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Possible Role of the Endocannabinoid System in Tourette Syndrome

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Abstract

Tourette syndrome (TS) is a neuropsychiatric disorder with childhood onset. The core symptoms are motor and vocal tics. The majority of patients also suffer from psychiatric comorbidities. The pathophysiology of TS is not clear, but changes in different neurotransmitter systems—in particular the dopaminergic system—have been confirmed. Since there is increasing evidence that cannabis-based medicine (CBM) is effective in the treatment of TS, an involvement of the endocannabinoid system in the pathophysiology of TS has been suggested. The purpose of this chapter is to present existing evidence suggesting a pathophysiological role of the endocannabinoid system in TS and to summarize available data on beneficial treatment effects of CBM in patients with TS.

Keywords: Tourette syndrome, cannabis-based medicine, tics, THC, cannabinoids, cannabis

1. Introduction

1.1. Symptoms of Tourette syndrome

Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder that is present in approximately 1% of the population [1]. For unknown reasons, it occurs 3–4 times more often in men than in women. To fulfill the diagnostic criteria for TS, multiple motor and at least one vocal tic must be present for a minimal period of 1 year before 18 years of age.

Tics are sudden, repetitive involuntary movements or vocalizations. Both vocal and motor tics can be further differentiated into a simple or complex presentation. Simple motor tics

involve only one group of muscles in a brief jerk-like movement, with examples such as eye blinking, head jerking or shoulder shrugging. Complex motor tics, on the contrary, involve multiple groups of muscles or resemble purposeful movements. Examples of complex motor tics are as follows: touching people or objects, echopraxia (mirroring another person's actions) or copropraxia (involuntary performing of obscene gestures). Simple vocal tics are short vocalizations, for example throat clearing, sniffing or grunting. Complex vocal tics involve the involuntary production of words or entire sentences, for example echolalia (repeating another person's words), palilalia (repeating one's own words) and coprolalia (involuntary pronunciation of obscene words). Although coprolalia is often associated with TS, it is only present in approximately 10% of patients [2]. The majority of patients report a premonitory urge that precedes the tics. This is often described as an "uncomfortable" physical sensation located in a particular body part or as a more generalized feeling [3]. Most (adult) patients are able to control their tics for a short period of time.

In almost 90% of TS patients, tics are accompanied by other co-occurring psychiatric disorders such as attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), self-injurious behaviors (SIB), anxiety disorders and depression [4].

1.2. Course and causes of Tourette syndrome

Tics typically first emerge between 5 and 7 years of age and increase in severity until they reach a peak in early adolescence (most often at the age of 10–12 years). After this worst-ever period, tics—in most cases—decrease until a mild to minimal degree of severity is reached in early adulthood [5]. At the same time, TS is characterized by spontaneous fluctuations and waxing and waning over time. The occurrence of tics is influenced by various environmental factors. While the majority of patients experience fewer tics when relaxing or concentrating (e.g. when practicing sports, playing musical instruments or computer games), tics often increase with stress, tiredness and infections.

To date, no single cause of TS was identified; instead, several lines of evidence suggested that TS is caused by an interplay between genetic [6] and environmental factors [7]. For example, there is clear evidence that prenatal and perinatal complications including low birth weight and maternal smoking during pregnancy [8, 9] may represent such epigenetic factors. In contrast, the influence of infections [7] and immunological factors [10] is still unclear. As for the pathophysiology of TS, most studies suggest a major involvement of the dopaminergic system [11–17]; however, several other neurotransmitter systems might play a role including the serotonergic [12, 18], histaminergic [19], glutamatergic [20], GABAergic [21], cholinergic [22], and noradrenergic systems [23]. Furthermore, it is believed that disturbances of cortico-striato-thalamo-cortical (CSTC) pathways play a role in the generation of tics [24].

