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Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study

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Objective: *Cannabis may alleviate some symptoms associated with multiple sclerosis (MS). This study investigated the effect of an orally administered standardized* Cannabis sativa *plant extract in MS patients with poorly controlled spasticity.*

Methods: *During their inpatient rehabilitation programme, 57 patients were enrolled in a prospective, randomized, double-blind, placebo-controlled crossover study of cannabis-extract capsules standardized to 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD) each. Patients in group A started with a drug escalation phase from 15 to maximally 30 mg THC by 5 mg per day if well tolerated, being on active medication for 14 days before starting placebo. Patients in group B started with placebo for seven days, crossed to the active period (14 days) and closed with a three-day placebo period (active drug dose escalation and placebo sham escalation as in group A). Measures used included daily self-report of spasm frequency and symptoms, Ashworth Scale, Rivermead Mobility Index, 10-m timed walk, nine-hole peg test, paced auditory serial addition test (PASAT), and the digit span test.*

Results: *In the 50 patients included into the intention-to-treat analysis set, there were no statistically significant differences associated with active treatment compared to placebo, but trends in favour of active treatment were seen for spasm frequency, mobility and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency ($P = 0.013$) and mobility after excluding a patient who fell and stopped walking were seen ($P = 0.01$). Minor adverse events were slightly more frequent and severe during active treatment, and toxicity symptoms, which were generally mild, were more pronounced in the active phase.*

Conclusion: *A standardized* Cannabis sativa *plant extract might lower spasm frequency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs.*

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Key words: *cannabinoids; cannabis; mobility; multiple sclerosis; muscle spasms; rehabilitation; spasticity; THC*

Introduction

Painful muscle spasms are among the most common and distressing symptoms of multiple sclerosis (MS) and have a major influence on the quality of life.[1] Physiotherapy helps reduce spasticity, but anti-spastic medication may also help many of these patients.[2] The latter includes oral preparations such as baclofen,[3] dantrolene,[4] tizanidine[5] and recently gabapentin,[6] and injections of neurotoxic agents,[7] or even surgical placement of an intrathecal baclofen pump.[8] However, some of these therapeutic options are expensive or sometimes unavailable. Moreover the available oral anti-spasticity medications often only give partial relief and have gastrointestinal or psychotropic side effects. Additional therapies, easy to administer and with tolerable side effects, are therefore needed.

Anecdotal evidence,[9] preclinical data,[10] small clinical reports[11–18] and phase 2 trials,[19,20] suggest that cannabis derivatives may play a useful role in alleviating muscle spasms, tremor, pain and bladder dysfunction associated with MS. However, although many MS patients claim to have benefited from self-medication with cannabis either by smoking,[9] drinking herbal infusions or eating home-made cookies, so far there are no controlled clinical trials supporting the reclassification of cannabis preparations as a prescription medicine.

Cannabis sativa (hemp) is the unique source of a set of more than 60 oxygen-containing aromatic hydrocarbon compounds known as cannabinoids.[21] Among these, Δ^9-tetrahydrocannabinol (THC) is largely responsible for the psychopharmacological properties and physical effects of cannabis. The detection of cannabinoid receptors throughout the CNS (CB1 receptors),[22] and in the peripheral immune system (CB2 receptors)[23] as the molecular targets of THC, has led to a better understanding of the possible mechanisms of action of the cannabinoids as well as of

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endogenous ligands (anandamides) of the CB-receptors. There is some evidence that other cannabinoids contribute to the therapeutic effects of THC. Cannabidiol (CBD), the second main cannabinoid, may also help alleviate pain, spasticity and fatigue. Furthermore, CBD may attenuate the psychotropic effects of THC, block heart rate acceleration due to THC, normalize the slowing of time perception induced by THC and reduce feelings of drowsiness, physical weakness and cognitive impairment when compared to THC alone.[24] It thus seems likely that a combination of THC and CBD (as is present in cannabis plant extracts) may give the drug more balance with regard to side effects that often limit the use of synthetic or isolated THC alone.

