Δ^9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: A 6-Week Randomized Trial

Kirsten R. Müller-Vahl, M.D.; Udo Schneider, M.D.; Heidrun Prevedel; Karen Theloe; Hans Kolbe, M.D.; Thomas Daldrup, M.D.; and Hinderk M. Emrich, M.D.

Background: Preliminary studies suggested that delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient of *Cannabis sativa* L., might be effective in the treatment of Tourette syndrome (TS). This study was performed to investigate for the first time under controlled conditions, over a longer-term treatment period, whether THC is effective and safe in reducing tics in TS.

Method: In this randomized, double-blind, placebo-controlled study, 24 patients with TS, according to DSM-III-R criteria, were treated over a 6-week period with up to 10 mg/day of THC. Tics were rated at 6 visits (visit 1, baseline; visits 2–4, during treatment period; visits 5–6, after withdrawal of medication) using the Tourette Syndrome Clinical Global Impressions scale (TS-CGI), the Shapiro Tourette-Syndrome Severity Scale (STSSS), the Yale Global Tic Severity Scale (YGTSS), the self-rated Tourette Syndrome Symptom List (TSSL), and a videotape-based rating scale.

Results: Seven patients dropped out of the study or had to be excluded, but only 1 due to side effects. Using the TS-CGI, STSSS, YGTSS, and video rating scale, we found a significant difference ($p < .05$) or a trend toward a significant difference ($p < .10$) between THC and placebo groups at visits 2, 3, and/or 4. Using the TSSL at 10 treatment days (between days 16 and 41) there was a significant difference ($p < .05$) between both groups. ANOVA as well demonstrated a significant difference ($p = .037$). No serious adverse effects occurred.

Conclusion: Our results provide more evidence that THC is effective and safe in the treatment of tics. It, therefore, can be hypothesized that the central cannabinoid receptor system might play a role in TS pathology.

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Received Feb. 25, 2002; accepted July 11, 2002. *From the Department of Clinical Psychiatry and Psychotherapy (Drs. Müller-Vahl, Schneider, and Emrich; and Mss. Prevedel and Theloe) and the Department of Neurology, Medical School of Hannover, Hannover, Germany (Dr. Kolbe); and the Institute of Legal Medicine, Heinrich Heine University, Düsseldorf, Germany (Dr. Daldrup).*

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Corresponding author and reprints: Kirsten R. Müller-Vahl, M.D., Department of Clinical Psychiatry and Psychotherapy, Medical School Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany (e-mail: mueller-vahl.kirsten@mh-hannover.de).

Gilles de la Tourette syndrome (TS) is characterized by multiple waxing and waning motor and 1 or more vocal tics. In many cases, it is associated with behavioral problems or psychopathologies. There is evidence that frontal-subcortical pathways are pathophysiologically involved. Although postmortem and functional imaging studies have suggested that dopamine might be involved in the pathobiology, many other neurotransmitters have been implicated as malfunctioning in TS. Presently, dopamine D_2 receptor antagonists (neuroleptics) are the most effective drugs for the treatment of tics. However, neuroleptics are not effective in all patients and, in many cases, are not well tolerated. Therefore, there is expanding interest in new therapeutic strategies.[1,2]

In 1988[3] and 1993,[4] anecdotal reports suggested that marijuana smoking improves tics and associated behavioral disorders in TS. These initial reports were supported by a retrospective survey using a standardized interview in a larger group of patients ($N = 64$).[5] Of 17 patients reporting prior use of marijuana, 14 (82%) experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and obsessive-compulsive behavior.

However, in Germany, use of marijuana is illegal, and cannabis herb is not licensed for clinical use. Therefore, we decided to use delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient of *Cannabis sativa* L., for further clinical trials. In an open, uncontrolled pilot study we treated 1 patient once with 10 mg of THC. This

treatment resulted in a tic reduction of about 80% lasting for 7 hours without causing any side effects.[6] These initial results were confirmed by a randomized, double-blind, placebo-controlled, crossover, single-dose trial of THC in 12 adult TS patients.[7,8] Self- and examiner rating scales demonstrated a significant improvement of motor and vocal tics and obsessive-compulsive behavior after treatment with THC compared with placebo. Five patients experienced transient, mild side effects.[8] Measuring cognitive functions, neuropsychological tests showed no significant differences after treatment with THC compared with placebo treatment.[7]

In this randomized, double-blind, placebo-controlled study in 24 adult TS patients, we examined whether oral treatment with THC is effective and safe in reducing tics over a period of 6 weeks.

