

An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis

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The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of *Cannabis sativa* in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ($P < 0.05$, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ($P < 0.05$, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS. Multiple Sclerosis (2004) 10, 425–433

Key words: cannabidiol; cannabis; delta-9-tetrahydrocannabinol; multiple sclerosis; neurogenic detrusor overactivity; neuropathic pain; sleep disorder; spasticity; urinary incontinence

Introduction

Ninety per cent of patients with multiple sclerosis (MS) develop lower urinary tract symptoms (LUTS) after 10 years of disease activity.¹ Urinary urgency and urge incontinence may affect quality of life and are often compounded by immobility. Standard treatment with anti-cholinergics and clean intermittent self-catheterization may be highly effective in the early stages, but with increasing disability indwelling catheterization, an intervention with significant morbidity, is often required. Additional therapies for refractory urinary symptoms in patients with advanced MS are required to prevent or postpone the need for long-term indwelling catheterization.

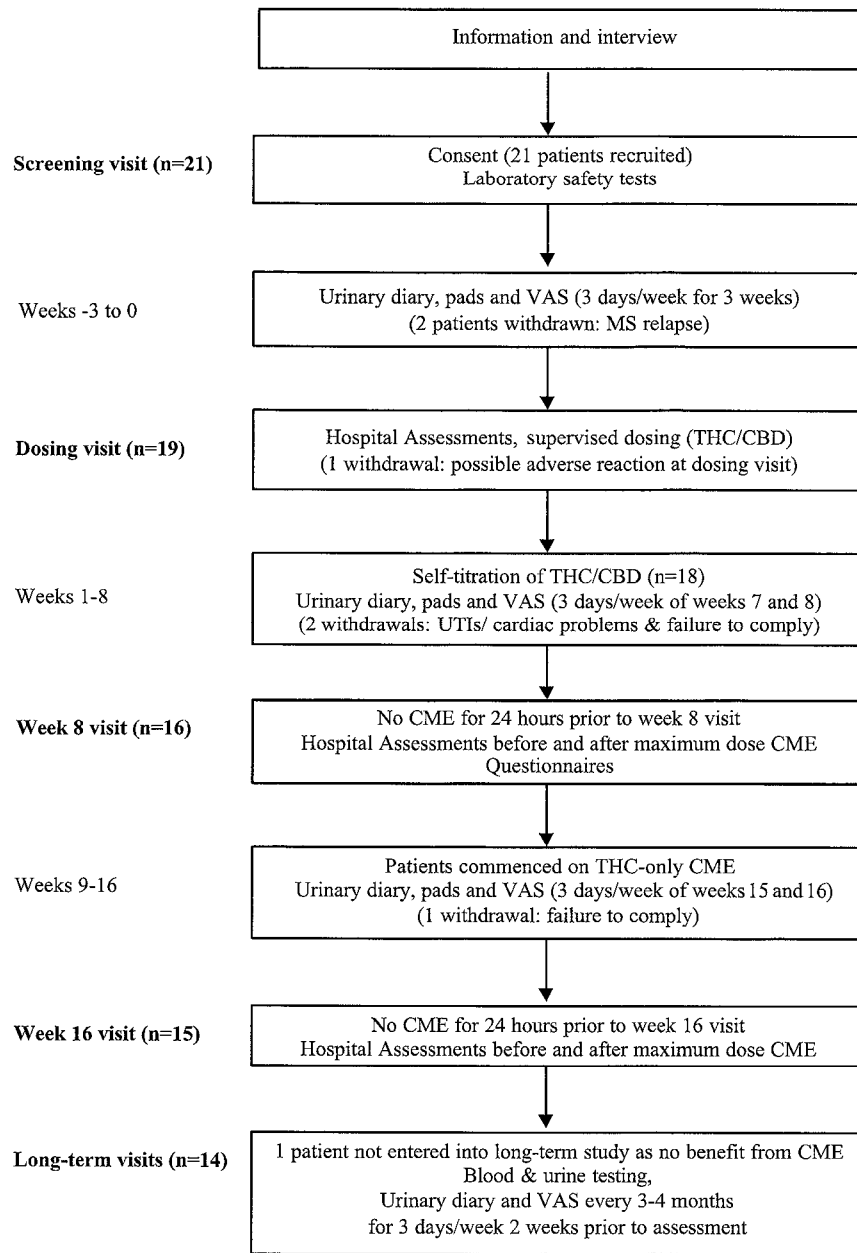
Some patients with MS use cannabis to alleviate urinary and other symptoms. In a survey of 112 patients who used 'street' cannabis as a medicine, 64%, 55% and 59% reported improvements in urgency, urge incontinence

