

Review

Efficacy of habit reversal training for the treatment of tics in patients with Tourette syndrome and other tic disorders

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SUMMARY

Introduction

Among hyperkinetic movement disorders, tic disorders can prove particularly challenging in terms of their clinical management. Habit reversal therapy (HRT) has been recommended as a behavioral intervention for the treatment of tics in patients diagnosed with Tourette syndrome (TS) or other tic disorders. This systematic literature review assessed the efficacy of HRT, either as a stand-alone or as the key component of a wider Comprehensive Behavioral Intervention for Tics (CBIT).

Methods

A comprehensive search was conducted according to the PRISMA guidelines across four databases (PubMed, PsycINFO, EMBASE, and OVID MEDLINE) for randomized controlled trials (RCTs) published between 2000 and 2024.

Results

Ten high-quality RCTs met stringent inclusion criteria. The geographical distribution of the studies was skewed, with 6/10 studies originating from North America. The findings consistently showed significant reductions in tic severity across children, adolescents, and adults with TS or other tic disorders treated with HRT. Treatment gains were consistently maintained at follow-up periods ranging from 3 to 10 months. Several studies reported additional benefits, including improvements in cognitive function and emotional regulation. Modified protocols, such as shortened interventions and group delivery formats, showed promising results for increasing accessibility while maintaining efficacy. No significant adverse effects were reported across studies.

Discussion

This review found robust evidence supporting the efficacy of HRT as a behavioral intervention delivered by trained psychologists for the treatment of tics. HRT has the potential to provide effective, safe, and possibly long-lasting benefits for tic management across different age groups. Future research should focus on larger-scale studies with extended follow-up periods, investigation of treatment response predictors, and strategies for widespread implementation across multiple geographical regions.

Key words: tics, Tourette syndrome, tic disorders, habit reversal therapy, Comprehensive Behavioral Intervention for Tics

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Introduction

Tourette syndrome (TS) and persistent motor/vocal tic disorders are neurodevelopmental disorders with onset in early life and chronic course ¹. TS is characterized by the presence of multiple motor tics and at least one vocal tic, whereas persistent motor/vocal tic disorders are truncated forms with motor or vocal tics only. Tics are defined as repetitive, involun-

tary, non-rhythmic, sudden movements or vocalizations performed in response to a subjective feeling of inner tension ('premonitory urge') that is temporarily relieved by tic expression². Simple motor tics involve discrete muscle groups, while complex motor tics simultaneously affect multiple muscles³. Simple vocal tics are brief sounds, whereas complex vocal tics are meaningful words, which in 10-30% of patients can take the form of involuntary swearing (coprolalia)⁴. Tics typically emerge in childhood between the ages of four and six years, and are 3-4 times more common in males⁵. A comprehensive understanding of the psychopathology of TS and other tic disorders is critical for the effective management patients with these conditions, as tic disorders are often accompanied by co-morbid conditions, most commonly tic-related obsessive-compulsive disorder, attention-deficit and hyperactivity disorder, anxiety and affective disorders^{1,6,7}. Both tics and associated behavioral problems can significantly impact health-related quality of life^{8,9}. With a prevalence of approximately 0.3-1% in children and adolescents, TS is a relatively common neuropsychiatric condition that extends beyond mere physical manifestations, often affecting social interactions, academic performance, and overall functioning^{10,11}.

Traditionally, the management of tic disorders has relied heavily on pharmacological interventions, including antidopaminergic agents and alpha-2 agonists. However, both the efficacy and the tolerability profiles of these medications can vary widely, particularly in pediatric populations. Among non-pharmacological approaches, habit reversal training (HRT) has emerged as a promising behavioral intervention for tic management¹². HRT is a structured behavioral therapy designed to address repetitive behaviors through three core components: awareness training, competing response training, and social support¹³. The theoretical framework underlying HRT suggests that the temporary relief experienced after tic expression reinforces the behavior, thereby increasing its likelihood of recurrence¹⁴. By interrupting the negative reinforcement cycle that maintains tics, HRT aims to reduce tic frequency and severity through targeted behavioral strategies.

