Treatments for Tourette syndrome in children and young adults: A systematic review

Tratamento da síndrome de Tourette em crianças e jovens adultos: Uma revisão sistemática

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ABSTRACT

Introduction: Tourette's Syndrome (TS) is a neurodevelopmental disorder characterized by motor and / or vocal tics for more than 12 months. TS affects about 0.8% of pediatric patients and is associated with great functional impairment and psychological distress. The present study aims to list and compare the effectiveness of therapies used in children and young people with TS.
Methods: PubMed / MEDLINE, Cochrane Library, ScienceDirect, SciELO and Lilacs were used from September 2020 to April 2021 to search for randomized clinical trials with pharmacological, behavioral, physical or alternative interventions for tics in children and young people with ST.
Results: 13 clinical trials were included, of which six pharmacological, six behavioral and one of other conformation. The global score on the Yale Global Tic Severity Scale showed evidence in favor of Habit Reversal Training (HRT) and Comprehensive Behavioral Intervention for Tics (CBIT). Evidence from two studies suggests that antipsychotic medications improve tic scores. Evidence from other interventions has shown no conclusive benefit.
Conclusions: The present study identified benefits with the use of antipsychotics. The study also found that HRT and CBIT showed improvement in reducing the severity of tics, in addition to not having any adverse effects. These therapies showed significant clinical improvement, but there is no comparison between the use of these isolated approaches in relation to their use associated with medications. In view of the different forms of therapy, further studies are needed to identify the effectiveness and the profile of adverse effects of these interventions.

Keywords: Tourette Syndrome, Therapeutics, Tics, Child, Adolescent.

RESUMO

Introdução: A Síndrome de Tourette (ST) é um distúrbio do neurodesenvolvimento caracterizado por tiques motores e/ou vocais por mais de 12 meses. A ST afeta cerca de 0,8% dos pacientes pediátricos e associa-se a grande comprometimento funcional e sofrimento psíquico. O presente estudo tem como objetivo listar e comparar a eficácia das terapias utilizadas em crianças e jovens com ST.
Métodos: PubMed/MEDLINE, Cochrane Library, ScienceDirect, SciELO e Lilacs foram usados desde setembro de 2020 até abril de 2021 para a busca de ensaios clínicos randomizados com intervenções farmacológicas, comportamentais, físicas ou alternativas para tiques em crianças e jovens com ST.
Resultados: 13 ensaios clínicos foram incluídos, dos quais seis farmacológicos, seis comportamentais e um de outra conformação. A pontuação global na Yale Global Tic Severity Scale, apresentou evidências a favor do Treinamento de Reversão de Hábito (TRH) e Intervenção Comportamental Abrangente para Tiques (ICAT). As evidências de dois estudos sugerem que medicamentos antipsicóticos melhoram os escores de tiques. Evidências de outras intervenções não mostraram nenhum benefício conclusivo.
Conclusões: O presente estudo identificou benefícios com o uso do antipsicóticos. O estudo também identificou que a TRH e a ICAT apresentaram melhora na redução da gravidade dos tiques, além de não apresentarem efeitos adversos. Essas terapias mostraram importante melhora clínica, mas não há comparação entre o uso dessas abordagens isoladas em relação ao seu uso associado com medicamentos. Diante das diferentes formas de terapia, mais estudos são necessários para identificar a eficácia e o perfil de efeitos adversos dessas intervenções.

Palavras-chave: Síndrome de Tourette, Terapêutica, Tiques, Criança, Adolescente.

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INTRODUCTION

Tourette's syndrome (TS) and Chronic tic disorder (CTD) are disorders characterised by the presence of combined or singular motor and vocal tics for more than 12 months with the onset before the age of 18 years[1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tics are sudden, fast, recurring, non-rhythmic movements or vocalisations usually preceded by a feeling of urgency, which is described as an intense desire to move or an internal tension before the movement[2,3]. The prevalence in paediatric patients has been estimated as 0.4%-0.8%, and both TS and CTD are associated with great functional impairment and psychological distress[4]. In general, tics start at around 6 to 7 years old, with clinical worsening between the ages of 8 and 12 years old. From adolescence and early adulthood tics decrease in severity, with a comparatively lower prevalence in adult life[5]. Tics can be simple or complex movements and, although they can affect any part of the body, they are more prominent on the face. Vocal tics include a variety of sounds and words, including coprolalia - inappropriate or involuntary use of words, sounds or phrases[3].