1.3. Treatment of Tourette syndrome

Both European [25–27] as well as Canadian [28] treatment guidelines for TS recommend application of behavioral psychotherapy techniques (either habit reversal training or exposure and response prevention training), pharmacotherapy and, in otherwise treatment resistant very severely affected patients, surgical intervention using deep brain stimulation. Like in the case

of many psychiatric disorders, treatment is only available on a symptomatic level. Available treatments for TS alleviate symptoms to more tolerable degree quite successfully, but cannot eradicate tics completely. However, treatment for tics is not necessary in all cases, but should be taken into consideration, when tics interfere with daily life functions or cause significant emotional distress. The drugs most often used in the treatment of tics are atypical antipsychotics including aripiprazole, risperidone, sulpiride, and (in Germany) tiapride. If these drugs are not effective or not well tolerated, only few alternative options remain, including alpha-2-agonists (in case of comorbid ADHD), topiramate, tetrabenazine and, rarely, botulinum toxin. While the antipsychotics are by far the most widely used drugs for the treatment of TS, they bring along considerable side effects load such as sedation, weight gain, metabolic changes, and acute dyskinesia [25].

In summary, a large number of patients with TS are unsatisfied with available treatments—either due to insufficient efficacy or because of clinically relevant side effects—and therefore, further treatment alternatives need to be developed.

2. Possible role of the endocannabinoid system in Tourette syndrome

The main function of the central endocannabinoid system (ECS) is inhibitory modulation of other neurotransmitter systems. Among other brain regions, cannabinoid type 1 receptors (CB1) are expressed with high density in the basal ganglia [29] indicating a paramount role of the ECS in the control of movements. In TS, there is substantial evidence for an involvement of the dopaminergic system. However, until today it is unclear, whether these alterations represent the primary cause of the disease or are related to secondary or compensatory changes. In addition to the dopaminergic hypothesis in TS, changes in several other transmitter systems have been suggested including the glutamatergic, GABAergic, serotonergic, noradrenergic and histaminergic systems. Since the ECS is a highly important modulatory system in the brain that influences and controls all important neurotransmitter systems, it can be speculated that TS might be caused by a dysfunction in the ECS system. This hypothesis is in line with studies reporting about an involvement of several different neurotransmitter systems in TS. In addition, alterations within the ECS would explain the complex clinical presentation of TS including both hyperkinetic movements with tics and a large variety of psychiatric manifestations.

Noteworthy, there is a strong interaction between the dopaminergic and the ECS [29, 30], particularly in basal ganglia regions including the striatum [31] and the globus pallidus [32]. Since there is substantial evidence for an involvement of the dopaminergic system in the pathobiology of TS, it, therefore, can also be speculated that CBM may inhibit dopaminergic activity in brain areas associated with motor control resulting in a reduction of hyperkinetic movements such as tics [33]. However, one might also speculate that the modulation of other neurotransmitter systems including glutamate and GABA might result in a reduction of tics.

Until today, only one neuroimaging study has been performed using single photon emission computed tomography (SPECT) and [123I]AM281 to investigate the ECS in patients with TS [34].

In this study, it could be demonstrated that CB1 receptor binding is reduced after treatment with THC. Since in this study, no control group has been included, no statement is possible, whether CB1 receptor binding is changed in patients with TS. So far, genetic analyses failed to demonstrate any genetic variations in the cannabinoid receptor gene (CNR1) in TS [35].

3. Cannabis-based medicine in patients with Tourette syndrome

3.1. Retrospective reports on self-medication

A substantial number of patients with TS report using cannabis illegally in order to improve their tics or comorbid psychiatric disorders. While doing so, most of these patients rely on their own judgment and self-medicate without a proper consultation with their treating physician. Such an observation was first described in two small case series published in 1988 and 1993 [36]. Sandyk et al. [37] described three male patients, who benefitted both in terms of tics and comorbid psychiatric symptoms after smoking 0.5–2 marijuana cigarettes per day. Hemming et al. [36] reported a case of a 36-year-old man, who smoked a marijuana cigarette every day and claimed to be symptom-free for 1 year. More recently, Müller-Vahl et al. [38] conducted a retrospective survey about self-medication with cannabis in 64 patients with TS seen at a specialized Tourette outpatient clinic in Germany. Seventeen patients indicated to use marijuana illegally as self-treatment for their symptoms, and 14 of them reported beneficial effects not only on tics, but also on different comorbidities. Interestingly, none of the patients reported clinically relevant adverse events (AEs) or a deterioration of tics after the use of marijuana. This effect was not influenced by concomitant use of antipsychotics or selective serotonin reuptake inhibitors (SSRIs).

