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Treatment of Tourette's Syndrome with Δ^9-Tetrahydrocannabinol (THC): A Randomized Crossover Trial

Anecdotal reports in Tourette's syndrome (TS) have suggested that marijuana (cannabis sativa) and delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana, reduce tics and associated behavioral disorders. We performed a randomized double-blind placebo-controlled crossover single-dose trial of Δ^9-THC (5.0, 7.5 or 10.0 mg) in 12 adult TS patients. Tic severity was assessed using a self-rating scale (Tourette's syndrome Symptom List, TSSL) and examiner ratings (Shapiro Tourette's syndrome Severity Scale, Yale Global Tic Severity Scale, Tourette's syndrome Global Scale). Using the TSSL, patients also rated the severity of associated behavioral disorders. Clinical changes were correlated to maximum plasma levels of THC and its metabolites 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC) and 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH). Using the TSSL, there was a significant improvement of tics (p=0.015) and obsessive-compulsive behavior (OCB) (p = 0.041) after treatment with Δ^9-THC compared to placebo. Examiner ratings demonstrated a significant difference for the subscore "complex motor tics" (p = 0.015) and a trend towards a significant improvement for the subscores "motor tics" (p = 0.065), "simple motor tics" (p = 0.093), and "vocal tics" (p = 0.093). No serious adverse reactions occurred. Five patients experienced mild, transient side effects. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration. Results obtained from this pilot study suggest that a single-dose treatment with Δ^9-THC is effective and safe in treating tics and OCB in TS. It can be speculated that clinical effects may be caused by 11-OH-THC. A more long-term study is required to confirm these results.

Introduction

Gilles de la Tourette's syndrome (Tourette's syndrome, TS) is a complex neurobehavioral disorder characterized by multiple motor tics and one or more vocal tics throughout a period of more than a year with an onset before the age of 18. Basal ganglia circuits projecting to frontal and limbic areas and the dopaminergic system seem to be pathophysiologically involved. Presently, dopamine antagonists are the most effective drugs for the treatment of tics [18, 22].

Anecdotal reports [5, 24] and a retrospective survey using a standardized interview [19] suggested a beneficial influence of smoking marijuana on tics and associated behavioral disorders in TS. Therefore, we treated one patient once in an open uncontrolled pilot study with 10 mg delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana. Using the Tourette's syndrome Global Scale [12], the total tic severity score was 41 before treatment, and was reduced to 7 two hours after treatment. The patient noted a tic improvement of 70% and felt an improvement in attention, impulse control, obsessive-compulsive behavior (OCB), and premonitory feeling without having any adverse reactions [20].

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This pilot study was carried out to confirm these preliminary results suggesting that Δ^9-THC might be successful in the therapy of TS. Therefore, we performed a randomized double-blind placebo-controlled crossover trial of Δ^9-THC in 12 adult patients suffering from TS.

Method

Patients

In this study, 12 adult patients (11 men, 1 woman, mean age = 34 ± 13 (SD) years, ranging 18 – 66 years) with TS according to DSM-III R criteria were included. Patients were recruited from our movement disorder clinic. Tic severity was measured according to the Shapiro Tourette's syndrome Severity Scale (STSS) [26], the Tourette's syndrome Global Scale (TSGS) [12], and the Yale Global Tic Severity Scale (YGTSS) [3] by one of the authors, who is very experienced in Tourette's syndrome and tic rating (KR MV). Before entering the study, tic severity (mean (± SD)/median) was 3.6 (± 1.2)/4 (STSS), 22.6 (± 22.0)/22 (TSGS), and 45.8 (± 17.3)/46 (YGTSS). Seven patients were unmedicated for at least two years and five were taking medication for the treatment of TS (two patients on pimozide (no. 1 and 4), one on tiapride (no. 11), one on diazepam (no. 3), and one on pimozide, clonazepam and fluoxetine (no. 9)). Medication was stable for at least two months before entering the study and during the course of the study. Patients who had significant concomitant illnesses, history of psychosis and schizophrenia, or were pregnant were excluded. In all patients, routine blood and urine tests and MRI were performed to exclude other diseases.

Seven patients reported prior use of marijuana: three (no. 2, 7, 10) had used marijuana only once or occasionally years ago, and four (no. 1, 5, 8, 12) were regular users but were asked to stop using marijuana at least one week before entering the study. Five patients (no. 3, 4, 6, 9, 11) had never used marijuana before.