and hesitancy, respectively.² In addition, Wade has recently reported that medicinal cannabis extracts produced improvements in bladder symptoms in some patients recruited for neurogenic symptoms in MS.³ Such effects are consistent with reports of the existence of cannabinoid receptors in rodent bladder, the activation of which reduces bladder motility,^{4–7} as well as in regions of the central nervous system associated with bladder control.⁸ Statistically significant improvements in MS-related neuropathic pain and improvements in spasticity in some patients have also been reported by Wade and Notcutt.^{3,9}

Because cannabis has not yet been licensed for medicinal use in the UK, patients have to use 'street' cannabis that has not been subjected to rigorous quality control, with obvious implications for safety. Cannabis medicinal extracts (CME) are whole-plant extracts of *Cannabis sativa* that are derived from plants bred selectively to contain fixed proportions of the abundant cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in particular. In addition to THC or CBD, the remainder (<5%) of the cannabinoid fraction of the extract contains other 'minor' cannabinoids that occur naturally in smaller quantities. The cannabinoid fraction of CME accounts for 50% of the extract, the balance being comprised of noncannabinoid substances such as flavinoids and terpenoids. Ethanol (50%) and propylene glycol (50%) dissolve the highly lipophilic extract and facilitate sublingual

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absorption.¹⁰ The rate of absorption of CME following sublingual administration is more rapid and predictable than by the oral route, and enables patients to self-titrate the dose of CME, balancing symptom control against side effects, such as intoxication.¹¹

The aim of this open-label, pilot study was to evaluate the safety, tolerability, dose range and efficacy of two preparations of CME on lower urinary tract and other troublesome symptoms in patients with advanced MS.

Patients and methods

Patient selection

Patients aged 18–65 with advanced MS (Kurtzke ≥ 6.5) and troublesome LUTS refractory to maximum conven-

tional treatment were eligible for recruitment. Other inclusion criteria included detrusor overactivity proven on cystometry and a Mini-Mental State Examination¹² score > 27 . All patients continued on maximum tolerated dose of anti-cholinergic medications and clean intermittent self-catheterization when applicable throughout the trial. Patients using street cannabis were required to stop four weeks prior to and during the study and urine tests for cannabis were carried out prior to recruitment. Exclusion criteria included detrusor failure, an indwelling catheter or inability to fulfil the requirements of the study protocol.

Study procedures

The study protocol, summarized in Figure 1, had local ethics committee approval. The trial was conducted under

a 'DDX' (Doctor's and Dentist's exemptions) license issued by the Medicines Control Agency, with several restrictions on protocol design. Initial approval was given for eight weeks' treatment with CBD/THC, followed by THC-only in the long-term. Following informed consent and physical examination, suitable patients were asked to perform baseline home assessments (Table 1) for three consecutive days per week for three weeks, to confirm eligibility. Patients at risk of recurrent urinary tract infections were advised to increase their fluid intake, as UTI is a potential confounding factor. We considered that precise measurement of fluid intake would be too difficult for these significantly disabled patients to undertake in addition to their many other daily outpatient assessments.

Urinary diary and VAS scores were repeated for three days per week during the last fortnight of each eight-week treatment period on CME (see below) and during the long-term safety and efficacy extension (Figure 1). Outpatient hospital assessments (Table 1) were also performed at baseline and at the end of each treatment period. The patients did not take CME for 24 hours prior to the outpatient hospital visit. Cystometry was performed to calculate maximum bladder capacity. The patients then took their maximum tolerated dose of CME and cystometry was repeated. Thus 'chronic' and 'acute' effects of CME on cystometric capacity were evaluated. In a similar manner, at the same outpatient visit the chronic and acute

effects of CME on spasticity were monitored using the Ashworth score, carried out by the same trained observer.

