Original Article

The treatment of spasticity with Δ^9 -tetrahydrocannabinol in persons with spinal cord injury

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Study design: Open label study to determine drug dose for a randomized double-blind placebo-controlled parallel study.

Objectives: To assess the efficacy and side effects of oral Δ^9 -tetrahydrocannabinol (THC) and rectal THC-hemisuccinate (THC-HS) in SCI patients.

Setting: REHAB Basel, Switzerland.

Method: Twenty-five patients with SCI were included in this three-phase study with individual dose adjustment, each consisting of 6 weeks. Twenty-two participants received oral THC open label starting with a single dose of 10 mg (Phase 1, completed by 15 patients). Eight subjects received rectal THC-HS (Phase 2, completed by seven patients). In Phase 3, six patients were treated with oral THC and seven with placebo. Major outcome parameters were the spasticity sum score (SSS) using the Modified Ashworth Scale (MAS) and self-ratings of spasticity.

Results: Mean daily doses were 31 mg with THC and 43 mg with THC-HS. Mean SSS for THC decreased significantly from 16.72 (± 7.60) at baseline to 8.92 (± 7.14) on day 43. Similar improvement was seen with THC-HS. We observed a significant improvement of SSS with active drug ($P=0.001$) in the seven subjects who received oral THC in Phase 1 and placebo in Phase 3. Major reasons for drop out were increase of pain and psychological side effects.

Conclusion: THC is an effective and safe drug in the treatment of spasticity. At least 15–20 mg per day were needed to achieve a therapeutic effect.

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Keywords: spinal cord injury; spasticity; pain; THC; cannabinoid; cannabis

Introduction

Preparations of the hemp plant (*Cannabis sativa* L.) have a long history in medical treatment of neurological disorders. The oldest reports of medicinal applications originate in China and Egypt two thousand years BC. A traditional Chinese herbal ascribed to the Emperor Shen-nung who lived in the third millennium BC recommends the use of cannabis for the treatment of pain and beriberi, among other indications. As beriberi, a vitamin deficiency disease of thiamine (vitamin B1), is accompanied by several neurological symptoms it can be assumed that cannabis was used to alleviate these problems.¹ In India the Ayurvedic tradition of using cannabis dates back to early pre-Christian centuries, its applications including epilepsy, neuralgic pain and tetanus. Indian hemp found its way into modern western medicine in the 19th century. Many physicians of the

time including Sir John Russell Reynolds, personal physician of Queen Victoria, praised the analgesic and muscle relaxing effects of the drug.²

It was not before the 1960s that the chemical structure of the main active compound of cannabis, (–)-trans- Δ^9 -tetrahydrocannabinol (THC, dronabinol) was characterized, allowing first clinical studies with exact doses. Surveys among patients with multiple sclerosis and spinal cord injury (SCI), who used cannabis to treat their symptoms,^{3–6} case reports^{7,8} and small clinical studies with dronabinol and other synthetic cannabinoids^{9–13} suggest that cannabis and single cannabinoids may be useful medicines in spasticity and spasms.

As the detection of an endogenous cannabinoid system consisting of specific cannabinoid receptors (CB₁ and CB₂) and their endogenous ligands, so called endocannabinoids, in the late 1980s and 1990s our understanding of the mechanisms of action of THC has considerably improved.¹⁴ THC binds to both CB₁ and

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CB₂ receptors. Both cannabinoid receptor types are coupled through inhibiting G proteins, negatively to adenylate cyclase and positively to mitogen-activated protein kinase. In addition, CB₁ receptors are coupled to several ion channels. CB₁ receptors are found in particularly high concentrations within the central nervous system. They are also present in certain peripheral organs and tissues, including peripheral nerve terminals.¹⁵ Within the central nervous system, the distribution pattern of CB₁ receptors is heterogeneous and can account for several prominent pharmacological properties of cannabinoid receptor agonists. For example, there is evidence that the basal ganglia are richly populated with CB₁ receptors and that these receptors mediate the well documented ability of CB₁ receptor agonists to alter motor function.¹⁶

Spasticity in SCI is difficult to treat with drugs that are currently available. In a review by Tarrico *et al*,¹⁷ intrathecal administration of baclofen resulted in a significant improvement in the Ashworth Scale and activities of daily living (ADL). Tizanidin resulted in improved spasticity scores, but did not improve ADL and side effects (sleepiness, xerostomia) were common. Other oral drugs (gabapentin, clonidin, diazepam and oral baclofen) were not shown to be efficacious compared to placebo. In addition to systemic treatment, focal treatment for spasticity in those with SCI includes injections with botulinum toxin and surgical interventions. In many cases treatment results are unsatisfactory, raising the need for new therapeutic options.

Recent larger placebo-controlled trials investigating the efficacy of cannabis and THC in spasticity have been restricted to MS patients.^{18–22} In contrast to spasticity in MS, that may be of supra-spinal and spinal origin, spasticity in patients with SCI is solely based on spinal

lesions. We conducted a double-blind placebo-controlled parallel study (Phase 3) of oral THC (dronabinol, MarinolTM) in patients with SCI to investigate its effects on spasticity of spinal origin (Phase 3). This double-blind trial was preceded by an open label dose finding study with oral THC (Phase 1) and an open label dose finding study with rectal THC-HS (Phase 2).

Patients and methods

Subjects

Twenty-five patients (two females, 23 males) with traumatic SCI aged 19–73 years (mean: 42.6 years) participated in the study (see Table 1). Eleven were paraplegics, 14 tetraplegics. Participants terminated taking all spasmolytic medication at least three half-life periods before enrolling in the study. They had to be free of illegal drugs, documented with a negative urine drug screen at baseline. Pregnant subjects or those with severe somatic and known psychiatric diseases were excluded. Spasticity without any spasmolytic treatment had to be ≥ 3 points on the Modified Ashworth Scale (MAS)²³ in at least one muscle group.

