

Original Reports

Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)

Mark A. Ware,^{*,†} Tongtong Wang,[‡] Stan Shapiro,^{‡,§} and Jean-Paul Collet[¶] for the COMPASS STUDY TEAM¹

Departments of *Anesthesia, †Family Medicine, ‡Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada.

§Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada.

¶Department of Pediatrics, University of British Columbia; Child and Family Research Institute, Vancouver, British Columbia, Canada.

Abstract: Cannabis is widely used as a self-management strategy by patients with a wide range of symptoms and diseases including chronic non-cancer pain. The safety of cannabis use for medical purposes has not been systematically evaluated. We conducted a prospective cohort study to describe safety issues among individuals with chronic non-cancer pain. A standardized herbal cannabis product (12.5% tetrahydrocannabinol) was dispensed to eligible individuals for a 1-year period; controls were individuals with chronic pain from the same clinics who were not cannabis users. The primary outcome consisted of serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Secondary efficacy parameters included pain and other symptoms, mood, and quality of life. Two hundred and fifteen individuals with chronic pain were recruited to the cannabis group (141 current users and 58 ex-users) and 216 controls (chronic pain but no current cannabis use) from 7 clinics across Canada. The median daily cannabis dose was 2.5 g/d. There was no difference in risk of serious adverse events (adjusted incidence rate ratio = 1.08, 95% confidence interval = .57–2.04) between groups. Medical cannabis users were at increased risk of non-serious adverse events (adjusted incidence rate ratio = 1.73, 95% confidence interval = 1.41–2.13); most were mild to moderate. There were no differences in secondary safety assessments. Quality-controlled herbal cannabis, when used by patients with experience of cannabis use as part of a monitored treatment program over 1 year, appears to have a reasonable safety profile. Longer-term monitoring for functional outcomes is needed.

Study registration: The study was registered with www.controlled-trials.com (ISRCTN19449752).

Received January 25, 2015; Revised July 18, 2015; Accepted July 28, 2015.

The study was funded by the Canadian Institutes of Health Research (MOL-66262). M.A.W. receives salary support from the FRQS and the Louise and Alan Edwards Foundation and has a research grant to his institution from CanniMed. M.L. is a founding board member of Panag Pharm Inc, a start-up company researching topical non-psychoactive cannabinoids for pain and inflammation, a medical advisor to Abide Therapeutics researching agents to modulate the endocannabinoid system for the treatment of pain, and a co-investigator on a clinical trial sponsored by Prairie Plant Systems. D.E.M. has received speaker's honoraria and/or consulting fees from Pfizer Canada, Eli Lilly Canada Inc, Janssen Pharmaceuticals, and Purdue Pharma Canada. A.B. discloses consultancies or advisory boards to Bedrocan, CanniMed, Jansen, Johnson & Johnson, Lilly, Merck, Mettrum, Pfizer, and Purdue Pharma. T.W., S.S., J.-P.C., A.G., C.O., and J.M.E. report no conflicts.

Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.

Address reprint requests to Dr. Mark A. Ware, MBBS, MRCP, MSc, A5.140 Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada. E-mail: mark.ware@mcgill.ca

¹ Aline Boulanger, MD, Department d'anesthésie, Université de Montreal, Montreal, Quebec, Canada; John M. Esdaile, MD, Division of Rheumatology, University of British Columbia, Vancouver, British Columbia, Canada; Allan Gordon, MD, Division of Neurology, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada; Mary Lynch, MD, Departments of Anesthesia, Psychiatry and Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada; Dwight E. Moulin, MD, Departments of Clinical Neurological Sciences and Oncology, Western University, London, Ontario, Canada; Colleen O'Connell, MD, Department of Physical Medicine and Rehabilitation, Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada.

1526-5900

© 2015 The Authors. Published by Elsevier Inc. on behalf of the American Pain Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jpain.2015.07.014>

Perspective: This study evaluated the safety of cannabis use by patients with chronic pain over 1 year. The study found that there was a higher rate of adverse events among cannabis users compared with controls but not for serious adverse events at an average dose of 2.5 g herbal cannabis per day.

© 2015 The Authors. Published by Elsevier Inc. on behalf of the American Pain Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key words: Cannabis, safety, chronic pain, adverse events, cohort study.

The medical use of cannabis is an issue of major public health importance. Several countries have policies to allow patients to possess and use cannabis for medical purposes. Recently, Health Canada released the *Marihuana for Medical Purposes Regulations*,⁸ which require a signed document from a health professional for a patient to access cannabis for medical purposes. A lack of data on the safety and efficacy of cannabis is a major barrier to physicians' involvement.

Several randomized controlled trials of smoked cannabis have shown efficacy in chronic pain and spasticity.^{1,4,17,18} These trials have been short (1–3 weeks of exposure) with small sample sizes (n = 20–60 participants). Several oral cannabinoid prescription medications are available, and adverse events from clinical trials of these compounds have been reviewed¹⁶; some have been studied for periods of up to 1 year.^{14,19} Given the potential health concerns of recreational cannabis use,⁷ more safety data on the long-term medical use of herbal cannabis are needed.

We conducted a multicenter cohort study to evaluate safety issues in patients with chronic pain using cannabis as part of their pain management regimen.

Methods

Objectives

The primary objective was to assess the risk of adverse events associated with cannabis when used in the treatment of chronic pain. Secondary objectives were to examine the effects of cannabis on pulmonary and neurocognitive function, and to explore the effectiveness of cannabis on chronic pain, including pain intensity and quality of life.

Study Design

A prospective cohort study with a 1-year follow-up was conducted in 7 clinical centers across Canada between January 2004 and April 2008.