Drug administration

At the initial supervised dosing visit, patients were instructed on how to recognize symptoms of intoxication. Under close observation and cardiomonitoring, they took up to four sprays of THC/CBD (2.5 mg of THC and 2.5 mg CBD per spray) as tolerated over 2 hours. The patients were monitored for 4 hours after the start of dosing. At home, patients took THC/CBD at night-time only for the first two weeks of treatment and were monitored by daily telephone contact to check on their ability to use the spray, and to advise on dose escalation and side effects. Thereafter, divided daytime dosing was introduced, with a maximum permitted daily dose of 120 mg each of THC and CBD (48 sprays). However, a conservative dosing regimen was followed over the first four weeks of treatment, with gradual dose escalation such that patients titrated symptom relief against the acute side effects of CME (intoxication). After four weeks patients were actively encouraged to experiment with their dosing regimen and to take the maximum tolerated dose of CME. After eight weeks' treatment on THC/CBD the patients were switched to the THC-only extract (2.5 mg THC per spray) for a further eight weeks. Adverse events and CME consumption were recorded daily throughout the study. At the conclusion of the trial, with ethics committee approval, patients were permitted to continue treatment with CME and were allowed to choose either extract in a long-term safety and efficacy study. Assessments including urinary diary and VAS were completed every 3–4 months.

Data analysis

Data from the first six weeks of each treatment period were not analysed because this period had been used for self-titration to arrive at a stable dose. Statistical calculations were performed using Wilcoxon's signed rank test (Graphpad Prism version 3.02).

Results

Previous use of cannabis

Ten patients had used cannabis as a medicine previously and four of these were considered 'regular' users (cannabis used as a medicine > 15 times) with smoking or ingestion of the drug within three months of recruitment. Urine testing for cannabis was negative prior to recruitment in all patients.

Recruitment and withdrawals

Twenty-one patients (4M:17F; mean age 48 years, range 31–64) were recruited. Mean (median) time from the date of formal diagnosis of MS was 11 (10) years and the mean duration from first onset of symptoms to diagnosis was 6 (3) years. Fourteen had primary or secondary progressive MS and the remainder had relapsing–remitting disease

Table 1 Assessments performed at home and during outpatient hospital visits

Home assessments

Frequency and volume chart, noting time and nature of each micturition event, whether voluntary void or incontinence episode and sensation (planned void, normal, strong or urgent desire to void)
Incontinence pad weights
Daily Visual Analogue Scale for each neurogenic symptom (identified at tape-recorded interview)

Hospital (outpatient) assessments

Laboratory safety tests

Full blood count
Renal profile
Liver profile
Urinalysis and urine culture, urinary HCG, urine screen for cannabis at screening visit

Questionnaires

Mini Mental State Examination¹²
Medical Outcomes Study Short Form 36 (generic quality of life)²⁵
Hospital Anxiety and Depression score²⁶
Multiple Sclerosis Impact score²⁷
Barthel Activities of Daily Living Index²⁸
International Continence Society BPH²⁹
Bristol Female Lower Urinary Tract Symptoms³⁰

Urological

Filling and voiding cystometry (baseline visit and before and after maximum tolerated dose)
Post void residual

Neurological

Tape-recorded interview to identify neurogenic symptoms and effect of CME
Ashworth scale for spasticity³¹
Global patient comfort score

that was considered stable. Mean Kurtzke score at entry to the trial was 7.0 (range 6.5–8.0).

All patients reported troublesome LUTS for >5 years. Eleven patients took Oxybutynin and seven took Tolterodine regularly. Five patients took Desmopressin in addition to an anti-cholinergic on an 'as required' basis. Two patients had found anti-cholinergics to be ineffective and one was unable to tolerate the side effects. The patients had varying degrees of detrusor dysfunction and detrusor sphincter dyssynergia with 11 requiring regular clean intermittent self-catheterization. Fifteen patients completed 16 weeks of treatment; the timing and reasons for withdrawal of the other six patients are detailed in Figure 1.

Duration of treatment and follow-up

Patients took THC/CBD for a mean (median) of 11 (10) weeks and THC-only for 10 (9) weeks during each treatment period. Fourteen patients were entered into the long-term safety and efficacy extension and all opted to take the THC-only extract. Mean (median) long-term follow-up with voiding diary and VAS scores was 31 (35) weeks. Eleven of these 14 patients continue to take CME in the long-term extension for a mean (median) of 27 (30) months (22.2 patient years) and 3 discontinued CME after physical deterioration necessitated an indwelling catheter.