Material

Active treatment consisted of oral synthetic THC (dronabinol, MarinolTM) containing either 2.5, 5 or 10 mg Δ^9 -THC in sesame oil and was delivered by Solvay (Unimed/Roxane) Pharmaceutical Inc., OH, USA. Solvay also delivered the placebo capsules containing only sesame oil. THC-HS suppositories were delivered by ElSohly Laboratories Inc., Oxford, MS, USA. THC-HS suppositories contained an equivalent of 5 and 10 mg THC.

Table 1 Patients' characteristics in study phases

Phases	Phase 1 open label	Phase 2 open label	Phase 3 parallel study randomized double-blind placebo-controlled	
Medication	Oral THC (Marinol TM) capsules	Rectal THC-HS suppositories	Oral THC or placebo	
N	22	8	13	
N			7 Placebo	6 Verum
<i>Patients characteristics</i>				
Age: mean (range)	40.9 year (19–73)	48.8 year (32–66)	39.0 year (29–66)	42.8 year (36–48)
Sex: male/female	20/2	8/0	6/1	5/1
Paraplegia ^a	11	3	4	4
Tetraplegia ^b	11	5	3	2
ASIA ^c (A/B/C/D)	6/4/4/8	1/3/2/2	3/1/0/3	2/0/2/2
Years postinjury	13.3 year (2–29)	15.5 year (5–28)	15.6 year (6–28)	13 year (3–29)
Drop outs	7	1	0	0
Completed phase	15	7	13	

^aParaplegic patients: levels of injury T4–T11

^bTetraplegic patients: levels of injury C4–C6

^cASIA (American Spinal Injury Association) Impairment Scale: assessment for defining the extent of SCI of motor and sensory pathways

Approvals

The export of the material from the USA has been approved by the Drug Enforcement Administration (DEA), and the import to Switzerland by the Swiss Federal Office of Public Health (BAG permit No. 92). The Ethics Committee of the University of Basel approved the study design (protocol No M3/96), which followed the Helsinki Declaration.

Outcome variables

To assess spasticity the MAS (see Table 2) was performed consecutively by two independent physicians. The original scale (0, 1, 1+, 2, 3, 4) has been recoded to 0–5. Tests were carried out bilaterally for six joints: arm abductors/adductors, elbow extensors/flexors, wrist extensors/flexors, hip extensors/flexors, knee extensors/flexors, foot extensors/flexors. For every joint, four values were documented (left/right/examiner 1 and 2). Spasticity sum score (SSS) was calculated by addition of all examinations divided by 4. Ergometry was performed with arm crank Ergoline Cardiovit AT-10/Schiller (Baar, Switzerland), pulmonary function tests were performed with a Spirovit SP-10/Schiller (Baar, Switzerland). Bladder cystomanometry was examined with UROSKOP D 3/Siemens (Munich, Germany) and included the following parameters: first desire to void (FDV), maximum cystometric capacity (MCC), intravesical pressure (IP), bladder compliance (BC), postvoid residual urine volume (PVV), volume at first detrusor contraction (VFC). The functional independence measure (FIM)²⁴ was used to assess ADL²⁴ and the Hamilton Rating Scale for Depression (HRSD)²⁵ to measure mood alterations.

Table 2 Modified Ashworth Scale

0 = No increase in muscle tone
1 = Slight increase in tone with a catch and release or minimal resistance at end of range
2 = As 2 but with minimal resistance through range following catch
3 = More marked increase tone through ROM
4 = Considerable increase in tone, passive movement difficult
5 = Affected part rigid

Standardized computerized neuropsychological tests included the continuous performance test (CPT)²⁶ for sustained attention and the Deux Barrages (DB)²⁷ test for selective spatial attention.

For self-ratings of spasticity, pain, attention, mood and side effects, a seven-point scale from 0 to 6 was used. For spasticity and pain it was 0 = no spasticity/pain, 1 = minimal, 2 = minor, 3 = moderate, 4 = strong, 5 = very strong, 6 = intolerable. Both mood and attention were scaled as follows: 0 = very bad, 1 = bad, 2 = rather bad, 3 = moderate, 4 = rather good, 5 = good, 6 = very good.

Procedure

Baseline examinations were performed on day 0. On day 1, patients received either oral THC (Phase 1) or rectal THC-HS (Phase 2) and were switched medications after completing the phase they began, including at least 1 week of a washout period. Phase 3 was a randomized, double-blind, placebo-controlled, parallel study with oral THC (see Table 3).

Initially we intended to perform a three arm study with 6 weeks of oral THC (Phase 1), 6 weeks of rectal THC-HS (Phase 2), followed by a 6 weeks randomized, double-blind, placebo-controlled crossover trial with oral THC and rectal THC-HS (Phase 3). Owing to logistical problems with the import of THC-HS we had to terminate Phase 2 after seven patients were enrolled. The design of Phase 3 was also modified from a crossover to a parallel study.

Most of the study participants were outpatients who entered the hospital on day 0 for baseline investigations, stayed there until the evening of day 1 or until day 2. Dose escalations were usually discussed with the patients by phone or during unscheduled visits to the hospital. On days 8 and 43 of each phase participants visited the hospital for interviews and examinations. Some of the study subjects were inpatients for longer periods.

Baseline investigation included blood tests (hemogram, CRP, GOT, GPT, γ -GT, alkaline phosphatase, creatine, urea, urea acid, sodium, potassium, urine test, urine drug screen), pulmonary function test, ergometry, physical and neurological examinations, bladder cystomanometry, neurological and physical examination, neuropsychological tests, FIM, HRSD (see Table 5).