METHOD

Patients

In this study, 24 adult patients (19 men, 5 women; mean ± SD age = 33 ± 11 years; range, 18–68 years) with TS according to DSM-III-R criteria were included. In all patients, diagnosis of TS was confirmed by one of the authors (K.R.M-V.). Fifteen patients were unmedicated for at least 6 months prior to the study, and 9 were taking medication for the treatment of TS (neuroleptics, N = 4; selective serotonin reuptake inhibitors [SSRIs], N = 2; and a combination of neuroleptics plus an SSRI and/or clonazepam, N = 3). Medication was stable for at least 1 year before entering the study. Patients were instructed not to change their medication during the course of the study. Those patients who had significant concomitant illnesses or a history of psychosis and schizophrenia, were pregnant, or were breast-feeding were excluded.

Seventeen patients reported that they had never used marijuana before. Four patients reported that they used marijuana occasionally (defined as 1–4 times monthly) and 3 were regular users (defined as 2 times or more weekly) during the last year. All patients were asked to stop using marijuana at least 6 weeks before entering the study. To exclude use of cannabis during the last 6 weeks before entering the study, in all patients, qualitative urine and quantitative serum tests of THC and its metabolites were done at the baseline visit.

This study was approved by the local ethics committee, the German Federal Institute for Drugs and Medical Devices (Federal Opium Agency), and the district authority. For all patients, an insurance policy was taken out. After complete description of the study to the subjects, written informed consent was obtained.

Treatment

The study was conducted as a prospective, randomized, double-blind, placebo-controlled trial. Patients were assigned randomly to receive THC (2.5- and 5.0-mg gelatin capsules; N = 12) or a placebo (N = 12) identical in taste and appearance. Patients assigned to the placebo group received placebo throughout the study. Randomization was done by a psychiatrist who was not involved in the study and kept the codes until completion of the study. None of the investigators or patients had access to the randomization codes during the study.

Patients were treated over a period of 6 weeks. The dosage was titrated to the target dosage of 10.0 mg THC. Starting at 2.5 mg/day, the dose was increased by increments of 2.5 mg/day every 4 days. The same dosing schedule was used to reduce medication at the end of the treatment period. If a subject could not tolerate the maximum dose, an adjustment could be made by decreasing study medication up to 5.0 mg until a tolerated dose was achieved. Patients were instructed to take medication once a day in the morning with breakfast.

The study consisted of 6 visits: visit 1 = baseline (1 or 2 days before treatment period was started), visit 2 = treatment day 9 (third day at dose of 7.5 mg to decide whether to increase to 10.0 mg), visit 3 = treatment days 20 to 22 (during maximum dose), visit 4 = days 30 to 31 (last day at maximum dose of 10.0 mg before dose reduction was started), visit 5 = day +1 or +2 (first or second day after study medication was stopped), and visit 6 = 5 to 6 weeks after study medication withdrawal. To avoid misuse, study medication was given to the patients in portions at visits 1, 2, 3, and 4.

At each visit tic severity was measured using different examiner rating scales: the Tourette's Syndrome Clinical Global Impressions scale (TS-CGI),[9] a 7-point ordinal scale ranging from "normal" to "extremely severe" based on all available information concerning the impact of TS symptoms on daily functioning; the Shapiro Tourette-Syndrome Severity Scale (STSSS),[10] a 5-item score that provides an overall index of tic severity; and the Yale Global Tic Severity Scale (YGTSS),[11] consisting of ratings for motor and vocal tics concerning number, frequency, intensity, complexity, and interference, plus an overall TS impairment rating. In addition, a videotape-based rating scale was performed.[12] This 12-minute film protocol includes near and far body views rating 5 domains: number of body areas involved, motor tic (MT) and phonic tic (PT) intensity, and frequency of MT and PT. All examiner ratings were done under blind conditions by one of the authors who is experienced in TS and tic rating (K.R.M-V.).