Dose of CME

Although the range of doses in use by the end of the initial self-titration treatment periods for THC/CBD or THC was quite wide across the group, the doses after the titration periods remained stable for each patient individually. Patients took 1–39 sprays/24 hours of THC/CBD (2.5–97.5 mg each/24 hours), with a daily mean of 33.7 mg (median 30.5) each. The number of sprays of THC-only extract was 1–30.2 sprays/24 hours (2.5–75 mg/24 hours) with a daily mean of 31.2 mg (median 29.4), significantly less than on THC/CBD ($P < 0.05$, Wilcoxon's signed rank test). The four patients who were previous regular users of cannabis as a medicine took a mean (median) of 52 mg (49) each of THC and CBD and 50 mg (55) of THC during the last two weeks of each eight week treatment period.

Patients took a mean (median) of 23.4 mg (16.3) of THC-only/24 hours during the long-term extension, which was significantly less than during the first eight weeks of treatment on THC/CBD. However, long-term dosing data from one patient with above average consumption were not available. There was no correlation between the dosage of CME in individual patients and the effect on bladder symptoms or VAS scores. Tolerance to CME (increasing doses required to achieve the same therapeutic benefit) did not occur in the long-term.

The body mass index (BMI) was available for 12 of the 15 patients who completed 16 weeks of treatment; mean (median, range) BMI was 24 (24, 17–30). The doses of CME taken by each patient were not related to their BMI.

Laboratory safety tests

There were no clinically significant changes in haematological, renal or hepatic indices throughout the study.

Side effects

As a result of the study design, most patients experienced symptoms of intoxication such as mild drowsiness, disorientation and altered time perception during the dose titration period. However three patients had single short-lived hallucinations (two visual and one auditory) that did not recur when they lowered their dose. Two patients appeared to be exquisitely sensitive to the psychoactive effects of CME and could tolerate no more than one spray of either extract daily, but still reported beneficial effects. One of these patients had improvement in spasms but neither tremor nor urinary symptoms improved. This patient continues to take CME with beneficial effects on spasms. The other patient had improvements in frequency and incontinence, but not in episodes of urgency or nocturia or VAS scores of pain, tremor or spasms. It is likely that these improvements were related to the placebo effect as this patient later discontinued CME without significant deterioration in symptoms.

All patients complained of a worsening of dry mouth (already present due to anti-cholinergic treatment) and two complained of mouth soreness at the site of drug administration.

Diary data

Functional bladder capacity and bladder emptying efficiency Voided (plus catheterized where applicable) urine volumes provide a measure of 'functional' bladder capacity. This measure did not increase significantly from baseline after eight weeks' treatment with either THC/CBD or THC-only or in the long-term study. Bladder emptying efficiency [volume voided \times 100/(volume voided + post void residual)] is a measure of detrusor function, but is affected by bladder outlet obstruction. For the eight patients who voided and catheterized throughout the study, mean (median) bladder emptying efficiency was 44% (45) at baseline and did not change significantly following eight weeks of treatment with either extract (44% (47), THC/CBD and 42% (48), THC-only) or in the long-term study (40% (41), THC-only).

Urinary incontinence, frequency, and total voided volumes The number of daily incontinence episodes, the volume of incontinence, nocturia and daytime urinary frequency all decreased significantly on both extracts after eight weeks of treatment ($P < 0.05$, Wilcoxon's signed rank test; Figure 2). Both extracts were comparable in terms of efficacy. In the long-term study, the number of incontinence episodes and daytime frequency also decreased significantly (Figure 2). The total daily volume of urine produced (assessed by adding voided, catheterized and incontinence pad weights) also decreased significantly from baseline after using THC/CBD for eight weeks (median 1800 versus 1464 mL, $P < 0.05$, Wilcoxon's signed rank test) and after eight weeks of THC-only (median 1334 mL, $P < 0.05$). The mean combined voided and catheterized volumes were similar across the treatment periods (1953, 1631, 1636 and 1589 mL for baseline, weeks 7 and 8, weeks 15 and 16 and the long-term respectively,