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

Design

The study was conducted as a double-blind placebo-controlled crossover trial. Patients were randomly assigned a single-dose of oral Δ^9-THC (gelatin capsules at 2.5 and 5.0 mg) first or a single-dose of identical placebo first on two days separated by a 4-week washout phase before they were crossed over to receive the other treatment. 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 received different doses of Δ^9-THC according to their body weight, sex, age and prior use of marijuana: females without prior use of marijuana and body weight ≤ 60 kg or age ≥ 50 years received 5.0 mg, otherwise 7.5 mg; men without prior use of marijuana and body weight ≤ 70 kg or age ≥ 50 years received 5.0 mg; men who used marijuana regularly, body weight > 70 kg and age < 50 years received 10 mg, all other men received 7.5 mg. Thus, four patients received 5.0 mg Δ^9-THC (no. 4, 6, 7, 10), six 7.5 mg (no. 2, 3, 5, 9, 11, 12) and two 10.0 mg (no. 1, 8).

The same experimental plan was applied on both days. Before medication, patients received a standardized breakfast to guarantee comparable enteral absorption of Δ^9-THC. Blood pressure and pulse were taken at baseline and every hour until 5 hours after medication. 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), blood samples were taken before and 30, 90, 150, 240, 360 and 1440 min (= 24 hours) after medication. Patients remained in hospital for one night.

Each patient rated tic severity on a self-rating scale according to the Tourette's syndrome Symptom List (TSSL) [12] before and 3 – 4 hours after treatment. Furthermore, tic severity was assessed before and 3 – 4 hours after treatment using different examiner ratings (STSS, YGTSS, and TSGS) by one of the authors (KR MV) in an interview session. Patients were unaware of the tic-rating. We analyzed not only total tic scores but also – dependent on the particular scale – subscores for the categories simple motor tics (SMT), complex motor tics (CMT), motor tics (MT = SMT + CMT), simple vocal tics (SVT), complex vocal tics (CVT), and vocal tics (VT = SVT + CVT). Using the TSSL, patients were additionally asked to rate severity of impulse control, OCB, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and premonitory experiences (PE) prior to the occurrence of tics before and after treatment (0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). The symptom "OCB" was subdivided into obsessions and compulsions such as checking, ordering, doing things just right, counting, rituals, washing, and doing things an exact number of times.

At the end of each examination day patients were asked to rate the global change (0, ±10%, ±20% etc. – ± 100%) and document adverse reactions. At the end of the second day, they were also asked which examination day they assessed overall as more positive (including global change and side effects; 0, 10%, 20% etc. – 100%).

The primary outcome measures were: tic scores according to the TSSL, STSS, YGTSS, and TSGS, scores of associated behavioral disorders measured by the TSSL, global change and plasma concentrations of THC, 11-OH-THC and THC-COOH.

Statistical analysis

To analyze results of self- and examiner's ratings, the differences were calculated between rating scores obtained before and after treatment either with Δ^9-THC or placebo. For all ratings, treatment, carry-over and phase effect were calculated using the method described by Hill and Armitage [7]. The significance of differences in self- and examiner's ratings after treatment with Δ^9-THC compared to placebo was assessed using the Mann-Whitney test. Differences were considered significant where the probability of error, p, was less than 0.05 and also where carry-over and phase effect were not significant. Correlations between changes in clinical rating scores and maximum plasma concentrations of THC, 11-OH-THC, and THC-COOH were tested using simple linear regression analysis. A value of $p < 0.05$ was used to determine statistical significance. All tests were used in an ex-

ploratory manner. There was no correction for multiplicity of testing. SPSS PC version 7.0 for Windows was used for data analysis.

Results

Six patients received Δ^9-THC followed by placebo, and another six patients received placebo followed by Δ^9 -THC. None of the patients dropped out.

Using the TSSL, there was a significant improvement of tics after treatment with Δ^9-THC compared with placebo ($p = 0.015$). Analyzing subscores of the TSSL, there was a significant improvement of SMT ($p = 0.026$), CMT ($p = 0.015$), MT ($p = 0.026$), and CVT ($p = 0.041$) (Table **1**).

