Pharmacologic Treatment of Comorbid Attention-Deficit/ Hyperactivity Disorder and Tourette and Tic Disorders

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KEYWORDS

• ADHD • Tics • Stimulants • α-Agonists • Tourette

KEY POINTS

- There is a bidirectional relationship between ADHD and tic disorders.
- A comprehensive medical and psychiatric evaluation is essential to treatment.
- Stimulants are the first-line pharmacotherapy to treat ADHD in patients with tic disorders.
- α-Agonists are added to simulants or used as monotherapy to treat ADHD and tics.

INTRODUCTION

Tics are defined as sudden, rapid, and recurrent, nonrhythmic motor movements or vocalizations.[1] Motor tics are movements, such as eye blinks or shoulder shrugs. Vocal, also known as phonic tics, are utterances or sounds, such as throat clearing.[2] The distinction is somewhat arbitrary, because vocalizations are produced by muscles. Both motor and phonic tics are classified as either simple or complex. Simple motor tics are brief and meaningless movements involving one muscle or muscle group, whereas complex motor tics are more purposeful and involve multiple muscle groups. Simple vocal tics, like simple motor tics, are fast and meaningless sounds. Complex vocal tics involve words or phrases, and may include obscenities (coprolalia). The Diagnostic and Statistical Manual, 5th edition, classifies motor and vocal tics based on their duration; if movements and/or sounds have been present for less than 1 year, they are classified as a provisional tic disorder. If either movements or sounds have persisted for greater than 1 year they are diagnosed as either a persistent motor or persistent vocal tic disorder.[1,2]

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Child Adolesc Psychiatric Clin N Am 31 (2022) 469–477
https://doi.org/10.1016/j.chc.2022.03.004 **childpsych.theclinics.com**

Tourette disorder (TD), also referred to as Tourette syndrome, is diagnosed when an individual has multiple motor tics and one or more vocal tics, although they need not be present at the same time. The tics must have been present for at least 1 year with onset before the age of 18. The disorder is named after the French neurologist George Gilles de la Tourette, who in 1885 published a case series of nine patients with tics.[3]

Tics typically begin in early childhood with an average age of onset of 5 to 7 years. Motor tics often emerge first with a head-to-toe progression. Phonic tics typically emerge 1 to 2 years later. Tics are usually not static, and the predominant tic or tics may change at different times in the same individual. The tics wax and wane over time, and there may be long periods during which the tics are minimal or even absent. Tics usually peak before puberty around the ages of 9 to 12 and attenuate significantly by early adulthood. Intense focus, such as playing a sport or instrument, may make the tics subside or even disappear entirely at least temporarily. Conversely, tics may worsen during periods of stress and illness. Patients typically report a premonitory urge, or unpleasant sensation they feel in their body or mind, which builds up before a tic and is subsequently relieved by completing the tic. Tics are briefly suppressed with effort, which can lead to an increase in the discomfort and potential for more intense bouts.

Individuals with tic disorders, and particularly TD, often have co-occurring or comorbid psychiatric symptoms or conditions. Estimates vary, but 50% to 80% of patents with TD also meet criteria for attention-deficit/hyperactivity disorder (ADHD).[4] The relationship between TD and ADHD is bidirectional; 20% of those with ADHD may meet criteria for a tic disorder. Proposed reasons for this high overlap include a core deficit in inhibition related to frontostriatal and frontoparietal network dysfunction in cortico-striatal-thalamic-cortical tracts. Imaging studies show hyperfunctioning/overactive circuits in the basal ganglia in TD resulting in motor/cognitive/emotional disinhibition, worsened by frontal hypoactivity in ADHD. That both disorders tend to improve with time may reflect increased myelinization of prefrontal regions.[5,6]

A comprehensive diagnostic evaluation is essential in patients with tic disorders, given the high comorbidity rate not just for ADHD, but with other disorders. Twenty percent to 60% of patients with TD have obsessive-compulsive disorder, approximately 25% have a learning disorder, and 20% have an anxiety disorder. Many of these patients also have other behavioral or impulse control disorders.[4]