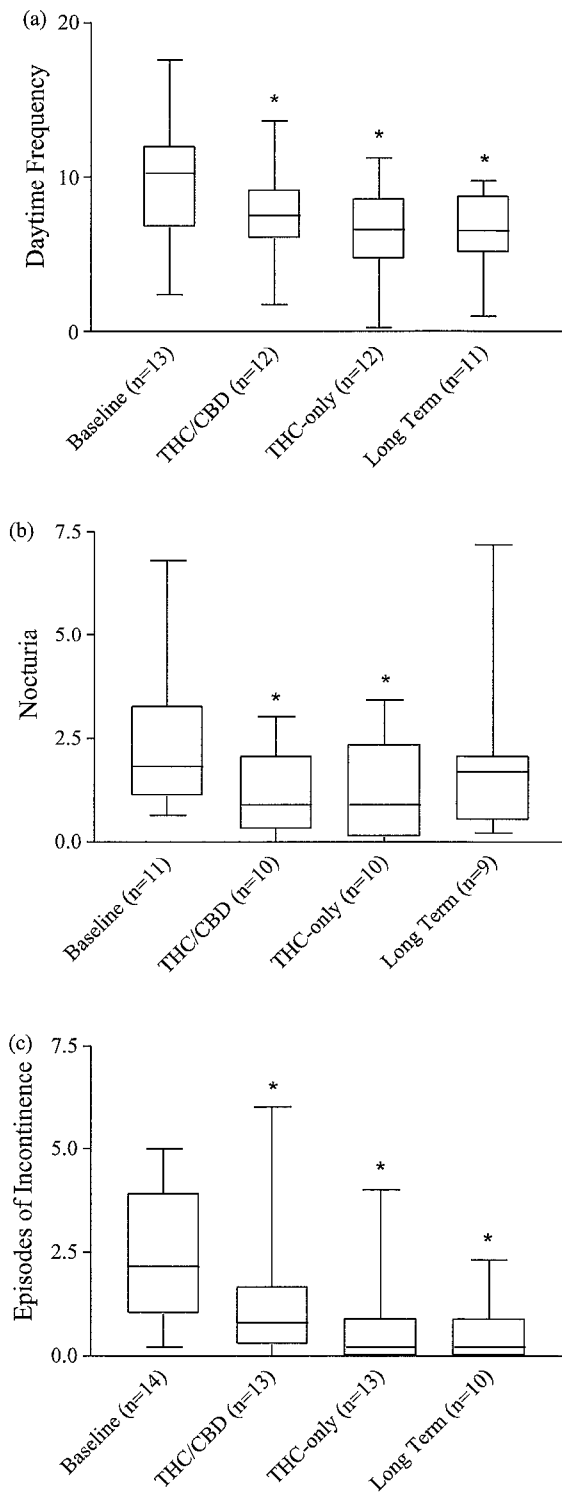


Figure 2 The effects of THC/CBD and THC-only on the total number of daytime (a) and night-time (b) voids, and the number of incontinence episodes/24 hours (c) as recorded in voiding diaries at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only). The box extends from the 25th percentile to the 75th percentile, with a line at the median; the whiskers extend above and below the box to show the highest and lowest values (* where $P < 0.05$ compared to baseline using Wilcoxon's signed rank test).

Figure 4) but the volumes recorded during weeks 7 and 8 were statistically significantly smaller than baseline volumes.

Bladder sensations The mean (median) proportion of voids for which the patient reported having the sensation of 'urgency' decreased significantly from 16% (11) to 6% (5) after eight weeks' treatment with THC/CBD, to 4% (2) after eight weeks of THC-only and to 2% (0.05) in the long-term. In concert, the proportion of 'planned or normal' voids increased significantly on both extracts following eight weeks' treatment and in the long-term ($P < 0.05$, Wilcoxon's signed rank test, Figure 3).

Other troublesome symptoms The most frequent additional troublesome symptoms that the patients identified during the tape recorded interview on entry to the study were spasticity, pain, tremor, difficulty sleeping and constipation (Table 2). Average VAS scores for pain ($n = 13$) improved after eight weeks' treatment with THC/CBD ($P < 0.05$, Wilcoxon's signed rank test). Scores for spasticity ($n = 13$), pain ($n = 12$) and difficulty sleeping ($n = 9$) all improved significantly ($P < 0.05$, Wilcoxon's signed rank test) after eight weeks' treatment with THC-only. No changes were noted for either tremor or constipation. Improvement in pain scores ($n = 10$) remained significant in the long-term for a mean (median) of 31(35) weeks. In addition, one patient complaining of severe idiopathic nausea refractory to all treatments had complete resolution of this symptom on both extracts, with continued benefit in the long-term. Improvements in other symptoms such as wellbeing were reported but the numbers were too small for analysis.

