JPPT | State of the Art Review

A Review of the Current Treatment of Tourette Syndrome

Mary F. Seideman, PharmD and Travis A. Seideman, AA

Tourette syndrome is a hyperkinetic movement disorder that presents before age 18 years and involves motor and phonic tics that may present with a wide range of severity. The severity and presentation of tics in an individual may fluctuate over time. Tourette syndrome may affect social relationships and school attendance, and may result in depression. Comorbidities are common, with attention-deficit/hyperactivity disorder and obsessive-compulsive disorder being most common. The literature supporting optimal treatment is limited but provides a framework for clinical decision-making. The focus of this review is to discuss the symptoms and possible causes of Tourette syndrome and current non-pharmacologic and pharmacologic treatment options, to help practitioners optimize care for pediatric patients with this disease.

ABBREVIATIONS AAN, American Academy of Neurology; ADHD, attention-deficit/hyperactivity disorder; BTX, botulinum toxin A; CBIT, comprehensive behavioral intervention for tics; CDC, Centers for Disease Control and Prevention; CGI, Clinical Global Impression; CNS, central nervous system; DBS, deep brain stimulation; FDA, US Food and Drug Administration; PMU, premonitory urge; THC, δ-9-tetrahydrocannabinol; VMAT2, vesicular monoamine transporter type 2; YGTSS, Yale Global Tic Severity Scale.

KEYWORDS behavioral therapy; pediatrics; pharmacotherapy; tics; Tourette syndrome

J Pediatr Pharmacol Ther 2020;25(5):401–412

DOI: 10.5863/1551-6776-25.5.401

Introduction

Tourette syndrome, first described by Gilles de la Tourette in 1885, is a hyperkinetic movement disorder diagnosed when multiple motor tics and at least 1 phonic tic have persisted for more than a year since the original onset, although not necessarily concurrently. These tics must begin before age 18 years and must not be attributable to other causal factors.[1] A tic is considered a sudden, recurring motor movement or vocal sound without rhythm. Across the population with a diagnosis of Tourette syndrome, the degree of impairment varies, and the type and severity of tics experienced by an individual may fluctuate over time.[2] Some tics cause muscle fatigue and pain due to the repetitive nature of contractions and movements. Attempting to physically hide or control tics during school may interfere with the ability to focus on learning. The presence of tics may impair social relationships, prompt bullying, negatively affect school attendance, and increase the risk of depression, making diagnosis and treatment of Tourette syndrome important for the overall safety and well-being of the youth.[2,3–7] Comorbidities are common, including attention-deficit/hyperactivity disorder (ADHD; 54.3%) and obsessive-compulsive disorder (50.0%).[8] Unfortunately, current literature identifying the specific etiology and pathophysiology of Tourette syndrome is limited, which complicates selection of a definitive treatment and makes it difficult to achieve consistent results with therapy. This review will present current pharmacologic treatments for Tourette syndrome–associated tics and the chief non-pharmacologic options to assist practitioners in optimizing care for these pediatric patients.

Etiology

Currently, there are insufficient data to identify the exact cause of Tourette syndrome. Although it remains speculative, recent research has revealed that tic disorders, including Tourette syndrome, might share a genetic etiology.[9] Although the underlying mechanisms causing Tourette syndrome–related tics have not been conclusively elucidated, some studies have suggested the possible involvement of serotonin. Unfortunately, studies investigating this theory have involved small numbers of patients and/or the presence of comorbid obsessive-compulsive disorder, which have made it difficult to confirm a role for serotonin.[10,11] It has also been postulated that dopaminergic activity might play a key role in the pathophysiology of the syndrome, but data remain insufficient.[12,13]

Tourette syndrome–related tics are associated with a premonitory urge (PMU). These are described as an uncomfortable feeling of increased tension that precedes the onset of the tic and is temporarily relieved after the tic has subsided.[14] Premonitory urges are an important component of tics, but their importance and physiologic cause have not been fully elucidated. Neuroimaging has also revealed that the motor circuit involved in Tourette syndrome is the same circuit involved in normal voluntary behaviors. Irregular activity in these areas is presumed to be causal at this time. Tourette syndrome–related tics are likely induced by

a combination of PMU, neurohormonal imbalances, abnormal neural pathway activity, and an inability to regulate physical tic motions.[13]

Prevalence

The prevalence of Tourette syndrome is difficult to determine because of a variety of factors, including stringent diagnostic criteria, varied assessment methodologies, the need for patients or caregivers to acknowledge the existence of tics, and the need for access to health care. Both Bitsko et al[15] and the CDC,[16] in separate phone call–based studies, found that Tourette syndrome is diagnosed in about 2 to 3 per 1000 children aged 6 to 17 years, translating to a prevalence of 0.19% to 0.3% in the United States. Tourette syndrome is almost 3 times more prevalent in males than females and about 2 times more prevalent in youth aged 12 to 17 years than those aged 6 to 11 years. Most symptoms are rated as mild by family members, rather than moderate or severe. Both studies reported that non-Hispanic white children are more likely to receive a diagnosis of Tourette syndrome. The CDC study authors suggested that data collection might be skewed by lack of community awareness or limited access to medical care.[15,16]

Pharmacologic Options

Despite the relative lack of conclusive, well-powered efficacy and safety studies, a wide range of agents have been used to reduce the severity and frequency of Tourette syndrome–related tics. Studies are challenged by the complexity of the disorder, the periodic waxing and waning of symptoms, the presence of associated comorbidities (e.g., ADHD and obsessive-compulsive disorder), and the lack of definitive target receptors for treatment. Only 3 agents (i.e., haloperidol, pimozide, and aripiprazole) have been approved by the FDA for the suppression of Tourette syndrome–related tics.[17–19] However, the range of drugs clinically used is broader and includes the α_2 adrenergic agonists (i.e., clonidine and guanfacine), typical and atypical antipsychotics, and, in specific situations, botulinum toxin A (BTX). Combination treatment is often used if sufficient tic suppression cannot be obtained with a single agent; however, data to support this approach are lacking. Common oral medications used in Tourette syndrome–related tic suppression are noted in the Table.

Because of the lack of a universally effective treatment, additional treatment options, including antiepileptic drugs, vesicular monoamine transporter type 2 (VMAT2) inhibitors, and cannabinoids, have been suggested; however, all require more study. The neurologic effect of cannabinoids on children and adolescents precludes their use in these age groups.[20] In an attempt to provide recommendations for treatment approaches, The American Academy of Neurology (AAN) published practice guidelines in 2019. These guidelines stratified assessment of interventions labeled as "probably" or "possibly" more effective than placebo, which demonstrates the lack of definitive treatment data.[20] In the absence of firm recommendations, pharmacologic treatment is ultimately selected by using a combination of available data, individual provider experience and preference, the presence of comorbid diagnoses, lifestyle considerations, and the side effect profiles of various agents.

