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Mark A. Ware, MBBS MRCP MSc, Tongtong Wang, BMed PhD, Stan Shapiro, PhD, Jean-Paul Collet, MD PhD, for the COMPASS study team, Aline Boulanger, MD, John M. Esdaile, MD, Allan Gordon, MD, Mary Lynch, MD, Dwight E. Moulin, MD, Colleen O'Connell, MD

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

Mark A. Ware MBBS MRCP MSc[1], Tongtong Wang BMed PhD[2], Stan Shapiro PhD[2,3], Jean-Paul Collet MD PhD[4] for the COMPASS study team*

*Aline Boulanger MD[5], John M. Esdaile MD[6], Allan Gordon MD[7], Mary Lynch MD[8], Dwight E. Moulin MD[9], Colleen O'Connell MD[10]

Institutional affiliations:

[1]Departments of Anesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada
[2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
[3]Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada
[4]Department of Pediatrics, University of British Columbia; Child and Family Research Institute, Vancouver, British Columbia, Canada
[5]Department d'anesthesie, Université de Montreal, Montreal, Quebec, Canada
[6]Division of Rheumatology, University of British Columbia, Vancouver, British Columbia, Canada
[7]Department of Neurology, University of Toronto, Toronto, Ontario, Canada
[8]Departments of Anesthesia, Psychiatry and Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada
[9]Departments of Clinical Neurological Sciences and Oncology, Western University, London, Ontario, Canada
[10]Department of Physical Medicine and Rehabilitation, Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada

Address for reprints and correspondence:

Dr. Mark A. Ware
A5.140 Montreal General Hospital
1650 Cedar Avenue
Montreal, Quebec H9S 4Y5
Canada

Tel: (514) 934-8222
Fax: (514) 934-8096
Email: mark.ware@mcgill.ca

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Abstract

Cannabis is widely used as a self-management strategy by patients with a wide range of symptoms and diseases including chronic noncancer 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 subjects with chronic noncancer pain. A standardized herbal cannabis product (12.5% THC) was dispensed to eligible subjects for a one-year period; controls were subjects with chronic pain from the same clinics who were not cannabis users. The primary outcome consisted of serious adverse events (SAEs) and non-serious adverse events (AEs). 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 seven clinics across Canada. The median daily cannabis dose was 2.5g/d. There was no difference in risk of SAEs (adjusted IRR=1.08, 95% CI=0.57-2.04) between groups. Medical cannabis users were at increased risk of non-serious AEs (adjusted IRR=1.73, 95% CI=1.41-2.13); most were mild to moderate. There were no differences in secondary safety assessments.

Quality-controlled herbal cannabis, when used by cannabis-experienced patients as part of a monitored treatment program over one year, appears to have a

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reasonable safety profile. Longer term monitoring for functional outcomes is needed.

Study registration

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

Perspective

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

Key words

Cannabis, safety, chronic pain, adverse events, cohort study

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Introduction

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 subjects). Several oral cannabinoid prescription medications are available, and adverse events from clinical trials of these compounds have been reviewed [16]; some have been studied for periods of up to one year [14,19]. Given the potential health concerns of recreational cannabis use [11], 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

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to explore effectiveness of cannabis on chronic pain, including pain intensity and quality of life.

Study design

A prospective cohort study with a one-year follow-up was conducted in seven 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 six months, with moderate to severe pain for which conventional treatments had been considered medically inappropriate or inadequate. Subjects using cannabis as part of their treatment formed the cannabis group, while subjects 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. Subjects were instructed not to drive a car or operate a motored 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. (PPS) and contained 12.5 (±1.5) % tetrahydrocannabinol (THC)(see S2-1). Cannabis subjects were able to use the delivery system with which they were most comfortable. Subjects were advised to take the first dose in the evening, begin with low doses and titrate upwards to maximum tolerated dose. An upper limit recommendation of 5 grams

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per day (g/d) was made to reduce 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. Prior to dispensing, subjects 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 (ICH) [11]. AEs were reported as serious (SAEs) or non-serious using ICH 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 WHO-UMC causality assessment system [13] and Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [3]. Serious and unexpected AEs were reported to Health Canada and the institutional research ethics boards (REBs).

Secondary outcomes

Neurocognitive function

Neurocognitive testing comprised two subtests of the Wechsler Memory Scale—Third Edition (WMS®-III) (Verbal Paired Associates I—recall and Verbal Paired Associates II, including recall and recognition) and two subtests of the Wechsler Adult Intelligence Scale—Third Edition (WAIS®-III) (Digit Symbol-coding, Picture Arrangement).

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Pulmonary function

Pulmonary function testing consisted of Slow Vital Capacity (SVC), Functional Residual Capacity (FRC), Residual Volume (RV), Total Lung Capacity (TLC), Forced Expiratory Volume in one second (FEV_1), 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, TSH).

Efficacy measures

Pain intensity was measured using visual analogue scales (VAS) (0: no pain – 10: worst pain possible) as 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 (MPQ), which measures sensory, affective and evaluative dimensions of pain. Other symptoms were measured using the modified Edmonton Symptom Assessment Scale (ESAS). Mood was measured using the Profile of Mood States (POMS). Quality of life was measured using the SF-36.

Study procedures

Baseline assessment

All subjects underwent baseline history and physical examinations, addiction screening (Drug Abuse Screening Test (DAST-20)), neurocognitive testing, and urine drug testing (ELISA). Blood tests and pulmonary function tests were conducted in the cannabis group only.