Table 1 Changes in global tic scores and subscores after treatment with Δ^9-THC and placebo are summarized. Medians and mean scores ± SD of 12 patients are given. t = treatment effect

Tic score	*Δ^9-THC*			*Placebo*			*t*
	Median	*Mean*	*± SD*	*Median*	*Mean*	*± SD*	*p*
STSS	−1.0	−1.00	1.00	0	−0.33	0.65	0.132
TSGS	−7.5	−10.00	8.61	0	−3.50	7.53	0.132
− SMT	−3.5	−4.25	3.91	0	−2.25	4.18	0.310
− CMT	−1.0	−2.08	2.94	0	0	0	0.015
− MT	−5.0	−6.25	5.19	0	−2.25	4.18	0.065
− SVT	−1.5	−2.50	2.43	0	−1.33	4.62	0.093
− CVT	0	−1.67	2.08	0	−0.08	0.29	0.132
− VT	−2.5	−3.67	3.89	0	−1.42	4.60	0.093
YGTSS	−6.0	−10.25	12.95	0	−3.75	9.12	0.132
− MT	−3.5	−3.42	3.85	0	−1.50	2.75	0.180
− VT	−2.0	−2.42	2.78	0	−0.58	1.16	0.093
TSSL	−12.5	−14.00	10.97	−2.5	−4.92	6.69	0.015
− SMT	−3.0	−5.67	5.69	−0.5	−2.00	3.16	0.026
− CMT	−3.0	−3.58	2.84	−0.5	−1.25	1.66	0.015
− MT	−6.5	−8.50	6.57	−1.5	−2.75	3.41	0.026
− SVT	−1.5	−3.08	4.01	0	−1.42	3.06	0.180
− CVT	−1.0	−1.58	1.93	0	−0.25	0.62	0.041
− VT	−4.5	−3.83	3.69	0	−1.58	3.03	0.132
− PE	−1.5	−2.17	2.25	0	−0.75	2.38	0.132
− impulsivity	−3.5	−3.33	3.45	−0.5	−1.42	2.11	0.093
− anxiety	0	−0.25	0.45	0	−0.17	0.39	0.589
− depression	−0.5	−0.58	0.67	0	−0.25	0.45	0.310
− ADHD	−0.5	−1.25	2.14	0	−0.25	0.87	0.093
− OCB	−3.5	−4.83	5.59	0	−1.33	2.50	0.041

Using examiner ratings, global tic severity scores demonstrated a much greater reduction after Δ^9-THC treatment compared with placebo, but differences did not reach statistical significance (Table **1**). However, when analyzing subscores, CMT (TSGS) demonstrated a significant improvement ($p = 0.015$) and there was a trend towards a significant difference for the subscores MT (TSGS, $p = 0.065$), SVT (TSGS, $p = 0.093$), and VT (TSGS, $p = 0.093$; YGTSS, $p = 0.093$).

Using the TSSL, there was also a significant improvement in OCB ($p = 0.041$). Other categories of behavioral disorders as well as premonitory experiences demonstrated an improvement after Δ^9-THC treatment, but results did not reach statistical significance (Table **1**).

We analyzed our data once again including only those patients who had received either 7.5 or 10.0 mg Δ^9-THC ($n = 8$). Using the TSSL ($p = 0.036$) and the subscore MT (YGTSS, $p = 0.036$), we found a significant improvement after Δ^9-THC treatment. Using the STSS ($p = 0.071$), the YGTSS ($p = 0.071$) and the subscores CMT (TSGS, $p = 0.071$) and MT (TSGS, $p = 0.071$), there was a trend towards significant improvement.

On the Δ^9-THC treatment day 10 of 12 patients experienced a global improvement (mean of +35% ± 28.0, range, 20–90%). Two patients noted no change (no. 7, 11). In contrast, only three patients (no. 6, 8, 10) reported a global improvement (mean of +7% ± 13.7, range, 10–40%) on the placebo day, and nine felt no change. At the end of the study, nine patients (no. 1, 2, 3, 4, 5, 8, 10, 11, 12) assessed the Δ^9-THC treatment day overall more positively than the placebo day (+43.3% ± 31.1, range, 10–100%). Three patients (no. 6, 7, 9) experienced the placebo day more positively (+21.7% ± 12.6, range, 10–35%).