α_2 Adrenergic Agonists. *Clonidine.* Clonidine is a centrally acting imidazoline derivative that stimulates the α_2 adrenergic receptors in the locus coeruleus in the brain stem, causing a reduced sympathetic outflow from the CNS.[21] It is thought to reduce tics through the resultant decrease of norepinephrine release and turnover.[22] Clonidine offers a therapeutic option without the risks of drug-induced movement disorders that can be associated with antipsychotic drugs. However, evidence supporting the efficacy of clonidine is inconsistent and is often based on small numbers of patients.

The strongest support for the use of clonidine in tic suppression comes from 2 larger studies. In the first study, The Tourette's Syndrome Study Group[23] conducted a multicenter, double-blind clinical trial of 136 children (aged 7–14 years) with ADHD and chronic tic disorder. Patients were randomized to either clonidine alone, methylphenidate alone, clonidine in combination with methylphenidate, or placebo. Dosing was titrated during a 4-week period to attain a level of optimal school function with an acceptable level of side effects. The maximal daily allowable dose was 60 mg for methylphenidate and 0.6 mg for clonidine. Doses were initiated at once daily, then subsequently divided into 2 to 3 doses per day, as dosing increased. The study used the Yale Global Tic Severity Scale (YGTSS) and YGTSS total scores to assess the effect of treatment. The YGTSS is a widely used, semi-structured and clinician-rated measure of the severity of tic characteristics, including the number, frequency, intensity, complexity, and their interference with lifestyle.[5,22] YGTSS total scores combine the measured effect on motor tic, vocal tic, and overall improvements. In addition, changes in Clinical Global Impression rating scale scores (CGI), which provide a separate improvement rating and a summation of YGTSS subscores, were also reported. Compared with placebo, YGTSS scores were improved in all active treatment groups at 16 weeks. Significant improvements in YGTSS total scores were reported for clonidine alone ($p = 0.003$) and methylphenidate alone ($p = 0.003$) compared with placebo. For CGI scores from investigator observers, the proportion of patients with an improvement in tics compared with placebo was highest for combined methylphenidate and clonidine treatment (75.0%, $p = 0.0004$). Improvement in tics was reported in 66.7% of patients with clonidine alone ($p = 0.002$) and 44.4% with methylphenidate alone ($p = 0.21$). Similar consistency was observed in CGI scores

Table. Common Oral Medications for Tourette Syndrome–Related Tic Suppression[17–20,25]

Drug	Dosage Information	Side Effects*	Comments	Effect on Tic Severity[20]
Clonidine	Initiate at 0.05 mg nightly and increase by 0.05 mg every 3–7 days Usual range: 0.05–0.4 mg/day divided into 2–3 daily doses Maximum dose: 0.6 mg/day	Sedation, dry mouth, dizziness, decreased blood pressure, decreased heart rate, skin irritation (with patch)	May provide benefit for tics and ADHD symptoms when both conditions are present. Some patients may benefit from a trial of patch once stabilized on oral daily dose. Discontinue dose gradually to avoid rebound hypertension.	Probably more effective than placebo
Guanfacine	Initiate at 0.25–0.5 mg nightly; increase weekly Usual range: 1.5–4 mg/day divided twice daily Maximum dose: 4 mg/day	Sedation, dry mouth, dizziness, headache, fatigue, decreased blood pressure, decreased heart rate, QTc interval prolongation (extended-release formulation)	May provide benefit for tics and ADHD symptoms when both conditions are present. Monitor for QTc prolongation. Discontinue dose gradually to avoid rebound hypertension.	Possibly more effective than placebo
Haloperidol	Initiate at 0.5 mg daily; increase by 0.5 mg weekly Usual range: 0.05–0.075 mg/kg/day divided in 2–3 daily doses Maximum dose: 3 mg/day	Drowsiness, movement disorders	FDA approved for TS-related tics. Reserved for significant treatment-resistant tics. Taper off during the course of weeks to months to avoid the risk of withdrawal dyskinesia.	Probably more effective than placebo
Pimozide	Initiate at 0.05 mg/kg nightly; increase every 3 days Usual range: 0.05–0.2 mg/kg/day (2–4 mg/day) Maximum dose: 10 mg/day	Drowsiness, movement disorders, QTc prolongation	FDA approved for TS-related tics. Reserved for significant treatment-resistant tics. Monitor for QTc prolongation before and during pimozide treatment. Taper off during the course of weeks to months to avoid the risk of withdrawal dyskinesia.	Possibly more effective than placebo
Aripiprazole	Initiate at 2 mg/day; increase as needed to the maximum dose Usual dose: 5 mg (<50 kg) 10 mg (≥50 kg) Maximum dose: 10 mg/day if <50 kg or 20 mg/day if ≥50 kg	Sedation, fatigue, weight gain, movement disorders	FDA approved for TS-related tics. Reserved for when other agents have failed or are contraindicated. May have less risk of movement disorders than other antipsychotics listed. May have more risk of weight gain compared with haloperidol or pimozide. Taper off during the course of weeks to months to avoid the risk of withdrawal dyskinesia.	Probably more effective than placebo
Risperidone	Initiate at 0.5 mg nightly; increase as needed to 3 mg/day Usual range: 0.5–3 mg/day divided twice daily Maximum dose: 3 mg/day	Sedation, fatigue, dizziness, weight gain, movement disorders	Reserved for treatment not responding to other agents. May have more risk of weight gain compared with haloperidol or pimozide. Taper off during the course of weeks to months to avoid the risk of withdrawal dyskinesia.	Probably more effective than placebo

ADHD, attention-deficit/hyperactivity disorder; TS, Tourette syndrome

* All antipsychotics carry increased risks of movement disorders, weight gain, adverse metabolic effects, increased prolactin levels, and neuroleptic malignant syndrome, but tendencies vary by agent and dose.

reported by parent and teacher observers. Worsening of tics was no more frequent in those treated with methylphenidate (20%) versus those treated with either clonidine (26%) or placebo (22%). However, worsening of tics limited further dose increases in those assigned to receive methylphenidate alone (35%) more than those receiving combined methylphenidate and clonidine treatment (15%) or clonidine alone (18%). The authors noted that self-exclusion of patients previously experiencing tic worsening with methylphenidate might have skewed results. Overall, both study drugs were generally well tolerated, although moderate to severe sedation was reported in 28% of those taking clonidine. Incomplete reporting of data limited this study. In addition, the comorbid ADHD in the study population makes it difficult to generalize results to non-ADHD Tourette syndrome patients.