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Follow-up

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

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. Subjects were not specifically instructed to abstain from cannabis use prior to any study visits.

Adverse event 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 subjects' hospital charts to ensure that serious events were not missed.

Sample size and power considerations

For the primary outcome, the incidence of adverse events among cannabis users was compared with controls. It was assumed that SAEs followed Poisson distributions in the two study groups. The intended sample size of this study (350 cannabis-using subjects and 350 controls (see 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 0.15 case/person-year, and at a power above 70% for the incidence

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rate of serious adverse event in the control group above 0.20 case/person-year. These estimates were derived from interim safety analyses during a protocol revision (see S-3) and are consistent with estimates from a meta-analysis of adverse events from prescription cannabinoids [16].

Statistical analysis

Primary analysis

Demographic and clinical characteristics were compared between 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" (SOC) and "preferred terms." (PT). 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 were 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 one AE and medical cannabis use. Odd ratios (ORs) with a 95% CIs were calculated.

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Subgroup analysis

To further control for confounding by past cannabis use, we estimated the stratified incidence rate of adverse events by past cannabis use in the cannabis and control groups. We grouped past cannabis use into three 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 baseline interview; “naïve users” were those who reported never having used cannabis prior to baseline interview. We carried out a Poisson regression analysis to explore whether the incidence rate was consistent among participants with different cannabis use histories.

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). No adjustments for multiple comparisons were made.

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Protocol modifications

The original protocol was modified during the study implementation to reduce the burden on study subjects 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 REB of each participating hospital and Health Canada. An independent Safety Monitoring Advisory Committee was formed to ensure consistency for objectively and systematically categorizing adverse events' seriousness, severity and causality (S-3).

Regulatory approval to use the supplied herbal cannabis 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 (Figure 1). Median duration of follow-up was 11.9 months (range, 7 to 551 days) in the cannabis group and 12.1 months (range, 28 to 567 days) in the control group (outliers in follow-up time were due to late final visits; Table S-1). The cannabis group included 141 (66%) "current cannabis users", 58 (27%) "ex-cannabis users", and 16 (7%) "cannabis naïve". Controls included 70 (32%) "ex-cannabis users" and 146 (68%) "cannabis naïve".

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

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users compared to the control group. Socioeconomic status did not differ between groups. The average pain intensity score at baseline was significantly higher in the cannabis group than the control group. Compared to cannabis users, more control patients were using opioids (55% in cannabis group vs. 66% in controls), 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 (Table S-2). However in the cannabis group, "cannabis naïve" [9 (56%)] or "ex-cannabis users" [26 (45%)] were more likely to withdraw from the study than "current cannabis users" [32 (23%)]. (X^2 (DF=2) =14.46, $p<0.001$) (S-2).

The median daily dosage among cannabis-using subjects was 2.5g/d, (range 0.1-13.4; IQR 1.5-3.0); 11 (5%) patients received doses of >3g/d. Fifty-eight subjects (27%) used smoking as the only route of administration, 130 (61%) used a combination of smoking, oral and vaporization, and 17 (8%) consumed cannabis orally only (see S-6; Tables S-3, S-4 and S-4a).

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Adverse events

Serious Adverse Events

Twenty-eight (13%) subjects 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 two groups (unadjusted OR=0.64, 95% CI=0.38-1.04). 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=0.82, 95% CI=0.46-1.46).

SAEs are shown in Table 2. The most common categories were “Surgical and medical procedures” and “Gastrointestinal disorders” in cannabis (n=10, 25% and n=10, 25% respectively) and control groups (n=11, 20%, and n=7, 13% respectively) (Table S-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 control subjects died over the course of the trial, one by suicide and the other a death in the operating room following emergency treatment for abdominal pain; there were no deaths in the cannabis group.

Treatment was permanently stopped 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.

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Non-serious adverse events

Most patients in the cannabis-treatment (190/215; 88.4%) and control (184/216; 85.2%) groups experienced at least 1 non-serious AE, with a median of 3 events per subject (range 0-16; interquartile range 2-5) among cannabis users and a median of 2 events per subject (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=0.75-2.32).

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 subjects, the occurrence of events, and corresponding rates within each MedDRA SOC 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 (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 (Figure 2). Mild (420, 51.3%) or moderate (390, 47.7%) events were more common than severe ones (8, 1.0%) in the cannabis group. Non-serious AEs occurring more than once among cannabis

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users and assessed as certainly/very likely related to cannabis were somnolence (n=5, 0.6%), amnesia (n=4, 0.5%), cough (n=4, 0.5%), nausea (n=4, 0.5%), dizziness (n=3, 0.4%), euphoric mood (n=3, 0.4%), hyperhidrosis (n=2, 0.2%) and paranoia (n=2, 0.2%) (Table S-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%), while four (0.7%) were categorized as "severe" (abdominal pain, breast cancer, pulmonary embolism, and upper respiratory tract infection) (Tables S-6, S-7, S-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=0.57-2.04). Increasing the daily dose of cannabis did not lead to higher risks of SAEs or AEs. (Table S-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 one year was found between cannabis users and controls (Table S-12).

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Pulmonary function tests

After adjusting for tobacco smoking and other covariates, we did not find a significant change of SVC, FRC, and TLC over one year in the cannabis users. Residual volume was reduced (mean reduction 142ml), and a mean decline of 54mL in FEV_1 and a mean of 0.78% decrease in the FEV_1/FVC ratio was noted. The $FEF_{25-75\%}$ was lower with a mean decrease of 0.2; no change was observed in FVC (Tables S-13, S-14).