Study Population

Patients 18 years of age or older were eligible if they experienced chronic non-cancer pain for at least 6 months, with moderate to severe pain for which conventional treatments had been considered medically inappropriate or inadequate. Patients using cannabis as part of their treatment formed the cannabis group; those who were not using cannabis formed the control group, matched by site. We excluded patients who were pregnant or breast-feeding, who had a history of psychosis, who exhibited significant and unstable ischemic heart

disease or arrhythmia, or who suffered from significant and unstable bronchopulmonary disease. Patients were instructed not to drive a car or operate a motor vehicle while under the effects of cannabis. Written informed consent was obtained from all participants.

Study Drug

Herbal cannabis was provided by Prairie Plant Systems Inc and contained $12.5 \pm 1.5\%$ tetrahydrocannabinol (THC) (see [Supplementary Material S-1](#)). Patients in the cannabis group were able to use the delivery system with which they were most comfortable. They were advised to take the first dose in the evening, begin with low doses, and titrate upward to the maximum tolerated dose. An upper limit recommendation of 5 g/d was made to reduce the risk of diversion; higher doses were allowed when deemed appropriate by the prescribing physician. Cannabis was dispensed by the site pharmacy at weekly intervals for the first month and then monthly for the remainder of the study. Before dispensing, patients returned unused cannabis for weighing and destruction.

Outcome Measures

Primary Outcome

The primary outcome of this study was the incidence of adverse events (AEs) as defined by the International Conference on Harmonization.⁹ AEs were reported as serious (SAEs) or non-serious using the International Conference on Harmonization guidelines, and coded using the Medical Dictionary for Regulatory Activities (MedDRA version 11.0). Causality and severity were assessed by the study physician using the World Health Organization-Uppsala Monitoring Centre causality assessment system¹³ and Common Terminology Criteria for Adverse Events v3.0.³ Serious and unexpected AEs were reported to Health Canada and the institutional research ethics boards.

Secondary Outcomes

Neurocognitive function. Neurocognitive testing comprised 2 subtests of the Wechsler Memory Scale—Third Edition (Verbal Paired Associates I—Recall and Verbal Paired Associates II, including recall and recognition) and 2 subtests of the Wechsler Adult Intelligence Scale—Third Edition (Digit Symbol-Coding, Picture Arrangement).

Pulmonary function. Pulmonary function testing consisted of slow vital capacity, functional residual capacity, residual volume, total lung capacity, forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC),

and forced expired flow over the middle half of the vital capacity (FEF_{25-75%}).

Other safety parameters. Blood tests measured hematological, biochemical, liver, kidney, and endocrine function (prolactin, testosterone, thyroid-stimulating hormone).

Efficacy measures. Pain intensity was measured using visual analog scales (0, no pain; 10, worst pain possible) as the average, highest, and lowest in the past 7 days, and current pain intensity at the time of visit. Pain quality was assessed using the McGill Pain Questionnaire, which measures sensory, affective, and evaluative dimensions of pain. Other symptoms were measured using the modified Edmonton Symptom Assessment Scale. Mood was measured using the Profile of Mood States. Quality of life was measured using the SF-36.

Study Procedures

Baseline Assessment

All patients underwent baseline history and physical examinations, addiction screening (Drug Abuse Screening Test [DAST-20]), neurocognitive testing, and urine drug testing (enzyme-linked immunosorbent assay). Blood tests and pulmonary function tests were conducted in the cannabis group only.

Follow-Up

Intended follow-up was for 1 year. Six clinical visits (1, 2, 3, 6, 9, and 12 months after baseline) and 3 telephone interviews (1, 2, and 3 weeks after the baseline visit) were scheduled for patients in the cannabis group; 2 clinical visits (6 and 12 months after baseline) and 5 telephone interviews (1, 2, and 3 weeks, 3 and 9 months after baseline) were scheduled for control patients.

Neurocognitive and efficacy assessments were conducted at 6 and 12 months in all patients. Pulmonary function tests were repeated in the cannabis group at 12 months. Blood tests were conducted in the cannabis group at 1, 6, and 12 months. Patients were not specifically instructed to abstain from cannabis use before any study visits.

AE Reporting

AEs were captured during interviews at clinic visits, during telephone contacts, or spontaneously by calling the study nurse. At site visits, the study monitor reviewed patients' hospital charts to ensure that serious events were not missed.

Sample Size and Power Considerations

For the primary outcome, the incidence of AEs among cannabis users was compared with controls. It was assumed that SAEs followed Poisson distributions in the 2 study groups. The intended sample size of this study 350 cannabis-using participants and 350 controls (see [Supplementary Materials S-3](#)) meant that a rate ratio of 1.5 could be detected at powers above 60% for a control group incidence rate of SAEs above .15 case/person-year, and at a power above 70% for the incidence rate of SAEs

in the control group above .20 case/person-year. These estimates were derived from interim safety analyses during a protocol revision (see [Supplementary Materials S-3](#)) and are consistent with estimates from a meta-analysis of AEs from prescription cannabinoids.¹⁶

Statistical Analysis

Primary Analysis

Demographic and clinical characteristics were compared between the cannabis and control groups using parametric and non-parametric statistics as appropriate. Reasons for withdrawals were tabulated for both groups. AEs were coded and tabulated using the MedDRA headings "system organ classes" and "preferred terms." AEs were characterized by severity, causality, and outcome.

For incidence rate estimates, cumulative person-years were calculated from the date of the baseline visit until the date of discontinuation, death, or completion of the study, whichever came first. The 95% confidence intervals (CIs) for the rates were calculated using the Poisson distribution assumption.

An overdispersed Poisson regression model was used to assess the occurrence of AEs among cannabis users or controls.^{2,5,10} The results of the regression analyses are presented as incidence rate ratios (IRRs) with corresponding 95% CIs. Logistic regression analysis was also performed to explore the association between the risk of having at least 1 AE and medical cannabis use. Odd ratios (ORs) with 95% CIs were calculated.