The development of a Comprehensive Behavioral Intervention for Tics (CBIT) centered around HRT has further expanded its therapeutic potential. CBIT incorporates additional elements such as psychoeducation, functional interventions, and stress management techniques, making it a more holistic approach to tic management¹⁴. In the American Academy of Neurology guidelines on the treatment of tics, CBIT is recommended as a first-line intervention for tics, either independently or in combination with medication¹⁵.

This systematic review provides a critical synthesis of

the existing literature on the effectiveness of HRT in the treatment of tics, including potential variations in treatment outcomes across different demographic and clinical contexts. By examining the current evidence base, this review seeks to provide clinicians, researchers, and patients with a nuanced understanding of the role of HRT in the management of tic disorders, potentially informing more targeted and personalized treatment approaches.

Methods

The present systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁶. A comprehensive search strategy was implemented across multiple electronic healthcare databases, including PubMed, PsycINFO, EMBASE, and OVID Medline, focusing on original studies published between January 2000 and June 2024. The following MeSH terms were used as part of the search strategy: ((Tourette syndrome)* OR (Tic)) AND (Habit reversal therapy)* OR (Comprehensive Behavioral Intervention for Tics)* OR (CBIT) using the "Map to Thesaurus" tool. We included in our review randomized controlled trials (RCTs) that used standardized diagnostic and tic severity rating methods, specifically the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and the Yale Global Tic Severity Scale (YGTSS). We reviewed studies involving individuals of all ages diagnosed with TS or other chronic tic disorders, with a primary focus on HRT either in isolation or as the main component of the CBIT. In addition to tic severity measured by validated scales such as the YGTSS, we assessed secondary outcomes including health-related quality of life, psychosocial functioning, and treatment adherence. Comparison groups included treatment as usual, waitlist controls, and alternative interventions such as supportive psychotherapy. Case reports, case series, non-controlled studies, or pilot studies were excluded from our review. We also excluded RCTs with fewer than 30 participants, studies focusing solely on co-morbid conditions, and studies published in languages other than in English.

Results

Our search strategy initially yielded 415 papers from all databases. A total of 136 records were automatically removed due to being either duplicates or ineligible. The title and abstract of the remaining 279 papers were individually screened and 109 studies were excluded from the review as they did not meet the inclusion criteria. A further 160 studies were excluded after review of the full text. As a result of this selection process, the systematic

literature review identified 10 high-quality original studies focusing on the efficacy of HRT and CBIT for the treatment of tics in patients with TS and other chronic tic disorders (Fig. 1). Data from a total of 640 participants from different age groups were analyzed. The behavioral intervention consistently demonstrated significant efficacy across the reviewed studies. While the primary focus was on tic reduction, some RCTs showed improvements in co-morbid symptoms, cognitive functioning, and emotional regulation.

The studies spanned two decades, as they were published between 2003¹⁷ and 2024¹⁸ (Tab. I). Most studies were conducted across specialist clinics located in North America ($n = 5$ in the United States^{17,19-22} and $n = 1$ in Canada¹⁸, with Holland²³, Denmark²⁴, Taiwan²⁵

and Israel²⁶ hosting one study each. Sample sizes were characterized by a wide variability, ranging from 29¹⁷ to 126²⁰. The majority of participants were males across all studies, with proportions ranging from 55.2%¹⁷ to 84.4%²². The target populations spanned childhood and adulthood: the mean ages of the participants ranged from 9 years²⁵ to 35 years¹⁹. Six studies also included follow-up data at 3 months^{23,25,26}, 6 months^{18,19}, and 10 months¹⁷. Post-treatment improvement in tic severity, as measured by decreases in YGTSS total tic scores, ranged from 18.3%²³ to 46.1%²⁵. The study by Zimmerman-Brenner et al.²⁶ was an outlier, reporting an initial 60.5% worsening in total tic severity driven by increased vocal tics following exposure to CBIT within a group setting.