Blood tests

Seventy-eight patients in the cannabis group had blood tests conducted at baseline and at one year. There were no changes observed in liver, renal, and endocrine function (Tables S-14, S-15, S-16).

Efficacy measures

Pain intensity

Compared to baseline, a significant reduction in average pain intensity over one year was observed in the cannabis group (change 0.92; 95% CI=0.62, 1.23) but not in controls (change 0.18; 95% CI=-0.13, 0.49). After adjusting for confounders, a greater reduction of pain was observed among cannabis users than controls (difference =1.10, 95% CI=0.72, 1.56) (Figure 3; Tables S-17, S-18).

Quality of life

With regard to the change in Physical Component Summary (PCS) score, a significant improvement from baseline was observed in both groups at the 6- and 12-month clinic visits. The analysis of the change in the PCS indicated greater

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improvement of physical function in cannabis users than in controls (2.36 point greater improvement at 6-month, 95% CI=0.84, 3.88; and 1.62 points at 1-year, 95% CI= 0.10, 3.14). No within-group nor between-group differences for the Mental Component Summary (MCS) were observed. (Table S-24).

Pain and other symptoms

The sensory component of pain was reduced over one year in cannabis users compared to controls (Tables S-19, S-20). The total symptom distress score of the ESAS was also improved in cannabis users over one year (Tables S-21, S-22). The total mood disturbance scale of the POMS showed significant improvement for cannabis users compared to controls, with improvements found in the tension-anxiety, depression-dejection, anger-hostility and fatigue-inertia subscales (Tables S-23, S-24).

Discussion

To our knowledge, this is the first cohort study of the long term safety of medical cannabis use ever conducted. Over one year, we identified 40 SAEs among 28 subjects, and 818 non-serious AEs among 190 subjects 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 to 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].

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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 AE 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 one year of follow-up compared to 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 FEV_1 and a mean 1% decrease in FEV_1/FVC ratio over one year.

Neurocognitive function improved in both groups. This finding differs from that found in recreational users of cannabis where a meta-analysis of 15 studies investigating the effects of recreational cannabis use on neurocognitive performance [6] suggested that long-term cannabis users performed significantly poorer on tests of memory and attention than short-term users [11]; in that study, both groups consumed similar amounts of cannabis (median 7 g/week, range: 0.3-57), and there was no difference on 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 one year.

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With respect to secondary efficacy measures, we noted significant improvements in pain intensity and the physical dimension of quality of life over one year among the cannabis users compared to controls; there was also significant improvement among cannabis users in measures of the sensory component of pain, symptom distress, and total mood disturbance compared to controls. These findings, while 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 subjects (177 person-years) in the cannabis group and 216 controls (204 person-years) 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 0.20 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 subjects 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”.

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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), subjects 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 with that of the controls.

Finally, confounding by indication due to selective prescribing is another potential source of bias [15]. This bias may exist in our study due to the fact that 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 two 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 as 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.

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Despite these limitations, this study improves our knowledge about the safety of medical cannabis. Caution should be exercised in interpreting these results to 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 adverse effects of medical cannabis are modest and comparable quantitatively and qualitatively to prescription cannabinoids. The results suggest that cannabis at average doses of 2.5g/d in current cannabis users may be safe as part of carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate. However, safety concerns in naïve users cannot be addressed. Moreover, long term effects on pulmonary functions and neurocognitive functions beyond one year cannot be determined. Further studies with systematic follow-up are required to characterize safety issues among new cannabis users, and should be extended to allow estimation of longer term risks.

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Safety Monitoring Advisory Committee

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

Adverse Event Adjutication Committee

Mark Ware, Mary Lynch

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Figure legends

Figure 1. COMPASS CONSORT Flow Diagram

Figure 2. Unadjusted Incidence Rate Ratios of non-serious adverse events by System Organ Class

Figure 3. Changes in pain intensity over one year (data only shown for subjects with complete data at all time points; n=145 (cannabis), n= 157 (controls)

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Figure 1. COMPASS CONSORT Flow Diagram

