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Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies

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Summary

Three Cannabis Based Medicinal Extracts (CBMEs) for sublingual use became available in 2000. A total of 34 'N of 1' studies were undertaken using this novel therapy for patients with chronic, mainly neuropathic, pain and associated symptoms to explore efficacy, tolerability, safety and dosages. Three CBMEs (Δ9 Tetrahydrocannabinol (THC), Cannabidiol (CBD) and a 1 : 1 mixture of them both) were given over a 12-week period. After an initial open-label period, the CBMEs were used in a randomised, double-blind, placebo controlled, crossover trial. Extracts which contained THC proved most effective in symptom control. Regimens for the use of the sublingual spray emerged and a wide range of dosing requirements was observed. Side-effects were common, reflecting a learning curve for both patient and study team. These were generally acceptable and little different to those seen when other psycho-active agents are used for chronic pain. These initial experiences with CBME open the way to more detailed and extensive studies.

Keywords *Cannabis. Delta 9 tetrahydrocannabinol. Cannabidiol. Multiple sclerosis. Pain*: chronic, neuropathic.

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Cannabis has been used for five millennia for the treatment of many conditions including pain, inflammation, neuralgia, migraine and dysmenorrhoea. It has also been used as an anticonvulsant, muscle relaxant and for restlessness and anxiety in terminal illness [1,2]. However, by 1971 it was deemed to be of little medical use and was removed from the formulary (UK). The synthetic cannabinoid nabilone was subsequently introduced for the treatment of chemotherapy-induced intractable nausea and vomiting.

More recently, basic science research has revealed the Endocannabinoid system [2], thereby providing a rationale for clinical research. Concurrently there has been an explosion of anecdotal evidence from patients of the therapeutic effects of cannabis.

A few single dose clinical studies on the use of cannabis for pain were conducted in the 1970s but the conclusions drawn are debatable [3]. Very little has been undertaken since because of four major obstacles.

1. The absence of reliable and standardised preparations

Materials obtained from controlled sources, having reliable standardised composition and prepared to pharmaceutical standards, have not previously been available.

2. Difficulties with delivery methods

Smoking is an efficient method of patient titration and delivery but modern medicine does not accept the inhalation of carcinogenic smoke from burning, dried plant material as a method of delivering a therapeutic agent. Not only are there health risks [4,5] but undertaking quality clinical research using this approach is almost impossible.

As an oily substance, cannabis is difficult to nebulise and as such is irritable to the larynx and trachea. Equipment for heating cannabis to produce a vapour for inhalation is available recreationally.

Whilst the oral route is often used recreationally, the onset of effect is slow (over one and a half hours), absorption is very variable and there is a significant first-pass effect. This makes accurate and rapid titration difficult for a patient with chronic pain, although this may become a practical route for the patient who is stabilised and who requires a constant intake of cannabinoid. Rectal administration has also been suggested as a possibility but probably confers no advantages over the oral route.

The sublingual route was first described by Marshall in 1897 [1]. It provides the possibility of acceptable rapid absorption for titration, combined with the absence of a first-pass effect. No clinical studies had previously been undertaken on this route of administration.

3. Political and legal difficulties

It is only recently that the issues of the recreational and the medicinal use of cannabis have been disentangled in the minds of the public, the medical profession and senior politicians [2,6,7].

4. Side-effects

The possibility of acute psycho-active, other psychological and physical side-effects [2,8,9,10] that have been observed with recreational cannabis use have discouraged clinical study.

Single chemical or plant extract

It has been suggested that the presence of cannabidiol (CBD) ameliorates the psycho-active effects of Δ9 tetrahydrocannabinol (THC) [11]. Patients have self-reported that they prefer milder forms of cannabis that have a significant CBD content. Other evidence suggests that patients prefer plant cannabis to dronabinol (an oral synthetic form of THC) when used for the control of nausea and vomiting associated with chemotherapy [7,12]. Similarly patients who had used cannabis for their chronic pain prior to trying nabilone (a synthetic analogue of THC) preferred the former [13].

There may be several reasons for this difference. CBD blocks the metabolism of THC to 11-hydroxy-THC, which is more psycho-active than THC and may produce dysphoria [2]. Alternatively, it may simply be that patients find titration easier with smoked cannabis. It is unknown whether any other ingredients of plant cannabis contribute to this effect.

It was decided to investigate the potential benefits of whole plant extracts rather than pure THC alone. Pharmaceutical grade Cannabis Based Medicinal Extracts (CBMEs) derived from cloned plants, yielding standardised quantities of cannabinoids for sublingual use, became available for clinical study in 2000 from GW Pharmaceuticals. We chose to investigate a 1 : 1 mixture of THC and CBD for chronic pain and to compare it with placebo, THC alone and CBD alone. Two recently completed CBME studies [14,15] were run in parallel with this study as part of the initial development program.

The primary objective of this study was to identify the therapeutic windows of three CBMEs. The secondary objectives were to study the effects of three CBMEs of varying constituent composition on patients suffering with chronic, refractory pain or defects of neurological function; to study safety and tolerability parameters for these CBMEs; and to determine the approaches to more extensive and detailed studies.

Methods

The study was approved by the Local Research Ethics Committee and by the Medicines Control Agency and was conducted under a 'Doctors and Dentists Exemptions' (DDX) licence. During the time of the study the CBMEs remained classified as Schedule 1 drugs. This required that the patients and the investigating team be licensed by the UK Home Office in London. Each patient gave written, informed consent at the start of the study. The study underwent independent external audit.

The study cannabinoids

The cannabinoids were derived directly from standardised cloned plants and were prepared to medicinal standards. Each extract contained > 95% of the specified cannabinoid(s), the remainder being a mixture of other plant chemicals (minor cannabinoids, terpenes and flavonoids). The materials were prepared as a sublingual spray and each actuation delivered 2.5 mg of THC, 2.5 mg CBD, or 2.5 mg THC + 2.5 mg CBD (THC : CBD) or matching placebo in 0.1 ml. The first six patients received the spray as an aerosol delivery system (excipients tetrafluoroethane 80%, ethanol 20%). Subsequent patients used a pump action spray (excipients ethanol 50%, propylene glycol 50%).

