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

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1. Introduction

1.1. Tics and tic disorders

Tics are 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.

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.

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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]).
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.

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, Placentin 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.

2.3.3. Follow-up and long-term outcomes
Two studies have followed-up individuals who responded to CBIT for up to 6 months. Placentin 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 systematically suppressing all tics. Subsequently, patients begin to focus 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].

3. Pharmacological interventions for tics
Studies investigating the pathophysiology of TD implicate abnormalities within the cortico-basal ganglia-thalamocortical (CBGTC) 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 anti-convulsants/movement disorder medications (see Pringsheim et al. [61], McGuire et al. [62], or Singer [63] for a 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 anti-convulsants/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 (YGTTSS) [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 psychiatric disorders, mood disorders, and moderate to severe OCD [70–72], whereas other trials have required co-occurring ADHD for 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 norepinephrine/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 benzotropine 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 benztrpine 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 receptor that activates GABA_A 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
Note the internet medicine approaches to deliver behavioral interventions over ple, behavioral interventions have been adapted to be workshops) made available to increase the number of clin-
are several training opportunities (i.e. seminars, institutes, access and availability of behavioral interventions. First, there 
of behavioral interventions.
ment. Thus, the first challenge confronting the evidence-based 
prohibited from receive behavioral interventions or at 
viders]. As a result, individuals with TD are often 
omplications 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. Limited therapeutic response to evidence-based treatments

The second challenge confronting the evidence-based man-
agement of TD is the limited therapeutic response to existing behavioral interventions and pharmacological treatments. Although many patients with TD experience significant reduc-
tions 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 sev-
eral therapeutic strategies that can be implemented to opti-
mize 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 pro-
cesses, it may improve outcomes for individuals with TD as well. Second, it may be possible to enhance therapeutic out-
comes 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

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

<table>
<thead>
<tr>
<th>Tier 1 treatments</th>
<th>Tier 2 and Tier 3 treatments</th>
<th>Treatments requiring further support in RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBIT [61,76]</td>
<td>Clonidine [61,76,77,79]</td>
<td>Neurofeedback [61,78]</td>
</tr>
<tr>
<td>HRT [61,76,78,80]</td>
<td>Risperidone [61,76,77,79]</td>
<td>Tetrabenazine [77,79]</td>
</tr>
<tr>
<td></td>
<td>Aniracetam [61,77,79]</td>
<td>Clonidine [61,77]</td>
</tr>
<tr>
<td></td>
<td>Pimozide [61,76,77,79]</td>
<td>Quetiapine [77,79]</td>
</tr>
<tr>
<td></td>
<td>Haloperidol [61,76,77,79]</td>
<td>Tetrabenazine [77,79]</td>
</tr>
<tr>
<td>Tiapride [61,77]</td>
<td>Topiramate [61,77,79]</td>
<td></td>
</tr>
<tr>
<td>Olanzapine [76,77]</td>
<td>Ziprasidon [79]</td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin [61, for adults [79]</td>
<td>Deep Brain Stimulation [61,76,80]</td>
<td></td>
</tr>
</tbody>
</table>

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 comprehen-
sively 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 beha-
vioral 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 beha-
vioral interventions [116]. This presents a considerable chal-
lenge 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 treat-
ment. 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 clini-
cians trained in evidence-based behavioral interventions [117-
117]. Second, several studies have explored different treatment delivery modalities to increase the access and avail-
ability of evidence-based behavioral interventions. For exam-
ple, 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 tele-
medicine 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.
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 fewer 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, tetrathydrocannabinol) [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, deutetabenzine, and valbenzine) [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).

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


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 clinicians convey this information to patients and families in an effective manner.


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

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.**


**Practice guidelines by the American Academy of Neurology for patients with Tourette’s Disorder.**


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**Note:** The text above represents a compilation of references from various sources, primarily related to Tourette syndrome and its treatment. The compilation includes studies on the efficacy of different medications and therapies in managing tic disorders. However, it's important to note that the text is a representation of a larger, more comprehensive compilation and does not include all the references cited in the original sources. The full texts of these studies can be found in academic databases and journals cited in the references.


