and adults ($p=0.01$) showed significant improvement in obsessive-compulsive symptoms based on the Leyton Obsessional Inventory, and 81% of the entire sample reported subjective improvement. Husted evaluated fluoxetine as well, dosing it up to 40 mg/day for eight weeks in 71 adults and 3 adolescents with OCD.[56] Outcomes were compared in 13 patients with co-morbid tics versus 61 patients without tics. The two groups had a significant ($p<0.0001$) and similar decrease in Y-BOCS scores, with approximately one-quarter showing clinically meaningful improvement. In a small pediatric study, Riddle evaluated fluoxetine 10 or 40 mg/day for 4–20 weeks in 10 youths aged 8-15 years with OCD.[57] Four children with primary OCD were compared to six children with TS and co-morbid OCD. Half of the patients in each group were considered treatment responders, and those with TS showed no change in tic severity. In another pediatric study, Geller evaluated paroxetine 10-60 mg/day in 335 youths aged 8–17 years

with OCD, many of whom had at least one co-morbid condition.[39] The response rate was 55% in the 51 patients with co-morbid tics, but this was significantly lower than the 71% who responded in the entire sample (p=0.004). Finally, Yaryura-Tobias investigated clomipramine at a mean dose of 113.3 mg/day in 17 patients aged 5 to 52 years with TS and obsessive-compulsive symptoms.[58] Outcomes were evaluated based on clinical evaluation, self-assessment, and family reports, and overall the authors reported that clomipramine controlled 80-90% of symptoms.

Only three small RCTs have evaluated the efficacy of SSRIs, specifically fluoxetine and sertraline, for treating obsessive-compulsive symptoms in patients with co-morbid tic disorders. We evaluated these trials using the USPSTF criteria, and each was rated as poor because the small sample size resulted in inadequate power.[8] March[59] conducted a secondary analysis on the influence of tics in the Pediatric OCD Treatment Study[47], a 12-week RCT comparing sertraline, CBT, the combination of sertraline and CBT, and placebo in 112 youths aged 7–17 years with OCD. In the entire sample, decreases in CY-BOCS scores were significantly greater with each of the three active treatments compared to placebo, and with combination treatment compared to each monotherapy. Only 17 subjects had a co-morbid tic disorder, and in this subsample the results were similar except that sertraline was not significantly better than placebo. Scahill performed a 20-week, double-blind, placebo-controlled, crossover trial of fluoxetine 20 mg/day in 11 patients aged 8-33 years with TS and obsessive-compulsive symptoms.[60] Only eight of these patients completed at least part of the crossover phase, and in this small group a trend was found favouring fluoxetine over placebo for obsessive-compulsive symptoms (p=0.06). Fluoxetine had no significant effect, however, on tics. Kurlan performed a four-month, double-blind, placebo-controlled, parallel-group trial of fluoxetine 20–40 mg/day in 11 boys aged 10–18 years with TS and obsessive-compulsive behaviours.[4] Improvement in OCD symptoms did not differ between the two groups, while tic severity measures generally showed a trend favouring fluoxetine.

PHARMACOLOGICAL RECOMMENDATIONS FOR TIC-RELATED OCD

RECOMMENDATION FOR SSRIS IN ADULTS

Weak Recommendation, Low-Quality Evidence. While good evidence supports the efficacy of SSRIs to treat adults with OCD in general, the evidence is limited for patients with co-morbid tic disorders. Our consensus group has made a weak recommendation given that the benefits, risks, and burdens are closely balanced, and the best action may differ depending on the circumstances for each patient. Other treatment alternatives may be equally reasonable.

RECOMMENDATION FOR CLOMIPRAMINE IN ADULTS

Category X. While good evidence supports the efficacy of clomipramine to treat adults with OCD in general, the evidence is very limited for patients with co-morbid tic disorders. Our consensus group concluded that this evidence is insufficient to enable a formal recommendation.

RECOMMENDATION FOR ANTIPSYCHOTIC AUGMENTATION IN ADULTS

Weak Recommendation, Low-Quality Evidence. Limited evidence suggests that antipsychotic augmentation of an SRI may be beneficial in reducing treatment-resistant obsessive-compulsive symptoms in adults with co-morbid tic disorders. The studies do not, however, adequately address the adverse effects associated with this intervention. Our consensus group agreed on a weak recommendation, given that other alternatives may be equally reasonable.

RECOMMENDATION FOR SSRIS IN CHILDREN & ADOLESCENTS

Weak Recommendation, Low-Quality Evidence. While good evidence supports the efficacy of SSRIS to treat children and adolescents with OCD in general, the evidence is limited for patients with co-morbid tic disorders. Our consensus group has made a weak recommendation given that the benefits, risks, and burdens are closely balanced, and the best action may differ depending on the circumstances for each patient. Other treatment alternatives may be equally reasonable.

RECOMMENDATION FOR CLOMIPRAMINE IN CHILDREN & ADOLESCENTS

Category X1. While some evidence supports the efficacy of clomipramine to treat children and adolescents with OCD in general, the evidence is very limited for patients with co-morbid tic disorders. Our consensus group concluded that this evidence is insufficient to enable a formal recommendation.

