Original Article

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain

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Abstract

This study compared the efficacy of a tetrahydrocannabinol:cannabidiol (THC:CBD) extract, a nonopioid analgesic endocannabinoid system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer. In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), *THC extract* (n = 58), *or placebo* (n = 59). *The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC:CBD compared with placebo (improvement of −1.37 vs. −0.69), whereas the THC group showed a nonsignificant change (−1.01 vs. −0.69). Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance. There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. No significant group differences were found in the NRS sleep quality or nausea scores or the pain control assessment. However, the results from the European*

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Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire showed a worsening in nausea and vomiting with THC:CBD compared with placebo ($P = 0.02$), whereas THC had no difference ($P = 1.0$). Most drug-related adverse events were mild/moderate in severity. This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids. J Pain Symptom Manage 2010;39:167–179.

Key Words
Cancer, pain, tetrahydrocannabinol, cannabidiol, Sativex®

Introduction

Cancer pain is a common problem, and 70%–90% of patients with advanced cancer experience significant pain.[1] Opioids remain the keystone for the treatment of moderate to severe cancer pain; however, some patients experience inadequate pain relief with opioids and standard adjuvant analgesics despite dose adjustments, and unacceptable side effects are common.[2,3]

Cannabis contains 60 or more cannabinoids (CBs). The main ones include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[4,5] There is evidence that both THC and CBD show promise in relieving cancer-related pain.[6,7] Sativex® (THC:CBD), an endocannabinoid system modulator, is produced by GW Pharma Ltd, United Kingdom. It is derived from strains of *Cannabis sativa* L. plants developed to produce high and reproducible yields of principal CBs (THC and CBD), with minor amounts of other CBs and terpenes in a solution containing ethanol, propylene glycol, and peppermint oil flavoring.[5] The named CBs constitute at least 90% of the total CB content of the extracts.

CBs act primarily through specific CB receptors: CB_1 receptors are predominantly distributed in the central nervous system, and CB_2 receptors are located primarily in the periphery (including the immune system). The principal pharmacological effects of THC include analgesia, muscle relaxation, antiemesis, appetite stimulation, and psychoactivity.[8] CBD has shown anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant, and antipsychotic activity, and has been also shown to reduce the anxiety and psychoactive effects of THC.[9,10] Preliminary tests of pharmacology and behavioral activity support the similarity of the endogenous CB anandamide to THC.[11] Both are partial agonists at the CB_1 receptor. CBD, in contrast, binds weakly to CB_1 and CB_2 but does show pharmacological potency as a neutral antagonist at each receptor,[12] that is, is silent at such receptors but can reverse both agonist and inverse agonist responses. CBD also has shown powerful anti-inflammatory, immunomodulatory,[13] and antioxidant properties in vitro.[14] It is a TRPV1 vanilloid receptor agonist in its own right, while modulating anandamide by inhibiting both its reuptake and hydrolysis.[15] Additionally, CBD increases adenosine A2A receptor signaling by inhibition of the adenosine transporter.[16] Both THC and CBD have shown analgesic efficacy in animal models.[10,17,18] In this study, both a THC:CBD extract and a THC-only extract were compared against placebo to ascertain if the inclusion of CBD provided a different efficacy or safety profile.

Campbell et al.[19] published a literature review of nine randomized controlled trials performed using CBs (any route of administration) in patients with acute, chronic nonmalignant, or cancer pain. Five studies that were described in four reports comprised 128 patients with cancer pain.[6,7,20,21] All of the trials conducted in patients with cancer pain were placebo-controlled trials. Four of the trials found CB as effective as codeine but with dose-limiting side effects. Thus, CBs have demonstrated efficacy comparable to selected opioids.

THC:CBD is the first endocannabinoid system modulator to undergo clinical development for pain. It has been approved in Canada for the relief of neuropathic pain in multiple sclerosis

and persistent background cancer-related pain. The formulation is an oromucosal spray that allows flexible, individualized dosing. Patients self-titrate their overall dose and pattern of dosing according to their response to, and tolerance of, the medicine, with administration of approximately 8–12 sprays/day, that is, 22–32 mg/day THC and 20–30 mg/day CBD. This study assessed the analgesic efficacy of THC:CBD and THC extracts compared with that of placebo in the management of patients with at least moderately severe cancer-related pain despite appropriate pharmacological management.

Methods

This two-week (two-day baseline and two-week treatment), multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluated the efficacy of THC:CBD extract and THC extract in the analgesic management of patients with moderate to severe cancer-related pain. There was a two-day baseline period. Adult male or female patients who had been using strong opioids for at least one week to relieve pain associated with incurable malignancy and who gave written informed consent were screened for study entry. Eligible patients recorded a pain severity score of 4 or above on a 0–10 Numerical Rating Scale (NRS) on both days of the two-day baseline period. Patients were excluded if they had cancers affecting the oral cavity; radiotherapy to the floor of the mouth; major psychiatric or cardiovascular disorders; epilepsy; renal or hepatic impairment; or if they were pregnant, lactating, or not using adequate contraception. Patients who had received therapies expected to confound the study outcome (epidural analgesia within 48 hours of screening; palliative radio-, chemo-, or hormonal therapy within two weeks of screening; or CBs within seven days of randomization) were also excluded. Patients taking levodopa, sildenafil, or fentanyl or patients with a hypersensitivity to CBs were excluded on safety grounds. Patients completed a study diary, recording pain score three times daily and background medication and all additional breakthrough analgesia on each day during the baseline period. Patients then returned for assessment, randomization, and dose introduction to one of the three treatment arms: THC:CBD extract, THC extract, or placebo (Fig. 1) in a 1:1:1 treatment allocation ratio. Patients were reviewed after 7–10 days (Visit 2) and at the end of study (14–20 days) or withdrawal (Visit 3). During the medication dosing period, the patients continued to complete the daily study diaries with the aforementioned information and the number of doses of study medication taken. The relevant regulatory authorities and research ethics committees approved the study.