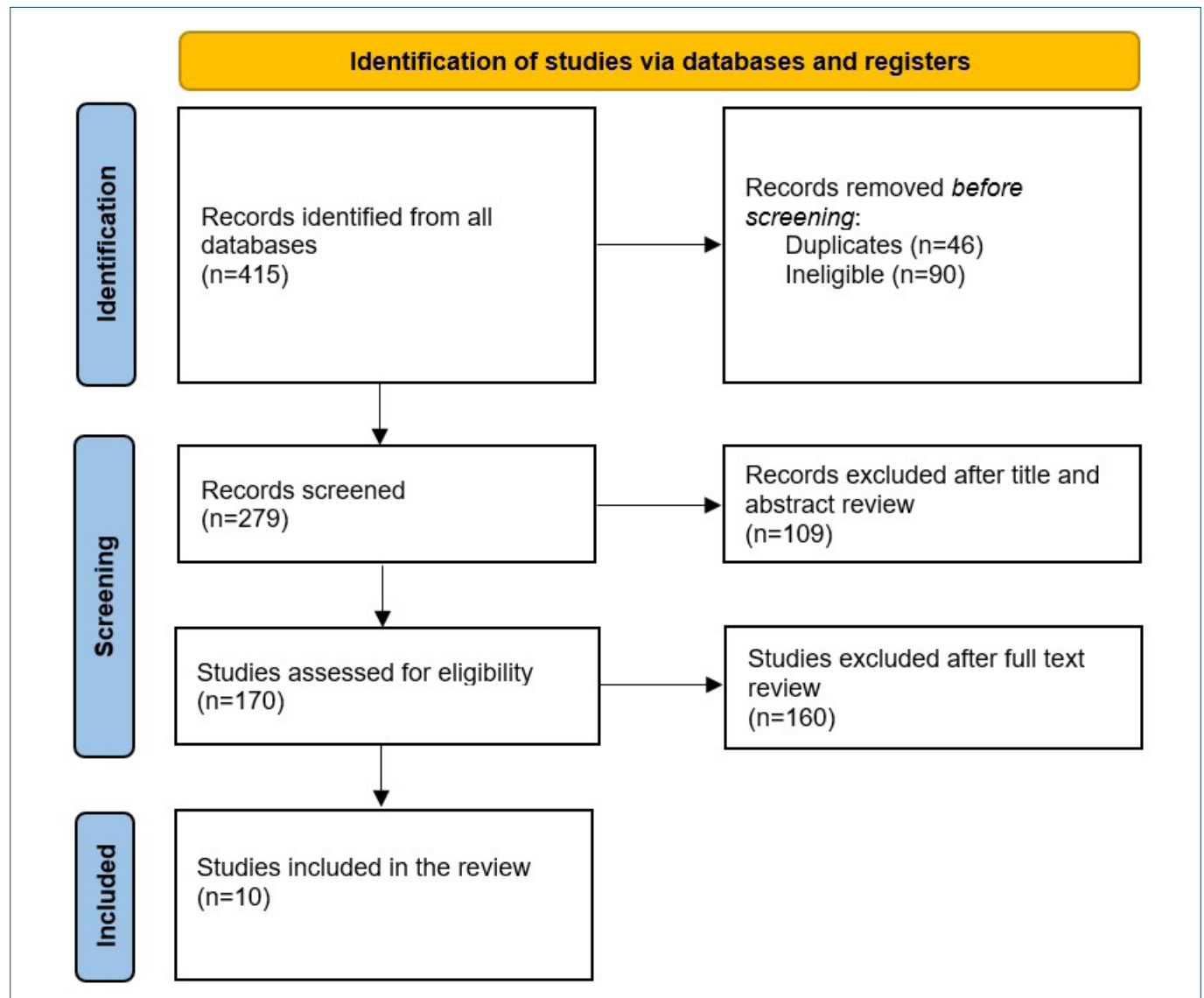


FIGURE 1. PRISMA flow diagram showing the study selection process for the systematic literature review.

TABLE I. Summary of the studies included in the systematic literature review.