The aim of this study was to determine the tolerability, safety and the clinical effects on spasm frequency of an add-on therapy with an orally administered standardized cannabis extract compared to placebo in patients with MS with persistent spasticity not responding to other drugs.

Methods

This was a randomized, double-blind, placebo-controlled cross-over parallel group study. It was carried out in a 60 bed in-patient rehabilitation centre in Switzerland that predominantly treats patients who have MS.

Patients were eligible for the study if they had clinically confirmed MS and clinically stable spasticity with at least one joint scoring ≥ 2 on the Ashworth scale.[25] They were excluded if they had significant neurological (other than MS), cardiovascular or infectious diseases; clinical disease exacerbation or treatment with steroids during the two months preceding study entry; history of alcohol or drug abuse; depression (Beck Depression Index > 11);[26] history of psychosis; use of cannabinoids during the week prior to inclusion; or significant cognitive impairment (Short Orientation Memory Concentration Test < 21).[27]

The study was approved by the Ethics Committee of the medical faculty of the University of Bern and by the Swiss Federal Office of Public Health. Eligible patients who gave written informed consent and had a urine test negative for cannabinoids were included.

The study design was subject to some practical time constraints. Patients were usually only admitted for 28 days and follow-up after that was not possible because most patients came from far away. After three days for taking informed consent, screening and baseline measures, five days for dose titration and an additional nine days on maintenance dose were needed to allow benefits to be seen. Therefore, just seven days for placebo phase and three days of wash-out between phases could be provided. Though the schedule of actions was not similar in timing between the two groups, neither the patients nor the assessing physician knew the exact association between a given schedule and its respective treatment regime.

The active drug was a whole-plant cannabis extract containing 2.5 mg THC and 0.9 mg CBD in a gelatine capsule to be taken orally as an add-on therapy. Placebo capsules were identical in shape, taste and colour.

Throughout the study, patients were given 12 capsules daily in three divided doses (four capsules – at noon, in the late afternoon and at bedtime together with a glass of milk), but the proportion of 'active' and 'placebo' capsules was varied by an unblinded study nurse according to (a) the patient's group, and (b) during the four-day dose escalation phase, according to the patient's report of side effects. During the dose escalation phase a patient started with six active capsules daily (equivalent to 15 mg THC/day). Each day the 'treating physician' (who was different to the 'assessing physiotherapist' rating treatment effects) asked the patient about his/her perception of benefits and side effects and requested the unblinded study nurse to increase or not to increase the dose accordingly. The maximum increase allowed was two capsules each day, with the overall maximum dose being 12 active capsules daily (equivalent to 30 mg THC/day). After 14 days of active treatment, patients were switched to placebo capsules without tapering the active dose. Consequently, the unblinded nurse knew the patient's group and status, but this information was not disclosed to any other person. Throughout the study, patients received rehabilitation from staff that were not aware of the patient's group, and all anti-spasticity medication was continued without change.

Randomization was by a randomization list established by the trial statistician using SAS® version 8.2 (SAS Inc., Cary, NC), and held by the principal investigator (CV), allocating sequentially the next randomization code to the next patient who had successfully passed screening measurements. Patients were randomized to early (group A) or late (group B) active treatment.

The assessments used at each assessment point were:

- The Ashworth scale of muscle tone,[25] which was the primary outcome measure (with 0 = normal, 1 = slight increase when the limb is moved, 2 = more marked increase but not restricting movement, 3 = considerable increase limiting passive flexion, and 4 = limb rigidity in flexion or extension). This was applied bilaterally to elbow flexors and extensors, wrist flexors and extensors, hip flexors, extensors and adductors, knee flexors and extensors, and foot plantar flexors and extensors. The mean scores over the left and right side were summed up over all eleven joints assessed, yielding an overall score for muscle tone of 0–88. Missing values for single joints were replaced for analysis by the patient's mean value from all other joints.
- The Rivermead Mobility Index (RMI)[28] and 10-m timed walk for people able to walk.[28]
- The nine-hole peg test (9HPT).[29]

In addition, the Nottingham Extended ADL Index (NEADL)[30] was recorded at the initial point referring to the month before admission, and at the start and end of the whole trial the EDSS,[31] the paced auditory serial addition test (PASAT)[32] and the digit span of the WAIS R intelligence scale[33] were recorded.