Subgroup Analysis

To further control for confounding by past cannabis use, we estimated the stratified incidence rate of AEs by past cannabis use in the cannabis and control groups. We grouped past cannabis use into 3 categories. "Current cannabis users" were those who reported using cannabis at the baseline interview; "ex-cannabis users" were those who reported having previously used cannabis but not at the baseline interview; "naive users" were those who reported never having used cannabis before the baseline interview. We carried out a Poisson regression analysis to explore whether the incidence rate was consistent among participants with different histories of cannabis use.

Secondary Analyses

A random effects model with a random intercept for patient was used to model neurocognitive and pulmonary function, pain, mood, symptom severity, and quality of life. Age, gender, disability status, average pain intensity, concomitant pain medication use, alcohol use (current vs former or never users), tobacco use (current vs former or never users), past cannabis use (ever vs never), and study sites were incorporated as covariates.

Statistical analyses were undertaken with SAS software (version 9.1; SAS Institute Inc, Cary, NC). No adjustments for multiple comparisons were made.

Protocol Modifications

The original protocol was modified during the study implementation to reduce the burden on the study participants and aid recruitment. Details of these modifications are found in the [Supplementary Materials \(S-3\)](#).

Ethics and Regulatory Approvals

The study was approved by the research ethics board of each participating hospital and Health Canada. An independent Safety Monitoring Advisory Committee was formed to ensure consistency for objectively and systematically categorizing the seriousness, severity, and causality of AEs ([Supplementary Materials S-4](#)).

Regulatory approval to use the herbal cannabis supplied was obtained from the Therapeutic Products Directorate of Health Canada.

Results

From January 2004 to April 2008, 431 patients were recruited, 215 in the cannabis group and 216 controls ([Fig 1](#)). Median duration of follow-up was 11.9 months (range = 7–551 days) in the cannabis group and 12.1 months (range = 28–567 days) in the control group (outliers in follow-up time were due to late final visits; [Supplementary Table 1](#)). The cannabis group included 141 (66%) “current cannabis users”, 58 (27%) “ex-cannabis users”, and 16 (7%) “cannabis-naive users”. Controls included 70 (32%) “ex-cannabis users” and 146 (68%) “cannabis-naive users”.

Baseline characteristics are presented in [Table 1](#). Patients in the cannabis group were younger, with a larger percentage of male, disabled, and tobacco or alcohol users compared with the control group. Socio-economic status did not differ between the groups. The average pain intensity score at baseline was significantly higher in the cannabis group than in the control group. Compared with cannabis users, more control patients were using opioids (55% in cannabis group vs 66% in the control group), antidepressants (47% vs 59%), or anticonvulsants (44% vs 55%) at baseline. Three (1.4%) cannabis users reported “intermediate severity” addiction problems as judged by the DAST-20 score.

Sixty-seven patients receiving study cannabis and 34 control patients discontinued the study before the full year of follow-up; data from all patients were included in the safety analysis.

There were no significant differences in baseline measures between patients who completed the study and those who did not ([Supplementary Table 2](#)). However, in the cannabis group, “cannabis-naive users” (9 [56%]) or “ex-cannabis users” (26 [45%]) were more likely to withdraw from the study than “current cannabis users” (32 [23%]) (χ^2 [DF = 2] = 14.46, $P < .001$) ([Supplementary Table 2](#)).

The median daily dosage among cannabis-using participants was 2.5 g/d (range = .1–13.4; interquartile range = 1.5–3.0); 11 (5%) patients received doses of >3 g/d. Fifty-eight participants (27%) used smoking as the only route of administration, 130 (61%) used a combination

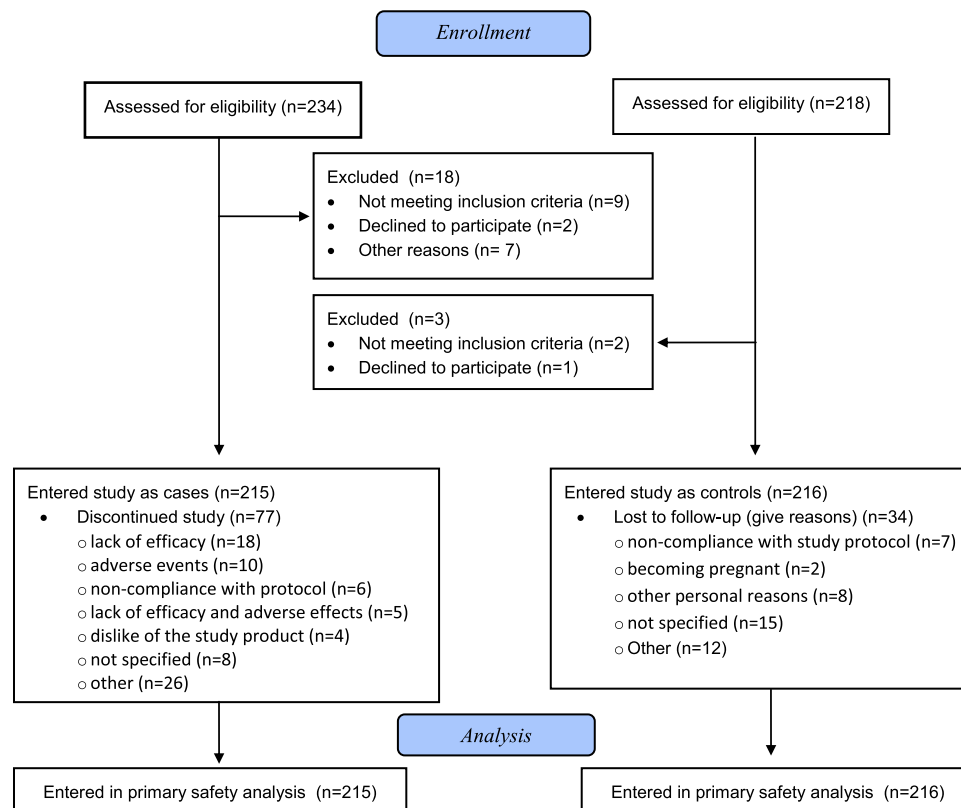


Figure 1. COMPASS CONSORT flow diagram.