Patient selection

Patients were either recruited from the local Pain Relief Clinic or directly referred by general practitioners or hospital consultants. Several volunteered directly with the agreement of their general practitioners.

The patients were all over 18 years old, with chronic, stable pain, poorly responsive to other modalities of control. Pain, other symptoms and medication use had to be stable over the 4 weeks preceding the start of the study. Patients were required to abstain from driving during the study and also required to ensure adequate contraception.

Patients with significant cardiovascular disease, oral disease or any other serious systemic disorders were excluded. Patients with any history of schizophrenia, other psychoses, other significant psychiatric disorder or any problem with drug or alcohol misuse/dependency were also excluded [10]. Depression secondary to their chronic pain was not an exclusion factor.

Patients with a past history of significant recreational cannabis use or who were continuing to use the drug in this manner were excluded. Patients who had current or previous experience of using cannabinoids as a medicine (illicit plant cannabis or nabilone) were included.

The rationale for recruiting patients who were non-naïve to cannabis was:

- The CBME preparations, the delivery system, and the sublingual route were new and untried in patients. There was no information on likely dose range.
- These patients would have knowledge of the benefits, effects and side-effects of cannabinoids. They would therefore be appropriately prepared and able to recognise these effects early.
- Some qualitative comparison with their preceding cannabinoid use and effect might be achievable.

As experience grew, more cannabinoid-naïve patients were recruited.

The study design (Fig. 1)

An 'N of 1' methodology was used. Two weeks of baseline assessments were followed by a 4-h supervised titration with open-label THC : CBD. CBME use was continued at home for a 2-week run-in period. A schedule of assessments was undertaken before and after each period. Throughout the study patients kept a daily diary of their worst two symptoms, each measured with a standard 10 cm visual analogue scale (VAS), and also of their sleep and any side-effects experienced.

If the patients showed some benefit in one or more of their assessments, they could proceed to the 8-week, randomised, double blind, placebo controlled, crossover part of the study. Each week for the first 4 weeks they randomly received a different CBME (THC, CBD, THC : CBD or placebo). At the start of each week, titration under supervision was undertaken as on the first day of the open-label period. Each CBME was then given again in random order over the next 4 weeks. Therefore each patient received each CBME and placebo for two separate 1-week periods.

Randomisation was undertaken externally and the schedule supplied to GW Pharmaceuticals. Un-blinding occurred at completion of each patient's study.

Cannabinoid escape medication

Seven frequent users of illicit cannabis for symptom control prior to the study were offered the THC : CBD mixture as escape medication during the crossover period. This was to ensure that they did not return to their use of illicit cannabis when receiving ineffective medication.

Patient assessment

At the first visit a full medical history was obtained including an assessment of the pain and associated symptoms, the past management, and the current drug therapy. The previous use of cannabis, recreational and medicinal, determining frequency, type, effectiveness and side-effects was explored. Further relevant information was obtained from local medical records and the patient's general practitioner. A physical examination was undertaken. Basic haematology, urea, electrolytes and liver function tests were performed and repeated at the end of the study.

Depression was assessed with the Beck Depression Inventory (BDI), which was applied at each visit. This was supplemented by the General Health Questionnaire 28 (GHQ28) at three points during the study (Fig. 1) [16].

Up to five significant pain or other symptoms were nominated by the patient and the severity of each was assessed at each visit using a standard VAS. The patients were familiarised with the assessment procedures and the daily diaries to be completed at home. The severity of the two worst symptoms was measured in the morning, at midday and in the evening on a daily basis. The remaining index symptoms were used to broaden the assessment of individual clinical effectiveness. Duration of

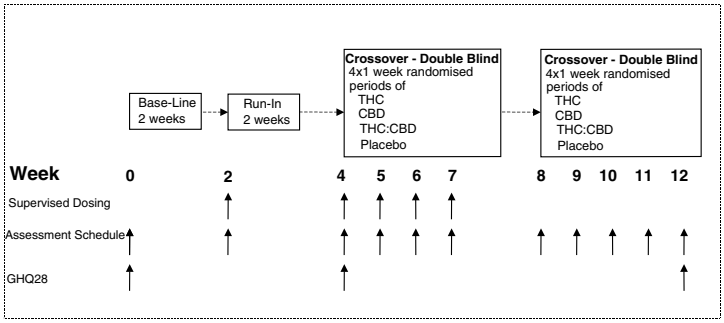

Figure 1 The structure of the study.

sleep (hours) and quality of sleep (Good, Fair, Poor) were recorded for each night. Appetite, bowel function, bladder function and activity levels were also monitored.

Patients were fully briefed on the possible psychoactive side-effects and the likely seven most common were identified in the diary. These were presented in the form of the question: ''Throughout the day have you experienced any of the following (please tick): Dry mouth, Time distortion, Dizziness, Panic/anxiety attacks, Drowsiness, 'High'/'Strange' feeling, Hallucinations''. Patients were also asked to record any other side-effects or new symptoms that they experienced whether or not they felt this was associated with the medication. No attempt was made to investigate tolerance, dependency or other longer-term psychiatric effects.

The use of concomitant medication was monitored. Patients were asked not to change their regular medication without prior discussion with the research team. The maintenance of a constant pharmacological background was considered important. Non-cannabinoid medication for breakthrough pain was allowed and documented. However, by definition, most patients were getting very little benefit from their previously prescribed medication.

Cannabinoid administration

The patients underwent 4-h dosing sessions at the hospital (Fig. 1) whenever a new CBME was introduced. Initially, one spray was given every 15 min. This interval had been determined from studies of the use of the spray in healthy volunteers. This interval was changed to 30 min after the first six patients had been studied.

Throughout these titrations, vital signs and side-effects were monitored at regular intervals. Tests of psychomotor and cognitive function were performed before the start and after 3 h (Trail Making Tests A & B [17], Adult Memory and Information Processing Battery (AMIPB) [18]).

At the end of 4 h, patients had received between two and four sprays (two and eight sprays for the first six patients), depending on their response (effects and side-effects). The patients were then discharged home with a relative if in a clinically satisfactory state. They were given a supply of the test CBME. During the initial 2-week run-in period patients were contacted daily for 7 days or longer (as necessary). At all times, a member of the team was available for contact in an emergency, to answer questions, etc.