In addition, patients rated severity of motor and vocal tics on a self rating scale according to the Tourette Syndrome Symptom List (TSSL)[9]. Furthermore, patients were asked to rate severity of "premonitory urges." At the baseline visit, self rating according to the TSSL was explained and practiced. Once before and daily during the treatment period (days 1–42), TSSL was performed at

home. After medication was stopped, self rating was continued once a week until visit 6.

At each visit, blood pressure, pulse, and blood samples for routine laboratory studies were taken. Furthermore, blood samples were used to measure plasma concentrations of THC and its metabolites, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-Δ^9-tetrahydrocannabinol–9-carboxylic-acid (THC-COOH). At visits 1, 3, 5, and 6, urine tests of THC and its metabolites were performed to exclude additional cannabis use and to control compliance.

The primary outcome measures were tic scores according to the TS-CGI, STSSS, YGTSS, video rating scale, and TSSL.

Statistical Analysis

Data were analyzed using SPSS PC version 10.0 for Windows (SPSS, Inc., Chicago, Ill.). Analyses assessing rates of change involved examinations of change scores (difference between scores at baseline visit 1 and visits 2–6). The significance of differences in THC and placebo group in tic scores at different examination days was assessed using Mann-Whitney U test. Differences were considered significant if the probability of error was $p < .05$. In addition, for the multiple comparisons (TS-CGI, STSSS, YGTSS, and video ratings) the unadjusted p value was compared with the Bonferroni adjusted α of 0.01 ($0.05 \div 5$).

Furthermore, we performed repeated-measures analysis of variance (ANOVA) to assess differences in tic scores during the treatment period (visits 2, 3, 4) between both groups. The level of significance was set at the 5% limit.

Analyses included data only from patients who completed the study and were not excluded for any reason.

Influences on tic scores by other parameters like patients' age and sex, co-medication, and prior use of cannabis were tested using a stepwise forward multiple regression analysis. A value of $p < .05$ was used to determine statistical significance.

RESULTS

Four patients dropped out (THC group, N = 3; placebo group, N = 1). One patient in the THC group stopped medication at day 4 (first day at dose of 5.0 mg) due to side effects like anxiety and restlessness. Two patients dropped out due to noncompliance, and in 1 patient, repeated qualitative THC urine tests over a 4-week period were positive although the patient asserted that he had stopped using marijuana weeks before. Three further patients had to be excluded after the study ended. At the end of the study, 1 patient reported that he had started medication with pimozide during the course of the study. One patient reduced study medication below the limit of 5.0 mg to the initial dose of 2.5 mg. Independent of the dosage, he reported side effects like dizziness, tiredness, and muzziness. One patient temporarily stopped THC medication, indicated by negative concentrations of THC and its metabolites in urine analysis.

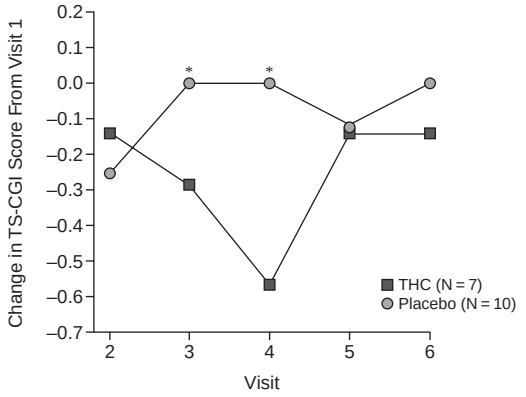
Therefore, further analyses were performed including a total of 17 patients: 7 in the THC group (6 men, 1 woman; mean ± SD age = 35 ± 15 years) and 10 in the placebo group (7 men, 3 women; mean age = 35 ± 9 years). Both groups were similar in terms of use of other medications (neuroleptics, N = 2; SSRI/clonazepam, N = 1). At the baseline visit, before study medication was started, tic severity (mean ± SD) according to the TS-CGI was 2.57 ± 0.79 in the THC group and 2.40 ± 0.52 in the placebo group. Tic scores obtained from the STSSS were: THC group = 3.29 ± 1.38, placebo group = 3.40 ± 1.26; scores from the YGTSS were: THC group = 44.71 ± 19.28, placebo group = 38.60 ± 18.56. Tic scores obtained from the video rating scale were: THC group body areas involved = 4.71 ± 1.60, MT intensity = 3.29 ± 0.95, PT intensity = 1.43 ± 1.40, MT frequency = 19.43 ± 10.31, PT frequency = 5.43 ± 8.40; placebo group body areas involved = 4.10 ± 2.13, MT intensity = 2.70 ± 1.25, PT intensity = 1.60 ± 1.35, MT frequency = 13.60 ± 12.06, PT frequency = 2.00 ± 1.49. Tic scores obtained from the TSSL were: THC group = 28.29 ± 14.47, placebo group = 23.50 ± 12.81.