The second study supporting clonidine in tic suppression examined the use of clonidine transdermal patches. Clonidine patches pose an attractive alternative to oral treatment, with the potential for reduced sedation due to more consistent blood levels and possible improved compliance compared with multiple daily dosing.[22] In a randomized, double-blind, multicenter placebo-controlled trial, Du et al[24] studied the effectiveness and safety of clonidine patches on tic reduction. The study included 437 patients (aged 6–18 years) with chronic motor or vocal tic disorders (40%), transient tic disorder (5%), or Tourette disorder (55%). Patients were randomized to either the treatment group (clonidine patch, n = 326) or control group (placebo patch, n = 111) for 4 weeks. Clonidine was dosed as a 1-mg patch (>20 kg but ≤40 kg), a 1.5-mg patch (>40 kg but ≤60 kg), or a 2-mg patch (>60 kg weight). One-day overlaps were required from new patch initiation to old patch removal, with patches replaced weekly. YGTSS and CGI scores were used to evaluate the severity of symptoms at the start of the study and at 7, 14, and 21 days. The composition of the study groups did not differ significantly related to demographics or baseline data for tic types (vocal or motor), symptom severity (CGI score), heart rate, or blood pressure. A total of 280 patients (treatment group) and 101 patients (placebo group) completed all 4 weeks of the study, with a significant decrease in the overall YGTSS score demonstrated in the clonidine adhesive patch group ($p = 0.03$). At the end of 4 weeks, the difference in the overall response rate between the 2 groups was statistically significant ($p < 0.0001$), with 68.85% (treatment) and 46.85% (placebo) of patients responding. Conclusions regarding efficacy specifically in Tourette syndrome–related tics are limited because of the large number of study participants (45%) with non–Tourette syndrome-associated tics.

For Tourette syndrome–related tic suppression, oral clonidine has been initiated at 0.05 mg nightly, titrated by 0.05 mg every 3 to 7 days, as tolerated, to the minimal effective dose. A typical dose ranges from 0.3 to 0.4 mg/day.[25] With immediate-release tablets, total daily dosing can be divided into 2 to 3 doses per day or, with smaller doses of 0.1 to 0.2 mg/day, given as a single nighttime dose. Once the effective daily dose is identified, the patient can be converted to a transdermal patch, which might be a convenient option in some cases. The most commonly reported side effect with clonidine is sedation. Additional side effects may include dry mouth, drowsiness, dizziness, constipation, and decreased blood pressure. A decrease in pulse rate occurs to some degree in most patients receiving clonidine, but it does not impair exercise response. Skin irritation with the adhesive patch may occur and subsequently lead to allergic reaction when clonidine is taken orally.[21] Most side effects with clonidine are mild, dose related, and resolve with continued treatment or dose reduction. Dosing schedules should be optimized for individual patients to balance tic reduction and side effects. For example, in school-age youth, nighttime dosing may reduce classroom sedation. However, if effectiveness wanes during the day, divided dosing regimens may control tics more effectively during school, but they may also increase the risk for daytime sedation. The AAN guidelines list clonidine as probably more effective than placebo, and support that the treatment effect of clonidine appears to be larger in children with comorbid ADHD, with clonidine contributing to an improvement in both tics and ADHD symptoms.[20]

Guanfacine. Guanfacine, another α_2 adrenergic agonist, has also been used clinically in Tourette syndrome. Scahill et al[26] studied guanfacine versus placebo in an 8-week randomized, double-blinded, placebo-controlled trial of 34 children (ages 7–14 years) with tic disorders and comorbid ADHD. They reported a mean reduction in the YGTSS scores for tic severity of 31% with guanfacine (from 15.2 to 10.7) versus 0% reduction in the placebo group ($p = 0.05$). The guanfacine study dose ranged from 1.5 to 3 mg, most commonly dosed as 1 mg in the morning, 0.5 mg in the mid-afternoon, and 1 mg in the evening. Reported side effects included sedation, dry mouth, constipation, decreased morning appetite, and mid-sleep awakening. Study limitations included small sample size and patients with only mild to moderate tics. Despite the authors citing potential benefit of the long half-life of guanfacine (average 10–30 hours, 13–14 hours in younger patients),[27] doses in the study were administered 3 times per day.

In a small pilot study of 24 children (ages 6–16 years), Cummings et al[28] conducted a 4-week, double-blind, placebo-controlled study of the efficacy of guanfacine on tic severity and neuropsychiatric functioning parameters in tic disorders. Of the 24 children studied, 23 met criteria for Tourette syndrome. Guanfacine was started at 0.5 mg each evening, increasing weekly to a maximum of 1 mg twice daily. No significant difference ($p = 0.48$) was demonstrated in mean YGTSS scores

from baseline (guanfacine, 32.08; placebo, 32.22) to after treatment (guanfacine, 23.25; placebo, 28.92). The authors suggested that targeting lower dosing to minimize sedation might have contributed to the lack of effectiveness. In another study, extended-release guanfacine was compared with placebo by Murphy et al[29] in a multisite, 8-week, randomized, double-blind, control study of 23 boys and 11 girls (ages 6–17 years) with chronic tic disorder. Guanfacine was dosed initially as 1 mg every morning. In participants ≤25 kg, dosing advanced by 1 mg every 14 days with a maximum of 3 mg, whereas those >25 kg advanced every 7 days to a maximum of 4 mg. Dosing continued as daily or was divided into 2 daily doses. The study did not demonstrate a significant change in YGTSS scores with guanfacine (decrease score 23.6 ± 6.42, p = 0.08). The reported difference in positive response in CGI scores of 19% (3 of 16) with guanfacine versus 22% (4 of 18) with placebo was also not statistically significant (p = 1.0). Side effects included fatigue, dry mouth, drowsiness, irritability, headache, abdominal pain, and decreased appetite. QTc interval prolongation was reported in 2 patients, and it was determined to not be clinically significant per cardiologist review. The study excluded patients with known QTc prolongation. Conclusion regarding efficacy specifically in Tourette syndrome–related tic suppression is significantly limited by the small sample size and a study population with the broader classification of chronic tic disorder.

Guanfacine has been clinically used for tic suppression in Tourette syndrome, despite a lack of robust data, with expectations of α_2 adrenergic agonist effects with potentially less sedation than clonidine. Dosing can be initiated with 0.25 to 0.5 mg orally at bedtime, increasing weekly as tolerated to a maximum daily dose of 4 mg/day divided into 2 daily doses. The typical dosing range is 1.5 to 4 mg/day.[25] The most common side effects are sedation and dry mouth, but may include dizziness, headache, fatigue, and constipation. Side effects are generally mild, decreasing with continued treatment or dose reduction. Postmarketing cases of spontaneous mania and aggressive behavior have been reported.[27] The current AAN guidelines note that guanfacine is possibly more effective than placebo. Furthermore, the guidelines recommend that patients taking extended-release guanfacine who 1) have a cardiac history; 2) are concurrently taking QTc-prolonging drugs; or 3) have a family history of prolonged QTc syndrome must undergo QTc monitoring at baseline and during treatment.[20]

Antipsychotics. Two typical antipsychotics, haloperidol and pimozide, have been the traditional pharmacologic treatment for Tourette syndrome–related tic suppression.[30] However, concerns regarding the risk of movement disorders with these agents led to interest in the potential use of atypical antipsychotics, including aripiprazole and risperidone. The antagonism of serotonin 5-hydroxytryptamine type-2 receptors together with tic suppression effects of dopamine D-2 receptor antagonism is thought to reduce the risks of movement disorders with these newer agents.[31] Several other atypical antipsychotics, including olanzapine and quetiapine, have shown promise in small open-label trials and case reports; however, there is a lack of sufficient rigorous studies to assess the place for these agents in tic reduction in Tourette syndrome.