Table 3 Study design

Phases	Phase 1 open label			Phase 2 open label			Phase 3 parallel study randomized double-blind placebo-controlled		
Medication	Oral THC (Marinol™)			Rectal THC (THC-HS)			Oral THC versus placebo		
Treatment duration	6 weeks			6 weeks			6 weeks		
Day of examination	1 ^a	8 ^b	43 ^c	1 ^a	8 ^b	43 ^c	1 ^a	8 ^b	43 ^c

^aFirst day of medication with a single dose of 10 mg THC

^bIndividual dose adjusted to tolerance of side effects and symptoms of spasticity

^cStable individual dose

Wash out period between the phases at least 1 week

Phase 1 Twenty-two patients received oral THC for 6 weeks. Phase 1 was completed by 15 participants (seven drop outs) (see Table 4). On day 1, a single dose of 10 mg oral THC was administered at 0900 hours after a standardized breakfast. Investigations of MAS, reflexes, heart rate and blood pressure were performed at 0900, 1000, 1100, 1300, 1400, 1700 and 1900 hours. On day 2, a dose titration phase was begun, which was usually completed after 10–14 days. Dose titration was performed on an individual basis without a fixed scheme until the maximum tolerated dose or the treatment aim was achieved. The treatment aim was a maximum reduction of spasticity and improvement of motor function, which had to be balanced against the loss of muscular strength by the medication. Daily doses were divided into 3–5 doses, the evening dose usually being higher than the other doses. On day 8, physical, neurological and neuropsychological examinations were performed. Spasticity according to the MAS was measured 2 h after administration of the morning dose. Mood alterations according to HRSD were examined;

side effects and self-ratings were monitored and discussed with the patients.

Self-ratings for spasticity, pain, attention, mood, side effects were documented by the patients on a daily basis to estimate mean symptom intensity during the proceeding 24 h.

All examinations of day 0 (baseline) were repeated on day 43 (last day of treatment).

Phase 2 Eight patients received rectal THC-HS for 6 weeks. Phase 2 was completed by seven participants (one drop out). Two dropped out after completing this phase. The same procedure as in Phase 1 was applied with regard to dosing and measurement procedures. Phase 2 had to be stopped due to logistical problems with the import of the study medication after finishing seven patients.

Phase 3 Thirteen patients were included in this randomized double-blind placebo-controlled parallel phase. Six patients received oral THC at their individual

Table 4 Procedure

		<i>Investigations</i>
Baseline without medication	Day 0 and Day 43	Physical and neurological examination including MAS Laboratory tests: blood picture, CRP, GOT, GPT, γ -GT, urine test, urine drug test Cystomanometry ECG Stress test (arm crank test) Pulmonary function test Neuropsychological tests: Continuous Performance Test (CPT), Deux Barrages Test (DB) Hamilton Depression Scale (HDRS) Functional Independence Measure (FIM) Self-ratings: spasticity, pain, mood, concentration
Phase 1 oral THC	Day 1	Baseline MAS Administration of 10 mg oral THC 1 h after application MAS 2 h after application MAS Followed by CPT und DB 4 h after application MAS 5 h after application MAS 8 h after application MAS 10 h after application MAS Self-ratings: spasticity, pain, mood, concentration
	Day 8	Two hours after individual morning medication Physical and neurological examination including MAS Laboratory tests: blood picture, CRP, GOT, GPT, γ -GT, urine test HDRS CPT and DB Self-ratings
Phase 2 rectal THC-HS	Day 43 Day 1 Day 8 Day 43	Two hours after application of oral THC same procedure as in baseline day 0 Same procedure as in Phase 1
Phase 3 oral THC <i>versus</i> placebo	Day 1 Day 8 Day 43	Same procedure as in Phase 1

Table 5 Detailed information on patients and completed study phases

Age	Sex	Type	Phase 1 open label oral THC				Phase 2 open label rectal THC			Phase 3 Parallel study r, db, pc*			Reasons for drop out
			0	1	8	43	1	8	43	1	8	43	
66	m	Tetra	x	x	x	x	x	x	x	x	x	x	
43	m	Para	x	x	x	x	x	x	x	x	x	x	
32	m	Tetra	x	x	x	x	x	x	x	x	x	x	
42	m	Para	x	x	x	x	x	x	x	x	x	x	
42	m	Para	x	x	x	x	(x)	(x)	(x)	—	—	—	Reduced compliance
29	m	Para	x	x	x	x	—	—	—	x	x	x	
43	m	Tetra	x	x	x	x	—	—	—	x	x	x	
31	f	Para	x	x	x	x	—	—	—	x	x	x	
43	m	Tetra	x	x	x	x	—	—	—	x	x	x	
47	m	Para	x	x	x	x	—	—	—	x	x	x	
45	m	Para	x	x	x	x	—	—	—	x	x	x	
29	m	Para	x	x	x	x	—	—	—	x	x	x	
36	f	Para	x	x	x	x	—	—	—	x	x	x	
48	m	Tetra	x	x	x	x	—	—	—	x	x	x	
31	m	Tetra	x	x	x	x	—	—	—	—	—	—	Increased pain
73	m	Tetra	x	x	x	—	—	—	—	—	—	—	Increased pain
29	m	Tetra	x	x	x	—	—	—	—	—	—	—	Anxiety, increased pain
53	m	Tetra	x	x	—	—	—	—	—	—	—	—	No cause
36	m	Tetra	x	x	—	—	—	—	—	—	—	—	Anxiety
40	m	Para	x	x	—	—	—	—	—	—	—	—	Several psychological adverse effects
43	m	Tetra	x	x	—	—	—	—	—	—	—	—	Decreased attention and mood
19	m	Para	x	(x)	—	—	—	—	—	—	—	—	Several psychological adverse effects
51	m	Tetra	x	—	—	—	x	x	x	—	—	—	Apoplexia
63	m	Tetra	x	—	—	—	x	x	x	—	—	—	Pain, decreased compliance
51	m	Tetra	x	—	—	—	(x)	(x)	—	—	—	—	pain
			25	22	17	15	8	8	7	13	13	13	

x Data complete

(x) Data incomplete

— No data available

^ar = randomized, db = double-blind, pc = placebo-controlled

maximum dose determined during the dose escalation phase of Phases 1, 7 patients received the corresponding placebo doses. The rhythm of examinations was the same as in Phases 1 and 2. Blinding and randomization for Phase 3 was performed by the Institute of Hospital Pharmacy, University Hospital, Bern, Switzerland.