Each patient recorded spasm-frequency scales five times daily referring to the preceding four hours (0 = no spasms; 1 = 1–3 spasms; 2 = 4–6 spasms; 3 = > 6 spasms). Finally each patient recorded daily, using diary-based questionnaires, their experience of tremor, micturition problems, and sleep disturbances.

The following means were used to reduce data variability and bias. The number of capsules administered daily was always 12 (four capsules three times daily); there was a sham dose escalation during placebo phase; patients were asked for tolerability every day throughout the treatment period – not just during true dose-escalation; and the measures were rated by an assessing physiotherapist not informed about tolerability and side effects obtained by the treating physician. The four physiotherapists were specially trained by a senior therapist (BG) using defined guidelines to ensure that the Ashworth rating would be performed in a reliable way throughout the study. Moreover, each individual patient was rated by the same physiotherapist throughout the study. There was at least a two hour interval between physiotherapeutic treatments and the assessment of spasticity.

Adverse events were recorded every day and rated as 'mild' (does not interfere with routine activities), 'moderate' (interferes with routine activities) and 'severe' (subject is unable to perform routine activities). All patients had physical examinations including cardiovascular assessments and body temperature every day. A questionnaire (derived from a drug reaction scale developed by Musty for cannabis-induced reactions[34]) within a diary was used to assess subjective changes as perceived by the patients themselves. It consisted of 16 statements concerning mainly a patient's emotional and psychical well being that could be rated on a Likert scale numbered from 0 ('not at all') to 10 ('extremely intense'). Patients had haematology and biochemical blood tests and urinalysis at screening day and after every treatment period. All patients had a standard electrocardiogram (ECG) at enrolment and all women of childbearing potential had a pregnancy test before study entry.

All analyses were performed with the statistical analysis system SAS® version 8.2 (SAS Inc., Cary, NC). The intention-to-treat analysis-set was defined as all patients who finished at least one study phase and provided at least minimal data on outcome for the second phase unless otherwise indicated. However, safety data were analysed from all patients, which received at least one dose of study medication.

The correlation between body weight and eventually tolerated dose was assessed by Spearman's rank correlation coefficient. The questionnaire regarding cannabis-induced toxicity, all laboratory parameters and vital signs were tested by t-tests for differences between treatment periods.

All efficacy parameters were analysed as change from baseline of each treatment period except for the 10-m timed walk and the patient's report of tremor. Mixed linear modelling[35] or the generalized estimating equations (GEE) within generalized linear models[36] were used. Available baseline values were included in the model as covariables. Period and carry-over effects, initially included in the statistical models, were removed from the final model if their effect was nonsignificant.[37] Missing observations were replaced by Last Observation Carried Forward.

No sample size calculation was performed because relevant data were not available, but it was anticipated that this study would give useful data on use and tolerability of the capsules, safety and some guidance on efficacy. No correction of the error levels for multiple testing has been performed. Thus, all tests comparing efficacy between active drug and placebo are reported with their local P-values, serving as flags for differences that would be statistically significant ($P < 0.05$) if chosen as primary efficacy criterion.

Results

During recruitment time between April 2000 and April 2001, 348 MS patients were routinely admitted to the rehab hospital, and the demographic and clinical baseline data of the 57 patients who underwent screening measurements and entered into this study are summarized in Table 1. Patients in group A tended to be more disabled, a divergence that reached significance for the Nottingham Extended ADL index ($P < 0.05$). Groups were balanced regarding the type of MS disease (13 primary progressive, 14 secondary progressive, 1 relapsing–remitting in group