Finally, Abi-Jaoude et al. [39] in Canada reported results from a retrospective analysis investigating efficacy and safety of smoked cannabis in 19 adults with TS. Patients experienced an average improvement of their tic severity measured with the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS) of approximately 60%. Altogether, 18 out of 19 patients experienced an improvement of their TS symptoms. All patients included in this study had used cannabis for self-medication for more than 1 year. Most often reported AEs were a feeling of “being high”, decreased concentration, increased anxiety, increased appetite, sedation, irritability, dry mouth, and dry eyes. However, no serious adverse events (SAEs) were reported.

3.2. Prospective case studies using different cannabis-based medicines

To date, there is a small number of prospective case studies available providing increasing evidence that CBM might be effective and well tolerated in adults with TS. Interestingly, in these case reports, different CBMs have been used. While most of these studies report about beneficial effects in adults, only very recently, first promising case reports in minors have been published.

3.2.1. Case studies using tetrahydrocannabinol

In 1999, Müller-Vahl et al. [40] published the first case of a 25-year old patient with TS treated with oral tetrahydrocannabinol (THC). This patient suffered from a complex TS and a number of additional psychiatric disorders such as ADHD, obsessive-compulsive behavior (OCB), SIB, anxiety disorder, and impulsivity. According to the patient's report, self-medication with smoked cannabis (2–3 g/day) caused a clinically relevant improvement of all these symptoms. Therefore, the patient was prospectively treated once with a single dose of 10 mg THC. This resulted in a significant reduction of tics of about 80% as well as an improvement in attention, impulse control, OCB, and premonitory urges. In addition, neuropsychological tests showed improvements in signal detection, sustained attention, and reaction time in the absence of AEs.

The same group described another case of a 24-year old female, who had an improvement of tics and premonitory urges after combined therapy of THC and the antipsychotic amisulpride [41]. The patient did far better on this combination than on monotherapy with either THC or amisulpride.

In addition, in 2011, Brunnauer et al. [42] reported the case of a 42-year-old male with TS, who suffered from multiple motor and vocal tics as well as OCB. Treatment with 15 mg THC resulted in a 75% tic reduction. As this patient was a professional driver, his driving abilities were assessed by professional computerized tests. Interestingly, the patient's concentration and visual abilities improved after THC administration.

Finally, Jakubovski and Müller-Vahl [43] reported about a 16-year old patient with vocal tics resembling stuttering-like phenomena accompanied by multiple simple and complex vocal tics as well as simple motor tics. Apart from tics, he was also experiencing further psychiatric problems including rage attacks, sleeping problems, tic-related anxiety and shame about speaking in public, depressed mood, and OCB (e.g., ordering of pencils, not just right feeling, and rumination) resulting in difficulties concentrating. Due to treatment resistance and intolerable AEs after established therapeutic interventions, it was decided to implement treatment with vaporized THC (up to a maximum dose of 22.4–33.6 mg THC/day). This leads to an improvement of his tics including complex vocal tics resulting in improved speech fluency. Moreover, coexisting psychiatric conditions improved.

3.2.2. Case studies using nabiximols

The first case report about effective treatment with nabiximols in a patient with TS was published by Trainor et al. [44] in 2016. This 26-year-old male suffered from treatment-resistant TS with severe motor and vocal tics, OCD, SIB, and depression. Administration of 4 puffs nabiximols (=10.8 mg of THC and 10 mg cannabidiol (CBD)) resulted in a 85% reduction of motor and 90% reduction of vocal tics after 4 weeks of treatment measured via the Rush Video Tape Rating Scale [45] and a 35% tic improvement according to the YGTSS-TTS. No AEs were reported.

Another single case study using nabiximols was reported by Kanaan et al. [46]. This was a 22-year-old male with complex and severe treatment resistant TS. Nabiximols (up-titrated to 9 puffs/day = 24.3 mg THC and 22.5 mg CBD) resulted in a reduction of tics measured with YGTSS-TTS, Tourette's Syndrome Symptom List (TSSL), and Rush Video Tape Rating Scale, premonitory urges, and a general improvement of quality of life without causing clinically relevant AEs.

3.2.3. Case studies using medicinal cannabis

Recently, Jakubovski and Müller-Vahl published a case report of a patient with TS treated with medicinal cannabis [43]. He suffered from a rare form of TS: a severe, impairing and treatment resistant vocal blocking and stuttering-like vocal tics as well as palilalia. These symptoms significantly impaired social contacts and daily living. The 19-year old patient received medicinal cannabis at a dose of 0.1 g cannabis once daily. After 8 months of follow-up, the symptoms improved significantly, especially speech fluency, but also other tics. After cannabis inhalation, beneficial effects lasted for about one and a half hour. Although the acute effect resolved thereafter, he experienced an overall positive effect during most time of the day. Only at the beginning of the treatment, he experienced a "high sensation" that resolved later on.

