REVIEW ARTICLE

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Different treatment methods for tics and Tourette Syndrome

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Abstract

Introduction and Objective. Tourette syndrome is a neuropsychiatric disorder that begins in childhood and reaches its peak just before adolescence. The disorder is severely troublesome for patients not only by the motor and phonic tics that occur, but also by the often co-occurring behavioural disorders. The review presents the treatment methods available today, including behavioural methods, as well as pharmacological and surgical methods.

Review Methods. Scientific publications were searched for articles using Pubmed and Google Scholar with the use of phrases 'Tourette Syndrome', 'Tourette Syndrome Treatment', 'tics treatment', 'deep brain stimulation' and 'Tourette Syndrome epidemiology'.

Brief description of the state of knowledge. Until recently, treatment of this disease was limited to the use of antipsychotic drugs only. With the development of knowledge about the pathophysiology of Tourette syndrome, drug groups, such as VMAT-2 inhibitors, lurasidone, ecopipam, noradrenergic drugs, and GABA-ergic drugs have also been introduced into treatment. The importance of educating parents, students and teachers around affected children was also highlighted. Botulinum toxin injections have also been proven to reduce the severity or even disappearance of tics. In refractory patients with severely severe tics, more invasive treatments, such as deep brain stimulation, are undertaken.

Summary. Treatment methods for tics and Tourette syndrome are constantly developing. However, intensive research is still needed to introduce new treatments and improve existing therapies. Any therapy, whether pharmacological or invasive, carries the risk of side-effects and complications.

Key words

Tourette Syndrome, tics, tic disorders

INTRODUCTION AND OBJECTIVE

Tourette syndrome (TS) is a neurodevelopmental disorder, the essence of which is the presence of motor and verbal tics lasting a minimum of one year and beginning before the age of 18 (Tab. 1) [1]. Tics are non-rhythmic movements or vocalizations that occur suddenly and repeatedly [2]. They may be categorized as simple or complex (Tab. 2) [3]. The majority of tics exhibit a fluctuating course, with discrete bouts lasting from weeks to months. Exacerbations may be caused by tensions, illnesses, injuries, or other factors; however, frequently, there is no recognizable cause [4]. Tics are usually preceded by a sensation of impending discomfort, and, after the tics fade, followed by a sense of relaxation. However, the tics themselves are controlled consciously, and allows the affected person to postpone them, although intentional suppression of tics sometimes results in higher internal tension and pain [5].

Although the etiology of TS remains only partially known, the suggested explanations cover both functional and structural alterations in the corticostriatal-thalamocortical circuitry inside the basal ganglia, alongside the dopaminergic nigrostriatal pathways. A complex interaction of noradrenergic, serotoninergic, cholinergic, histaminergic, glutaminergic, and GABAergic systems is the neurochemical basis [4]. The course of TS is variable, but usually the peak of symptoms occurs before puberty and decreases thereafter [6].

The aim of the review is to demonstrate available treatment of tics and TS with various methods (Fig. 1).

Epidemiology. The prevalence of TS in the general population is estimated at 0.3–1%, with males three times more likely to be affected than females. Tics primarily affect young people (before the age of 18) and usually have a fluctuating cycle, while more persistent course appears in adults [2]. Some studies show that up to 80% people diagnosed with tics disorder before the age of ten experienced a considerable decrease in tics during adolescence [7]. Psychiatric comorbidities are frequently developed among individuals with TS over their lifetime. The most common comorbidity in children is ADHD. Other disorders that co-occur in TS (abbreviation) are anxiety disorders, depressive disorders, autism spectrum disorders and sleep disorders [8]. The risk of death in people with TS and comorbidities has been proven to be higher than in patients without comorbidities [9].