About 85% of patients with TS have one or more neuropsychiatric disorders, such as Obsessive-Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD), anxiety and depression[6,7]. The pathophysiology associated with TS is still not well understood, but it is probably caused by striatal-thalamic-cortical circuit interruption due to aberrant neural activity and consequent inhibition of somatosensory impulses and movements [8].

Cognitive-behavioural and pharmacological therapies are indicated for young people with TS who have, due to tics, impaired quality of life and daily functioning[8]. The cognitive-behavioural therapy and the psychoeducation is based on improve the knowledge of the patient and their families about TS, as a result, the knowledge deconstructs misconceptions about the syndrome, prepares the patient for possible more invasive therapeutic approaches, and educates the patient and his family [9].

Pharmacological approaches are based on experience *one on one,* but it is also influenced by the comorbidities of the paciente and the way of the spectrum of TS. In general lines, a pacient with TS may be treated with antipsychotic drugs first and second-generations, α-2-agonists, botulinum toxin or Δ-9-tetrahydrocannabinol showing different levels of evidence, quality of treatment and recommendation[8,9].

Most of the time these therapies show significant improvement in TS[9], however, there are other treatment options in cases of refractoriness, such as deep nerve stimulation, provided it meets a list of criteria based on recommendations of North American and European groups of study[10]. When choosing the treatment for TS, the interaction between tics and other comorbidities, such as OCD and ADHD, should be considered[11].

Systematic reviews and meta-analyzes on the treatment of tics are rarely found. Some studies have evaluated the effectiveness of treatments in both children and adults[12, 13], but it is known that children and adults may have different responses to the same drugs, both in terms of effectiveness and in susceptibility to adverse effects[14].

The current review aimed to list and compare the efficacy of the therapies used in children with TS, as well as their benefits and damages.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA).

Data base

The keywords used for the search in databases were obtained from Health Sciences Descriptors in the Virtual Health Library. The databases used for the research were PubMed/MEDLINE, Cochrane Library and ScienceDirect, with the keywords “Tourette syndrome”' and “Treatment”, and in the Scientific Electronic Library Online (SciELO) and Latin American and Caribbean Literature in Sciences of Health (Lilacs) with the same keywords in Portuguese, Spanish and English. Searches were conducted from September to December 2020 and updated in April 2021. Articles published in national and international journals in the last 20 years in English, Portuguese and Spanish were included. Book chapters, editorials, case reports and review studies were excluded from the analysis.

Eligibility criteria

PICO strategy was used to determine the inclusion and exclusion criteria.

Population: aged < 19 years old with a clinical diagnosis of TS or chronic tics disorder, according to DSM-5 criteria. Patients with transient tics (duration < 12 months) were excluded. Studies that included patients older than 19 years were not enrolled even if the average age of the study was < 19 years, due to possible associated biases.

Intervention: pharmacological treatments, psychological, behavioural, educational and psychosocial therapies, as well as physical and alternative therapies.

Comparison: placebo or other pharmacological therapies, psychological, behavioural, educational and psychosocial therapies, as well as physical and alternative therapies. Head-to-head studies were excluded.

Outcome: severity of tics assessed by the Yale Global Tic Severity Scale (YGTSS).

Only Randomised Clinical Trials (RCTs) were considered eligible. Decisions about inclusion criteria and classification of interventions were agreed by all authors before data extraction.

Eligibility criteria

Relevant data for the research were added to a table by one of the reviewers and this information was later verified by a second reviewer using a pilot form in Microsoft Excel 2017. As several scales have been described, the analysis priority has been given to YGTSS, which is the most used. After searching and choosing the articles, the risks of bias were analysed for each of the studies, evaluating whether any source of bias had a significant impact on the results.

Yale Global Tic Severity Scale (YGTSS)

The main subscale used for comparison was the YGTSS - total tic score (YGTSS-TTS), since most of the articles analysed used the values resulting from this assessment as their main result. When this value was not available in the study, YGTSS motor tic severity and YGTSS phonic tic severity were used, but this does not affect the comparison between the effectiveness of treatments, since YGTSS total tic score derives from YGTSS motor tic severity and YGTSS phonic tic severity [15].