3.2.4. Treatment of minors with Tourette syndrome using cannabis-based medicines

Until today, only three single case studies are available reporting about treatment of minors with TS using CBM. The first report was published by Hasan et al. [47] in 2010. They described a 15-year old adolescent with severe and treatment resistant TS and comorbid ADHD. In this boy, augmentation of preexisting medication with risperidone (1 mg), aripiprazole (10 mg), and methylphenidate (15 mg) with oral THC (gradually up-titrated to 15 mg/day during 9 weeks) resulted in a significant tic reduction (global score of the YGTSS (range, 0–100) decreased from 97 to 54) and improved quality of life. The only AE observed was mild and transient euphoria.

The first ever case report of a child with TS treated with CBM was published only recently by Szejko et al. [48]. This 7-year-old boy suffered from severe tics and comorbid ADHD, which prevented him to attend school and finally resulted in social isolation, depression, and suicidal ideation. As all previous therapies including behavioral interventions and various medications (including risperidone, aripiprazole, tiapride, methylphenidate, and guanfacine) turned out to be unsuccessful, THC was proposed as a therapy of last choice. THC (in combination with risperidone (2 mg/day) and guanfacine (2 mg/day)) were gradually up-titrated to a maximal dose of 29.4 mg/day. Follow-up for more than 4 months demonstrated not only a clinically relevant improvement of tics, but also of accompanying psychiatric symptoms resulting in overall improved quality of life and social performance. Despite the relatively high dose of THC, no AEs were reported.

Furthermore, there is another single case report available describing beneficial effects of a combined treatment with vaporized medicinal cannabis and oral THC in a 12-year-old boy with TS (unpublished data, under revision). The boy complained of severe motor tics causing

significant insomnia. Therefore, the boy's parents—both of whom were medical doctors—decided to medicate their son with 0.02 g vaporized cannabis (Bedrocan® variety containing 22% THC and 1% CBD, corresponding to a dose equivalent of 4.4 mg THC). This resulted—according to their reports—in a tremendous symptom improvement. Because of a further tic increase, the family presented at our Tourette outpatient clinic. Since the family reported about an ongoing effect while using cannabis with a relevant tic decrease, we decided to implement a combined treatment with vaporized medicinal cannabis (up to 0.1 g cannabis per day, varieties Bedrocan® and Amnesia Haze®, corresponding to 22 mg THC/day) plus oral THC drops (up to 12.5 mg/day). This combined therapy resulted not only in a marked tic reduction, but also an improvement of premonitory urges without any AEs.

Thus, currently, the database for treatment of minors with TS using CBM is very limited. However, from available preliminary results, it is suggested that CBM is effective and well tolerated even in this age group. At present time, no long-term follow-up data are available, and therefore, no statement is possible about positive and possible negative long-term effects, in particular with respect to detrimental effects on the developing brain. From observational oncological studies in children, however, it is also suggested that controlled application of CBM is safe and well tolerated. It is unknown, whether in children with TS the risk for psychosis is increased after treatment with CBM comparable to the increased risk in healthy children after excessive recreational cannabis use. Assuming a dysfunction in the ECS in TS, it can also be speculated that CBM may have beneficial effects on the course of the disease.

