

Influence of Treatment of Tourette Syndrome with Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) on Neuropsychological Performance

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Previous studies have suggested that marijuana (cannabis sativa) and delta-9-tetrahydrocannabinol (Δ^9 -THC), the major psychoactive ingredient of marijuana, are effective in the therapy of tics and associated behavioral disorders in Tourette Syndrome (TS). Because there is also evidence that cannabis sativa may cause cognitive impairment in healthy users, we performed a randomized double-blind placebo-controlled crossover trial for Δ^9 -THC in 12 adult TS patients to investigate whether treatment of TS with a single dose of Δ^9 -THC at 5.0 to 10.0 mg causes significant side effects on neuropsychological performance. Using a variety of neuropsychological tests, we found no significant differences after treatment with Δ^9 -THC compared to placebo treatment in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance, or mood. Only when using the Symptom Checklist 90-R (SCL-90-R) did our data provide evidence for a deterioration of obsessive-compulsive behavior (OCB) and a trend towards an increase in phobic anxiety. However, these results should be interpreted with caution as SCL-90-R has known limitations on measuring OCB. We suggest that the increase in phobic anxiety is mainly due to the fact that a single-dose treatment rules out the possibility of administering the dosage slowly. In contrast to results obtained from healthy marijuana users, a single-dose treatment with Δ^9 -THC in patients suffering from TS does not cause cognitive impairment. We therefore suggest that further investigations should concentrate on the effects of a longer-term therapy of TS with Δ^9 -THC.

Introduction

Gilles de la Tourette Syndrome (Tourette syndrome, TS) has been recognized as a neurobehavioral disorder associated with motor and vocal tics and a spectrum of behavioral and cognitive features. Commonly observed behavioral disorders are attention deficit hyperactivity disorder (ADHD), obsessive-compulsive behavior (OCB), self-injurious behavior, affective disorders, anxiety disorders, addiction, learning disabilities, conduct disorder, and sleep disorders [8].

Until today, therapy of TS has remained difficult and, in many patients, unsatisfactory. Neuroleptics are the treatment of choice for the suppression of tics. However, therapy with neuroleptics is limited, as some patients do not benefit from

their use, they cause significant side effects in others, and, in addition, they are not efficacious in the therapy of associated behavioral disorders [33].

More recently, there was increasing evidence that marijuana (cannabis sativa) or its ingredients might be useful in the therapy of movement disorders [7,9,10,24,37,42,44,48,49,56]. In TS, anecdotal reports suggested a beneficial influence of marijuana smoking on tics and associated behavioral disorders [24,48]. These initial reports were supported by a study using a standardized interview: of 17 patients reporting prior use of marijuana, 14 (82%) patients experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and OCB [42]. Therefore, we had treated one TS patient in an open uncontrolled trial once with 10 mg delta-9-tetrahydrocannabinol (Δ^9 -THC), the major psychoactive ingredient of marijuana, resulting in a marked reduction of tic severity of more than 80%. The patient himself noted not only an improvement of tics but also an amelioration in attention, impulse control, OCB, and premonitory feeling with no adverse reactions [44]. These preliminary results were confirmed in a randomized double-blind placebo-controlled crossover trial of Δ^9 -THC in 12 adult patients suffering from TS. Using self- and examiner-rating scales, we found a significant improvement of motor and vocal tics and OCB after single-dose treatment with Δ^9 -THC compared with placebo [43].

This study was carried out to investigate whether treatment of TS with a single dose of Δ^9 -THC causes significant side effects on neuropsychological performance. To date, there is a controversial debate as to whether the use of cannabis causes neuropsychological effects in healthy subjects [32]. We therefore performed a variety of neuropsychological tests after treatment with Δ^9 -THC compared with placebo treatment in patients suffering from TS.

Materials and Methods

Patients

In this study, 12 adult patients (11 men, 1 woman, mean age = 34 ± 13 (SD), ranging from 18 to 66) with TS according to DSM-III R criteria were included. Patients were recruited from our outpatient movement disorder clinic. The diagnosis was made

by one of the authors (KR MV). At the time of investigation, seven patients had not been medicated for at least two years, and five patients were taking medication for TS treatment (two patients [No.1 and 4] pimozide, one tiapride [No.11], one diazepam [No. 3], and one pimozide, clonazepam and fluoxetine [No. 9]). In these five patients, medication was stable for at least two months before entering the study and during the course of the study.