Treatment methods. Treatment of tics and TS in each patient requires a strictly individualised approach. Moreover, due to the co-occurrence with tics of multiple behavioural disorders, such as obsessive-compulsive disorder or attention deficit hyperactivity disorder (ADHD), treatment must be

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Table 1. Classification and criteria of tics and TS [6]

	PARENT CATEGORY	CRITERIA OF CHRONIC OR PERSISTENT MOTOR AND/OR VOCAL TIC DISORDER	CRITERIA OF TOURETTE SYNDROME
DSM-5	• Neurodevelopmental disorders	• Onset before the age of 18 • The course may fluctuate, but is present at least 1 year before the onset • Not caused by any substance or disease • Presence of one or more motor or vocal tics at some time, but not both • No prior TS history • State if the tics are motor or verbal	• Onset before the age of 18 • The course may fluctuate, but is present at least 1 year before the onset • Not caused by any substance or disease • At some point, presence of one or more vocal tics and multiple motor tics
ICD-11	• Nervous system disorders: primary • Mental and behavioural disorders: secondary • Obsessive–compulsive disorders and related • Neurodevelopmental disorders	• Last 12 months • Symptoms include one or more verbal and motor tics	• Last 12 months • One or more vocal and/or motor tics appear simultaneously

DSM-5 – The Diagnostic and Statistical Manual of Mental Disorders 5th edition; ICD-11 – The International Statistical Classification of Diseases and Related Health Problems, 11th edition

