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LEADING TOPIC

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Cannabis-based medicine in treatment of patients with Gilles de la Tourette syndrome

Natalia Szejko[1,2,3], Kamila Saramak[2], Adam Lombroso[4], Kirsten R Müller-Vahl[5]

[1]Department of Neurology, Medical University of Warsaw, Warsaw, Poland
[2]Department of Bioethics, Medical University of Warsaw, Warsaw, Poland
[3]Department of Neurology, Yale University, New Haven, Connecticut, United States
[4]Child Study Centre, Yale School of Medicine, New Haven, Connecticut, United States
[5]Clinic of Psychiatry, Social Psychiatry and Psychotherapy, Hanover Medical School, Hanover, Germany

ABSTRACT

Introduction. Gilles de la Tourette syndrome (GTS) is a childhood onset disorder characterised by the presence of motor and vocal tics. The guidelines of both the American Academy of Neurology (AAN) as well as the European Society for the Study of Tourette Syndrome (ESSTS) recommend behavioural therapy and pharmacotherapy, mainly with antipsychotics, as first line treatments for tics. In spite of these well-established therapeutic approaches, a significant number of patients are dissatisfied because of insufficient tic reduction or intolerable side effects. Previous studies have suggested that cannabis-based medicine (CBM) might be an alternative treatment in these patients.

Material and methods. Two reviewers (KS, NS) searched the electronic database of PubMed on 1 July, 2021 for relevant studies using the search terms: ('Tourette syndrome' [MeSH Terms] OR 'Gilles de la Tourette syndrome' [MeSH Terms] OR 'tic disorders' [MeSH Terms] OR 'tics' [MeSH Terms] OR 'tic disorders' [Title/Abstract]) AND ('cannabis-based medicine' [Title/Abstract] OR 'cannabis' [Title/Abstract] OR 'dronabinol' [Title/Abstract] OR 'nabiximols' [Title/Abstract] OR 'tetrahydrocannabinol' [Title/Abstract] OR 'THC' [Title/Abstract] OR 'cannabidiol' [Title/Abstract], limit: 'humans'. These studies were further reviewed for additional relevant citations. The titles and abstracts of the studies obtained through this search were examined by two reviewers (KS, NS) in order to determine article inclusion. Discrepancies were addressed by the reviewers through discussion and eventually conversation with the senior reviewer (KMV).

Results. Although the amount of evidence supporting the use of CBM in GTS is growing, the majority of studies are still limited to case reports, case series, and open uncontrolled studies. To date, only two small randomised controlled trials (RCTs) using tetrahydrocannabinol (THC, dronabinol) have been published demonstrating the safety and efficacy of this intervention in the treatment of tics in patients with GTS. On the other hand, another RCT with Lu AG06466 (formerly known as ABX-1431), a modulator of endocannabinoid neurotransmission, has failed to prove effective in the therapy of GTS. Accordingly, under the guidelines of both the ESSTS and the AAN, treatment with CBM is categorised as an experimental intervention that should be applied to patients who are otherwise treatment-resistant.

Conclusions. Increasing evidence suggests that CBM is efficacious in the treatment of tics and psychiatric comorbidities in patients with GTS. The results of ongoing larger RCTs, such as CANNA-TICS (ClinicalTrials.gov Identifier: NCT03087201), will further clarify the role of CBM in the treatment of patients with GTS.

Key words: Gilles de la Tourette syndrome, tics, cannabis-based medicine, THC, dronabinol, tetrahydrocannabinol, obsessive-compulsive disorder, attention deficit/hyperactivity disorder

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Address for correspondence: Natalia Szejko, Department of Neurology, Medical University of Warsaw, Warsaw, Poland; e-mail: natalia.szejko@wum.edu.pl

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Introduction

Gilles de la Tourette syndrome (GTS) is a childhood onset neuropsychiatric disorder characterised by the presence of vocal and motor tics. In the majority of patients, psychiatric comorbidities co-exist. The most common ones are attention deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), depression, anxiety, and autism spectrum disorder [1]. The prevalence of GTS is estimated to be 0.3-1%, depending on the study population [2, 3]. The pathophysiology of GTS is still unknown. It is postulated that tics occur as a result of an imbalance in cortico-striato-thalamo-cortical loops [4]. It is believed that GTS is caused by imbalances in diverse neurotransmission systems including the dopaminergic [5], the GABA-ergic [6], the glutaminergic [7], the serotoninergic [8], the histaminergic [9], and the endocannabinoid systems [10].

As yet, there is no cure for GTS, and treatment is only symptomatic. Although the majority of patients do not require treatment or respond well to behavioural therapy or pharmacotherapy as recommended by the European Society for the Study of Tourette Syndrome (ESSTS) [11–13] and the American Academy of Neurology (AAN) [14], nonetheless in some patients the reduction of tics and psychiatric comorbidities is not satisfactory, or treatments are not well tolerated.