Table 1 Demographic and baseline data

Item	*Group A*, n = *28*	*Group B*, n = *29*	*Total*, n = *57*
Male:female	13:15	12:17	28:29
Age mean (SD) years	53.8 (9.4)	56.1 (10.6)	54.9 (10.0)
EDSS median (range)	7.5 (5.5)	7.0 (5.5)	7.0 (6.0)
Disease duration mean (SD) years	17.1 (7.3)	17.0 (9.5)	17.0 (8.4)
Ashworth mean (SD); range	12.4 (6.2); 26	12.5 (6.4); 25.5	12.5 (6.2); 26
Spasm frequency score mean (SD)	1.04 (0.78)	1.06 (0.69)	1.05 (0.73)
PASAT number correct mean (SD)	16.7 (17.2)	22.5 (23.6)	19.9 (20.9)
NEADL score mean (SD)*	8.8 (5.8)	11.7 (4.4)	10.4 (5.2)
RMI score mean (SD)	4.3 (4.4)	5.8 (4.2)	5.1 (4.3)
FIM score mean (SD)	90.8 (27.1)	101.0 (18.0)	96.1 (23.2)
Previously used cannabis	15	18	33

*Difference between groups A and B: $P < 0.05$.

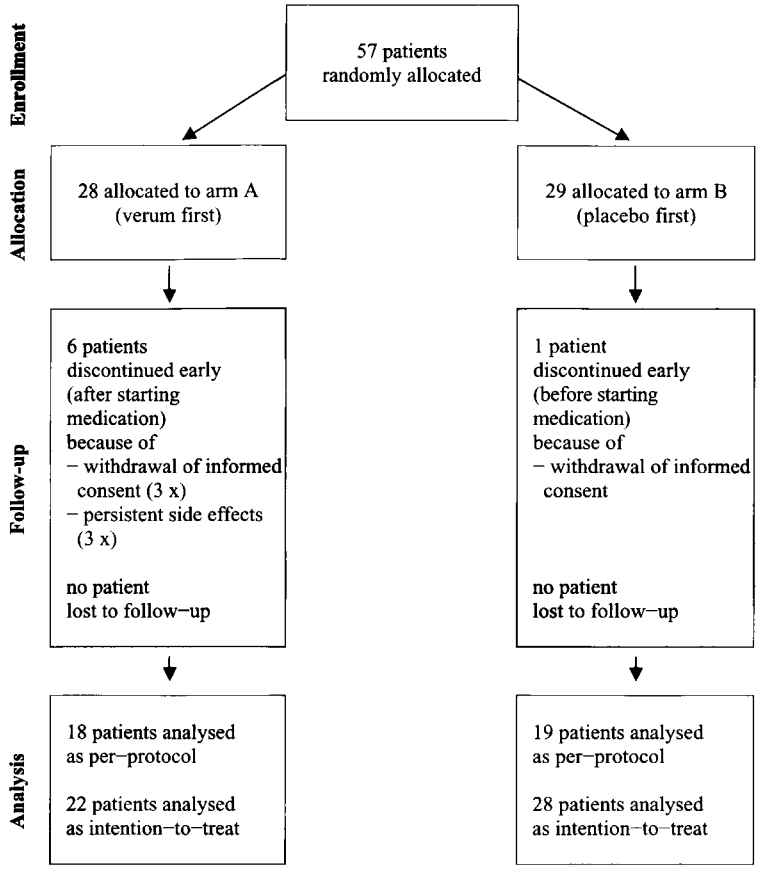

Figure 1 *CONSORT – flow diagram.*

A, 16/12/1 in group B). No urine sample tested positive for cannabinoids at entry or in any nontreatment phase.

The flow and loss of patients through the trial is shown as CONSORT diagram (Figure 1). Five of the six patients who withdrew on starting with active medication (group A) had no previous exposure to cannabis. Other clinical characteristics of the seven drop-outs were not different from the 50 patients who were included in the intention-to-treat analysis set. Thirty-seven patients finished their study participation per-protocol (i.e., took 90% or more of prescribed dose).

