Safety, tolerability, and efficacy of orally administered cannabinoids in MS

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Abstract—The authors conducted a randomized, double-blind, placebo-controlled, twofold crossover study in 16 patients with MS who presented with severe spasticity to investigate safety, tolerability, and efficacy of oral Δ^9-Tetrahydrocannabinol (THC) and Cannabis sativa plant extract. Both drugs were safe, but adverse events were more common with plant-extract treatment. Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC and plant-extract treatment worsened the participant's global impression.

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Evidence suggests that cannabinoids can relieve muscle spasticity and other symptoms in MS.[1-3] The hemp plant (*Cannabis sativa*) is the unique source of compounds known as cannabinoids, including the major psychoactive Δ^9-Tetrahydrocannabinol (THC) and the nonpsychoactive cannabidiol (CBD).[4] Discovery of both the cannabinoid receptors, present throughout the CNS and the peripheral immune system, and the endogenous cannabinoid system has strengthened scientific interest in the field.[4] Many patients with MS are already using cannabis to alleviate their symptoms.[4] However, results of the few small- and short-term clinical trials have been equivocal, and the majority of patients experienced unpleasant side effects.[2,4,5] We performed an additional study analyzing two products—synthetic THC and a cannabis plant extract with THC and CBD.

Methods. We studied 16 patients with progressive MS (10 with secondary progressive [SP] and six with primary progressive [PP] MS). Patients were eligible for study if they had disease duration >1 year, severe spasticity (mean Ashworth spasticity score[6] of 2 or more in at least one limb) during screening, and Expanded Disability Status Scale (EDSS) score between 4 and 7.5. Exclusion criteria included other disease of clinical importance, use of other investigational drug, disease exacerbation, steroid treatment or use of cannabinoids in the 2 months preceding study entry, and history of alcohol or drug abuse, depression, psychosis, or schizophrenia. The study was approved by the Ethics Committee of the VU Medical Center, and patients gave written informed consent.

After a screening visit, regular visits were scheduled at days 1, 14, and 28 and weeks 8, 10, 12, 16, 18, and 20. Patients received identical-appearing capsules containing dronabinol (THC = Marinol®, Unimed Pharmaceuticals, Inc.), *C sativa* plant extract (standardized THC content = 20 to 30% CBD and <5% other cannabinoids, Society for Oncological and Immunologic Research, Germany), and placebo for 4 weeks each.

During the first 2 weeks, study medication was administered in two daily doses of 2.5 mg THC or plant extract, containing the same level of THC. If well tolerated, the dose was elevated to 5 mg twice a day for the next 2 weeks. Patients were asked to take the capsules exactly 1.5 hours before the planned assessments during visit days. There was a 4-week washout between treatment periods. Patients underwent physical examinations and safety blood and urine tests throughout the study. An EKG was performed at enrollment, and women underwent pregnancy tests. Patients were not allowed to drive or to operate machinery while taking the drugs. To avoid unmasking, a "treating" physician was responsible for general medical care and safety management, whereas an "assessing" physician was responsible for the neurologic tests.

Muscle tone was measured using the Ashworth scale[6] (0 = normal, 1 = slight increase, 2 = more marked increase, 3 = considerable increase, 4 = limb rigidity in flexion or extension) for elbow flexors, extensors, pronators, and supinators; wrist and finger flexors; hip adductors; knee flexors and extensors; and foot plantar flexors bilaterally. Disability/impairment was measured using the EDSS, including functional systems, and a composite score (MSFC) of leg function/ambulation (timed 25-foot walk), arm/hand function (Nine-hole Peg Test), and cognition (Paced Auditory Serial Addition Test).[7] Subjective changes

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Table *Incidence and severity of adverse events at least possibly related to placebo, THC, or cannabis plant-extract treatment*

Treatment	Adverse event (frequency)	Mild	Moderate	Severe
Placebo	Total (20)	14	6	0
	Somnolence (4)	3	1	
	Increased spasticity (3)	1	2	
	Dizziness (3)	3		
	Headache (3)	3		
	Others (7)	4	3	
THC	Total (20)	18	2	0
	Dry mouth (5)	5		
	Headache (4)	4		
	Others (11)	9	2	
Plant extract	Total (41)	32	8	1
	Dizziness (6)	6		
	Increased spasticity (5)	2	3	
	Somnolence (5)	5		
	Headache (5)	4	1	
	Ataxia (3)	3		
	Dry mouth (3)	3		
	Emotional lability (3)	2	1	
	Others (11)	7	3	1