In these treatment-resistant patients, experimental therapy is suggested. In this context, deep brain stimulation (DBS) can be taken into consideration. Alternatively, novel — and less invasive — pharmacological approaches can be considered, among them, cannabis-based medicine (CBM) [15]. The initial evidence in this regard came from patients who reported improvements in a wide spectrum of symptoms after self-medication with cannabis [16]. Following these findings, Müller-Vahl et al. postulated for the first time a 'cannabinoid hypothesis' of GTS [17]. Subsequently, the effectiveness and tolerability of CBM in GTS was confirmed in independent case series [18–20] and small randomised controlled trials (RCTs) [16, 21]. Importantly, treatment with different types of CBM was effective not only in the treatment of tics, but also in the improvement of different psychiatric comorbidities [10].

The aim of this review was to present current data and knowledge on the treatment of patients with GTS using CBM as well as its underlying mechanisms, and to provide state-of-the-art information on the use of CBM in the treatment of patients with GTS. Importantly, we present results regarding therapy of tics as well as psychiatric comorbidities, and allude to studies examining the involvement of the endocannabinoid system (ECS) in the pathophysiology of GTS.

Material and methods

Two reviewers (KS, NS) searched the electronic database of PubMed on 1 July, 2021 for relevant studies using the search terms: ('Tourette syndrome' [MeSH Terms] OR 'Gilles de la Tourette syndrome' [MeSH Terms] OR 'tic disorders' [MeSH Terms] OR 'tics' [MeSH Terms] OR 'tic disorders' [Title/Abstract]) AND ('cannabis-based medicine' [Title/Abstract] OR 'cannabis' [Title/Abstract] OR 'dronabinol' [Title/Abstract] OR 'nabiximols' [Title/Abstract] OR 'tetrahydrocannabinol' [Title/Abstract] OR 'THC' [Title/Abstract] OR 'cannabidiol' [Title/Abstract], limit: 'humans'.

These studies were further reviewed for additional relevant citations. The titles and abstracts of the studies obtained through the search were examined by the same two reviewers (KS, NS) in order to determine article inclusion. Discrepancies were addressed by the reviewers through discussion and eventually conversation with the senior reviewer (KMV). Reviews and meta-analyses in the area were further searched for relevant citations. In addition, the reference lists of the articles identified were reviewed for additional studies. In addition to the studies identified through systematic review, in order to make the publication list as comprehensive as possible, studies still in press and not yet published were added by the authors (i.e. through precedent knowledge about relevant publications).

We have organised the publications presented in this review according to the level of evidence (ranging from 1a to 4, with 1a being the highest level of evidence). As a consequence, the following categories emerged: 1a (systematic review of randomised controlled trials); 1b (individual randomised controlled trials with narrow confidence intervals); 2a (systematic review of homogeneous cohort studies); 2b (individual cohort study and low-quality randomised control studies); 3a (systematic review of homogeneous case-control studies); 3b (individual case-control studies); 4 (case series and case reports); and 5 (expert opinions based on non-systematic reviews). In the subsequent sections of the review, we added designators describing the level of evidence for each category of study. In addition, information regarding the level of evidence is set out in Table 1, which contains all studies included in this paper.

Results

Evidence for involvement of endocannabinoid system (ECS) in Gilles de la Tourette syndrome

The ECS is one of the most important systems involved in the regulation of neurotransmission. The two main receptors regulating the function of the ECS are the cannabinoid receptors type 1 (CB1) and type 2 (CB2) [22, 23]. Although CB1 receptors are mainly located in the central nervous system (CNS), and CB2 receptors are mainly expressed in the peripheral nervous system and the immunological system, the distribution of these receptors is much wider than initially thought (Figs. 1 and 2). For example, only recently it has been shown that the CB2 receptor is also expressed in the brain (Fig. 2) [24]. This robust representation reflects the fact that the ECS influences the functioning of almost every system in the human body.

Table 1. Studies examining safety and efficacy of cannabis-based medicine in Gilles de la Tourette syndrome (according to level of evidence and chronological order)