RECOMMENDATION FOR ANTIPSYCHOTIC AUGMENTATION IN CHILDREN & ADOLESCENTS

Category X1. Only very limited evidence supports the efficacy of antipsychotic augmentation of an SRI in children and adolescents with treatment-resistant OCD and co-morbid tic disorders. Our consensus group concluded that this evidence is insufficient to enable a formal recommendation.

DISCUSSION

The main finding of this review is that evidence for pharmacological treatment of tic-related OCD symptoms is quite limited in both children and adults. Pharmacotherapy studies for OCD often exclude patients with co-morbid tics, and those that focus on tic-related OCD are few and of poor quality. In fact, we found only three RCTS of pharmacotherapy for tic-related OCD, including one secondary analysis and one crossover trial, and they involved a total of 39 patients.[4,59,60] While none of these trials found that SSRI treatment was significantly better than placebo, all three were underpowered and one found that the combination of an SSRI and CBT was superior to CBT alone.[59] A number of retrospective studies and prospective open-label trials do suggest that SSRIS and clomipramine may be beneficial for tic-related OCD; however, in two of the four studies that compared OCD outcomes in patients with and without co-morbid tics, those with tics showed less improvement.[53,61] Evidence supporting antipsychotic augmentation of SRIS for tic-related OCD is also modest, with all the RCT data limited to adults.[14,15]

Given the limited evidence on pharmacotherapy for tic-related OCD, clinicians must rely on research involving OCD patients who mainly do not have tics. Substantial evidence supports the efficacy of SRIs for uncomplicated OCD in both children[34,62–64] and adults,[12] but an important question is whether the presence of co-morbid tics influences pharmacotherapy outcomes. Ultimately this is an empirical question that requires further investigation, but it is at least plausible that pharmacological interventions could have different effects for tic-related OCD compared to OCD without tics. This is because a number of other differences have already been found between the two types of OCD. For example, tic-related OCD has an earlier age of onset and is more common in males, whereas OCD without tics is more likely to present later and is associated with an equal sex distribution or even female predominance.[65,66] Co-morbidity patterns also appear to differ, as studies have found that patients with tic-related OCD have higher rates of ADHD, other disruptive behaviour disorders, trichotillomania, and body dysmorphic disorder.[67,68] Finally, some evidence suggests that the two groups of patients tend to have different types of OCD symptoms.[65,66,69] Patients with tics appear to have more aggressive, sexual, religious, and symmetry-related obsessions, as well as counting, ordering, touching, blinking, hoarding, and self-damaging compulsions. Patients without tics, on the other hand, appear to have more obsessive-compulsive symptoms related to dirt, contamination, and cleaning. Given all these differences in the clinical presentation of OCD depending on the presence or absence of tics, it would not be surprising if response to medications were different as well.

The paucity of research on pharmacotherapy for tic-related OCD is striking given how frequently OCD is associated with tic disorders. In children and adolescents with OCD, prevalence estimates for a lifetime history of tic disorders have ranged from 26% to 59%.[70] Little information is available about rates of tic disorders in adult-onset OCD, but approximately 15% of adults with OCD, including child- and adult-onset cases, have been found to have a history of tics.[66,71] The association between OCD and tic disorders is also high in the other direction, with OCD occurring in approximately 40% of patients with TS.[2,7] In fact, family studies suggest that TS and child-onset OCD may represent variable phenotypic expressions of the same underlying illness, and the two conditions are thought to have a common neurobiological basis that involves disturbances in fronto-striatal circuits.[72] The presence of OCD in many patients with tic disorders is highly relevant clinically, as the OCD symptoms can account for considerable psychosocial impairment.[7] Indeed, for many patients with tic disorders, the focus of treatment is not on the tics, which are often mild and non-interfering, but on addressing symptoms of OCD, ADHD, and other associated conditions.[73] Therefore, the development of effective and safe treatments for tic-related OCD and other co-morbidities is of utmost importance.

AUTHORS' CONCLUSIONS

Treatment of co-morbid OCD in patients with tic disorders is a common clinical challenge, but evidence supporting pharmacological interventions is sparse for both children and adults. As a result, clinicians must rely primarily on studies that have been conducted in OCD patients who, for the most part, do not have tics. While such studies support the efficacy of SSRIs and clomipramine for OCD symptoms, it is unclear whether the results can be extrapolated to patients with tic-related OCD, and some evidence suggests that SSRIs

may be less beneficial in this population. Clearly, more research is required to determine whether tic status influences response to pharmacotherapy for OCD. In the meantime, we advocate a judicious approach to pharmacotherapy for OCD in patients with tic disorders. Medication treatment may be reasonable in certain circumstances, especially when OCD symptoms are severely impairing, but clinicians and patients should strongly consider starting with CBT. Particular caution is warranted with antipsychotic augmentation of an SRI, as evidence supporting this intervention is modest in adults and virtually non-existent in children. Moreover, antipsychotics are associated with significant adverse effects, including metabolic abnormalities, extrapyramidal symptoms, and tardive dyskinesia.

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