

Psychopathological and Cognitive Effects of Therapeutic Cannabinoids in Multiple Sclerosis: A Double-Blind, Placebo Controlled, Crossover Study

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Objectives: To study possible psychopathological symptoms and cognitive deficits, abuse induction, as well as general tolerability and effects on quality of life, fatigue and motor function in cannabis-naïve patients with multiple sclerosis (MS) treated with a free-dose cannabis plant extract (Sativex).

Methods: In an 8-week, randomized, double-blind, placebo-controlled, parallel group crossover trial, 17 cannabis-naïve patients with MS were assessed at baseline and at the end of the cannabis and placebo phases of the trial (each of 3 weeks) by means of Symptom Checklist-90 Revised, Self-rating Anxiety Scale, Multiple Sclerosis Functional Composite (of which 1 dimension is the Paced Auditory Serial Additional Test that was used to evaluate cognition), Visual Analogue Scale on health-related quality of life, Multiple Sclerosis Impact Scale-29, and Fatigue Severity Scale.

Results: Postplacebo versus postcannabinoid scores showed that no significant differences could be detected on all the variables under study. A significant positive correlation was found between Δ -9-tetrahydrocannabinol blood levels and scores at the General Symptomatic Index and at the “interpersonal sensitivity,” “aggressive behaviour,” and “paranoiac tendencies” subscales of the Symptom Checklist-90 Revised. No serious adverse events, abuse tendencies, or direct withdrawal symptoms were reported. Increased desire for Sativex with secondary depression was reported in 1 subject.

Conclusions: Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patients with MS. However, the positive correlation between blood levels of Δ -9-tetrahydrocannabinol and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoiac features might arise, although greater statistical power would be necessary to confirm this finding.

Key Words: cannabinoids, psychosis, anxiety, cognition, multiple sclerosis

(*Clin Neuropharm* 2009;32: 41–47)

Psychopathological symptoms and cognitive impairment are often reported as possible side effects of recreational cannabis use. In population surveys, anxiety and psychotic symptoms are commonly experienced after cannabis use.^{1,2} The psychotomimetic effect of cannabis, which was proved in ex-

perimental studies reporting transient positive and negative psychotic symptoms together with other psychopathological phenomena,³ is greater in subjects predisposed for psychosis^{4,5} and probably in adolescent smokers due to a greater vulnerability of the developing brain.⁶ On the other hand, cannabis use has been frequently reported in anxiety disorders⁷; it might precipitate psychosis,^{5,8} and the overall risk of developing psychotic symptoms has been described as increasing 3-fold in cannabis users.⁶

The acute administration of cannabis was reported to produce transient effects on several neuropsychological functions (eg, attention, memory, visual-motor coordination, verbal fluency, and psychomotor speed).^{3,9,10} In “heavy users” (eg, subjects smoking several joints per day, during periods of many years), a long-term, mild cognitive impairment was reported.^{11,12} Although no significant cognitive deficits were reported in frequent but moderate users of cannabis,¹³ the persistent effects of cannabis on cognition remain uncertain.¹⁴

Cannabinoids have recently been suggested for the treatment of neurodegenerative disorders, vascular and inflammatory diseases, cancer, and central pain,¹⁵ and they are currently suggested for the treatment of spasticity and chronic pain in multiple sclerosis (MS). In the light of this potential therapeutic role, studies focusing on psychological and cognitive tolerability of cannabinoids in MS are eagerly awaited.¹⁶ At the moment, some studies on general tolerability of cannabis treatment in MS are available,¹⁷ whereas, at least in our knowledge, no specific data have been published on its cognitive and psychopathological tolerability.

Consequently, the aims of this study were (i) to characterize the effects of a 3-week cannabinoid treatment with a cannabis plant extract containing Δ -9-tetrahydrocannabinol (Δ -9-THC) and cannabidiol (CBD) in equal proportions on several psychopathological dimensions, including psychotic symptoms and anxiety, and cognitive performances in cannabis-naïve patients with MS; (ii) to evaluate the tolerability and possible abuse induction; and (iii) to study the effects of cannabis on quality of life-related dimensions, on fatigue and motor function.