YGTSS was the tool chosen because it is the score most commonly used for TS and it is also considered the gold standard in the tics evaluation[12]. YGTSS includes a symptom validation list for motor and vocal tics[15]. Tics are assessed for the number, frequency, intensity, complexity and interference of symptoms on a scale of 0–5. The scores for each dimension are totaled to reflect the severity of motor tics (range 0–25), vocal tics (range 0–25) and combined tics (range 0–50)[16]. YGTSS also includes a classification of general impairment such as experienced suffering and disability in the interpersonal, academic and occupational spheres[17].

RESULTS

After excluding duplicate texts, 916 articles were identified and, of these, 254 were selected for full text screening. Thirteen articles published between 2001 and 2021 met eligibility criteria (Figure 1). Of the 13 selected clinical trials, six articles were pharmacological interventions, six were behavioural interventions and one was physical intervention.

The characteristics of these studies, as well as the benefits and potential damages of each therapy, are present in Tables 1, 2 and 3. All the studies analysed involved patients diagnosed with TS or chronic tics, with targeted treatment for these conditions

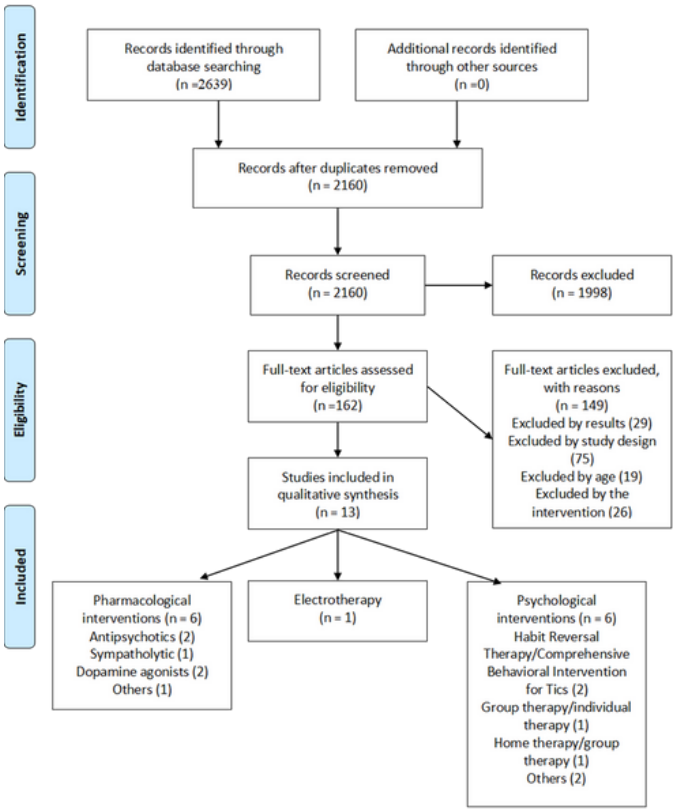

Figura 1. Flow diagram of preferred reporting items for systematic and meta-analysis.

Pharmacological interventions

Aripiprazole[18] in high dose (n = 45) and low dose (n = 44) compared to placebo (n = 44) resulted in significant clinical improvement. Patients were treated for 8 weeks and followed up for an average period of 30 days thereafter. There was a significant improvement in YGTSS-TTS in patients who used a low dose of aripiprazole (p = 0.002; 95% CI = -10.2 to -2.3) and in those who used high doses (p <0.0001; 95% CI = - 13.8 to -5.9) compared to placebo. Patients who used high doses of aripiprazole had a statistical difference in the improvement of tics according to YGTSS-TTS compared to placebo during all 8 weeks of treatment, and except for the second week of treatment, low doses of aripiprazole also showed this improvement. At the end of the 8th week, patients who used a low dose of aripiprazole had a mean change from baseline in YGTSS-TTS of - 13.4 ± 10.36, while those who used high doses had a change of -16.9 ± 9, 46. Patients who used placebo had a mean variation of -7.1 ± 10.36 in YGTSS-TTS. There was an improvement of 45.9% and 54.2% in YGTSS-TSS with the use of low and high doses of aripiprazole, respectively.