Diagnoses for TD and ADHD are made based on the clinical history. Structured or semistructured diagnostic interviews, such as the DISC or K-SADS, can help with reliability. The Tic Symptom Self Report is a screening questionnaire individuals and families can complete to identify tics. Clinician-scored rating scales help qualify and quantify disorder severity. The Yale-Global Tic Severity Scale (YGTSS) is considered the gold standard rating scale for tics, and assesses the following tic domains: number, frequency, intensity, complexity, and interference and tic-related impairment.[6]

It is imperative to assess the patient's self-esteem and how he or she is functioning academically, socially, and within the family. This history, along with quantitative symptom assessments, can identify which symptoms are most impairing and bothersome to the patient and family. Patients with persistent tic disorders and ADHD have more peer problems and reduced quality of life than those with either disorder alone. Indeed, much of the associated psychopathology (behavioral, emotional, neurocognitive) in TD is secondary to ADHD.[7] Given that tic disorders tend to remit independent of ADHD, and outcomes of ADHD are problematic without intervention, treatment of ADHD is usually the priority when comorbidity is present.[8]

This article next reviews current pharmacologic evidence for treatment of ADHD and tic disorders, and discusses clinical implications and treatment strategies.

RESEARCH AND CURRENT EVIDENCE IN PHARMACOTHERAPY FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TIC DISORDERS

Stimulants

In clinically referred individuals with ADHD and tic disorders, ADHD symptoms are usually more impairing than tics, and thus treatment of ADHD should be prioritized. Stimulants remain the most effective pharmacologic choice for children with ADHD, and are considered first-line. Children with ADHD and comorbid tics respond equally to stimulants as children with ADHD without tics.[9]

However, the Food and Drug Administration (FDA) lists "patients with motor tics or with a family history or diagnosis of Tourette syndrome" as a contraindication for Ritalin, and the following warning/precaution for Adderall: "Amphetamines have been reported to exacerbate motor and phonic tics and Tourette syndrome. Therefore, clinical evaluation for tics and Tourette syndrome in children and their families should precede use of stimulant medications." Cohen and colleagues[10] explain the history of case reports from the 1970s and 1980s, which led to the FDA label in 1983. These warnings have likely limited the use of an effective treatment of children with ADHD and tic disorders.[10]

There have since been several randomized controlled trials (RCTs) showing no deleterious effect of stimulants on tics. The Cohen meta-analysis examined 22 RCTs involving 2385 participants to determine the risk of new onset or worsening tics in patients with ADHD taking stimulants compared with placebo. The results showed no increase in new onset or worsening of tics in those taking stimulants. New onset or worsening of tics were reported in 5.7% of children in the stimulant group, compared with 6.5% in the placebo arm. The authors conclude that overall the risk of new onset or tic worsening associated with stimulants is similar to that of placebo. Moreover, stimulant type (methylphenidate vs amphetamine derivative), duration of action (short-acting vs long-acting), dose, and duration of treatment were not associated with a more frequent onset or worsening of tics. Crossover trials did report a greater association of new onset or worsening of tics compared with parallel-group studies, although neither group reported an association between tics and stimulant use. The study concluded that the number needed to harm from new onset or worsening tics with stimulants is 1000.[10] Thus, 1000 people would need to take a stimulant before one person would be expected to develop new or worsening tics.

α-Agonists

The α_2-agonists clonidine and guanfacine are often considered first-line pharmacologic treatment for tics.[11] Several RCTs have looked at whether they are effective at treating ADHD and comorbid tic disorders.

In 1991 Leckman and colleagues[12] reported a 26% improvement over baseline ratings in the patients treated with clonidine compared with placebo, as measured by the Tourette Syndrome Global Scale; in addition they reported a 48% reduction in the "impulsive-hyperactive" factor on the ADHD Conners Parent Questionnaire in the clonidine group compared with 6% in the placebo group.[12]

In the Treatment of ADHD and Chronic Tics (TACT) study, the Tourette Syndrome Study group reported that the combination of methylphenidate and clonidine conferred the greatest treatment effect for ADHD (1.09) and tic symptoms (0.75) compared with either medication alone or placebo.[9,13]

In contrast, Singer and colleagues[14] in a 1995 study did not show benefit of clonidine over placebo on either tic severity on the Hopkins Scale or Tourette Syndrome Severity Scale, or on ADHD on the parent global linear analogue rating of hyperactivity.