Using the TS-CGI at visits 3 ($p = .05$) and 4 ($p = .008$), we found a statistically significant difference between THC and placebo groups. ANOVA demonstrated a trend toward a significant difference between both groups ($p = .079$) (Figure 1). Using the STSSS, we found a significant difference between both groups at visit 4 ($p = .033$) and a trend toward a significant difference at visit 3 ($p = .067$) (Figure 2). The YGTSS demonstrated a trend toward a significant difference between THC and placebo groups at visit 4 ($p = .061$). Repeated-measures ANOVA, as well, showed a trend toward a significant difference ($p = .077$) (Figure 3). When using the subscore "motor global scale" of the YGTSS we found a significant difference at visit 4 ($p = .040$).

Using the TSSL at 10 different treatment days (days 16, 19, 29, 31, 32, 33, 35, 36, 37, and 41), we found a significant difference ($p < .05$) between placebo and THC group, and, in addition, at a further 13 days (days 15, 17, 18, 20, 23, 24, 26, 27, 28, 30, 34, 38, and 42), there was a trend toward a significant difference ($p < .10$). ANOVA demonstrated a significant difference between both groups ($p = .037$) (Figure 4). Although rating of premonitory urges did not show significant differences ($p = .131$), graphically, a difference is obvious, demonstrating a reduced feeling of premonitory urges in the THC but not the placebo group (Figure 5).

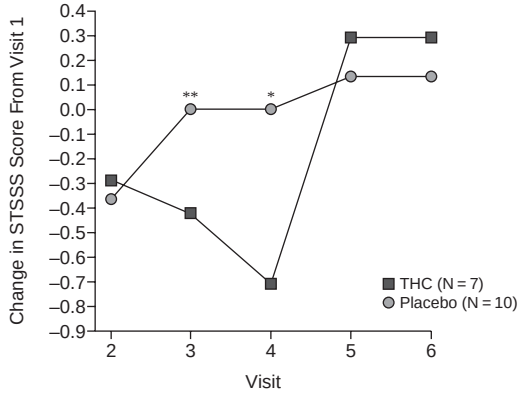
The videotape-based rating scale demonstrated a trend toward a significant group difference for the score "motor tic intensity" at visit 2 ($p = .083$) and a significant differ-

Figure 1. Changes in TS-CGI Scores From Visit 1 to Visits 2–6 in Patients Treated With THC Compared With Placebo[a]



[a]Visit 1 = baseline, visit 2 = treatment day 9, visit 3 = treatment days 20–22, visit 4 = treatment days 30–31, visit 5 = 1 day after medication stopped, visit 6 = 5 weeks after medication stopped. ANOVA: p = .079.
*p ≤ .05.
Abbreviations: THC = tetrahydrocannabinol, TS-CGI = Tourette's Syndrome Clinical Global Impressions scale.