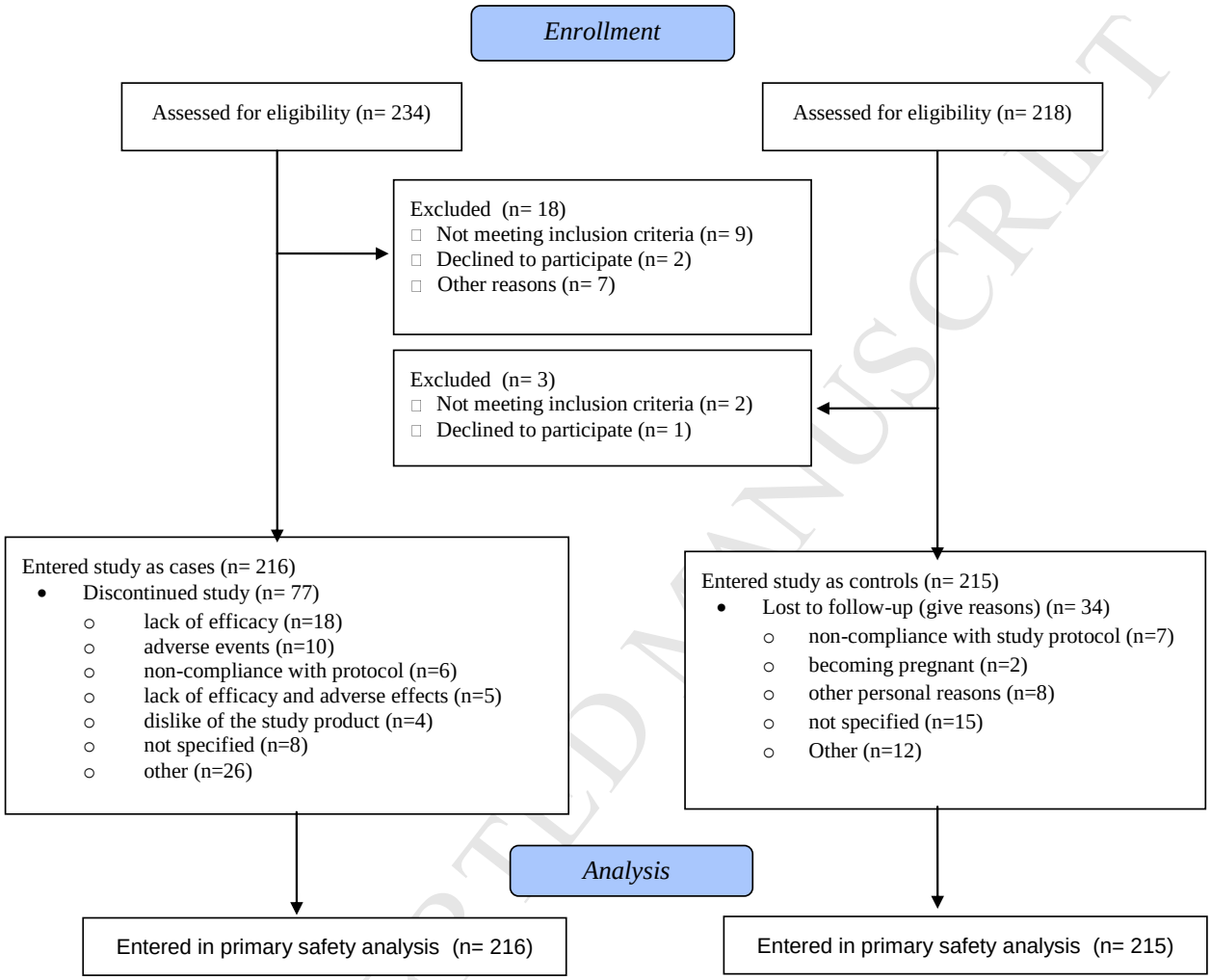

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Figure 2. Unadjusted Incidence Rate Ratios of non-serious adverse events by MedDRA System Organ Class

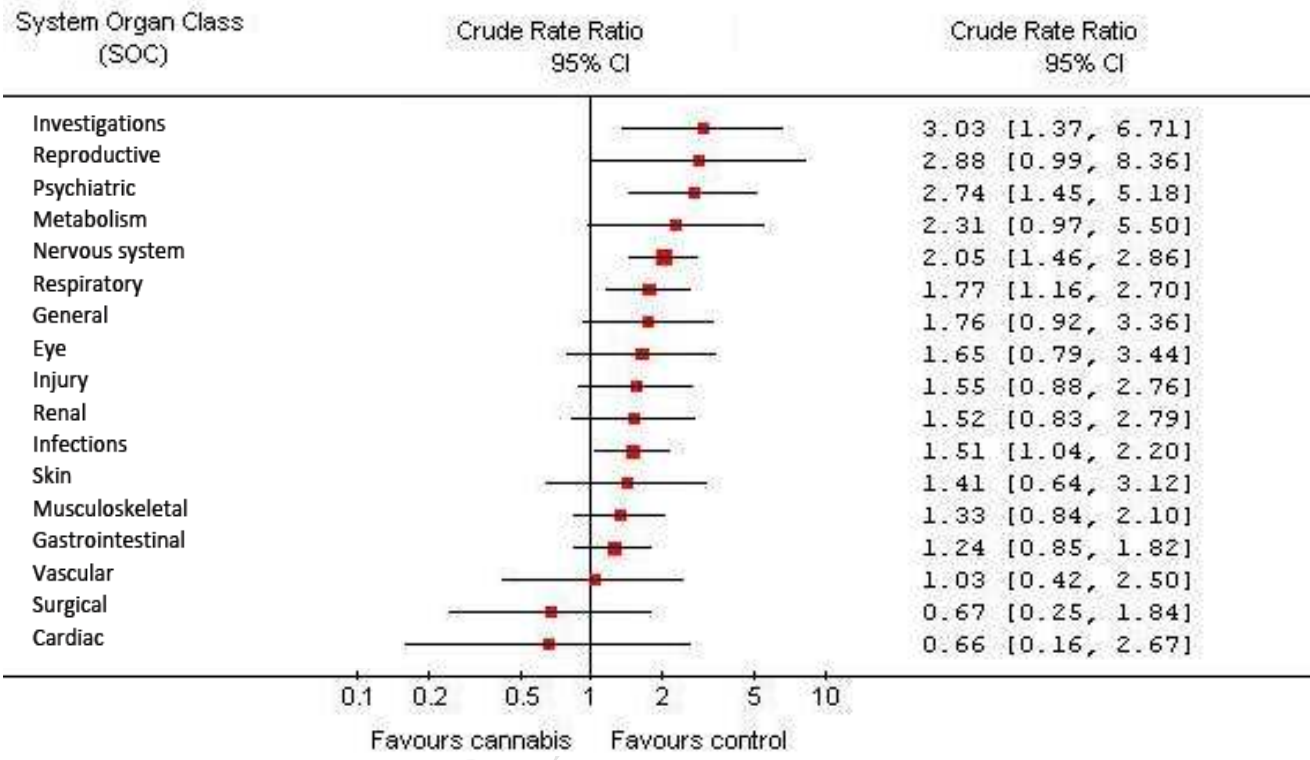

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Figure 3. Changes in pain intensity over one year