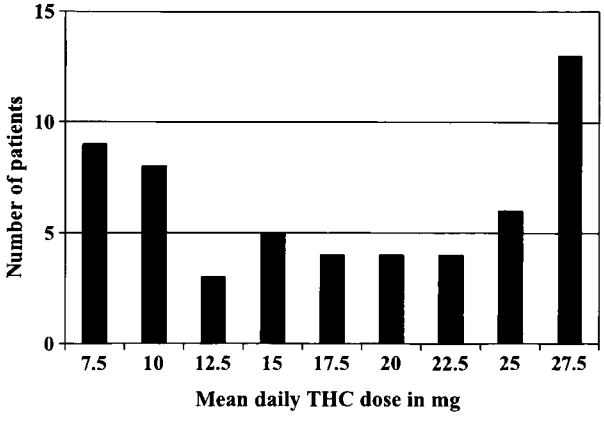

Figure 2 *Mean dosage of THC in the cannabis phase.*

As shown in Figure 2, the maximally tolerated THC dose exhibited a bimodal distribution. In the 50 patients of the ITT set, there was a weak but significant correlation between the mean tolerated dose during the dose maintenance phase and body weight ($r = 0.31$, $P < 0.05$). On average, patients in group A tolerated significantly higher doses than patients in group B (20.0 ± 9 mg/day versus 14.5 ± 8.7 mg/day; $P < 0.01$). At baseline, THC-naive patients tolerated the same or even slightly higher THC doses than patients with regular or occasional cannabis use in their history, with the exception of the five THC-naive patients mentioned above who withdrew early with side effects.

In general, cannabis extract was well tolerated. No serious adverse events emerged during the trial. Adverse events (AEs) were slightly more frequent and more severe during active treatment (Table 2). One patient in group B fell on her shoulder during the initial placebo phase and could not use her stick for walking which limited her mobility. She nevertheless insisted on continuing to take the study medication. The daily questionnaire for the assessment of cannabinoid toxicity – represented as the arithmetic mean of the 16 statements concerning emotional and physical states – was generally rated very low but showed a significantly higher toxicity level during active treatment (mean intraindividual difference between cannabis and placebo period 0.3 ± 0.4 units; $P < 0.001$).

No clinically relevant changes were observed in physical examinations, including pulse, blood pressure and

Table 2 Frequency and severity (mild/moderate/severe) of all adverse events reported

Adverse event	*Verum*		*Placebo*	
	Frequency	*Severity*	*Frequency*	*Severity*
Dizziness	11	5/4/2	10	7/2/1
Euphoria, 'high'	10	3/6/1	8	7/1/0
Difficulty concentrating	10	3/6/1	9	7/2/0
Nausea, feeling sick	4	2/2/0	1	1/0/0
Constipation	1	0/1/0	5	5/0/0
Pain in extremities	1	1/0/0	2	1/1/0
Dry mouth	2	1/1/0		
Blurred vision	2	0/2/0		
Tremor or shakes	1	0/1/0		
Flu-like symptoms	1	0/1/0		
Inadequate laughing	1	1/0/0		
Sleepiness	1	0/0/1		
Sleeplessness			2	0/2/0
Feeling aggressive			1	1/0/0
Palpitations			1	1/0/0
Headache			1	1/0/0

body temperature, or in any haematology or biochemistry parameter.

The effect of active treatment on the clinical measures is shown in Tables 3 and 4. Generally, there were no statistically significant differences associated with active treatment phase. The trend for improvement in spasm frequency associated with active treatment ($P = 0.058$ in the ITT set) became more obvious when restricting analysis to the 37 patients who took treatment consistently throughout the active phase ($P = 0.013$ in the per-protocol set). Patients also tended to fall asleep more easily while on active treatment ($P = 0.07$). The slight trend in improvement in the RMI ($P = 0.15$) became significant ($P = 0.003$ in the ITT set) on removal of the patient who lost mobility following a fall in her placebo phase. There was a significant improvement over the whole trial period for both measures of concentration/attention, the PASAT ($P = 0.0003$) and the digit span test ($P = 0.0014$), but there were no significant differences between the two treatment regimes.