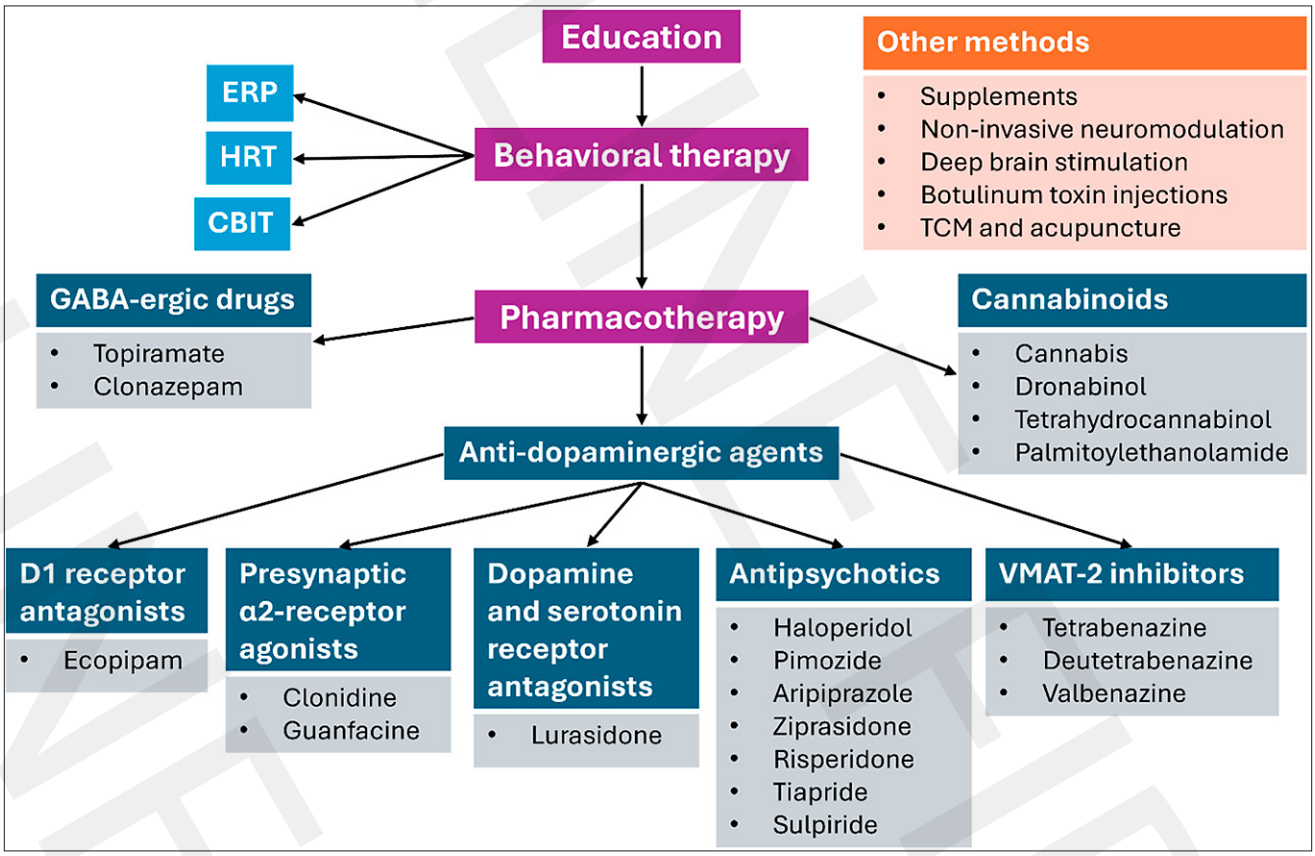

Figure 1. Figure 1. Available treatment of tics and Tourette Syndrome [2]. ERP - Exposure and Response Prevention; HRT - Habit Reversal Training; CBIT - Comprehensive Behavioral Intervention for Tics; TCM – Traditional Chinese Medicine.

multidisciplinary [2]. Since the 1960s, antipsychotic drugs have been widely used to treat tics and TS, thought to be the only effective treatment. However, it has been noted that this therapy has a lot of side-effects in the form of dyskinesias, akathisia, drug-induced parkinsonism, and also leads to metabolic disorders. Therefore, it was decided to look for new therapies with fewer side-effects on the body. Currently, a combination of behavioural, educational, pharmacological and, in refractory cases, surgical methods, are used in treatment [10].

The education of patients, their families and people close to them is also important for the success of treatment and helps them understand the disease. The Tourette Association of America provides parents, students, and teachers with educational resources that teach different attitudes toward patients affected by the disease [6]. This allows them to learn more about the problems of those affected and teaches them how to deal with and communicate better.

Behavioural Therapy. Behavioural therapy is widely regarded as the most effective psychotherapy technique for treating tic disorders. Numerous randomized controlled trials have confirmed its effectiveness, and there have been no known adverse effects [11]. Behavioural strategies in tic control give patients skills to change the internal and external factors that cause and maintain tics. The most empirically supported behavioural therapies include habit reversal training (HRT), Comprehensive Behavioural Intervention for Tics (CBIT), as well as exposure and response prevention (ERP) [12].

Exposure and Response Prevention (ERP). Involves the individual suppressing tics for extended periods of time (response prevention), followed by gradually increasing exposure to premonitory urges and environmental factors (e.g. situations and activities) that are likely to induce tics, with the goal of increasing urge tolerance and thus reducing tics.

In order to analyze the effectiveness of ERP, Verdellen et al. (2004) conducted a randomized study on a mixed-age group of 43 people with tic disorders. The participants were then randomly assigned to either fourteen 2-hour ERP sessions or twelve 1-hour HRT treatments. Individuals with concomitant mental problems and those using tic-reduction medication were eligible to participate. The Yale Global Tic Severity Scale (YGTSS; range 0 – 50 [higher scores indicate greater severity of symptoms]) was used by a masked independent evaluator to assess results. Therapists were closely monitored, but no treatment integrity data was published. Both groups' tics improved after treatment, but there was no significant group × time interaction, indicating that the two therapies were equally effective. Despite exhibiting equal efficacy to the well-established HRT, ERP individuals obtained more than twice as much therapy as HRT participants, albeit the authors adjusted for this disparity in the analyses [12].