Seven patients reported prior use of marijuana. Of these, three had used marijuana only once or occasionally several years ago (No. 2, 7, 10). The other four were regular users, but had stopped using marijuana at least one week before entering the study (No.1, 5, 8, 12). These four patients used marijuana for therapeutic reasons. Two of them had stopped less effective medical treatment with pimozide, and one patient used both pimozide and marijuana for treating TS. Five patients had never used marijuana before.

The study was approved by the local ethics committee, the German Federal Institute for Drugs and Medical Devices (Federal Opium Agency), and the district authority. An 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 randomized double-blind placebo-controlled crossover trial. All patients were treated once with a single dose of Δ^9 -THC (gelatin capsules containing 2.5 and 5.0 mg Δ^9 -THC) and once with a visually identical placebo on two days separated by a 4-week washout phase. According to their body weight, sex, and prior use of marijuana, patients received 5.0, 7.5 or 10.0 mg Δ^9 -THC. 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). Six patients received Δ^9 -THC followed by placebo and another six patients placebo followed by Δ^9 -THC.

Patients were admitted in the morning and received a standardized breakfast to guarantee comparable enteral absorption of Δ^9 -THC. Beginning one hour after medication, the neuropsychological tests were performed as described below. Results obtained from placebo treatment were used as reference values in TS patients. All patients remained in hospital for one night. After a 4-week washout phase, they were readmitted and the same experimental schedule was performed.

The Tests

1. German version of the Auditory Verbal Learning Test (VLMT) to assess verbal memory and learning. It consists of five presentations with recall of a 15-word list, one presentation of a second 15-word list and a sixth recall trial [23].
2. Digit Span (subtest of the Hamburg-Wechsler Intelligence Scale) to assess short-term memory. In this test, patients were required to reproduce increasingly longer strings of digits in the order presented and reversed [60, 61].
3. Multiple choice vocabulary test (Mehrfachwahl-Wortschatztest, MWT-B) to measure verbal intelligence. In a 37-item list containing five words per item (one correct

word and four nonsense words), the correct word has to be identified [38].

4. Benton Visual Retention Test to measure immediate and visual memory. This test requires the retention of visual information in iconic form over very brief periods [2].
5. Signal Detection: this test indicates speed of information processing and vigilance. White squares are presented on a black screen. Single squares appear and disappear in randomized order. Subjects have to press a response button if squares form a specific pattern [58].
6. Vienna Reaction Time to measure motor, recognition and total reaction time. Subjects have to press a button in response to the successive presentation of 15 single or combined visual/auditory stimuli. Stimuli are presented in randomized sequence as light (single visual stimulus) or tone (single auditory stimulus).
7. Sustained Attention (based on the Pauli test [1]). Subjects have to add or to subtract simple digits presented in random order on a screen by means of a PC keyboard.
8. Divided Attention. In this binary-choice reaction test, subjects have to react differentially to a distinct tone and a specific pattern of white squares on a black screen. Tones and white squares are presented in random order. Reaction time and errors reflect both motor speed and decision-making process [66].
9. Hamilton Depression Scale to identify depression and to quantify the degree of depression (21 item version) [20, 21].
10. Symptom Checklist 90-R (SCL-90-R): This self-rating test was used to identify and rate the following symptoms: somatization, OCB, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism. In addition, a general symptomatic index (GSI), a positive symptom total (PST) and a positive symptom distress index (PSDI) were calculated [12, 13].

Statistical analysis

Data were analyzed using SPSS PC version 7.0 for Windows. The significance of differences in neuropsychological tests after treatment with Δ^9 -THC compared with placebo was assessed using the Mann-Whitney test. A non-parametric test was used to compare the two groups of data, as our sample size was relatively small and this test makes no assumptions about the distribution of the data. Treatment, carry-over and phase effect for all tests were calculated using the method described by Hill and Armitage [26]. Differences were considered significant if the probability of error was $p < 0.05$ and, in addition, carry-over and phase effect were not significant.

Results

Compared with placebo treatment, there were no statistically significant differences after medication with Δ^9 -THC using the following tests: VLMT, digit span, MWT-B, Benton Test, signal detection, Vienna reaction time, sustained attention, divided attention, and Hamilton Depression Scale. Using SCL-90-R, we found no differences in the items: somatization, interpersonal sensitivity, depression, anxiety, anger-hostility, paranoid ideation, psychoticism, GSI, PST, and PSDI. Only OCB demonstrated a significant deterioration after Δ^9 -THC treatment ($p = 0.041$) and for phobic anxiety, there was a trend towards a significant deterioration ($p = 0.093$). Results of all tests are summarized in Tables 1 and 2.