In comparing clonidine with risperidone, Gaffney and colleagues[15] showed that clonidine reduced tic severity by 26% on the YGTSS and reduced ADHD severity by 38% on the ADHD-RS. In a different study comparing clonidine with levetiracetam, Hedderick and colleagues[16] showed a small but significant decrease in mean Total Tic Score (25.2 baseline vs 21.8), but not mean total YGTSS (48.7 vs 43.1) in the clonidine group, and no difference in ADHD-RS. The latter study was limited by only including two patients with ADHD; neither study had a placebo comparator.[16]

There have been three studies that have shown a benefit for transdermal clonidine in tic disorders, but did not include any secondary ADHD outcome measures.[17–19]

In 2001 Scahill and colleagues[20] showed a 37% decrease on the teacher-rated ADHD-RS for guanfacine compared with 8% in the placebo group. For tics, the guanfacine group had a 31% decrease in tic severity on the YGTSS versus 0% in the placebo group. In contrast, a 2017 study that examined guanfacine extended release compared with placebo failed to show a significant effect of guanfacine in tic reduction compared with placebo.[21]

A 2013 meta-analysis of available studies showed α-agonists to have a significant benefit in reduction of tics compared with placebo, with a standardized mean difference (SMD) of 0.31. This study examined the impact of a comorbid ADHD diagnosis, and found that in studies that enrolled patients with tics plus ADHD, the SMD jumped to a clinically significant 0.68 for α-agonists. In studies where ADHD was excluded the SMD was 0.15. Studies that had a greater percentage of subjects with ADHD showed a greater efficacy from α-agonists in tic reduction.[11]

Overall, studies in which α-agonists have been effective reduce tic severity by about 30%, an effect likely moderated by the presence of comorbid ADHD.

Other Agents

There are two studies that examined atomoxetine. In 2005 Allen and colleagues[22] showed a decrease of 5.5 points on the YGTSS Total Tic Score in the atomoxetine group compared with 3 points in the placebo group. This difference approached but did not reach significance with a calculated effect size of 0.3. The study measured ADHD response using the ADHD-RS and found an effect size of 0.6.[22] A 2008 study did show a significant difference in response in the atomoxetine group, with a YGTSS Total Tic Score decrease of 5.1 points compared with 2 points in the placebo, yielding an effect size of 0.4. The atomoxetine group experienced a decrease in the ADHD-RS-IV-Parent:Inventory total score of 10.4 points compared with 4.4 points in the placebo arm, with an effect size of 0.57.[23] These small but statistically significant decreases may be clinically meaningful for patients depending on baseline tic severity and specific areas of improvement.

Two RCTs evaluated the tricyclic antidepressant desipramine in patients with ADHD and tic disorders after several case reports were published. Singer and colleagues[14] in 1995 reported that patients with ADHD and TD treated with desipramine had a statistically significant decrease in the parent global linear analogue comparing the child's current tics with tics anytime in the past. In contrast, participants in the desipramine group did not show a decrease in any of the standardized tic ratings used. In this same study desipramine was also superior to clonidine and placebo in reducing hyperactivity on the parent-completed global linear analogue rating scale and the hyperactivity subscale of the CBCL.[14]

In 2002 a second study reported a 30% decrease from baseline in the YGTSS global severity scores in participants treated with desipramine compared with those on placebo. Desipramine was also effective in reducing ADHD symptoms by 42% from baseline relative to placebo on the ADHD-RS.[24]

DISCUSSION

The first step in the pharmacologic treatment of individuals with comorbid ADHD and tics is a comprehensive medical and psychiatric evaluation; information should be obtained from the primary care physician, patient, parents, the school, and any involved clinicians or other services. Neuropsychological or psychometric assessment may also be helpful in disentangling ADHD symptoms from executive function difficulties and/or specific learning disorders. A thorough, detailed and multidisciplinary evaluation qualifies and quantifies problematic symptoms in the patient. This facilitates identification of which symptoms are the most problematic or distressing to prioritize for intervention.