Table 1. Baseline Characteristics of Study Participants by Exposure Status

CHARACTERISTICS	CANNABIS GROUP (N = 215)	CONTROL GROUP (N = 216)	P
Age at enrollment*	45.5 (19–82)	52.4 (21–83)	<.001
Gender (% male)†	110 (51.2%)	76 (35.2%)	<.001
Education (% university/college)‡	111 (51.6%)	122 (56.5%)	.14
Married; n (%)†	133 (61.9%)	140 (64.8%)	.52
Disabled; n (%)†	129 (60.0%)	102 (47.2%)	.01
Tobacco status‡§			.01
Current tobacco users	91 (42.3%)	67 (31.0%)	
Ex-tobacco users	77 (35.8%)	73 (33.8%)	
Never users	47 (21.9%)	76 (35.2%)	
Alcohol status‡			.05
Currently drinking	166 (77.2%)	149 (69.0%)	
Not currently drinking	49 (22.8%)	67 (31.0%)	
Past cannabis use†			<.001
Current cannabis users	141 (65.6%)	0	
Ex-cannabis users	58 (27.0%)	70 (32.4%)	
Naive users	16 (7.4%)	146 (67.6%)	
Drug Abuse Screening Test¶			<.0001
N/A (DAST = 0)	59 (27.4%)	133 (62.1%)	
Low (DAST = 1–5)	153 (71.2%)	81 (37.9%)	
Intermediate (DAST = 6–10)	3 (1.4%)	0	
Substantial (DAST = 11–15)	0	0	
Severe (DAST = 16–20)	0	0	
Type of pain†			.40
Nociceptive	35 (16.3%)	39 (18.1%)	
Neuropathic	83 (38.6%)	70 (32.4%)	
Both	97 (45.1%)	107 (49.5%)	
Average pain intensity*	6.6 (0–10)	6.1 (0–10)	.002
Duration of pain (years)‡	8.0 (0–54)	7.0 (0–82)	.42
Medications			
Opioids†	118 (54.9%)	143 (66.2%)	.02
Antidepressants†	101 (47.0%)	128 (59.3%)	.01
Anticonvulsants†	94 (43.7%)	118 (54.6%)	.02

*Mean (range), Student t-test.

†Number of patients (proportion), χ^2 .

‡Median (range), the Wilcoxon rank sum test.

§“Current smokers” were those who reported smoking at the baseline interview; “ex-smokers” were those who reported abstinence from cigarettes at baseline; “never smokers” were those who reported never smoking at the baseline interview.

||“Current cannabis users” were those who reported using cannabis and were still using at the baseline interview; “Ex-cannabis users” were those who reported using cannabis but were not using at the baseline interview; “naive users” were those who reported never using cannabis before the baseline interview.

¶Fisher's exact test.

of smoking, oral, and vaporization, and 17 (8%) consumed cannabis orally only (see [Supplementary Materials S-6; Supplementary Tables 3, 4, and 4a](#)).

AEs

SAEs

Twenty-eight (13%) patients in the cannabis group reported at least 1 SAE, compared with 42 (19%) in the control group. The risk of having at least 1 SAE was not significantly different between the 2 groups (unadjusted OR = .64, 95% CI = .38–1.04). The total number of SAEs

was similar in the cannabis and control groups (40 and 56, respectively). The incident rates of SAEs were 22.6 and 27.5 events per 100 person-years of follow-up in the cannabis and control groups, respectively (unadjusted IRR = .82, 95% CI = .46–1.46).

SAEs are shown in [Table 2](#). The most common categories were “Surgical and medical procedures” and “Gastrointestinal disorders” (n = 10, 25%; n = 10, 25%, respectively) in the cannabis group and (n = 11, 20%; n = 7, 13%) in the control group ([Supplementary Table 5](#)). The most common SAEs in the cannabis group were abdominal pain (n = 3, 12%), intestinal obstruction (n = 3, 12%), and nephrolithiasis (n = 3, 12%). None of the SAEs was considered to be “certainly/very likely” related to study cannabis. One SAE (convulsion) was considered “probably/likely” related to study cannabis. Two participants in the control group died over the course of the trial, 1 by suicide and the other died in the operating room after emergency treatment for abdominal pain; there were no deaths in the cannabis group.

Treatment was stopped permanently for 2 patients due to SAEs (1 convulsion and 1 alcohol problem). At the end of the study, 31 (77.5%) of the SAEs in the cannabis group had been fully resolved.

Non-serious AEs

Most patients in the cannabis group (190 of 215; 88.4%) and the control group (184 of 216; 85.2%) experienced at least 1 non-serious AE, with a median of 3 events per participant (range = 0–16; interquartile range = 2–5) among cannabis users and a median of 2 events per participant (range = 0–14, interquartile range = 1–4) among controls. The risk of having at least 1 AE did not differ significantly between cannabis users and controls (unadjusted OR = 1.32, 95% CI = .75–2.32).

A total of 818 non-serious AEs were reported in the cannabis group, resulting in an incidence rate of 4.61 events/person-year. This rate was significantly higher than in the control group in which there were 581 non-serious AEs and an incidence rate of 2.85 events/person-year (unadjusted IRR = 1.64, 95% CI = 1.35–1.99) ([Table 3](#)).