Reference	Number of patients and gender	Age [years]	Substance	Study design	Level of evidence	Outcome
Müller-Vahl et al. 2002 (II) [16]	11 male 1 female	18–66	THC	Randomised double-blind placebo-controlled crossover trial	1b	Reduction of tics; improvement of OCB
Müller-Vahl et al. 2003 [61]	19 male 5 female	18–68	THC	Randomised, double-blind, placebo-controlled trial	1b	Reduction of tics
Jakubovski et al. 2020 [67]	96 patients	≥ 18	Nabiximols	Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase IIb trial (CANNA-TICS)	1b	To be announced
Müller-Vahl et al. 2021 [64]	41 males, 8 females	≥ 18	Lu AG64066 (formerly known as ABX-1431)	Multicentre, randomised, placebo-controlled, double-blind trial	1b	No effect on tics
Müller-Vahl et al. 2021 [63]	16 males, 4 females	≥ 18	Lu AG64066 (formerly known as ABX-1431)	Single-dose phase 1b study	1b	Reduction of tics and premonitory urges
Thaler et al. 2018 [20]	33 males 9 females	20–73	Various CBM	Retrospective data analysis and telephone survey	3b	Reduction of tics
Milosev et al. 2019 [18]	84 males 14 females	18–79	Various CBM (street cannabis, nabiximols, THC, medicinal cannabis)	Retrospective data analysis and prospective online survey	3b	Reduction of tics; reduction of psychiatric comorbidities; improvement of quality of life
Hemming et al. 1993 [37]	1 male	36	Cannabis	Case report	4	Complete remission
Müller-Vahl et al. 1998 [38]	55 male 9 female	15–64	Cannabis	Case series	4	Reduction or complete remission of tics; reduction of psychiatric comorbidities
Müller-Vahl et al. 1999 [44]	1 male	25	THC	Case report	4	Reduction of tics; reduction of psychiatric comorbidities
Müller-Vahl et al. 2002 (I) [45]	1 female	24	THC	Case report	4	Reduction of tics
Hasan et al. 2010 [55]	1 male	15	THC	Case report	4	Reduction of tics; improvement of quality of life
Brunnauer et al. 2011 [46]	1 male	42	THC	Case report	4	Reduction of tics; improvement of driving ability
Trainor et al. 2016 [48]	1 male	26	Nabiximols	Case report	4	Reduction of motor and vocal tics
Abi-Jaoude et al. 2017 [19]	16 males 3 females	18–64	Medicinal cannabis	Case series	4	Reduction of tics
Jakubovski et al. 2017 [52]	2 male	16, 19	THC, medicinal cannabis	Case report	4	Reduction of tics, including complex vocal tics; reduction of psychiatric comorbidities
Kanaan et al. 2017 [50]	1 male	22	Nabiximols	Case report	4	Reduction of tics, improvement of quality of life
Szejko et al. 2018 [56]	1 male	8	THC	Case report	4	Reduction of tics; reduction of psychiatric comorbidities; improvement of quality of life
Szejko et al. 2019 [57]	1 male	12	THC, medicinal cannabis	Case report	4	Reduction of tics; improvement in sleeping problems

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Table 1 cont. Studies examining safety and efficacy of cannabis-based medicine in Gilles de la Tourette syndrome (according to level of evidence and chronological order)

Reference	Number of patients and gender	Age [years]	Substance	Study design	Level of evidence	Outcome
Pichler et al. 2019 [53]	1 female	47	Tincture with THC and CBD	Case report	4	Reduction of tics; improvement of quality of life
Milosev et al. 2019 [18]	84 males 14 females	18–79	Various CBM (street cannabis, nabiximols, THC, medicinal cannabis)	Retrospective data analysis and prospective online survey	3b	Reduction of tics; reduction of psychiatric comorbidities; improvement of quality of life
Müller-Vahl et al. 2021 [54]	1 male	≥ 18	Various CBM including medicinal cannabis	Case report	4	Tic reduction by > 95%, improvement of quality of life, improvement of social and professional life

THC — tetrahydrocannabinol; OCB — obsessive-compulsive behaviour; CBM — cannabis-based medicine; CBD — cannabidiol; Levels of evidence:1a — systematic review of randomised controlled trials; 1b — individual randomised controlled trials with narrow confidence intervals; 2a — systematic review of homogeneous cohort studies; 2b — individual cohort study and low-quality randomised control studies; 3a — systematic review of homogeneous case-control studies; 3b — individual case-control studies; 4 — case series and case reports; 5 — expert opinions based on non-systematic reviews

