Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Evidence-based treatment of Tourette's disorder and chronic tic disorders

Joey Ka-Yee Essoe, Marco A. Grados, Harvey S. Singer, Nicholas S. Myers & Joseph F. McGuire

To cite this article: Joey Ka-Yee Essoe, Marco A. Grados, Harvey S. Singer, Nicholas S. Myers & Joseph F. McGuire (2019): Evidence-based treatment of Tourette's disorder and chronic tic disorders, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2019.1643236

To link to this article: https://doi.org/10.1080/14737175.2019.1643236

Accepted author version posted online: 11 Jul 2019.
Published online: 17 Jul 2019.

EXPERT REVIEW OF NEUROTHERAPEUTICS
https://doi.org/10.1080/14737175.2019.1643236

Taylor & Francis
Taylor & Francis Group

REVIEW

Evidence-based treatment of Tourette's disorder and chronic tic disorders

Joey Ka-Yee Essoe[a], Marco A. Grados[a], Harvey S. Singer[b], Nicholas S. Myers[a,c] and Joseph F. McGuire [a]

[a]Division of Child and Adolescent Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [b]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [c]Department of Psychology, Towson University, Towson, MD, USA

ABSTRACT

Introduction: Chronic Tic Disorders and Tourette's Disorder (collectively referred to as TD) are characterized by sudden, rapid, and repetitive motor movements or vocalizations called tics. Children, adolescents, and adults with TD often experience co-occurring psychiatric symptoms and impairments in multiple domains. As a result of tics and other symptoms, patients with TD can develop negative self-views, require considerable accommodations, and experience a poor quality of life. Therefore, the efficient and effective management of TD bears considerable importance.

Areas covered: This expert review evaluated the empirical support for behavioral and pharmacological interventions based on the results of randomized controlled trials (RCTs). Behavioral interventions evaluated include habit reversal training (HRT), comprehensive behavioral intervention for tics (CBIT), and exposure response prevention (ERP). Reviewed pharmacological interventions included alpha-2 agonists, antipsychotics, and anticonvulsants.

Expert opinion: This review identified several efficacious behavioral and pharmacological interventions for TD. However, several gaps in the management of TD include: (1) the access/availability of behavioral interventions, (2) novel and more efficacious treatment approaches, and (3) the development of more comprehensive interventions to manage TD. In order to advance the treatment of TD, additional research is necessary to efficiently, effectively, and comprehensively develop and evaluate new treatments for patients with TD.

ARTICLE HISTORY
Received 10 May 2019
Accepted 10 July 2019

KEYWORDS
Tourette's disorder; behavior therapy; comprehensive behavioral intervention for tics; pharmacotherapy; randomized controlled trials

1. Introduction

1.1. Tics and tic disorders

Tics are sudden, rapid, and repetitive movements or vocalizations that are non-rhythmic [1]. Tics are often discussed in terms of type (e.g. motor and vocal) and complexity (e.g. simple and complex). Tics that involve physical movements are referred to as motor tics, whereas tics that produce sounds are labeled vocal tics. Simple tics are quick and purposeless movements or sounds. In comparison, complex tics often involve multiple muscle groups and may consist of combinations of simple tics, posturing, and pauses. Regardless of type and complexity, tics are relatively common among children and adolescents, with up to 20% of school- age children exhibiting tics for a period of time [2,3]. Despite its common occurrence, many tics will naturally remit over a period of months. Tic disorders are classified based on the age of onset, function, type of tic, and presence of medical conditions or substance use. The diagnoses of Provisional Tic Disorder, Chronic Motor/Vocal Tic Disorder, and Tourette's Disorder all require the onset of symptoms prior to 18 years of age, and the absence of other contributing medical conditions or substances. A Provisional Tic Disorder further requires either single or multiple tics to be present for less than one year. The diagnosis of a Chronic Motor or Vocal Tic Disorder is appropriate when only motor tics or only vocal tics have been present for more than one year, respectively. The diagnosis of Tourette's Disorder is warranted when concurrent multiple motor and one or more vocal tics have been present for longer than one year [1,4].

Chronic Tic Disorders and Tourette's Disorder (collectively referred to as TD henceforth) affect many children and adolescents, but prevalence estimates vary widely (0.03–5.26%) [5]. For instance, Scahill, Sukhodolsky, Williams, and Leckman [6] reported 1–2% of children are affected by TD, whereas Knight and colleagues [7] suggested that TD affects less than 1% of children. Meta-analytic investigations and expert reviews suggest the actual prevalence of TD is likely between 0.3–0.9% in children and adolescents [5,8]. For youth with TD, tics typically emerge between ages 4 and 8, and often begin with simple motor tics. Tics often progress in type and complexity to include simple vocal tics, and complex motor and vocal tics [9]. While most recognizable and socially stigmatizing, coprolalia (obscene language) and copropraxia (obscene gestures) only occurred in up to 20% of individuals with TD [10,11]. Patients with TD report that tics peak in severity during early adolescent years (around 10.5 years old), but often diminish in the late adolescence or early adulthood [12,13]. While tics are the overt behavioral characteristic of TD, many individuals with TD also report experiencing internal unpleasant sensory phenomena called premonitory urges (up to 92% of adults, and 79% of children [14–16]). Premonitory

CONTACT Joseph F. McGuire jfmcguire@jhmi.edu Division of Child and Adolescent Psychiatry, Johns Hopkins University. 1800 Orleans St, Baltimore MD 21287, USA

Article highlights

- Patients with TD and co-occurring conditions experience significant distress and impairment. The efficient and effective management of TD and co-occurring conditions is essential to alleviate distress and impairment associated with TD.
- There are two primary interventions for patients with TD: behavioral and pharmacotherapy treatment. The evidence for these approaches based on randomized controlled trials (RCTs) was reviewed.
- Behavioral treatments such as habit reversal training (HRT), the comprehensive behavioral intervention for tics (CBIT), and exposure response prevention (ERP) were found to be efficacious in RCTs during short-term treatment phases and long-term follow-up periods.
- Pharmacological interventions (i.e. antipsychotics and alpha-2 agonists) were found to be efficacious in RCTs during short-term treatment periods.
- Despite the efficacy of existing interventions, several treatment challenges remain. These challenges include improving the accessibility and response rate of existing interventions and developing comprehensive treatment approaches for the management of TD.

urges precede tics and are transiently reduced by the performance of tics [16,17]. The pattern of urge-relief plays an important role in the neurobehavioral treatment model of tics discussed later.

1.2. Co-occurring conditions, functional impairment, and quality of life

In addition to tics and premonitory urges, most individuals with TD experience one or more co-occurring psychiatric conditions. The most common of these conditions are obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD), with anxiety, mood disorders, and disruptive behaviors also often reported [18]. Tics and co-occurring psychiatric conditions lead individuals with TD to experience health problems (e.g. bodily harm due to tics), social problems (e.g. poor self-perception, peer teasing, bullying), emotional difficulties (e.g. anxiety, depression, aggression, suicidal ideations), and school/work challenges (e.g. difficulties completing assignments, paying attention) [19]. Several studies have documented that TD causes impairment in multiple domains of functioning [20,21]. As a result of tics and co-occurring symptoms, many children with TD have a negative self-view [22], require considerable accommodations to function [23], and experience a poor quality of life [24–26]. Although tics may remit in adulthood, a considerable portion of individuals with TD experience persisting impairment from childhood tics [27]. Therefore, the efficient and effective management of TD in childhood has implications across the lifespan.

This expert review examines the empirical support for interventions to manage TD in randomized controlled trials (RCTs). Based on the efficacy of findings, expert recommendations for the management of TD are provided. Afterward, key gaps in management of TD are identified and discussed. While strategies to optimize existing interventions are presented, there is a need for further research on treatment approaches that comprehensively address all affected domains: reduce tic severity, minimize impairment, cultivate resilience, and improve quality of life for individuals with TD.

2. Behavioral interventions for tics

Behavioral interventions for TD are based on the neurobehavioral model for tics [19,28]. This model acknowledges the genetic, biological, and neurological basis of tics, but suggests that internal and external factors influence the expression of tics. For instance, most patients experience an aversive somatosensory sensation called a premonitory urge that precede tics and cause distress (92% in adults [14]; 79% in children [16]). Patients with TD report that premonitory urges are reduced by the expression of tics [14], which has been confirmed in several experimental studies [29–31]. Consequently, tic expression becomes negatively reinforced due to the reduction in the aversive premonitory urge, which makes this pattern more likely to occur when a premonitory urge is experienced again. This same relationship holds true for external factors as well. Individuals with TD may have difficulty managing tics during certain undesirable activities (e.g. completing homework assignments) [23,32,33]. This can result in the disruption, early discontinuation, and/or avoidance of the activities. As these undesired activities are avoided or discontinued early, the expression of tics in these situations becomes negatively reinforced. Behavioral interventions such as habit reversal training (HRT), the comprehensive behavioral intervention for tics (CBIT), and exposure with response prevention (ERP) aim to interrupt this reinforcement pattern using different therapeutic approaches. Below, we provide a brief description of each behavioral treatment approach and describe the short- and long-term outcomes in clinical trials.