Habit Reversal Training (HRT). HRT is divided into two main sections:1) awareness training – consists of various methods to make tic expression and related premonitory drives more conscious; 2) competing response training, which prevents tics from expressing themselves by identifying and using physically incompatible responses [13]. HRT improves participants' awareness of impending tics. Individuals acquire a tic-stopping behaviour when the impulse occurs, and each bothersome tic may be controlled more effectively with practice. HRT has evolved into a manualized CBIT. In multiple studies, HRT has proved to be effective; for example, Yates et al. (2016) randomly assigned 33 chronic tic disorder (CTD) and TS children aged 9–13 years into 2 groups: HRT and psychoeducation. Both groups saw reduced tic severity and higher quality of life, with HRT outperforming psychoeducation in terms of lowering motor tic symptoms [14]. In a 12-month follow-up study of 28 children, Dabrowski et al. (2018) found that HRT and psychoeducation improved long-term tic symptoms, quality of life, and school attendance. The HRT group had a significantly lower total tic score than the psychoeducation intervention group [15].

Continuous Built-In Test (CBIT). A personalized, multi-component approach to treating tic symptoms [13] which trains patients to become more conscious of their tics. In this method, patients engage in a competing habit whenever they experience premonitory desires [4]. The CBIT trials for children and adults found that an 8-session regimen was effective; however, individuals with limited tic awareness, treatment motivation, severe tics, or significant clinical comorbidity may require a longer period of therapy.

Children and adults (aged 9 years or above) who initially respond positively to CBIT, typically sustain their treatment gains for 6 months. There is limited evidence to support the effectiveness of CBIT in children under 9 years of age [6]. According to research, age is said to be a predictor of tic suppression [16], which means that a developmentally appropriate adaptation may be necessary, because young children may not have the self-awareness and self-control needed to successfully implement CBIT techniques.

In order to determine the effects of group-CBIT, research was conducted aimed at comparing pre- and post-intervention ratings for the symptom scale related to tics to those of the control group. Group CBIT resulted in significant improvements in motor tic interference, impairment, and overall severity score, compared to the control group. The intervention group outperformed the control group in terms of motor tic interference and overall score, aligning with a prior study that found improvement in severity [12].

TREATMENT METHODS – DRUGS

Anti-dopaminergic agents – Vesicular monoamine transporter-2 (VMAT2) inhibitors. Although dopamine receptor blocking drugs can effectively reduce tics, they can also lead to serious and long-term consequences, such as tardive dyskinesia. Dopamine-depleting medicines that inhibit VMAT2 can treat hyperkinetic movement disorders, such as tics, without producing tardive dyskinesia. Tetrabenazine, deutetrabenazine and valbenazine are included in this group of agents [17].

Tetrabenazine, a medication approved by Food And Drug Administration (FDA) for Huntington's chorea, has been demonstrated to effectively treat tics associated with TS in open-label trials. The drug is effective for treating hyperkinetic movement disorders, although it can cause adverse effects, such as sleepiness, parkinsonism, depression, and akathisia [18]. Dopamine depletors such as deutetrabenazine and valbenazine are also being studied for treating TS. In a pilot open-label trial conducted by Jankovic et al. (2016), 23 adolescent patients with moderate-to-severe tics from TS were titrated over a 6-week period and maintained for 2 weeks at a mean dose of 32.1 mg (range: 18–36 mg) of deutetrabenazine. An independent blinded rater evaluated tic severity using the Yale Global Tic Severity Scale (YGTSS) and tic effect using the TS-Clinical Global Impression questionnaires. The YGTSS Total Tic Score improved by 37.6%, with significant improvements in secondary outcomes, such as TS-Clinical Global Impression, TS-Patient Global Impression of Change, Tic-Related Impairment Score, Beck Depression Inventory II, and the Children's Yale-Brown Obsessive Compulsive Scale. There were no serious or severe side-effects recorded [17].

Preliminary findings indicate that studies with valbenazine in TS did not meet their intended primary aim. T-Force studies include T-Force GREEN (paediatric phase 2), T-Force GOLD (paediatric phase 3), and T-Forward (adult phase 2). The causes for these failures are unclear, but may be due to methodological issues, such as including minor cases and underdosing. According to Jankovic et al. (2020), to-date, no randomized, double-blind, placebo-controlled trials have been published; however, VMAT2 inhibitors are commonly utilized as a first-line treatment for patients with TS who have significant tics [19].