Data analysis

This study was primarily observational and each patient's data were evaluated individually. The use of placebo and blinding was to provide greater rigour to the observational data. Data from the individual 'N of 1' studies have been aggregated to give an indication of the scale of the benefits seen, the occurrence of side-effects, etc. Similarly a comparison of the effectiveness of the three CBMEs and placebo was undertaken.

Where clinical benefit could be shown for individual patients, they were offered the opportunity to continue into a long-term safety extension study (CBME SAFEX). It had been a requirement of the Local Research Ethics Committee for the patients to be able to continue treatment unless clinical, pharmaceutical or regulatory requirements deemed otherwise.

Results

Patients

A total of 34 patients were studied. Demographic details, underlying diagnosis, main problem symptoms, and previous medicinal use of cannabis are shown in Table 1. The high number of female patients reflected the prevalence of multiple sclerosis. The patients have been grouped for analysis (Fig. 2).

Only seven patients used THC : CBD as rescue medication during the crossover part of the study (Group CRM). Therefore data from these patients have only been included for the assessment of the run-in periods. The first two patients had inadequate data from the baseline period.

Out of the total of 34, 24 patients completed the crossover period without cannabinoid rescue medication (Group NoRM) (Fig. 2). They provide the comparative information on effects and side-effects.

One patient, who experienced a vasovagal episode, continued single-blind without the THC periods for the remainder of the crossover period. Therefore only data on dosage used are included (Table 2).

Two patients were withdrawn from the study (Table 2). One failed to tolerate the THC : CBD at the lowest dose during the run-in and the other could not cope with the study requirements.

Dose titration sessions

The initial rate of titration was too rapid for two of the first six patients who developed dysphoria and lightheadedness. Both recovered fully over the following 2 h. Subsequently, the interval between sprays was changed from 15 to 30 min. This gave the patients adequate opportunity to terminate their titration safely if they started to experience side-effects.

The tests of psychomotor and cognitive function (Trail Tests and AMIPB) yielded unexpectedly equivocal results, requiring a more detailed analysis than planned. There were often improvements in performance after CBME [19]. Therefore the results will be presented separately.

Table 1 Patient details.

No.	Sex	Age	Diagnosis	Years	Site of pain/ symptom (S1)	Site of pain/ symptom (S2)	Prev cann. use*	Rescue CBME**	Global outcome***
1	M	51	MS	12	Lumbar pain	Leg spasms	3	CRM	2
2	M	43	Spinal cord tethering, laminectomy	13	Low lumbar pain	Posterior leg pain (L)	3	CRM	3
3	F	58	MS	6	Thigh pain (L) & spasms	Hip pain (L)	2	CRM	3
4	M	55	Low back, sciatica, post laminectomy	36	Lumbar pain	Posterior leg pain (B)	3	CRM	2
5	F	53	MS	11	Whole leg pain	Neck, arm (L) pain	2	CRM	2
6	F	52	MS	15	Knee pain (B)	Head, face (L)pain	1	CRM	0
7	F	33	Disc degeneration, laminotomy × 2	3.5	Posterior thigh (R)	Low back pain	0	NoRM	1
8	F	44	MS, post cystectomy, ileostomy	18	Urethral pain	Pelvic floor pain	1	NoRM	3
9	F	51	MS	7	Thigh (L), lower legs pain	Chest tightness	N	None	X
10	F	50	MS	1.5	Leg pain (R)	Right leg spasm	1	None	X
11	F	53	Spinal fusion	18	Posterior leg pain (B)	Low back pain	2	NoRM	3
12	F	55	MS	10	Lower leg pain	Lumbar pain	0	NoRM	0
13	F	32	Degenerative Disc, post laminotomy	6	Leg (B) pain	Back pain	0	NoRM	2
14	M	64	Paraplegia, AV malformation of cord	10	Leg pain (B)	Foot (R) stabbing pain	1	NoRM	2
15	F	46	MS	13	Leg pain	Sacro-iliac pain	0	None	3
16	M	41	MS	10	Leg spasms	Bladder urgency	1	NoRM	3
17	F	41	MS	23	Leg spasms	Hip pain (R)	1	NoRM	2
18	M	50	Brachial Plexus Avulsion injury	14	Arm (R) aching pain	Arm, shooting pains	0	NoRM	1
19	M	48	Femoral Plexopathy from phenol inj.	7	Lumbar pain	Leg, scrotum (L) pain	2	NoRM	2
20	F	30	Laminectomy L1-5 × 2	9	Lumbar pain	Leg (L) pain	0	NoRM	1
21	F	46	MS	3	Retro-orbital pain (B)	Arm (R) pain	1	NoRM	3
22	M	53	MS	4	Legs spasticity	Leg (B) pain	1	NoRM	1
23	M	48	Myopathy	4	Leg (B) pain	Upper arms	3	NoRM	2
24	F	35	CRPS1 post ankle trauma	9	Ankle (R) aching pain	Ankle (R) stabbing pain	0	NoRM	1
25	F	26	CRPS1	4	Neck, arm ache	Neck, scapula shooting pain	N	NoRM	1
26	F	41	Polyarthralgia	20	Spinal pain	Knee pain (B)	2	NoRM	0
27	F	26	Disc degeneration, post discectomy	5.5	Lumbar pain	Posterior leg pain (L)	0	NoRM	1
28	F	47	MS	7	Neck, thorax pain	Arm pain (R)	0	NoRM	2
29	F	56	Radiculopathy, cervical fusion	11	Arms, C5-8 pain	Inter-scapular pain	0	NoRM	2
30	F	44	Diffuse systemic Atrophy	11	Jaw pain	Tremor in limbs	2	NoRM	2
31	F	50	MS	10	Neck pain	Lower leg pain (B)	0	NoRM	2
32	F	66	MS	3	Leg pain (B)	Hand pain (B)	0	NoRM	0
33	M	62	Massive Trauma Left Arm	26	Lateral forearm pain (L)	Wrist allodynia (L)	1	NoRM	1
34	M	38	Stiff Man Syndrome	15	Hands, wrists pain	Buttocks, hips pain	3	CRM	2

MS = Multiple Sclerosis; CRPS = Complex Regional Pain Syndrome; R = Right; L = Left; B = Bilateral.
*Previous medicinal cannabis use: 3 = frequent, 2 = sometimes, 1 = occasional, 0 = none, N = nabilone.
**Rescue CBME: CRM = Rescue CBME group; NoRM = No Rescue CBME group; None = others.
***Global Outcome: 3 – Substantial; 2 – Moderate; 1 – Some; 0 – No Benefit; X – Didn't complete.