The study medication was delivered using a pump action oromucosal spray. Each 100-μL actuation of the pump containing the THC:CBD extract delivered a dose containing 2.7 mg THC and 2.5 mg CBD. Each 100-μL actuation of the pump containing the THC extract delivered a dose containing 2.7 mg THC, and each actuation of placebo delivered only excipients plus colorants. The maximum permitted dose of all study medication was eight actuations in any three-hour period and 48 actuations in any 24-hour period.

Patients self-titrated to their optimal dose over the seven days of Week 1, based on efficacy, tolerability, and the maximum permitted dose. Patients could increase the total number of sprays each day by a maximum of 50% until they either had satisfactory relief of their symptoms or developed unwanted effects, such as intoxication ("high"). The total number of sprays was spread over the day with a minimum of 15 minutes between any two sprays. If unwanted effects developed on a new number of sprays, the patient would not take any further sprays for three to four hours. The patient would then go back to taking their further sprays at a similar level to the previous day. Once the patient had found the maximum number of sprays per day that they tolerated well or the number that provided good symptom relief, they continued with approximately the same number of sprays per day for the remainder of the study.

The coprimary endpoints were the change from baseline in NRS pain score and use of breakthrough analgesia. The NRS, a widely used and validated measure of pain severity, is capable of showing clinically and statistically significant changes in pain disorders.[22,23] The NRS question "indicate your level of pain"

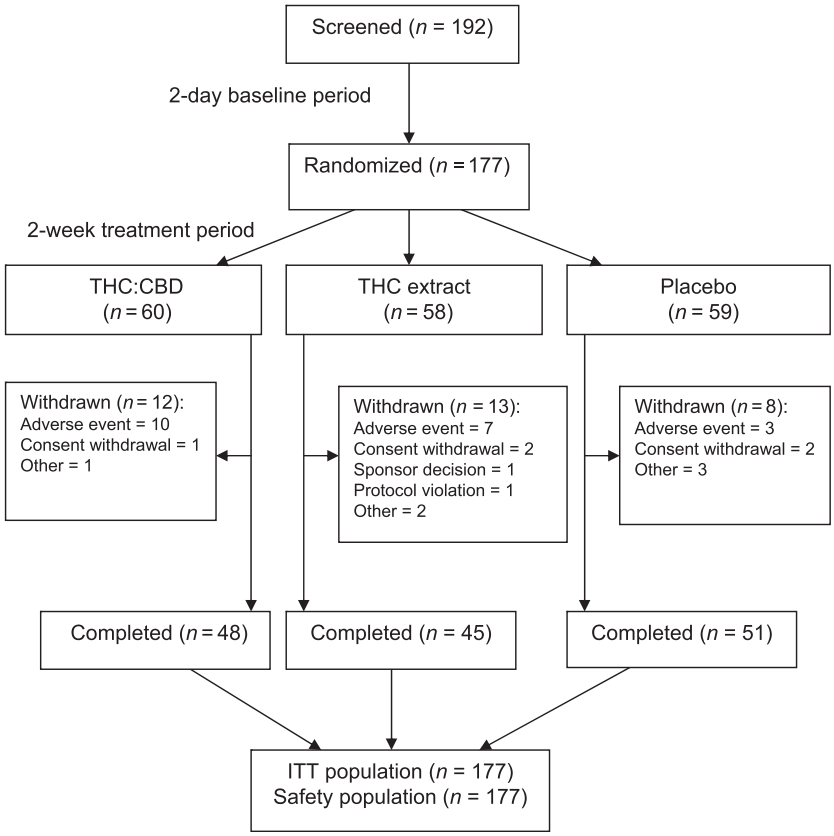

Fig. 1. Study design (Consolidated Standards of Reporting Trials [CONSORT] diagram). ITT = intent to treat.

was answered by patients three times daily (in the morning on waking, at lunchtime, and in the evening before retiring), using the anchors 0 = no pain and 10 = very bad pain. Patients were allowed to use their breakthrough analgesia as required, and this was recorded daily in the diary. Patients maintained background medication for the duration of the study. The secondary endpoints included the use of opioid background medication, patient assessments of sleep quality, nausea, memory, concentration, and appetite over the previous 24 hours using diary NRSs. The Brief Pain Inventory-Short Form (BPI-SF) and The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) Version 3 were completed by patients at Visit 1 and at the end of the study.[24,25] The BPI-SF consists of nine questions; eight have a single response, and Question 9 is subdivided into seven parts. The Total BPI (Questions 3–6) is the unweighted sum of the four pain scores and represents the pain intensity. The Total BPI for Question 9 is the unweighted sum of the seven assessments and represents the effect of pain. The EORTC QLQ-C30 cancer questionnaire consists of 30 questions that cover global health status, functional scales (e.g., physical functioning), and symptoms (e.g., fatigue).

Adverse events (AEs) and use of concomitant medications were reported by patients at study visits throughout the trial. Predefined categories for determining the intensity and the relationship to study medication were used. The expert clinical judgment from the investigating study physicians was used in determining intensity and causal relationship of AEs and serious AEs.