The MWT-B was used to measure verbal intelligence. Six TS patients were assessed as moderately intelligent (IQ 91–109), four as highly (IQ 110–127) and two as very highly intelligent (IQ \geq 128). Furthermore, we investigated whether the results of neuropsychological tests in TS patients were within the normal range. Therefore, we compared the results after placebo treatment with respective reference values for each test. Thus, in the following tests results of all patients were found within the normal range: VLMT, digit span, signal detection, Vienna reaction time, sustained attention and divided attention. One patient (No.9) in the Benton Test and in the Hamilton Depression Scale (No.8) each was found below the normal range. The SCL-90-R (after placebo treatment) demonstrated psychopathological self-ratings in TS patients regarding the items somatization ($n=2$), OCB ($n=2$), interpersonal sensitivity ($n=2$), depression ($n=3$), anxiety ($n=3$), anger-hostility ($n=2$), phobic anxiety ($n=5$), paranoid ideation ($n=3$), psychoticism ($n=2$), GSI ($n=2$), PST ($n=3$), and PSDI ($n=3$). Of these patients, three were on medication for TS, two were regular marijuana users and another two were neither medicated nor regular users (Table 3).

Discussion

Previous investigations in TS provided evidence that treatment with Δ^9 -THC reduces tics and associated behavioral disorders like OCB [43]. In this study, we investigated whether a single-dose treatment of TS with Δ^9 -THC causes alterations in

neuropsychological performance. Our results demonstrated that there was no effect of Δ^9 -THC on short-term verbal and visual memory, recognition, verbal learning, intelligence, information processing, vigilance, reaction time, sustained attention or divided attention. Furthermore, treatment with Δ^9 -THC did not result in a deterioration of depression, somatization, interpersonal sensitivity, anxiety, anger-hostility, paranoid ideation, or psychoticism. However, using SCL-90-R, our data provided evidence for a deterioration of OCB and a trend towards an increase in phobic anxiety.

Results of tests obtained from placebo treatment demonstrated that TS patients participating in this study had intellectual functions within the average range of the general population, as has been described before [53]. In addition, the SCL-90-R – even as a poor measure – confirmed that TS is often associated with behavioral disorders such as depression, anxiety, phobic anxiety, and anger-hostility. Seven out of twelve TS patients demonstrated one or more pathological measurements in items according to SCL-90-R. Three of these patients were taking medication for TS and two were regular marijuana users who had stopped treatment with pimozide when starting marijuana use. We therefore suggest that pathological items of SCL-90-R were found in those patients more severely affected, and were not due to prior use of marijuana.

During the last few years, there has been a controversial debate as to whether cannabis sativa causes neuropsychological

test	Δ^9 -THC		placebo		t	c	p
VLMT 1	5.6 \pm 1.3		5.8 \pm 1.2		n.s.	n.s.	n.s.
VLMT 5-1	5.6 \pm 2.2		5.3 \pm 2.3		n.s.	n.s.	0.044
VLMT 6	13.4 \pm 1.5		13.5 \pm 1.6		n.s.	n.s.	n.s.
Digit span, n correct	10.8 \pm 2.0		11.3 \pm 1.7		n.s.	n.s.	n.s.
MWT-B, n correct	30.5 \pm 3.0		30.5 \pm 3.3		n.s.	n.s.	0.026
Benton-Test, n correct	7.7 \pm 1.6		7.9 \pm 1.2		n.s.	n.s.	n.s.
Benton-Test, n errors	3.2 \pm 2.6		2.6 \pm 1.6		n.s.	n.s.	n.s.
Signal detection, hits	45.8 \pm 4.3		48.0 \pm 6.8		n.s.	n.s.	0.026
Vienna reaction time,							
recognition time, ms	433.2 \pm 96.1		423.9 \pm 75.6		n.s.	n.s.	n.s.
total reaction time, ms	610.9 \pm 139.8		595.1 \pm 95.9		n.s.	n.s.	n.s.
motor time, ms	168.1 \pm 60.3		170.5 \pm 54.8		n.s.	n.s.	n.s.
Sustained attention, n correct	330.9 \pm 82.2		333.8 \pm 65.3		n.s.	n.s.	0.009
Divided attention, ms	741.9 \pm 78.4		748.5 \pm 70.4		n.s.	n.s.	n.s.
hits	27.5 \pm 4.0		28.5 \pm 3.5		n.s.	n.s.	n.s.
Hamilton depression scale	4.2 \pm 8.3		4.4 \pm 8.7		n.s.	n.s.	n.s.