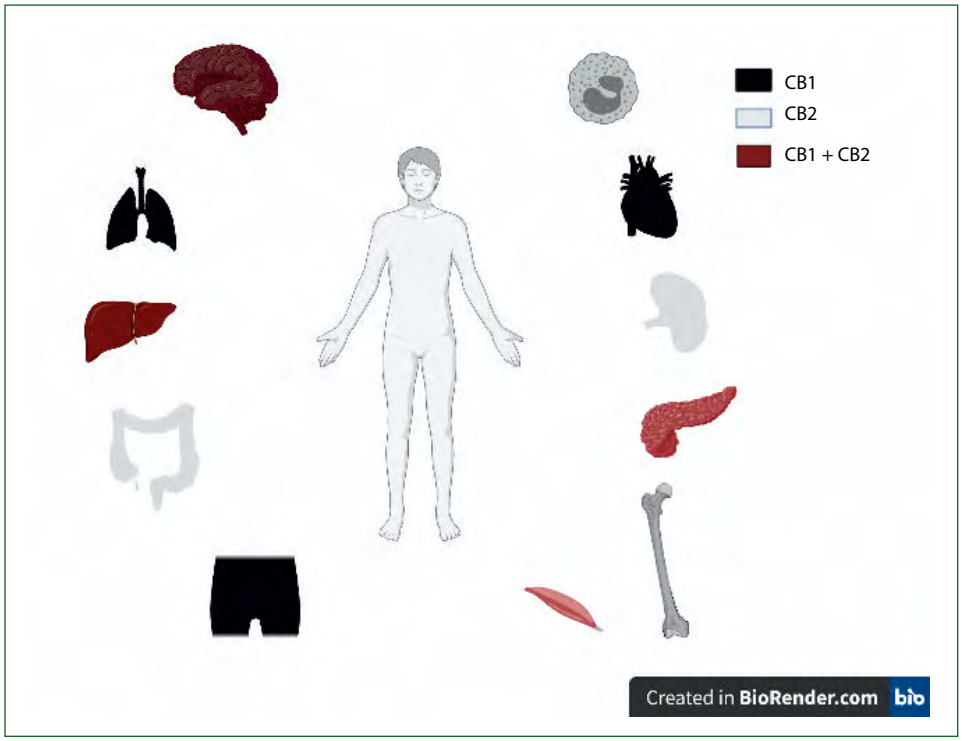

Figure 1. Distribution of cannabinoid receptor type 1 (CB1) and 2 (CB2) in human body

Just recently, a number of further receptors have been identified that also belong to the ECS: the G protein-coupled receptor 118 (GPR18) [25], GPR55 [26], GPR119 [25], and Transient Receptor Potential Vanilloid 1 (TRPV1) [27, 28]. Previous studies have demonstrated that the density of central CB1 receptors is especially high in the basal ganglia [29], which further suggests that the ECS is involved in motor control. The ECS has been identified as the most important neuromodulatory system in the brain [30, 31]. Therefore, it has been speculated that disturbances in the ECS lead to dysfunctional dopaminergic neurotransmission which, in turn, may cause tics [32]. Just recently, Müller-Vahl et al. [32] published the results of a study in which they measured cerebrospinal fluid (CSF) levels of different endocannabinoids in a sample of adult patients with GTS (n = 20) compared to controls (n = 19). CSF levels of different endocannabinoids ("N" —arachidonoylethanolamine (AEA, anandamide), 2-arachidonoylglycerol (2-AG), the endocannabinoid-like molecule palmitoyl ethanolamide (PEA), and the lipid arachidonic acid (AA)), were significantly increased in GTS compared to controls. Levels of

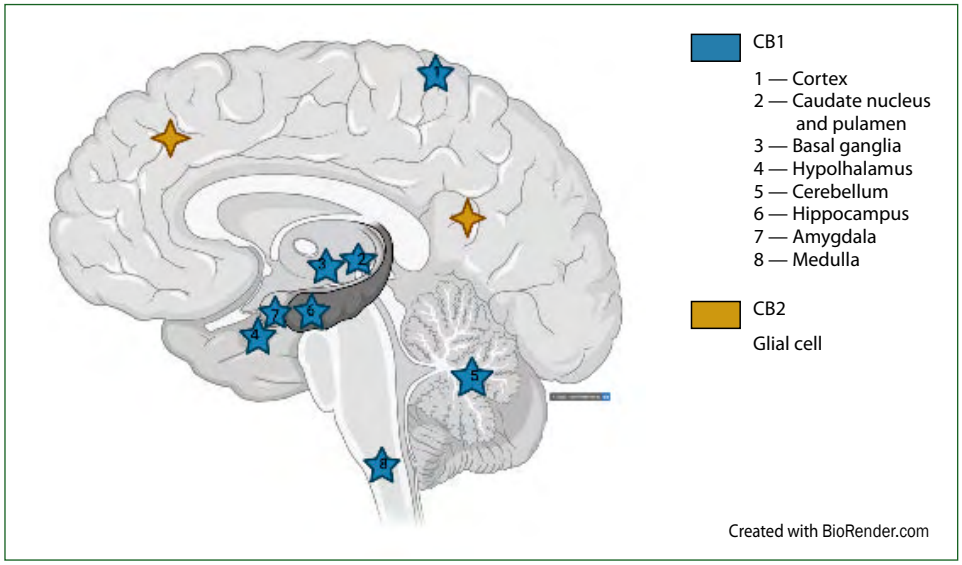

Figure 2. Distribution of cannabinoid receptor type 1 (CB1) and 2 (CB2) in brain

2-AG were correlated with the severity of comorbid ADHD. The authors speculated that elevated endocannabinoid levels may represent either an epiphenomenon or secondary changes in order to compensate for alterations in other neurotransmitter systems such as the dopaminergic system or, alternatively, may represent the primary cause of GTS.

Further evidence regarding the involvement of the ECS in the pathophysiology of GTS has been provided by neuroimaging studies. Berding et al. [33] performed single photon emission computed tomography (SPECT) and [123I]AM281 in six patients with GTS. As a result, it could be demonstrated that CB1 receptor binding is reduced after treatment with tetrahydrocannabinol (THC, dronabinol). Unfortunately, no control group was included in this study and therefore it is not possible to determine whether CB1 receptor binding is changed in patients with GTS. As for genetic analyses, they have been inconclusive so far. While one study failed to show any genetic variations in the cannabinoid receptor gene (CNR1) in GTS [34], another [35] found a significant association of GTS clinical phenotype with the rs2023239 variant of CNR1.