2.1. Habit reversal training

2.1.1. Description

Habit reversal training (HRT) was first described by Azrin and Nunn [34] as a method for eliminating nervous habits and tics. This intervention consists of multiple components that can include psychoeducation, awareness training, competing response training, generalization training, self-monitoring, relaxation training, behavioral rewards, motivational procedures, and social support [35]. However, evidence suggests that there are three central components to HRT: awareness training, competing response training, and social support [36]. Awareness training focuses on building awareness to the occurrence of tics (response detection), physical expression of tics (response description), and eventually to detect the early tic movements or the premonitory urge that precedes the tic (early detection). Competing response training focuses on developing and implementing a competing response that is contingent upon the early detection of the tic. A competing response is a behavior that is physically incompatible with the tic, socially discrete, and could be maintained for up to one minute. After tics are detected, patients perform competing responses to inhibit tic expression. Thereafter, social support can be applied to reinforce the competing response. In social support training, a social support person (usually a caregiver or partner) is trained to help implement awareness training and competing responses outside of the clinic. The social support person is encouraged to provide developmentally appropriate praise for correct implementation. This helps

the therapeutic skills learned in the clinic to generalize to other situations and locations. As individuals with TD practice these skills in clinic and other settings, these skills become easier to apply to manage tics. The therapeutic skills taught in HRT aim to disrupt the reinforcement cycle that maintains tic expression. Specifically, as the tic no longer serves to provide relief from the aversive antecedent (i.e. premonitory urge), the tic would be expressed less and the urge-tic relationship would be weakened or discontinued.

2.1.2. Short-term outcomes

Over the past 40 years, HRT has been studied in patients as young as 5 [37] and as old as 75 years of age [38]. There have been at least eight randomized clinical trials that have compared HRT to waitlist conditions (in which no treatment or therapeutic contact was provided) [39,40] and active comparison conditions (in which a comparison treatment was provided) [41–46]. When compared to waitlist conditions, HRT was found to exhibit significantly greater reductions in tic frequency and tic severity [39,40]. However, when comparing HRT to active comparison conditions, findings have been mixed. HRT was found to exhibit greater reduction in clinician-rated tic severity in comparison to supportive therapy (i.e. an intervention in which clinicians did not impart tic management skills, but provided coping and problem-solving skills) [43,44], and greater reductions in tic frequency in comparison to mass negative practice (in which patients voluntarily perform tics for an extended period of time) [41]. Meanwhile, HRT was found to produce comparable reductions in clinician-rated tic severity when compared to ERP (in which patient use tic suppression to reduce tic severity, see section 2.3 below for a full description of ERP) [42,46] and psychoeducation [45].

When examining these non-significant studies, a few confounding factors were identified. First, ERP and HRT share similar therapeutic targets of discontinuing the reinforcement cycle in which tic expression produces relief from premonitory urges [42,46]. Thus, it may be anticipated that these interventions produced comparable benefit. Second, there is a considerable difference in therapeutic contact between the 12 two-hour ERP sessions and the 10 one-hour HRT sessions reported in Verdellen et al. [42]. While another study found that 1- and 2-h ERP sessions provide comparable benefit [47], the differences in therapeutic contact complicate the findings of Verdellen et al. [42]. Finally, Yates and colleagues [45] delivered both psychoeducation and HRT in a group format, which is noticeably different from the individual format in all other studies. Indeed, Rizzo et al. [46] found limited improvement in clinician-rated tic severity from psychoeducation when it was delivered in an individual format, which may suggest that there is something unique about the group format for psychoeducation. Taken together, while these studies suggest that HRT produces comparable therapeutic benefit to ERP and psychoeducation, there are methodological differences that raise questions about the generalizability of these findings.

2.1.3. Follow-up and long-term outcomes

Several studies have followed individuals who received HRT in clinical trials over a period of months. Verdellen and colleagues [42] re-assessed participants three months after the initial treatment phase, but interpretations are confounded by the cross-over design of treatment (e.g. the HRT group received ERP after the initial treatment phase). Wilhelm et al. [43] and Deckersbach et al. [44] re-assessed participants who received HRT ten and six months after the initial weekly treatment phase, respectively. These studies found that participants who received HRT continued to exhibit long-term reductions in clinician-rated tic severity compared to supportive therapy up to 10 months after treatment. Finally, Azrin et al. [41] found that participants who received HRT continued to experience reduced tic frequency up to 18 months after the initial treatment phase. Despite improvement by many participants receiving HRT compared to comparison conditions, Dabrowski and colleagues [48] re-assessed after 12 months participants who received group HRT or group psychoeducation in Yates et al. [45] and found that both groups continued to improve after the initial treatment phase.

2.2. Comprehensive behavioral intervention for tics

2.2.1. Description

The comprehensive behavioral intervention for tics (CBIT) is a natural extension of HRT and represents its successor in many ways [28]. For instance, CBIT incorporates the core therapeutic components of HRT protocols: psychoeducation about the TD, awareness training, competing response training, social support, and a developmentally appropriate behavioral reward system to reinforce skill practice. However, CBIT includes the additional therapeutic techniques of relaxation training and functional assessment/intervention to further target internal and external factors that influence tic expression. In addition to providing HRT skills to disrupt the negative reinforcement cycle, CBIT teaches relaxation training skills to manage internal mood states that are associated with tic expression (i.e. anxiety, stress). The functional assessment and intervention component aim to address external factors that influence tic expression. The functional assessment systematically evaluates situations and environments (i.e., antecedents) that are associated with worsening tic severity, and inquiries about outcomes of those situations in which tics are worse (i.e., consequences). Afterward, the functional intervention applies targeted strategies to either decrease antecedents that worsen tic severity, or decrease the socially mediated consequences that may be maintaining/exacerbating tics (i.e. avoidance or early discontinuation of less preferred activities) and promote adaptive skill use instead (i.e. use of HRT skills). Similar to HRT, the therapeutic skills aim to disrupt the reinforcement cycle that maintains tic expression. However, CBIT targets both internal (i.e. premonitory urges, anxiety, stress) and external factors (i.e. specific situations and contexts) that reinforce tic expression, whereas HRT primarily targets only internal factors (i.e. premonitory urges). As the reinforcement cycle for internal and external factors is disrupted, tics are usually expressed less and the urge-tic relationship is weakened and/or discontinued.

2.2.2. Short-term outcomes

There have been three randomized clinical trials that have compared CBIT to either a waitlist condition [49] or the active comparison of supportive therapy [50,51]. The two active comparison trials were large multi-site randomized clinical

trials of CBIT compared to supportive therapy in children [50] and adults [51]. In parallel fashion, participants with TD were randomly assigned to receive eight sessions of CBIT or psychoeducation and support therapy (PST) over a period of 10 weeks. Both multi-site trials found CBIT to be superior to PST in reducing clinician-rated tic severity and improving global outcomes; however, there were some slight differences in the magnitude of treatment effects and response rates. In children and adolescents, Piacentini and colleagues [50] found a moderate-to-large treatment effect (scaled difference between pre- and post-treatment severity) for CBIT (d = 0.68) and a 53% treatment response rate. Meanwhile, in older adolescents and adults, Wilhelm and colleagues [51] found a comparable moderate-to-large treatment effect for CBIT (d = 0.57), but a lower treatment response rate of 38%. CBIT was not associated with any adverse consequences such as symptom substitution or worsening of tic symptoms across trials [52]. Finally, Ricketts et al. [49] compared CBIT delivered over the internet to a waitlist condition and found that CBIT significantly reduced clinician-rated tic severity and had a 33% treatment response rate in comparison to the waitlist condition.

2.2.3. Follow-up and long-term outcomes

Two studies have followed-up individuals who responded to CBIT for up to 6 months. Piacentini et al. [50] and Wilhelm et al. [51] both found that reductions in clinician-rated tic severity were maintained up to 6 months after initial treatment with CBIT. Moreover, participants followed-up after the initial treatment phase exhibited improved psychosocial outcomes [53,54]

2.3. Exposures with response prevention

2.3.1. Description

Exposure with response prevention (ERP) is a behavioral therapy that relies upon tic suppression to reduce tic severity. Many individuals with TD report the ability to suppress tics for some period of time which can be influenced by contextual factors [55] and reinforcement patterns [29–31]. ERP seeks to capitalize on this natural ability and extend the duration of tic suppression periods over increasingly longer intervals of time. This treatment begins with a training phase in which patients practice systemically suppressing all tics. Subsequently, patients begin to focusing on premonitory urges during sessions and engage in tic suppression. Over successive sessions, the intensity of treatment is increased by focusing the attention to the part of the body in which the urge is experienced, and exposure (either imagined or in vivo) to situations in which tics are often expressed – all while engaging in tic suppression. Tic suppression skills in ERP aim to disrupt the reinforcement cycle that maintains tic expression and help patients habituate to premonitory urges [56].

