# Tourette's Syndrome

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**Abstract** Tourette's syndrome (TS) is a chronic disorder characterized by motor and vocal tics and a variety of associated behaviour disorders. Because current therapy is often unsatisfactory, there is expanding interest in new therapeutic strategies that are more effective, cause less side effects and ameliorate not only tics but also behavioural problems. From anecdotal reports and preliminary controlled studies it is suggested that – at least in a subgroup of patients – cannabinoids are effective in the treatment of TS. While most patients report beneficial effects

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when smoking marijuana (*Cannabis sativa L.*), available clinical trials have been performed using oral $\Delta^9$-tetrahydrocannabinol (THC). In otherwise treatment-resistant TS patients, therefore, therapy with THC should not be left unattempted. To date, it is unknown whether other drugs that interact with the endocannabinoid receptor system might be more effective in the treatment of TS than smoked marijuana or pure THC. Since it has been suggested that abnormalities within the endocannabinoid receptor system might underlie TS pathophysiology, it would be of interest to investigate the effect of substances that for example bind more selectively to the central cannabinoid receptor or inhibit the uptake or the degradation of different endocannabinoids.

**Keywords** Tourette's syndrome • Tic • Attention obsessive compulsive disorder • OCD

## Abbreviations

| | |
|---|---|
| 2AG | 2-Arachidonoylglycerol |
| ADHD | Attention deficit hyperactivity disorder |
| GCIS | Global clinical impression scale |
| GP | Globus pallidus |
| MRI | Magnetic resonance imaging |
| NL | Neuroleptics |
| PD | Parkinson's disease |
| PET | Positron emission tomography |
| OCB | Obsessive compulsive behaviour |
| SSCP | Single-strand conformation polymorphism |
| SSRI | Selective serotonin-reuptake inhibitors |
| STSS | Shapiro Tourette-syndrome severity scale |
| TS | Tourette's syndrome |
| TSGS | Tourette's syndrome global scale |
| TSSL | Tourette syndrome symptom list |
| YGTSS | Yale global tic severity scale |

# 1 Tourette's Syndrome

## *1.1 The Clinical Picture of Tourette's Syndrome*

Tourette's syndrome (TS) is defined as a childhood-onset chronic neuropsychiatric disorder characterized by multiple motor and one or more vocal tics (The Tourette

Syndrome Classification Study Group 1993). Tics are sudden, repetitive, stereotyped movements or phonic productions that predominantly involve facial, shoulder or upper limb muscles. Salient features of tics are premonitory urges preceding the tics and the ability to suppress the tics for a short period of time. Beside such simple tics, complex tics can occur including copro- and echophenomena. In the majority of patients behavioural problems are associated such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive behaviour (OCB), self injurious behaviour, depression, anxiety disorder, rage, learning disorders, conduct disorder, oppositional deficient disorder, and addiction. Most typically, tics start between the age of 6–8 years, reach their maximum between the age of 10–14 years, and decrease spontaneously in the further course of the disease (Robertson 2000; Singer 2000).

## *1.2 The Aetiology of Tourette's Syndrome*

The neurobiology of TS is still unknown. Findings from in vivo neuroimaging studies provided evidence that different parallel circuits that connect frontal association areas with the basal ganglia are pathophysiologically involved (Gerard and Peterson 2003). It is thought that these loops are involved in the selection, programming, initiation, and control of movement (Alexander et al. 1990). Furthermore, it has been suggested that abnormal function of basal ganglia circuits with abnormal excessive activity of multiple discrete sets of striatal neurons can produce tics (Mink 2001). However, recent findings from magnetic resonance imaging (MRI) studies provided evidence that TS is primarily caused by anomalous frontal lobe association and projection fibre bundles resulting in both basal ganglia function abnormalities and disinhibition of the cingulate gyrus (Müller-Vahl 2006).

Most neurotransmitters involved in frontal-subcortical circuits have been suggested to play a role in the pathobiology of TS, including the dopaminergic, GABAergic, glutamatergic, cholinergic, serotonergic, noradrenergic, opiod, second messenger, and cannabinoid receptor systems (Singer and Wendtlandt 2001; Müller-Vahl et al. 1998). Although multiple clinical and laboratory studies favour an involvement of the dopaminergic system, to date no characteristic dopaminergic dysfunction has been consistently identified. Therefore, it has been speculated that dysfunctions in other transmitter systems might underlie TS pathology and changes in the dopaminergic system might be secondary to these defects (Singer and Wendtlandt 2001).