Statistical analysis

The following comparisons were made:

- intraindividual comparisons of outcomes in patients within the two open label phases (Phases 1 and 2) at different times of investigations (comparisons of baseline values with values under treatment on days 1, 8 and 43),
- intraindividual comparisons of outcomes in patients who received oral THC in Phase 1 and rectal THC-HS in Phase 2 (five patients),

- intraindividual comparisons of outcomes in patients who received oral THC in Phase 1 and placebo in Phase 3 (seven patients),
- intraindividual comparisons of outcomes in patients who received oral THC in Phase 1 as well as in Phase 3 (six patients).

We decided not to compare the outcome on the six patients who received oral THC and the seven patients who received placebo in Phase 3 because there was a major difference in baseline scores on the SSS (18.8 versus 11.6). Our analysis was restricted to intraindividual comparisons within the Phases 1 and 2 (comparison a), between Phases 1 and 2 (comparison b) and between Phases 1 and 3 (comparisons c and d).

Analysis of variance (ANOVA) with repeated measures was applied to evaluate the treatment effect between baseline (day 0) and day 1, 8 and 43 over time. Individual mean scores for each trial period were compared using the corresponding contrast of the

repeated measure ANOVA or nonparametric Wilcoxon test (if the sample size was relatively small). Treatments during the double-blind phase were also compared using repeated measure ANOVA with phase as within and patient and treatment as between factors. Relations between ratings of the two examiners were calculated by means of Spearman rank correlation. Differences between scores were evaluated with the Wilcoxon matched-paired test. Results of all statistical tests were considered significant at P -values <0.05 and trend at P -values <0.1 . Owing to the multiple interdependencies of the variables, we did not correct the P -values of these calculations. Their results therefore have to be considered as exploratory. All data analyses were performed with SPSS 10.07 of SPSS Inc., Chicago.

Results

Mean dosage

After dose adaptation the average daily dose of oral THC was 31 mg (range: 15–60 mg), the average daily dose of rectal THC-HS was 43 mg (range: 20–60 mg).

Analysis of Ashworth scores

Two hours after administration of a single dose of 10 mg oral THC on day 1 (Phase 1, $N=15$), spasticity was significantly reduced ($P<0.001$) (see Table 6). On day 8, a highly significant reduction of the SSS was seen 2 h after administration of the THC dose ($P<0.001$). There was a significant reduction of spasticity on day 43 ($P<0.05$). Mean SSS for oral THC decreased by 7.8 points, from 16.72 (± 7.60) to 8.92 (± 7.14) from baseline to day 43.

In Phase 2 (rectal THC-HS, $N=7$), reduction of spasticity was significant at all points of investigation (see Table 6). Mean SSS decreased from 22.71 (± 11.68) to 9.21 (± 9.25) from baseline to day 43.

Seven patients of Phase 1 received a placebo in Phase 3. Spasticity was significantly lower with active treatment in Phase 1 on day 1 after 1, 2, 8 and 10 h after

administration of oral THC in this group compared to placebo in Phase 3 (see Figure 1). After 1 h mean values of SSS were 12.00 (± 6.11) with placebo compared to 7.57 (± 7.37) with oral THC. The SSS with placebo showed an increase 1 h after dose administration while it was reduced with oral THC. Comparing the spasticity scores during the whole treatment period, they were reduced on average by 4.89 points with verum compared to placebo ($P=0.001$, ANOVA with repeated measures) (see Figure 2).

There were no significant differences in the spasticity scores of the five patients who completed both Phases 1 and 2 after oral THC and rectal THC-HS (see Figure 3).

To investigate the intraindividual fluctuation of spasticity, we compared the baseline spasticity scores of the 13 patients who underwent both Phases 1 and 3. There were minimal, nonsignificant differences between

Figure 1 SSS on day 1 in patients who received oral THC in Phase 1 and placebo in Phase 3 ($N=7$). The asterisk indicates a significant difference ($P<0.05$) in the Wilcoxon test

Figure 2 Course of SSS during the 6 weeks of treatment in patients who received oral THC in Phase 1 and placebo in Phase 3 ($N=7$). There was an overall highly significant reduction of SSS with oral THC compared to placebo ($P=0.001$), (ANOVA with repeated measures)

Table 6 Reduction of SSS by oral THC (Phase 1) and rectal THC-HS (Phase 2) (ANOVA with repeated measures)

	Phase 1 open label oral THC $N=15$	Phase 2 open label rectal THC-HS $N=7$
Baseline	16.7 (± 7.6)	22.7 (± 11.7)
Day 1	7.8 (± 7.0)**	9.9 (± 8.2)*
Day 8	8.9 (± 6.8)**	12.0 (± 8.1)*
Day 43	8.9 (± 7.1)*	9.2 (± 9.3)*

Day 1: SSS as measured 2 h after a single dose of 10 mg oral THC or 10 mg rectal THC-HS

Days 8 and 43: SSS as measured 2 h after administration of the individual THC doses

* $P<0.05$ (compared to baseline)

** $P<0.001$ (compared to baseline)

the baseline values (15.4 ± 7.2 versus 14.7 ± 6.2). There was a nearly parallel course of the spasticity scores in the six patients who received oral THC both in Phases 1 and 3 (see Figure 4). The observed difference of a higher SSS on day 1 in Phase 3 was due to a single subject who presented with an extensor spasticity, which had a strong subjective component.