Urodynamic data

The maximum cystometric capacity (MCC) increased, but not significantly, from a mean of 296.6 mL (median 292,

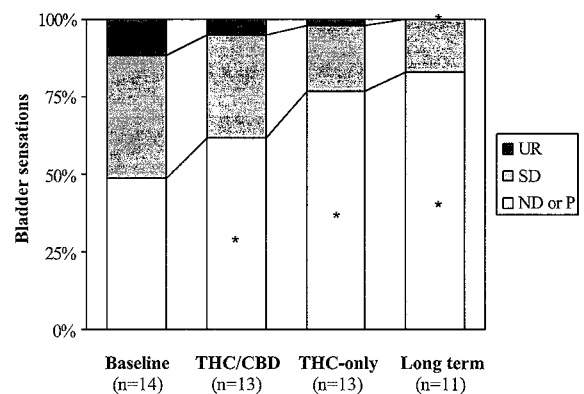


Figure 3 The effects of THC/CBD (weeks 7 and 8) and THC-only (weeks 15 and 16, long-term) on the proportion of bladder sensations recorded in frequency/volume charts. UR =urgency, SD =strong desire to micturate, ND/P are normal desire to micturate and planned voids. The asterix denotes a statistically significant difference from baseline values ($P < 0.05$, Wilcoxon's signed rank test). Data from one patient with concomitant severe sensory urgency that persisted throughout the trial has been excluded.

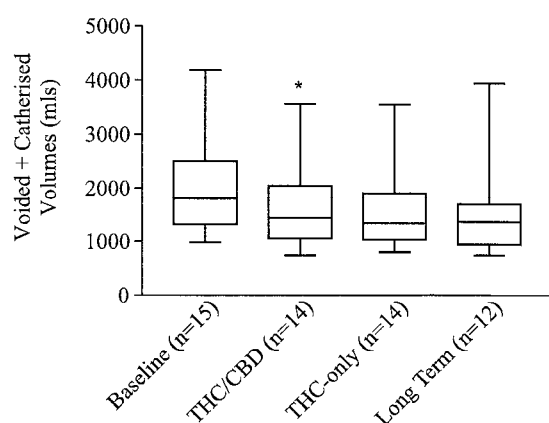


Figure 4 Mean total voided and catheterized volumes/24 h at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only). (* where $P < 0.05$ compared to baseline using Wilcoxon's signed rank test).

range 45–608, $n = 15$) at baseline to 339 mL (312, 103–665, $n = 14$) after chronic treatment with THC/CBD. Chronic treatment with THC-only resulted in a significant increase in mean MCC to 394 mL (294, 126–781, $n = 14$; $P < 0.05$, Wilcoxon's signed rank test). Acute treatment with the maximum tolerated dose of THC/CBD (mean dose, 10) increased mean MCC to 394 mL (324.5, 105–814, $n = 14$) but this was not significant. However acute treatment with THC-only (mean dose, 7.5) significantly increased the mean MCC to 426 mL (384, 142–812, $n = 12$; $P < 0.05$).

Urinary symptom questionnaires

Responses to the questions relating to urinary frequency (Q1), nocturia (Q2) and urge incontinence (Q4) and to the impact of urinary symptoms on life (Q30 ICS-BPH, Q31 BFLUTS) changed significantly after eight weeks of treatment with both extracts ($P < 0.05$, Wilcoxon's signed rank test), and reflected the improvements reported in diary data and pad tests. In addition, significant improvements were also noted in the responses to questions 3 (urgency) and 6 (number of incontinent episodes, BFLUTS only) after eight weeks' treatment with THC-only.

General and neurological assessments

There were no significant changes in any of the questionnaire based measures (SF36, MS Impact score, Barthel

activities of daily living, Hospital Anxiety and Depression score) after eight weeks' treatment with THC/CBD. Ashworth and global comfort scores did not change after eight weeks' treatment with either extract (the patients having fasted from CME for 24 hours) or acute treatment with the maximum tolerated dose.

The physical examination measures remained unchanged in all patients. Mean Kurtzke score did not change throughout the early part of the trial (eight weeks' treatment each with THC/CBD and THC-only). No change in mean Ashworth scores from baseline were noted at the 8- and 16-week assessments, either following a 24-hours fast from CME or following maximum tolerated dose of CME.