The study was powered assuming an underlying treatment difference of 1 point on an NRS and a standard deviation (SD) of 1.6 (estimated from previous studies), with 80% power and two-sided 5% significance.[26,27] After allowing for 15% dropouts, 58 subjects per group

were required. For the two coprimary efficacy variables (NRS pain score and use of breakthrough medication), the Hochberg[28] method was used to test the global hypothesis for a treatment effect on pain. The null hypothesis was to be rejected if either coprimary variable produced two-sided $P \leq 0.025$ or both produced $P \leq 0.05$. The daily pain NRS score was the mean of the three daily assessments. The change in mean NRS pain score from baseline (all days in run-in period) to the end of treatment (last three days on treatment) was analyzed using analysis of covariance (ANCOVA), with baseline pain as a covariate and grouped study center and treatment as factors.[29,30] The proportions of responders (patients with ≥30% improvement from baseline to end of study NRS pain score) were compared between treatments. Use of breakthrough medication (number of days of use during last three days on treatment) was analyzed using logistic regression with a cumulative logit model. In addition, the change from baseline in mean number of doses of escape medication was analyzed using ANCOVA.

Results

A total of 192 patients were screened over 25 months, leading to 177 patients randomized to treatment (Fig. 1) at 28 European centers. The mean (SD) duration of cancer in these patients was 3.5 years (2.8 [3.27], 3.2 [4.27], and 4.5 [5.25] years, respectively, in the THC:CBD, THC, and placebo groups, respectively). The mean age, gender distribution, previous cannabis use, primary disease sites, and pain classification were similar among the three treatment groups (Table 1). The most common type of cancer pain was of mixed pathophysiology, followed by bone and neuropathic pain (Table 1). At baseline, the mean daily dose of opioid background medication in the whole study population was 271 mg of oral morphine equivalents. The median oral morphine equivalent dose was slightly lower in the THC:CBD group at baseline compared with the THC and placebo groups (Table 2). For all three treatment groups, the predominant primary reason for discontinuing the study was AEs (Fig. 1).

Table 1
Patient Demographics

Demographics	THC:CBD	THC	Placebo	Total
Gender, *n* (%)				
Male	33 (55)	30 (52)	32 (54)	95 (54)
Female	27 (45)	28 (48)	27 (46)	82 (46)
Ethnic origin, *n* (%)				
Caucasian	59 (98)	57 (98)	58 (98)	174 (98)
Other	1 (2)	1 (2)	1 (2)	3 (2)
Previous cannabis use, *n* (%)	6 (10)	6 (10)	7 (12)	19 (11)
Age (years), mean (SD)	59.4 (12.1)	61.3 (12.5)	60.1 (12.3)	60.2 (12.3)
Duration of cancer (years), mean (SD)	2.8 (3.3)	3.2 (4.3)	4.5 (5.3)	3.5 (4.4)
BMI, mean (SD)	23.1 (4.2)	23.5 (5.2)	24.1 (4.3)	23.6 (4.6)
Primary cancer sites, *n* (%)				
Breast	12 (20)	8 (14)	9 (15)	29 (16)
Prostate	6 (10)	8 (14)	10 (17)	24 (14)
Lung	7 (12)	9 (16)	4 (7)	20 (11)
Pain classification, *n* (%)				
Mixed	31 (52)	28 (48)	30 (51)	89 (50)
Bone	16 (27)	24 (41)	25 (42)	65 (37)
Neuropathic	11 (18)	11 (19)	17 (29)	39 (22)
Visceral	14 (23)	12 (21)	11 (19)	37 (21)
Somatic/incident	7 (11)	5 (9)	6 (10)	18 (10)
Baseline morphine equivalents[a]				
Median (mg)	80.0	120.0	120.0	120.0
Range	0–6,000	0–1,280	0–6,000	0–6,000
Mean (+SD)	258.4 (789.47)	188.2 (234.49)	367.0 (886.38)	271.2 (698.98)
1st–3rd quartile	30–180	50–213	40–240	40–240

BMI = body mass index.
[a]Oral morphine equivalence data are sourced from Refs. 43–45.

Table 2
Change in Dose of Opioid Background Medication (Oral Morphine Equivalents) and Strong Opioid Breakthrough Medication

Opioid Characteristics	THC:CBD	THC	Placebo	All
Opioid background medication: change from baseline to last 3 days on study medication (patients with data available, excluding 3 patients receiving intrathecal opioids)				
n (% ITT population)	60 (100)	58 (100)	58 (98)	176 (99)
Median	0.0	0.0	0.0	0.0
Range	−627 to 300	−27 to 1,088	−1,200 to 400	−1,200 to 1,088
Mean (±SD)	−3.5 (108.44)	26.9 (152.00)	−41.4 (201.27)	−6.4 (160.60)
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Opioid background medication: categorized change from baseline in oral morphine equivalents per day				
Increase, *n* (%)	6 (12)	6 (12)	4 (7)	16 (10)
No change, *n* (%)	41 (79)	40 (77)	43 (80)	124 (78)
Decrease, *n* (%)	5 (10)	6 (12)	7 (13)	18 (11)
Strong opioid breakthrough medication: categorized change from baseline in number of doses taken				
N (% ITT population)	22 (37)	18 (31)	19 (32)	59 (33)
Increase, *n* (%)	2 (9)	4 (22)	7 (37)	13 (22)
No change, *n* (%)	12 (56)	10 (56)	12 (63)	34 (58)
Decrease, *n* (%)	8 (36)	4 (22)	0	12 (20)

ITT = intent to treat; SD = standard deviation.