Finally it is worth noting that patients improved markedly over the whole study period. For example, the Ashworth score improved from a mean (SD) of 13.3 (6.2) to 11.1 (6.3) ($P = 0.0018$), the spasm frequency from 1.1 (0.7) to 0.7 (0.6) ($P = 0.0002$; Figures 3 and 4), and the RMI from 5.0 (4.3) to 5.5 (4.6) ($P = 0.005$).

Discussion

This randomized, double-blind, placebo-controlled crossover study of an orally administered standardized *Cannabis sativa* plant extract in patients with MS-induced spasticity has found the extract to be safe and well tolerated, and that it may reduce spasm frequency. The major limitations were the small number of patients,[57] the short phase of active treatment (14 days), and the general limitations in the measurement of spasticity.

The constraints on study design and duration made this study a preliminary and exploratory one, able to investigate safety and efficacy but unlikely to reach firm conclusions. Furthermore, this was an investigation of cannabis extract when added to existing treatments, the only ethically appropriate design, but a design that makes proving efficacy more difficult.

Side effects during active and placebo treatment were rather similar in frequency but, as expected, more pronounced in severity during plant-extract treatment. However, the generally low incidence of cannabinoid-related

Table 3 Efficacy parameters – changes over total trial (ITT analysis set)

	Total trial period		*Difference*	*Statistics*	
	Begin	*End*		*Test value*	*Probability*
Parameter [*n*]					
Ashworth [50]	13.3 ± 6.2[a]	11.1 ± 6.3[a]	− 2.2 ± 1.4[c]	− 3.31[e]	0.0018
EDSS [49]	7.09 ± 1.13[a]	7.09 ± 1.12[a]	− 0.01 ± 0.04[c]	− 0.57[e]	0.5691
FIM [48]	94.2 ± 23.9[a]	95.5 ± 23.7[a]	0.4 ± 0.7[c]	1.13[e]	0.2648
RMI [50]	5.0 ± 4.3[a]	5.5 ± 4.6[a]	0.6 ± 0.4[c]	2.92[e]	0.0053
9-HPT [47]	64.9 ± 54.0[a]	58.7 ± 52.7[a]	− 5.6 ± 10.2[c]	− 1.10[e]	0.2749
Pasat [38]	20.8 ± 21.1[a]	37 ± 26.7[a]	17.9 ± 9.1[c]	3.97[e]	0.0003
Digit span [46] [50]	12.1 ± 3.7[a]	13.7 ± 4.3[a]	1.5 ± 0.9[c]	3.41[e]	0.0014
Diary					
Spasms [49]	1.1 ± 0.7[a]	0.7 ± 0.6[a]	2.86 (1.76–4.63)[d]	14.14[f]	0.0002
Micturition [36]	2.1 ± 0.8[a]	2.0 ± 0.8[a]	1.05 (0.53–2.12)[d]	0.02[f]	0.8820
Tremor [36]	0.43 ± 0.51[b]	0.19 ± 0.4[b]	3.15 (1.33–7.46)[d]	4.80[f]	0.0285
Falling asleep fast [50]	0.58 ± 0.5[b]	0.62 ± 0.49[b]	1.18 (0.55–2.54)[d]	0.18[f]	0.6698
Waking up again [50]	0.76 ± 0.43[b]	0.72 ± 0.45[b]	1.23 (0.61–2.49)[d]	0.33[f]	0.5637

[a]Arithmetic mean ± standard deviation.
[b]Ratio of patients answering affirmatively to the corresponding question ± standard deviation.
[c]Mean change from trial begin ± 95% confidence interval.
[d]Odds ratio for being in a more favourable class during cannabis treatment (plus 95% confidence range).
[e]Student's *t*-value.
[f]χ^2-value.