3.2.5. *Controlled trials using tetrahydrocannabinol*

Up to this date, only two small controlled studies have been conducted in adult patients with TS using CBM. Both of them were performed by Müller-Vahl's group. Dr. Müller-Vahl is an internationally renowned expert in the field of TS and tic disorders. She introduced CBM in the treatment of TS, conducted the first randomized controlled trials in this group of patients in the early 2000s, and since then dedicated a large part of her research endeavors in this area. In both controlled studies, efficacy and safety of pure THC have been investigated. The first one, published in 2002 by Müller-Vahl et al. [48], was a randomized double-blind placebo-controlled cross-over single-dose trial using 5.0, 7.5 or 10 mg of THC. The trial included 12 adult TS patients with a mean age of 34 ± 13 years. Tic severity was assessed both via a self-rating (TSSL) and different examiner-rating scales (Shapiro Tourette's syndrome Severity Scale (STSSS) and YGTSS). The Tourette's syndrome Global Impression Scale (TS-CGI) was used to assess global disease severity. To assess changes in psychiatric comorbidities (including OCB, ADHD, and anxiety), the self-assessment of the TSSL was used. According to TSSL, there was a significant improvement of tics and OCB compared to placebo. According to examiner rating scales for the assessment of tic severity, there was an improvement in the subscore "complex motor tics" and a trend toward a reduction in the subscores "motor tics," "simple motor tics" and "vocal tics." The following AEs were recorded: headache, nausea, dizziness, tiredness, cheerfulness, dry mouth, anxiety, sensitivity to noise and light, ataxia and poor concentration, but no SAEs were reported. Plasma levels of the THC metabolite 11-hydroxy-delta-tetrahydrocannabinol correlated with tic reduction as assessed by TSSL.

In 2003, Müller-Vahl et al. published results of a randomized, double-blind, placebo-controlled follow-up trial [49]. In this study, 24 adult patients with TS were treated for a period of 6 weeks with up to 10 mg THC/day. Tic severity was evaluated at six different time points. For tic assessment, both self-rating scales as well as examiner rating scales were used (TSSL, YGTSS, STSSS, and Rush Video-Based Tic Rating Scale) [45]. Nearly all rating scales indicated a significant superiority of the THC arm compared to placebo at visits 3 and 4. The Rush Video-Based Tic Rating Scale also showed a significant difference or trends toward significant group differences at visits 2 and 4 for the items “motor tic intensity” and “motor tic frequency,” respectively. Seven patients dropped out of the study, but only one due to AEs (restlessness and anxiety). Five patients in the THC group reported AEs (tiredness, dry mouth, dizziness and fuzziness), while three in the placebo group (tiredness, dizziness, anxiety, depression) in the absence of SAEs.

3.2.6. Efficacy of cannabis-based medicines in the treatment of psychiatric comorbidities in patients with Tourette syndrome

Up to 90% of patients with TS suffer from psychiatric comorbidities and studies investigating quality of life in these patients clearly demonstrate that most patients are more impaired by ADHD, OCD, and depression, respectively, than their tics. Thus, in the majority of patients with TS, effective treatment of comorbidities is even more important than treatment of tics. Until today, however, there is no treatment strategy known that improves both tics and comorbidities. Therefore, in patients with complex TS combined therapy using different treatment strategies in parallel is inevitable.

Interestingly, from all available case studies and controlled trials, it is suggested that CBM improves not only tics, but also psychiatric symptoms. Therefore, it can be speculated that CBM might be the first treatment strategy that is useful in the treatment of the complete spectrum of symptoms. More specifically, there is preliminary evidence that CBM also improves ADHD [39], OCB/OCD [40] impulsivity [43], depression [50], sleeping problems [51], and anxiety [43].

For example, in the retrospective survey by Abi-Jaoude et al. [39], all patients reported in addition to the tic improvement also an improvement of psychiatric symptoms after treatment with cannabis including sleeping disturbances, anxiety, OCB, impulsivity, irritability and rage attacks. With respect to comorbid ADHD, only one out of 13 patients demonstrated no improvement of ADHD symptoms. This data in patients with TS is in line with preliminary results in patients suffering from pure ADHD (without tics or TS). In 2017, Cooper et al. [52] published results of a randomized placebo-controlled pilot study using nabiximols in patients with ADHD. In this trial, 30 adults with ADHD were included, and cognitive performance was assessed using an objective assessment for inattention, hyperactivity, and impulsivity (Qb-Test). Although for the primary outcome, no significant difference was observed, several secondary outcomes demonstrated superiority of nabiximols compared to placebo with improvements in hyperactivity, impulsivity and inattention, respectively. In the active group, three mild AEs and one SAE (muscular spasms/seizures) were recorded, while in the placebo group, one SAE (cardiovascular problems) occurred.

Although most patients with TS treated with CBM report about an improvement of one or even more psychiatric comorbidities, larger controlled trials are needed to confirm these promising, but preliminary results.