The mean (SD) number of sprays taken per day, which had stabilized by the end of the first week (Days 1−7) ending the titration phase, were THC:CBD extract, 8.75 (5.14); THC extract, 8.34 (5.17); and placebo, 9.61 (4.67) (Fig. 2). Overall, for the entire treatment period, the mean (SD) number of sprays used daily in the placebo group (10.88 [5.81]) was higher than those in the THC:CBD (9.26 [5.53]) and THC groups (8.47 [5.46]).

Efficacy

The mean (SD) baseline NRS pain scores were similar among treatment groups and within grouped centers (THC:CBD extract = 5.68 [1.24], range = 2.33−8.25; THC extract = 5.77 [1.33], range = 2.87−9.33; placebo = 6.05 [1.32], range = 3.5−9.56). The adjusted mean reduction in NRS (ANCOVA) for THC:CBD, THC, and placebo groups at the end of the treatment were −1.37, −1.01, and −0.69 points, respectively.[31] The adjusted mean treatment difference from placebo was statistically significant for a reduction in pain with the THC:CBD extract (0.67 points, $P = 0.014$) but not the THC extract (0.32 points, $P = 0.245$). The ANCOVA did not have normally distributed residuals, but the nonparametric analysis gave a similar result. The median changes from baseline for THC:CBD, THC, and placebo groups were −1.36, −1.00, and −0.60, respectively. The median difference from placebo was statistically significant for a reduction in pain, which was in favor of THC:CBD extract (0.55 points, $P = 0.024$) but not for the THC extract (0.24 points, $P = 0.204$). Sensitivity analyses of the change from baseline in the mean NRS scores concurred with the primary analysis.

In chronic pain trials, it is recommended that the percentages of patients obtaining reductions in pain intensity of at least 30% on a pain NRS (responders) should be documented.[32] A reduction in pain NRS of approximately 30% is considered to represent a clinically important difference.[23] In the intent-to-treat responder analysis, approximately twice as many patients in the THC:CBD group had a reduction from baseline NRS of at least 30% compared with the placebo and THC groups (THC:CBD = 23 [43%] vs. THC = 12 [23%], placebo = 12 [21%]). The odds ratio for the comparison of responders between THC:CBD and placebo was 2.81 (95% confidence interval [CI] = 1.22, 6.50; $P = 0.006$), and between THC and placebo was 1.10 (95% CI = 0.44, 2.73; $P = 0.28$) (Fig. 3).

The number of days on which any breakthrough medication was used was similar among all treatment groups, with no significant differences observed in this clinical trial of brief duration (THC:CBD vs. placebo: $P = 0.70$). There was a reduction observed in the mean number of daily doses of all breakthrough medication (THC:CBD extract = −0.19; THC extract = −0.14; placebo = −0.15)

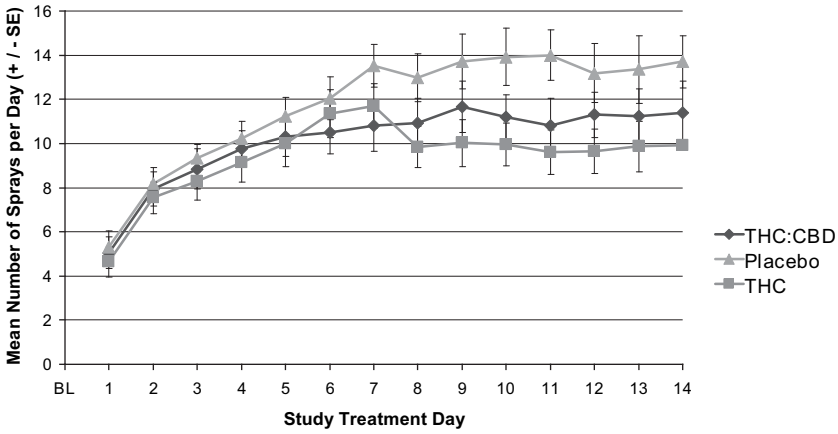

Fig. 2. Exposure to study medication—mean number of sprays per day. SE = standard error.

by the end of the study period, but the difference in change from baseline between treatment groups was not statistically significant. More specifically, there was no change from baseline to the last three days of treatment in the median oral morphine equivalent dose of opioid background medications in 124 (78%) patients for whom the data were available. Doses were increased for 16 patients (10%) and reduced for 18 (11%); these changes were evenly distributed across the three treatment groups (Table 2). During the baseline period or last three days on treatment, strong opioid breakthrough medication was recorded by 59 patients (33%); of these, 34 (58%) showed no change in the number of doses taken when comparing baseline with last three days of treatment, 13 (22%) increased the number of doses, and 12 (20%) reduced the number of doses taken. A greater proportion

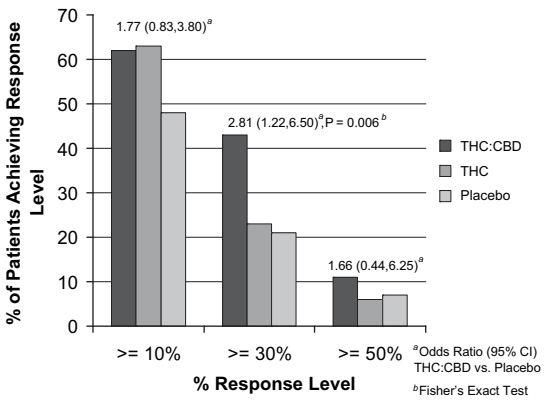

Fig. 3. Pain 0–10 Numerical Rating Scale scores: responder analysis (ITT analysis). [a]Odds ratio (95% CI) THC:CBD vs. placebo; [b]Fisher's exact test.

of patients in the THC:CBD group (eight patients) reduced breakthrough doses; conversely, the highest proportion of increases in dose was in the placebo group (seven patients), which was statistically significantly greater than those in the THC:CBD group ($P = 0.004$).