## *1.3 Treatment of Tourette's Syndrome*

In 1961, haloperidol was proven to be effective in the treatment of tics in patients suffering from TS. Since then, dopamine receptor blocking drugs (neuroleptics, NL) such as haloperidol, pimozide, sulpiride, risperidone, tiapride,

and other typical and atypical NL are considered the most effective agents in the treatment of tics. However, treatment with neuroleptic drugs is often unsatisfactory due to low efficacy or significant side effects (sedation, drowsiness, impaired motivation, weight gain, depression, akathisia, and acute dystonic reactions). Therefore, NL are recommended particularly in those patients who are significantly impaired and/or suffer from severe tics. Alternatively, only a limited number of substances can be used in the treatment of tics including clonidine, an α-adrenoceptor agonist, and dopamine receptor agonists such as pergolide. To date, there is no therapy known that is not only effective in the treatment of tics, but also improves associated behavioural disorders. Therefore, selective serotonin-reuptake inhibitors (SSRI) are recommended for the treatment of associated OCB, and psychostimulants such as methylphenidate are the treatment of choice in patients suffering from additional ADHD. In patients with severe and complex symptoms combined treatment with several drugs is often inevitable (Müller-Vahl 2002).

### *1.4 Future Perspectives in the Treatment of Tourette's Syndrome*

At present, therapy of TS often remains unsatisfactory. There is no drug known that is curative. All available drugs are associated with potentially disabling adverse effects. Although there is general agreement that available drug therapy should be limited to those patients who are significantly impaired by their symptoms, it is well known that not only severe, but also mild, tics can be functionally disabling. In the treatment of TS, therefore, new therapeutic strategies are desirable that (1) are more effective in the treatment of tics, (2) cause less adverse effects, and (3) improve not only tics but also associated behavioural disorders such as ADHD and OCB.

Against this background, many TS patients seek alternative or complementary medicine including special diets and nutritional supplements (Mantel et al. 2004; Müller-Vahl et al. 2008) as well as legal and illegal drugs such as nicotine, alcohol and *Cannabis sativa* (Müller-Vahl et al. 1997a, b). Based on such self-monitoring, further investigations were stimulated on the therapeutic use of cannabinoids in the treatment of TS.

## 2 Treatment of Tourette's Syndrome with Cannabinoids

### *2.1 Anecdotal Reports*

In 1988 Sandyk and Awerbuch and in 1993 Hemming and Yellowlees for the first time suggested that the use of smoked marijuana (*Cannabis sativa*) might be useful in the treatment of TS. Sandyk and Awerbuch (1988) reported on three 15–39-year-old male patients who experienced an improvement not only of their tics and the

preceding urge to tic, but also of several associated behavioural problems such as self-mutilatory behaviour, attention span, and hypersexuality when smoking 1/2 to 2 marijuana cigarettes per day. Five years later, Hemming and Yellowlees (1993), in addition, described a single case of a 36-year-old man suffering from TS who reported that he had been symptom-free for more than 1 year when taking one "cone" of marijuana per night.

These initial case reports were corroborated by results obtained from a retrospective survey that has been performed at a specialized TS outpatient clinic (Clinic of Psychiatry, Hannover Medical School) in 1998 (Müller-Vahl et al. 1998). Using a standardized questionnaire, 64 consecutive adult TS patients were interviewed about the use and the potential effect of cannabinoids on their symptoms. Of 17 patients reporting prior use of marijuana, 14 (82%) experienced a reduction or complete remission of motor and vocal tics and/or an amelioration of premonitory urges, OCB, and ADHD. None of these patients reported serious side effects or a deterioration of symptoms when smoking marijuana. Beneficial effects were noted not only in drug-free patients, but also in patients with ongoing treatment.

## *2.2 Uncontrolled Single Case Studies*

Because in Germany use of marijuana is illegal and the cannabis herb is not licenced for clinical use, consecutive clinical trials investigating the therapeutic effect of cannabinoids in TS were performed using $\Delta^9$-tetrahydrocannabinol (THC), the most psychoactive ingredient of *Cannabis sativa*.