2.3.2. Short-term outcomes

There have been at least two randomized clinical trials that have compared ERP to HRT [42,46]. When compared to HRT, ERP was found to exhibit comparable reductions in clinician-rated tic severity in both trials [42,46]. Although the findings from one trial are confounded by greater therapeutic contact in the ERP group relative to the HRT group (12 two-hour ERP sessions versus 10 one-hour HRT sessions) [42], the other trial had comparable therapeutic contact between treatment groups [46]. There is also some evidence from an open-trial that suggests one-hour and two-hour sessions of ERP produce comparable therapeutic benefit [47]. Although some clinicians may be concerned that tic suppression could result in a 'tic rebound' effect after therapy sessions, there was no increase in tic severity following treatment with ERP [57].

2.3.3. Follow-up and long-term outcomes

Unfortunately, there have been no follow-up or long-term studies of individuals who received ERP in clinical trials. While Verdellen et al. [42] re-assessed participants who received ERP and HRT three months after the initial treatment phase, these interpretations are confounded by the cross-over design of treatment (e.g. HRT group received ERP after the initial treatment phase). Fortunately, there is a large clinical trial that is currently underway that will provide information on the long-term outcomes of ERP delivered over the internet [58].

3. Pharmacological interventions for tics

Studies investigating the pathophysiology of TD implicate abnormalities within the cortico-basal ganglia-thalamo-cortical (CBGSC) circuit and related neurotransmitter systems (e.g. dopamine, glutamatergic, GABAergic, noradrenergic, serotonergic, histaminergic, etc). The CBGTC is a complex circuit connecting the frontal cortex to the basal ganglia, to the thalamus, and back to the cortex [59]. The CBGTC has also been implicated in other psychiatric disorders that commonly co-occur with TD, such as OCD and ADHD (see Peters et al. [60] for a review). Recent reviews have provided an update on the relationship between the pathophysiology and pharmacotherapy for TD [59].

Several neurotransmitters are involved in CBGTC circuit, and medications targeting these neurotransmitters have been investigated for pharmacological intervention. RCTs of pharmacological agents have primarily focused on three classes of medications: alpha-2 agonists, antipsychotics, and anticonvulsants/movement disorder medications (see Pringsheim et al. [61], McGuire et al. [62], or Singer [63] for comprehensive review of all open-label and RCTs for TD). Meta-analyses have shown efficacy for some alpha-2 agonists [64] and antipsychotics [64,65] in comparison to placebo for reducing tic severity; however, there is inconsistent evidence that anticonvulsant/movement disorder medications reduce tic severity compared placebo [61,66].

The RCTs for the aforementioned three classes of medications are presented and efficacy of individual medications within these classes reviewed. Most studies have focused on the short-term outcomes of RCTs, with few studies following patients over the long-term use of these medications within clinical trials. The short-term outcomes of RCTs are presented, with the follow-up/long-term outcomes provided when available. While RCTs represent the gold standard by which pharmacological interventions are evaluated, there are several methodological and design challenges that can produce

variability in study outcomes and limit the broader interpretation of findings. First, there is variability in the primary outcome measure used in RCTs for TD. While most RCTs in the past few decades have utilized the clinician-administered Yale Global Tic Severity Scale (YGTSS) [67], RCTs conducted prior to its development have used measures of tic severity that are different and may not entirely be comparable to one another (e.g. other clinician-rated scales, self-reports or observed tic frequency; see McGuire et al. [68] for a comprehensive review of TD assessments). Second, due to the resource-intensive nature of RCTs, sample sizes for many clinical trials are small and may have less than the desired statistical power to detect differences between medications and placebo. Third, tics naturally wax and wane in severity which highlights the importance of including a placebo/control condition in clinical trials. While the placebo response across clinical trials is often small (d = .16), it can affect up to 19% of participants with TD [69]. Thus, if a trial has a small sample size and a high placebo response, the true efficacy of a medication may be underestimated and underappreciated. Finally, there is considerable heterogeneity in the sample characteristics across RCTs for TD. For instance, some clinical trials have excluded individuals with TD who have co-occurring psychotic disorders, mood disorders, and moderate to severe OCD [70–72], whereas other trials have required co-occurring ADHD for study participation [73–75]. Thus, the findings from one many not accurately generalize to another study.

Based on recommendations provided by treatment guidelines [61,76–80], this section begins with a review of the evidence for first-line TD medications – alpha-2 agonists. This section then proceeds to review the second- and third-line medication options in the following order: atypical antipsychotic medications, typical antipsychotic medication, anticonvulsants, and other medications. Practice guidelines have provided varied recommendations for second- and third-line treatments [61,76,77,79], and there is also growing interest in several other pharmacological interventions that are discussed further in the expert opinion section.

3.1. Alpha-2 agonists

Alpha-2 agonists are antihypertensive medications that affect the central and peripheral nervous system. Broadly, these medications suppress the sympathetic nervous system and reduce arousal. While education and behavioral therapy are recommended by most guidelines as first-line treatment for TD [76,78–80], alpha-2 agonists are generally recommended as first-line medicines based on their safety profile [76,79]. Alpha-2 agonists such as clonidine and guanfacine are approved by the FDA to treat ADHD, and there have been at least 15 RCTs that investigated the efficacy of clonidine and guanfacine for reducing tic severity.

3.1.1. Clonidine

Clonidine is an alpha-2 agonist that indirectly inhibits the release of norepinephrine. There have been at least 13 RCTs that have examined the efficacy of clonidine compared to either a placebo [75,81–84] or active medication condition (e.g. desipramine [73], haloperidol [85–88], levetiracetam [89], risperidone [90], and tiapride [91]). In comparison to placebo, clonidine has been found efficacious for reducing clinician-rated tic severity in four studies [75,81–83], while one trial found that clonidine did not reduce observed tic frequency to a greater degree than placebo [84]. In most drug comparison trials, clonidine did not significantly differ from other medications. Specifically, clonidine, risperidone [90], haloperidol [85–88], and tiapride [91] were all found to reduce clinician-rated tic severity, but there were no statistically significant differences between medication groups at post-treatment in these trials. As noted above, this may likely be due to the small sample sizes of these clinical trials. In a trial of patients with TD and co-occurring ADHD, desipramine, but not clonidine, reduced clinician-rated tic severity [73]. Clonidine was found to reduce clinician-rated tic severity to a greater degree as compared to levetiracetam [89]. Across RCTs that included clonidine, common side effects included sedation and/or fatigue [75,82,89,90], faintness and/or dizziness [75,82,85,86,90], irritability [75,82,89], dry mouth [75,82,90], hypotension [85,86], and insomnia [83,89]. In these RCTs, the treatment period ranged between 4 and 16 weeks, with no published reports on the durability of the initial treatment gains from maintenance on clonidine in these clinical trials.

3.1.2. Guanfacine

Guanfacine is another alpha-2 agonist that reduces the excitation of the peripheral sympathetic system. There have been at least three RCTs that have examined the efficacy of guanfacine compared to placebo with mixed results [74,92,93]. Guanfacine was found to be efficacious in reducing clinician-rated tic severity in youth with TD and co-occurring ADHD [74]. However, two other RCTs found that guanfacine [92] and extended-release guanfacine [93] were no more efficacious than placebo in reducing tic severity. Notably, these two latter clinical trials excluded participants if they were receiving pharmacotherapy for co-occurring conditions such as ADHD [92,93]. Across clinical trials with guanfacine, common side effects included sleepiness and/or drowsiness [92,93], fatigue [92,93], headache [92,93], dry mouth [93], and some reduction in blood pressure and pulse [74]. The short-term treatment period in these trials ranged between 4 and 8 weeks, with no published reports on the durability of the initial treatment gains from maintenance guanfacine in these trials. To the authors' knowledge, there are no direct comparison studies between clonidine and guanfacine.

3.2. Antipsychotics

Currently, the only medications approved by the United States Food and Drug Administration (FDA) for the treatment of tics are all antipsychotics: haloperidol, pimozide, and aripiprazole. Typical antipsychotics primarily affect dopamine in the central nervous system. Dopamine is a key neurotransmitter in the CBGTC circuit and motor system, and thus is a logical neurotransmitter to target in the management of TD (see Mogwitz et al. [94] and Augustine and Singer [59] for further discussion on the role of dopamine in TD). Meanwhile, atypical antipsychotics affect the dopamine and serotonin systems.

3.2.1. Atypical antipsychotics

3.2.1.1. Aripiprazole. There have been at least four RCTs that have examined the efficacy of aripiprazole compared to placebo [70,71] and active comparison medications (e.g. risperidone, tiapride) [95–97]. In comparison to placebo, aripiprazole has been efficacious in reducing clinician-rated tic severity [70,71]. However, when compared to other medications, no significant differences have been observed. Specifically, aripiprazole, risperidone [95,97], and tiapride [96] were all found to reduce clinician-rated tic severity, but there were no statistically significant differences between medication groups at post-treatment. Across these clinical trials, common side effects of aripiprazole include weight gain and/or appetite increase [71,95], gastrointestinal complaints [95], sedation, drowsiness, or fatigue [70,95], somnolence [70], and blurred vision [95]. In these RCTs, the short-term treatment period ranged between 8 and 12 weeks, with no published reports on the durability of the initial treatment gains from maintenance aripiprazole.