The number of patients, the occurrence of events, and corresponding rates within each MedDRA system organ class category are shown in [Table 3](#). The most common AE categories in the cannabis group were nervous system (n = 165, 20%), gastrointestinal (n = 109, 13.4%) and respiratory disorders (n = 103, 12.6%). Compared with controls, the rate of nervous system disorders (unadjusted IRR = 2.05, 95% CI = 1.46, 2.86), respiratory disorders (unadjusted IRR = 1.77, 95% CI = 1.16, 2.70), infections disorder (unadjusted IRR = 1.51, 95% CI = 1.04, 2.20), and psychiatric disorders (unadjusted IRR = 2.74, 95% CI = 1.45, 5.18) were significantly higher in the cannabis group ([Fig 2](#)). Mild (420, 51.3%) or moderate (390, 47.7%) events were more common than severe events (8, 1.0%) in the cannabis group. Non-serious AEs occurring more than once among cannabis users and

Table 2. SAEs Categorized by System Organ Class

SERIOUS AEs	CANNABIS GROUP		CONTROL GROUP	
	SYSTEM ORGAN CLASS (MEDDRA)	NUMBER OF EVENTS	RATE*	NUMBER OF EVENTS
Surgical and medical procedures	10	5.65	11	5.39
Gastrointestinal disorders	10	5.65	7†	3.43
Musculoskeletal and connective tissue disorders	5	2.82	6	2.94
Injury, poisoning, and procedural complications	4	2.26	1	.49
Renal and urinary disorders	3	1.69	1	.49
Nervous system disorders	2	1.13	4	1.96
Respiratory, thoracic, and mediastinal disorders	1	.56	7	3.43
Infections and infestations	1	.56	5	2.45
Vascular disorders	1	.56	3	1.47
Metabolism and nutrition disorders	1	.56	2	.98
Psychiatric disorders	1	.56	2‡	.98
Investigations	1	.56	0	.00
General disorders and administration site conditions	0	.00	3	1.47
Blood and lymphatic system disorders	0	.00	1	.49
Eye disorders	0	.00	1	.49
Hepatobiliary disorders	0	.00	1	.49
Immune system disorders	0	.00	1	.49
Total	40	22.60§	56	27.45§
Total number of patients	28	13.02%	42	19.44%

*Unit: n/100 person-years.

†One patient died in the operating room.

‡One patient committed suicide.

§The rates of serious AEs did not differ significantly between these 2 groups (Unadjusted incidence rate ratio = .82, 95% CI = .46–1.46).

||The risk of having reported at least 1 SAE was not significantly different between 2 groups (Unadjusted odds ratio = .62, 95% CI = .37–1.04).

assessed as certainly/very likely related to cannabis were somnolence (n = 5, .6%), amnesia (n = 4, .5%), cough (n = 4, .5%), nausea (n = 4, .5%), dizziness (n = 3, .4%), euphoric mood (n = 3, .4%), hyperhidrosis (n = 2, .2%), and paranoia (n = 2, .2%) (Supplementary Table 7).

In the control group, gastrointestinal disorders (n = 101, 17.4%) and nervous system disorders (n = 93, 16.0%) were the most frequently reported (Table 3). The majority of AEs among controls were mild (57.3%) or moderate (42.0%); 4 (.7%) were categorized as “severe” (abdominal pain, breast cancer, pulmonary embolism, and upper respiratory tract infection) (Supplementary Tables 6–8).

Multiple Regression Analyses

The association between cannabis use and the rate of AEs is summarized in Table 4. Medical cannabis users had an increased risk of non-serious AEs (adjusted IRR = 1.74, 95% CI = 1.42–2.14) but not SAEs (adjusted IRR = 1.08, 95% CI = .57–2.04). Increasing the daily dose of cannabis did not lead to higher risks of SAEs or AEs (Supplementary Table 10).

Neurocognitive Tests

Significant improvements were observed in all neurocognitive subtests after 6 and 12 months in cannabis users and controls (Table 5). After adjusting for age, gender, education, alcohol history, disability status, concurrent average pain intensity, quality of life, and clinic sites, no difference in neurocognitive function after 1 year was found between cannabis users and controls (Supplementary Table 12).

Pulmonary Function Tests

After adjusting for tobacco smoking and other covariates, we did not find a significant change in slow vital capacity, functional residual capacity, and total lung capacity over 1 year among the cannabis users. Residual volume was reduced (mean reduction 142 mL), and a mean decline of 54 mL in FEV₁ and a mean decrease of .78% in the FEV₁/FVC ratio were noted. The FEV_{25–75%} was lower with a mean decrease of .2; no change was observed in FVC (Supplementary Tables 13 and 14).

Blood Tests

Seventy-eight patients in the cannabis group had blood tests conducted at baseline and at 1 year. No changes in liver, renal, and endocrine function were observed (Supplementary Tables 15 and 16).

Efficacy Measures

Pain Intensity

Compared with baseline, a significant reduction in average pain intensity over 1 year was observed in the cannabis group (change = .92; 95% CI = .62–1.23) but not in the control group (change = .18; 95% CI = –.13 to .49). After adjusting for confounders, a greater reduction in pain was observed among cannabis users than among controls (difference = 1.10, 95% CI = .72–1.56) (Fig 3; Supplementary Tables 17 and 18).