Ecopipam[19] showed significant results compared to placebo after 16 days (p = 0.01; 95% CI = 0.9 to -6.5) and 30 days of treatment (p = 0.03; 95% CI = -6.1 to 0.3). The mean was reduced from 32.8 ± 7.1 at baseline to 27.7 ± 8.8 in 16 days and to 27.2 ± 9.1 in 30 days with the use of ecopipam. With the placebo, the results varied from 33.7 ±

6.7 to 31.6 ± 7.7 and 30.3 ± 8.6, respectively, in the same periods of time. Both motor and vocal tics showed significant improvement with the use of ecopipam.

Guanfacine[20] did not show promising results when compared to placebo. In the group that used guanfacine (n = 16), the YGTSS-TTS decreased from 26.25 ± 6.61 to 23.56 ± 6.42 (p = 0.08), after 8 weeks of treatment, while in the control group (n = 18) there was a similar reduction from 27.67 ± 8.7 to 24.72 ± 10.54 after the same period of time. Thus, there was no significant reduction between the two groups in the YGTSS-TTS.

N-acetylcysteine[21] (n = 17) did not show any significant reduction in tics assessed by YGTSS-TTS compared with the control group (n = 14) after 12 weeks of treatment. The group that used N-acetylcysteine showed a variation from 27.1 ± 7.2 before treatment to 24.3 ± 7.9 after 12 weeks, while the placebo group varied from 26.3 ± 7.7 to 21.3 ± 4.6 (p = 0.815) in the same period of time.

Pergoline[22] showed a small improvement of symptoms in YGTSS-TSS. There was an average reduction of 8.8 points in the YGTSS-TSS (p = 0.05; 95% CI = 0.1 to 17.6) in the group that used pergoline (n = 36), varying from 50.6 ± 13.1 before treatment to 36.4 ± 16.5 after 8 weeks. In the placebo group (n = 15) there was a decrease in YGTSS-TTS from 45 ± 13 to 39.6 ± 19.4 in 8 weeks. The decrease in symptoms with pergoline did not reach clinically significant levels.

Psychological / psychosocial interventions

In the study by Yates et al.[23], patients were divided into 2 groups, one group (n = 17) participated in the Habit Reversal Training (HRT) and another (n = 16) in the educational group treatment. There was a reduction from 16.31 ± 3.03 to 15.88 ± 2.28 in the YGTSS motor tic severity (percentage improvement of 2.6%) and from 12.63 ± 5.93 to 11.13 ± 5.82 in the YGTSS phonic tic severity (improvement of 10.5%) in patients who participated in the educational group after 6 therapy sessions. In the HRT group, there was a change from 17.65 ± 4.74 to 15.12 ± 4.3 in the YGTSS motor tic severity (improvement of 14.5%) and from 12.71 ± 6.99 to 12.71 ± 5.61 in the YGTSS phonic tic severity (without percentage improvement) after the eighth session.

In the study by Dabrowski et al.[24], 28 of the 33 participants in the study by Yates et al.[23] were reevaluated, comparing YGTSS motor tic severity and YGTSS vocal tic severity after one month and after 12 months of treatment. Thirteen participants from the educational group and 15 from the HRT group were reevaluated. In the educational group there was a reduction from 15.54 ± 2.33 (95% CI = 14.13 - 16.95) to 13.77 ± 2.24 (95% CI 11.08 - 16.46 in the motor YGTSS tic severity and from 11.15 ± 6.35 (95% CI 7.32 - 14.99) to 9.23 ± 7.28 (95% CI 4.83 - 13.63) in the YGTSS phonic tic severity. In HRT group there was a decrease from 12.33 ± 5.64 (95% CI = 9.21 - 15.46) to 10 ± 7.1 (95% CI = 6.07 - 13.93) in the YGTSS phonic tic severity, while the YGTSS motor tic severity went from 14.73 ± 3.83 (95% CI = 12.61 - 16.85) to 12.2 ± 5.07. An average reduction of 8 points in the YGTSS-TSS was observed between the first evaluation (one month before the starting treatment) and the last one (12 months later) in those in HRT group, while in the educational group there was a reduction of 6 points in the same period of time.