In an uncontrolled single case study beneficial effects of a single dose treatment with 10 mg THC orally were reported in a 25-year-old male patient who suffered from TS in association with ADHD, OCB, anxiety, lack of impulse control, and self injurious behaviour (Müller-Vahl et al. 1999). For several years he had used marijuana (2–3 g per day) illegally and reported a marked improvement of his tics and behavioural problems when smoking marijuana. In this prospective single case study, for the first time, valid and reliable rating scales were used to assess the clinical effect of THC in TS. At the time of investigation, the patient was unmedicated and had stopped smoking marijuana 3 days before. Using the tic section of the Tourette's Syndrome Global Scale (TSGS) (Leckman et al. 1988), the total tic severity score was 41 before treatment and was reduced to 7 two hours after THC treatment. Both motor and vocal tics improved and coprolalia disappeared. The improvement began 30 min after treatment and lasted for about 7 h. No adverse effects occurred. Measuring cognitive functions, neuropsychological tests showed improved signal detection, sustained attention, and reaction time after treatment. The patient himself noted an improvement of motor and vocal tics of about 70%. Furthermore, he felt an amelioration in attention, impulse control, OCB, and premonitory feeling.

In another single case study, THC in combination with a neuroleptic medication was described as superior to THC or NL alone with respect to the treatment of tics (Müller-Vahl et al. 2002a). In this 24-year-old female suffering from extreme motor

and vocal tics, treatment with 10 mg/day THC plus 1200 mg/day amisulpride (an atypical neuroleptic drug) was found to be the most effective treatment. However, due to NL-induced side effects such as galactorrhoea, weight gain, and sedation, later on she decided to discontinue pharmacotherapy. Nonetheless, from this clinical observation it is suggested that THC might augment anti-tic effects of dopamine receptor blocking drugs. These results are in line with animal studies in rats demonstrating that hypokinesia induced by the dopamine receptor antagonist haloperidol significantly increases after co-administration of THC (Moss et al. 1984). It, therefore, has been suggested that combined treatment with cannabinoids and NL might be of therapeutic value in hyperkinetic movement disorders such as TS (Moss et al. 1989).

## *2.3 Controlled Single-Dose Trial*

Based on these initial case reports, a randomized double-blind placebo-controlled crossover single-dose trial of THC in TS was performed (Müller-Vahl et al. 2002b). In this study 12 adult patients (11 men, 1 woman, mean age = 34 ± 13 (SD) years, range 18–66 years) were included. Patients were randomly assigned a single dose of oral THC first or a single dose of visually identical placebo first on two days separated by a 4-week washout phase before they were crossed over to receive the other treatment. According to their body weight, sex, age and prior use of marijuana, patients were treated with 5, 7.5 or 10 mg THC. Both self (Tourette Syndrome Symptom List (TSSL) (Leckman et al. 1988)) and examiner rating scales (Shapiro Tourette-Syndrome Severity Scale (STSS) (Shapiro et al. 1988), Yale Global Tic Severity Scale (YGTSS) (Harcherik et al. 1984) and TSGS (Leckman et al. 1988)) were used to determine the effect of THC. Using the TSSL, there was a significant global tic improvement after THC compared with placebo ($p = 0.015$). Examiner ratings demonstrated a significant improvement ($p = 0.015$) for complex motor tics (TSGS). Using the TSSL, in addition, there was a significant improvement of OCB ($p = 0.041$). Including only those patients who had received either 7.5 or 10.0 mg THC ($n = 8$), data became more robust suggesting that higher dosages are more effective. On the THC treatment day, 10 of 12 patients experienced a global improvement (mean +35% ± 28.0, range 20–90%). In contrast, on the placebo day only three patients reported a global improvement (mean of +7% ± 13.7, range 10–40%). No serious adverse reactions occurred. Five patients experienced transient mild side effects lasting for 1–6 h. Four of them reported headache, nausea, dizziness, hot flush, tiredness, poor powers of concentration, and cheerfulness. One patient who was treated with 10 mg THC experienced dizziness, anxiety, tremble, sensitivity to noise and light, dry mouth, and ataxia lasting for about half an hour.

In addition, a variety of neuropsychological tests was performed to investigate the influence of a single-dose treatment of THC on neuropsychological performance (Müller-Vahl et al. 2001). No detrimental effect of THC was found on short-term verbal and visual memory, recognition, verbal learning, intelligence,

information processing, vigilance, reaction time, sustained attention and divided attention. In healthy cannabis users there is evidence that cannabis use causes cognitive impairments that correlate with frequency and duration of cannabis use (Solowij et al. 1995; Block and Ghoneim 1993). Since it has been suggested that the central cannabinoid system might be involved in the pathophysiology of TS (Müller-Vahl et al. 1998, 1999), it can be hypothesized that the effect of THC on neuropsychological performance may be different in patients suffering from TS compared to healthy users.