Haloperidol and Pimozide. Both haloperidol and pimozide are FDA approved to decrease Tourette syndrome–associated tic severity. Studies have attributed the tic reduction effects to the dopamine D2 receptor-blockade characteristics of these drugs.[32,33] Haloperidol is FDA approved for use in children ages ≥3 years, with a dosage of 0.05 mg/kg/day to 0.075 mg/kg/day divided into 2 or 3 daily doses. Dosages may be started at 0.5 mg/day, increasing by 0.5 mg per dose at weekly intervals as tolerated to the minimal effective dose.[17] Pimozide is FDA approved for children ages ≥12 years.[18] Dosing can be initiated at 0.05 mg/kg at bedtime, increasing as tolerated every third day to a maximum of 0.2 mg/kg daily, not to exceed 10 mg per day. A typical dosing range for pimozide is 2 to 4 mg/day.[25] Side effects with these agents include sedation, drowsiness, dizziness, restlessness, and headache. Pimozide is associated with an increased risk of QTc interval prolongation, and electrocardiography is recommended prior to and during treatment. In addition, both drugs carry the risk of extrapyramidal side effects, such as tardive dyskinesia, a potentially irreversible movement disorder. Because of the risk of side effects, haloperidol and pimozide are reserved for Tourette syndrome–related tics that have failed other therapies. The AAN guidelines indicate haloperidol is probably more effective, and pimozide is possibly more effective, than placebo.[20]

Aripiprazole. This agent is FDA approved for the treatment of tics in Tourette syndrome for children as young as 6 years.[19] Several small, open-label studies have previously shown a positive effect for aripiprazole in Tourette syndrome–related tics.[34,35] A large phase 3 multicenter randomized, double-blinded, placebo-controlled trial by Sallee et al[36] contributed to FDA approval. The study recruited 133 patients (ages 7–17 years) from 76 practice sites in the United States, Canada, and Italy. A total of 119 patients completed the study testing low doses of aripiprazole (5 mg/day if <50 kg, 10 mg/day if ≥50 kg) to high doses (10 mg/day if <50 kg, 20 mg/day if ≥50 kg) versus placebo for 8 weeks. Patients were initiated at 2 mg/day, increased to 5 mg/day after 2 days, and then increased stepwise to the study dose based on weight. Using the YGTSS, a significant improvement in tic severity was reported with aripiprazole, with a decrease from baseline of 45.9% (low dose, p = 0.002) and 54.2% (high dose, p < 0.0001). When compared with placebo, the YGTSS score significantly decreased with

aripiprazole (low dose −7.1, p = 0.0033; high dose −9.5, p = 0.0001). A greater proportion of high-dose versus low-dose patients withdrew from the study due to adverse events. Extrapyramidal symptoms (e.g., akathisia, resting tremor, tremor) were reported in more patients with aripiprazole (low dose: n = 1, 2.3%; high dose: n = 6, 13.3%) than those with placebo (n = 0). Overall, the most common side effects reported included sedation, somnolence, increased appetite, fatigue, headache, and nausea. The mean ± SD weight gains were 1.8 ± 2 kg, 1 ± 2 kg, and 0.6 ± 2.1 kg for low-dose aripiprazole, high-dose aripiprazole, and placebo, respectively. The authors acknowledged that although the study sample is relatively small compared with those of other phase 3 trials, it constitutes the largest body of supporting evidence for the usage of aripiprazole, providing an alternative antipsychotic choice for treatment of tic disorder. In a second randomized, placebo-controlled trial, 61 children and adolescents (ages 6–18 years) with Tourette syndrome were enrolled in a 10-week study of aripiprazole by Yoo et al.[37] A total of 89% of patients completed the study. The study demonstrated a significant reduction in mean total tic score of the YGTSS versus placebo (−15.0 vs −9.6, p = 0.0196). The CGI severity of illness score was also significantly improved with aripiprazole versus placebo (p = 0.0321).

Because irreversible movement disorders may occur with antipsychotic medications, labeling advises limiting use of aripiprazole to patients for whom other equally effective but potentially less harmful treatments are not available or appropriate. Because the risk of tardive dyskinesia is believed to increase with the duration of antipsychotic treatment, regular reassessment for the need to continue treatment is recommended. Labeling recognizes the increased risk of suicidal ideation and recommends close monitoring for unusual changes in behavior or suicidality. In addition, monitoring for weight gain, a concern with atypical antipsychotics, is recommended. Dosing can be initiated at 2 mg/day, increasing as needed and tolerated to a maximum of 10 mg/day (<50 kg) or 20 mg/day (≥50 kg). Recommended dosing for Tourette syndrome–related tics is 5 mg/day if <50 kg or 10 mg/day if ≥50 kg.[19] The AAN guidelines identify aripiprazole as probably more likely than placebo to reduce tic severity.[20]

Risperidone. Most studies of the effectiveness of risperidone for Tourette syndrome–related tics include only adults or adolescents. However, a small, randomized, double-blind, placebo-controlled trial of 34 patients by Scahill et al[31] included 26 children age <18 years (mean age, 11.1 ± 2.2 years). The study demonstrated significant improvements (p = 0.002) in YGTSS Total Tic Scores with risperidone (32%) versus placebo (7%). In the children randomized to risperidone (n = 12) compared with placebo (n = 14), a significant reduction (p = 0.004) in tics was reported with risperidone (36%) versus placebo (9%). Side effects, including sedation, fatigue, and increased appetite, were considered transient and decreased with either time or dose reduction. No extrapyramidal symptoms were reported. A mean weight gain of 2.8 kg was reported in this study.