To examine the reliability of the MAS and the performance of the two assessing physicians, all baseline values of all patients ($N=22$) were compared. There was a highly significant correlation in the assessments produced by the two examiners ($P=0.001$, correlation coefficient: 0.94). Mean SSS was 1.3 points lower in physician 2 during the whole study.

Figure 3 Course of SSS in patients who received both oral THC in Phase 1 and rectal THC-HS in Phase 2 ($N=5$). No significant differences were observed between oral THC and rectal THC-HS. Asterisks indicate differences compared to baseline, one asterisk a level of significance of $P < 0.05$, two asterisks a level of $P < 0.01$ (ANOVA)

Figure 4 Course of SSS during the 6 weeks of treatment in patients who received oral THC in Phases 1 and 3 ($N=6$). There was an overall highly significant reduction of SSS with oral THC compared to baseline in both phases ($P=0.001$, (ANOVA with repeated measures)

Self-rating of spasticity

Self-ratings were compared in seven patients who received oral THC in Phase 1 and placebo in Phase 3 (see Figure 5). Baseline ratings were almost identical (3.9 versus 3.7 points). On day 1, spasticity was perceived as minor (1.9 points) with oral THC and as strong and unaltered (3.7 points) with placebo ($P=0.033$, Wilcoxon test). On days 8 and 43, there were no significant differences between the values with oral THC and placebo. There were no significant differences in self-ratings of spasticity between Phases 1 and 3 in patients who received oral THC in both phases (data not presented).

Self-ratings of pain, mood and attention

Patients of Phase 1 perceived a significant reduction of pain with oral THC on day 1 compared to baseline ($P=0.047$). However, there was no significant reduction of pain compared to placebo on day 8 and day 43. There were no significant differences in mood and attention between oral THC and placebo, nor between baseline values and values on treatment days. However, there was a trend ($P=0.066$) to a worsened attention with oral THC compared to placebo on treatment day 1, but this trend disappeared despite continued treatment.

Bladder cystomanometry

Data were available for 12 patients who received oral THC in Phases 1 and 6 patients with rectal THC-HS in Phase 2. Four patients could not be included due to bladder pacemaker, ileum conduit, permanent catheterization and one refusal. All patients presented with an upper motor neuron bladder (UMNB). Half of the patients of Phase 1 showed an increase and half a decrease of MCC. So there were no significant changes compared to baseline in this subgroup. Of the six

Figure 5 Self-rating of spasticity by patients who received oral THC (dronabinol) in Phase 1 and placebo in Phase 3 ($N=7$). The asterisk indicates a significant difference of $P < 0.05$ between Phases 1 and 3 on day 1 (Wilcoxon, matched paired test)

patients who received rectal THC-HS, five showed an increase and one a decrease in MCC, resulting in a trend for improved MCC in patients of Phase 2 ($P=0.075$). There were no significant changes or trends in other parameters.

Pulmometry, ergometry

After 6 weeks of treatment with oral THC, 13 patients of Phase 1 showed a significant improvement of vital capacity from 65 to 71% of the nominal value ($P=0.028$). Results from two patients could not be evaluated. Seven patients who received the placebo in Phase 3 also had a significant improvement in their vital capacity from 71 to 78%; thus, the improvement in pulmonary function could not be interpreted as a treatment effect.

Five of the seven patients who received oral THC in Phase 1 and placebo in Phase 3 were available for analysis of their arm crank test. Two of the participants could not be included due to poor motor function of their hands. No significant improvement in physical work capacity and no alterations of the ECG were seen. With oral THC, maximum systolic blood pressure decreased from 146 at baseline to 140 mmHg (-4%) after 6 weeks of treatment, while it increased with placebo from 146 to 159 mmHg ($+9\%$). Differences between the values after 6 weeks of treatment were marginally significant in the Wilcoxon test ($P=0.04$).

Hamilton depression scale

No significant differences were observed between baseline, placebo and active treatment in all groups.

Neuropsychological tests

Five of the seven patients who received oral THC in Phase 1 and placebo in Phase 3 were available for analysis. Two persons with tetraplegia could not perform the tests because of compromised motor function of their hands. There were no differences in the Continuous CPT between active treatment and placebo, demonstrating that attention and sustained attention were unaffected by THC. In the Divided Attention Test, reaction time decreased both with THC and placebo during the 6 weeks of treatment, possibly due to a training effect. However, reaction time with active treatment was worse compared to placebo on day 43 ($P=0.043$). In the DB test, the number of correct marks increased during the 6 weeks with both oral THC and placebo. On day 1, there were significantly more correct marks with THC, but also more omissions ($P=0.043$). As with the other neuropsychological tests we observed a training effect in both Phases 1 and 3 in the DB test.

Laboratory findings

All parameters were stable with the exception of a transient mild increase of liver transaminases in one

Table 7 Self-report of physiological and psychological side effects at the end of oral THC in Phase 1 ($N=22$, including drop outs)

<i>Adverse physiological effects</i>	<i>%</i>	<i>Adverse psychological effects</i>	<i>%</i>
Dry mouth	32	Sleepiness	36
Increase of pain	23	Anxiety	32
Unpleasant body sensations	14	Disturbance of attention	27
Impaired vision	9	Dizziness	23
Feeling of paralysis	9	Worsened mood	9
Adynamia	5	Loss of control	9
Increase of spasticity	5	Disturbance of perception	5

patient, who received oral THC. Urine drug screen at baseline was negative in all subjects.

Functional independence measure

No significant changes were found in ADL functions. Still, there was some benefit for some patients. For example, one tetraplegic could perform self-catheterization for the first time in several years due to an improved motor coordination of his hands.

Side effects

While four patients (18%) noted pain relief, five subjects (23%) reported pain augmentation and four of them dropped out (see Table 7). Thus, the increase in pain was one of the major reasons for dropping out. Xerostomia was reported by seven patients (32%), sleepiness by eight patients (36%) and anxiety by seven patients (32%).