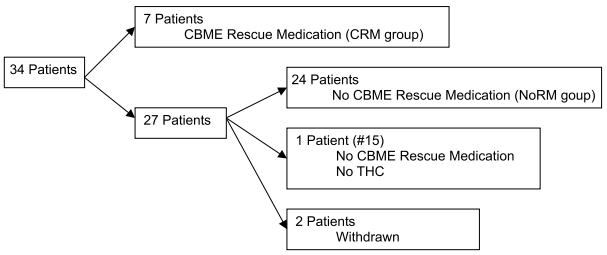

Figure 2 The progress of the 34 patients through the study.

Run-in period symptom control

The two main symptoms (S1, S2) were measured (VAS) at the start and at completion of the 2-week run-in period for all 34 patients. The scores were aggregated and the median and interquartile ranges are shown (Fig. 3). Sixteen of the 34 patients had a decrease in VAS of greater than 50% for either S1 or S2. Of these, 10 patients had a greater than 50% reduction in VAS for both S1 and S2.

Of the 34 patients, 32 recorded the VAS of S1 and S2 at midday on each day of the baseline and run-in periods (2 weeks each). The results have been aggregated (Fig. 4) and the median and interquartile range presented.

Crossover period symptom control

During the crossover period, the cumulative S1 scores for 24 patients in group NoRM measured three times/day (median (interquartile range)) were placebo 5.9 (2.8–7.3), CBD 5.45 (3.6–7.4), THC 4.63 (1.74–6.06) and THC : CBD 4.4 (2.6–5.8). ($p < 0.001$, overall test for significance, Friedman). THC : CBD and THC were

Table 2 Details of the patients who either failed to complete the study or for whom the randomization code was broken.

Patient ID	Reason
#9	Very frail from MS. Could not tolerate the lowest dose of the spray during the open-label period and became too sedated. She was withdrawn at this point.
#10	Travel to the study centre was too distressing for her. 3 weeks into the crossover part of the study she was withdrawn. The randomization was broken. There had been no evidence of benefit during the crossover period.
#15	She experienced a vasovagal episode during titration with THC. Her vital signs had been checked 10 min previously and reflected the pre-dosing results. She recovered uneventfully and was able to return home about 2 h later. The THC periods of the crossover period were omitted and she continued single-blind.
#19	He became very depressed and distressed towards the end of the crossover period having had no benefit for 5 weeks following initial success. Breaking the randomization code it was discovered that only the THC : CBD period had been beneficial. He continued the last 2 weeks single-blind, which included the second THC : CBD period. Later we learned that he was on the verge of divorcing his wife who had a psychiatric disorder, coincidental to the study.
#32	She had an episode of abdominal pain and vomiting in week 2 of the crossover period. Randomization was broken. A diagnosis of gastroenteritis was made. A break from the medication was allowed and she then continued single-blind.

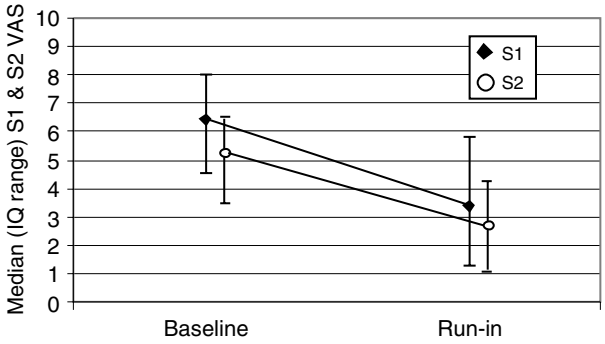

Figure 3 Change in median (interquartile range) VAS for symptom S1 & S2 recorded at the start (baseline) and at completion of the 2-week run-in period for 34 patients with open-label THC : CBD.

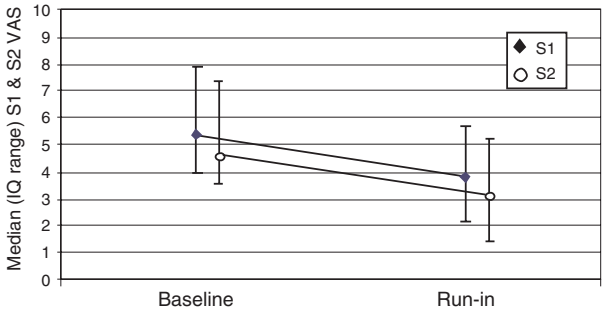

Figure 4 Change in median VAS recorded in the daily diaries at noon for symptom (S1 & S2) & (interquartile range) during 2 weeks base-line period and 2 weeks open-label THC : CBD (Patients #3 to #34).

both significantly better than placebo ($p < 0.05$ and $p < 0.01$, Wilcoxon with Bonferroni correction) (Fig. 5).

Similarly, the S2 scores (median (interquartile range)) for placebo, CBD, THC and THC : CBD were 4.98 (2.61–7.50), 5.03 (3.16–6.88), 4.08 (1.33–5.43) and 4.28 (2.33–5.51), respectively ($p < 0.001$ overall test for significance, Friedman). THC and THC : CBD were significantly better than placebo ($p < 0.001$ and $p = 0.054$, Wilcoxon with Bonferroni correction).