In another double-blind, randomized, placebo-controlled trial, Dion et al[38] reported a decrease in the Global Severity Rating of the Tourette Syndrome Severity Scale, which measures disease severity and social function disruption, with risperidone. In the risperidone group 60.8% of patients showed improvement in at least 1 point in the Global Severity Rating of the Tourette Syndrome Severity Scale versus 26.1% in the placebo group (p < 0.05). However, the study only included adolescents and adults (n = 48), 12 of which (9 study drug, 3 placebo) withdrew prior to study completion. In addition to the small sample size, the possibility of participant symptom suppression during observational data gathering might have resulted in underreporting tic frequency. The most frequently reported side effects included mild to moderate fatigue and somnolence. Importantly, Parkinson Factor scores indicated significantly more hypokinesia in the risperidone group versus placebo (p = 0.006). Tremors were significantly increased (p = 0.005) in the population that began the study with above-average baseline scores for tremor. No significant increase in tremor was shown for patients beginning the study with average baseline tremor scores or no baseline tremor. Of risperidone patients 39.1% (9 of 23) required pharmacologic treatment for Parkinson-like movement (extrapyramidal symptoms) versus 8.7% (1 of 23) of placebo patients (p = 0.04). Four patients terminated the study early because of adverse events. Depression (at any level) was reported in 26.1% (6 of 23) of those treated with risperidone versus 4.4% (1 of 23) of placebo patients (p = 0.10). Overall, the most commonly reported side effects in this study included fatigue and somnolence. Two participants were hospitalized for depression possibly related to treatment, whereas 2 others terminated the study early because of depressed mood. Doses ranged from 1–6 mg/day (median dose, 2.5 mg/day) at day 56 of the study, starting low and titrating upward based on clinical response and tolerability. The effect on tic suppression of risperidone was compared with clonidine in a small, double-blind pilot study of children and adolescents (n = 21, ages 7–17 years).

Gaffney at al[39] reported that both agents showed improvement in tic symptoms, with no significant difference in the percentage of clinical responders between groups. Doses were slowly titrated upward during the course of 3 to 4 weeks as tolerated with a maximum dose of 0.005 mg/kg (0.35 mg/day) for clonidine and 0.06 mg/day for risperidone. Side effects were reported in 58% of clonidine patients, with sedation most common (n = 5; 42%), and in 33% of risperidone patients, with stiffness most common (n = 2; 22%). The stiffness was reported as not Parkinson-like in nature. All adverse

events were considered mild to moderate in severity and resolved with continued dosing or dose reduction, in particular sedation and dizziness. The small size of this study and lack of a placebo comparator limit the generalizability of results. In addition, the authors state the lack of a placebo makes it difficult to distinguish between true drug effect and the normal waxing and waning of tic symptoms.

Overall, risperidone is well tolerated in the treatment of Tourette syndrome–related tics. Dosing can be initiated at 0.5 mg orally at bedtime, increasing as needed and tolerated to 3 mg/day divided into 2 daily doses. As with other antipsychotics, the benefits of treatment with risperidone should be weighed against the risk of side effects, which may include sedation, dizziness, weight gain, and potential movement disorders.[25] The AAN categorizes risperidone as probably more effective than placebo in reduction of tic severity.[20]

Botulinum Toxin A. In an effort to suppress tics and reduce risks associated with systemic drug exposure, studies have examined the efficacy of BTX injection. When injected into muscle, BTX inhibits acetylcholine release from peripheral motor nerve terminals, causing partial chemical denervation, resulting in local neuromuscular paralysis.[40] Release of other neurotransmitters is also decreased. It has been conjectured that local tic suppression for prolonged periods might reduce tic frequency or cause permanent termination. Studies have examined treatment of primarily phonic and simple motor tics. As with numerous other treatments for tics, there is a relative lack of well-powered conclusive studies, with small numbers of participants. Generalizability of results is hampered by the use of inconsistent doses and predominantly single-dose tests. Importantly, studies have only included adolescents and adults. A recent Cochrane review[41] found only 1 study meeting their rigorous criteria for randomized placebo (or treatment drug) controlled trials.

Marras et al[42] studied 20 patients, 18 of whom completed the study and 14 of whom received a diagnosis of Tourette syndrome (all with mild, non-disabling tics). Participants received a single localized injection of either BTX or saline placebo. Outcomes were measured via blinded videotape or clinical assessment of motor tics, as well as PMU during the course of 12 weeks after dose. Once tics returned to baseline, participants were crossed over to the other study arm. A significant reduction in tics per minute was reported in the treatment phase (39% BTX vs 5.8% placebo). Premonitory urge scores also significantly decreased with BTX versus placebo ($p = 0.02$). Side effects following treatment included local weakness (9 BTX, 2 placebo) and neck discomfort (3 BTX, 1 placebo). Replacement tics ($n = 2$) and increased PMU ($n = 2$) were also reported. Study limitations included small sample size, self-reporting of PMU, and difficulties with blinding BTX recipients (as noted by reports of muscle weakness after dose). Inclusion of patients with only mild tics limit the ability to extrapolate findings to patients with more severe tics.

Other studies on BTX in tic suppression show promise, but they are hampered by a lack of controlled trials and case reports. Larger randomized controlled trials studying the efficacy of repeated dosing, especially in more severe tics, as well as efficacy and safety in children, are needed to more fully determine the role of BTX in Tourette syndrome–related tic suppression. A single BTX treatment may last 12 to 16 weeks. Side effects may include local muscle weakness, local muscular discomfort, replacement tics, and increased PMU. The AAN concluded that BTX treatment for Tourette syndrome–related tics was probably more effective than placebo in adolescents and adults and stated the PMU might also improve. Furthermore, they delineate the role of BTX for bothersome simple motor tics and severely disabling or aggressive vocal tics when benefits outweigh the risks. No recommendation for use in children can be made at this time.[20]

Cannabinoids. Self-treatment with cannabinoids by some patients for a variety of diagnoses, including Tourette syndrome–related tics, makes understanding these agents important for practitioners. The endocannabinoid system affects synaptic neurotransmission[43]; therefore, testing cannabinoids for tic suppression has gained interest. Cannabinoids affect specific receptors: cannabinoid receptor type 1 located in the CNS, and cannabinoid receptor type 2, primarily in immune tissues.[44] *Cannabis sativa* (marijuana) comprises more than 60 cannabinoids,[43] with varying strengths and concentrations, leading to heterogeneous composition of test drug, making comparative studies difficult. The main pharmacologically active cannabinoids include the psychoactive component δ-9-tetrahydrocannabinol (THC) and the non-psychoactive component cannabidiol.