Long-term safety and efficacy extension

CME did not have any adverse effects on laboratory safety blood tests after a mean of 36 weeks of follow-up. Three patients, all of whom were wheelchair bound at the time of recruitment, suffered significant MS-related physical deterioration during the long-term extension.

Discussion

In this open-label, pilot study in a select group of patients with advanced MS we investigated the safety and efficacy of self-titrated sublingual whole plant extracts of *C. sativa* for treatment of refractory lower urinary tract and other chronic symptoms. Side effects were minimal and tolerable, and over the short- and long-term periods of observation many symptoms improved and none worsened. Thus, self-titrated treatment with CME appears safe and efficacious.

Treatment with CME improved several MS-related urinary symptoms, with decreases in frequency, nocturia, incontinence and urgent voids, and increases in the proportion of voids that were 'planned' or occurred with a normal desire to void. However, total urinary output also decreased significantly during treatment with either extract, indicating that the patients were drinking less fluid. This may of course have contributed to the improvements in frequency, nocturia and episodes of incontinence, although it cannot have caused the observed increase in MCC that may also underlie these findings. The reduction in the number of urgent micturition events might also be related to decreases in fluid intake or the rate of bladder filling.

Table 2 Mean (SD) VAS scores for troublesome secondary neurogenic symptoms at baseline, weeks 7 and 8 (THC/CBD), weeks 15 and 16 (THC-only) and in the long-term (THC-only)

	n	Baseline	n	THC/CBD	n	THC-only	n	Long-term
Spasticity	14	43.57 (18.74)	13	35.00 (22.59)	11	30.18 (16.17)	10	34.60 (24.95)
Pain	13	57.92 (21.17)	12	42.75 (22.41)	11	41.91 (24.39)	10	39.9 (23.53)
Tremor	10	43.90 (22.57)	9	40.22 (26.38)	8	39.75 (29.97)	6	48.67 (25.12)
Sleep	9	49.78 (26.05)	9	32.00 (25.95)	8	28.50 (26.33)	6	37.5 (30.19)
Constipation	6	50.50 (18.83)	6	36.33 (23.00)	6	37.17 (25.56)	6	34.33 (31.53)

Bold indicates statistically significant difference from baseline score ($P < 0.05$, Wilcoxon's signed rank test).

An important aspect of this trial was the use of self-titration to establish a dosage most appropriate for each individual patient. This approach has also been used by both Nottcutt and Wade,^{3,9} however, in our study patients were encouraged to gradually increase the dose of CME over a longer period (four weeks) until they had identified their maximum tolerated dose. The large dose range observed appeared to be determined by sensitivity to the side effects rather than by the amount of medication required to control LUTS, as there was no relation to final stable dose on either extract and baseline urological parameters, such as MCC. Similarly, patients who responded to CME in terms of symptom control were not all on a higher than average dose of CME, however the number of patients in this pilot study is too small for detailed analysis of responder and nonresponder groups.

The incidence of events due to intoxication (e.g., hallucinations) was low even though patients were encouraged to take the maximum tolerated dose. This suggests that the favourable pharmacokinetic profile of CME using the sublingual route allows patients to adjust their dose quite precisely such that symptom relief is achieved with minimal side effects, although it is possible that with such a large final dose range of CME, some patients might have been using a suboptimal dose. There was little inpatient variation in the daily dose of either extract over time, which suggests that tolerance to CME did not occur and that efficacy was maintained at a stable dose.

All of the patients entered into the long-term safety and efficacy extension chose to take the THC-only extract as they found it more effective in controlling their urinary symptoms, particularly by reducing the intensity of urinary urgency. However no significant differences in efficacy between the extracts were identified on data analysis. In addition, patients preferred THC-only to THC/CBD as they took significantly less of this preparation to achieve the same therapeutic effect.

The positive effects of treatment on urinary symptoms, spasticity, pain and difficulty sleeping suggests that CME acts at numerous sites in the nervous system. Cannabinoids have been shown to inhibit gastrointestinal and uterine smooth muscle contraction and it is possible that CME has a direct inhibitory effect on detrusor contraction.^{5-7,13,14} In addition, interaction of CME with the cholinergic receptor system and/or synergism with anticholinergic medication represent further mechanisms of action.¹⁵⁻¹⁷

The duration of action of cannabis on detrusor function or muscle spasticity is unknown. Anecdotally, many patients smoke cannabis for the rapid relief of acute symptoms (e.g., muscle spasms), or to attenuate chronic symptoms (e.g., tremor, pain), rather than as a preventative measure. This pattern of drug usage is probably related to the pharmacokinetic profile of the cannabinoids. However, we wanted to identify any chronic effects of the drug on parameters such as the Ashworth score and cystometric capacity, and therefore performed these measures after 24 hours off CME. Notwithstanding the obvious limitations of an open-label trial, given the half-life of the

preparation (4-6 hours), a significant change from baseline could reasonably be attributed to chronic effects. We then assessed the acute effects of CME on these parameters following maximum tolerated dose.