Application of cannabis-based medicine in treatment of Gilles de la Tourette syndrome

Here, we present current evidence regarding the use of CBM in GTS. For each section, we assign a level of evidence according to the standards of evidence-based medicine.

Retrospective reports on self-medication (level 4)

The first cases of (illegally conducted) self-medication with cannabis were reported by Sandyk and Awerbuch [36] in 1988. Three male patients aged between 15 and 39 years, who had experienced incomplete responses to conventional medications, noted the alleviation of tics as well as various psychiatric comorbidities when smoking 0.5-2 cannabis cigarettes per day. In 1993, Hemming et al. [37] described the case of a 36-year-old man who observed complete remission of symptoms while smoking one cannabis cigarette per day.

In 1998, Müller-Vahl et al. [38] published the results of a retrospective questionnaire-based study on self-medication with cannabis. Sixty-four patients with GTS (55 males and nine females, age range 15–64) were included, of whom 17 reported having used cannabis as self-treatment for their symptoms. The amount of drug administered, as well as the duration and frequency of use, varied considerably among participants, from two cigarettes over a lifetime to regularly smoking 3-4 cigarettes per day. Fourteen patients experienced amelioration or complete remission of vocal and motor tics. Moreover, an improvement of premonitory urges, obsessive compulsive symptoms (OCS), and/or ADHD was reported by patients. None of the participants noted clinically relevant adverse events (AEs) or exacerbation of symptoms.

In 2017, Abi-Jaoude et al. [39] retrospectively evaluated the effectiveness and tolerability of cannabis administered to 19 adults (16 males and three females, age range 18–64) with GTS. Overall, all patients experienced relief of symptoms. In 18 patients, an average improvement of approximately 60% of tic severity, as measured by the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) [40], was observed. All participants reported substantial amelioration of comorbidities. Most commonly noted AEs were a feeling of a "high", decreased concentration, increased anxiety, and increased appetite. None of the patients reported serious adverse events (SAEs).

Thaler et al. [41] interviewed 42 patients with GTS (33 males and nine females, age range 20-73), who used cannabis in different forms for at least one year. Improvement of symptoms was assessed using a Likert scale [42]. The average

tic improvement was 3.85/5 points showing a clinically relevant influence on tics. Only four patients noted no effect of cannabis, while six stopped using cannabis for various reasons, including AEs with one subject experiencing a self-reported acute psychotic episode. Other relevant AEs included hallucinations (four patients), irritability or confusion (six), and cognitive decline (seven).

Finally, Milosev et al. [43] performed a retrospective study including 98 patients with GTS (84 males and 14 females, age range 18-79) using different kinds of CBM in various doses. The most frequently used CBM was street cannabis, followed by nabiximols, THC, and medicinal cannabis. Overall, the use of CBM resulted in a subjective reduction of tics (of about 60% in 85% of patients). The majority of patients (55%) also experienced an improvement of comorbidities (mainly OCS/OCD, ADHD, and sleep problems) as well as quality of life. Side effects were reported by 50% of patients, but all of these were rated as mild or moderate. Overall, most patients (66%) preferred cannabis flowers over other CBM such as THC and nabiximols, since it was felt to be more effective and better tolerated. Interestingly, patients reported THC-rich strains as being the most effective.

Prospective case studies using different cannabis-based medicines (level 4)

To date, the number of prospective case studies focusing on the effectiveness and tolerability of various types of CMB in GTS is very limited. The vast majority of case reports include adults. Only a very few case studies have been published reporting treatment effects of CBM in minors with GTS.

Case studies using THC (level 4)

In 1999, Müller-Vahl et al. [44] described the case of a 25-year-old male who suffered from GTS and psychiatric comorbidities including ADHD, OCS, and anxiety. When self-medicating with cannabis, he reported an alleviation of all these symptoms. Three days before entering the study, he stopped smoking cannabis. Thereafter, he was treated with a single dose of 10 mg THC orally. Treatment effects were assessed prospectively. Two hours after THC administration, a tic reduction of approximately 80% according to the Tourette's Syndrome Global Scale was observed. The patient noted an improvement of attention, impulse control, OCS, and premonitory urges, without relevant AEs.

In another single case study, Müller-Vahl et al. [45] reported on a 24-year-old female whose tics were best controlled after combined treatment with THC (10 mg per day) and the dopamine receptor antagonist amisulpride (1,200 mg per day) compared to each treatment alone.

In 2011, Brunnauer et al. [46] published the case of a 42-year-old lorry driver who underwent experimental therapy with THC (15 mg per day), resulting in tic reduction of 75% measured with the YGTSS-TTS. THC treatment also had a positive influence on the patient's driving abilities, with improved concentration and visual perception.