Antipsychotic drugs. The FDA has authorized three medications to treat TS: haloperidol, pimozide, and aripiprazole, all of which block dopamine receptors. Haloperidol and pimozide were found to be beneficial in reducing the frequency and intensity of tics in double-blind, placebo-controlled trials. However, these medications should

be avoided due to side-effects, such as metabolic syndrome, prolonged QT interval or torsades de pointes [10].

In addition to these three neuroleptics, several additional medications that block dopamine receptors have also been used to treat TS, including ziprasidone and risperidone. Risperidone's neurotransmission effects may treat comorbid symptoms like aggressiveness or obsessive-compulsive symptoms in treating children with TS. However, additional research is needed to determine its effectiveness in treating mental comorbidities [5].

The two most often used first-line medications for adults are risperidone and aripiprazole. One of the main pharmacologic characteristics that sets aripiprazole apart from serotonin-dopamine antagonists is that it is a partial agonist of the D2 dopamine receptor. Aripiprazole has been shown to alleviate extrapyramidal symptoms (EPS) and hyperprolactinaemia. It acts as a partial agonist of serotonin 5-HT1A receptors and as an antagonist of 5-HT2A receptors [20]. Side-effects that were often reported were weight gain, nausea, and drowsiness. However, research indicates that aripiprazole is well-tolerated and rarely leads to withdrawal due to adverse effects [21].

Tiapride is a selective antagonist of dopamine D2 receptors and has a weak antipsychotic effect. Because of its success clinically, it is widely used in Europe to treat tics [22]. According to a study by Yang et al (2019), the most prevalent adverse effects of tiapride were dry mouth, nausea and dizziness [23]. Tiapride, in addition to inhibiting the striatal supersensitive D2 receptor, is also thought to have some 5HT-3 and 5HT-4 blocking properties. Its primary side-effects are weight gain, temporary hyperprolactinaemia, and sleepiness. Since 1970, studies have also documented benefits of sulpiride on the treatment of tic symptoms. It is a very specific D2 receptor blocker, and additionally has been demonstrated to have modest anxiolytic, antidepressant, and antipsychotic properties [5].

Dopamine and serotonin receptor antagonists. Lurasidone – an atypical antipsychotic medication – is authorized for the treatment of schizophrenia in adults and adolescents 13 years of age and older [24]. A case series were conducted which suggested that an additional therapy with lurasidone may be effective in treating complex forms of TS with obsessive symptoms and aggressive behaviour resistant to antipsychotic monotherapy, or other psychopharmacological treatments. Nevertheless, due to very limited data, further research is necessary to evaluate the long-term tolerance and efficacy of polypharmacy [25].

D1-receptor antagonists. Ecopipam is a first-in-class selective dopamine D1 receptor antagonist that appears to minimize side-effects while treating tics. Current research indicates that ecopipam may be an effective alternative to presently available drugs for tics. The most frequent side-effects include nausea, vomiting, somnolence, headaches, sleeplessness and upper abdominal pain; however, the medication was overall well-tolerated, with no signs of weight gain or movement disorders induced by drugs [26].

Presynaptic α2-receptor agonists. Alpha agonists, including clonidine and guanfacine, are commonly administered by paediatricians and psychiatrists as 'first-tier' drugs for newly- diagnosed TS patients. Research suggests that these medications can effectively treat mild tics alongside mild ADHD and impulse control disorders [19]. In a 16-week, multi-centre, randomized, double-blind clinical study, 136 children with ADHD and chronic tic disorder were randomly assigned to receive clonidine alone, methylphenidate alone, or a combination of the two drugs, or placebo. The combined therapy of clonidine and methylphenidate showed the greatest benefit in improving tics and attention. Although 28% of patients experienced moderate or severe drowsiness with clonidine, the medication was usually well-tolerated [27].