Study	Sample size (% M), mean age	Country	Setting	Tic disorder diagnostic criteria	Outcome measures	YGTSS total tic severity scores, change (%)	Main findings
Wilhelm et al., 2003 ¹⁷	n = 29 (55.2% M), 34 years	USA	Specialist clinic	DSM-IV-TR	YGTSS, CGI	- HRT (n = 16): 30.5 (pre) 19.8 (post), -10.7 (35.1%) 21.0 (10 months), -9.5 (31.1%) - SP (n = 13): 26.6 (pre) 26.9 (post), 0.3 (1.1%) 23.8 (10 months), -2.8 (11.8%)	- HRT significantly more effective than SP in reducing tic severity and functional impairment - Effects of HRT maintained at 10-month follow-up
Verdellen et al., 2004 ²³	n = 43 (79.1% M), 21 years	Holland	Specialist clinic	DSM-IV-TR	YGTSS	- HRT (n = 22): 24.1 (pre) 19.7 (post), -4.4 (18.3%) 13.5 (3 months), -10.6 (44.0%) - ERP (n = 21): 26.2 (pre) 17.6 (post), -8.6 (32.8%) 14.0 (3 months), -12.2 (46.6%)	- HRT and ERP equally effective in reducing tic severity - Improvements in tic severity maintained at the 3-month follow-up
Deckersbach et al., 2006 ¹⁹	n = 30 (56.7% M), 35 years	USA	Specialist clinic	DSM-IV-TR	YGTSS, CGI	- HRT (n = 15): 29.3 (pre) 18.3 (post), -11.0 (37.5%) 18.4 (6 months), -10.9 (37.2%) - SP (n = 15): 27.7 (pre) 26.8 (post), -0.9 (3.2%) 26.6 (6 months), -1.1 (4.0%)	- HRT significantly more effective than SP in reducing tic severity - Effects of HRT maintained at 6-month follow-up - Improved life satisfaction and psychosocial functioning with both HRT and SP
Piacentini et al., 2010 ²⁰	n = 126 (78.6% M), 12 years	USA	Specialist clinic	DSM-IV-TR	YGTSS, PTQ, CGI	- CBIT (n = 61): 24.7 (pre) 17.1 (post), -7.6 (30.8%) - PST (n = 65): 24.6 (pre) 21.1 (post), -3.5 (14.2%)	- CBIT significantly more effective than SP in reducing tic severity - Effects of CBIT maintained at 6-month follow-up
Wilhelm et al., 2012 ²¹	n = 122 (63.9% M), 32 years	USA	Specialist clinic	DSM-IV-TR	YGTSS, ATQ, CGI	- CBIT (n = 63): 24.0 (pre) 17.8 (post), -6.2 (25.8%) - SP (n = 59): 21.8 (pre) 19.3 (post), -2.5 (11.5%)	- CBIT significantly more effective than SP in reducing tic severity - Effects of CBIT maintained at 6-month follow-up

TABLE I. Continued from previous page

Study	Sample size (% M), mean age	Country	Setting	Tic disorder diagnostic criteria	Outcome measures	YGTSS total tic severity scores, change (%)	Main findings
Morand-Beaulieu et al., 2022 ²²	n = 32 (84.4% M), 11 years	USA	Specialist clinic	DSM-IV-TR	YGTSS, CGI	- CBIT (n = 16): 23.8 (pre) 16.9 (post), -6.9 (29.0%) - PST (n = 16): 24.4 (pre) 24.9 (post), 0.5 (2.0%)	- CBIT significantly more effective than treatment-as-usual in reducing tic severity - EEG markers of cognitive control not associated with treatment outcome or affected by CBIT
Zimmerman-Brenner et al., 2022 ²⁶	n = 55 (81.7% M), 11 years	Israel	Specialist clinic	DSM-5	YGTSS, PTQ	- Group CBIT (n = 28): 24.8 (pre) 39.8 (post), 15.0 (60.5%) 18.4 (3 months), -6.4 (25.8%) - Group PST (n = 27): 22.0 (pre) 37.1 (post), 15.1 (68.6%) 21.8 (3 months), -0.2 (0.9%)	- Both group CBIT and group educational intervention for tics effective in reducing tic severity (at 3-month follow-up) and co-morbid behavioral symptoms - Initial increase in tic severity across both group interventions driven by increased vocal tics - Children with behavioral problems and lower intellectual abilities benefitting less from group CBIT
Leclerc et al., 2024 ¹⁸	n = 98 (63.3% M), 20 years	Canada	Specialist clinic	DSM-5	YGTSS, GAF	- CBIT (n = 51): 20.6 (pre) 14.9 (post), -5.7 (27.7%) 11.6 (6 months), -9.0 (43.7%) - CoPs (n = 47): 19.8 (pre) 14.7 (post), -5.1 (25.8%) 13.8 (6 months), -6.0 (30.3%)	- Both CBIT and cognitive psychophysiological treatment effective in reducing tic severity - Both treatments showing similar efficacy for children and adults