Most of the NRS diary symptom scores and investigator-assessed pain control showed no significant treatment differences between the three groups (Table 3). A statistically significant difference in improvement with placebo was observed in the diary NRS concentration and memory scores, whereas the placebo group showed a mean improvement from baseline in concentration score (−0.35) and the THC:CBD group showed a deterioration (0.33, $P = 0.02$), as did the THC group (0.29, $P = 0.03$). The memory score showed no change in the placebo group (0.01), but a deterioration in the THC:CBD group (0.63, $P = 0.045$) and in the THC group (0.66, $P = 0.053$). Similarly, the appetite diary NRS score showed a mean improvement from baseline in the placebo group, and there was a slight reduction in appetite score in both THC:CBD and THC groups (−0.59 vs. 0.24, $P = 0.016$; and −0.59 vs. 0.06, $P = 0.056$, respectively) (Table 3).

The QLQ-C30 showed, as expected, few differences among treatment groups in the two-week follow-up. Of the 16 items assessed, the only statistically significant observations were reductions in cognitive function score when compared with placebo (THC:CBD extract = −5.33 vs. 3.68, $P = 0.02$; THC extract = −6.77 vs. 3.68, $P = 0.01$) and a worsening of

Table 3

Primary and Secondary Endpoints Showing Baseline Score, Change from Baseline, Treatment Difference, and Statistical Significance of the Difference in Change From Baseline for THC:CBD, THC, and Placebo

				Comparison with Placebo	
Endpoint	Treatment Group	Baseline	Change From Baseline	Treatment Difference	Statistical Significance, *P*-value
Mean pain severity NRS score (coprimary)	THC:CBD	5.68	−1.37	−0.67[a]	0.014
	THC	5.77	−1.01	−0.32[a]	0.245
	Placebo	6.05	−0.67	—	—
Breakthrough medication: no. of days used (coprimary)	THC:CBD	—	—	OR = 0.96[a]	0.697
	THC	—	—	OR = 1.20[b]	0.555
	Placebo	—	—	—	—
Breakthrough medication: mean daily dose	THC:CBD	0.91	−0.19	−0.04[a]	0.688
	THC	1.10	−0.14	0.01[b]	0.899
	Placebo	0.80	−0.15	—	—
Mean sleep quality NRS score	THC:CBD	4.33	−0.57	−0.31[a]	0.346
	THC	4.46	−0.24	0.02[b]	0.95
	Placebo	4.17	−0.26	—	—
Mean nausea NRS score	THC:CBD	2.44	0.26	0.49[b]	0.110
	THC	2.04	0.24	0.46[b]	0.126
	Placebo	1.98	−0.22	—	—
Mean memory NRS score	THC:CBD	3.02	0.63	0.65[b]	0.045
	THC	2.98	0.66	0.62[b]	0.053
	Placebo	2.90	0.01	—	—
Mean concentration NRS score	THC:CBD	3.59	0.33	0.68[b]	0.021
	THC	3.53	0.29	0.64[b]	0.028
	Placebo	3.37	−0.35	—	—
Mean appetite NRS score	THC:CBD	4.83	0.24	0.83[b]	0.016
	THC	4.58	0.06	0.66[b]	0.056
	Placebo	4.98	−0.59	—	—
Pain control assessment proportion with pain controlled	THC:CBD	50%	1%	OR = 1.70	0.488
	THC	54%	−2%	OR = 1.76	0.400
	Placebo	36%	−4%	—	—
Mean BPI-SF total pain in last 24 hours	THC:CBD	20.88	−0.17	−1.04[a]	0.619
	THC	21.29	−3.20	−4.07[a]	0.048
	Placebo	23.48	0.87	—	—
Mean BPI-SF total interference by pain in last 24 hours	THC:CBD	46.63	−3.53	−4.84[a]	0.325
	THC	39.39	−4.50	−5.81[a]	0.275
	Placebo	51.05	1.31	—	—
Mean QLQ-C30 global health status	THC:CBD	29.74	7.23	2.47[a]	0.443
	THC	27.05	5.60	0.84[a]	0.793
	Placebo	25.29	4.77	—	—
Mean QLQ-C30 physical functioning	THC:CBD	40.34	−6.92	−4.23[b]	0.108
	THC	35.56	−3.94	−1.25[b]	0.631
	Placebo	34.14	−2.69	—	—
Mean QLQ-C30 role functioning	THC:CBD	29.02	−0.02	3.31[a]	0.415
	THC	28.65	−0.12	3.21[a]	0.434
	Placebo	25.00	−3.33	—	—
Mean QLQ-C30 emotional functioning	THC:CBD	24.44	7.70	6.73[a]	0.084
	THC	22.41	6.19	5.22[a]	0.174
	Placebo	25.37	0.98	—	—
Mean QLQ-C30 cognitive functioning	THC:CBD	50.57	−5.33	−9.01[b]	0.022
	THC	56.32	−6.77	−10.46[b]	0.008
	Placebo	50.85	3.68	—	—
Mean QLQ-C30 social functioning	THC:CBD	29.02	3.19	1.61[a]	0.679
	THC	29.89	9.66	8.08[a]	0.038
	Placebo	25.71	1.58	—	—
Mean QLQ-C30 fatigue	THC:CBD	71.55	−3.92	−2.71[a]	0.422
	THC	70.69	−1.36	−0.15[a]	0.965
	Placebo	64.56	−1.21	—	—
Mean QLQ-C30 nausea and vomiting	THC:CBD	25.57	5.13	8.56[b]	0.020
	THC	22.13	−3.41	0.02[b]	0.997
	Placebo	21.75	−3.43	—	—
Mean QLQ-C30 pain	THC:CBD	83.62	−15.64	−6.34[a]	0.107
	THC	79.60	−15.71	−6.41[a]	0.103
	Placebo	81.64	−9.30	—	—