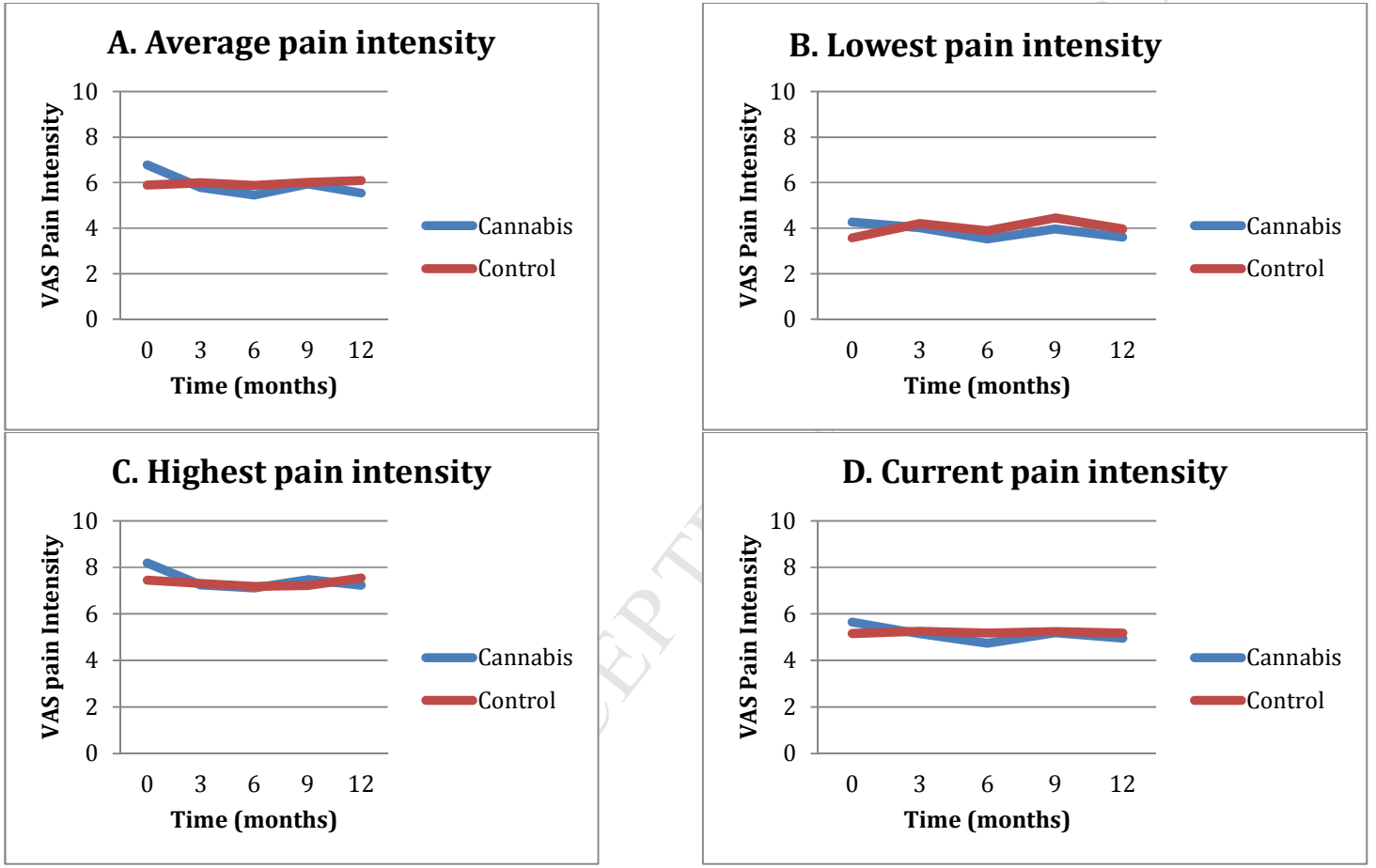

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Table 1. Baseline characteristics of study subjects, by exposure status

Characteristics	**Cannabis group (N=215)**	**Control group (N=216)**	**P**
Age at enrollment[1]	45.5 (19-82)	52.4 (21-83)	<0.001
Gender (% male)[2]	110 (51.2%)	76 (35.2%)	<0.001
Education (% University/College)[2]	111 (51.6%)	122 (56.5%)	0.14
Married; N (%)[2]	133 (61.9%)	140 (64.8%)	0.52
Disabled; N (%)[2]	129 (60.0%)	102 (47.2%)	0.01
Tobacco status[2,4]			0.01
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[2]			0.05
Currently drinking	166 (77.2%)	149 (69.0%)	
Not currently drinking	49 (22.8%)	67 (31.0%)	
Past cannabis use[2,5]			<0.001
Current cannabis users	141 (65.6%)	0	
Ex-cannabis users	58 (27.0%)	70 (32.4%)	
Naïve users	16 (7.4%)	146 (67.6%)	
Drug Abuse Screening Test[6]			<0.0001
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[2]			0.40
Nociceptive	35 (16.3%)	39 (18.1%)	
Neuropathic	83 (38.6%)	70 (32.4%)	
Both	97 (45.1%)	107 (49.5%)	
Average pain intensity[1]	6.6 (0-10)	6.1 (0-10)	0.002
Duration of pain (years)[3]	8.0 (0-54)	7.0 (0-82)	0.42
Medications			
Opioids[2]	118 (54.9%)	143 (66.2%)	0.02
Antidepressants[2]	101 (47.0%)	128 (59.3%)	0.01
Anticonvulsants[2]	94 (43.7%)	118 (54.6%)	0.02