One of the studies compared the effectiveness of behavioural therapy (n = 25), psychoeducational therapy (n = 24) and pharmacological treatment (n = 47) with risperidone or aripiprazole[25]. Patients who used Behavioural Therapy (BT) and pharmacology therapy showed a reduction in the severity of tics according to YGTSS-TTS (and its subscales), while the group that underwent psychoeducational therapy did not show considerable improvement. The volunteers were evaluated three times, the first (T0) before the starting treatment, the second (T1) after 10 weeks and the third (T3) 3 months after the end of BT or psychoeducational therapy and 5 months after starting pharmacological therapy. Patients who participated in BT had a reduction from 35.4 ± 17.78 at T0 to 19.84 ± 14.38 at T1 and 19.96 ± 13.68 at T2 at YGTSS-TTS, while those who used pharmacological treatment increased from 36.38 ± 16.70 in T0 for 23.47 ± 12.64 in T1 for 22.26 ± 11.23 in T2 with p <0.05 in both approaches. On the other hand, patients who used psychoeducational therapy went from 34.25 ± 14.34 in T0 to 35.00 ± 14.89 in T1 to 33.12 ± 13.88 in T2 in YGTSS-TTS.

One of the studies compared the effectiveness of individual therapy with group therapy[26], using in both approaches HRT and tic exposure therapy. Individual therapy group used HRT (n = 31) and the group that received group therapy was submitted to exposure therapy (n = 28). Patients who participated in individual therapy (n = 31) had an average of 51.52 13.04 in YGTSS-TTS before the beginning of treatment, while those who were allocated for group therapy (n = 28) had an average of 48 12.12. After eight therapy sessions, there was a decrease of 9.48 7.84 points in individual therapy and 7.48 5.44 points in group therapy. Both treatments presented clinical improvement (p < 0.0001). There was no significant difference in the clinical response between the two groups considering YGTSS-TTS.

A research by Singer, McDermott, Ferenc, Specht and Mahone[27] produced videos and an instructional guide that should be administered by parents (based on home psychotherapy) and compared its effectiveness with therapy administered by a therapist after 10 weeks of treatment. The patients who used the first method (n = 8) had, on average, in YGTSS-TTS, 27.75 ± 3.62 points before treatment and 18.75 ± 5.7 after 10 weeks of treatment (p <0.001) . Patients who had the therapy administered in person by a therapist had a score of 28.2 ± 4.56 before the start of treatment and 20.70 ± 6.34 after 10 weeks of treatment (p = 0.010).

The study by Piacentini et al.[28] compared Comprehensive Behavioural Intervention for Tics (CBIT)

(n = 61) in relation to educational and supportive therapy (n = 65) in the reduction of chronic tics for 10 weeks. The CBIT group had an average of 24.7 ± 6.2 points in YGTSS-TSS before the starting treatment and 17.1 ± 2 after the 10 weeks of treatment, while those who participated in the control group had 24.6 ± 6 before treatment and 21.1 after 10 weeks. There was an average decrease of 7.6 points in YGTSS-TTS in patients undergoing HCT compared to a decrease of only 3.5 points in the other group (p <0.001; 95% CI = 2 to 6.2).

Other types of interventions

A study conducted by Wen-Jun et al.[29] evaluated the effectiveness of electrotherapeutic stimulation in reducing tics compared to a false procedure ("sham procedure"). Patients who underwent electrotherapeutic stimulation (n = 29) scored an average of 30.41 ± 5.89 on the YGTSS-TTS before the starting treatment and 20.62 ± 6.44 after 40 sessions. Patients who participated in the sham procedure scored 30.04 ± 5.52 before the starting the procedure and 23 ± 7.37 after 40 sessions. Participants who underwent electrotherapy showed an average improvement of 31.66% in YGTSS-TTS, while the sham group had an improvement of 23.96%, which resulted in a non-significant difference between the groups.

A study by Zheng et al.[30] compared 5-ling-granule (5-LGr), a herbal medicine, (n = 363) with tiapride (n = 123) and placebo (n = 117) for 8 weeks, evaluating the clinical response in the 2nd and 8th week. In the 2nd week of treatment, there was no statistical difference between the groups evaluating the YGTSS-TSS, but in the 8th week a significant difference was found. Patients who used tiapride showed a variation in the YGTSS-TSS from 23.1 ± 6.9 before treatment to 10.1 ± 6.4 after the 8th week of treatment (p <0.001 compared to placebo). The 5-LGr group varied the YGTSS-TSS score from 23.7 ± 6.8 to 10.6 ± 6.8 (p <0.001 compared to placebo and 0.489 compared to tiapride). Variation in the placebo group was 22.7 ± 6.7 to 14.4 ± 7.5 after the 8th week of treatment initiation.