(*Continued*)

Table 3
Continued

Endpoint	Treatment Group	Baseline	Change From Baseline	Comparison with Placebo: Treatment Difference	Comparison with Placebo: Statistical Significance, *P*-value
Mean QLQ-C30 dyspnea	THC:CBD	40.23	−1.09	−0.80[a]	0.846
	THC	43.27	4.21	4.49[b]	0.282
	Placebo	34.46	−0.28	—	—
Mean QLQ-C30 insomnia	THC:CBD	52.30	−6.15	−1.05[a]	0.833
	THC	51.15	−0.41	4.69[b]	0.347
	Placebo	51.41	−5.10	—	—
Mean QLQ-C30 appetite loss	THC:CBD	60.34	−3.69	−0.88[a]	0.857
	THC	54.60	−1.19	1.62[b]	0.743
	Placebo	59.32	−2.81	—	—
Mean QLQ-C30 constipation	THC:CBD	50.00	−5.74	−7.97[a]	0.077
	THC	33.33	−3.11	−5.35[a]	0.233
	Placebo	40.68	2.23	—	—
Mean QLQ-C30 diarrhea	THC:CBD	13.22	−2.15	−1.57[a]	0.615
	THC	8.62	0.56	1.15[b]	0.713
	Placebo	12.99	−0.58	—	—
Mean QLQ-C30 financial difficulties	THC:CBD	58.05	−5.58	−1.70[a]	0.714
	THC	59.20	−8.93	−5.05[a]	0.276
	Placebo	57.06	−3.88	—	—

[a]In favor of active treatment.
[b]In favor of placebo.

"nausea and vomiting" score in the THC:CBD, although not in the THC only group, when compared with placebo (THC:CBD = 5.13 vs. −3.43, $P = 0.02$; THC = −3.41 vs. −3.43; $P = 1.0$). A trend toward improvement was seen in both active treatment groups in the QLQ-C30 pain assessment score (THC:CBD extract = −15.64 vs. −9.30, $P = 0.11$; THC extract = −15.71 vs. −9.30, $P = 0.10$) and in the constipation score (THC:CBD = −5.74 vs. 2.23, $P = 0.08$; THC = −3.11 vs. 2.23, $P = 0.23$).

Safety and Tolerability

The active compounds were generally well tolerated, and no safety concerns were identified during this study. Treatment-related AEs were reported by 106 (60%) patients. Common treatment-related AEs (three or more patients) were similar to those seen in other THC:CBD clinical trials: somnolence, dizziness, and nausea, mostly of mild or moderate severity (Table 4).[26,27,33–38] The incidence of death in this advanced cancer population was similar across treatment groups (eight THC:CBD, eight THC, seven placebo), and all were considered because of progression of underlying disease. None of the cases from the 10 patients who reported nonfatal serious AEs (SAEs) raised any concerns regarding the safety of CBs. The nonfatal SAEs of urinary retention, tumor-related pain, worsened nausea, weakness, tumor hemorrhage, and somnolence were experienced by five patients in the THC:CBD group, all of which were unrelated to study medication. Three events were moderate in severity, and four events were severe. Five subjects who received THC experienced the nonfatal SAEs of metastases to brain, gastric ulcer hemorrhage, syncope, bronchopneumonia, hyperglycemia, confusion, oral candidiasis, somnolence, tremor, and disorientation. All events were unrelated to study medication, with the exception of a single episode of syncope, which was probably related to THC. Two events were moderate in severity, and eight events were severe. No patients from the placebo group reported a nonfatal SAE.

Discussion

Unrelieved cancer pain can result in significant distress and disability.[1,39] The results of this study show that the THC:CBD extract is an efficacious adjunctive treatment for cancer-related pain in patients who are not achieving an adequate analgesic response to opioids.