[1]Mean (range), Student T-test

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[2]Number of patients (proportion), Chi-square
[3]Median (range), the Wilcoxon Rank Sum Test
[4]"Current smokers" were those who reported smoking at baseline interview; "ex smokers" were those who reported abstinence from cigarettes at baseline; "never smokers" were those who reported never smoking at baseline interview.
[5]"Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported using cannabis but were not using at baseline interview; "naïve user" were those who reported never using cannabis prior to baseline interview.
[6] Fisher's Exact Test

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Table 2. Serious adverse events (SAEs) categorized by System Organ Class (SOC)

Serious Adverse Events	**Cannabis group**		**Control group**	
System Organ Class (MedDRA)	**Number of events**	**Rate[1]**	**Number of events**	**Rate[1]**
Surgical and medical procedures	10	5.65	11	5.39
Gastrointestinal disorders	10	5.65	7 [2]	3.43
Musculoskeletal and connective tissue disorders	5	2.82	6	2.94
Injury, poisoning and procedural complications	4	2.26	1	0.49
Renal and urinary disorders	3	1.69	1	0.49
Nervous system disorders	2	1.13	4	1.96
Respiratory, thoracic and mediastinal disorders	1	0.56	7	3.43
Infections and infestations	1	0.56	5	2.45
Vascular disorders	1	0.56	3	1.47
Metabolism and nutrition disorders	1	0.56	2	0.98
Psychiatric disorders	1	0.56	2[3]	0.98
Investigations	1	0.56	0	0.00
General disorders and administration site conditions	0	0.00	3	1.47
Blood and lymphatic system disorders	0	0.00	1	0.49
Eye disorders	0	0.00	1	0.49
Hepatobiliary disorders	0	0.00	1	0.49
Immune system disorders	0	0.00	1	0.49
Total	**40**	**22.60 [4]**	**56**	**27.45 [4]**
Total number of patients	**28**	**13.02% [5]**	**42**	**19.44% [5]**

[1]Unit: n/ 100 person-years
[2]One patient died in the operating room.
[3]One patient committed suicide.
[4]The rates of serious adverse events did not differ significantly between these two groups (Unadjusted incidence rate ratio=0.82, 95% CI=0.46-1.46).
[5]The risk of having reported at least 1 SAE was not significantly different between two groups (Unadjusted odds ratio=0.62, 95% CI=0.37-1.04).

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Table 3. Summary of non-serious adverse events (SAEs) categorized by System Organ Class (SOC)

Non-serious adverse events	Cannabis group			Control group		
System Organ Class (MedDRA)	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	0.93	71	93	0.46
Gastrointestinal disorders	66	109	0.62	70	101	0.50
Respiratory, thoracic and mediastinal disorders	77	103	0.58	49	67	0.33
Infections and infestations	63	89	0.50	49	68	0.33
Musculoskeletal and connective tissue disorders	49	77	0.44	50	67	0.33
Psychiatric disorders	47	57	0.32	21	24	0.12
General disorders and administration site conditions	29	35	0.20	20	23	0.11
Injury, poisoning and procedural complications	23	31	0.18	21	23	0.11
Renal and urinary disorders	23	29	0.16	18	22	0.11
Skin and subcutaneous tissue disorders	18	22	0.12	17	18	0.09

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Non-serious adverse events	Cannabis group			Control group		
System Organ Class (MedDRA)	**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)**
Investigations	21	21	0.12	8	8	0.04
Eye disorders	16	20	0.11	13	14	0.07
Reproductive system and breast disorders	11	15	0.08	5	6	0.03
Metabolism and nutrition disorders	14	14	0.08	7	7	0.03
Vascular disorders	8	8	0.05	9	9	0.04
Surgical and medical procedures	6	7	0.04	10	12	0.06
Cardiac disorders	4	4	0.02	7	7	0.03
Blood and lymphatic system disorders	4	4	0.02	0	0	0.00
Ear and labyrinth disorders	3	3	0.02	5	5	0.02
Immune system disorders	1	2	0.01	3	3	0.01
Hepatobiliary disorders	2	2	0.01	1	1	0.00
Endocrine disorders	1	1	0.01	0	0	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0.00	3	3	0.01
Total	191	818	4.62	186	581	2.85
Unadjusted odds ratio (95% CI)	1.28 (0.72, 2.28)			1		
Unadjusted incidence rate ratio (95% CI)	1.62 (1.34, 1.97)			1		

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Table 4: Unadjusted and adjusted rate ratios of adverse events for medical cannabis

	Cannabis	Control	Unadjusted IRR (95% CI)	Adjusted IRR[1] (95% CI)
All patients				
Number of patients	215	216	--	--
Cumulative person-years	176.9	204.1	--	--
Number of SAEs	40	56	0.82 (0.46-1.46)	1.08 (0.57-2.04)
Number of AEs	816	574	1.64 (1.35-1.99)	1.74 (1.42-2.14)
Patients excluding "current cannabis users"[2] at baseline				
Number of patients	74	216	--	--
Cumulative person-years	52.2	204.1	--	--
Number of SAEs	20	56	1.40 (0.66-2.93)	1.77 (0.72-4.32)
Number of AEs	316	574	2.15 (1.69-2.74)	2.07 (1.59-2.70)

IRR=Incidence rate ratio; 95% CI=95% confidence interval;
SAE=serious adverse event; AE=non-serious adverse event

1. 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.
2. "Current cannabis users" were those who reported using cannabis and were still using at baseline interview.