Adverse effects associated with treatment

Given the relatively small samples found in the studies, every evidence that there was an increased risk for adverse effects was considered. Although antipsychotics are associated with increased risks of sedation and extrapyramidal side effects[31] the studies analysed did not associate any serious adverse effects to antipsychotics when compared to placebo. Patients who used high doses of aripiprazole had more side effects, with thirty-four participants experiencing at least one adverse effect. Twenty-nine patients who used low doses of aripiprazole and eighteen of the placebo group had at least one adverse effect.

Guanfacine also had considerable adverse effects compared to placebo, especially fatigue, drowsiness, headache, abdominal pain, decreased appetite, depressed mood, dry mouth, and irritability. These symptoms were most frequently reported within the first four weeks of treatment. Other drugs analysed in this research, as well as electrotherapy, did not present statistically significant adverse effects when compared to placebo.

Some studies did not provide information on adverse effects caused by the treatments applied, and therefore, it was not possible to assess their safety profile.

DISCUSSION

HRT is considered the first treatment line for TS and for CTD in children and young people[32]. Our results support this recommendation, with evidence that other Behavioural therapies, such as CBIT, have a similar magnitude of effect to medications. CBIT approach basically consists of awareness training for tics and premonitory desire, competitive response training to provide tic substitutive behaviour and functional intervention to help identify changes in daily activities that could be beneficial in reducing tics. The absence of collateral damage is a factor that benefits CBIT practice[7, 33, 34], as well as its long term effect of reducing tics. The main guidelines of the United States, European Union and Canada recommend HRT as the first line of treatment for tics[32, 33, 35]. Despite this, for many people with tics and TS, pharmacological treatment should be considered either because of the lack of treatment response to HRT or limited access to therapy. Antipsychotics are widely used for TS and aripiprazole, in our results, showed an important clinical response compared to placebo, even at low doses. In comparison to the control group, there was no increased risk of clinically significant adverse effects. These findings may suggest that aripiprazole is a useful and safe drug for children with tics, with a similar effect to other antipsychotics. Educational therapies presented no significant clinical improvement, especially when compared to Behavioural therapies and pharmacological treatment. Treatment combining both HRT and exposure therapy was effective in individual and group therapy.

Antipsychotics, such as olanzapine, have not been evaluated in RCTs, only in head-to-head studies, which have a low comparative potential for effectiveness. Thus, to assess its efficacy, as well as its safety profile in paediatric patients with TS, further studies are needed.

Ecopipam showed an important clinical improvement in patients with tics, reducing both vocal and motor tics. In addition, ecopipam appears to be well tolerated in TS, with the absence of neuroleptic conditions common in other dopamine antagonists. Alpha-2-agonists, such as clonidine and guanfacine, are commonly used in children with CTD and are even considered first-line for TS[36-41]. The selection of clonidine and guanfacine occurs

partly because of their more favourable side effect profile when compared to antipsychotics[13]. The study analysed in this review[20] differed from other findings in the literature, since it concluded that there was no significant clinical improvement in patients who used guanfacine compared to placebo. However, this study had a sample of only 34 participants and, therefore, it may not have considerable statistical power to conclude the effectiveness of guanfacine. Another drug that did not show significant clinical improvement in TS in children and adolescents, according to the results obtained in this research, was N-acetylcysteine. Other previous studies concluded that N-acetylcysteine has a significant clinical benefit in the treatment of trichotillomania in adults, however, the same efficacy results were not observed in children with TS evaluated in Bloch's research[37].

5-LGr provided a significant clinical improvement over the placebo, in addition to demonstrating an efficacy in reducing tics similar to what occurs with tiapride. The effectiveness of 5-LGr observed in this study may be related to its multiple pharmacological and therapeutic properties. Preclinical studies have shown that this substance was able to decrease the affinity of the striatal D2 receptor and decrease the metabolic level of dopamine, while suppressing tics-like behaviour in mice [30].