THC = Δ^9-Tetrahydrocannabinol.

were assessed using questionnaires including the MS-specific Fatigue Severity Scale, the Medical Outcomes Study Short Form 36,[8] and a health-related quality of life questionnaire.[9] In addition, daily Visual Analogue Scales were used to assess changes in spasticity, pain, tremor, fatigue, concentration, micturition, walking, vision, mood, and participant's global impression.

Statistical analysis. Incidence of adverse effects (AE) was analyzed by Cochran–Mantel–Haenszel tests. Efficacy was analyzed using a mixed linear model in case of interval data. Categorical and binary data were assessed by generalized estimating equations within a generalized linear model. p Values <0.1 were considered as statistical trend, and p values <0.05 as significant.

Results. Mean age was 46 years (SD = 7.9), mean disease duration was 15 years (SD = 10.7), and mean EDSS score was 6.2 (SD = 1.2). Six patients had used cannabis before, none on a regular basis. All patients completed the study, and none of the scheduled visits was missed.

Safety and tolerability. Both THC and plant-extract capsules were tolerated well. No serious AE emerged. AE were more common during plant-extract treatment compared with placebo treatment (OR = 1.9, $\chi^2 = 6.6$, $p = 0.01$). Five patients reported increased spasticity during plant-extract treatment (table 1). One AE was rated as severe—acute psychosis lasting for 5 hours after the scheduled dose increase of plant extract. No clinically relevant changes were observed for physical examinations or in hematology or chemistry measurements.

Efficacy. Compared with placebo, active treatment did not result in significant differences of muscle tone (figure 1) or EDSS score. However, worsening was found in the brainstem functional systems score (F = 4.3, $p = 0.08$) during plant-extract treatment, as well as in the total MSFC score (F = 4.6, $p = 0.09$) and the Nine-hole Peg Test score (F = 7.6, $p = 0.02$) during THC treatment. No significant change was found in fatigue. Although the Medical Outcomes Study Short Form 36 "mental health" subscale score (F = 8.1, $p = 0.02$) and the health-related quality of life questionnaire domain "psychological status" (F = 8.1, $p = 0.02$) improved during THC treatment, this was offset by worsening of the Visual Analogue Scale "subject's global impression" score (THC: F = 9.2, $p = 0.01$; plant extract: F = 7.1, $p = 0.02$; figure 2). During THC treatment, a trend for deterioration was found in the Visual Analogue