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Table 5. Neurocognitive measures in cannabis-exposed and control subjects over one year[1]

	Group	Number of subjects	Baseline	6 months	12 months
WMS®-III [2]					
Verbal paired associates I					
Recall	Cannabis	77	16.92 (7.69)	20.97 (8.01)	22.97 (7.56)
(Max: 32 points)	Control	53	17.42 (7.85)	19.25 (8.70)	22.72 (8.53)
Verbal paired associates II					
Recall	Cannabis	76	5.67 (2.35)	6.29 (2.05)	6.54 (1.81)
(Max: 8 points)	Control	53	5.45 (2.55)	6.02 (2.45)	6.64 (1.95)
Recognition	Cannabis	76	23.80 (0.80)	23.92 (0.32)	23.78 (1.41)
(Max: 24 points)	Control	53	23.94 (0.23)	23.98 (0.14)	23.98 (0.14)
WAIS®-III [3]					
Digit symbol-coding	Cannabis	72	52.21 (21.60)	53.31 (23.64)	55.90 (23.11)
(Max: 133 points)	Control	53	49.94 (18.82)	54.64 (20.26)	55.00 (17.65)
Picture arrangement	Cannabis	76	11.64 (3.91)	13.67 (5.03)	14.18 (4.36)
(Max: 22 points)	Control	53	11.42 (4.65)	13.32 (5.14)	14.24 (5.53)

[1]Data are presented as mean (SD).
[2]WMS®-III: Wechsler Memory Scale – Third Edition
[3]WAIS®-III: Wechsler Adult Intelligence Scale – Third Edition

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

Supplementary materials

Mark A. Ware MBBS MRCP MSc[1], Tongtong Wang BMed PhD[2], Stan Shapiro PhD[2,3], Jean-Paul Collet MD PhD[4] for the COMPASS study team*

*Aline Boulanger MD[5], John M. Esdaile MD[6], Alan Gordon MD[7], Mary Lynch MD[8], Dwight E. Moulin MD[9], Colleen O'Connell MD[10]

Institutional affiliations:

[1]Departments of Anesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada
[2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
[3]Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada
[4]Department of Pediatrics, University of British Columbia; Child and Family Research Institute, Vancouver, British Columbia, Canada
[5]Department d'anesthesie, Université de Montreal, Montreal, Quebec, Canada
[6]Division of Rheumatology, University of British Columbia, Vancouver, British Columbia, Canada
[7]Department of Neurology, University of Toronto, Toronto, Ontario, Canada
[8]Departments of Anesthesia, Psychiatry and Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada
[9]Departments of Clinical Neurological Sciences and Oncology, Western University, London, Ontario, Canada
[10]Department of Physical Medicine and Rehabilitation, Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada

Address for reprints and correspondence:

Dr. Mark A. Ware
E19.145 Montreal General Hospital
1650 Cedar Avenue
Montreal, Quebec H9S 4Y5
Canada
Tel: (514) 934-8222
Fax: (514) 934-8096
Email: mark.ware@mcgill.ca

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1 Study drug

Cannabis was provided to the site pharmacies as a milled herbal product with 10mm grind size and 15% humidity in sealed 30g gold foil packages, certified free of contaminants and impurities.

2 Statistical plans

2.1 Adverse event analysis

A Poisson Regression model was used to examine the association between medical cannabis use and adverse events compared with controls. Specific variables concerning cannabis use and AEs were examined to identify potential confounders or effect modifiers. These variables included age, gender, disability status, past cannabis use, tobacco use, alcohol use, baseline pain intensity, concomitant medication use (opioids, antidepressants, anticonvulsants) and study sites. Potential confounders and effect modifiers were examined in the final regression model. Goodness of Fit was assessed to evaluate overdispersion.

We calculated the proportion of patients who experienced at least one event, serious, and non-serious adverse events in both groups.

2.2 Neurocognitive test analyses

Raw and scaled scores of each subtest of neurocognitive function were considered as a continuous measure to compare their changes over time. Only subjects with complete raw scores of each subtest at both time points were included in each analysis. A random effects model with a random

intercept for patient was fitted to look at effects of exposure, follow-up time, and interaction of exposure and follow-up time after adjusting for potential confounders or covariates. Follow-up time was defined as a dummy variable with baseline as a reference group (i.e. 6 months vs. baseline, and 12 months vs. baseline). A separate multiple regression analysis was performed for each of the neurocognitive subtests, except for Verbal Paired Associates II—Recognition test since 95% of participants obtained a maximum score of 24 on this test. As analysis of both raw and scaled scores gave virtually identical results, only the raw scores are presented in the tables.