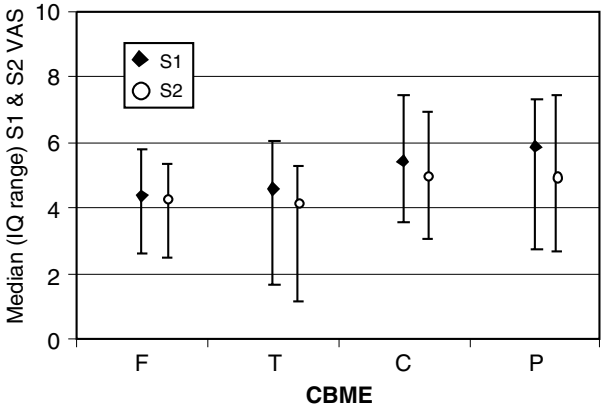

Figure 5 Crossover period aggregated symptom S1 and S2 VAS measured 3 times/day (median, (interquartile range)) for the four pairs of weeks for each CBME and placebo. F = THC : CBD; T = THC; C = CBD; P = Placebo.

Of these 24 patients, nine had a decrease in VAS of more than 50% for either S1 or S2 when using one of the three active preparations, compared with placebo. All nine experienced this with THC and/or THC : CBD. Of these, three patients also achieved this reduction with CBD.

Effectiveness of medication in comparison with run-in THC : CBD

At the weekly visit the patients were asked to compare their current test medication with the THC : CBD received during the initial run-in period of the study. Fourteen of 24 patients in group NoRM found the

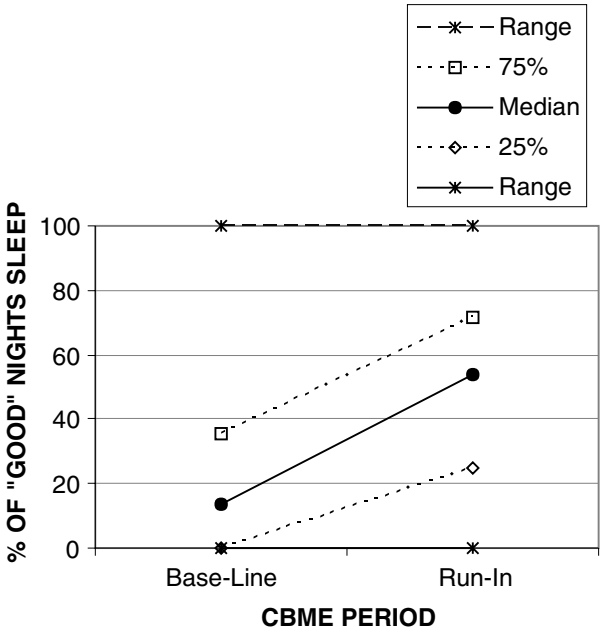

Figure 6 Percentage of nights when sleep was of ''good'' quality for 32 patients (#3 to #34) comparing the 14-day baseline and run-in periods (median, interquartile range, range).

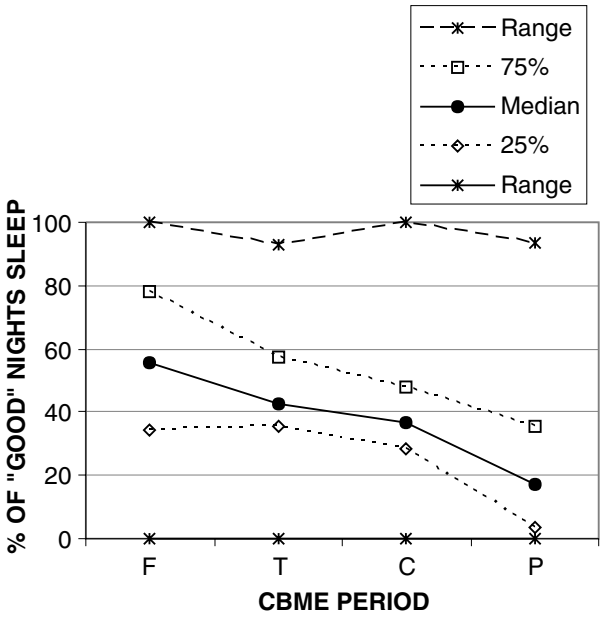

Figure 7 Percentage of nights when sleep was of ''good'' quality for 24 patients (Group NoRM) comparing the 14 days of each CBME used during the crossover periods (median, interquartile range, range).

THC : CBD (nine patients) and/or the THC (eight patients) as equal or more effective for symptom control. Four of these patients also found CBD as effective as the original medication. No patient found the placebo as effective as the original medication.

Quality of sleep

The percentage of nights that each patient described as 'good quality sleep' were compared for the baseline and the run-in periods. The results from 32 of 34 patients are presented (median, IQR, range). The median (IQR) rose from 13.4% (35.7, 0) to 53.5% (71.4, 25) (Fig. 6).

Similarly. the percentage of 'good' nights was calculated for the 24 patients of group NoRM for the crossover part of the study, comparing the three different CBMEs and placebo (median, IQR, range). (Fig. 7). The median (IQR) for THC : CBD was 55.4% (78, 34.5), for THC was 42.9% (57.2, 35.7), for CBD was 36.9% (47.9, 28.6), and for placebo 17.0% (35.7, 3.6). ($p < 0.001$ overall test for significance, Friedman). THC : CBD, THC and CBD were all significantly better than placebo ($p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively, Wilcoxon with Bonferroni correction).

Duration of sleep

The duration of sleep for each of the 24 patients in group NoRM for each of the CBMEs and placebo during the crossover part of the study was calculated. The mean (SD) sleep duration in hours for THC : CBD, THC, CBD and placebo were 6.8 (1.3), 6.7 (1.3), 6.4 (1.4) and 6.3 (1.6), respectively (Fig. 8).

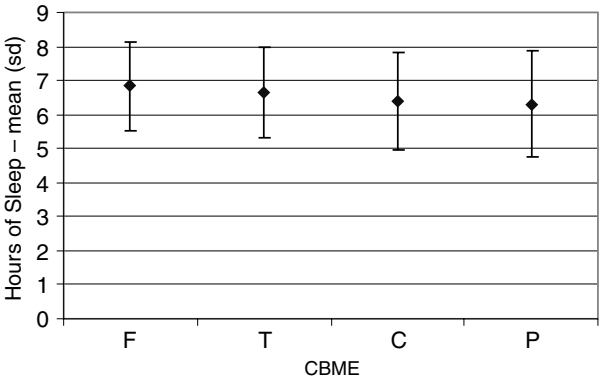

Figure 8 Duration of sleep in hours (mean, SD) for 24 patients (Group NoRM) comparing the 14 days of each CBME used during the crossover periods. F = THC : CBD; T = THC; C = CBD; P = Placebo.