Case studies using nabiximols (level 4)

So far, only two studies have been reported regarding experimental therapy of GTS with nabiximols. Nabiximols (tradename Sativex®) is marketed in the form of an oromucosal spray containing 2.7 mg THC and 2.5 mg cannabidiol (CBD) per puff [47]. It is officially licensed in most European countries for the treatment of spasticity in multiple sclerosis. In 2016, Trainor et al. [48] described the case of a 26-year-old male with severe GTS with significantly impaired quality of life. After a 4-week treatment with nabiximols at a dose of 2 x 2 puffs/day (= 10.8 mg of THC and 10 mg CBD), a marked reduction of motor (85%) and vocal (90%) tics occurred as measured by the Rush Video Rating Scale (RVRS) [49]. The YGTSS-TTS showed a tic improvement of 35%. No AEs were reported.

An even higher dose of nabiximols, of 3 x 3 puffs/day (= 24.3 mg THC and 22.5 mg CBD), was administered to a 22-year-old male with GTS in a single case study published by Kanaan et al. [50]. Importantly, no AEs were reported. Treatment resulted in a tic reduction of 22% as measured by the YGTSS-TTS. In addition, the patient's quality of life showed a marked improvement of 70% according to the GTS-Quality of Life Scale (GTS-QoL) [51].

Case studies using medicinal cannabis (level 4)

Jakubovski et al. [52] described the case of a 19-year-old male who suffered from a complex form of GTS with severe speech impairment due to palilalia and vocal blocking tics resembling stuttering. Despite speech therapy and the use of anti-tic medication, speech blocking tics deteriorated over time, which finally had a detrimental effect on the patient's quality of life. Treatment with vaporised medicinal cannabis (Bedrocan®, containing 22% THC and 1% CBD) was started at a dose of 0.1 g daily and was gradually increased to 0.6 g per day. Follow-up over eight months revealed marked improvement of blocking tics, reduction of premonitory urge, and significant improvement in quality of life, since the patient was able to hold normal conversations with near-normal speech fluency. Almost complete remission of symptoms lasted for c.90 minutes after the use of cannabis, while a 70% tic reduction was observed during the whole day in the absence of significant AEs.

Pichler et al. [53] presented the case of a 47-year-old female with GTS who had started self-medicating by smoking home-grown cannabis and THC, after treatments with risperidone (4 mg per day) and aripiprazole (35 mg per day) had proved ineffective. After consulting a specialist, risperidone and aripiprazole were replaced by treatment with a standardised oral tincture containing 0.3 mg of THC and 0.6 mg of CBD per drop. The patient received 3 x 34 drops daily (= 10 mg THC and 20 mg CBD). After two months of therapy, a significant tic reduction was observed (YGTSS global score decrease from 73 to 44) as well as a subjective improvement in quality of life. No AEs were observed.

Just recently, Müller-Vahl published an interview with an adult patient treated with a different CBM, but who eventually decided on treatment with medicinal cannabis, because it was felt to be more effective [54]. The patient reported a tic reduction of more than 95%, improvement in quality of life, as well as improved social and professional life after his use of cannabis.

Treatment of minors with GTS using cannabis-based medicines (level 4)

The first study reporting the use of CBM in the treatment of tics in minors was published by Sandyk and Awerbuch [36]. Their first case was of a 15-year-old boy suffering from severe motor tics co-existing with OCD and SIB. Previous treatments with haloperidol and clonidine had been ineffective, but he noticed by accident that smoking cannabis caused general relaxation and improvement of his tics. According to the patient's family, motor tics improved by 50%. In addition, they noticed a modest reduction of SIB. After discontinuation of cannabis smoking, a significant rebound of tics was observed. The second case described by Sandyk and Awerbuch was of a 17-year-old boy who had experienced severe vocal and motor tics from the age of seven. Prior therapies with clonidine and haloperidol were badly tolerated. On several occasions, the patient noticed a reduction of his tics of 60-70% for several hours, as well as an improvement of his attention span, when smoking cannabis.

In 2010, Hasan et al. [55] reported the first case of a minor who received therapy with a CBM. In this 15-year-old boy with GTS and concomitant ADHD, treatments with risperidone (1 mg), aripiprazole (10 mg), and methylphenidate (30 mg/day) had not resulted in sufficient tic reduction or were not well tolerated. Therefore, treatment with THC was initiated at a dose of 5 mg/day, which was increased to 15 mg/day over nine weeks. This resulted in a marked tic reduction (of 44% as measured by YGTSS). In addition, an improvement in quality of life was observed, in the absence of SAEs. As a consequence, the patient could attend school for the first time in several years.

Jakubovski et al. [52] published the case of a 16-year-old boy with GTS and a wide range of psychiatric comorbidities including speech problems with palilalia, vocal blocking, and a change of melody and rhythm of speech. Due to the ineffectiveness of other medications, treatment with vaporised THC was initiated at a dose of 3 x 8 drops daily (= 16.8 mg THC). At an eight months follow-up appointment, a marked reduction of motor and vocal tics could be observed, with only minimal vocal blocking tics. No AEs occurred. In addition, comorbidities improved, with amelioration of impulsive behaviours, rage attacks, anxiety and OCS. As a result, the patient's academic performance and social life improved.