A meta-analysis of published research on alpha-2 agonists for treating TS indicated that they had a medium-to-large effect on tics in participants with co-existing ADHD, but had a non-significant effect on tics in studies that excluded ADHD [28]. Clonidine may aid in sleep initiation at night, but its ability to reverse daytime sedation with the central nervous system (CNS) stimulants restricts its use. Guanfacine is chosen over clonidine in treating comorbid ADHD and impulsive control due to its lower sedative effects. Both α2 agonists have limited efficacy in treating tics. In a trial of 34 children with persistent tic disorder, extended release of guanfacine did not significantly reduce multiple tic scores compared to placebo [29].

In addition to drowsiness, α2 agonists may cause weariness, dry mouth, headaches, irritability, bradycardia, and orthostatic hypotension. α2 agonists have limited efficacy, but may be beneficial for individuals with minor tics that require medication [30].

GABA-ergic drugs – Topiramate (TPM). Although topiramate is an antiepileptic drug, it is also used with success for various off-label indications including mental diseases. TPM promotes GABA-mediated neurotransmission through GABA-A receptors. TPM usage can cause difficulty in word-finding, mental processing, concentration, and memory [31]. According to a meta-analysis by Yu et al. (2020), TPM is more effective and causes fewer side-effects than both haloperidol and tiapride in treating children with TS. It is now indicated for mild cases of TS or when patients experience troublesome side-effects from other therapies [32].

Benzodiazepines (BDP). The most prevalent BDP drug for TS treatment is clonazepam, indicated for moderate to severe tics [14]. Although clonazepam can be beneficial, it should not be used as the primary treatment [33]. Unfortunately, only two single-blind comparison studies regarding clonazepam have been conducted. The first trial found that clonazepam was more effective than clonidine in tic suppression, whereas the second study proved that patients with a high ratio of red blood cells to plasma choline reacted better to clonazepam than haloperidol [5]. These medications should be taken with caution due to numerous commonly experienced side-effects, such as fatigue, lethargy and sleepiness [34].

Cannabis-based medications (CBM). The potential use of cannabis to treat tics in severe TS was studied in a double-blind, crossover trial of 22 adult patients. The result was reduction in total tic score in both active and placebo groups which was measured by the YGTSS. A linear mixed-effects model revealed a significant interaction between treatment (active/placebo) and visit number on the tic score, indicating a higher drop (improvement) in tics with active treatment [35].

Results from some studies are promising, e.g. a study by Barchel et al. reported a notable enhancement in

patients' quality of life, employment status and reduction of medications taken, despite lack in tics frequency or general mood improvement [36]. Another study by Serag et al. demonstrated that CBM can effectively reduce the intensity of tics and premonitory desires; however, extensive trials employing stringent methodology, standardized pharmacological components, and set dosages, are essential for reliably assessing their efficacy [37].

Other methods – Supplements. Researchers at Catania University in Italy carried out an open-label trial that examined the effectiveness of L-theanine and vitamin B6 supplementation in reducing tics and anxiety. The study involved a group of children and indicated that both treatments help reduce tics and anxiety symptoms according to the YGTSS and the Multidimensional Anxiety Scale for Children (MASC). Further trials still need to be undertaken [38]. Another study reported that magnesium helps reduce both verbal and motor tics. Renal magnesium deficiency in some cases of patients diagnosed with TS may be associated with the 11q23 chromosomal site. It has been reported that certain environmental substances and conditions that result in magnesium shortage might induce or worsen the symptoms of TS [39].

Non-invasive neuromodulation. Clinical studies have been conducted on the use of non-invasive brain stimulation to alleviate the symptoms of TS, with the focus mainly on the motor cortex area. Methods such as transcranial direct current stimulation and transcranial magnetic stimulation have been used for this purpose. Both methods are safe, but according to current guidelines, they are not recommended for alleviating symptoms of TS [40].