This study involved patients with advanced cancer, who had a mean disease duration of more than three years and moderate to severe levels of pain at entry (>4 on an NRS pain

Table 4
Most Common Treatment-Related Adverse Events (Reported by Three or More Patients)

Description of Event	THC:CBD *n* (%)	THC extract *n* (%)	Placebo *n* (%)
Somnolence	8 (13)	8 (14)	6 (10)
Dizziness	7 (12)	7 (12)	3 (5)
Confusion	4 (7)	1 (2)	1 (2)
Nausea	6 (10)	4 (7)	4 (7)
Vomiting	3 (5)	4 (7)	2 (3)
Raised gamma GT	2 (3)	5 (9)	1 (2)
Hypercalcemia	0	0	3 (5)
Hypotension	3 (5)	0	0

Gamma GT = gamma glutamyl transferase.

scale), despite ongoing opioid treatment. After two weeks of receiving study medication adjunctive to all other treatments, the THC:CBD extract group showed a statistically significant reduction in pain severity when compared with placebo, with a reduction in mean pain NRS scores from baseline of 1.37 points (22.6%). The pain NRS data were not normally distributed; hence, parametric and nonparametric analyses were conducted. This had no influence on the significance of the results. The heterogeneity in the distribution of the pain scores (many large negative and large positive results), combined with consensus-based recommendations,[32] highlight the importance of the responder analysis. These recommendations are primarily based on the results of an analysis of relationships between changes in pain intensity and patient reports of overall improvement in 10 clinical trials of chronic pain, with patients of diverse diagnoses, in which a clinically relevant response was defined as a reduction of pain of at least 30% from baseline to end of study.

In this current study population, 43% of patients taking the THC:CBD extract achieved a 30% or greater improvement in their pain score (equated to a mean improvement of 2.71 boxes), approximately twice the number of patients who achieved this response in the THC and placebo groups. The results of the responder analysis and the mean change from baseline must be interpreted remembering that the study medications were adjunctive to existing treatments, including strong opioids, for the duration of the trial. Larger treatment differences from placebo may be noted in a study of longer duration, as evident in other conditions.[23,24]

At baseline, the mean daily use of opioid background medication was relatively high (271 mg of oral morphine equivalents). The change in number of daily doses of breakthrough medication between baseline and end of study showed a slight trend toward reduction and no relevant differences between treatment groups. Only a small number of patients recorded taking strong opioid breakthrough medication in their daily diaries during the baseline period or last three days on treatment. Of these, most showed consistent dosing patterns; the changes that did occur showed a trend toward a decrease in the number of doses taken in the THC:CBD group and an increase in the placebo group. There was a large range in the dose of background oral morphine equivalent treatment. These findings may be a reflection of different treatment models used in the participating countries and illustrates the need to include a more specific eligibility criteria of minimum opioid treatment in future studies. Less variation in the existing treatment regimens would enhance the interpretation of the efficacy result but would make recruitment to the study more challenging.

No statistically significant differences in patient-assessed sleep quality or nausea NRS scores or investigator-assessed pain control assessment were noted between the study medications and placebo. There was a significant improvement in the BPI-SF total score for THC but not for THC:CBD. Studies of longer duration in other indications have regularly shown that the quality of sleep in the THC:CBD group needs to be improved.[26,27,33,40] The differences between treatment groups in the memory, concentration, and appetite NRS diary scores are partly attributable to an apparent improvement in the placebo group.

The QLQ-C30 showed few differences between study medications and placebo. Considering the follow-up duration and the patient population, this is unsurprising. There were marginal improvements in QLQ-C30 pain scores but significantly reduced cognitive function scores with the THC:CBD and THC groups compared with those of the placebo group. The statistically significant worsening in the QLQ-C30 nausea and vomiting score seen with the THC:CBD extract compared

with placebo was not seen in the diary scores for nausea and is confounded by a median change of 0 between the groups, making interpretation of this result difficult. Similarly, the changes in appetite reported in the patient diaries were not seen in the QLQ-C30.

The few statistically significant results of the secondary endpoints should be interpreted with caution because of the multiple analyses performed on the questionnaire and the overlap in content between some of the NRS scales and questionnaire items. However, there is a consistent impairment of cognitive function reported by patients in this study. Although the clinical significance of this finding is unclear, it warrants further careful assessment in long-term studies. It is accepted that there will be limitations and potential inaccuracies of patient-completed diary data, and future studies will look to refine this method of data completion.

The AEs seen in this study were similar to those seen in other clinical trials[26,27,33–38] Of the AEs leading to permanent cessation of study medication (17%, 12% and 3%, respectively, for THC:CBD extract, THC extract, and placebo), approximately half were considered to be related to study treatment. None of the 33 reported SAEs raised concerns regarding treatment safety. The incidence of death was comparable among treatment groups, and there were no treatment-related deaths. Despite some uncertainty in the total morphine equivalent dose received by patients, the safety profile adds evidence that this was a population with advanced disease; 13% of patients died during the study because of their underlying disease.

The THC:CBD and the THC medications were well tolerated. Patients were fully titrated at one week and maintained stable dosing throughout the treatment period, that is, there was no observed tendency to increase dose with time. This corresponded to a reduction in pain NRS score over the same period. The clinical response to pain with THC:CBD extract oromucosal spray has not demonstrated tolerance in several clinical trials of longer duration.[26,27,33–38]

There is evidence of synergy between THC and morphine in pain, and THC may modulate endogenous opioid tone.[41] However, in this study, the THC:CBD combination showed a more promising efficacy profile than the THC extract alone. This finding is supported by evidence of additional synergy between THC and CBD. CBD may enhance the analgesic potential of THC by means of potent inverse agonism at CB_2 receptors,[14] which may produce anti-inflammatory effects, along with its ability to inhibit immune cell migration.[42] Additionally, CBD may modulate the potential unwanted effects of THC by means of antagonism at CB_1 receptors,[39] which potentially would provide a better safety profile for the THC:CBD medication in chronic use.