MATERIALS AND METHODS

Subjects

Seventeen patients with MS were recruited from the MS Outpatient Clinic at “Sapienza” University. After obtaining written informed consent, subjects underwent a baseline neurological and psychiatric assessment. To be eligible for inclusion into this study, patients had to fulfill the following criteria: male or female subjects between 18 and 60 years of age; right-handed with normal right-hand function; a baseline Expanded Disability Status Scale¹⁸ score ranging from 3.5 to

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DOI: 10.1097/WNF.0b013e3181633497

6.5; a stable disease for at least 30 days before study entry and nosystemic corticosteroid therapy within 4 weeks of randomization; significant spasticity in at least 2 muscle groups; antispastic and immunomodulatory agents (dosage, frequency, and route of administration) stable, before the study entry, for at least 1 and 6 months, respectively; no history of epilepsy of alcohol or substance abuse and no major medical illnesses; absence of psychiatric disorders or cognitive impairment at first evaluation; no history of psychiatric disorders; no concomitant therapy with psychoactive drugs; no female patient who was pregnant, lactating, or planning pregnancy during the course of the study; and no previous use of cannabis. This study was approved by the local Ethical Committee. Patients were informed about the potential for psychosis, anxiety, and panic, and they gave their informed consent to be included into the trial.

Study Drug

Patients received cannabis-based medicine extract (Sativex, GW Pharma, UK) presented in a pump action sublingual spray. Sativex is composed of whole cannabis plant extract, containing Δ -9-THC (27 mg/mL) and CBD (25 mg/mL), in ethanol/propylene glycol (50:50) excipient. Each actuation delivers 100 μ L of spray, containing THC 2.7 mg and CBD 2.5 mg. Placebo had the appearance, smell, and taste of the active formulation in ethanol/propylene glycol (50:50) excipient but contained no active components.

Study Design

This 8-week, randomized, double-blind, placebo-controlled, crossover trial was part of a larger study on functional magnetic resonance imaging and electrophysiological correlates of cannabinoid effect in MS patients experiencing spasticity (Pozzilli C et al, personal communication).

Patients taking immunomodulatory, antispastic, and/or any other pharmacological treatment were admitted in the study if therapy intake was stable for at least 6 and 1 months, respectively, before the study entry and were requested to maintain the intake of these pharmacological agents at fixed dosage, route, and time of administration. Trial assessments were scheduled at fixed times to be performed under standardized identical conditions (eg, daytime, interval to the last administration of antispastic, immunomodulatory compounds, and others).

Screening assessment was followed by randomization and dose introduction. Patients were randomly assigned to 2 counter-balanced groups starting either with Sativex or with placebo as the first drug. After 3 weeks, the first treatment was discontinued, and patients entered a washout phase of 2 weeks, before starting the second treatment phase of 3 weeks. During each treatment period, all patients had to reach the optimal, individualized dosage to subjectively relief spasticity. The number of daily actuations was recorded.

As shown in Figure 1, all patients completed the psychopathological and cognitive measures before starting therapy and at the end of both Sativex and placebo treatment phases. A withdrawal was done at the end of each treatment phase to evaluate the THC and CBD levels in the blood. Patients were recontacted and asked to estimate their desire for cannabis and whether they had noted any new medical or psychiatric problem twice after the end of the study, 2 weeks, and 2 months later, respectively.

Outcome Measures

At each visit, all patients were asked to complete rating scales to assess fatigue, disability, psychopathology, cognitive functioning, and the physical and psychological impact of MS on quality of life.

Specifically, psychopathological symptoms were assessed using 2 self-reporting devices: the Symptom Checklist-90 Revised (SCL-90-R)¹⁹ and the Self-rating Anxiety Scale (SAS).²⁰ The SCL-90-R is a 90-item symptom inventory; the subject rates each item on a 5-point scale of distress, from 0 "not-at-all" to 4 "extremely." The 90 items are scored and interpreted in terms of 9 primary symptom dimensions and 1 global severity index of distress named General Symptomatic Index. The dimensions are labeled as somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The SAS is a 20-item symptom inventory specifically designed to study anxiety; the subject rates each item on a 4-point scale of distress, from 1 "none or a little of the time" to 4 "most or all of the time."