General Health Questionnaire 28 (GHQ28)

The GHQ28 assesses the patient's health in general over the preceding few weeks. It has four components (Somatic Symptoms, Anxiety & Insomnia, Social Dysfunction, Severe Depression) and it is recognised that these are not independent of each other. The lower the

Table 3 Median values (interquartile range [range]) of the four elements, the total score and the caseness of the GHQ28 and of the BDI at the start, the end of the run-in and at the end of the study.

General Health Questionnaire (GHQ28)							
Period	Somatic Symptoms	Anxiety & Insomnia	Social Dysfunction	Severe Depression	Total (Maximum 84)	Caseness	BDI
Baseline	8.5 (13,4.5 [19,2])	9 (11.5,5.5 [18,1])	9 (13.5,7.5 [18,1])	3 (12,1 [20,0])	36 (44,23 [69,11])	13 (17,5 [25,0])	16 (26.7,9.7 [42,3])
End of Run-In	5 (6,4 [10,0])	5 (8,2 [9,0])	7 (8,5.5 [11,1])	1 (6.5,0 [10,0])	18 (26,13 [36,8])	2 (6,1 [9,0])	7 (16.25,5 [43,0])
End of Study	6 (7.5,5 [14,1])	7 (8,4 [13,0])	7 (9.5,5.5 [17,0])	1.5 (6.5,0 [12,0])	24.5 (31.5,16.5 [41,2])	4 (10,0.5 [14,0])	8 (20,4.75 [42,0])

score, the 'healthier' the patient. The median scores (interquartile range [range]) for the 24 patients in group NoRM measured at the start, at the end of the run-in period and at the end of the study are shown (Table 3). The 'Caseness', derived from the patient's score, is an indication of psychological/psychiatric disturbance.

Depression

For the 24 patients in group NoRM, the median (IQR) of the BDI score measured at the start, at the end of the run-in period and at completion of the study are shown (Table 3). Fourteen patients changed the severity of their depression between the start and the end of the study. Seven patients moderate → mild; three patients moderate → minimal; two patients severe → moderate; one patient severe → mild; one patient minimal → mild. [BDI score: Minimal 0–9, Mild 10–16, Moderate 17–29, Severe 30–63].

Daily intake of CBME

At the start of the run-in period each of the patients titrated themselves to their optimum dose over a period of several days. The amount was partly determined by the onset of side-effects and partly the improvement in symptoms. During the crossover period the patients reached their optimum dose more quickly.

The two patients who used six or more sprays as a single dose found it difficult to retain sublingually because of salivation. This caused some of the CBME to be swallowed, theoretically altering the absorption profile. Across the 34 patients there was a range of use of between one and eight sprays as a single dose.

For 25 patients (Group NoRM + patient #15), the average daily intake of CBME for the last 4 days of the run-in and each pair of CBME treatment weeks during the crossover period was calculated (median, IQR, range) (Fig. 9). This assumed a level of stability in the dose used towards the end of each week.

Side-effects

In their daily diaries the patients recorded episodes of the seven specified side-effects. For 24 patients (Group NoRM) the number of days on which the three commonest side-effects occurred during the run-in period and the 2 weeks of use of each CBME and placebo during crossover are shown (Fig. 10). Unfortunately data on the incidence of the designated side-effects (e.g. dry mouth, drowsiness) during the baseline period was substantially incomplete due to an error in data collection and is not presented.

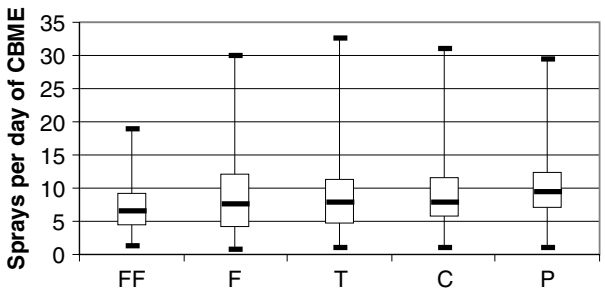

Figure 9 Box and whisker plot of the median (interquartile range, range) number of sprays/day used by 25 patients (Group NoRM + patient #15). The last 4 days of the run-in period and the last 4 days of each of the pairs of weeks of each CBME were averaged. FF = Run-In THC:CBD; F = THC : CBD; T = THC; C = CBD; P = Placebo.

Drowsiness and euphoria/dysphoria ('high') were common in the first 2 weeks of the run-in period while patients tried to find an appropriate dose and were more frequent with CBMEs containing THC. Dizziness followed a similar pattern but was less of a problem. Episodes of panic and anxiety were infrequent. They were commonest during the run-in period and not exclusive to those who were cannabinoid naïve. Time distortion was infrequent but occurred with CBMEs containing THC. Hallucination was recorded by only one patient and was not reported as severe.

The most common symptom that patients complained of was a dry mouth (Fig. 10). However, most patients were taking other medications which could contribute to this, indicated by the high occurrence when using placebo.

Some patients experienced a stinging sensation on use of the spray, particularly with the initial formulation. Many did not like the taste. No sublingual mucosal changes were observed.