In conclusion, THC:CBD extract, a nonopioid analgesic, endocannabinoid system modulator, has been shown to be a useful adjunctive treatment for relief of pain in patients with advanced cancer who experience inadequate analgesia despite chronic opioid therapy. The reductions in pain scores were neither because of a change in opioid background medications nor because of an increase in use of breakthrough medication. Therefore, we can conclude that the observed reduction in pain scores is attributable to the positive analgesic effects of THC:CBD extract. These results are very encouraging and merit further study.

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References

1. Glare P. Choice of opioids and the WHO ladder. In: Davis M, Glare P, Hardy J, eds. Opioids in cancer pain. Oxford, UK: Oxford University Press, 2005: 221–234.

2. Scottish Intercollegiate Guidelines Network. Control of pain in patients with cancer: A National Clinical Guideline. Edinburgh, Scotland: SIGN 44, 2000. 1–79.

3. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330:592–596.

4. House of Lords Select Committee on Science and Technology. Cannabis: The scientific and medical evidence, 9th Report. Session 1997–98. London, UK: House of Lords, 1998. Available from http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15101.htm. Accessed January 4, 2008.

5. GW, Pharma Ltd. Product monograph: Sativex®, Ottawa, Canada. Health Canada, 2007. Available from http://cpe0013211b4c6d-cm0014e88ee7a4.cpe.net.cable.rogers.com/dpdonline/searchRequest.do. Accessed March 4, 2008.

6. Noyes R, Brunk SF, Baram DA, et al. Analgesic effect of delta 9-tetrahydrocannabinol. J Clin Pharmacol 1975;15:139–143.

7. Noyes R, Brunk SF, Avery DA, et al. The analgesic properties of delta 9-tetrahydro-cannabinol and codeine. Clin Pharmacol Ther 1975;18:84–89.

8. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. Pharmacol Ther 1997;74: 129–180.

9. Pertwee RG. Neuropharmacology and therapeutic potential of cannabinoids. Addict Biol 2000;5: 37–46.

10. Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabinol. Med Hypotheses 2006; 66:234–246.

11. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. Eur J Pharmacol 1993;231: 313–314.

12. Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB(1) and CB(2) receptor agonists in vitro. Br J Pharmacol 2007;150:613–623.

13. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci USA 2000; 97:9561–9566.

14. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)delta 9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA 1998;95:8268–8273.

15. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001;134:845–852.

16. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA 2006;103: 7895–7900.

17. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006;147(Suppl 1): 163–171.

18. Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol 2001;63:569–611.

19. Campbell FA, Tamer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systemic review. BMJ 2001;323:1–6.

20. Jochimsen PR, Lawton RL, VerSteeg K, Noyes R. Effect of benzopyranoperidine, a delta-9 THC congener, on pain. Clin Pharmacol Ther 1978;24(2): 223–227.

21. Staquet M, Gantt C, Machin D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. Clin Pharmacol Ther 1978;23(4):297–401.

22. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007–1019.

23. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.

24. Cleeland CS, Ladinsky JL, Serlin RC, et al. Multidimensional measurement of cancer pain: comparisons of US and Vietnamese patients. J Pain Symptom Manage 1988;3:23–27.

25. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality if life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–376.

26. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65:812–819.

27. 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.

28. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75:800–802.

29. Conover WJ, Inam RL. Analysis of covariance using the rank transformation. Biometrics 1982;38: 715–724.

30. Hodges JL Jr, Lehmann EL. Estimates of location based on rank tests. Ann Math Statist 1963;34: 598–611.

31. Johnson JR, Wright ST. Cannabis-based medicines on the treatment of cancer pain: a randomised, double blind, parallel group, placebo controlled, comparative study of the efficiency, safety, and tolerability of Sativex and Tetranabinex in patients with cancer-related pain. J Support Oncol 2005;3(Suppl 3):21.

32. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

33. Collin C, Davies P, Mutiboko I, et al. Randomised controlled trial of cannabis based medicine in spasticity caused by multiple sclerosis. Eur J Neurol 2007;14:290–296.

34. Wade DT, Makela P, Robson P, et al. 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;10:1–8.

35. Wade DT, Makela PM, House H, et al. Long–term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler 2006;12:639–645.

36. Barnes MP. Sativex® clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother 2006;7:607–615.

37. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133: 210–220.

38. Rog D, Nurmikko TJ, Young CA. Oromucosal delta-9-tetrahrdrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther 2007;20:2068–2079.

39. Ripamonti C, Dickerson ED. Strategies for the treatment of cancer pain in the new millennium. Drugs 2001;61:955–977.

40. Russo E, Guy G, Robson P. Cannabis, pain and sleep: lessons from therapeutic clinical trials of Sativex cannabis based medicine. Chem Biodivers 2007;4:1729–1743.

41. Cox ML, Haller VL, Welch SP. Synergy between delta 9-tetrahydrocannabinol and morphine in the arthritic rat. Eur J Pharmacol 2007;12:125–130.

42. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: D9-tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin. Br J Pharmacol 2008;153: 199–215.

43. Twycross R, Wilcock A, Charlesworth S, et al, eds. Palliative care formulary, 2nd ed Oxford, UK: Radcliffe Publishing, 2002.

44. Fallon M. Opioid switching and rotation. In: Sykes N, Fallon MT, Patt RB, eds. Clinical pain management: Cancer pain. London, UK: Hodder Arnold, 2003: 157–165.

45. Hanks G, Cherney N, Fallon M. The management of pain. In: Doyle D, Hanks G, Cherny N, Calman K, eds. Oxford textbook of palliative medicine, 3rd ed Oxford, UK: Oxford University Press, 2005.