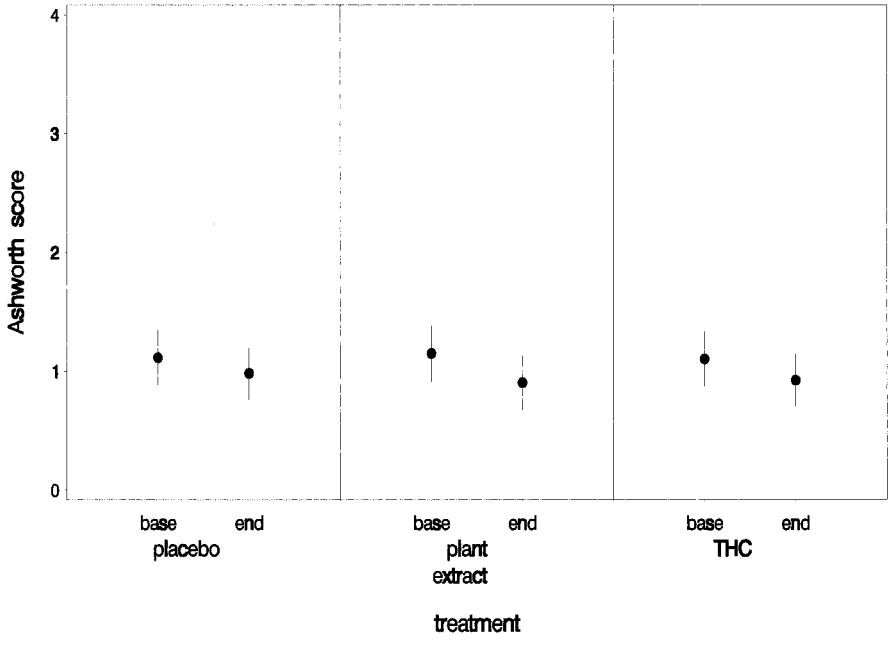

Figure 1. Change in Ashworth score in 16 patients with MS after 4 weeks of treatment (placebo, Cannabis sativa *plant extract, and Δ^9-Tetrahydrocannabinol). Mean and 95% CI are shown. The mean muscle tone score was calculated by dividing the sum score by the number of joints assessed. Decreasing scores represent improvement of spasticity. There were no significant differences in changes during active treatment compared with placebo.*

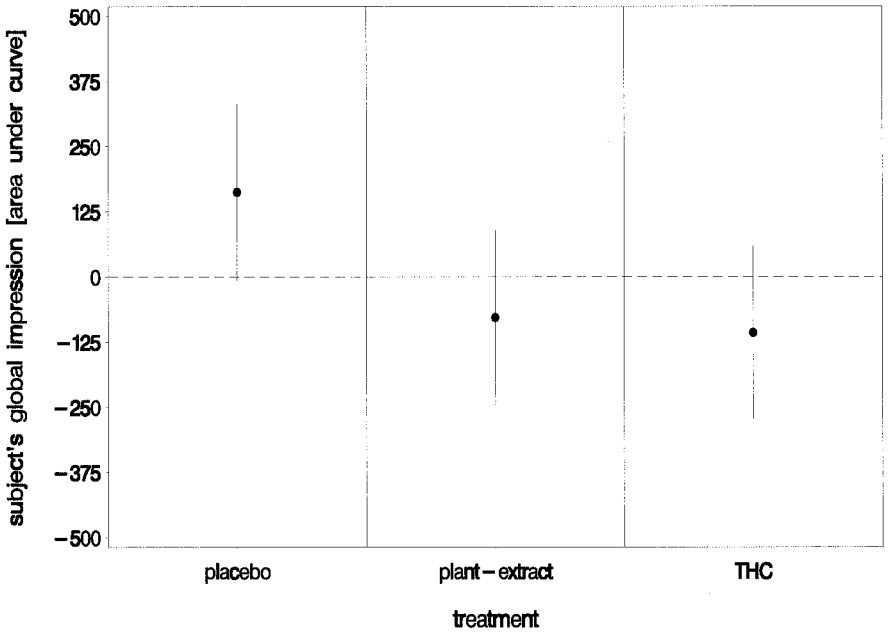

Figure 2. Change in daily Visual Analogue Scale "subject's global impression" score in 16 patients with MS after 4 weeks of treatment (placebo, Cannabis sativa *plant extract, and* Δ^9*-Tetrahydrocannabinol). Mean and 95% CI are shown. Scores less than zero represent worsening of a "subject's global impression" compared with baseline. Compared with placebo, both THC (F = 9.2,* p = *0.01) and plant-extract (F = 7.1,* p = *0.02) treatment resulted in lower scores.*

Scale "walking" score (F = 5.0, p = 0.08). No significant differences were found in Visual Analogue Scale scores rating spasticity.

Both patients and "treating" physician often guessed correctly whether the patients were on active treatment. However, the assessing physician guessed correctly only 25% of the time during placebo treatment and 31% of the time during plant extract and THC treatment, and stated "do not know" 50% of the time on average.

Discussion. No safety concerns emerged during the trial, and most AE were rated as mild. Because of the limited sample size no definite conclusions can be drawn. However, the results do not suggest therapeutic benefit of either THC or plant-extract treatment.

A recent report suggested that cannabinoids can alleviate spasticity in mice with chronic relapsing experimental autoimmune encephalomyelitis.[1] However, the compounds were used at concentrations that are not likely to be tolerated in humans.[10] Results of an early study in patients with MS (n = 9) suggested that single doses of either 5 or 10 mg oral THC reduced spasticity.[2] In a second pilot study with oral THC (n = 13), objective outcome measures were unchanged. However, the patients' self-report was that spasticity significantly improved.[3] In a single-dose study of smoked cannabis involving 10 healthy volunteers and 10 patients with MS, some patients noted subjective improvement.[5] However, objective measurements of posture and balance showed that the drug impaired these functions in both the healthy volunteers and the patients.