Discussion

Both oral THC (dronabinol, Marinol™) and rectal THC-HS proved to reduce spasticity in spinal cord injured patients in our study. Maximum effects following a single dose of 10 mg oral THC administered on day 1 were noted between 1 and 5 h after drug administration. In contrast to several other trials in SCI and MS patients, which found no or minor effects on objective spasticity measures,^{18,20,21,28} there were significant differences between placebo and verum as well as between baseline and treatment values in the SSS.

From previous research on the bioavailability of rectal THC-HS compared to oral THC, we expected considerably lower maximum doses for the rectal administration. Brenneisen *et al*¹³ determined an almost doubled bioavailability of rectal THC-HS compared to oral THC. However, in our study the mean daily tolerated doses for oral THC of 31 mg, which was somewhat lower than for rectal THC-HS (mean: 43 mg).

Possibly, the physical loss of the medication in patients with anal sphincter incontinence was the reason for the comparatively high rectal THC-HS doses observed in our study.

There may be three major reasons for a significant influence of THC on objective measures of spasticity in our study compared to previous reports: (1) individual dose titration, (2) comparatively high daily THC doses and (3) discontinuation of antispastic medication before inclusion into the study.

Many earlier studies used low and sometimes fixed doses of THC that may have been an important reason for lack of efficacy. Killestein *et al*²⁸ applied a capsulated cannabis extract and oral dronabinol to 16 MS patients with maximum daily doses of 2×5 mg. No differences in spasticity scores were found compared to placebo. Ungerleider *et al*¹⁰ in his study with 13 MS patients found that at least single doses of 7.5 mg oral THC were necessary to achieve a significant reduction in spasticity. As there is a low margin between sought after therapeutic effects and psychological side effects, and because there is a high interindividual variability in susceptibility to THC, a flexible design with individually adjusted doses and dosing intervals is required to get optimum results in the treatment of spasticity.²⁹ Pertwee²⁹ suggested starting with at least 2.5 or 5 mg oral THC twice daily. Even higher single doses may be tolerated at the beginning of a study. Brenneisen *et al*¹³ treated two patients with 10–15 mg of oral THC without causing relevant side effects. The interindividual variability of THC effects is appreciated for several indications. In a study by Clifford,³⁰ two of eight MS patients with severe tremor showed objective improvement, one with a single dose of 5 mg oral THC, the other with a single dose of 15 mg THC, 5 and 10 mg being completely ineffective in this patient.

Daily doses in recent studies on spasticity in MS and SCI varied between 5 and 10 mg oral THC,²⁸ 10–25 mg,¹⁹ 15–30 mg²¹ and 2.5–120 mg,²⁸ underlining the high interindividual variability. In our study, we determined comparatively high tolerated daily doses of 15–60 mg for oral THC, the mean dose being 31 mg compared to average daily doses of 0.46 mg THC/kg body weight. In addition to interindividual variability, susceptibility to THC may vary in different patients' groups. Helwig *et al*³¹ determined a maximum daily dose of 0.15 mg THC/kg body weight in advanced cancer patients. However, higher doses may be tolerated by some subjects in this patients' group.

In contrast to many other studies, in which previous medication was continued,^{19,21,32} participants in our investigation had to stop their antispastic drugs before inclusion in the study. Thus, we were able to compare oral THC with placebo without interference due to interaction effects with other medications. The benefit of discontinuing other medications for the treatment of spasticity is twofold. First, it is much more difficult to achieve additional measurable therapeutic effects if antispastic medication is continued. As side effects of THC and other antispastic medication may be additive,

for example, sedation and dizziness with baclofen and benzodiazepines, it may also be more difficult to achieve higher doses if concomitant medication is administered.

The Ashworth Scale was shown to be a reliable tool for the measurement of spasticity, as proven in our study by the high correlation between the spasticity scores determined by the two examiners. However, the Ashworth Scale may not be sensitive enough to reveal small changes. Several studies did not find objective changes in spasticity but subjective improvement. Spasticity is a very complex phenomenon, with contributions from patient symptoms, physical functioning and psychological impact.³³ The validity of the Ashworth Scale has been questioned since it is a rather rough measure and may not include all relevant aspects of spasticity. Shakespeare *et al*¹⁸ suggested that sensitive, validated spasticity measures need to be developed. It is unclear why there were no subjective improvements in spasticity with oral THC compared to placebo at the end of the study period, while there was a significant difference on the first treatment day. A possible reason may be a habituation to the improved state that was no longer perceived as an improvement or tolerance to the treatment effects may have developed. However, the second explanation seems unlikely since the development of tolerance should also have been detected in the spasticity scores over the study.

The exact mechanism of the antispastic effects of THC is not known. In spasticity there is increased activity of alpha motoneurons and excitatory interneurons, and decreased activity of inhibitory interneurons.³⁴ This results in facilitation of excitatory glutamate neurons, and inhibition of inhibitory GABA neurons.³⁵ A separate ceruleus–spinal projection also modulates the activity of spinal motoneurons via a noradrenergic mechanism.³⁵ Besides spasticity, flexor and extensor spasms, clonus and ataxia, as well as acute, chronic and paroxysmal pains are often features of MS and SCI.