3.2.1.2. Risperidone. There have been at least six RCTs that have investigated the efficacy of risperidone compared to placebo [72,98] and active comparison medications (e.g. pimozide, aripiprazole, clonidine) [90,95,99,100]. Similar to other antipsychotic medications, risperidone has demonstrated considerable efficacy in reducing clinician-rated tic severity compared to placebo [72,98]. Meanwhile, when compared directly to other psychotropic medications, the findings have been mixed. Risperidone and pimozide were compared in at least two RCTs. Although both medications reduced clinician-rated tic severity [99,100], risperidone was found to be more effective than pimozide in one study [100], but comparable in another [99]. However, no significant differences in clinician-rated tic severity were found between clinical trials that compared risperidone to either aripiprazole [95] or clonidine [90]. In these studies, common side effects of risperidone included increased appetite and/or weight gain [72,95,98–100], sedation, drowsiness, fatigue [72,90,95,98–100], somnolence [98,99], depression [99], and headache [98,100]. The short-term treatment period in these clinical trials varied between 4 and 8 weeks, with no published report examining the durability of initial treatment gains from maintenance risperidone.

3.2.1.3. Ziprasidone. Ziprasidone is an atypical antipsychotic medication that affects dopamine, serotonin, and epinephrine/norepinephrine receptors. There has been at least one RCT evaluating the efficacy of ziprasidone compared to placebo [101]. Ziprasidone was found to be efficacious in reducing clinician-rated tic severity compared to placebo. In this clinical trial, a common side effect of ziprasidone was sedation [101]. The short-term treatment period in this trial lasted eight weeks, and there has been no published report on the durability of initial treatment gains from maintenance ziprasidone within clinical trials.

3.2.2. Typical antipsychotics

3.2.2.1. Haloperidol. Haloperidol was the first antipsychotic medication approved for the management of TD and has been well studied in patients with TD. There have been at least five RCTs that have compared haloperidol to placebo [102–104] and active comparison conditions (e.g. clonidine, tiapride, pimozide) [85,102,103,105]. The efficacy of haloperidol has been mixed in comparison to placebo and other medications. In comparison to placebo, haloperidol was found to be more efficacious in reducing clinician-rated tic severity in one study [102] but not in another [103]. While haloperidol was found to be efficacious in reducing clinician-rated tic severity [85,102,105], there was no difference in symptom reduction when compared to tiapride [105]. Similarly, a single report found haloperidol to yield smaller symptom reduction when compared to clonidine [85]. Furthermore, in comparison to pimozide, one RCT reported that haloperidol was slightly more efficacious in reducing clinician-rated tic severity than pimozide [102], another RCT reported that it was less efficacious than pimozide [103], yet another RCT with a small sample reported that its efficacy did not differ from pimozide [104]. Across these RCTs, common side effects of haloperidol included extrapyramidal symptoms (e.g. motor restlessness, muscle rigidity, muscle spasms and contractions) [102–104], anticholinergic side effects (e.g. blurred vision, constipation, dry mouth) [104], dizziness [85], somnolence, and depression [85,103]. In general, the short-term treatment period for these studies ranged between 4 and 12 weeks, with at least one report following patients for up to a period of 20 months. Specifically, Ross & Moldofsky [104] reported that the two participants who received haloperidol continued to exhibit improvement up to 20 months after the initial treatment phase, but both required benztropine mesylate to control extrapyramidal effects.

3.2.2.2. Pimozide. There have been at least six RCTs with over five participants, which have investigated the efficacy of pimozide compared to placebo [102,103,106] and active medication conditions (e.g. risperidone, haloperidol) [99,100,102–104]. In comparison to placebo, pimozide was found to be more efficacious in reducing clinician-rated tic severity [102,103,106]. However, the efficacy of pimozide relative to other antipsychotic medications has been mixed. While pimozide and risperidone have both been found to reduce clinician-rated tic severity [99,100,104], pimozide was found to be less effective than risperidone in one study [100], but comparable in another [99]. Similarly for the comparison of pimozide and haloperidol, findings have also been mixed. While pimozide and haloperidol both reduce clinician-rated tic severity, one study found that pimozide had lower post-treatment tic severity relative to haloperidol [103], another study found the opposite pattern at post-treatment [102], and the third found no between group differences at post-treatment [104]. Across these RCTs, common side effects of pimozide include extrapyramidal side effects [99,102–104,106], increased appetite and/or weight gain [99,100,103], anticholinergic side effects [104,106], dizziness and/or fatigue [99,100], somnolence [99], and depression [99]. In general, the short-term treatment period for these studies ranged from 4 to 12 weeks, with at least one report following patients for up to a period of 20 months. Ross and Modofsky [104] found that amongst the seven patients treated with pimozide, six continued to exhibit improvement up to 20 months after the initial treatment

phase. Although none reported lethargy or akinesia, two required benztropine mesylate to control extrapyramidal effects and two reported transient depression.

3.2.2.3. Ecopipam.

Ecopipam is a highly selective antagonist for D1 (excitatory) dopamine receptors, which is in contrast to targeting the D2 (inhibitory) dopamine receptors associated with antipsychotics medications. There has been at least one RCTs that has examined the efficacy of ecopipam compared to placebo [107], and another placebo-controlled RCT (NCT02102698) is ongoing. Ecopipam was found to be more efficacious than placebo in reducing clinician-rated tic severity in children with TD. In this RCT, short-term efficacy of ecopipam was measured after four weeks of treatment, with no report the durability of initial treatment gains.

3.3. Anticonvulsants

Anticonvulsants are a broad class of medications initially developed to treat seizures. Amongst several mechanisms, anticonvulsants can target the receptors of two major neurotransmitters in the CBGTC pathways, inhibitory gamma-aminobutyric acid (GABA) receptors, and excitatory glutamate receptors. GABA and glutamate modulate motor movements via intricate interactions with other neurotransmitters in the CBGTC pathways including dopamine, histamine, and acetylcholine. The mechanism of action for this class of medications is complex and multi-factorial, and interested readers should see a comprehensive review for further detail (see Augustine and Singer [59]). At least two anticonvulsant medications have been evaluated in patients with TD in small RCTs [89,108,109].

3.3.1. Topiramate

Topiramate is a broad-spectrum antiepileptic that increases cerebral $GABA_A$ concentration and selectively blocks some glutamate receptors. There have been at least one RCT that has examined the efficacy of topiramate compared to placebo [108]. In this trial, topiramate has been found to be more efficacious in reducing clinician-rated tic severity than placebo [108]. Side effects of topiramate such as somnolence, cognitive problems, and weight loss were not reported to occur more often than placebo in this trial. The short-term treatment period lasted 10 weeks, and there has been no published report on the durability of initial treatment gains from maintenance topiramate within clinical trials.

3.3.2. Levetiracetam

Levetiracetam is a broad-spectrum antiepileptic medication with atypical GABAergic effects. Although the exact mechanism of action is unknown, levetiracetam binds to synaptic vesicle protein SV2A and inhibits the release of neurotransmitters. There have been at least two RCTs that have examined the efficacy of levetiracetam compared to placebo [109] and active medication (clonidine) [89]. Levetiracetam did not reduce clinician-rated tic severity in comparison to either placebo [109] or clonidine [89]. The common side effects of levetiracetam in these trials included irritability, sadness/depression, anxiousness, tiredness, and insomnia [89,109]. In these RCTs, short-term efficacy of levetiracetam was measured between 4 and 6 weeks of initial treatment, with no published report the durability of these initial treatment gains.

3.4. Other medications

3.4.1. Baclofen

Baclofen is a muscle relaxant often prescribed to treat muscle spasms, clonus, rigidity, and spasticity. It is a $GABA_B$ analog that activates $GABA_B$ receptors. There has been at least one small RCT that has examined the efficacy of baclofen compared to placebo [110]. While baclofen was found to reduce tic-related impairment, there was no difference in clinician-rated tic severity reductions between baclofen and placebo [110]. The side effects of baclofen were transient and included stomach complaints, anxiety, constipation, and headaches. The short-term efficacy of baclofen was measured over a period of four weeks, with no published report on the durability of initial treatment gains.

4. Summary of studies and treatment recommendations

This review examined the empirical support of interventions to manage TD in randomized controlled trials. Based on the findings of this review, there are several medications and behavioral interventions were found to demonstrate short-term efficacy and positive follow-up/long-term outcomes for reducing tic severity. Table 1 provides a summary of these findings, which are organized by the recommendations of practice parameter papers and expert guidelines [61,76–80]. These guidelines recommend psychoeducation when tics are transient and/or mild in severity. Meanwhile, behavioral interventions (i.e. ERP, HRT, or CBIT) are recommended when tic severity is moderate or greater. Finally, medications such as alpha-2 agonists and antipsychotics are recommended in combination with behavioral interventions when tics are severe [61,76,78,80]. For those individuals with TD who are unresponsive to multiple evidence-based medications and behavioral interventions, there are a few alternative treatment approaches that have shown promises in open-label trials or case reports (e.g. botulinum toxin, deep brain stimulation, transcranial magnetic stimulation, and investigational medications such as VMAT-2, ecopipam, fluphenazine; see Sharp and Singer [111] or Martino and Pringsheim [112]) [113–115]. However, there is limited information on the short-term and follow-up/long-term outcomes of these approaches in RCTs.