Figure 2. Changes in STSSS Scores From Visit 1 to Visits 2–6 in Patients Treated With THC Compared With Placebo[a]

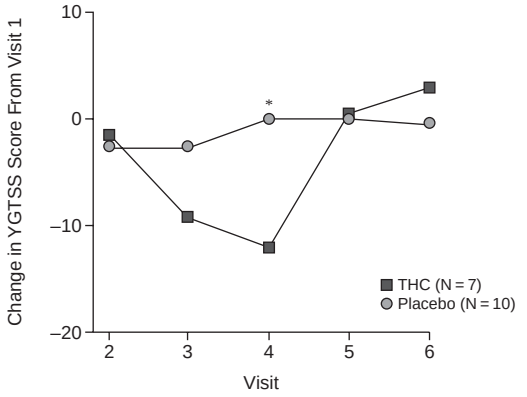


[a]Visit 1 = baseline, visit 2 = treatment day 9, visit 3 = treatment days 20–22, visit 4 = treatment days 30–31, visit 5 = 1 day after medication stopped, visit 6 = 5 weeks after medication stopped.
*p < .05.
**p < .10.
Abbreviations: STSSS = Shapiro Tourette-Syndrome Severity Scale, THC = tetrahydrocannabinol.

ence at visit 4 (p = .030). The score "frequency of motor tics" demonstrated a trend toward a significant difference at visit 4 (p = .078). ANOVA demonstrated a trend toward a significant difference for the score "motor tic intensity" (p = .055). Comparing our results with the Bonferroni adjusted α, we found a significant group difference using the TS-CGI at visit 4 (p = .008).

No serious adverse reactions occurred. Blood pressure and pulse did not change. Five patients in the THC group

Figure 3. Changes in YGTSS Score From Visit 1 to Visits 2–6 in Patients Treated With THC Compared With Placebo[a]



[a]Visit 1 = baseline, visit 2 = treatment day 9, visit 3 = treatment days 20–22, visit 4 = treatment days 30–31, visit 5 = 1 day after medication stopped, visit 6 = 5 weeks after medication stopped. ANOVA: p = .077.
*p < .10.
Abbreviations: THC = tetrahydrocannabinol, YGTSS = Yale Global Tic Severity Scale.

reported mild side effects like tiredness, dry mouth, dizziness, and muzziness. However, none of these patients reduced study medication below 7.5 mg due to these side effects, because none felt seriously impaired. Three patients in the placebo group reported adverse effects like tiredness, dizziness, anxiety, and depression.

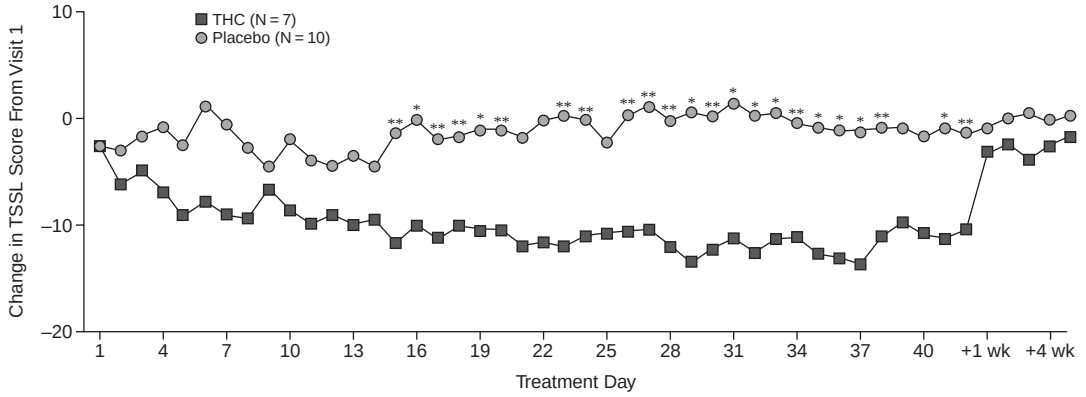
Urine and serum analyses for THC and its metabolites demonstrated that no patient in the placebo group used marijuana additionally. A stepwise forward multiple regression analysis demonstrated no influence on tic scores by patients' age and sex, comedication, or prior use of cannabis.

DISCUSSION

Our results confirm preliminary data suggesting that THC reduces tics in patients suffering from TS. Global as well as detailed examiner ratings, a self rating scale, and a videotape-based rating scale demonstrated a significant or a trend toward a significant reduction in tics during 6 weeks of treatment with THC.