No serious adverse reactions occurred. Blood pressure and pulse did not change significantly. After treatment with Δ^9-THC, seven patients (no. 5, 7, 8, 9, 10, 11, 12) reported no side effects. Five patients (no. 1, 2, 3, 4, 6) experienced mild transient adverse reactions lasting between 1 and 6 hours (Table **2**). Two patients (no. 10, 11) reported mild side effects (headache) after placebo treatment.

Table 2 Adverse events after Δ^9-THC treatment in 5 patients are summarized. In addition, the particular dosages of Δ^9-THC are given and whether patients had prior use of marijuana.

Patient no	*Dosage [mg Δ^9-THC]*	*Adverse events*	*Prior use of cannabis sativa*
1	10	headache, nausea	occasionally (for the last time 2 weeks ago)
2	7.5	dizziness, hot flush	occasionally (for the last time 3 years ago)
3	7.5	dizziness, anxiety, tremble, sensitivity to noise and light, dry mouth, ataxia	No
4	5	tiredness, poor powers of concentration	No
6	5	tiredness, cheerfulness	No

Maximum THC plasma levels were measured 30 ($n = 2$), 90 ($n = 4$) and 150 min ($n = 5$) after medication (in one patient, no level could be measured), of 11-OH-THC after 90 (n=5), 150 ($n = 6$) and 240 min ($n = 1$), and of THC-COOH after 90 ($n = 4$),

150 (n = 5) and 240 min (n = 3). In 3 patients (no. 5, 8, 12) plasma concentrations of THC, 11-OH-THC and THC-COOH were already positive before treatment with Δ^9-THC, indicating that these patients had used marijuana within the last 4 – 6 weeks before entering the study.

Simple linear regression analysis demonstrated a significant correlation between tic improvement (measured by STSS, TSGS, and YGTSS, respectively) and maximum plasma concentration of 11-OH-THC. Furthermore, there was a significant correlation between the oral dose of Δ^9-THC and the maximum plasma level of 11-OH-THC. When only those nine patients exhibiting negative values before entering the study are included, there was also a significant correlation between the oral Δ^9-THC dose and the maximum level of THC-COOH (Table **3**). There was no correlation between plasma concentration of THC and its metabolites and changes in OCB after Δ^9-THC treatment.

Table 3 Correlation between oral dose of THC, maximum plasma concentration of THC and its metabolites 11-OH-THC and THC-COOH and changes in clinical rating scores

	Oral dose of THC	*TSSL*	*STSS*	*TSGS*	*YGTSS*
Oral dose of THC		r = 0.035 (n. s.)	r = 0.364 (n. s.)	r = 0.529 (p = 0.077)	r = 0.279 (n. s.)
THC	r = 0.526 (p = 0.079)	r = 0.203 (n. s.)	r = 0.057 (n. s.)	r = 0.017 (n. s.)	r = 0.114 (n. s.)
THC*	r = 0.476 (n. s.)	r = 0.307 (n. s.)	r = 0.215 (n. s.)	r = 0.523 (n. s.)	r = 0.383 (n. s.)
11-OH-THC	r = 0.691 (p = 0.013)	r = 0.062 (n. s.)	r = 0.754 (p = 0.005)	r = 0.674 (p = 0.016)	r = 0.764 (p = 0.004)
11-OH-THC*	r = 0.866 (p = 0.003)	r = 0.187 (n. s.)	r = 0.780 (p = 0.013)	r = 0.694 (p = 0.038)	r = 0.845 (p = 0.004.)
THC-COOH	r = 0.389 (n. s.)	r = 0.010 (n. s.)	r = 0.045 (n. s.)	r = 0.108 (n. s.)	r = 0.130 (n. s.)
THC-COOH*	r = 0.673 (p = 0.047)	r = 0.273 (n. s.)	r = 0.551 (n. s.)	r = 0.322 (n. s.)	r = 0.448 (n. s.)

* indicates that only patients are included demonstrating negative plasma values before treatment with Δ^9-THC (n = 9).