Cognitive performances were evaluated using the Paced Auditory Serial Additional Test (PASAT), 1 of the 3 dimensions of the Multiple Sclerosis Functional Composite (MSFC).²¹ PASAT is a measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability. The dependent variable is the sum of correct answers given by the subject (out of 60 possible). The other 2 dimensions of the MSFC are the Timed 25-Foot Walk (T25FW), which is a quantitative measure of leg function and ambulation, and the 9-Hole Peg Test (9HPT), a quantitative measure of arm and hand function. To calculate the overall MSFC, scores for each component are converted to z scores using a specific formula. All these 3 independent clinical dimensions contribute equally to the overall MSFC score.

Quality of life and physical and psychological impact of MS from the patients' perspective were studied by means of 3 instruments: the Visual Analogue Scale on health-related quality of life,²² the Fatigue Severity Scale,²³ and the 29-item Multiple Sclerosis Impact Scale.²⁴ Visual Analogue Scale on health-related quality of life consists of a straight line of a specified length with verbal descriptors at each end consisting of short and easily understood phrases that describe the variable being measured. Fatigue Severity Scale is a 9-item questionnaire that assesses the effect of fatigue on daily living. Each item is a

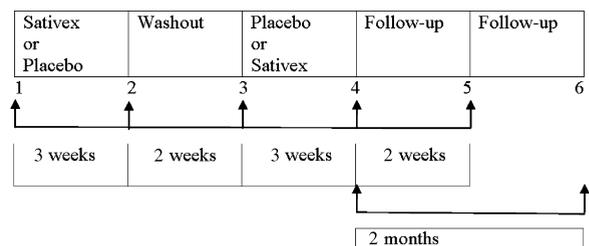


FIGURE 1. Study design. 1 = Screening assessment and randomization; administration of clinical, cognitive, and psychopathological questionnaires; first-phase treatment introduction. 2 = First-phase treatment discontinuation; administration of clinical, cognitive, and psychopathological questionnaires; first blood withdrawal; assessment of possible side effects. 3 = Administration of clinical, cognitive, and psychopathological questionnaires; second-phase treatment introduction. 4 = Second-phase treatment discontinuation; administration of clinical, cognitive, and psychopathological questionnaires; second blood withdrawal; assessment of possible side effects. 5 = Clinical assessment; evaluation of possible long-lasting side effects and of possible desire/craving for cannabinoids. 6 = Clinical assessment; evaluation of possible long-lasting side-effects and of possible desire/craving for cannabinoids.

statement on fatigue that the subject rates from 1 “completely disagree” to 7 “completely agree.” Patients with a mean score of 4 or more were defined as suffering from significant fatigue. The 29-item Multiple Sclerosis Impact Scale is an instrument measuring the physical (20 items) and psychological (9 items) impact of MS. The 2 summary scores are generated by summing individual items and then transformed to a 0 to 100 scale. High scores indicate worse health.

THC and CBD Plasma Measurement

Tetrahydrocannabinol and CBD levels in the plasma were measured according to the LC-MS/MS spectrometric method (Liquid Chromatography with tandem Mass Spectrometer detection) of Valiveti and Stinchcomb,²⁵ with slight modifications. Chromatographic analyses were carried out using a High-Performance Liquid Chromatography with tandem Mass Spectrometer detection (HPLC-MS/MS) system. Negative electrospray ionization was used and all analyses were performed in Multiple Reaction Monitoring (MRM) mode. The transition were *m/z* 313—245 for THC and CBD. The limit of quantitation was 0.1 ng/mL for Δ -9-THC and CBD.

Statistical Analysis

We assigned patients to treatment sequence by using an independent statistician-generated randomization code. Investigators allocated patients consecutively by time of inclusion at the study site.

9HPT task periods were averaged over the 2 trials for each hand, averaging together both the dominant and nondominant hand trials. T25FW trial periods were averaged over the 2 trials. MSFC scores were calculated using test results from the baseline visit from all patients. Analyses for MSFC were conducted without replacing data values as well.

For all variables measured except for MSFC PASAT, 9HPT, and T25FW, Wilcoxon’s matched pairs signed-rank tests were used to compare variables measured at the end of each 3-week treatment period (postplacebo vs post-Sativex) given that all variables except those listed above are defined by finite scoring systems that do not fit a normal distribution. For MSFC PASAT, 9HPT, and T25FW, paired *t* tests were conducted to compare the variables postplacebo versus post-Sativex levels, given that these 3 variables are defined by a continuous, normally distributed time scale.