It is important to highlight the scarcity of evidence for alternative treatments that are often used for CTD and TS. The only research found that assessed the efficacy of acupuncture was a head-to-head study[42] compared to haloperidol and had a low impact of evidence. No studies were found on the use of dietary supplements, vitamins or yoga.

There is no evidence of the effectiveness of electrotherapeutic stimulation in reducing tics in children and adolescents. Although the study by Wu et al.[29] concluded that this approach is safe, there was no significant improvement in relation to the sham group. It should also be considered that, in addition to a small sample, the patients in this study continued to use medications for tics, which may explain the clinical improvement in both groups - even in those who did not undergo electrotherapy.

It should be noted that the great effectiveness of behavioural therapies was due to the research that used CBIT, since it was the study with the most significant sample. Despite consistent evidence of the efficacy of Behavioural therapies and the low risk of associated adverse effects, difficulties with access and financial constraints may make it impossible to adhere to this type of treatment. An alternative proposed for these situations is home psychotherapy. Usually little used in practice, this approach consists of an instructional video based on HRT and written instructions to be followed by patients and parents at home[7]. One study concluded that there is a significant clinical improvement in tics using videos and, despite being a small sample study, this alternative is promising, especially for cases where there is no possibility of face-to-face therapy. Further studies are needed to prove the effectiveness of this approach.

Associated disorders are very common in TS and in patients with chronic tics. These conditions were identified in 10 of the 13 RCTs evaluated in this review, it is noteworthy that the three studies did not include comorbidities in the data analysis.

Psychoeducational therapy showed no improvement when compared to pharmacological treatment and Behavioural therapy. The psychoeducational approach uses cognitive behavioural strategies to work on topics that interfere in the quality of life of these patients, such as the tics themselves and the TS, self-esteem, school, anger and anxiety. The objective is to reinforce coping strategies, reduce anxiety and emphasise the patient's strengths[43].

Thus, the approach chosen to treat tics depends on the degree and types of disability[4]. A commonly used approach is behavioural therapy, often HRT. With regard to pharmacological therapy, alpha-adrenergic agonists are indicated as the first line, these being clonidine and guanfacine. Other therapeutic options include risperidone, aripiprazole, tetrabenazine, pimozide, haloperidol and fluphenazine[3].

Some limitations must be considered, mainly the number of studies and the sample of some of these studies, and this diminishes the strength of the evidence and conclusions. In addition, many of the interventions were only studied on a short-lived RCT, with modest sample sizes. The number of studies and the size of the samples were reduced, so there is doubt about which treatments are the best and the magnitude of their effects. Many interventions had poor quality evidence. Most studies have compared the short-term post-treatment effects, and the long-term effectiveness of interventions is not well known.

Most studies did not report changes in comorbid conditions, focusing on changes in tics. Thus, it is not possible to conclude the effect of interventions on symptoms of comorbidity related to TS. Adverse effects were not considered in all studies evaluated, thus preventing a more detailed critical assessment of the studies. Finally, as long as there is evidence to support the effectiveness of various treatments, knowledge gaps remain and there is still a great need for controlled RCTs for tic interventions to assess long-term efficacy and safety.

CONCLUSION

Regarding pharmacological therapies, the present study identified benefits with the use of aripiprazole and ecopipam. Pergoline shows a slight improvement in tics compared to placebo. The results showed no benefit in the use of guanfacine, considered a first-line medication for the treatment of tics in children and young people, diverging

from other findings in the literature. Similarly, no reduction in tics was observed when evaluating the effectiveness of N-acetylcysteine. HRT has been shown to be slightly superior to educational therapy, being a good alternative due to the absence of adverse effects. It was also noted that behavioural and pharmacological therapy (risperidone and aripiprazole), when compared to psychoeducational intervention, rates expressive reductions in symptoms.

Given, as likely, some behavioural and pharmacological options, it seems reasonable to consider the patient's choice and financial possibilities when choosing therapy. Other treatments may become the option after the lack of response to the therapies mostly commonly used. A therapy considered an alternative, 5-LGr, obtained good results – similar to tiapride. Considering that young people and their parents can seek alternative treatments, it is important to emphasise that their use is not supported by strong evidence to date. We conclude that among the various forms of therapy, the most studies are indicated to identify the efficacy and the profile of adverse effects of these actions, in order to guide the best method for each patient and their comorbidities.

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