There are many reports indicating that CB₁ receptor agonists enhance GABA function in the brain.³⁶ It is generally accepted that CB₁ receptor agonists reduce transmitter release, via decreasing calcium-channel conductance, decreasing action potential generation and via increasing potassium-channel conductance.¹⁵ Also, CB₁ receptor agonists have been found to inhibit presynaptic glutamic acid release. In animal models of MS, CB₁ receptor agonists improved specific signs of spasticity and tremor, while a CB₁ receptor antagonist not only reversed the effects of agonists but administered alone caused an exacerbation of both symptoms, indicating that the endocannabinoid system is tonically active.³⁷

The strength of our study results is limited by the small number of subjects eligible for analyses. Owing to logistical problems, we had to modify the study design. Originally, we intended to conduct a double-blind crossover study in Phase 3 after finishing two open label phases with oral and rectal THC-HS. Fortunately, the baseline spasticity scores in Phases 1 and 3 had a

similar level, which allowed us to make intraindividual comparisons between the spasticity scores following the administration of oral THC and placebo. The changes in the Ashworth Scale were so impressive that, even with the low number of patients, there was a highly significant difference between verum and placebo. There is a limited amount of data available on THC effects on spasticity in SCI. Most of studies have studied the effects of THC in MS patients. Our results support previous investigations with SCI patients.^{11,13,38} Maurer *et al*¹¹ found significant effects of 5 mg oral THC in one SCI patient on sleep, pain and spasticity. Brenneisen *et al*¹³ observed improvements in joint function and mobility in two spastic patients, one with MS and one with SCI following 10–15 mg oral THC. Wade *et al*³⁸ included subjects with different ailments in his pilot study (MS, SCI, brachial plexus convulsion) and found improvements in pain and spasticity.

A problem that is difficult to treat in MS and SCI patients is lower urinary tract symptoms or hyper-reflexive bladder. Anecdotal reports suggest that cannabinoids may alleviate bladder dysfunction,^{5,6,39} conducted an open trial with cannabis and THC in 21 patients with advanced MS and refractory lower urinary tract symptoms. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment.³⁹ In our study, we only observed minor effects that may have occurred by chance alone – that is, a trend for increased MCC in patients receiving rectal THC-HS. Some participants experienced subjective improvement of micturition.

For a considerable number of patients, psychological side effects are a major problem in the treatment with high doses of THC. Müller-Vahl *et al*⁴⁰ found no significant side effects on neuropsychological performance of single dose of oral THC at 5.0–10.0 mg in 12 patients with Tourette's syndrome. There were no significant differences after treatment with verum compared to placebo in verbal and visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance or mood. In our study, several participants dropped out due to anxiety and other psychological problems, but those who completed at least one phase showed remarkably low impairment in the applied neuropsychological test battery. Thus, THC may be a very effective antispastic agent for that proportion of patients who tolerate comparatively high doses. No subjects dropped out due to lack of drug efficacy.

An unusual observation, in contrast to previous trials, was the increase of pain in five participants compared to a decrease in four subjects. Neuropathic pain may be an important indication for the treatment with THC and cannabis. There are several reports of pain reduction in MS by THC^{19,41,42} and cannabis,^{38,19} in central neuropathic pain from brachial plexus avulsion⁴³ and in neuropathic pain in HIV positives.⁴⁴ However, Attal *et al*⁴⁵ were not able to confirm the efficacy of THC in chronic refractory neuropathic pain in an open study

with eight patients who received daily doses of up to 25 mg dronabinol. In healthy subjects, increase in pain intensity is a common observation. Clark *et al*⁴⁶ found hyperalgesic effects with cannabis after thermal stimuli in 16 regular cannabis users. Hill *et al*⁴⁷ made similar observations following an electrical stimulus. Naef *et al*⁴⁸ used heat, cold, pressure, single and repeated transcutaneous electrical stimulation to investigate the analgesic effects of oral THC in 12 healthy subjects. The cannabinoid did not significantly reduce pain. In the cold and heat tests it even produced hyperalgesia. Raft *et al*⁴⁹ treated eight subjects who underwent tooth extractions with intravenous THC (0.022 and 0.044 mg/kg body weight). Two experienced analgesia, the other six hyperalgesia. To our knowledge, there is only one clinical study with cannabinoids in chronic pain patients that found increased pain perception.⁵⁰ Jochimsen *et al*⁵⁰ conducted a double-blind, 5-way crossover designed study with placebo, two doses of codeine sulfate (60 and 120 mg), and two doses of benzopyranoperidine (2 and 4 mg), a synthetic derivative of THC with 35 patients who required analgesics for chronic pain due to malignancies. The cannabinoid appeared to augment pain. Our study with SCI patients confirms that cannabinoid receptor agonists may cause hyperalgesia in some pain patients.

Conclusion and recommendations

THC may be a useful drug in the treatment of spasticity in patients with SCI. In particular, patients with tetraplegia who present with decreased pulmonary function may benefit from a medication with a cannabinoid because it will not depress respiration.⁵¹ However, many patients may not tolerate the doses needed. Comparatively high doses of at least 15–20 mg of the drug were required in our study to achieve a therapeutic effect. As tolerance to the psychological effects shows a high interindividual variability, this is one of the major limiting factors and makes the cannabinoid unsuitable for a number of patients. To our surprise, not only anxiety, but also augmentation of pain was an important reason for a drop out. We recommend starting with low doses with subsequent slow dose escalation over days or weeks to find the appropriate individual dosage and to minimize the occurrence of adverse events. For some patients our entrance dosage of a single dose of 10 mg oral THC may have been too high, and necessitate starting with a lower dose. Psychological side effects may decrease in the course of a treatment with THC, as tolerance develops. The systemic bioavailability of rectal THC-HS is about twice as high as that of oral THC. However, there may be no advantage of the rectal preparation due to the physical loss and lack of availability of the medication due to anal sphincter incontinence. Further clinical studies are needed to define the role of THC in the treatment of spasticity in SCI. THC should not only be compared to placebo, but it should also be evaluated against established antispastic medications.