For correlations with CBD and Δ -9-THC serum levels, all dependent variables except for MSFC PASAT, 9HPT, and T25FW measured during the post-Sativex period were correlated using Spearman rank correlations given the nonparametric nature of these variables as stated above. For MSFC PASAT, 9HPT, and T25FW values measured during post-Sativex periods, Pearson correlations were evaluated to correlate with CBD and Δ -9-THC serum levels.

All tests are reported with their local *P* values, thus identifying differences that would have potential statistical significance ($P < 0.05$), if chosen as the primary efficacy criterion. For the correlation statistics, Bonferroni correction was not used because the comparisons did not fall within a single joint family of comparisons by definition.

RESULTS

All the 17 patients who entered the study completed the trial and were included in the analysis.

Baseline demographic and clinical characteristics are reported in Table 1. Baseline assessment did not reveal significant cognitive problems. All the included patients had taken

antispastic and immunomodulatory compounds in their clinical history, with generally poor results. During the study, only 5 patients were taking immunomodulatory compounds (interferon-beta, copolymer-1, or azathioprine) and 10 were taking antispastic drugs (baclofen, dantrolene sodium, chlorhydrate tizanidina, or botulinum toxin). All patients maintained the intake of these pharmacological agents at fixed dosages, route, and time of administration in relation to the assessment points of the trial.

The number of daily actuations used was significantly higher during the placebo than during the Sativex period (15.16 + 4.51 vs 8.20 + 3.15; $t = 5.31$, $P < 0.001$).

Postplacebo versus post-Sativex scores are reported in Table 2. It is shown that neither psychopathological nor cognitive scores differed between the Sativex and the placebo period. Although objective measures did not reveal any cognitive impairment, 11 patients during the Sativex administration and 2 subjects during the placebo period reported subjective drowsiness and sense of “slower-thinking”; 1 of the 11 subjects who reported this symptom experienced transient mental confusion with temporal and spatial disorientation. Measures of fatigue, leg and arm function, quality of life, and

TABLE 1. Baseline Demographic and Clinical Characteristics (n = 17)

Characteristics	Mean (\pm SD)
Age (range)	49.8 (\pm 6.64)
Sex (Female/Male)	11:6
Disease duration, yr	20.76 (\pm 8.42)
Disease course	17 SP
EDSS score	6.1 (\pm 0.3)
MSFC (PASAT)	35.76 (\pm 13.22)
MSFC (9HPT)	29.66 (\pm 8.21)
MSFC (T25FW)	26.85 (\pm 14.51)
MSIS-29 (physical items)	53.64 (\pm 11.83)
MSIS-29 (psychological items)	36.54 (\pm 20.51)
FSS	5.61 (\pm 0.97)
VAS QoL	4.29 (\pm 2.08)
SAS	36.38 (\pm 6.42)
SCL-90 GSI	0.63 (\pm 0.28)
SCL-90 Somat	10.61 (\pm 4.17)
SCL-90 Obsess	6.61 (\pm 4.36)
SCL-90 Sens	4.46 (\pm 4.31)
SCL-90 Depr	12.76 (\pm 6.59)
SCL-90 Anx	4.46 (\pm 3.45)
SCL-90 Aggr	2.46 (\pm 1.66)
SCL-90 Phob	4.3 (\pm 3.32)
SCL-90 Para	2.92 (\pm 3.61)
SCL-90 Psychosis	4.23 (\pm 2.42)

SP indicates secondary progressive MS; EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; PASAT, Paced Auditory Serial Additional Test; 9HPT, 9-Hole Peg Test; T25FW, Timed 25-Foot Walk; MSIS-29, Multiple Sclerosis Impact Scale; FSS, Fatigue Severity Scale; VAS QoL, Visual Analogue Scale for Quality of Life; SAS, Self Rating Anxiety Scale; SCL-90, Symptom Checklist-90 Revised; GSI, General Symptomatic Index; Somat, somatized anxiety; Obsess, obsessive-compulsive features; Sens, sensitivity; Depr, depression; Anx, anxiety; Aggr, aggressive behaviour; Phob, phobic anxiety; Para, paranoiac tendencies; Psychosis, psychotic symptoms.