Furthermore, treatment with THC did not result in a deterioration of depression, somatization, interpersonal sensitivity, anxiety, anger–hostility, paranoid ideation, and psychoticism. Using the Symptom Checklist 90-R (SCL-90-R) (Derogatis et al. 1973; Derogatis 1977), data provided evidence for a deterioration of OCB and a trend towards an increase in phobic anxiety. However, limitations of the SCL-90-R in measuring OCB are known. From other studies, in contrast, it is suggested that cannabinoids may even improve OCB (Müller-Vahl et al. 1998, 1999). The increase in phobic anxiety is probably due to the study design, because the dosage could not be administered slowly.

## *2.4 Six-Week Randomized Trial*

Based on these encouraging results, a randomized, double-blind, placebo-controlled study was performed to confirm these findings (Müller-Vahl et al. 2003a, b). In this study 24 adult patients (19 men, 5 women, mean age = 33 ± 11 (SD) years, range 18–68 years) with TS were included. Patients were treated over a period of 6 weeks with 5–10 mg THC. The dosage was titrated to the target dosage of10 mg THC. Starting at 2.5 mg/day, the dosage was increased by increments of 2.5 mg/day every 4 days. The study consisted of six visits (visit 1 = baseline, visits 2–4 during treatment, visits 5 and 6 after withdrawal). At each visit tic severity was measured using different examiner rating scales (Global Clinical Impression Scale, GCIS) (Leckman et al. 1988), STSS, YGTSS, and a videotape-based rating scale (Goetz et al. 1987) as well as a self rating (TSSL).

Using the GCIS at visits 3 and 4 there was a significant difference ($p < 0.05$) between the THC and placebo group. At visit 4, in addition, a significant difference between both groups was found when using the STSS ($p = 0.033$), the subscore "motor global scale" of the YGTSS ($p = 0.040$) and the videotape-based rating scale ($p = 0.030$). The TSSL demonstrated a significant difference ($p < 0.05$) between the placebo and THC group at 10 treatment days (between day 16 and 41). ANOVA also demonstrated a significant difference between both groups ($p = 0.037$). Several other measures, in addition, demonstrated a trend towards a significant difference ($p < 0.1$) at visits 2, 3, and 4, respectively, either in global tic scores or in several subscores.

Seven patients dropped out of the study or had to be excluded, but only one due to side effects. No serious adverse effects occurred. Five patients in the THC group reported mild side effects (tiredness, dry mouth, dizziness, and muzziness) and

three patients in the placebo group (tiredness, dizziness, anxiety, and depression). One patient in the THC group stopped medication at day 4 (first day at dose 5 mg) due to side effects like anxiety and restlessness.

In addition, the influence of a 6-week THC treatment on neuropsychological performance was investigated (Müller-Vahl et al. 2003). To measure cognitive functions the following tests were used: (1) German version of the Auditory Verbal Learning Test (VLMT) (Helmstaedter and Durwen 1990), (2) Benton-Visual-Retention-Test (BVRT) (Benton 1945), (3) Divided Attention (TAP) (Zimmermann and Fimm 1989), and (4) multiple choice vocabulary test (Mehrfachwahl-Wortschatztest, MWT-B) (Merz et al. 1975). Neither during medication, nor immediately after medication was stopped, nor 5–6 weeks after withdrawal, were any detrimental effects seen on learning curve, interference, recall and recognition of word lists, immediate visual memory span, and divided attention. Measuring immediate verbal memory span, there was even a trend towards a significant improvement during and after treatment. Furthermore, no significant influence on OCB, anxiety, depression and "the current emotional state" was found [unpublished data].

## 3 Adverse Effects

Based on the available data it can be concluded that in most TS patients treatment with THC causes only mild adverse reactions. Overall, adverse effects were comparable to those seen in other groups of patients including headache, dry mouth, nausea, dizziness, muzziness, hot flush, tiredness, poor powers of concentration, and cheerfulness. Previous studies were afflicted with a low drop-out rate due to side effects. Only rarely more significant adverse effects were observed such as anxiety, tremble, ataxia, and restlessness. In contrast to other studies, neuropsychological tests did not demonstrate detrimental effects on cognition in TS patients. Since it has been suggested that changes in the cannabinoid receptor system might be involved in the pathophysiology of TS, it can be speculated that in TS patients cognitive functions are less impaired (or even improved) by THC compared to healthy users.