Recently, Szejko et al. [56] presented the case of a 7-year-old boy with severe tics and comorbid ADHD, which had a detrimental effect on his education and mental health. Treatment attempts such as behavioural interventions and pharmacotherapy (including risperidone, aripiprazole, tiapride, methylphenidate, and guanfacine alone or in combination) were ineffective. Therefore, the authors decided to augment treatment with risperidone (2 mg/day) and guanfacine (2 mg/day) with oral THC in the form of oil-based drops (initial dose of 0.7 mg/ day, increased to 18.2 mg/day over a period of 16 weeks). Occasionally, even higher doses of THC, of up to 29.4 mg/day, were used. At follow-up examination after four months, a clinically relevant reduction of tics and psychiatric comorbidities was observed, without relevant AEs, resulting in a tremendous improvement in the patient's quality of life and school performance.

The same authors [57] published the case of a 12-year-old boy affected by severe motor tics resulting in insomnia. His parents, both of whom were medical doctors, initiated treatment with 0.02 g vaporised medicinal cannabis (Bedrocan®, corresponding to a dose of 4.4 mg THC). According to their reports, this therapy caused a significant reduction in symptoms. Due to a further deterioration, the parents decided to modify the therapy by adding a second cannabis variety, increasing the dose of vaporised medicinal cannabis (up to 0.1 g cannabis per day, varieties Bedrocan® and Amnesia Haze®, corresponding to 22 mg THC) and finally adding oral THC (up to 12.5 mg/day, divided into two doses). After several weeks of treatment, at a visit to our clinic, both the parents and the patient reported the beneficial effects of combined treatment with cannabis and THC, with reduced tics, improved concentration and sleep, as well as the remission of headaches. A variety of clinical assessments before, and 30 minutes after, vaporisation of 0.15 g cannabis (Amnesia Haze®, equivalent to 33 mg THC) was performed, demonstrating a marked reduction of tics (by 35%), and of premonitory urges (by 35%) and a very marked improvement in quality of life (by 95%) as assessed by YGTSS-TTS, RVRS, Premonitory Urge for Tics Scale (PUTS) [58], and GTS-QoL. No AEs were reported or observed.

Controlled trials using THC (level 1b)

The first RCT using THC in GTS was conducted in 2002 by Müller-Vahl et al. [59], and included 12 adult patients with GTS (11 males and one female, age range 18–66, mean age 34 ± 13). In this randomised double-blind placebo-controlled single-dose crossover trial, doses of 5.0, 7.5 or 10 mg of THC were administered orally according to the patient's body weight, sex, age, and prior use of cannabis. Tic severity was assessed before, and 3-4 hours after, a single dose of THC using both self-assessment tools (Tourette Syndrome Symptom List, TSSL) and examiner-based ratings such as the Shapiro Tourette Syndrome Severity Scale (STSS) [60], the Tourette Syndrome Global Scale (TSGS), and the YGTSS. Psychiatric comorbidities (OCS, ADHD, and anxiety) were self-evaluated using the TSSL. Blood samples were taken to measure plasma concentrations of THC and its metabolites. Treatment with THC resulted in a significant reduction of tics and OCS (according to TSSL) compared

to a placebo. Moreover, a significant reduction in 'complex motor tics' and a trend towards a significant improvement was observed for 'motor tics', 'simple motor tics' and 'vocal tics' (according to TSGS). This improvement significantly correlated with maximum plasma concentration of THC metabolites (11-hydroxy-Delta-(9)-tetrahydrocannabinol (11-OH-THC) and 11-nor-Delta(9)-tetrahydrocannabinol-9-carboxylic acid (THC-COOH)). The following AEs were reported: headache, nausea, dizziness, tiredness, excessive cheerfulness, dry mouth, anxiety, sensitivity to noise and light, ataxia and poor concentration. All AEs were rated as mild or moderate.

One year later, Müller-Vahl et al. [61] published the results of a randomised, double-blind, placebo-controlled follow-up trial, in which THC at a dose of up to 10 mg per day was administered orally over a period of six weeks. This study included 24 patients (19 males and five females, age range 18-68). Tic severity was evaluated during six visits which took place at different times during the treatment period, as well as during withdrawal. The evaluation was conducted using both self-rating scales (TSSL) and examiner rating scales (Tourette's Syndrome Clinical Global Impression Scale (TS-CGI) [62], YGTSS, STSS, and RVRS). When comparing TS-CGI scores, there was a statistically significant improvement in the THC group compared to the placebo group at visits 3 and 4. The rest of the examiner rating tools (YGTSS, STSS and RVRS) also showed a significant difference, or a trend towards significant difference, at visits 2, 3 and 4. When comparing THC to placebo groups, TSSL scores on the tenth treatment day revealed a significant symptom reduction in favour of the THC group. Seven patients dropped out of the study. However, only one participant discontinued the medication due to AEs, which included restlessness and anxiety. Side effects were reported in the THC group by five patients (tiredness, dry mouth, dizziness, and fuzziness) and in the placebo group by three patients (tiredness, dizziness, anxiety, and depression). No SAEs were observed.