TABLE 2. Postplacebo Versus Post-Sativex Clinical Scales Scores (n = 17)

Scales	Postplacebo (mean ± SD)	Post-Sativex (mean ± SD)	Statistic
MSFC (PASAT)	43.0 (±11.8)	42.4 (±13.6)	$t = 0.28, P = 0.79$
MSFC (9HPT)	28.4 (±8.66)	28.75 (±9.37)	$t = -0.33, P = 0.75$
MSFC (T25FW)	26.2 (±16.9)	25.1 (±15.1)	$t = 0.51, P = 0.62$
MSIS-29 (physical items)	63.0 (±16.8)	62.3 (±13.1)	$z = 0.57, P = 0.57$
MSIS-29 (psychological items)	47.8 (±17.8)	46.3 (±15.9)	$z = -0.47, P = 0.64$
FSS	5.58 (±1.50)	5.89 (±0.93)	$z = -0.16, P = 0.88$
VAS QoL	3.65 (±2.29)	4.00 (±2.00)	$z = 1.01, P = 0.31$
SAS	37.7 (±8.67)	35.7 (±7.69)	$z = -1.26, P = 0.21$
SCL-90 GSI	0.76 (±0.43)	0.77 (±0.43)	$z = -0.12, P = 0.91$
SCL-90 Somat	12.11 (±7.25)	12.94 (±5.62)	$z = 0.60, P = 0.55$
SCL-90 Obsess	7.94 (±6.2)	8.11 (±5.39)	$z = -0.19, P = 0.85$
SCL-90 Sens	4.52 (±4.62)	4.76 (±4.57)	$z = -0.03, P = 0.98$
SCL-90 Depr	16 (±9.13)	15.58 (±8.65)	$z = -0.45, P = 0.65$
SCL-90 Anx	5.41 (±4.78)	6.05 (±5.65)	$z = 0.65, P = 0.52$
SCL-90 Aggr	3.11 (±3.01)	2.29 (±1.89)	$z = -0.92, P = 0.36$
SCL-90 Phob	6.11 (±4.97)	6.64 (±4.85)	$z = 0.25, P = 0.81$
SCL-90 Para	2.88 (±3.46)	3.17 (±3.74)	$z = 0.36, P = 0.72$
SCL-90 Psychosis	5 (±3.8)	4.23 (±3.63)	$z = -0.46, P = 0.65$

Refer to Table 1 for the explanations of abbreviations.

physical and psychological impairment due to MS did not differ between the 2 treatment periods.

Correlation between clinical scores and plasma levels of CBD and Δ -9-THC are reported in Table 3. A significant positive correlation was found between the Δ -9-THC blood levels and scores at the General Symptomatic Index and at the “Interpersonal sensitivity,” “Aggressive behaviour,” and “Paranoiac tendencies” of the SCL-90-R. No correlations were found between the other major component of Sativex (CBD) and the studied variables.

No serious adverse events (hospitalization, death) occurred during the study. Side effects reported during the placebo and Sativex phases were generally mild (Table 4). During the Sativex administration, 1 patient required treatment in the emergency department because of transient mental confusion with temporal and spatial disorientation, tachycardia, increased blood pressure, and mydriasis. Symptoms recovered in few hours without requiring hospitalization, and the patient was able to continue the study without further problems.

All patients were recontacted twice after the end of the study, 2 weeks, and 2 months later, respectively. At the 2-week but not at the 2-month visit, one 56-year-old lady reported intense desire to reintroduce Sativex after withdrawal and developed depressive symptoms (successfully treated with sertraline 50 mg/die), probably related to the impossibility to keep taking Sativex. None of the other patients reported craving for cannabis, dependence, and withdrawal effects, as well as any new medical or psychiatric problems.

DISCUSSION

The primary aim of this study was to explore the onset of psychopathological symptoms and cognitive deficits in cannabis-naïve patients with MS treated with a cannabis plant extract (Sativex) for relieving their spasticity. General tolerability, possible abuse induction, and the effects of cannabinoids on quality of life, fatigue, and motor function were also studied.