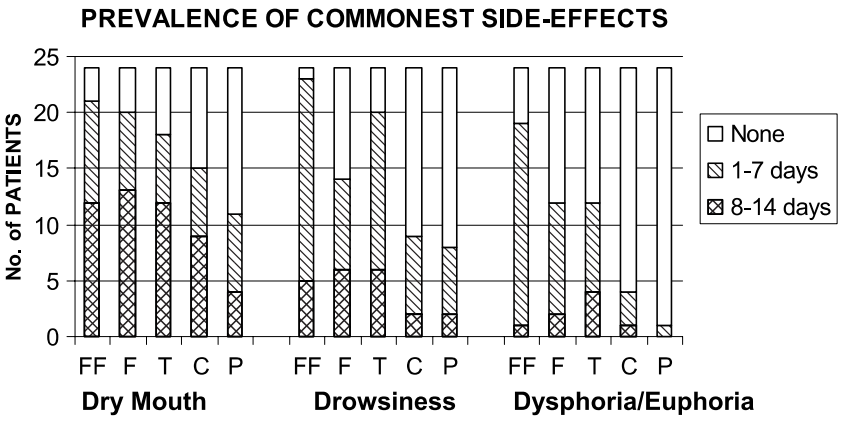

Figure 10 Prevalence of daily episodes of dry mouth, drowsiness and dysphoria/euphoria ("high") during run-in (14 days) and crossover periods (7 + 7 days). None = No episodes. 1–7 days = Episodes on <51% of days. 8–14 days = Episodes on >50% of days. FF = Run-In THC : CBD; F = THC : CBD; T = THC; C = CBD; P = Placebo.

Patient #15 had a vasovagal episode during a dosing session. It occurred 1 h after the third spray when using THC for the first time (as revealed on immediate unblinding) (Table 2). The reaction was probably due to a combination of prolonged sitting and excessive dosing. No other cardiovascular side-effects were observed for any patients.

A change in neural function was observed in two patients who had had previous spinal surgery. One had a return of an absent ankle reflex (patient #11). The second (patient #2) discovered that touch sensation reappeared in a previously anaesthetic fifth lumbar dermatome. He also found that his ability to maintain an erection was dramatically improved, leading to the accidental pregnancy of his partner and birth of a daughter.

No other side-effects related to the use of CBME emerged during the study.

The patients were weighed at the beginning and the end of the study in normal clothing. The median change in weight for 27 of 34 patients (interquartile range [range]) was 0.5 kg (−2 to 0.6 kg [−5.6 to 4 kg]). Of the remaining seven, two patients terminated the study early, one patient was paraplegic and unweighable, and data were unrecorded on four.

Full blood count, urea and electrolytes and liver function tests remained within normal limits for 33 patients. One patient had transient changes in alanine transaminase and alkaline phosphatase which may have been related to the use of erythromycin for a vaginal abscess.

During the 3 months of the study, other events occurred which were unassociated with CBME but would be likely to have an effect on outcomes (significant marital disharmony (two), husband made redundant (one), wife undergoing chemotherapy (one), pregnancy and misdiagnosis of a major genetic abnormality (one), flare up of MS (one), other (two)). The randomization was broken for two patients and both continued single-blind (Table 2).

Preferences

The 28 patients who obtained benefit were asked which CBME they had preferred. Eleven preferred THC : CBD; 14 found THC and THC : CBD equally satisfactory; two preferred THC; and one found THC and CBD equally satisfactory.

At the end of each individual study the senior clinician made a clinical assessment of the overall benefit for each patient to decide on progression to the safety extension study. This subjective assessment included the control of symptoms S1 and S2 and other identified symptoms, sleep, mood and GHQ28 (Table 1).

Discussion

This was the first clinical study of both the use of CBMEs and of their delivery via the sublingual route. The objectives were to obtain an initial indication of the efficacy, safety and tolerability. We had no firm knowledge of the extent of the therapeutic effect, the likely dose range, the frequency and pattern of administration, the incidence of and threshold for side-effects or the tolerability of the CBME spray.

Designing the study

In designing the study six major factors were taken into consideration.

1 Chronic pain is a heterogeneous problem with multiple and variable pathophysiological mechanisms coexisting in the patient and varying over time. Different mechanisms for pain genesis probably exist within a single clinical diagnostic group, leading to the need for different treatment strategies [20,21].

2 There has been a pressure to use cannabinoids in patients for whom all other therapy has failed. These are usually the most difficult and complex patients to study.

3 The effect of cannabinoids on pain is likely to be at variable sites in the nervous system ranging from the peripheral neurone to the cerebral cortex.
4 Previous and current therapy is usually heterogeneous.
5 Differences between healthy volunteers and patients in side-effect profile were anticipated.
6 Differences in therapeutic dose, effect and in side-effect profile between patients were expected, as seen with morphine and many other psycho-active drugs.

For multiple sclerosis (MS), the aetiology of the pain may be central neuropathic, somatic muscle spasm and spasticity, visceral muscle spasm (e.g. bladder), mechanical (spinal), mechanical (immobility) or even unrelated to MS. The pain may be markedly aggravated by psycho-social factors such as depression, immobility, employment loss, burden on the family and variable progression of the disease. To these must be added the effects of a variety of other problems including defects of vision, co-ordination, strength, sensation, bladder control, and sexual function.

There were three specific reasons for focussing on patients with MS. Firstly, there is extensive anecdotal evidence of the benefits of illicit cannabis for symptom control in this disease. Secondly, there is a perception that cannabinoids should be used for treating neuropathic pain, although there is no strong evidence to support this opinion. We therefore saw no reason to exclude others with a variety of other intractable pain problems. All patients exhibited multiple pains of nociceptive, neuropathic and/or uncertain pathophysiology. Two patients nominated a symptom that was not specifically painful (tremor, bladder urgency). Third, it was expedient to focus on this group to obtain agreement to initiate studies of CBMEs. However, choosing the most intractable problems for the clinical trial of a new drug for pain is far from ideal.

With all these difficulties we decided that a classical parallel or crossover group study was inappropriate [22]. We opted to use an 'N of 1' approach, which has been described as a developer's tool and has been recommended for studying new therapy in chronic pain [23,24] and cannabinoids [7]. The method has already been used by others for the study of the medicinal use of cannabinoids in individuals [25,26].

The patients are studied as individuals but with the rigour of double-blind placebo controlled crossover techniques. Each individual patient study stands by itself and indeed is much closer to everyday clinical practice than is the classical parallel trial of a new pharmacological treatment. It allows both for the heterogeneity of patients and their varied responses. The capture of data can be individualised, allowing a variety of endpoints. Variable dosing patterns are acceptable, enabling the patients to individually customise their usage to different endpoints.