Table 1 Neuropsychological tests in TS patients after treatment with Δ^9 -THC compared with placebo treatment (means \pm SD). t = treatment effect, c = carry-over effect, p = phase effect (p-value)

Items of the SCL-90-R	Δ^9 -THC		placebo		t	C	p
Somatization	49.4 \pm 11.3		47.9 \pm 11.0		n.s.	n.s.	n.s.
OCB	55.2 \pm 9.4		50.8 \pm 12.6		0.041	n.s.	n.s.
Interpersonal sensitivity	56.5 \pm 9.0		52.8 \pm 9.9		n.s.	n.s.	n.s.
Depression	52.5 \pm 8.4		49.3 \pm 11.9		n.s.	n.s.	n.s.
Anxiety	53.3 \pm 11.4		51.8 \pm 12.7		n.s.	n.s.	n.s.
Anger-hostility	55.8 \pm 13.3		52.2 \pm 10.3		n.s.	n.s.	n.s.
Phobic anxiety	60 \pm 12.0		56.4 \pm 12.7		n.s.	n.s.	n.s.
Paranoid ideation	53.9 \pm 9.6		54.0 \pm 12.5		n.s.	n.s.	n.s.
Psychoticism	51.3 \pm 8.5		51.3 \pm 9.3		n.s.	n.s.	n.s.
GSI	54.8 \pm 9.7		51.8 \pm 12.2		n.s.	n.s.	n.s.
PST	50.8 \pm 20.1		51.6 \pm 13.2		n.s.	n.s.	n.s.
PSDI	57.8 \pm 14.1		52.8 \pm 15.2		n.s.	n.s.	n.s.

Table 2 Different items of the SCL-90-R in TS patients after treatment with Δ^9 -THC compared with placebo treatment (t-value, means \pm SD). t = treatment effect, c = carry-over effect, p = phase effect (p-value)

Table 3 SCL-90-R in TS patients after placebo treatment outside the normal range. Additionally medication for TS and regular use of marijuana are given

Patient no.	pathological items	medication	regular use of marijuana
4	somatization, depression, PST	pimozide	no
6	PSDI	no	no
7	anxiety, phobic anxiety, paranoid ideation, psychoticism, PSDI	no	no
8	OCB, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, psychoticism, GSI, PST, PSDI	no	yes
9	depression, anxiety, phobic anxiety, paranoid ideation, GSI, PST	pimozide, fluoxetine, clonazepam	no
11	phobic anxiety	tiapride	no
12	somatization, OCB, interpersonal sensitivity, anger-hostility, phobic anxiety	no	yes

effects in healthy users [32]. Interpreting results given in the literature, the following aspects have to be taken into account: duration and frequency of cannabis use, acute vs. long-lasting effects, and co-existence of neuropsychiatric disorders [46]. In addition, data should be differentiated regarding the different cannabinoids, as it has to be assumed that they will cause different cognitive effects.

Acute psychotropic effects of cannabis are influenced by set, setting, dose, and type of application. The most common psychiatric side effects in healthy users are a feeling of drowsiness and being "high" [27]. Adverse reactions such as anxiety, panic reactions, restlessness, dysphoria, and sedation seem to occur mainly after use of higher doses [19]. These side effects may occur both after occasional and (less frequently) after regular use. Cannabis use may aggravate an existing psychosis, but it is still unclear whether it may cause a "marijuana psychosis" [27]. Acute use may cause impairments in cognitive functions such as alterations in associative [3] and perceptual processes [15,32,51], attention and information processing [32].

Although there are numerous studies available investigating neuropsychological effects of cannabis use, it remains unclear whether cannabis use may cause long-term cognitive impairments [32]. Some studies have provided evidence that cognitive impairments correlate with frequency and duration of cannabis use [4,57]. *Solowij et al.* [57] found that "light use" (defined as use up to twice a week) did not alter selective attention, while more frequent use did. *Block and Ghoneim* [4] found that "heavy use" (defined as use seven times weekly or more) was associated with deficits in mathematical skills, verbal expression, and selective impairment. However, "light use" (defined as use one to four times weekly) and "intermediate use" (defined as use five to six times weekly) were not associated with cognitive impairments. Furthermore, it has

been demonstrated that heavy marijuana use is associated with residual neuropsychological effects on attention and executive functions [47]. Compared with normal controls, heavy users were found to react slowly in perceptive-motor tasks while intelligence and memory tests did not differ [59]. *Schwartz et al.*, however, found that cannabis-dependent adolescents have selective short-term memory deficits [52].