We investigated changes in bladder function following treatment with CME using voiding diaries and cystometry. There was a considerable range in MCC and functional bladder capacity at baseline across the group and the numbers are insufficient to permit analysis of subgroups of bladder dysfunction, for example those patients with a very small bladder capacity or those with incomplete bladder emptying and a large residual. However all patients had detrusor overactivity. Although chronic treatment with THC-only produced significant increases in MCC, the increase seen with chronic treatment with THC/CBD did not reach statistical significance. This might be related to a failure to power the study adequately. Acute treatment with either extract did not further increase mean MCC significantly. Bladder emptying efficiency, an indirect measure of both detrusor contractility and outlet obstruction, did not change.

The improvements in urinary urgency in the absence of increasing voided volumes might be due to the action of cannabinoids on the putative suburothelial mechanosensory apparatus.¹⁸ The endocannabinoid anandamide is an agonist at the vanilloid receptor (TRPV1) and it has recently been demonstrated that the density of TRPV1-immunoreactive c-fibres in the suburothelium is increased in patients with spinal cord lesions and bladder overactivity.¹⁹⁻²¹ It is possible that cannabinoids or their metabolites in the blood or urine have an effect on vanilloid receptor-expressing afferent C fibres in the suburothelium. CME might also act directly on afferent fibers⁶ or at the level of the spinal cord. It has been shown that intrathecal anandamide attenuates inflammation-induced bladder overactivity in an animal model.²² Finally, cannabinoid receptors in the pons and other parts of the CNS involved in the control of micturition represent other potential pharmacological targets.²³

Treatment with CME improved troublesome chronic neurological symptoms, in keeping with the results of other pilot studies using CME.^{3,9} None of the other symptoms worsened. We observed significant improvements in VAS scores for pain, spasticity and ability to sleep after eight weeks' treatment with THC-only CME. Treatment with THC/CBD also significantly improved pain, but improvements in spasticity and sleeping did not reach statistical significance, probably a result of the small numbers of patients in the study. In the long-term study, there was a significant improvement in pain VAS only. The mean VAS scores for spasticity and quality of sleep decreased, but not significantly, in the long-term (Table 2). This is probably related to sample size, as patients did not take significantly less CME during this period. Other investigators have also reported improvements in these symptoms.^{3,9} The positive results of VAS scores of spasticity and negative results of Ashworth scores complement the findings of Wade, and may reflect the limitations of the Ashworth scale in terms of its sensitivity.³ In addition, whilst the Ashworth scale has

good intraobserver reliability, the results can be influenced by several factors (for example a long travelling time to the hospital in a seated position). Killestein has also reported negative results in Ashworth scores following treatment with both whole plant cannabis extracts and THC (Marinol) taken orally, although these results might be related to unpredictable bioavailability from the gastrointestinal tract as well as limitations in the Ashworth score itself.²⁴

Weaknesses of this study are that there was no control group and it was not blinded. However, this is a potential problem in all such studies of novel treatments. An open-label design was necessary because this form of cannabis had not been used in a medical setting before and the dosage and onset of the symptoms of intoxication were unknown. Because of the open-label trial design, we were able to help patients identify symptoms of intoxication at an early stage during the dose titration period. A multi-centre, placebo-controlled trial is now in progress.

Conclusion

In this open-label pilot study, treatment with cannabis-based medicinal extracts produced sustained improvements in urinary symptoms, in particular urinary urgency and urge incontinence, with significant improvements in symptom-specific quality of life scores. Decreased urinary output during treatment might account for part of the improvements in frequency and nocturia. Patient-reported pain, spasticity and quality of sleep all improved significantly in the short-term. The improvements in pain scores persisted in the long-term study. Unpleasant side effects such as hallucinations were uncommon and other side effects such as dry mouth were well tolerated.

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