Abbreviations: ATQ, Adult Tic Questionnaire; BATS, Beliefs About Tics Scale; CGI, Clinical Global Impression; CoPs, Cognitive Psychophysiological treatment; DSM, Diagnostic and Statistical Manual; EEG, Electroencephalography; ERQ, Emotion Regulation Questionnaire; GAF, Global Assessment of Functioning scale; HMVTS, Hopkins Motor/Vocal Tic Scale; HRT, Habit Reversal Training; ICD, International Classification of Diseases; M, Males; PST, Psychoeducation/Supportive Therapy; PTQ, Parent Tic Questionnaire; PUTS, Premonitory Urge for Tics Scale; SP, Supportive Psychotherapy; TS, Tourette Syndrome; YGTSS, Yale Global Tic Severity Scale.

Two early studies by Wilhelm et al.¹⁷ and Deckersbach et al.¹⁹ were characterized by a similar design, comparing 14 sessions of HRT to 14 sessions of psychoeducation and supportive therapy (PST) to treat tic disorders in relatively small adult samples. In both studies, HRT resulted in greater post-treatment reductions in tic severity compared to the control group. Regarding secondary outcomes, Wilhelm et al.¹⁷ found that the HRT group experienced a more significant reduction in YGTSS tic-related impairment compared to the sup-

portive therapy group. Similarly, Deckersbach et al.¹⁹ reported that treatment also resulted in improvements in general psychosocial functioning, life satisfaction, depression, and obsessive-compulsive symptoms, though these improvements were not exclusive to the HRT group. The study by Wilhelm et al.¹⁷ involved independent evaluators to assess outcomes, however they were not masked to the condition.

In the early 2000s, researchers expanded on initial HRT findings to develop and test CBIT¹⁴. In the original CBIT

study, Piacentini et al.²⁰ randomized 126 youth with tic disorders to receive either eight sessions of CBIT or a PST control condition. All assessments were conducted by independent evaluators who were blinded to the group assignments. The CBIT group showed greater reductions in tic severity and tic-related impairment (as measured by the YGTSS) compared to the PST group, although there were no unique improvements in measures of attention-deficit, hyperactivity, disruptive behavior, depression, anxiety, or obsessive-compulsive symptoms²⁷. Moreover, participants who responded to CBIT after 10 weeks did not show improvements in family functioning, caregiver strain, or social adjustment following treatment. Woods et al.²⁷ separately reported 6-month follow-up data from the Piacentini et al.²⁰ study to assess the long-term durability of CBIT. Six months after treatment, youth who initially responded to CBIT generally maintained their reduction in tics and showed decreases in overall behavior problems, anxiety, depression, and disruptive behavior. A more recent 11-year follow-up study by Espil et al.²⁸ confirmed that while tics improved in both treatment groups, those who initially responded to CBIT improved more rapidly and maintained their gains over the 11 years, even after accounting for intermediate interventions. Together, these findings suggest that CBIT is a lasting intervention that may potentially alter the long-term trajectory of tic disorders.

In a similar design to the Piacentini et al.²⁰ child trial, Wilhelm et al.²¹ randomized 122 adults with tic disorders to either CBIT or PST. CBIT led to greater reductions in tic severity compared to PST by the end of the acute phase. CBIT also resulted in greater pre-post reduction in tic-related impairment as measured by the YGTSS, but there was no differential benefit of CBIT over PST in improving symptoms of psychiatric co-morbidities, family functioning, social adjustment, or anger disability compared to PST. A separate study on the same sample documented short-term therapeutic benefit of CBIT for co-occurring obsessive symptoms, whereas long-term benefits were found to include reduced inattention and disability²⁹. Wilhelm et al.²¹ reported that 80% of initial CBIT responders maintained treatment benefits at six-month follow-up. However, this study lacked a controlled long-term follow-up, making it uncertain whether the observed improvements were due to the maintenance of gains, the use of other treatments, or the natural passage of time. A study by McGuire et al.³⁰ on the combined data from Piacentini et al.²⁰ and Wilhelm et al.²¹ showed that CBIT was significantly more effective than PST in reducing the severity of the tics rated as more bothersome by the participants. The presence of baseline urge was associated with tic remission for CBIT, but not PST. In addition to providing confirmation that CBIT

was significantly more effective than treatment-as-usual in reducing tic severity in children with tic disorders, Morand-Beaulieu et al.²² found that neurophysiological markers of cognitive control were not associated with treatment outcome or affected by CBIT.