Comparisons of results across groups of patients cannot reach the same level of statistical significance as with homogeneous, parallel group studies. Therefore the analyses undertaken are an attempt to summarise some of the data from the 34 individual studies. Furthermore, the patients were desperate to participate in the study because of the failure of past symptom control. The attention from the study team further complicates the evaluation. It was not surprising that all but one patient could show some benefit at the end of the run-in period. Therefore the data only allows for generalizations to be drawn, thereby providing information for individual clinical practice and for the design of future and more focussed studies.

The progress of patients in a 'steady state' in the subsequent extension study will complement the information given here (paper in preparation). Future studies might give tighter indications of the likely success of CBMEs in treating the specific symptoms of specific diseases, although we are still far from being able to predict accurately the outcome of most therapy in chronic pain.

The 1-week periods of the crossover part were too short. However, periods of 2 weeks or more would have extended this study unacceptably. Alternatively, we could have eliminated one or more CBMEs. However, as we had no hard evidence on the optimum CBME, we compromised. We did not include washout periods, as cannabinoids have a long half-life in the body even though their clinical effect may only last a few hours.

Dosing

Although healthy volunteers in the Phase 1 studies could tolerate titration at 15-min intervals, our patients proved different. This vindicated our use, at the beginning of the study, of patients who had previous experience of medicinal cannabis use.

In general, patients initially titrated to the limit of tolerability (drowsiness, dysphoria) rather than benefit. The tests of psychomotor and cognitive function served mainly as a reassurance for discharging the patients home (19). The wide range of dosage parallels that seen with morphine and many other psycho-active drugs.

As the study progressed, the instructions for home usage of the CBMEs evolved. Because of our concerns over safety, we instructed patients to initially use, as a single dose, 30–50% less than they had received during the titration session. They were allowed to use the CBME up to 6 times per day, as required. Over the days, the patients' dosage and pattern of use was customised to their need from their response. For example, some might

prefer a higher dose at night. With experience and confidence, the patients quickly moved to their optimum dosing schedule.

Pain and other symptoms

No attempt has been made to analyse effects of the CBME on specific pain symptoms. The VAS scores do not differentiate between improvements due to direct effects on neural pathways, effects on sleep and mood, and the benefit of the supportive environment of the study. Equally some patients found the study tiring, tedious and frustrating, whilst others experienced domestic upheavals etc.

The overall trends seen with the use of THC and THC : CBD were encouraging. We anticipated that CBD would have little effect by itself in this study, but it may have other therapeutic roles, particularly in inflammatory pain [14,27].

All eight patients with residual pain associated with the failure of spinal surgery obtained benefit and this is an exciting prospect for further study in this notoriously difficult group to treat.

Sleep and mood

The CBME seemed to have little effect on the recorded number of hours of sleep. However, the change in quality from 'poor' or 'fair' to 'good' was unexpectedly high. The quality of sleep is a subjective global assessment and includes duration, depth and disturbance. It is more important for the patient than duration alone. Others have analysed nocturia [15] and shown a reduction in its frequency with the use of THC. The effects of CBMEs on sleep may prove to be one of the major benefits of the use of cannabinoids in chronic pain and MS.

The GHQ28 indicated that the use of CBME had had a broad effect even though it was only applied on three occasions across the study. The changes in the 'Caseness' of the GHQ28 and in the BDI show valuable improvement in mood.

Side-effects

The psycho-active side-effects of cannabinoids are the main focus of objection to this group of drugs. We specifically targetted the common acute side-effects by recording their daily occurrence. Whilst we did not measure intensity or duration directly, the daily occurrence gives an indication of prevalence (Fig. 10).

Patients were free to record any other perceived effects. However, except for the oral effects of the spray itself, no other side-effects emerged.

In general, the side-effects were manageable, tolerable and similar to those seen clinically with most other psycho-active drugs used in pain management. They were most prevalent during the run-in period as patients learnt to titrate themselves to an appropriate level. Realistically, the weekly periods of the study were too short to allow time for the patients to fully customise their use and their side-effect management.

Drowsiness and dizziness induced by the CBMEs were common, but manageable for all but one patient (Table 2). It was used to positive advantage at night time to improve sleep (as with tricyclic antidepressants, morphine, etc.).

Dysphoria and mild euphoria were common during the run-in period. Some patients were pleased to experience a feeling of relaxation and well-being, especially if they had had a bad day with pain. Some found the distancing effect beneficial. However, no patient wanted to exchange the disabling effect of chronic pain for that of immobility from being dysphoric/euphoric.

At the start of the study and before the dose titration sessions, the patients were briefed about the possibility of panic attacks. We had no information about their incidence or at what point they might appear. No severe panic attacks occurred, although some became anxious at the onset of dysphoria. It may be that these are primarily a feature of uncontrolled dosing, particularly in the novice recreational user.

A dry mouth was a common oral problem. However, many patients were using other drugs which could contribute to this effect. No specific oral lesions were seen, although they have occurred in patients in other studies (GW Pharmaceuticals).

Cannabis is known to stimulate appetite. However, only one patient showed a substantial increase in weight. The loss of 5.6 kg by another probably reflected substantial marital disharmony.

Preferences

The initial open-label titration with THC : CBD proved to be a guide to the optimum dose of THC. Although CBD and placebo had limited effect, patients did not titrate themselves much further than they had with the original THC : CBD. Prior to the study we had expected to find that the THC : CBD mixture would be optimal, that we would see more side-effects with THC, and that CBD alone would be almost ineffective. Whilst there was a preference for THC:CBD, the differences were not as marked as we anticipated. The lack of effect of CBD by itself may just reflect either the narrow range of pain problems studied and/or the need for a substantially higher dose of CBD.

In conclusion, this study has been a first step in gaining confidence in the use of CBMEs. THC and THC : CBD were effective in relieving pain and improving sleep in a

small group of patients. As experience was gained in dosing, the spray proved easy and convenient for the patients to use. They were able to medicate in public without attracting unwelcome attention from others. Side-effects were not substantially different to those seen with most other psycho-active drugs used in pain management.

Studying CBMEs in patients with a wider variety of pain problems, exploring specific areas, and deepening the clinical experience are the next steps. The potential uses in a variety of other, non-pain areas (neuro-protection, psychiatric disease, tumour therapy, inflammation, AIDS, etc.) are exciting prospects for the future now that we have some confidence and experience in the use of these materials.

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