Our study evaluated the effects of cannabinoids on cognition by means of PASAT, which is widely used to test sustained attention, divided attention, concentration, and information processing speed in MS patients.²⁶ We found no significant differences between Sativex and placebo in the PASAT scores, although we found a higher frequency of subjective drowsiness and sense of “slower-thinking” in the cannabinoid phase of the study. Tacking into consideration the

TABLE 3. Relationship Between Plasma Levels of CBME Components and Clinical Scores

Indexes	CBD, ng/mL	Δ -9-THC, ng/mL
MSFC (PASAT)	-0.23 ($P = 0.37$)	-0.17 ($P = 0.52$)
MSFC (9HPT)	0.06 ($P = 0.82$)	-0.01 ($P = 0.97$)
MSFC (T25FW)	0.07 ($P = 0.80$)	0.26 ($P = 0.33$)
MSIS-29 (physical items)	0.14 ($P = 0.59$)	0.34 ($P = 0.19$)
MSIS-29 (psychological items)	0.11 ($P = 0.68$)	0.17 ($P = 0.51$)
FSS	0.14 ($P = 0.60$)	0.24 ($P = 0.35$)
VAS QoL	0.20 ($P = 0.44$)	-0.01 ($P = 0.96$)
SAS	-0.02 ($P = 0.93$)	0.19 ($P = 0.47$)
SCL-90 GSI	0.17 ($P = 0.52$)	0.52 ($P = 0.03$)
SCL-90 Somat	0.19 ($P = 0.47$)	0.46 ($P = 0.06$)
SCL-90 Obsess	0.23 ($P = 0.37$)	0.43 ($P = 0.09$)
SCL-90 Sens	0.42 ($P = 0.09$)	0.67 ($P < 0.01$)
SCL-90 Depr	0.03 ($P = 0.91$)	0.36 ($P = 0.16$)
SCL-90 Anx	0.19 ($P = 0.46$)	0.44 ($P = 0.07$)
SCL-90 Aggr	0.30 ($P = 0.24$)	0.57 ($P = 0.02$)
SCL-90 Phob	-0.19 ($P = 0.47$)	0.06 ($P = 0.81$)
SCL-90 Para	0.27 ($P = 0.30$)	0.59 ($P = 0.01$)
SCL-90 Psychosis	-0.05 ($P = 0.86$)	0.29 ($P = 0.25$)

Refer to Table 1 for the explanations of abbreviations.

TABLE 4. Side Effects Reported During the 2 Treatment Periods

	Sativex Phase (n = 17)	Placebo Phase (n = 17)
Mouth dryness or burning	5	0
Depression	1	1
Fatigue	6	3
Euphoria	1	1
Headache	3	3
Nausea and vomiting	2	1
Drowsiness and/or slower thinking	11	2
Dizziness and vertigo	8	0
Tremor	1	0
Lower limb weakness	3	0

high sensitivity of PASAT for revealing cognitive deficits, we are prone to interpret this finding as of no significant impact on cognition in our cohort. Although a previous study reported an improvement on PASAT performances during a period of 2 weeks,²⁷ our results are in accordance with a 4-week study, which did not find any difference compared with placebo.²⁸ Our findings support the hypothesis that cannabinoids taken as a treatment for MS symptoms do not affect cognition, at least in the short term. Note that research on long-term recreational cannabis users (mean length of regular use >10.3 years) showed that slower cognitive processing rates in PASAT performances are more common among long-term rather than short-term users,¹¹ suggesting that although cognitively safe, a note of caution is needed in the long-term administration. Another aspect to be considered as of potential impact on cognition is the dosage. Our findings suggest that in the range of therapeutic dosages (mean daily puffs 8.20 + 3.15, approximately corresponding to 22 mg of Δ -9-THC), cannabinoids do not significantly affect cognition, and this is in accordance with results from a study reporting no significant cognitive deficits in frequent but moderate users of cannabis.¹³ Although we did not find any significant correlation between Δ -9-THC and CBD plasma levels and PASAT scores at the end of the Sativex treatment, which suggests that at these moderate dosages, there is no dose effect on cognition; cognitive tolerability at higher dosages cannot be predicted on the basis of our data because the study was not designed to detect such an effect.