Beyond the exploration of the general effectiveness of CBIT, Chen et al.²⁵ examined the potential usefulness of an abbreviated, four-session version of CBIT added to the routine clinical care of Taiwanese children with tic disorders. Their results showed that the modified four-session CBIT could achieve similar efficacy to standard CBIT interventions, suggesting the potential for more streamlined treatment approaches. Zimmerman-Brenner et al.²⁶ tested the efficacy of CBIT in a group setting. They found that both group CBIT and group educational intervention for tics were effective in reducing total tic severity at 3-month follow-up, following an initial increase in tic severity across both group interventions driven by a transient exacerbation in vocal tics. A separate study by Gur et al.³¹ on the same sample reported that group CBIT significantly improved regulation abilities (cognitive inhibition and emotion regulation) and resulted in decreased impulsivity and better behavior inhibition.

Finally, the efficacy of HRT was compared with other behavioral interventions for tic control in different clinical settings. An early study by Verdellen et al.²³ compared HRT with exposure and response prevention (ERP) and found the two interventions to be equally effective in reducing tic severity, with improvements maintained at the 3-month follow-up assessment. Likewise, Nissen et al.²⁴ found that a combination of HRT and ERP was effective in reducing tic severity when delivered either individually or in groups, resulting in increased patient-perceived control over their tics. Recently, Leclerc et al.¹⁸ found that both CBIT and cognitive psychophysiological treatment significantly reduced tic severity, with similar efficacy for children and adults.

Discussion

The present systematic literature review aimed to comprehensively assess the efficacy of HRT and CBIT in the treatment of tics in the context of TS and other chronic tic disorders. Ten high-quality RCTs met rigorous inclusion criteria. The collective findings revealed a robust and promising approach to tic management. Collectively, the reviewed studies supported the efficacy of HRT or CBIT as a specific monotherapy for reducing tics and possibly tic-related impairment. By including control conditions that accounted for the passage of time, the relative superiority of HRT or CBIT to these conditions suggests that the effects of the behavioral intervention were not simply due to natural symptom fluctuation (waxing and waning pattern of tics). No significant

adverse effects were reported in any of the studies. The results consistently demonstrated significant reductions in tic severity across children, adolescents, and adults with TS or other tic disorders. Such treatment gains were consistently sustained during follow-up periods ranging from 3 to 10 months, suggesting the long-term effectiveness of HRT and CBIT. These findings are consistent with a clinically significant change, as all RCTs - with the exception of the one by Verdellen et al.²³ - showed a reduction of at least 25% in YGTSS scores³². Moreover, the behavioral intervention demonstrated remarkable versatility, showing effectiveness across diverse age groups and clinical settings.

A few studies shed light on broader psychological and functional improvements beyond tic symptom management. The clinical sample who took part in the study by Deckersbach et al.¹⁹ reported improvements in life satisfaction and psychosocial functioning. Nissen et al.²⁴ documented that their participants consistently reported increased feelings of control over their tics, a critical psychological outcome that transcends mere symptomatic relief. Gur et al.³¹ noted significant improvement in cognitive inhibition and emotional regulation, within a group therapy setting. These findings collectively underscore the potential of behavioral interventions to provide meaningful clinical improvements across various patient populations providing comprehensive beneficial effects that extend beyond tic control.