Psychostimulants are the recommended first-line pharmacologic treatment of ADHD symptoms in patients with comorbid tic disorders. To state again, in patients whose ADHD symptoms are most problematic, stimulants should be prescribed first.

The Cohen meta-analysis makes clear that stimulants were associated with neither new onset nor worsening of tics in patients with ADHD and tic disorders. Some individuals may be particularly sensitive to the effects of stimulants and experience a transient tic increase after starting a stimulant or increasing the dose. FDA warning labels remain on many stimulants, and it is essential to discuss with the family the possibility of tic onset or increase. Attention to family history of tic disorders and/or obsessive-compulsive disorder is essential, because this may identify individuals at higher risk for the development of tics, independent of exposure to stimulants. Additionally, tics typically onset at around the same age as ADHD is recognized or diagnosed, and their onset may be entirely coincidental. Furthermore, tic fluctuations with waxing and waning are characteristic of the natural history, and it is possible that a waxing period is simultaneously occurring at the time of medication initiation. Conversely, an incidental waning period may be confused with clinical improvement on the stimulant. It is helpful to understand each individual patient's typical pattern of tic fluctuations in advance of starting treatment. Discussion of these possibilities with families before starting medication is strongly recommended.

Methylphenidate is recommended as the initial stimulant choice in this population. In the only head-to-head study of methylphenidate versus dextroamphetamine, increases in tic severity were sustained for those on high doses of dextroamphetamine.[25] For individuals treated with a stimulant in the past who experienced an increase in tics, rechallenge with a stimulant should be considered if the ADHD symptoms are not adequately controlled with nonstimulants. Methylphenidate is initiated at 5 mg for children and 10 mg for adolescents and titrated up gradually. Patients should be closely monitored for any worsening of tics. An immediate-release formulation may be helpful to start with low doses and then switched to a long-acting preparation once an effective and tolerable dose is reached. Long-acting stimulants may be less likely than their immediate-release counterparts to be associated with a tic increase, although there are no controlled studies examining this directly.

Although this article is focused on pharmacologic interventions for ADHD and tic disorders, it is important to acknowledge that there is an effective evidence-based therapy for tics called comprehensive behavioral intervention for tics (CBIT). A therapist trained in CBIT uses habit reversal training to help the patient identify premonitory urges or sensations, and to implement competing responses in lieu of the tics. By breaking the cycle of negative reinforcement, tic urges and tics themselves decrease. CBIT also helps identify antecedents and familial responses that may be reinforcing tics. CBIT has been shown to reduce tic severity by 50% and is often the first-line

treatment in patients whose tics are causing significant impairment or distress.[4] These patients can address their ADHD symptoms with stimulants and tics through CBIT.

If the ADHD symptoms improve during stimulant titration but tics worsen, CBIT can facilitate reduction of tics. The stimulant dose is held or temporarily reduced while monitoring the tics. The stimulant is retitrated later on when the tics improve. If ADHD symptoms are not adequately improved and the tics have worsened, an α-agonist is added.

α-Agonists are an excellent alternative option in patients with ADHD and tic disorders. Patients with higher levels of impulsivity and hyperactivity would be ideal candidates. α-Agonists do seem to be markedly more effective in treatment of tics in patients with ADHD compared with those without; this suggests that ADHD is a moderating factor and renders α-agonists an especially appealing monotherapy in this patient population.

Guanfacine is often preferred over clonidine because it is less sedating and has a longer half-life, although there are times where sedation is a desired benefit. In choosing short- versus long-acting guanfacine, extended-release guanfacine failed to separate from placebo in the treatment of tics in its one RCT. It should be noted that dosing only went to 4 mg with a mean daily dose of 2.6 mg in the long-acting guanfacine trial, and higher doses in adolescents (up to 7 mg) were shown to be more effective when extended-release guanfacine was used to treat ADHD. Given the negative trial results, however, short-acting guanfacine would be recommended first.