The other major element under study was the effect of cannabinoid treatment on psychopathology. Psychopathological symptoms were often found in recreational cannabis users,^{1,2} and cannabis use had been frequently reported in anxiety⁷ and psychotic disorders.²⁹ Our finding that psychopathological scores did not differ between cannabinoids and placebo apparently contrasts with the report of transient “positive” and “negative” psychotic symptoms, perceptual alterations, euphoria, and anxiety in healthy volunteers.³ However, in that study, the authors evaluated the acute effect of 2 fixed dosages of intravenously injected Δ -9-THC in subjects who had previously smoked cannabis, whereas in our study patients were cannabis naïve, they took a free-dosage oral-administered cannabis extract that also contains CBD, and the effects on psychopathology were evaluated after 3 weeks of treatment. These differences in the study design make a direct comparison of these 2 studies difficult. To our knowledge, there was no previous study specifically focused on the evaluation of psycho-

pathological phenomena in MS patients. However, a few psychiatric disturbances were reported among other side effects. In particular, euphoria was the most frequently reported symptom, ranging from 3.2% to 26.6% of the treated subjects,^{30–34} whereas other phenomena were found sporadically (hyperactivity,³⁰ dissociation,³² feeling “paranoid,” and hallucinations³⁴).

In our study, euphoria was reported only by 1 patient in the treatment group (5.8%), and its rate was comparable to that reported in the placebo group. This finding does not differ considerably from previous studies. However, neither our nor previous studies used standardized questionnaires to measure euphoria, and further studies with more objective and sensitive measures are thus required.

Having found no differences in the SCL-90 and SAS scores, our study suggests that in the short term, Sativex administered to cannabis-naïve patients for therapeutic purposes does not increase the risk of main psychopathological symptoms. However, we found a moderate but significant positive correlation between the plasma levels of Δ -9-THC (the principal active ingredient of cannabis) and some of the SCL-90 scales. This suggests that although at the low therapeutic levels used in this study, cannabinoids do not induce the onset of psychopathological symptoms, at higher dosages, the risk of worsening interpersonal sensitivity (eg, the tendency of experiencing feeling of inadequacy in the relationship with others), aggressiveness, and paranoid thoughts cannot be excluded. This possibility, together with previous reports of sporadic symptoms like feeling “paranoid” and hallucinations³⁴ in patients with MS treated with cannabinoids, suggests that a careful evaluation of history of psychosis should be done in all patients addressed to cannabinoids treatment. Finally, the correlation between Δ -9-THC and aggressiveness found in our study contrasts with a previous research that excluded aggressive feelings in 50 MS patients treated with cannabis-derived drug.³¹ Considering that the relationship between cannabis use and aggressiveness is still debated,^{35,36} future studies on larger samples of patients taking cannabinoids as a therapy are needed.

Another aim of the study was the evaluation of the impact of cannabinoid treatment on some physical problems related to MS (eg, reduced leg and arm function, fatigue), as well as on quality of life and physical and psychological impairment. Our findings suggest that in the short term, none of these variables changed significantly. These results are in line with current literature showing that administered for a 2- to 4-week treatment period, cannabis does not significantly improve arms and legs mobility²⁷ and fatigue,³⁷ whereas they differ from those of Killestein and colleagues,³⁷ who found a significant worsening in the total MSFC and 9HPT scores. Our findings also confirm previous studies showing how cannabis use did not covary with general scores on quality of life,^{37–39} whereas a positive slight trend benefit was found on legs motility (T25FW) in long-term studies.³⁹ More promising results have been previously reported with subjective reports: cannabis was reported to relief fatigue and dysfunction of walking and balance and to improve emotional dysfunction.⁴⁰ However, the fact that findings with objective measurements are mostly conflicting suggests that studies on larger cohorts are needed to evaluate the impact of cannabinoid treatment on these variables.

Another issue to be evaluated was the general tolerability. All subjects included in the study completed the 3 weeks of trial, and no serious adverse events occurred during the study. Side effects were slightly more frequent during active treatment than during placebo. No clinically relevant changes were observed in physical examinations, with the exception of transient

increased blood pressure in 1 patient. No changes were found in hematology or biochemistry parameters. Finally, although some possible effects of Sativex are similar to those reported with antispasmodics (eg, drowsiness, mouth dryness, dizziness, vertigo, and fatigue) and consequently could have been responsible of a summatory effect, this was not found in our study.