Table 4 Efficacy parameters – differences between treatments in change over treatment period (ITT analysis set)

	Placebo period		*Cannabis period*		*Difference*	*Statistics*	
	Begin	*End*	*Begin*	*End*		*Test value*	*Probability*
Parameter [*n*]							
Ashworth [50]	13.1 ± 6.3[a]	11.5 ± 6.1[a]	12.2 ± 6.4[a]	11.6 ± 6.5[a]	− 0.8 ± 1.3[c]	− 1.2[f]	0.2379
RMI [46]	5.3 ± 4.4[a]	5.3 ± 4.4[a]	4.8 ± 4.4[a]	5.3 ± 4.7[a]	− 0.3 ± 0.5[c]	− 1.46[f]	0.1524
9-HPT [46]	58.2 ± 41[a]	59.5 ± 48.3[a]	63.8 ± 51.3[a]	64.3 ± 63.5[a]	− 3.5 ± 16.6[c]	− 0.43[e]	0.6705
10-m walk [18][h]	–	50.7 ± 65[a]	–	60.0 ± 87.5[a]	− 9.3 ± 12.9	− 1.53[f]	0.1454
Pasat [38]	25.5 ± 23.7[a]	31.0 ± 26.1[a]	23.9 ± 23.4[a]	28.5 ± 25.8[a]	3.6 ± 7.9[c]	0.92[f]	0.3618
Digit span [46]	12.7 ± 3.7[a]	12.9 ± 3.9[a]	12.4 ± 4[a]	13.2 ± 3.4[a]	− 0.5 ± 1.0[c]	− 1.09[f]	0.2813
Diary							
Spasms [49]	0.9 ± 0.7[a]	0.8 ± 0.7[a]	1.0 ± 0.8[a]	0.7 ± 0.5[a]	1.78 (0.99–3.19)[c]	3.59[g]	0.0583
Micturition [34]	2.1 ± 0.8[a]	2.1 ± 1.0[a]	2.1 ± 1.0[a]	2.0 ± 0.9[a]	1.06 (0.42–2.7)[c]	0.02[g]	0.8986
Tremor [26][h]	–	0.21 ± 0.41[b]	–	0.21 ± 0.42[b]	0.95 (0.42–2.15)[e]	0.01[g]	0.9082
Falling asleep fast [50]	0.62 ± 0.49[b]	0.64 ± 0.48[b]	0.66 ± 0.48[b]	0.78 ± 0.42[b]	2.13 (0.95–4.74)[e]	3.21[g]	0.0730
Waking up again [50]	0.76 ± 0.43[b]	0.74 ± 0.44[b]	0.76 ± 0.43[b]	0.66 ± 0.48[b]	1.69 (0.63–4.59)[e]	1.04[g]	0.3082

[a]Arithmetic mean ± standard deviation.
[b]Ratio of patients answering affirmatively to the corresponding question ± standard deviation.
[c]Difference between treatments regarding change over treatment periods ± 95% confidence interval.
[d]Difference between measurements at the end of each treatment period ± 95% confidence interval.
[e]Odds ratio for being in a more favourable class at the end of the cannabis period (plus 95% confidence range).
[f]Student's *t*-value.
[g]χ^2-value.
[h]No baseline data are reported as they were only irregularly recorded.

toxicity was surprising given the fact that 27 patients (54% of ITT set) had a maintenance dose of 20 mg THC/day or above, which is, within the limited range of current clinical experience, quite a lot for oral administration.

Previous reports have shown that THC gives rise to concentration difficulties and many study patients reported these. However, the cognitive tests improved steadily during the study and by even more than 6 points compared to what can be expected from bare practice effects well known for the PASAT.[38] As we did not perform any trials before entering the study, the observed improvement in the PASAT is, however, mostly due to a practice effect.

The benefits on spasm frequency, though nonsignificant, are consistent with other studies,[20] as are the beneficial effects upon sleep.[20] It should be noted that the Ashworth score, although being a reliable and most acknowledged tool, may not be sensitive enough to record changes that still might be clinically relevant as suggested by a recent Cochrane review.[39] Furthermore, it must be questioned if disturbance of muscle tone by strong antispastic agents is in every case clinically meaningful as disability in MS patients seems more clearly related to weakness than to spasticity.[40]