5. Conclusion

Over the past 40 years, research has identified several pharmacological and behavioral interventions that are efficacious for reducing tic severity in TD. However, therapeutic improvement from these interventions is less than desired, with treatment responders often remaining symptomatic, and few interventions exist to address the psychosocial impairments associated with TD. Thus, while the field had made progress in the past few decades, there is still considerable further

Table 1. Behavioral and pharmacological treatments recommended by two or more practice guidelines.

Tier 1 treatments	Tier 2 and Tier 3 treatments	Treatments requiring further support in RCT
CBIT [61,76]	Clonidine [61,76,77,79]	Neurofeedback [61,78]
ERP [78,80]	Guanfacine [61,76,77,79]	Repetitive Transcranial Magnetic Stimulation [61,76,80]
HRT [61,76,78,80]	Risperidone [61,76,77,79]	Tetrahydrocannabinol [61,77], *for adults* [79]
	Aripiprazole [61,77,79]	Baclofen [61,77,79]
	Ziprasidone [61,76,77]	Levetiracetam [61,77]
	Pimozide [61,76,77,79]	Quetiapine [77,79]
	Haloperidol [61,76,77,79]	Tetrabenazine [77,79]
	Tiapride [61,77]	Topiramate [61,77,79]
	Olanzapine [76,77]	Ziprasidone [79]
	Botulinum toxin [61], *for adults* [79]	Deep Brain Stimulation [61,76,80]

Note. This table presents a list of treatments mentioned in two or more guidelines. The practice guidelines included the following: the 2019 American Academy of Neurology [61], the 2013 American Academy of Child & Adolescent Psychiatry Practice Parameters [76], the 2012 Canadian Journal of Psychiatry Guidelines: Pharmacotherapy guideline [79] and other therapies [80], the 2011 European Child and Adolescent Psychiatry Guideline: Pharmacotherapy guideline [77] and behavioral/psychosocial guideline [78].

Tiers 1, 2, and 3 treatments were organized by side-effect profile (low to high), then support for efficacy (high to low) as found in published guidelines. Treatments awaiting definitive RCT support are arranged by invasiveness or side-effect profile (low to high).

research necessary to efficiently, effectively, and comprehensively provide relief to patients with TD.

6. Expert opinion

While this review identified the efficacy of pharmacological and behavioral interventions to reduce tic severity, there remain several challenges to management of TD. This section discusses these challenges and provides emerging solutions to address them.

6.1. Limited access and availability of behavioral treatments

First, while meta-analyses demonstrate the efficacy of behavioral interventions [38] and experts recommend it as an initial therapeutic approach to manage tic severity, there are a limited number of clinicians trained in evidence-based behavioral interventions [116]. This presents a considerable challenge to implementing the recommended guidelines because of the limited availability and accessibility of trained treatment providers [117]. As a result, individuals with TD are often prohibited from receive behavioral interventions or at a minimum experience long wait times before initiating treatment. Thus, the first challenge confronting the evidence-based management of TD is the limited accessibility and availability of behavioral interventions.

There are several innovative approaches to increase the access and availability of behavioral interventions. First, there are several training opportunities (i.e. seminars, institutes, workshops) made available to increase the number of clinicians trained in evidence-based behavioral interventions [117-117]. Second, several studies have explored different treatment delivery modalities to increase the access and availability of evidence-based behavioral interventions. For example, behavioral interventions have been adapted to be delivered in a group format [45,118], as well as in an intensive individual format [119]. Perhaps most promising, several research groups have used and/or are beginning to use telemedicine approaches to deliver behavioral interventions over the internet [49,58,120–123], and via digital recordings [124,125]. While these strategies collectively have shown considerable promise, future research is still needed to explore approaches to increase the accessibility and availability of behavioral interventions for individuals with TD.

6.2. Limited therapeutic response to evidence-based treatments

The second challenge confronting the evidence-based management of TD is the limited therapeutic response to existing behavioral interventions and pharmacological treatments. Although many patients with TD experience significant reductions in tic severity in RCTs [38,64], evidence-based treatments rarely result in complete tic remission [126,127]. Thus, while treatment effects are large in many cases, there is considerable room to improve the efficacy of these treatments.

6.2.1. Approaches to enhance therapeutic outcomes for behavioral interventions

There are several possible approaches to enhance therapeutic outcomes for behavioral interventions. First, it may be possible to enhance therapeutic outcomes by optimizing the learning processes underlie behavioral interventions. For instance, associative learning and reward learning are two processes that are implicated in behavioral interventions. There are several therapeutic strategies that can be implemented to optimize these learning processes during psychosocial interventions for children and adolescents [128]. Alternatively, these learning processes may be enhanced using pharmacological augmentation. For instance, cognitive enhancers such as d-cycloserine have shown promise to enhance therapeutic outcomes and/or expedite therapeutic gains when paired with psychosocial interventions [129,130]. As these psychosocial treatments rely on similar learning processes, it may improve outcomes for individuals with TD as well. Second, it may be possible to enhance therapeutic outcomes by increasing use of behavioral intervention skills on a regular basis (i.e. increased homework compliance). Given that behavioral intervention skills (i.e. competing response or tic suppression) only reduce tic severity when used, it could be inferred that increased practice would generalize to greater severity reductions. Unfortunately, little is known about the relationship between homework compliance with behavioral

intervention skills and therapeutic outcomes. Thus, given the importance of practicing behavioral intervention skills beyond the clinic, future research should examine the relationship between skills use (i.e. homework compliance) and treatment outcomes and explore innovative ways in which to enhance behavioral skill use.

6.2.2. Approaches to enhance therapeutic outcomes for pharmacological treatments

Although several medications demonstrate a varying degree of efficacy for reducing tic severity, most are accompanied by side effects that can impede long-term use. Moreover, the long-term consequences of continued medication use remain unstudied among individuals with TD. As our understanding regarding the neurobiology of TD continues to advance [59,131], it is important that novel medications and new therapeutic targets be investigated to reduce tic severity with few side effects. While this review focused on evidence from RCTs, there are medications and treatment approaches that have shown considerable promise that were not discussed because they require further evaluation within an RCT.

First, several neurotransmitters and receptors have been implicated in the neurobiology of TD, but have been relatively understudied in RCTs (e.g. glutamate [132], endocannabinoids [133]; see Sharp and Singer [111] or Martino and Pringsheim [112]). Future research should examine the potential benefit of medications that target these transmitters and receptors (e.g. d-serine; riluzole; cannabidiol, tetrahydrocannabinol) [134,135]. Second, several existing efficacious medications target dopamine receptors but are accompanied by side effects that limit long-term tolerability. Future research should explore promising compounds that reduce tic severity and have a favorable side effect profile relative to antipsychotic medications. These include medications such as the aforementioned ecopipam as well as vesicular monoamine transporter 2 (VMAT-2) inhibitors (e.g. tetrabenazine, deutetrabenazine, and valbenazine) [107,136,137]. VMAT-2 inhibitors deplete dopamine by preventing the formation of presynaptic vesicles that contain dopamine and have shown promise for alleviating symptoms in movement disorders including patients with TD–based on open-label trials, chart reviews, and case reports [136,138–144]. Finally, most TD medications have focused on reducing tic severity, but have not examined whether these medications also influence premonitory urges. Given the role that premonitory urges play in behavioral interventions, it would be interesting to examine whether medications have differential efficacy for reducing and/or discontinuing premonitory urges.

6.2.3. Investigation of novel therapeutics

Novel non-pharmacological therapeutics such as transcranial magnetic stimulation (TMS), botulinum toxin, acupuncture, and biofeedback have also shown some potential for reducing tic severity (see Table 1, and Sharp and Singer [111]). For example, Grados, Huselid, and Duque-Serrano [145] reviewed open-label studies of TMS as a therapeutic for patients with TD. Although findings across reports were mixed, TMS trials targeting the supplementary motor area have positive effects for reducing clinician-rated tic severity especially in the presence of co-existing ADHD and/or OCD [145].

6.3. The need to address patient well-being beyond tics

The predominant focus of evidence-based interventions for TD has been on reducing tic severity. Although reductions in tic severity are important, this focus implies that tic severity is entirely responsible for the distress, impairment, and poor quality of life experienced by individuals with TD. Many individuals experience significant benefit from evidence-based interventions for TD, but a considerable percentage continues to experience distress from tics and associated challenges (e.g. health problems, social problems, emotional difficulties, and school/work challenges). As complete tic remission is uncommon with any evidence-based intervention, patients with TD have to develop effective coping skills to manage the daily challenges associated with TD and co-occurring conditions. Therefore, the third challenge confronting evidence-based management of TD is the development of comprehensive interventions that reduce impairment, develop adaptive coping skills, effectively managing co-occurring neuropsychiatric conditions, and improve the quality of life.