Taken together, these findings suggest that Sativex was well tolerated. Long-term studies confirm the good tolerability profile of cannabinoids for therapeutic use.^{17,39}

Finally, a crucial point that is usually a matter of concern when the therapeutic use of cannabinoids is proposed is the possibility that cannabis may induce dependence and abuse. At this regard, our study was in a good position to observe these possible phenomena, being on cannabis-naïve subjects and allowing for free dosages. Interestingly, none of the patients abused the use of Sativex during the treatment phase, the mean daily dosage being quite low (23–25 mg) and the number of daily actuations being significantly higher in the placebo than in the cannabis phase (suggesting that when patients had reached the therapeutic daily dosage, they spontaneously interrupted the dosage augmentation of Sativex without craving induction, whereas in the case of placebo, they continued to increase the number of daily actuations trying to reach active effects). Different motivations of the user (recreational vs therapeutic) might partially explain our findings that cannabinoid treatment in MS does not induce tolerability and dosage increase. However, in the case of other psychoactive substances (eg, benzodiazepines, tramadol, and zolpidem), some tendency to induce tolerability is also found in therapeutic settings with consequent increased risk of dosage augmentation and dependence,^{41–44} suggesting that our findings may be not completely due to the above-mentioned factor. A related but different factor is that in recreational use of cannabis, the route of administration (inhalation) usually maximizes the C_{max} and shortens the T_{max} in order to increase the psychoactive effect, whereas Sativex (sublingual/oromucosal administration) reaches a low C_{max} and has a fairly long T_{max}.⁴⁵ Different pharmacokinetics might be responsible for less gratifying subjective experiences due to the delayed psychoactive effect of Sativex, thus explaining (at least in part) why patients were not driven to increase the dosage.

Furthermore, direct withdrawal symptoms were not reported, as expected.¹⁷ However, some days after the end of the trial, 1 patient experienced desire to reintroduce Sativex. Whether this desire was driven by a perceived effective treatment (she explained it as a reaction to the impossibility to continue the treatment that she considered very helpful, and in effect, she presented a significant leg mobility improvement, with a 57% drop of T25FW scores) or whether it represented a withdrawal symptom cannot be addressed by a single case. Two months after the termination of the study, all the subjects included in the study had not increased desire to be treated again with Sativex and did not present any new medical or psychiatric problem. However, long-term studies are needed in larger samples to evaluate the possible dependence induced by cannabinoid therapy.

There are some limitations in our study, which need to be considered in the interpretation of our findings. The sample size was quite small to address completely all the questions arising from a study evaluating the psychopathological impact of cannabinoids. However, the power of the study was enough to evaluate the effect of Sativex on physical symptoms (eg, spasticity) and its electrophysiological and imaging counterpart. The study duration of treatment was relatively short, again aimed to provide pilot information about the study drug.

As a consequence, direct generalization of these data to larger clinical populations is not viable, and more focused studies are needed to investigate the safety of cannabinoids on cognitive and psychopathological domains in patients with MS. Cognitive performances were studied with 1 test (PASAT), and no other information about cognition in this cohort was available. More detailed test batteries should be included in future studies. Finally, the oromucosal route of administration of cannabis might have induced unpredictable interindividual and intraindividual variability in plasma Δ -9-THC levels, not detectable with blood tests.

In conclusion, cannabinoids prescribed for therapeutic reasons to cannabis-naïve patients with MS did not induce onset of psychotic or anxiety symptoms and did not impair cognition. Safety and tolerability were generally good, drug tolerance and dose increasing were not reported during the trial, and desire for Sativex or abuse was not present at follow-up. However, the positive correlation between blood levels of Δ -9-THC and psychopathological scores suggests that at dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoid features might arise. Finally, the effects of cannabinoids on quality of life, fatigue, and motor function of MS patients were non-significant, suggesting that the effective impact of cannabinoids in these patients as well as the most proper target symptoms remain to be better ascertained.

ACKNOWLEDGMENTS

Sativex was kindly provided by GW Pharma Ltd, Salisbury, England. The grant has been supported as the Project of University Research (ex-quota 60%)—year 2004—by the University “Sapienza” of Rome.

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