In general, cannabinoids are contraindicated in patients suffering from a psychotic illness and significant cardiac disorder. THC should be used with caution in patients with a history of substance abuse. Patients receiving treatment with THC should be warned not to drive or operate machinery until it is established that they are able to tolerate the drug. In addition, THC should not be used in pregnant and breast-feeding women and children because there is evidence that frequent cannabis use in young people is associated with increased rates of psychotic symptoms, depression and anxiety (Fergusson et al. 2003; Patton et al. 2002). However, in a small study in eight children (3–13 years) suffering from hematologic cancers, treatment with $\Delta^8$-THC was well tolerated (Abrahamov et al. 1995). The authors suggested that in children side effects may occur less frequently because the central cannabinoid $CB_1$ receptor system is not fully developed.

## 4 Central Cannabinoid Receptor (*CNR1*) Gene in Tourette's Syndrome

Based on the beneficial effects of cannabinoids in the treatment of TS, it has been hypothesized that the central cannabinoid ($CB_1$) receptor system is involved in the pathophysiology of TS. Therefore, the central cannabinoid receptor gene (*CNR1*) encoding the $CB_1$ was considered as a candidate gene for TS and systematically screened by single-strand conformation polymorphism (SSCP) analysis and sequencing. However, investigating 40 TS patients and 81 healthy controls and, in addition, two subsequent cohorts of 56 TS patients and 55 controls, and 64 patients and 66 controls, there was no evidence suggesting that TS is caused by genetic variations of the *CNR1* gene (Gadzicki et al. 2004).

## 5 In Vivo Imaging of Central Cannabinoid $CB_1$ Receptors in TS Using [$^{123}$I]AM281 and SPECT

In vivo neuroimaging using positron emission tomography (PET) and single photon emission computed tomography (SPECT) to investigate different aspects of the cannabinoid $CB_1$ receptor system is in a very preliminary state. Although some ligands that are suitable for measuring specific binding to $CB_1$ receptors in vivo in humans are already forthcoming, there is only a single study available investigating central cannabinoid $CB_1$ receptors in TS using the $CB_1$ antagonist [$^{123}$I]AM281 (*N*-(morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-[$^{123}$I]iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide) and single photon emission computed tomography (SPECT) (Berding et al. 2004). [$^{123}$I]AM281 was employed in six TS patients before and after THC treatment and specific over nonspecific partition coefficients V3" were calculated. Although mean V3" did not change significantly after THC treatment, V3" clearly declined in the only patient with a marked clinical response after THC treatment. Results from this first study, therefore, suggest that specific binding of [$^{123}$I]AM281 to $CB_1$ receptors can be detected in patients using SPECT. Because in this study a control group is lacking, the question as to whether $CB_1$ receptor binding sites are pathologically changed in TS patients as measured by [$^{123}$I]AM281 and SPECT remains unanswered.

## 6 Possible Explanations for Beneficial Effects of Cannabinoids in TS

In TS, positive effects of THC in the treatment of tics may be explained by different mechanisms. In the CNS, the highest densities of $CB_1$ receptors were found in the basal ganglia, cerebellum, and hippocampus (Herkenham et al. 1990; Glass et al. 1997). Within the basal ganglia, $CB_1$ receptors are particularly

prominent in the globus pallidus (GP) and substantia nigra pars reticulata – the indirect and direct output pathways (Herkenham et al. 1990). In TS there is evidence for an involvement of both the basal ganglia and the limbic system. This might account for the effects of cannabinoids on tics and behavioural problems in TS.

There are several lines of evidence suggesting a complex interaction between the $CB_1$ receptor system and the dopaminergic system, which is suggested to be overactive in TS patients. In rats it has been demonstrated that the release of the endocannabinid anandamide was eight-fold increased in the dorsal striatum after administration of a $D_2$-like dopamine receptor agonist (Giuffrida et al. 1999). This response could be prevented by administration of a $D_2$-like receptor antagonist. Pretreatment with the cannabinoid antagonist rimonabant enhanced the stimulation of motor behaviour elicited by a $D_2$-like dopamine receptor agonist, while administration of rimonabant alone had no effect on motor activity. It therefore can be speculated that the endocannabinoid system may act as an inhibitory feedback mechanism countering dopamine stimulation of motor activity (Giuffrida et al. 1999). In addition, it has been demonstrated that anandamide increases the release of dopamine both in the striatum (Cadogan et al. 1997) and in the mesolimbic system (Gessa et al. 1998). Treatments with the dopamine $D_2$ receptor antagonist haloperidol and sulpiride resulted in significantly increased cannabinoid receptor mRNA levels in the caudate-putamen. Therefore, it has been suggested that the expression of the cannabinoid receptor gene in the striatum is under the negative control of dopamine receptor-mediated events (Mailleux and Vanderhaeghen 1993).