Dronabinol, a synthetic THC with consistent composition, has been used in some studies. A Cochrane review only found 2 small studies meeting their stringent criteria, including randomized, controlled trial and comparison against placebo. These studies, together, comprised a total of only 28 adult patients, 8 of whom participated in both studies. Both studies reported positive effects on tic reduction and severity, although the authors of the 6-week study admit the results were not significant when a Bonferroni correction is performed. The studies had a large number of dropouts, inducing the risk of patient selection bias. In addition, the psychoactive effects of THC make true blinding difficult. The reviewers concluded that although some positive outcomes were reported, the size of the studies and potential biases did not provide enough evidence to warrant recommending cannabinoid treatment for tic reduction in adults.[43] The cannabinoid dose-related effect on neurologic deficits, including memory impairment, eye-hand coordination, and changes in percep-

tion and time, led to concerns for long-term neurologic effects, especially in children and adolescents. The AAN guidelines state that limited evidence suggests THC may possibly be more effective than placebo. Cannabinoid treatment should be avoided in children and adolescents because of the lack of data and the association with negative long-term cognitive effect.[20]

Miscellaneous Drugs. With their lack of risk of tardive dyskinesia, antiepileptic drugs have drawn interest in the continued search for agents to effectively suppress Tourette syndrome–related tics. However, sufficient studies are currently lacking. Benefit for topiramate in tic suppression was suggested by a small (n = 20; mean age, 16.5 years) double-blind, randomized control trial comparing placebo with topiramate. During the 70-day trial period, The Total Tic Score improved by 14.29 points with topiramate versus a 5.00-point improvement with placebo (p = 0.0259).[45] Adverse reactions with topiramate can include drowsiness and cognitive difficulties. The current AAN guidelines identified topiramate as possibly more effective than placebo in the reduction of tic severity.[20] Additional studies of antiepileptic agents are needed to identify safety and benefit in tic reduction. VMAT2 inhibitors (e.g., tetrabenazine) are dopamine depletors used in some other hyperkinetic disorders. Although there has been increasing interest in their use for Tourette syndrome–related tics, there is currently insufficient data to support use. Ongoing studies may provide more information regarding their role in treatment. The AAN guidelines identify a wide range of other drugs currently being studied, but with insufficient evidence as yet for Tourette syndrome–related tic suppression, including levetiracetam, *N*-acetylcysteine, and omega-3 fatty acids.[20] Future and ongoing research may provide more information regarding optimal pharmacologic treatment of Tourette syndrome–related tics.

Non-Pharmacologic Options

Several non-pharmacologic treatments for Tourette syndrome–related tics have also been studied. The 2 main approaches recommended by the AAN are deep brain stimulation (DBS) and behavioral therapy. The primary type of behavioral therapy used is comprehensive behavioral intervention for tics (CBIT). Non-pharmacologic treatments offer the avoidance of systemic drug side effects and potential alternatives for patients failing drug therapy.[20]

Deep Brain Stimulation. DBS, a relatively new method of treating Tourette syndrome, involves inserting an electrode into the brain at or near a specific target, enabling electrical activity to alter functions in precise brain regions and neuromodulating improperly functioning areas. DBS is approved by the FDA for some other movement-related disorders, although it is not yet approved for Tourette syndrome. However, the AAN recognizes DBS as a possible treatment option in certain specific cases of multidrug treatment failure, acknowledging that few studies examining the safety and efficacy of DBS have been done in children. Available data for DBS in Tourette syndrome–related tics are predominantly from adult and adolescent patients. Data collection is challenged by the few procedures performed yearly.[20]

A randomized and blinded study for DBS by Welter at al[46] demonstrates the difficulty in assessing this modality. Although 20 patients (ages 18–60 years) were recruited, only 16 finished due to either infection or non–study-related personal issues. The study included a 3-month double-blind period, followed by a 6-month open-label period, using a stimulation level below the side effect threshold to maintain binding. No significant improvements were observed in YGTSS scores between the control and stimulation groups (p = 0.39) during the blinded period. 15 serious adverse events were recorded (7 from the surgery, 4 infections). This study was limited by the short period of blinding and the small sample size. The authors suggested that the use of low stimulation levels might have contributed to the inability to reproduce beneficial effects reported in other studies.

Contrary to these negative findings, other reports have shown potentially positive treatment effect for DBS. The International Deep Brain Stimulation Database and Registry conducted a 4-year study attempting to discover the efficacy of DBS, the ideal location to stimulate, and the safety of DBS. This study included 185 patients (ages 13–58 years) from 10 different countries. After excluding patients without both 6- and 12-month postprocedure follow-up data, 171 participants were included in the final data pool (134 males, 37 women). Specific brain targets were found to yield better results, but none achieved statistical significance. However, collectively DBS treatment induced a significant decrease in both motor and phonic tics (p < 0.001 for both), with an improvement of YGTSS total scores (p < 0.001). During the year following the procedure, 35.4% (56 of 158) of patients had an adverse effect, primarily dysarthria or paresthesia caused by the stimulation. Adverse events related to the surgery included intracranial hemorrhage (n = 2; 1.3%) and infection (4 patients with 5 events total; 3.2%). Significant study limitations included the observational open-label nature, use of unregulated screening procedures, and lack of data related to medications used by patients at the time of the treatment.[47]

In a meta-analysis of peer-reviewed case reports and clinical trials published since 1999, Baldermann et al[48] reported that DBS is an effective treatment for Tourette syndrome. Using 57 studies totaling 150 patients (ages 15–60 years, median age 30 ± 9.8 years at time of surgery), a significant improvement in the YGTSS total score (p < 0.001) was reported, with progress mostly occurring in the first postoperative months. An ideal electrode placement location was unable to be identi-

fied. Data were insufficient to study adverse effects. The meta-analysis was limited by availability of only open-label small studies without controls and the variability in the brain targets. Johnson et al[49] conducted a retrospective study of imaging and clinical data from treatment-refractory Tourette syndrome to assess the efficacy of DBS and determine the maximal location for electrode placement. A total of 110 patients from 13 international sites were analyzed in the final data set. A documented YGTSS total score preoperatively and at least one postoperatively were required for study inclusion to assess the improvement in tic severity. A significant improvement ($p < 0.0001$) in tic severity was reported, with a median of 13 months required to reach 40% tic improvement (the parameter for being considered a responder). No significant difference between brain targets was identified. Limitations included use of open-label data and retrospective data collection.

Overall, current literature suggests DBS is a viable treatment option in some adult and adolescent patients with Tourette syndrome. However, recommendations are challenging, because of the lack of well-designed, sufficiently powered studies controlling for significant variables, such as stimulation location, participant medication use, and blinding. Future studies should attempt to identify ideal brain target areas for DBS to maximize effectiveness while minimizing risks. Without studies directly assessing the use of DBS in children, no data-driven recommendations can be made at this time in that population. The AAN guidelines state that patients with severe, multitreatment-resistant Tourette syndrome may benefit from DBS, but they emphasize that a multidisciplinary review to identify appropriate patient selection is paramount to success.[20]

Behavioral Therapy. Specifically, CBIT is recommended as a non-invasive initial treatment for Tourette syndrome. CBIT comprises 3 formerly separate types of therapy: habit reversal training, relaxation therapy, and awareness training. Other methods of behavioral therapy have been used, including exposure with response prevention, hypnosis, and massed negative practice, but no data to support use in Tourette syndrome are available at this time.[20]