Discussion

This pilot study is in line with previous results suggesting that cannabis sativa and Δ^9-THC both have a beneficial influence on the symptoms of TS [5,19,20,24]. Our findings demonstrated a significant reduction of motor and vocal tics and OCB using a self-rating scale (TSSL). Using examiner's ratings (STSS, TSGS and YGTSS), there was a significant improvement in the subscore CMT and a trend towards significant improvement in MT, SVT and VT. We believe that the reason that global tic severity scores failed to reach statistical significance when using examiner ratings was that examiner ratings are less sensitive to changes than a self-rating scale [9,10]. A variety of clinical characteristics of TS make objective quantification of "disease severity" difficult, such as heterogeneity and complexity of tics, the waxing and waning course of the disease, and the possibility of voluntarily tic suppression [11]. Even when performed under standardized conditions, examiner ratings always are limited to an isolated and relatively brief time period.

Interpreting our findings, some aspects have to be taken into account. The sample size (n = 12) was relatively small. Nevertheless, 9 of 12 patients assessed that Δ^9-THC treatment was more successful than placebo treatment (mean global improvement: 43 %). We used a crossover design due to the sample size. However, the crossover effect was not significant, indicating that the 4-week wash-out phase had prevented such an influence.

Because there was no previous experience in the therapy of TS with Δ^9-THC, patients were treated only once with a single dose of Δ^9-THC. Thus, it was not possible to administer one exact dosage to each patient. We therefore analyzed our data once again, but excluded those patients who had received a dosage of only 5.0 mg Δ^9-THC (n = 4). Although this sample included only eight patients, the results became more robust suggesting that dosages of 7.5 and 10.0 mg Δ^9-THC, respectively, may be more effective in the therapy than lower doses.

Five patients experienced mild adverse effects. More significant side effects such as headache, nausea, ataxia and anxiety were reported by those patients who had received 7.5 and 10.0 mg Δ^9-THC, respectively. However, only two out of seven patients who had used marijuana before reported side effects, but three out of five patients without prior use. Therefore, it might be speculated that side effects will decrease after more long-term treatment and will occur even less frequently when dosages are administered slowly.

It is well known that after oral administration, Δ^9-THC absorption is slow, erratic and depends on the intake of food [8]. Therefore, we did not only correlate changes in clinical rating scales after Δ^9-THC treatment to the oral dose of THC but also to maximum plasma levels of Δ^9-THC and its metabolites, 11-OH-THC and THC-COOH. In agreement with previous studies, there was no correlation between clinical effects and plasma levels of Δ^9-THC [1,16,17]. However, we found a highly significant correlation between maximum plasma levels of 11-OH-THC and all examiner ratings used, indicating that clinical improvement in TS may be caused by this highly active metabolite. Accordingly, previous studies found high plasma concentrations of 11-OH-THC after oral dosing - in contrast to administration by intravenous and smoking routes [27,28]. Furthermore, it has been suggested that after oral administration 11-OH-THC exerts significant clinical effects on the central nervous system [4,13,14,25].

Since central cannabinoid CB1 receptors have been found to be located with high concentrations in the output nuclei of the basal ganglia, it has been suggested that cannabinoids regulate motor activity [6,15]. There is much evidence that a general role of the endogenous cannabinoid transmission is the manipulation of other transmitter systems, predominantly to limit the extent of glutamate activation and GABA inhibition [2,23]. Furthermore, cannabinoid receptors are co-localized with dopamine receptors, suggesting that cannabinoids influence dopaminergic processes [6,15].

Our results suggest that clinical effects of cannabis sativa and Δ^9-THC in TS are due to a specific action on CB1 receptors, and do

not support the hypothesis that the beneficial effects are due to unspecific mechanisms such as sedation, reduction of anxiety or the fact of using an illegal drug. Furthermore, we hypothesize that the endogenous cannabinoid system might be involved in TS pathology. Interestingly, the neuroanatomical structures that are probably involved in TS pathology are heavily associated with the CB1 receptor system. Considering an involvement of the dopamine system in TS pathophysiology, it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine mechanisms. However, it can also be hypothesized that cannabinoids might influence motor control and behavior by modulating other transmitter systems such as GABA, glutamate, and serotonin.

In conclusion, our findings suggest that a single-dose treatment with Δ^9-THC is effective and safe in the therapy of tics and OCB in TS. However, due to the small sample size and lack of experience in the treatment of TS with Δ^9-THC, this study was conducted as a crossover trial using a single-dose treatment. Therefore, results should be interpreted as preliminary. To confirm these results, a prospective, double-blind, placebo-controlled follow-up study is needed involving a longer term therapy and a larger sample size.

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