3.2.7. Safety profile and influence on psychomotor functioning in patients with Tourette syndrome

From the available preliminary results, it is suggested that—on average—the AE profile of CBM in the treatment of patients with TS is very similar to that in other groups of patients. In line with data from recent meta-analyses including mixed patients' groups [52], for example, in the retrospective study by Abi-Jaoude et al. [53], a relatively high number of AEs were reported in patients with TS, but most AEs were mild and transient, respectively. Most often reported AEs after use of cannabis in patients with TS were a “feeling of high,” decreased concentration, decreased short-term memory, increased anxiety, increased appetite, sedation, irritability, dry mouth and eyes, and wheezing.

Contrary to these reports from open uncontrolled studies, from preliminary controlled data, it is suggested that the impact of THC on neuropsychological performance in adults with TS may differ as compared to both healthy people and other patient groups. In two controlled studies investigating the effects of THC in patients with TS, additionally, neuropsychological tests were performed. In the first study [54], the influence of a single dose treatment of THC on neuropsychological performance was investigated. However, no negative impact of THC compared to placebo was found on verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, and vigilance. In another study, Müller-Vahl et al. [55] investigated the influence of a 6-week THC treatment as compared to placebo on neuropsychological performance using different neuropsychological tests to assess verbal learning, attention, and memory. Again, THC had no detrimental effects on neuropsychological performance and immediate verbal memory span even improved after treatment with THC.

These results are completely in line with observations in two open uncontrolled single case studies. In 2007, Strohbeck-Kühner et al. [56] published a case of a 28 year-old male with ADHD (without TS), who benefitted from treatment with THC, and, moreover, his fitness to drive improved after treatment. A similar case was reported by Brunnauer et al. [42] some years later. They described an effective treatment with THC in a 42 year-old male. Furthermore, his driving ability (concentration and visual abilities) was better under treatment with THC as compared to the off-medication state. The authors, therefore, suggested that in TS, CBM such as THC may have beneficial effects on psychomotor functions related to driving performance. Thus, from this preliminary data, it is strongly suggested that the influence of CBM on neuropsychological performance in patients with TS may differ from effects in healthy people and other groups of patients.

Finally, until today, very little is known about safety of CBM in children and adolescents with TS [47–49]. However, from available preliminary case reports, it is suggested that in this group of patients CBM such as THC is well tolerated or even better tolerated than in adults. This observation is in line with reports in other groups of young patients. For example when using CBM in antineoplastic therapy [30] it has been suggested that CBM—even at high doses—are well tolerated in children.

3.2.8. Practical clues for the treatment of patients with Tourette syndrome using cannabis-based medicines

Despite lack of clear evidence, recent European [25] and Canadian treatment guidelines [28] for TS acknowledged available data and recommend CBM in otherwise treatment resistant adult patients with TS. Most experts suggest treatment with CBM, before taking surgical treatment with deep brain stimulation into consideration. Comparable to most other indications, until today it is unclear, which CBM is the most effective and best tolerated in patients with TS. However, from available data, it is suggested that pure CBD is not effective in the treatment of tics. Data obtained from both a retrospective and prospective survey performed at the Tourette outpatient clinic at Hannover Medical School, Germany, provide preliminary evidence that medicinal cannabis might be superior to pure THC and nabiximols (unpublished data). Currently, treatment with CBM in minors with TS should be only taken into consideration in otherwise treatment resistant and severely affected patients.

With respect to the dose, no clear recommendation can be given. In any case, starting dose should be low (corresponding to 2.5 mg THC/day) and up-titration should be slow, for example by 2.5 mg THC every 3–5 days. Maximal dose differs from patient to patient, but usually ranges from 0.1 to 1 g cannabis/day, corresponding to about 2.5–30 mg THC/day. However, in individual patients, maximal doses can be much higher.

An overview on all available studies investigating efficacy and safety of CBM in TS is given in **Table 1**.