Comprehensive Behavioral Intervention. Piacentini et al[50] studied youth ages 9 to 17 years with moderate or greater tics, finding that CBIT was more effective than control. During the course of 3 years, 126 patients (61 treatment, 65 control) were recruited; attrition rate was 10% (treatment) and 11% (control). Treatment was administered during the course of 10 weeks during 8 sessions, with the length of treatment sessions controlled. Randomization was modified to ensure each group had an equal number of patients using pharmacologic aids. Independent evaluators of tic severity were used to maintain blinding. After 10 weeks, the therapy group had significant improvement in YGTSS scores ($p < 0.001$). Of the 200 adverse events recorded, none were considered study related (i.e., broken bones offsite). Spontaneous tic worsening was recorded once. The key limitation was the inability to blind observers, patients, therapists, and parents regarding the type of therapy administered. Wilhelm et al[51] performed a CBIT efficacy study in patients with moderate to severe tics, in a 10-week randomized controlled trial of 122 patients (ages 16–69 years, 78 male, 44 female). Follow-up assessments at months 3 and 6 were performed on those showing improvement. Independent and blinded evaluators used the YGTSS and CGI for assessment, reporting significant improvements in YGTSS total score in the CBIT group ($p < 0.001$). Attrition of patients was not significantly different (17% control; 11% CBIT), and 223 adverse events were reported, although they were determined to be unrelated to treatment. Abnormal tic worsening was reported by 4 patients. A significant limitation of this study was non-blinded therapists or patients, in addition to excluding non-responders from follow-up data.

Overall, CBIT is an understudied treatment for Tourette syndrome, with only 2 available studies of sufficient sample size, limiting reliability. Additionally, blinding therapists and patients in CBIT studies is difficult. Some studies have attempted to identify behavioral intervention efficacy by combining the results of CBIT and habit reversal training. However, because of differences in these therapies, this can lead to inaccurate conclusions. According to the AAN guidelines, CBIT is more likely than psychoeducation or supportive therapy to reduce tic severity. In addition, this non-invasive treatment avoids the risks of systemic adverse drug events or surgery and should be considered as the first treatment option. For cases in which CBIT delivery in person is not available, other options may include secure Internet or teleconference provision of care.[20]

Summary

The literature supporting definitive treatment of Tourette syndrome–related tics is limited. Diagnosis of Tourette syndrome can be challenging, requiring specific diagnostic criteria to be met. Treatment is complicated by the waxing and waning of symptoms, existence of comorbid disorders, and a lack of robust studies identifying treatment with consistent outcomes. CBIT may assist in reduction of tic severity and help avoid systemic medication and potential side effects. It should be advocated for use as a primary treatment option and in conjunction with pharmacotherapy. Alpha-2 adrenergic agonists, including clonidine and guanfacine, are often considered a first-line pharmacologic option in Tourette syndrome–related tic suppression.[25] For patients with comorbid ADHD, treatment with clonidine, alone or combined with methylphenidate, or guanfacine may decrease both tic severity and ADHD symptoms. Although haloperidol and pimozide are FDA approved for tic reduction, newer antipsychotics, including aripip-

razole and risperidone, have been increasingly used because of concerns of movement disorders associated with older antipsychotics. Aripiprazole is the only other medication currently FDA approved for Tourette syndrome. However, an increased risk of movement disorders, including tardive dyskinesia and Parkinson-like movement disorder, exists with both first- and second-generation antipsychotics.

A number of alternate agents, such as antiepileptics and VMAT2 inhibitors, may offer alternatives for drug-resistant Tourette syndrome, but studies are needed to determine their efficacy. Patients failing optimal tic suppression or experiencing dose-limiting side effects with single-drug therapy may benefit from combination treatment using agents from different drug categories. Botulinum toxin A may provide relief for specific cases of severely disabling focal motor or phonic tics and PMU in adolescents, but it carries the risk of muscle weakness and laryngeal paralysis. Botulinum toxin A cannot be recommended in children at this time. The beneficial effect from a single treatment may last 12 to 16 weeks and must be repeated periodically. Long-term studies determining the effect of repeated treatment or the risk of effect reduction are not available. Cannabis cannot be recommended for children or adolescents for tic suppression. In addition to the lack of available studies in this age group, the long-term neurologic effect in growing youth continues to be a concern with cannabis. Patients reporting self-treatment with cannabis should be counseled regarding behavioral and drug treatment options and the potential long-term effect on cognitive function. Referral to a medical cannabis provider for more information may be warranted. DBS is not an approved treatment for Tourette syndrome–related tics at this time, although the AAN guidelines suggest it may be an alternative in severe, multidrug-resistant or self-injurious forms.

Overall, the choice of therapy, both non-pharmacologic and pharmacologic, must be individualized based on severity of symptoms, lifestyle, side effects, and response to previous treatment. With the potential negative psychosocial and learning effect associated with Tourette syndrome, pharmacists are in a unique position to provide optimization of pharmaceutical treatment and education for patients and caregivers on potential alternatives for tic suppression. Future studies may assist in identifying consistent approaches to the treatment of Tourette syndrome–related tics.

ARTICLE INFORMATION

Affiliations At the time of submission Mary Seideman, PharmD was at Banner Desert Medical Center (MFS), Mesa, AZ.

Correspondence Mary F. Seideman, PharmD; mrseideman@msn.com

Disclosures The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Ethical Approval and Informed Consent Given the nature of this study, the manuscript was exempt from institution review board/ethics committee review.

Accepted March 1, 2020

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Claussen AH, Bitsko RH, Holbrook JR, et al. Impact of Tourette syndrome on school measures in a nationally representative sample. *J Dev Behav Pediatr*. 2018;39(4):335–342.
3. Scahill L, Sukhodolsky DG, Williams SK, Leckman J. Public health significance of tic disorders in children and adolescents. *Adv Neurol*. 2005;96:240–248.
4. Storch EA, Murphy TK, Chase RM, Keeley M, et al. Peer victimization in youth with Tourette's syndrome and chronic tic disorder: relations with tic severity and internalizing symptoms. *J Psychopathol Behav Assess*. 2007;29:211–219.
5. Debes N, Hjalgrim H, Skov L. The presence of attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder worsen psychosocial and educational problems in Tourette syndrome. *J Child Neurol*. 2010;25(2):171–181.
6. Zinner SH, Conelea CA, Glew, GM, et al. Peer victimization in youth with Tourette syndrome and other chronic tic disorders. *Child Psychiatry Hum Dev.* 2012; 43(1):124–136.
7. Piedad JCP, Cavanna AE. Depression in Tourette syndrome: a controlled and comparison study. *J Neurol Sci*. 2016;364:128–132.
8. Hirschtritt M, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and etiology of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry*. 2015;72(4):325–333.
9. Dongmei Y, JaeHoon S, Fotis T, et al. Interrogating the genetic determinants of Tourette's syndrome and other tic disorders through genome-wide association studies. *Am J Psychiatry.* 2019;176(3):217–227.
10. Wong DF, Brasic JR, Singer HS, et al Mechanisms of dopaminergic and serotonergic neurotransmission in Tourette syndrome: clues from an in vivo neurochemistry study with PET. *Neuropsychopharmacology.* 2008;33(6):1239–1251.
11. Muller-Vahl KR, Szejko N, Wilke F, et al. Serotonin transporter binding is increased in Tourette syndrome. *Neurosci Lett.* 2005;385(2):120–125.
12. Hienert M, Gryglewski G, Stamenkovic M, et al. Striatal dopaminergic alterations in Tourette's syndrome: a meta-analysis based on 16 PET and SPECT neuroimaging studies. *Transl Psychiatry.* 2018;8(1):143. doi:10.1038/s41398-018-0202-y