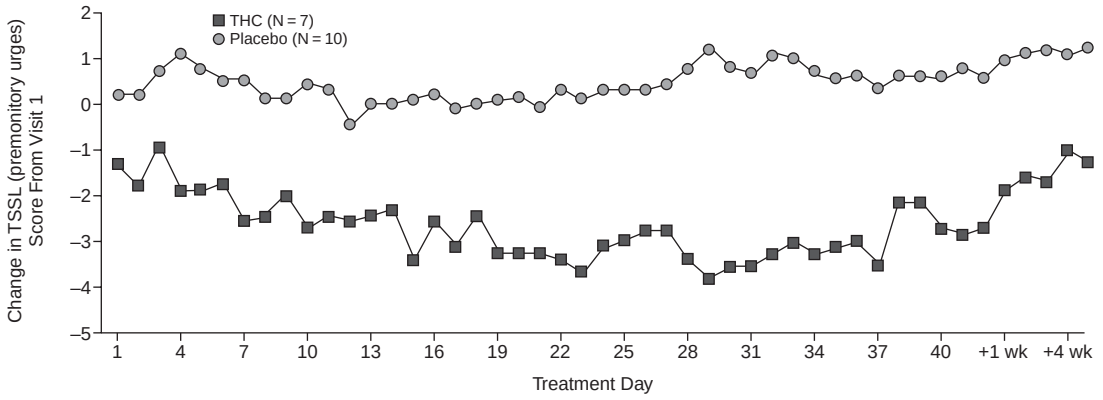
A total of 7 patients dropped out of the study or had to be excluded afterwards. However, only 1 patient dropped out due to significant side effects like anxiety and restlessness. One patient reduced the THC dose to 2.5 mg due to adverse effects like dizziness and tiredness, which were reported independently of the dosage, while blood pressure and pulse remained unchanged. In this 68-year-old man, serum concentrations of THC, 11-OH-THC, and THC-COOH were higher compared to most other patients, suggesting a reduced metabolism rate. Thus, one might speculate that THC will be less tolerated at an advanced age.

Figure 4. Changes in TSSL (tic rating) Scores From Visit 1 (baseline) to Treatment Days 1–42 and 1–5 Weeks After Stopping Treatment With THC or Placebo[a]



[a]ANOVA: p = .037.
*p < .05.
**p < .10.
Abbreviations: THC = tetrahydrocannabinol, TSSL = Tourette Syndrome Symptom List.

Figure 5. Changes in TSSL (premonitory urges rating) Scores From Visit 1 (baseline) to Treatment Days 1–42 and 1–5 Weeks After Stopping Treatment With THC or Placebo



Abbreviations: THC = tetrahydrocannabinol, TSSL = Tourette Syndrome Symptom List.

Most rating scales used demonstrated a marked tic reduction at visit 3 and even further improvement at visit 4. This indicates that THC reaches effectiveness after a treatment period of about 3 weeks, which persists or even increases after more than 4 weeks. It can be speculated that changes between visits 3 and 4 might be due to a delayed pharmacologic effect, because THC is a lipophilic compound, accumulates in deeper compartments, and is redistributed from fatty tissue. An habituation with decreased effect on tics was not seen within the 6-week treatment period. That no differences between both groups were found after medication was stopped, corroborates that differences at visits 3 and 4 were caused by THC medication. In addition, that other symptoms often associated with TS such as anxiety, depression, and obsessive-compulsive behavior did not change during treatment (data not shown), further substantiates that tic improvement was not caused by a placebo effect. Our data provide no evidence that results were influenced by other parameters like patients' age, sex, prior use of marijuana, and comedication with other centrally acting drugs.

The major limitation of this study is the relatively small sample group. In addition, when comparing our results with the Bonferroni adjusted α, we found a significant group difference only when using the TS-CGI at visit 4. However, from our data, there is no evidence that this "global improvement" is caused by other factors than tic improvement. Due to ethical reasons, we included only adult patients in this study. Therefore, at present, no statement can be made whether in children THC might be effective and safe as well.

Our results provide evidence that in some patients, THC significantly reduces tics, while other patients do not benefit from this medication. So far, it is unclear how this subgroup is clinically characterized. Some patients reported that THC is superior to different neuroleptics such as pimozide, because it is more effective, causes fewer or no side effects, and, in addition, reduces associated behavioral problems such as obsessive-compulsive behavior, self-injurious behavior, and depression. One patient, therefore, decided to use illegal marijuana regularly instead of taking neuroleptics.