The reviewed studies consistently identified certain tic characteristics as particularly challenging. McGuire et al.³⁰ observed that motor tics and those accompanied by strong premonitory urges were most bothersome to patients, with complex vocal manifestations like coprolalia also causing significant distress. This nuanced understanding provided critical insights for targeted intervention strategies. Notably, a few of the reviewed RCTs explored various intervention modalities, including individual and group therapy formats, as well as modified treatment protocols, such as shorter interventions. These findings highlight the importance of personalized treatment approaches. Zimmerman-Brenner et al.²⁶ documented the long-term beneficial effects of CBIT delivered within a group therapy setting, noting that treatment effectiveness varied based on individual characteristics such as cognitive abilities and comorbid conditions. Children with behavioral difficulties and lower intellectual abilities showed less benefit from CBIT, emphasizing the need for more individualized treatment strategies. Chen et al.²⁵ demonstrated the potential of a modified four-session CBIT that showed similar efficacy to standard CBIT protocols, suggesting potential for more streamlined and accessible treatment approaches. This finding is particularly significant from a healthcare perspective, offering potential cost-effec-

tive and time-efficient alternatives to established longer interventions. The study by Verdellen et al.²³ provided an interesting comparative perspective, showing that both HRT and ERP were effective in reducing tics, with ERP displaying marginally superior outcomes. Nissen et al.²⁴ further expanded this research line by comparing individual and group delivery methods of a behavioral intervention comprising both HRT and ERP, highlighting the flexibility of these interventions in addressing diverse clinical needs and resource constraints.

The main strength of the present systematic literature review lays in its comparative approach, revealing similar effectiveness for both children and adults. The methodological approach demonstrated both consistency and nuance across the reviewed studies. Researchers utilized standardized diagnostic criteria and validated rating scales (DSM and YGTSS, respectively), ensuring robust and comparable assessments. However, the variability in study designs and measurement tools further underscores the necessity for more standardized research protocols. Overall, the reviewed literature was characterized by other limitations, including the relatively small sample sizes. All the reviewed studies were conducted in specialist clinical settings, with selection/referral bias potentially limiting the generalizability of the overall findings, as the study samples may not have been representative of the broader tic disorder population. The predominance of RCTs conducted in Western research settings suggests a need for more diverse, cross-cultural studies to replicate initial findings and to validate the widespread applicability of the behavioral interventions under study. Although the research protocols incorporated psychometrically sound outcome measures, clinical data were not consistently collected by masked independent evaluators. Moreover, the relatively short-term follow-up periods suggest that the findings of the present review require cautious interpretation and additional research to establish definitive clinical conclusions. Finally, the reviewed studies support not only the efficacy of HR and CBIT, but also their effectiveness in various real-world settings. Specifically, individualized, in-person treatment delivery by trained psychologists appears to be a durable, specific treatment for reducing tics and tic-related impairment in both children and adults with TS and other chronic forms of tic disorders. However, the effectiveness studies have all been relatively small and were not designed according to well-accepted practices in effectiveness research³³.

In conclusion, this systematic review presents solid evidence supporting the efficacy of HRT, either in isolation or as the core component of CBIT, for managing tics in patients with TS and other chronic tic disorders. The consistent positive findings across the reviewed stud-

ies suggest that these approaches represent a valuable non-pharmacological treatment option. Despite the uneven geographical distribution of the studies, with 6 out of 10 RCTs conducted in North America, the collated findings support the effectiveness of HRT as a behavioral intervention, when delivered by trained psychologists. HRT and CBIT appear to offer effective, safe, and potentially long-lasting benefits for tic management across various age groups. Modified protocols, such as shorter interventions and group delivery formats, showed promising outcomes for enhancing accessibility while maintaining efficacy. While all the reviewed studies employed the YGTSS, a standardized outcome measure which provided a consistent measurement approach, there remains a need for more comprehensive assessment methods that can fully capture the complex nature of tic disorders. These include, but are not limited to, the physical subscale of disease-specific health-related quality of life measures such as the GTS-QOL (adults) and C&A-GTS-QOL (children and adolescents)³⁴⁻³⁷. There is also room for the development of more sophisticated measurement tools that can more accurately reflect the nuanced clinical presentations of patients with TS and other chronic tic disorders. From

a methodological perspective, future research should prioritize larger-scale, multi-center RCTs with extended follow-up periods, exploration of predictors of treatment response, and strategies for broader implementation in different geographical regions. There is a clear need for more comprehensive long-term studies that can definitively establish the sustained efficacy of HRT and CBIT. Additionally, exploring potential combination approaches with pharmacological treatments could provide more comprehensive management strategies to improve clinical outcomes and health-related quality of life.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by R.M. The first draft of the manuscript was written by R.M. and A.E.C., and all authors read and approved the final manuscript.

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