Quality of Life

With regard to the change in Physical Component Summary (PCS) score, a significant improvement from

Table 3. Summary of Non-serious AEs Categorized by System Organ Class

NON-SERIOUS AEs	CANNABIS GROUP			CONTROL GROUP		
	NUMBER OF PERSONS REPORTING SYMPTOMS	NUMBER OF EVENTS REPORTED	RATE (EVENTS/PERSON-YEAR)	NUMBER OF PERSONS REPORTING SYMPTOMS	NUMBER OF EVENTS REPORTED	RATE (EVENTS/PERSON-YEAR)
Nervous system disorders	101	165	.93	71	93	.46
Gastrointestinal disorders	66	109	.62	70	101	.50
Respiratory, thoracic, and mediastinal disorders	77	103	.58	49	67	.33
Infections and infestations	63	89	.50	49	68	.33
Musculoskeletal and connective tissue disorders	49	77	.44	50	67	.33
Psychiatric disorders	47	57	.32	21	24	.12
General disorders and administration site conditions	29	35	.20	20	23	.11
Injury, poisoning, and procedural complications	23	31	.18	21	23	.11
Renal and urinary disorders	23	29	.16	18	22	.11
Skin and subcutaneous tissue disorders	18	22	.12	17	18	.09
Investigations	21	21	.12	8	8	.04
Eye disorders	16	20	.11	13	14	.07
Reproductive system and breast disorders	11	15	.08	5	6	.03
Metabolism and nutrition disorders	14	14	.08	7	7	.03
Vascular disorders	8	8	.05	9	9	.04
Surgical and medical procedures	6	7	.04	10	12	.06
Cardiac disorders	4	4	.02	7	7	.03
Blood and lymphatic system disorders	4	4	.02	0	0	.00
Ear and labyrinth disorders	3	3	.02	5	5	.02
Immune system disorders	1	2	.01	3	3	.01
Hepatobiliary disorders	2	2	.01	1	1	.00
Endocrine disorders	1	1	.01	0	0	.00
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	0	.00	3	3	.01
Total	191	818	4.62	186	581	2.85
Unadjusted OR (95% CI)		1.28 (.72–2.28)			1	
Unadjusted IRR (95% CI)		1.62 (1.34–1.97)			1	

baseline was observed in both groups at the 6- and 12-month clinic visits. Analysis of the change in the PCS indicated greater improvement of physical function in cannabis users than in controls (2.36 point greater

improvement at 6 months, 95% CI = .84–3.88; and 1.62 points at 1 year, 95% CI = .10–3.14). No within-group or between-group differences for the Mental Component Summary were observed (Supplementary Table 25).

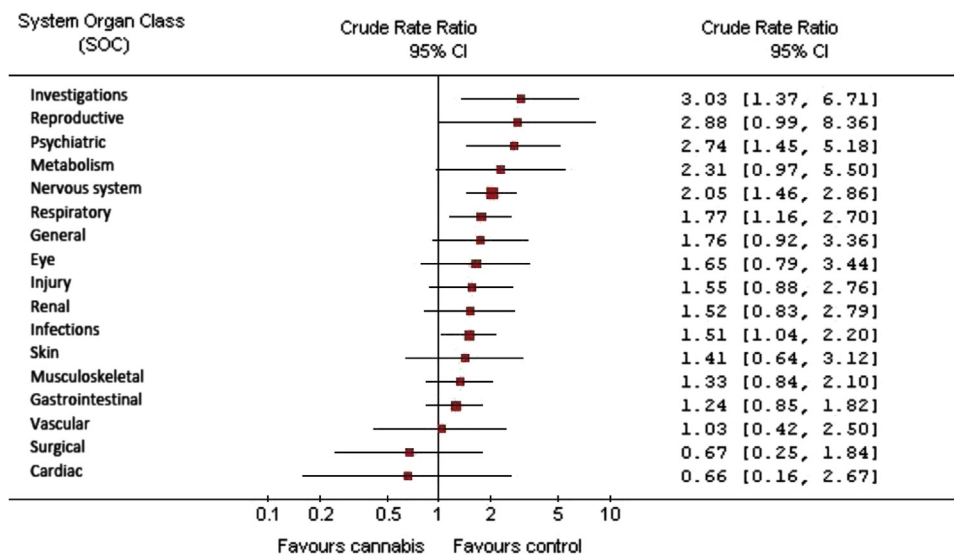


Figure 2. Unadjusted incidence rate ratios of non-serious adverse events by system organ class.

Table 4. Unadjusted and Adjusted Rate Ratios of AEs for Medical Cannabis

	CANNABIS	CONTROL	UNADJUSTED IRR (95% CI)	ADJUSTED IRR* (95% CI)
All patients				
Number of patients	215	216	–	–
Cumulative person-years	176.9	204.1	–	–
Number of SAEs	40	56	.82 (.46–1.46)	1.08 (.57–2.04)
Number of AEs	818	574	1.64 (1.35–1.99)	1.74 (1.42–2.14)
Patients excluding “current cannabis users”† at baseline				
Number of patients	74	216	–	–
Cumulative person-years	52.2	204.1	–	–
Number of SAEs	20	56	1.40 (.66–2.93)	1.77 (.72–4.32)
Number of AEs	316	574	2.15 (1.69–2.74)	2.07 (1.59–2.70)

*Adjusted for age at enrollment, gender, baseline pain intensity, baseline concomitant pain medication (yes/no), disability status (yes/no), tobacco use (current vs former or never smokers), alcohol use (current vs former or never users), past cannabis use (ever/never), and study sites.

†“Current cannabis users” were those who reported using cannabis and were still using at the baseline interview.

Pain and Other Symptoms

The sensory component of pain was reduced over 1 year in cannabis users compared with controls (Supplementary Tables 19 and 20). The total symptom distress score of the Edmonton Symptom Assessment Scale was also improved in cannabis users over 1 year (Supplementary Tables 21 and 22). The total mood disturbance scale of the Profile of Mood States showed significant improvement for cannabis users compared with controls, with improvements found in the tension-anxiety, depression-dejection, anger-hostility, and fatigue-inertia subscales (Supplementary Tables 23 and 24).