The fact that the spasm frequency reduction was more marked for patients in group A who tolerated a significantly higher THC dose (mean 15 versus 10 mg/day) confirms previous observations that efficacy may be dose related. In one study, beneficial effects were only observed for doses of $\geq$ 7.5 mg THC/day.[18] Conversely, Killestein *et al.* failed to demonstrate a clinical benefit of synthetic THC (Marinol®) and cannabis extract compared to placebo with a fixed dose of 5 mg THC/day for two weeks followed by 10 mg THC/day for a further two weeks.[19]

The lack of any general effect on disability is unsurprising. Spasticity is only one of several impairments affecting

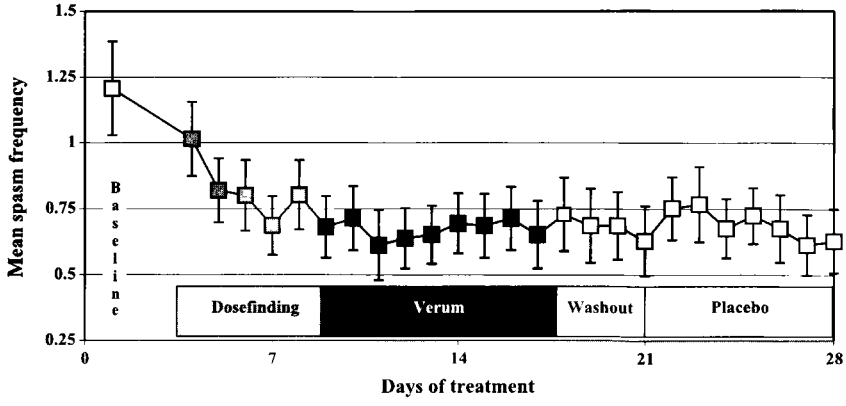

Figure 3 *Spasm-Frequency-Protocol (arm A): mean of five observation periods per day. Values are mean ± SEM. (0 = no spasm; 1 = 1–3 spasms; 2 = 4–6 spasms; 3 = > 6 spasms).*

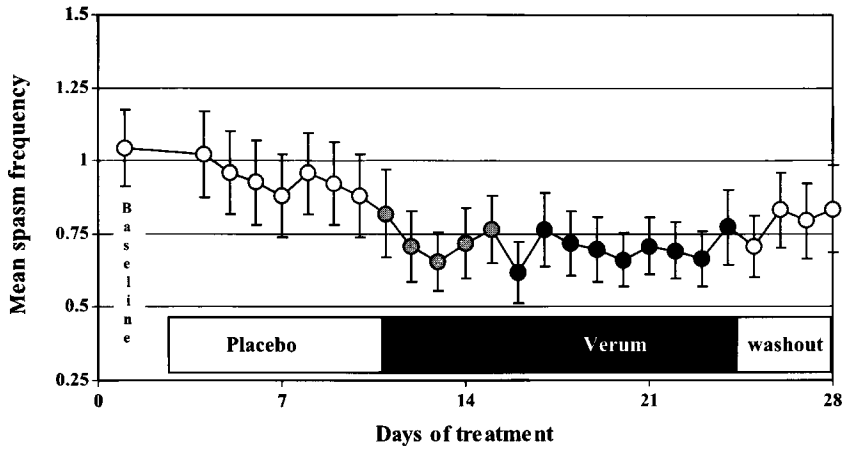

Figure 4 *Spasm-Frequency-Protocol (arm B): mean of five observation periods per day. Values are mean ± SEM. (0 = no spasm; 1 = 1–3 spasms; 2 = 4–6 spasms; 3 = > 6 spasms).*

activities such as mobility. Moreover, the short study time would not allow any patient to capitalize upon any potential benefit. Indeed it is surprising that secondary analysis suggested that there may have been an effect upon mobility as measured using the RMI.

In conclusion, this randomized, double-blind, placebo-controlled explorative study suggests that a *Cannabis sativa* plant extract might be beneficial to lower spasm frequency and to increase mobility with tolerable side effects. Future research is needed to investigate the efficacy and safety of cannabis derivatives in patients with MS using, if at all possible, improved ways of measuring spasticity in larger patient groups over a longer period of time.

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