Reference	Number of patients (sex)	Age	Substance	Study design	Outcome
Sandyk et al. 1988	3 (male)	15, 17, 39	<i>Cannabis sativa</i> L.	Case report	Reduction of tics, premonitory urges and self-injurious behavior; general relaxation; improvement of attention and hypersexuality
Hemming et al. 1993	1 (male)	36	<i>Cannabis sativa</i> L.	Case report	Symptom free
Müller-Vahl et al. 1998	64 (55 male, 9 female)	15-64	Medical cannabis	Case series	Tic reduction or remission; premonitory urges; improvement of OCB and ADHD
Müller-Vahl et al. 1999	1 (male)	25	THC	Case report	Tic reduction, premonitory urges; improvement of attention, impulse control, and OCB
Müller-Vahl et al. 2002a	1 (female)	24	THC (in combination with amisulpride)	Case report	Tic reduction, premonitory urges
Müller-Vahl et al. 2002b	24 (19 male, 5 female)	18-68	THC	Randomized double-blind parallel group placebo-controlled trial	Tic reduction; global improvement

Reference	Number of patients (sex)	Age	Substance	Study design	Outcome
Müller-Vahl et al. 2003b	12 (11 male, 1 female)	18-66	THC	Randomized double-blind placebo-controlled crossover trial	Tic reduction; improvement of OCB
Hasan et al. 2010	1 (male)	15	THC (in combination with aripiprazole and risperidone)	Case report	Tic reduction, improvement of quality of life; treatment with methylphenidate was tolerated without tic increase
Brunnauer et al. 2011	1 (male)	42	THC	Case report	Reduction of tics, improvement of concentration and visual perception
Trainor et al. 2016	1 (male)	26	Nabiximols	Case report	Reduction of motor and vocal tics
Abi-Jaoude et al. 2017	19 (16 males, 3 females)	18-51	Medical cannabis	Case series, structured interview	Reduction of tics
Jakubovski and Müller-Vahl. 2017	2 (male)	16, 19	THC, medical cannabis	Case report	Improvement of tics including complex vocal tics resulting in improved speech fluency, co-existing psychiatric conditions improved
Kanaan et al. 2017	1 (male)	22	Nabiximols	Case report	Reduction of tics, improvement of quality of life
Szejko et al. 2018	1 (male)	8	THC	Case report	Reduction of tics, improvement of comorbid psychiatric conditions (ADHD, depression), improvement of quality of life
Szejko et al. (submitted to Frontiers in Psychiatry)	1 (male)	12	THC, medical cannabis	Case report	Reduction of tics, improvement of sleeping problems

Table 1. Case studies employing CBM in TS.

4. Future directions

Larger well-designed controlled studies are urgently needed to confirm available preliminary results. Further studies should investigate not only the efficacy of CBM in the treatment of tics, but also their potency to improve typical psychiatric comorbidities in TS including ADHD, OCB, depression, anxiety, sleeping disorders, and rage attacks. Finally, the AE profile should be investigated in detail, since from available data, it is suggested that neuropsychological performance may improve—and not deteriorate—after treatment with CBM in this group of patients. So far, it is unknown, which CBM is the most effective and best tolerated in patients with TS. However, based on available reports, patients with TS seem to prefer CBM with median to high THC content.

Currently, a large randomized controlled trial in Germany is recruiting to further investigate efficacy and safety of nabiximols in patients with TS (ClinicalTrials.gov Identifier: NCT03087201). In this study, in addition, patients' fitness to drive will be investigated after treatment with nabiximols.

While all published studies investigated the effects of different synthetic or plant-derived cannabinoids in the treatment of TS, unpublished data from a single dose pilot study in 20 adult patients suggests that also modulators of the endocannabinoid system—such as inhibitors of the monoacylglycerol lipase (MGLL)—might be effective in the treatment of TS (ClinicalTrials.gov Identifier: NCT03058562).

5. Conclusions

There is increasing evidence that CBM might be a promising new treatment strategy for patients with TS. However, larger well-designed controlled studies are urgently needed to confirm preliminary results. However, already today, a substantial number of patients use CBM, either prescribed off-label or no-label under the guidance of the treating physician or as a self-medication without supervision of a medical doctor. Physicians, who treat patients with tic disorders and TS, should actively ask their patients about possible use of cannabis, since it is well known that many patients with TS use complementary or alternative treatments without informing their doctor [57]. If patients with TS report about (illegal) self-medication with cannabis, treating physicians should inform their patients about legal treatment options and available routes of intake without the risks associated with smoking.

Conflict of interest

KMV has received payment for consulting from Abide Pharmaceuticals and Fundacion Canna and support for research from GW and Almirall. She is carrying out studies in cooperation with Abide Pharmaceuticals, GW and Almirall. She is a member of the Scientific Advisory Board of Therapix and a second chairwoman of the International Association for Cannabinoid Medicine (IACM).

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