Recommended dosing of immediate-release guanfacine is 0.5 mg to 1 mg nightly for children and adolescents, respectively. Guanfacine can be increased by 0.5 to 1 mg every 3 to 7 days, alternating morning and night, with the higher dose given at night to facilitate onset of sleep. It should be noted that Scahill and colleagues prescribed guanfacine three times a day, with the most common dosing schedule 1 mg at 8 AM, 0.5 mg at 3 PM, and 1 mg at 8 PM. Clinical realities make twice a day dosing much more convenient and practical for families and is therefore recommended.

Atomoxetine is another good option for patients who cannot tolerate stimulants, prefer monotherapy, have a contraindication, or for whom targeted pharmacotherapy with a stimulant plus an α-agonist has not been effective. Dosing follows the typical ADHD recommendations discussed elsewhere in this issue.

Although there is some evidence for efficacy of desipramine in patients with ADHD and tic disorders, its use is not recommended, given potential adverse effects, including cardiovascular, and the availability of safer and effective alternatives.

The antipsychotic medications aripiprazole, pimozide, and haloperidol all have FDA indications for treatment of tics in TD. There is also evidence to support the use of risperidone, a second-generation antipsychotic. The second-generation medications are generally preferred over first generations (typical) when antipsychotics are used. This class of medications is better studied for TD than ADHD, although a few studies have looked at comorbidity and shown some benefit.[26–28] Moreover, antipsychotics do usually show a greater benefit in tic reduction compared with α-agonists.[4]

However, we prefer starting with α-agonists, given their preferable adverse effect profile and higher rate of response in individuals with both TD and ADHD. Antipsychotics are good options in patients unresponsive to α-agonists and CBIT, or whose tic severity impacts their safety and well-being. In patients in which antipsychotics are added to stimulants for other reasons, tics and polypharmacy can be reduced.

Lastly, there are limited data on the use of nutraceuticals for tic disorders. Two studies from Spain showed benefit from magnesium and vitamin B_6, with the caveats that in one trial the supplements were administered intravenously, and the oral administration study was an open-label one.[29,30] A study looking at *N*-acetylcysteine

showed no evidence for efficacy in reducing tics.[31] Omega-3 fatty acids did not reduce tic severity but did reduce tic impairment.[32] There is currently no evidence to support the use of cannabidiol or medical marijuana in the treatment of TD.

SUMMARY

It is essential to understand the frequent and bidirectional overlap of tic disorders and ADHD. A full comprehensive medical and psychiatric evaluation is necessary to separate tic symptoms from ADHD, and to prioritize the most problematic symptoms for intervention. Stimulants are the recommended first-line pharmacotherapy to treat ADHD symptoms in patients with tic disorders. CBIT is an effective behavioral therapy, which is generally considered the first-line treatment of persistent tic disorders. α-Agonists are added to stimulants if tics increase or used as monotherapy to target ADHD and tics. Atomoxetine is also an excellent option to treat ADHD and tics.

CLINICS CARE POINTS

- When evaluating patients with tic disorders, evaluate for comorbidities, such as ADHD, obsessive-compulsive disorder, anxiety, and learning disorders.
- Identify the most problematic symptoms the patient is having and treat those first.
- If tics worsen after starting a stimulant, the medication is held or temporarily reduced, retitrating when they improve.

DISCLOSURE

R.J. Jaffe: research support from Emalex and Teva/Nuvelution. B.J. Coffey Disclosures Past 12 Months: American Academy of Child and Adolescent Psychiatry, honoraria; Emalex, research support; Florida Children's Medical Services, grant support; Harvard Medical School/Psychiatry Academy, honoraria; NIMH, research support; Partners Healthcare, honoraria; Skyland Trail, advisory board; Teva/Nuvelution, research support; Scientific Advisory Board, Tourette Association of America, co-chair; Medical Advisory Board, TAA-cdc Partnership.

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