Although the sample size is too small to be conclusive, our study is currently the largest and the longest study addressing cannabinoid therapy in MS. A possible explanation for the lack of efficacy could be the route of administration. THC is absorbed reasonably well from the gut, but the process is slow, with a large range between and within individuals.[4] A second possible explanation could be the prescribed dose. However, the number of AE, especially during plant-extract treatment, does not support the use of higher dosing regimens. The plant extract used in this study contained 20 to 30% CBD. Animal studies have demonstrated that CBD administration interferes with drug metabolism in the liver and was associated with a substantial increase in CNS concentrations of THC. The increase in AE during plant-extract treatment was not accompanied by a positive trend in efficacy, therefore making it unlikely that persistent higher CNS concentrations of THC would be well tolerated and would lead to more favorable results.

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Prevalence and incidence of cluster headache in the Republic of San Marino

Abstract—Based on a preceding survey performed in 1985, the authors estimated the prevalence and incidence of cluster headache (CH) in the Republic of San Marino (26,628 inhabitants at 31 December 1999). All cases were diagnosed by direct interview according to International Headache Society criteria. The prevalence rate was 56/100,000 (95% CI 31.3 to 92.4), and the incidence rate was 2.5/100,000/year (95% CI 1.14 to 4.75). Most cases showed rare clusters. This is the first prospective study on the incidence of CH.

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Few studies have addressed the descriptive epidemiology of cluster headache (CH), focusing mainly on prevalence.[1-3] Only one retrospective incidence study was performed in Olmstead County, MN,[4] yielding an estimated incidence of CH of 9.8/100,000 population/year.

Here we present the results of a prospective study performed in the Republic of San Marino. The basis of this study was the previous survey performed 15 years ago.[5]

Methods. The Republic of San Marino is a small independent state situated within northeast Italy, near the Adriatic coast. All residents are entitled to free medical service, even if they consult doctors elsewhere. In this case, diagnosis and treatment are recorded in the patient's file. In the previous survey, we found 15 cases of CH with a prevalence rate of 69 cases/100,000 population at 31 January 1985. The population of the Republic of San Marino was 21,792 (10,893 men and 10,899 women) at 31 December 1985.

From 1 July to 31 December 1999, we carried out a new epidemiologic survey in the Republic of San Marino. The method was substantially the same as that used in the previous survey. As of 31 December 1999, the population was 26,628 (13,008 men and 13,620 women). Two neurologists of the San Marino Hospital reviewed all clinical records of neurologic, ophthalmologic, and otorhinolaryngologic consultations over the past 15 years to identify cases of suspect CH.

In July 1999, we sent a letter to each of 15 family physicians of the Republic of San Marino with a description of the clinical features of CH, asking them to contact us if they had in their records any case of suspected CH. Then we sent the same 1985 letter containing an explanation of the main characteristics of CH to every inhabitant of San Marino:

> We are searching for patients with a particular type of headache. This headache may be described as follows: . . . The pain is very severe, in the region of one eye and around it, always on the same side. Each attack usually lasts no more than 1–2 hours. These attacks occur once or more a day for shorter or longer periods.

Then we invited patients or relatives who had experienced a similar headache to be examined by a neurologist expert on headache.

Finally, two neurologist experts on headache examined all cases of suspected CH and made the diagnoses of CH according to the International Headache Society (IHS) criteria.[6]

As in the previous survey for the estimation of prevalence, we included patients with at least one typical period of CH in the past 15 years.

Results. We identified 43 patients with suspected CH, and the diagnosis was confirmed in 15 of them. Suspected and confirmed CH cases according to sources are shown in table 1.

In nine cases (Patients 1 to 9), the onset of CH was between 1 January 1985 and 31 December 1999. All patients were men. Mean age at onset was 29.6 years (range 15 to 53 years). Five patients (Patients 1, 2, 4, 6, and 9) had only one cluster. The other four had two (Patients 5, 7, and 8) or three (Patient 3) clusters with long periods of remission (see table 2).

Another six patients (Patients 10 to 15) were found in the previous survey (Patients 12, 10, 9, 13, 4, and 6 of the

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