Controlled trials using nabiximols (level 1b)

Only recently, CANNA-TICS, a large multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase IIb study was initiated to investigate the efficacy and safety of a 13-week-treatment with nabiximols on tics and a large variety of psychiatric comorbidities in patients with GTS [61]. Since the recruitment of 97 patients is already complete, results are expected by the end of this year. In the CANNA-TICS trial, in addition, plasma levels of endocannabinoids and the influence of nabiximols on patient driving ability will be measured.

Controlled trials using endocannabinoid modulator and MAGL inhibitor Lu AG06466 (formerly known as ABX-1431, level 1b)

In a small single-dose phase 1b study (n = 20, 16 males, mean age 34 ± 11), the safety and efficacy of Lu AG06466 (formerly known as ABX-1431) was investigated. Lu AG06466 is an endocannabinoid modulator and inhibitor of the monoacylglycerol lipase (MAGL), which degrades the endocannabinoid 2-AG. The use of Lu AG06466 results in increased levels of 2-AG, which is thought to cause a stimulation of the ECS. In this pilot study, a single dose of Lu AG06466 was found to be effective in the reduction of tics and premonitory urges [63]. Only mild to moderate AE, and no SAEs, were observed.

Based on this preliminary but encouraging data, the same group initiated a larger and longer-term multicentre parallel-group randomised double-blind placebo-controlled trial to confirm the efficacy of Lu AG06466 in tic reduction. In this follow-up study, 49 adults (43 male, mean age 32.9 ± 10.9) with GTS were included [64]. However, after a 12-week treatment period, no beneficial effects on tics, premonitory urges, OCD, or quality of life could be detected. In a small group of patients with comorbid ADHD, a non-significant reduction of ADHD symptoms was observed. Overall, there were no safety concerns.

A summary of all available studies examining the efficacy and safety of CBM in GTS is set out in Table 1.

Recommendations regarding treatment of patients with GTS with CBM

The ESSTS [13], the Canadian [65], and the AAN guidelines [14] recommend CBM for the treatment of tics in otherwise treatment-resistant adult patients with GTS. Following this line of evidence, most experts recommend the implementation of CBM prior to surgical intervention with DBS. However, it is still not clear which type of CBM, which dose, and which route of administration (i.e. orally versus inhalation) are preferable, because studies comparing different CBM in GTS are lacking. However, based on the available data, it is suggested that either pure THC (dronabinol) or combinations of THC with CBD in different ratios should be used. So far, there is not a single case report available suggesting that pure CBD might be effective in the treatment of tics or psychiatric comorbidities in GTS. Interestingly, there is preliminary evidence from both retrospectively and prospectively collected data suggesting that the inhalation of cannabis flowers might be superior compared to oral THC and nabiximols [18].

With respect to age, there is only very limited data available suggesting that CBM might be effective and safe in minors. In any case, the final decision regarding treatment must be individual. However, we recommend considering CBM in otherwise treatment-resistant, severely affected, children and adolescents with substantial impairment in quality of life, before considering surgical treatment with DBS.

Regarding dosage, we recommend starting with a low dose (1.0 to 2.5 mg THC/day or 25-50 mg cannabis flowers) and slowly up-titrating with 2.5 mg THC (or 25-50 mg cannabis flowers) every 3-5 days based on tolerability, comorbidities, co-medications, and patient age.

Treatment strategies for CBM should always follow the maxim 'start low, go slow' to induce tolerance and thus reduce

side effects. So far, no maximal dose has been determined. Treatment with CBM is individual, with doses usually ranging from 0.1 to 1 g cannabis/day and 2.5–30 mg THC/day, respectively. However, in single cases, doses of up to 5 g cannabis/day and 40-50 mg THC/day may be needed for symptom control and may be well tolerated.

Conclusions

CBM should still be regarded as an experimental treatment in patients with GTS, as suggested by the 2019 guidelines of the AAN [14] and the 2021 guidelines of the ESSTS [13]. A recently published meta-analysis examining the potential therapeutic benefits of CBM in psychiatric disorders in general, including GTS, demonstrated limited evidence for their effectiveness due to a lack of robust data from RCTs [66]. Moreover, the results of RCTs are conflicting, as smaller studies with THC showed significant tic reduction, while another study using the endocannabinoid modulator Lu AG06466 failed to demonstrate efficacy in tic reduction.

Therefore, it can be expected that the results from the CANNA-TICS trial [67] will provide some of this urgently needed additional data on efficacy and safety of CBM in this group of patients. With respect to the safety profile, there is general agreement that CBMs can be considered as safe and well-tolerated drugs when adhering to the strategy of 'start low, go slow' [68].

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She has served as a guest editor for 'Frontiers in Neurology' on the research topic 'The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects', is an associate editor for 'Cannabis and Cannabinoid Research' and an Editorial Board Member of 'Medical Cannabis and Cannabinoids' and 'MDPI-Reports' and a Scientific Board Member for 'Zeitschrift für Allgemeinmedizin'.

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