Furthermore, it has been demonstrated that constitutive hyperdopaminergia in dopamine transporter (DAT) knockout (KO) mice, an animal model linked with hyperdopaminergia, is associated with a significant decrease of striatal anandamide levels (Tzavara et al. 2006). These results further support that hyperdopaminergia leads to alterations of the endocannabinoid system and suggest that normalization of decreased anandamide levels might constitute an alternative therapeutic strategy for disorders associated with hyperdopaminergia such as TS (Tzavara et al. 2006).

In the reserpine-treated rat, an animal model for Parkinson's disease, a seven-fold increase in the levels of the endocannabinoid 2-arachidonoylglycerol (2AG) was observed in the GP. Administration of a dopamine $D_2$ receptor agonist increased locomotion accompanied by reduced 2AG and anandamide levels in the GP (Di Marzo et al. 2000). In humans, it has been shown that nabilone, a classical synthetic THC analogue, ameliorates levodopa-induced dyskinesia in PD (Sieradzan et al. 2001). Therefore, it can be speculated that THC inhibits dopaminergic activity in motor-control centres and, through this, reduces tics in TS.

On the other hand several other neurotransmitters involved in frontal-subcortical circuits have been suggested to play a role in the pathobiology of TS including the GABAergic, glutamatergic, cholinergic, serotonergic, noradrenergic, opiod, and second messenger systems. There is experimental evidence that the activity of most of these transmitters – both excitatory neurotransmitters

such as glutamate and inhibitory transmitters such as GABA and glycine – is affected by cannabinoids as well. Therefore, beneficial effects of THC in TS might also be explained by a modulation of one or several of these neurotransmitter systems.

## 7 Conclusions and Perspective

Available results from a limited number of case reports and preliminary studies consistently provide evidence for beneficial effects of *Cannabis sativa* and THC, respectively, in the treatment of tics and possibly behavioural problems (OCB, attention span, impulsivity, autoaggression) in TS patients. Based on the available data, it can be speculated that even low dosages (5–10 mg) are effective in this group of patients. In most TS patients treated with THC observed adverse effects were mild. Overall, adverse reactions were comparable to those seen in other groups of patients. However, in TS patients no detrimental effects of THC on neuropsychological tests were observed. Since it has been suggested that changes in the cannabinoid receptor system might be involved in the pathophysiology of TS, it can be speculated that the effect of exogenous cannabinoids on the endocannabinoid $CB_1$ receptor system might be different compared to healthy people. Such a hypothesis might explain why cannabinoids may induce different effects in different groups of patients.

In many cases, TS is associated with comorbid ADHD. The two main behavioural features of this disorder are impaired attention and an impulsive–hyperactive behavioural trait. From case reports it is suggested that impaired attention in TS patients may improve after smoking marijuana (Sandyk and Awerbuch 1988; Müller-Vahl et al. 1998) or the intake of oral THC (Müller-Vahl et al. 1999, 2003a, b). These clinical observations are in line with results from an animal model of ADHD (spontaneously hypertensive rat) suggesting that enhanced impulsivity is associated with a reduced cortical density of cannabinoid $CB_1$ receptors. In these rats impulsivity could be normalized with acute administration of a cannabinoid receptor agonist (WIN55212-2) (Adriani et al. 2003). In addition, there is a single uncontrolled case study available reporting a 28-year-old male suffering from ADHD who demonstrated a significant improvement of his driving-related performance after the oral intake of THC (Strohbeck-Kühner et al. 2007). The authors, therefore concluded that "... in persons with ADHD THC may have atypical and even performance-enhancing effects".

To date it is unknown whether herbal cannabis, cannabis extracts, other cannabinoid receptor agonists that bind more selectively to the central cannabinoid $CB_1$ receptor, or agents that interfere with the inactivation of endocannabinoids by inhibiting the uptake or the degradation might be superior to pure THC in the treatment of tics. There is some evidence that THC might augment the anti-tic effect of neuroleptic drugs. Further studies would be desirable investigating the

effect of different drugs that interact with the endocannabinoid receptor system on different clinical features in patients suffering from TS.

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