Discussion

To our knowledge, this is the first cohort study of the long-term safety of medical cannabis use ever conducted. Over 1 year, we identified 40 SAEs among 28 patients, and 818 non-serious AEs among 190 patients using medical cannabis. Headache, nasopharyngitis, nausea, somnolence, and dizziness were the most common AEs reported. Medical cannabis use did not increase the risk of SAEs compared with controls but was associated

with an increased risk of non-serious AEs, particularly with respect to nervous system and psychiatric disorders. This adverse event profile is similar to pharmaceutical cannabinoids.¹⁶

We found 78 respiratory events in the cannabis group and 56 in the control group, and most were considered mild or moderate. No increase in risk of serious respiratory AEs associated with medical cannabis use was detected (1 SAE in the cannabis group, and 7 in the control group). Medical cannabis users had a higher rate of developing non-serious respiratory AEs during 1 year of follow-up compared with controls. This is consistent with reports that long-term cannabis smoking is associated with an increased risk of chronic bronchitis.¹² In our study, cannabis users had a mean 50-mL decrease in FEV₁ and a mean 1% decrease in the FEV₁/FVC ratio over 1 year.

Neurocognitive function improved in both groups. This finding differs from that found in recreational users of cannabis; a meta-analysis of 15 studies investigating the effects of recreational cannabis use on neurocognitive performance⁶ suggested that long-term cannabis users performed significantly poorer on tests

Table 5. Neurocognitive Measures in Cannabis-Exposed and Control Individuals Over 1 Year*

	GROUP	NUMBER OF PATIENTS	BASELINE	6 MONTHS	12 MONTHS
WMS-III †					
Verbal paired associates I					
Recall (max 32 points)	Cannabis	77	16.92 (7.69)	20.97 (8.01)	22.97 (7.56)
	Control	53	17.42 (7.85)	19.25 (8.70)	22.72 (8.53)
Verbal paired associates II					
Recall (max 8 points)	Cannabis	76	5.67 (2.35)	6.29 (2.05)	6.54 (1.81)
	Control	53	5.45 (2.55)	6.02 (2.45)	6.64 (1.95)
Recognition (max 24 points)	Cannabis	76	23.80 (.80)	23.92 (.32)	23.78 (1.41)
	Control	53	23.94 (.23)	23.98 (.14)	23.98 (.14)
WAIS-III ‡					
Digit symbol-coding (max 133 points)					
	Cannabis	72	52.21 (21.60)	53.31 (23.64)	55.90 (23.11)
	Control	53	49.94 (18.82)	54.64 (20.26)	55.00 (17.65)
Picture arrangement (max 22 points)					
	Cannabis	76	11.64 (3.91)	13.67 (5.03)	14.18 (4.36)
	Control	53	11.42 (4.65)	13.32 (5.14)	14.24 (5.53)

*Data are presented as mean (SD).

†WMS-III, Wechsler Memory Scale, Third Edition.

‡WAIS-III: Wechsler Adult Intelligence Scale, Third Edition.

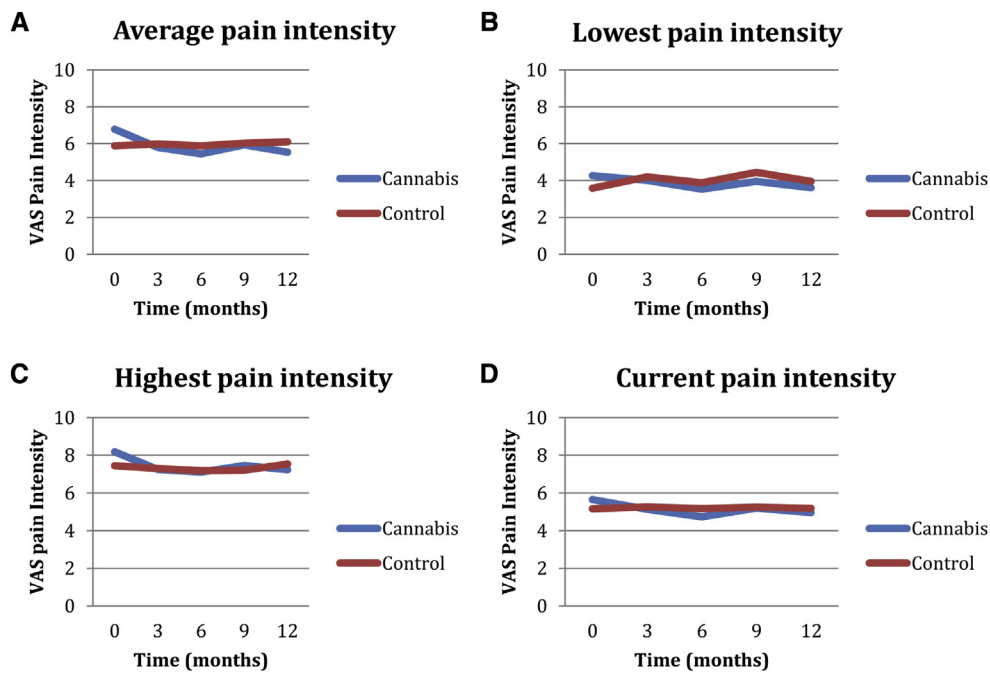


Figure 3. Changes in pain intensity over 1 year (data only shown for patients with complete data at all time points; $n = 145$ (cannabis), $n = 157$ (controls). Abbreviation: VAS, visual analog scale.

of memory and attention than short-term users.¹¹ In that study, both groups consumed similar amounts of cannabis (median = 7 g/wk, range = .3–57 g/wk), and there was no difference in memory and attention between short-term users and non-cannabis users. Longer-term follow-up of the neurocognitive effects of medical cannabis use is needed.

We found no impact of medical cannabis use on measures of hematological, biochemical, liver, renal, and endocrine function among 78 patients followed over 1 year.

With respect to secondary efficacy measures, we noted significant improvements in pain intensity and the physical dimension of quality of life over 1 year among the cannabis users compared with controls; there was also significant improvement among cannabis users in measures of the sensory component of pain, symptom distress, and total mood disturbance compared with controls. These findings, although not the primary outcomes of the study, are nevertheless important in considering the overall risk-benefit ratio of medical use of cannabis.