The neurobiology of TS is still unknown. Most neurotransmitters involved in frontal-subcortical circuits have been suggested to be involved in the pathobiology of TS.[13] Multiple clinical and laboratory studies favor an involvement of dopamine in TS. To date, however, 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 may be secondary to these defects.[13]

Only some years ago, a brain cannabinoid (CB1) receptor[14] and 2 endogenous ligands (endocannabinoids: anandamide and 2-arachidonylglycerol [2-AG]) were identified.[15,16] The highest densities of CB1 receptors in humans were found in the basal ganglia, cerebellum, hippocampus, and cerebral cortex.[17,18] Within the basal ganglia, CB1 receptors are particularly prominent in the globus pallidus and substantia nigra pars reticulata—the indirect and direct output pathways.[17]

There is substantial evidence for a close functional relationship between endocannabinoids and dopamine.[19] Dopamine acting at D_2-like receptors stimulates anandamide release in the dorsal striatum, suggesting that the endocannabinoid system participates in dopaminergic regulation of striatal function.[20] In the reserpine-treated rat, a model for Parkinson's disease, a 7-fold increase in the levels of 2-AG was observed in the globus pallidus. Administration of a dopamine D_2 receptor agonist increased locomotion accompanied by reduced 2-AG and anandamide levels in the globus pallidus.[19] Therefore, a participation of the endocannabinoid system in neuropsychiatric disorders that involve dysregulated dopamine neurotransmission—as in Parkinson's disease and as assumed in TS—has been suggested.[20]

There is much evidence that endocannabinoids act as neuromodulators by modulating the biosynthesis, release, and action of several classical neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate.[21–24] Animal studies have demonstrated that cannabimimetic agents decrease spontaneous activity,[25] cause catalepsy,[25] potentiate reserpine-induced hypokinesia,[26] attenuate spontaneous and induce stereotypic behaviors,[27] reduce amphetamine-induced hyperactivity,[28] and exert antidystonic effects in mutant dystonic hamsters.[29] In CB1 receptor knockout mice, reduced locomotor activity and increased catalepsy were observed.[30]

In humans, beneficial effects of different cannabinoids have been reported in patients suffering from dystonia, levodopa-induced dyskinesias in Parkinson's disease, and tremor in multiple sclerosis (see Müller-Vahl et al.[31] for review). In Huntington's disease a massive loss of cannabinoid receptor binding has been found in all regions of the basal ganglia in advance of other receptor changes, suggesting a causative role of the cannabinoid system in the progression of neurodegeneration. Clinical results, however, are contradictory (see Müller-Vahl et al.[31] for review).

Taking all these data together, there is substantial evidence that cannabinoids regulate motor activity in the basal ganglia.[17,18] From our results, it is suggested that THC reduces tics in patients suffering from TS. One might speculate that these beneficial effects are due to a specific action on CB1 receptors. Therefore, it can be hypothesized that the endogenous cannabinoid system might be involved in TS pathology. Interestingly, neuroanatomical structures that are suggested to be involved in TS pathology[32] are found to be heavily associated with the CB1 receptor system.[17,18] Considering an involvement of the dopamine system in TS pathophysiology, it can be speculated that tic improvement by THC might be caused by an interaction between cannabinoid and dopamine mechanisms. However, it can also be hypothesized that cannabinoids might influence motor control by modulating other transmitter systems like GABA and glutamate. By this means, it is conceivable that cannabinoids may reduce cortical input to the striatum or increase intrastriatal inhibition and, therefore, reduce tics in TS.

In conclusion, this is the first study suggesting that in TS THC is effective and safe in the treatment of tics over a longer-term treatment period. Our data further support the hypothesis of a causative role for endocannabinoids in basal ganglia–related movement disorders. Further clinical studies are needed to confirm these data. Future investigations should also attend to the question of whether THC, a combination of different cannabinoids, or cannabis herb is most effective and has the fewest side effects.

Drug names: clonazepam (Klonopin and others), pimozide (Orap), reserpine (Serpalan and others).

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