In contrast, our results in patients suffering from TS did not demonstrate significant alterations in neuropsychological functions after a single-dose treatment with Δ^9 -THC compared with placebo treatment. Interpreting these results, however, it has to be taken into account that only twelve patients were included in this study. Furthermore, it can be speculated that the dosages of Δ^9 -THC used in this study were too low and the duration of treatment too short to cause cognitive impairments. It has to be emphasized that only such low doses as 5.0 to 10.0 mg Δ^9 -THC seem to be necessary to reduce tics in TS [43,44]. Since it has been suggested that the central cannabinoid system might play a major role in TS pathology [42,44], in addition, it can be hypothesized that the effect of Δ^9 -THC on neuropsychological performance may be different in patients suffering from TS compared to healthy users. This hypothesis is supported by the fact that previous studies have provided evidence that cannabis sativa and Δ^9 -THC may improve not only tics but also attention in TS [42,44,48], whereas it has been suggested that cannabis use deteriorates attention in healthy users [47,57]. Results from this study indicate that a single-dose treatment with Δ^9 -THC does not deteriorate sustained and divided attention.

Using SCL-90-R, we found a significant deterioration of OCB. However, this result should be interpreted with caution, as there is much evidence that SCL-90-R is a poor measure of OCB and not sensitive in assessing changes in it [30,63]. In contrast, previous reports have suggested that use of marijuana may improve OCB in TS [42,44]. Using a self-rating scale (subscale of the Tourette Syndrome Symptom List [34]) accordingly, it has been demonstrated that a single-dose treatment with Δ^9 -THC causes a significant improvement in OCB [43].

Furthermore, SCL-90-R has shown a trend towards a significant increase in phobic anxiety. Anxiety reactions have also been found to be sequels of cannabis use among healthy users, but they seem to occur mainly after higher doses [19]. It can therefore be speculated that the increase in phobic anxiety is mainly a consequence of the study design, as it is not possible to administer an individual dosage to each patient gradually in a single-dose study. It can be hypothesized that anxiety reactions will occur less frequently when dosages are administered slowly.

So far, the function of the endogenous cannabinoid system is poorly understood. Central cannabinoid CB1 receptors have been found with high concentrations in the output nuclei of the basal ganglia, in forebrain areas associated with higher cognitive functions, in the molecular layers of the cerebellum, hippocampal dentate gyrus, and other parts of the hippocampal formation [25]. Cannabinoid receptors seem to regulate neurotransmission in a complex manner: cannabinoids influence dopaminergic processes in the basal ganglia [25,35], activate mesolimbic dopaminergic neurons [16] and increase the dopamine turnover in the prefrontal cortex [28]. They

reduce GABA reuptake in the globus pallidus lateralis [36], regulate the activity of substantia nigra pars reticulata (SNr) neurons by inhibition of GABA inputs [6,40], inhibit the release of glutamate from the subthalamic nucleus in the SNr [39,50] and in hippocampal neurons [54,55], and interact with the serotonergic system [31,41]. Anandamide, identified as an endogenous ligand of the cannabinoid receptor [14], has been found to reduce locomotor activity [11]. Accordingly, beneficial effects of cannabinoids have been reported in dystonia [10,37,49], tremor [7,9,10] and L-DOPA-induced dyskinesia in Parkinson's disease [56]. Furthermore, it has been suggested that cannabinoid receptors play a role in memory storage [22] and regulate monoaminergic neuron-mediated psychomotor activation [18].

To date, the nature of the neurobiological lesion in TS remains unknown. It has been suggested that dysfunctional dopaminergic basal ganglia circuitry may underlie TS pathology [45]. However, there is also evidence for an involvement of the nucleus accumbens/limbic system [5], the cingulate/orbitofrontal cortex [62] and a frontocortical dysfunction [29,64,65]. Because there is much evidence that cannabis sativa and Δ^9 -THC are successful in the therapy of tics and associated behavioral disorders, we suggest that the central cannabinoid system plays an active role in the neurobiology of TS. Our results indicate that a single-dose treatment of 5.0 to 10.0 mg Δ^9 -THC does not effect neuropsychological performance in patients suffering from TS. Therefore, we suggest that Δ^9 -THC is both effective and safe in the treatment of TS. A follow-up study involving a longer term Δ^9 -THC therapy is needed to confirm these preliminary results.

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