Despite its recognition, there has been little research aimed at psychosocial interventions to reduce tic-related impairment, develop adaptive coping skills, and improve the quality of life for individuals with TD. Storch et al. [146] piloted a modular cognitive behavioral protocol aimed at promoting resiliency and building coping skills in an open-label case series of children with TD. This initial work was extended by McGuire et al. [147] who further refined this modular treatment protocol and evaluated its efficacy in a randomized controlled trial. Youth with TD receiving this intervention exhibited reduced tic-related impairment and improved quality of life compared to the waitlist control condition, with therapeutic gains maintained for at least one month after initial treatment phase. While this demonstrates the promise of psychosocial interventions to develop adaptive coping skills [147] this research has entirely focused on youth. Additional research is needed to further develop and evaluate psychosocial interventions for adults with TD. Moreover, there are few comprehensive treatment protocols that offer guidance to simultaneously address the treatment of tics and related co-occurring neuropsychiatric conditions. The development of such comprehensive treatment protocols could facilitate communication and collaboration between clinicians across specialties (i.e. psychology, psychiatry, neurology).

Funding

This paper was not funded.

Declaration of interest

JF McGuire has received support from the Tourette Association of America, American Academy of Neurology, the Brain Research Foundation, American Psychological Foundation, and the Hilda and Preston Davis Family Foundation. He also receives royalties from Elsevier and serves as a consultant for Bracket, Syneos Health, and Luminopia. MA Grados serves as a member of the Cornelia de Lange Syndrome Foundation (CdLS) Medical Advisory Board. He also receives research/grant support from the Palo Alto Health Sciences, Inc. and the Centers of Disease Control and Prevention through the Tourette Association of America. HS Singer serves as a consultant for Cello Health BioConsulting,

ClearView Healthcare Partners, Teva, Abide Therapeutics, and Trinity Partners. He receives research/grant support from the Tourette Association of America and royalties from Elsevier Inc. Dr. Essoe recieves support from the Tourette Association of America. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Joseph F. McGuire http://orcid.org/0000-0002-6128-8138

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub: Washington, DC; 2013.
2. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: A community-based study. Neurology. 2002;59:414–420.
3. Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome: part 1: the epidemiological and prevalence studies. J Psychosom Res. 2008;65:461–472.
4. Wu MS, McGuire JF. Psychoeducation about tic disorders and treatment, in the clinician's guide to treatment and management of youth with Tourette syndrome and tic disorders. Academic Press: Cambridge (MA); 2018. p. 21–41.

•• **Provides an overview on psychoeducation relevant for patients and families with Tourette's Disorder and other tic disorders. This chapter provides sample dialogue and role plays to help clinicans convey this information to patients and families in an effective manner.**

5. Scharf JM, Miller LL, Gauvin CA, et al. Population prevalence of Tourette syndrome: A systematic review and meta-analysis. Mov Disord. 2015;30:221–228.
6. Scahill L, Sukhodolsky DG, Williams SK, et al. Public health significance of tic disorders. Behav Neurol Mov Disord. 2005;96:240.
7. Knight, T., T. Steeves, L. Day, et al. Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr neurol. 2012;47:77–90.
8. Scahill L, Specht M, Page C. The prevalence of tic disorders and clinical characteristics in children. J Obsessive Compuls Relat Disord. 2014;3:394–400.
9. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette syndrome: the first two decades. Pediatr English Ed. 1998;102:14–19.
10. McGuire JF, Nyirabahizi E, Kircanski K, et al. A cluster analysis of tic symptoms in children and adults with Tourette syndrome: clinical correlates and treatment outcome. Psychiatry Res. 2013;210:1198–1204.
11. Freeman RD, Zinner SH, MÜLLER-VAHL KR, et al. Coprophenomena in Tourette syndrome. Dev Med Child Neurol. 2009;51:218–227.
12. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med. 2006;160:65–69.
13. Groth C, Debes NM, Rask CU, et al. Course of Tourette syndrome and comorbidities in a large prospective clinical study. J Am Acad Child Adolesc Psychiatry. 2017;56:304–312.
14. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry. 1993;150: 98–102.
15. Banaschewski T, Woerner W, Rothenberger A. Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. Dev Med Child Neurol. 2003;45:700–703.
16. McGuire JF, McBride N, Piacentini J, et al. The premonitory urge revisited: an individualized premonitory urge for tics scale. J Psychiatr Res. 2016;83:176–183.
17. Woods DW, Piacentini J, Himle MB, et al. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with tic disorders. J Dev Behav Pediatr. 2005;26:397–403.
18. Freeman RD, Fast DK, Burd L, et al. An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. Dev Med Child Neurol. 2000;42:436–447.
19. McGuire JF, Murphy TK, Piacentini J, et al. Introduction to treatment and management of youth with Tourette disorders and tic disorders, in the clinician's guide to treatment and management of youth with Tourette Syndrome and tic disorders. Academic Press: Cambridge (MA); 2018. p. 1–20.
20. Storch EA, Lack CW, Simons LE, et al. A measure of functional impairment in youth with Tourette's syndrome. J Pediatr Psychol. 2007;32:950–959.
21. Cloes KI, Barfell KSF, Horn PS, et al. Preliminary evaluation of child self-rating using the child Tourette Syndrome impairment scale. Dev Med Child Neurol. 2017;59:284–290.
22. Hanks CE, McGuire JF, Lewin AB, et al. Clinical correlates and mediators of self-concept in youth with chronic tic disorders. Child Psychiatry Human Dev. 2016;47:64–74.
23. Storch EA, Johnco C, McGuire JF, et al. An initial study of family accommodation in children and adolescents with chronic tic disorders. Eur Child Adolesc Psychiatry. 2017;26:99–109.
24. Conelea CA, Woods DW, Zinner SH, et al. Exploring the impact of chronic tic disorders on youth: results from the Tourette syndrome impact survey. Child Psychiatry Hum Dev. 2011;42:219–242.
25. Storch EA, Merlo LJ, Lack C, et al. Quality of life in youth with Tourette's syndrome and chronic tic disorder. J Clin Child Adolesc Psychol. 2007;36:217–227.
26. Cutler D, Murphy T, Gilmour J, et al. The quality of life of young people with Tourette syndrome. Child Care Health Dev. 2009;35:496–504.
27. Conelea CA, Woods DW, Zinner SH, et al. The impact of Tourette syndrome in adults: results from the Tourette syndrome impact survey. Community Ment Health J. 2013;49:110–120.
28. Woods DW, Piacentini J, Chang SW, et al. Managing Tourette Syndrome: A behavioral intervention for children and adolescents. Treatments that work. New York: Oxford University Press; 2008.

•• **Treatment manual that provides a structured approach to the application of the Comprehensive Behavioral Intervention for Tics (CBIT).**

29. Himle MB, Woods DW, Conelea CA, et al. Investigating the effects of tic suppression on premonitory urge ratings in children and adolescents with Tourette's syndrome. Behav Res Ther. 2007;45:2964–2976.
30. Capriotti MR, Brandt BC, Turkel JE, et al. Negative reinforcement and premonitory urges in youth with Tourette syndrome an experimental evaluation. Behav Modif. 2014;38:276–296.
31. Specht MW, Woods DW, Nicotra CM, et al. Effects of tic suppression: ability to suppress, rebound, negative reinforcement, and habituation to the premonitory urge. Behav Res Ther. 2013;51:24–30.
32. Himle MB, Capriotti MR, Hayes LP, et al. Variables associated with tic exacerbation in children with chronic tic disorders. Behav Modif. 2014;38:163–183.
33. Capriotti MR, Piacentini JC, Himle MB, et al. Assessing environmental consequences of ticcing in youth with chronic tic disorders: the tic accommodation and reactions scale. Children's Health Care. 2015;44:205–220.
34. Azrin N, Nunn R. Habit-reversal: a method of eliminating nervous habits and tics. Behav Res Ther. 1973;11:619–628.
35. McGuire JF, Ricketts EJ, Piacentini J, et al. Behavior therapy for tic disorders: an evidenced-based review and new directions for treatment research. Curr Dev Disord Rep. 2015;2:309–317.
36. Woods D, Miltenberger R, Lumley V. Sequential application of major habit-reversal components to treat motor tics in children. J Appl Behav Anal. 1995;29:483–493.

37. Prabhakar D. Behavioral management of Tourette's disorder in a 5-year-old child. Prim Care Companion CNS Disord. 2014;16.
38. McGuire JF, Piacentini J, Brennan EA, et al. A meta-analysis of behavior therapy for Tourette syndrome. J Psychiatr Res. 2014;50:106–112.