There are several limitations of our study. First, the relatively small sample size and short follow-up time prevented our study from identifying rare SAEs. Following 215 patients (177 person-years) in the cannabis group and 216 (204 person-years) in the control group enabled us to detect a rate ratio of 1.5 at powers above 50% for an incidence rate of SAEs in the control group above .20 case/person-year.

Second, we observed a significant drop-out rate, which may be a source of selection bias. Losses to follow-up were estimated at 30% over a median follow-up of 12 months. Factors associated with drop-out included AEs, perceived lack of efficacy, and/or a dislike of the study product. However, patients lost to

follow-up were comparable with patients who finished the entire study.

Third, most study participants in the cannabis group (66%) were experienced cannabis users. Due to the small number of cannabis-naïve patients in the study, the safety of medical cannabis use in cannabis-naïve individuals cannot be addressed. Moreover, our results indicate that the rate of non-serious AEs among “current cannabis users” was lower than that among “ex-cannabis users” or “naïve users.” We would likely have observed a higher rate of AEs for cannabis if only new cannabis users had been included.

Fourth, observational bias could come from ascertainment of outcomes. Given the difference in follow-up (9 visits after baseline in the cannabis group vs 7 in the control group), patients in the cannabis group may have reported AEs otherwise neglected by controls. The effect of this limitation is likely to lead to more exaggerated estimates of AEs among medical cannabis users than among the controls.

Fifth, confounding by indication due to selective prescribing is another potential source of bias.¹⁵ This bias may exist in our study because herbal cannabis was authorized for refractory patients who had more pain and disability than controls. Information on determinants of prescription choices was unmeasured, but pain intensity and disability were considered as the most important factors influencing the decision to use medical cannabis. Adjusting for these 2 variables in the final model of our study helped to control indication bias.

With respect to the observed improvements in secondary efficacy measures, we interpret these with caution because the study was not a randomized controlled trial and allocation was not blinded. It is possible that

improvements in these efficacy measures resulted from regression to the mean, natural history of disease or the effect of being in the study. However, these biases would apply to both groups, yet still we noted difference between groups.

Despite these limitations, this study improves our knowledge about the safety of medical cannabis. Caution should be exercised in interpreting these results for all medical cannabis use as patients in this study used a standardized, quality-controlled herbal cannabis product with a reliable THC potency of 12.5%.

In conclusion, this study suggests that the AEs of medical cannabis are modest and comparable quantitatively and qualitatively with prescription cannabinoids. The results suggest that cannabis at average doses of 2.5 g/d in current cannabis users may be safe as part of a carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate. However, safety concerns in naive users cannot be addressed. Moreover, long-term effects on pulmonary functions and neurocognitive functions beyond 1 year cannot be determined. Further studies with systematic follow-up are required to characterize safety issues among new cannabis users

References

1. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL: Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 68: 515-521, 2007
2. Agresti A: *Categorical Data Analysis*, 2nd ed. Hoboken, NJ, John Wiley, 2002
3. Common terminology criteria for adverse events v3.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf. Accessed July 25, 2013
4. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B: Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 184:1143-1150, 2012
5. Gardner W, Mulvey EP, Shaw EC: Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. *Psychol Bull* 118: 392-404, 1995
6. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T: Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc* 9: 679-689, 2003
7. Hall W, Degenhardt L: Adverse health effects of non-medical cannabis use. *Lancet* 374:1383-1391, 2009
8. Health Canada. Marihuana for medical purposes regulations. Available at: <http://gazette.gc.ca/rp-pr/p2/2013/2013-06-19/html/sor-dors119-eng.php>. Accessed May 14, 2014
9. ICH: Definitions and standards for expedited reporting. Available at: <http://www.ich.org/cache/compo/276-254-1.html>. Accessed October 1, 2005

and should be extended to allow estimation of longer-term risks.

Acknowledgments

We gratefully acknowledge the support and contributions of Anna Passariello, Nicole Poitras, and Linda Ferguon (study coordinators); Ann Robinson (study monitor); Randa Zamrini (data manager); Myrna Yazer, Sylvie Toupin, Ann Rusnov, Charlene Bartha, Marilyn Galonski, Selena Roy, Susan Brophy, Joanne Stewart (study nurses); Thierry Ducruet (statistical support); Peter Fried (neuropsychiatry consultant); Don Boudreau (pulmonology consultant); Kam Shojania (rheumatology), and all the patients who made the study possible.

Safety Monitoring Advisory Committee.

Robin O'Brien (chair), Lawrence Joseph, Jock Murray.

Adverse Event Adjudication Committee.

Mark Ware, Mary Lynch.

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpain.2015.07.014>.

10. SAS Institute: *SAS/STAT User's Guide*, version 9. Cary, NC, SAS Institute, 2007
11. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J: Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 287:1123-1131, 2002
12. Tashkin DP: Effects of marijuana smoking on the lung. *Ann Am Thorac Soc* 10:239-247, 2013
13. The use of the WHO-UMC system for standardised case causality assessment. Available at: <http://who-umc.org/Graphics/24734.pdf>. Accessed July 25, 2013.
14. Wade DT, Makela PM, House H, Bateman C, Robson P: Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 12:639-645, 2006
15. Walker AM, Stampfer MJ: Observational studies of drug safety. *Lancet* 348:489, 1996
16. Wang T, Collet JP, Shapiro S, Ware MA: Adverse effects of medical cannabinoids: a systematic review. *CMAJ* 178: 1669-1678, 2008
17. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP: Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ* 182:E694-E701, 2010
18. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S: A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 9:506-521, 2008
19. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, Nunn AJ, Teare LJ, Fox PJ, Thompson AJ: Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 76:1664-1669, 2005