13. Wang Z, Miaia TV, Marsh R, et al. The neural circuits that generate tics in Gilles de la Tourette syndrome. *Am J Psychiatry.* 2011;186(12):1326–1337.
14. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. *Am J Psychiatry.* 1993;150(1):98–102.
15. Bitsko RH, Holbrook JR, Visser SN, et al. A national profile of Tourette syndrome, 2011-2012. *J Dev Behav Pediatr.* 2014;35(5):317–322.
16. Centers for Disease Control and Prevention (CDC). Prevalence of diagnoses Tourette syndrome in persons aged 6-17 years-United States, 2007. *MMWR Morb Mortal Wkly Rep.* 2007;58(21):581–585. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5821a1.htm. Accessed May 20, 2019.
17. Haloperidol [package insert]. Greenville, SC; Pai Pharmacuetical Associates, Inc; 2016.
18. ORAP [package insert]. Sellersville, PA: Teva Pharmacueticals USA; 2008.
19. Abilify [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co, Ltd; 2019.
20. Pringsheim T, Okun MS, Muller-Vahl K, et al. Practice guidelines recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology.* 2019;92(19):896–906.
21. Clonidine Hydrochloride [package insert]. Rockford, IL: Mylan Institutional Inc; 2015.
22. Song PP, Jiang L, Li XJ, et al. The efficacy and tolerability of the clonidine transdermal patch in the treatment of children with tic disorders: a prospective, open, single-group, self-controlled Study. *Front Neurol.* 2017;8:32. doi:10.3389/fneur.2017.00032
23. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics a randomized controlled trial. *Neurology*. 2002;58(4):527–536.
24. Du YS, Li HF, Vance A, et al. Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. *Aust N Z J Psychiatry.* 2008;42(9):807–813.
25. Qasaymeh MM, Mink JW. New treatments for tic disorders. *Curr Treat Options Neurol.* 2006;8(6):465–473.
26. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry.* 2001;158(7):1067–1074.
27. Tenex [package insert]. Bridgewater, NJ: Promius Pharma; 2013.
28. Cummings DD, Singer HS, Krieger M, et al. Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: a pilot study. *Clin Neuropharmacol.* 2002;25(6):325–332.
29. Murphy TK, Fernandez TV, Coffey BJ, et al. Extended-release guanfacine does not show a large effect on tic severity in children with chronic tic disorders. *J Child Adolesc Psychopharmacol.* 2017;27(9):762–770.
30. Pringsheim T, Marras C. Pimozide for tics in Tourette's syndrome. *Cochrane Database Syst Rev.* 2009;(2):CD006996. doi:10.1002/14651858.CD006996.pub2
31. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology.* 2003;60(7):1130–1135.
32. Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette syndrome and other tic disorders, part II: pharmacological treatment. *Eur Child Adolesc Psychiatry.*2011;20(4):173–196.
33. Shapiro E, Shapiro AK, Fulop G, et al. Controlled study of haloperidol, pimozide, and placebo for the treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry*. 1989;46(8):722–730.
34. Yoo HK, Lee JS, Paik KW, et al. Open-label study comparing the efficacy and tolerability of aripiprazole and haloperidol in the treatment of pediatric tic disorders. *Eur Child Adolesc Psychiatry*. 2011;20(3):127–135.
35. Rizzo R, Eddy CM, Cali P, et al. Metabolic effects of aripiprazole and pimozide in children with Tourette syndrome. *Pediatr Neurol.* 2012;47(6):419–422.
36. Sallee F, Kohegyi E, Zhao J, et al. randomized, double-blind, placebo controlled trial demonstrates the efficacy and safety of oral aripiprazole for the treatment of Tourette's disorder in children and adolescents. *J Child Adolesc Psychopharmacol*. 2017; 27(9):771–781.
37. Yoo HK, Joung YS, Lee JS, et al. A multicenter, randomized, double-blind placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry.* 2013;74(8):e772–e780.
38. Dion Y, Annable L, Stat D, et al. Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol.* 2002;22(1):31–39.
39. Gaffney GR, Perry PJ, Lund BC, et al. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry.* 2002;41(3):330–336.
40. BOTOX [package insert]. Madison, NJ: Allergan USA; 2019.
41. Pandey S, Srivanitchapoom P, Kirubakaran R, Berman B. Botulinum toxin for motor and phonic tics in Tourette's syndrome. *Cochrane Database Syst Rev.* 2018;(1):CD012285. doi:10.1002/14651858.CD012285.pub2
42. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology*. 2001;56(5):605–610.
43. Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's syndrome. *Cochrane Database Syst Rev.* 2009;(4):CD00656. doi:10.1002/14651858.CD006565.pub2
44. Muller-Vahl KR. Treatment of Tourette syndrome with cannabinoids. *Behav Neurol.* 2013;27(1):119–124.
45. Jankovic J, Jimenez-Shahed J, Brown LW. A randomized, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. *J Neurol Neurosurg Psychiatry.* 2010;81(1):70–73.
46. Welter ML, Houeto JL, Thobois S, et al. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. *Lancet Neurol.* 2017;16(8):610–619.
47. Martinez-Ramirez D, Jiminez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep bran stimulation public database and registry. *JAMA Neurol.* 2018;75(3):353–359.
48. Baldermann JC, Schuller T, Huys D, et al. Deep brain stimulation for Tourette-syndrome: a systematic review and meta-analysis. *Brain Stimul.* 2016;9(2):296–304.

49. Johnson KA, Fletcher PT, Servello D, Bona A, et al. Image-based analysis and long-term clinical outcomes of deep brain stimulation for Tourette syndrome: a multisite study. *J Neurol Neurosurg Psychiatry.* 2019;90(10):1078–1090.
50. Piacentini J, Woods DW, Scahill L. Behavior therapy for children with Tourette disorder: a randomized controlled trial. *JAMA.* 2010; 303(19):1929–1937.
51. Wilhelm S, Peterson AL, Piacentini J, et al. Randomized trial of behavior therapy for adults with Tourette's disorder. *Arch Gen Psychiatry*. 2012;69(8):795–803.