One study of both affected adolescents and adults showed a reduction in tic severity after rhythmic peripheral somatosensory stimulation of the median nerve [41]. Considering the significant adverse effects and refractoriness associated with traditional medication, TS patients may require innovative therapeutic options. In the light of emerging insights into underlying mechanisms associated to the onset and regulation of tics on the neuroanatomical ans neurophysiological level, neurostimulation appears promising and achievable [42].

Deep Brain Stimulation (DBS). DBS (abbreviation) is an invasive treatment for severe, refractory cases of tics in the course of TS (abbreviation) [43]. In this method electrodes are implanted in particular areas of the brain and create electric currents that control neuron activity. The European clinical recommendations TS (abbreviation) stipulate that DBS should be conducted in adults only when the patient has not responded to behavioral therapy and several pharmacological treatments, with tic symptoms enduring for a minimum of 5 years and severe symptoms present for at least 1 year [44]. In instances resistant to behavioral therapy and pharmacotherapy, DBS of the globus pallidus interna or centromedial thalamus may be considered. The most common known adverse effects are paresthesia and dysarthria, however more serious incidents such as hemorrhages may occur. More research is needed to determine the optimal target, benefits and hazards, indications, timing of the treatment, and stimulation settings [45].

Botulinum toxin injections. Botulinum toxin is a neurotoxin that inhibits the presynaptic release of acetylcholine at the neuromuscular junction, resulting in reversible chemodenervation of muscle fibres. Its mechanism of action in tic disorders may be related to the muscular weakening that occurs during injection, or to an influence on the premonitory desires that precede tics [46].

Botulinum toxin injections are a promising treatment for motor tics and phonic tics. A Randomized Double Blind Placebo Control Trial (RDBPCT) study involving 18 patients with motor tics was conducted. The patients were given botulinum toxin injections. It was shown that 39% of the patients improved and reduced the severity of their tics, while an increase in tics was observed in patients who took a placebo [47]. When it comes to side-effects, botulinum toxin can cause brief pain, minor muscular weakness, and hypophonia when applied in the throat to treat vocal tics. In Europe, this method is only recommended for older adolescents and adults who have not responded well to previous therapies [10].

Traditional Chinese Medicine (TCM) and acupuncture. TCM is a type of alternative medicine practiced in many countries to prevent and cu*e mental disorders, including TS. TCM medication may be prescribed as a customized formula, frequently in the form of liquid decoctions. Alternatively, it may be prescribed as pre-made dry decoctions, granules, or tablets, based on a standard formula including certain medical components for particular diagnosis or medical goals [48].

Acupuncture, as a part of Chinese medicine, is known for its potential efficacy. Traditional Chinese medical theory defines acupuncture as the insertion of tiny needles into acupoints. According to reports, acupuncture can help regulate brain function in people with tic disorders. A study by You et al. (2021) implies that acupuncture appears to be more effective for treating verbal motor tics than motor tics and general impairments [49]. With its promising efficacy, acupuncture appears to be just as well-known as TCM, and several publications suggested that combining the two would maximize the treatment's success [50].

CONCLUSIONS

Treatment of tics and TS is based on behavioural, pharmacological, surgical and acupuncture methods, with a combination of the various methods being necessary to achieve a therapeutic effect. In the treatment of TS, a multidisciplinary approach is necessary due to the co-occurring ailments that significantly reduce patients' quality of life. The role of the education of patients to better understand the disease and respond adequately is also emphasized. Many groups of drugs have found use in the management of tics in TS, although patients encounter a number of side-effects when using them. Supplementation with L -theanine and vitamin B6 has also been shown to help reduce tics and anxiety symptoms in children. A promising treatment for motor and phonic tics is botulinum toxin injections, which have a purely local effect and fewer side- effects compared to other pharmacological methods. More extensive research is needed to improve the effectiveness of existing treatments and minimize complications and side-effects.

TS is a disease that significantly reduces patients' quality of life, affecting many areas of life and making it difficult to function in society. This is the reason why it is so important to constantly seek new and improve existing treatments.

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