•• **A meta-analysis of randomized controlled trials of behavior therapy for patients with Tourette's Disorder and chronic tic disorders.**

39. O'Connor K, Brault M, Robillard S, et al. Evaluation of a cognitive-behavioural program for the management of chronic tic and habit disorders. Behav Res Ther. 2001;39:667–681.
40. Azrin NH, Peterson AL. Treatment of Tourette syndrome by habit reversal: A waiting-list control group comparison. Behav Ther. 1990;21:305–318.
41. Azrin NH, Nunn RG, Frantz S. Treatment of hairpulling (trichotillomania): a comparative study of habit reversal and negative practice training. J Behav Ther Exp Psychiatry. 1980;11:13–20.
42. Verdellen CW, Keijsers GP, Cath DC, et al. Exposure with response prevention versus habit reversal in Tourettes's syndrome: a controlled study. Behav Res Ther. 2004;42:501–511.
43. Wilhelm S, Deckersbach T, Coffey BJ, et al. Habit reversal versus supportive psychotherapy for Tourette's disorder: a randomized controlled trial. Am J Psychiatry. 2003;160:1175–1177.
44. Deckersbach T, Rauch S, Buhlmann U, et al. Habit reversal versus supportive psychotherapy in Tourette's disorder: a randomized controlled trial and predictors of treatment response. Behav Res Ther. 2006;44:1079–1090.
45. Yates R, Edwards K, King J, et al. Habit reversal training and educational group treatments for children with tourette syndrome: a preliminary randomised controlled trial. Behav Res Ther. 2016;80:43–50.
46. Rizzo R, Pellico A, Silvestri PR, et al. A Randomized controlled trial comparing behavioral, educational, and pharmacological treatments in youths with chronic tic disorder or tourette syndrome. Front Psychiatry. 2018;9:100.
47. van de Griendt JM, van Dijk MK, Verdellen CW, et al. The effect of shorter exposure versus prolonged exposure on treatment outcome in Tourette syndrome and chronic tic disorders–an open trial. Int J Psychiatry Clin Pract. 2018;22:262–267.
48. Dabrowski J, King J, Edwards K, et al. The long-term effects of group-based psychological interventions for children with Tourette syndrome: a randomized controlled trial. Behav Ther. 2018;49:331–343.
49. Ricketts EJ, Goetz AR, Capriotti MR, et al. A randomized waitlist-controlled pilot trial of voice over Internet protocol-delivered behavior therapy for youth with chronic tic disorders. J Telemed Telecare. 2016;22:153–162.
50. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: A randomized controlled trial. J Am Med Assoc. 2010;303:1929–1937.
51. Wilhelm S, Peterson AL, Piacentini J, et al. Randomized trial of behavior therapy for adults with Tourette syndrome. Arch Gen Psychiatry. 2012;69:795–803.
52. Peterson AL, McGuire JF, Wilhelm S, et al. An empirical examination of symptom substitution associated with behavior therapy for Tourette's Disorder. Behav Ther. 2016;47:29–41.
53. Woods DW, Piacentini JC, Scahill L, et al. Behavior therapy for tics in children: acute and long-term effects on psychiatric and psychosocial functioning. J Child Neurol. 2011;26:858–865.
54. McGuire JF, Ricketts EJ, Scahill L, et al., Effect of Behavior Therapy for Tourette's Disorder on Psychiatric Symptoms and Functioning. 2019
55. Conelea CA, Woods DW, Brandt BC. The impact of a stress induction task on tic frequencies in youth with Tourette syndrome. Behav Res Ther. 2011;49:492–497.
56. Verdellen CW, Hoogduin CA, Kato BS, et al. Habituation of premonitory sensations during exposure and response prevention treatment in Tourette's syndrome. Behav Modif. 2008;32:215–227.
57. Verdellen CW, Hoogduin CA, Keijsers GP. Tic suppression in the treatment of Tourette's syndrome with exposure therapy: the rebound phenomenon reconsidered. Mov Disord. 2007;22:1601–1606.
58. Hall CL, Davies EB, Andrén P, et al. Investigating a therapist-guided, parent-assisted remote digital behavioural intervention for tics in children and adolescents—'online remote behavioural intervention for tics'(ORBIT) trial: protocol of an internal pilot study and single-blind randomised controlled trial. BMJ Open. 2019;9:e027583.
59. Augustine F, Singer HS. Merging the pathophysiology and pharmacotherapy of tics. Tremor Other Hyperkinet Mov. 2018;8.

• **An up-to-date comprehensive review on the pathophysiology and pharmacotherapy for tics and Tourette's Disorder.**

60. Peters SK, Dunlop K, Downar J. Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. Front Syst Neurosci. 2016;10:104.
61. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology. 2019;92:896–906.

•• **Practice guidelines by the American Academy of Neurology for patients with Tourette's Disorder. Recommends behavioral therapies as the first-line treatment for patients with Tourette's Disorder.**

62. McGuire J, Hanks C, Murphy T, et al. Pharmacological and behavioral management of Tourette disorder and chronic tic disorders. Minerva Psichiatrica. 2014;55:161–180.
63. Singer HS. Treatment of tics and tourette syndrome. Curr Treat Options Neurol. 2010;12:539–561.
64. Weisman H, Qureshi IA, Leckman JF, et al. Systematic review: pharmacological treatment of tic disorders - Efficacy of antipsychotic and alpha-2 adrenergic agonist agents. Neurosci Biobehav Rev. 2013;37:1162–1171.
65. Liu Y, Ni H, Wang C, et al. Effectiveness and tolerability of aripiprazole in children and adolescents with Tourette's disorder: a meta-analysis. J Child Adolesc Psychopharmacol. 2016;26:436–441.
66. Yang CS, Zhang LL, Zeng LN, et al. Topiramate for Tourette's syndrome in children: A meta-analysis. Pediatr Neurol. 2013;49:344–350.
67. Leckman JF, Riddle MA, Hardin MT, et al. The yale global tic severity scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989;28:566–573.
68. McGuire JF, Kugler BB, Park JM, et al. Evidence-based assessment of compulsive skin picking, chronic tic disorders and trichotillomania in children. Child Psychiatry Human Dev. 2012;43:855–883.
69. Cubo E, González M, Singer H, et al. Impact of placebo assignment in clinical trials of tic disorders. Mov Disord. 2013;28:1288–1292.
70. 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;27:771–781.
71. 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:e772–e80.
72. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology. 2003;60:1130–1135.
73. Singer HS, Brown J, Quaskey S, et al. The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: A double-blind placebo-controlled study with clonidine and desipramine. Pediatrics. 1995;95:74–81.
74. 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.
75. Group, T.s.S.S. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002;58:527.
76. Murphy TK, Lewin AB, Storch EA, et al. Practice parameter for the assessment and treatment of children and adolescents with tic disorders. J Am Acad Child Adolesc Psychiatry. 2013;52:1341–1359.
77. 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;20:173–196.
78. Verdellen C, Van De Griendt J, Hartmann A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part III:

behavioural and psychosocial interventions. Eur Child Adolesc Psychiatry. 2011;20:197–207.
79. Pringsheim T, Doja A, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. Can J Psychiatry. 2012;57:133–143.
80. Steeves T, McKinlay BD, Gorman D, et al. Canadian guidelines for the evidence-based treatment of tic disorders: behavioural therapy, deep brain stimulation, and transcranial magnetic stimulation. Can J Psychiatry. 2012;57:144–151.
81. Zhong YQ, Zhou WZ, Hu WG. [Randomized double-blind controlled study on treatment of tic disorders in children with transcutaneous patch of clonidine]. Chin J Pediatr. 2007;45:785–787. Zhonghua er ke za zhi
82. Leckman JF, Hardin MT, Riddle MA, et al. Clonidine treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry. 1991;48:324–328.
83. 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;42:807–813.
84. Goetz CG, Tanner CM, Wilson RS, et al. Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. Ann Neurol. 1987;21:307–310.
85. Kang H, Zhang YF, Jiao FY, et al. Efficacy of clonidine transdermal patch for treatment of Tourette's syndrome in children. Chin J Contemp Pediatr. 2009;11:537–539.
86. Jiao F, Zhang X, Zhang X, et al. Clinical observation on treatment of Tourette syndrome in Chinese children by clonidine adhesive patch. Eur J Paediatr Neurol. 2016;20:80–84.
87. Zhang H, Lin Y, Liu M, et al. Clinical trial of the clonidine adhesive patch for the treatment of tic disorders. J Pediatr Pharm. 2006;12:8–16.
88. Guo J-M, Shi -X-X, Yang S-W, et al. [Efficacy of clonidine transdermal patch in treatment of moderate to severe tic disorders in children]. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19:786–789.
89. Hedderick EF, Morris CM, Singer HS. Double-blind, crossover study of clonidine and levetiracetam in Tourette syndrome. Pediatr Neurol. 2009;40:420–425.
90. 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;41:330–336.
91. Lu J, Comparative study in treatment of tic disorders by clonidine and tiapride. China National Knowledge Infrastructure (CNKI). Unknown
92. Cummings DD, Singer HS, Krieger M, et al. Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: A pilot study. Clin Neuropharmacol. 2002;25:325–332.
93. 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;27:762–770.
94. Mogwitz S, Buse J, Wolff N, et al. Update on the pharmacological treatment of tics with dopamine-modulating agents. ACS Chem Neurosci. 2018;9:651–672.
95. Ghanizadeh A, Haghighi A. Aripiprazole versus risperidone for treating children and adolescents with tic disorder: a randomized double blind clinical trial. Child Psychiatry Human Dev. 2014;45:596–603.
96. Wang Y, Chen Z, Wang X. The efficacy of aripiprazole and tiapride for Tourette disorders in children. Shandong Med J. 2013;53:58–59.
97. Zhang H, Huang H, Lin G. A randomized, controlled study of aripiprazole and risperidone for tic disorders. Clin Focus. 2015;30:1393–1396.
98. Dion Y, Annable L, Sandor P, et al. Risperidone in the treatment of Tourette syndrome: A double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2002;22:31–39.
99. Bruggeman R, Van der Linden C, Buitelaar JK, et al. Risperidone versus pimozide in Tourette's disorder: A comparative double-blind parallel-group study. J Clin Psychiatry. 2001;62:50–56.
100. Gilbert DL, Batterson JR, Sethuraman G, et al. Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. J Am Acad Child Adolesc Psychiatry. 2004;43:206–214.
101. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: A pilot study. J Am Acad Child Adolesc Psychiatry. 2000;39:292–299.
102. 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;46:722–730.
103. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. Am J Psychiatry. 1997;154:1057–1062.
104. Ross MS, Moldofsky H. A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. Am J Psychiatry. 1978;135:585-7.
105. Yang Z-J. The therapeutic efficacy and safety of tiapride and haloperidol in treatment of Tourette syndrome [J]. J Clin Pediatr. 2012;30:1051-3.
106. Shapiro AK, Shapiro E. Controlled study of pimozide vs. placebo in Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1984;23:161–173.
107. Gilbert DL, Murphy TK, Jankovic J, et al. Ecopipam, a D1 receptor antagonist, for treatment of tourette syndrome in children: A randomized, placebo-controlled crossover study. Mov Disord. 2018;33:1272–1280.
108. Jankovic J, Jimenez-Shahed J, Brown LW. A randomised, double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. J Neurol Neurosurg Psychiatry. 2010;81:70–73.
109. Smith-Hicks CL, Bridges DD, Paynter NP, et al. A double blind randomized placebo control trial of levetiracetam in Tourette syndrome. Mov Disord. 2007;22:1764–1770.
110. Singer HS, Wendlandt J, Krieger M, et al. Baclofen treatment in Tourette syndrome: A double-blind, placebo-controlled, crossover trial. Neurology. 2001;56:599–604.
111. Sharp AN, Singer HS. Standard, complementary, and future treatment options for tics. Curr Dev Disord Rep. 2018;5:101–7.
112. Martino D, Pringsheim TM. Tourette syndrome and other chronic tic disorders: an update on clinical management. Expert Rev Neurother. 2018;18:125–137.
113. Selles RR, Jukes T, McConnell M, et al. Relapse Prevention Strategies And Guidance On Refractory Cases, In The Clinician's Guide To Treatment And Management Of Youth with Tourette Syndrome and tic disorders. Academic Press: Cambridge (MA); 2018. p. 347–374.
114. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep brain stimulation public database and registry. JAMA Neurol. 2018;75:353–359.
115. Marras C, Andrews D, Sime E, et al. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology. 2001;56:605–610.
116. Woods DW, Conelea CA, Himle MB. Behavior therapy for Tourette's disorder: utilization in a community sample and an emerging area of practice for psychologists. Prof Psychol. 2010;41:518.
117. Scahill L, Woods DW, Himle MB, et al. Current controversies on the role of behavior therapy in Tourette syndrome. Mov Disord. 2013;28:1179–1183.
118. Nissen JB, Kaergaard M, Laursen L, et al. Combined habit reversal training and exposure response prevention in a group setting compared to individual training: a randomized controlled clinical trial. Eur Child Adolesc Psychiatry. 2019;28:57–68.
119. Flancbaum M, Rockmore L, Franklin ME. Intensive behavior therapy for tics: implications for clinical practice and overcoming barriers to treatment. J Dev Phys Disabil. 2011;23:61–69.
120. Himle MB, Freitag M, Walther M, et al. A randomized pilot trial comparing videoconference versus face-to-face delivery of behavior therapy for childhood tic disorders. Behav Res Ther. 2012;50:565–570.
121. Conelea CA, Wellen BC. Tic treatment goes tech: a review of TicHelper. com. Cognit Behav Pract. 2017;24:374–381.
122. Jakubovski E, Reichert C, Karch A, et al. The ONLINE-TICS study protocol: a randomized observer-blind clinical trial to demonstrate

the efficacy and safety of internet-delivered behavioral treatment for adults with chronic tic disorders. Front Psychiatry. 2016;7:119.
123. Andrén P, Aspvall K, de la Cruz LF, et al. Therapist-guided and parent-guided internet-delivered behaviour therapy for paediatric Tourette's disorder: a pilot randomised controlled trial with long-term follow-up. BMJ Open. 2019;9:e024685.
124. Singer HS, Rajendran S, Waranch HR, et al. Home-based, therapist-assisted, therapy for young children with primary complex motor stereotypies. Pediatr Neurol. 2018;85:51–57.
125. Specht MW, Mahone EM, Kline T, et al. Efficacy of parent-delivered behavioral therapy for primary complex motor stereotypies. Dev Med Child Neurol. 2017;59:168–173.
126. Storch EA, De Nadai AS, Lewin AB, et al. Defining treatment response in pediatric tic disorders: a signal detection analysis of the yale global tic severity scale. J Child Adolesc Psychopharmacol. 2011;21:621–627.
127. Jeon S, Walkup JT, Woods DW, et al. Detecting a clinically meaningful change in tic severity in Tourette syndrome: A comparison of three methods. Contemp Clin Trials. 2013;36:414–420.
128. McGuire JF, Storch EA. An inhibitory learning approach to cognitive-behavioral therapy for children and adolescents. Cognit Behav Pract. 2019;26:214–224.
129. McGuire JF, Wu MS, Piacentini J, et al. A meta-analysis of d-cycloserine in exposure-based treatment: moderators of treatment efficacy, response, and diagnostic remission. J Clin Psychiatry. 2017;78:196.
130. McGuire JF, Lewin AB, Storch EA. Enhancing exposure therapy for anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder. Expert Rev Neurother. 2014;14:893–910.
131. Felling RJ, Singer HS. Neurobiology of Tourette syndrome: current status and need for further investigation. J Neurosci. 2011;31:12387–12395.
132. Singer HS, Morris C, Grados M. Glutamatergic modulatory therapy for Tourette syndrome. Med Hypotheses. 2010;74:862–867.
133. Artukoglu BB, Bloch MH. The potential of cannabinoid-based treatments in Tourette Syndrome. CNS Drugs. 2019;33:417–30.
134. Lemmon ME, Grados M, Kline T, et al. Efficacy of glutamate modulators in tic suppression: a double-blind, randomized control trial of D-serine and riluzole in Tourette Syndrome. Pediatr Neurol. 2015;52:629–634.
135. Müller-Vahl KR, Schneider U, Prevedel H, et al. Δ9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. J Clin Psychiatry. 2003;64:459-65.
136. Jankovic J, Jimenez-Shahed J, Budman C, et al. Deutetrabenazine in tics associated with Tourette syndrome. Tremor Other Hyperkinet Mov. 2016;6:422-9.
137. Niemann N, Jankovic J. Real-world experience with VMAT2 inhibitors. Clin Neuropharmacol. 2019;42:37–41.
138. Jankovic J, Glaze DG, Frost JD. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology. 1984;34:688.
139. Jankovic J, Rohaidy H. Motor, behavioral and pharmacologic findings in Tourette's syndrome. Can J Neurosci Nurs. 1987;14:541–546.
140. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. Neurology. 1988;38:391.
141. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology. 1997;48:358–362.
142. Paleacu D, Giladi N, Moore O, et al. Tetrabenazine treatment in movement disorders. Clin Neuropharmacol. 2004;27:230–233.
143. Sweet RD, Bruun R, Shapiro E, et al. Presynaptic catecholamine antagonists as treatment for Tourette syndrome: effects of alpha methyl para tyrosine and tetrabenazine. Arch Gen Psychiatry. 1974;31:857–861.
144. Vieregge P. Tetrabenazine in the treatment of senile vocal tics. J Neurol. 1987;235:126–127.
145. Grados M, Huselid R, Duque-Serrano L. Transcranial magnetic stimulation in Tourette syndrome: a historical perspective, its current use and the influence of comorbidities in treatment response. Brain Sci. 2018;8:129.
146. Storch EA, Morgan JE, Caporino NE, et al. Psychosocial treatment to improve resilience and reduce impairment in youth with tics: an intervention case series of eight youth. J Cognit Psychotherapy. 2012;26:57–70.
147. McGuire JF, Arnold E, Park JM, et al. Living with tics: reduced impairment and improved quality of life for youth with chronic tic disorders. Psychiatry Res. 2015;225:571–579.