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References

- Mechoulam R. The pharmacohistory of *Cannabis sativa*. In: Mechoulam R (ed). *Cannabinoids as Therapeutic Agents*. CRC Press: Boca Raton.
- Reynolds JR. Therapeutic uses and toxic effects of *Cannabis indica*. *Lancet* 1890; **1**: 637–638.
- Dunn M, Davis R. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 1974; **12**: 175.
- Malec J, Harvey RF, Cayner JJ. Cannabis effect on spasticity in spinal cord injury. *Arch Phys Med Rehabil* 1982; **63**: 116–118.
- Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997; **38**: 44–48.
- Consroe P, Tillery W, Rein J, Musty RE. Reported marijuana effects in patients with spinal cord injury. *1998 Symposium on the Cannabinoids*. International Cannabinoid Research Society: Burlington 1998, p 64.
- Petro DJ. Marijuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 1980; **21**: 81–85.
- Meinck HM, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *J Neurol* 1989; **236**: 120–122.
- Petro DJ, Ellenberger C. Treatment of human spasticity with Δ^9 -tetrahydrocannabinol. *J Clin Pharmacol* 1981; **21**: 413–416.
- Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Δ^9 -THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse* 1987; **7**: 39–50.
- Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows anti-spastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiat Clin Neurosci* 1990; **240**: 1–4.
- Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet* 1995; **345**: 579.
- Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta-9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther* 1996; **34**: 446–452.
- Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokin* 2003; **42**: 327–360.
- Pertwee RG. Sites and mechanisms of action. In: Grotenhermen F, Russo E (eds). *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Haworth Press: Binghamton NY 2002, pp 73–87.
- Saáudo-Peña MC, Tsou K, Walker JM. Motor actions of cannabinoids in the basal ganglia output nuclei. *Life Sci* 1999; **65**: 703–713.
- Tarrico M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury (Cochrane Review). *Cochrane Database Syst Rev* 2000; **2**: CD001131.
- Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev* 2001; **4**: CD001332.
- Zajicek J et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362**: 1517–1526.
- Zajicek J. The cannabinoids in MS study – final results from 12 months follow-up. *Mult Scler* 2004; **10**(Suppl 2): 115.
- Vaney C et al. 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. *Mult Scler* 2004; **10**: 417–424.
- Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004; **10**: 434–441.
- Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987; **67**: 206–207.
- Granger CV, Hamilton BB, Linacre JM, Heinemann AW, Wright BD. Performance profiles of the functional independence measure. *Arch Phys Rehabil* 1993; **72**: 84–89.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56–62.
- Baker DB, Taylor CJ, Leyva C. Continuous performance tests: a comparison of modalities. *J Clin Psychol* 1995; **51**(4): 548–551.
- Zazzo R. Test de deux barrages. *Actualités pédagogiques et psychologique* Vol. 7. Delachaux et Nestlé: Neuchâtel 1974.
- Killestein J et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; **58**: 1404–1407.
- Pertwee RG. Prescribing cannabinoids for multiple sclerosis. *CNS Drugs* 1999; **11**: 327–334.
- Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Ann Neurol* 1983; **13**: 669–671.
- Helwig S, Fronk EM, Reif M, Schnelle M, Hoffmann J. Maximally tolerated dose (mtd) of standardized cannabis extract in palliative cancer patients: preliminary results from an open label, on-randomized phase I/II trial. *Second Conference on Cannabis and Cannabinoids* International Association Cannabis as Medicine, Cologne, September 12–13, 2003.
- Kogel RW, Johnson PB, Chintam R, Robinson CHJ, Nemchausky BA. Treatment of spasticity in spinal cord injury with dronabinol, a tetrahydrocannabinol derivate. *Am J Ther* 1995; **2**: 799–805.
- Riazi A, Fox P, Vickery J, Thompson AJ, Zajicek J, Hobart JC. Developing a patient-based measure of the impact of spasticity in multiple sclerosis. *Mult Scler* 2003; **9**: 151.
- Noth J. Trends in the pathophysiology and pharmacotherapy of spasticity. *J Neurol* 1991; **238**: 131–139.
- Gilman S, Newman SW (eds). *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology* 9th edn. Philadelphia: FA Davis Company 1996.
- Musty RE, Consroe P. Spastic Disorders. In: Grotenhermen F, Russo E (eds). *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Haworth Press: Binghamton NY 2002, pp 195–197.
- Baker D et al. Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J* 2001; **15**: 300–302.

- 38 Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* 2003; **17**: 18–26.
- 39 Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkely KJ, Fowler CJ. An open label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler* 2004; **10**: 425–433.
- 40 Müller-Vahl KR, Koblenz A, Jobges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry* 2001; **34**: 19–24.
- 41 Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; **329**: 253–260.
- 42 Young CA, Rog DJ. Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis. *IV. Congress of the European Federation of IASP Chapters (EFIC)* September 2–6, 2003, Prag.
- 43 Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; **112**: 299–306.
- 44 Abrams DI et al. The effects of smoked cannabis in painful peripheral neuropathy and cancer pain refractory to opioids. *IACM 2nd Conference on Cannabinoids in Medicine* Cologne, September 12–13, 2003.
- 45 Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? *Eur J Pain* 2004; **8**: 173–177.
- 46 Clark WC, Janal MN, Zeidenberg P, Nahas GG. Effects of moderate and high doses of marijuana on thermal pain: a sensory decision theory analysis. *J Clin Pharmacol* 1981; **21**(8–9 Suppl): 299–310.
- 47 Hill SY, Schwin R, Goodwin DW, Powell B. Marijuana and pain. *J Pharmacol Exp Ther* 1974; **188**: 415–418.
- 48 Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain* 2003; **105**: 79–88.
- 49 Raft D, Gregg J, Ghia J, Harris L. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. *Clin Pharmacol Ther* 1977; **21**: 26–33.
- 50 Jochimsen PR, Lawton RL, VerSteeg K, Noyes Jr R. Effect of benzopyranoperidine, a delta-9-THC congener, on pain. *Clin Pharmacol Ther* 1978; **24**: 223–227.
- 51 Zwillich CW, Doekel R, Hammill S, Weil JV. The effects of smoked marijuana on metabolism and respiratory control. *Am Rev Respir Dis* 1978; **118**: 885–891.