2.3 Respiratory function

Paired t-tests were performed to examine the effects of cannabis on pulmonary function.

3 Modifications to Protocol

Expected incidences in the control group required for a specified power (0.5, 0.6, 0.7, 0.8, and 0.9) were estimated at a 5% level of statistical significance. A rate ratio of 1.5 can be detected with over 80% power for an incidence rate of SAEs in the control group above 0.15 case/person-year. The initial sample size target was 350 cannabis-using subjects and 1050 (3:1) subjects in the control group matched by age, disease and site (see Protocol modifications, below).

However, early in the implementation of the study, the feasibility of recruiting 1050 controls (an average of 150 controls per clinic) was questioned. In addition, clinic visit scheduling was perceived to be too much

of a burden for the patients. The protocol was therefore revised with respect to the following points:

1. Remove the requirement for cannabis users recruited after March 1st 2006 to undergo blood testing at baseline and during follow-ups;
2. Remove the requirement for baseline and follow-up neurocognitive testing in all subjects recruited after March 1st 2006 in both the cannabis users and the control group;
3. Decrease the number of control subjects from 1050 to 350;
4. Switch the 2-, 3- and 9-month clinic visits for subjects in the cannabis group recruited after March 1st 2006 to telephone interviews instead.

All protocol modifications were approved by all appropriate regulatory and ethics committees.

4 Adjudication of adverse events

To identify and address any differences in the way study sites classified the causality and severity of adverse events, an Adjudication Committee was established to review the classification of adverse events reported during this study. Two clinical reviewers independently assessed the seriousness, severity and causality of each event. The committee then met to compare assessments and to discuss the discrepancies and means to resolve them. Suggestions for amendments to the database were passed on to the Steering Committee for approval and any necessary database changes made.

5 Study withdrawals

The most common reasons for early discontinuation of study drug in cannabis group were lack of efficacy (18 patients), adverse events (10), non-compliance with the protocol (6), lack of efficacy and adverse effects (5), dislike of the study product (4), and not specified (8). Seventeen patients discontinued the study due to non-medical reasons, for example, moving to other cities and family reasons. The most common reasons for early discontinuation among control patients were non-compliance with the study protocol (7), becoming pregnant (2), other personal reasons (8), and not specified (15).

Adverse events led to treatment interruptions in 24 (60%) events, among which 22 were temporary suspensions with a median of 3 days (range 1-37 days).

6 Additional dosing data

“Current cannabis users” (median 2.8 g/d; range: 0.2-13.4) consumed more cannabis than “ex-cannabis users” (median: 1.8 g/d; range: 0.1-3.7) or “cannabis-naïve” (2.0 g/d; range: 0.1-3.4) over the course of the study ($p<0.0001$).

7 Adverse event reports

Severe AEs among cannabis users included diverticulitis, haematemesis, joint arthroplasty, mania, motor dysfunction, multiple sclerosis, muscle spasms, and vomiting. Of these, only mania was considered as “certainly/very likely” related to the study cannabis.

The most common AEs in the cannabis group were headache (n=41, 5.01%), nasopharyngitis (n=37, 4.52%), nausea (n=36, 4.40%), somnolence (n=29, 3.55%) and dizziness (n=27, 3.30%) (Table S-8).

Three hundred and eight non-serious AEs, considered as "certainly/very likely", "probably/likely" or "possibly" related to the study cannabis, were reported by 126 patients. Those assessed as "certainly/very likely" related to the study cannabis were somnolence (5), amnesia (4), cough (4), nausea (4), dizziness (3), euphoric mood (3), hyperhidrosis (2), paranoia (2), anxiety (1), cognitive disorder (1), confusional state (1), decreased appetite (1), headache (1), increased appetite (1), lethargy (1), mania (1), oral discomfort (1), rash (1), sedation (1), vision blurred (1), and vomiting (1) (Table S-7).

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8 Additional tables

Table S-1: Duration of follow up, according to study groups

Duration	Cannabis (N=215)	Control (N=216)
<30 days	3 (1.4%)	3 (1.4%)
30 days to <3 months	6 (2.8%)	0
3 months to <6 months	10 (4.6%)	3 (1.4%)
6 months to <9 months	28 (13.0%)	13 (6.0%)
9 months to <12 months	20 (9.3%)	15 (6.9%)
> 12 months	148 (68.8%)	182 (84.3%)
Range (days)	7-551	28-567
Total person-years (years)	176.9	204.1

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Table S-2. Baseline characteristics of subjects, by discontinuation status[1]

Characteristics	**Completed subjects (N=330)**	**Discontinued subjects (N=101)**	**P**
Age at enrollment (years) [2]	49.5 (10.5)	47.2 (11.5)	0.09
Gender (% of male)	138 (41.8%)	48 (47.5%)	0.31
Education (% of University/College)[3]	171 (53.2%)	62 (63.2%)	0.08
N (%) of being married	211 (63.9%)	62 (61.4%)	0.64
N (%) of being disabled	178 (53.9%)	53 (52.5%)	0.80
Tobacco status at enrollment			0.50
Current smokers	116 (35.2%)	42 (41.6%)	
Ex smokers	117 (35.4%)	33 (32.7%)	
Never smokers	97 (29.4%)	26 (25.7%)	
Alcohol status at enrollment			0.07
Current drinking	234 (70.9%)	81 (80.2%)	
Ever/never drinking	96 (29.1%)	20 (19.8%)	
Past cannabis use[4]			
Control group	N=182	N=34	0.05
Ex cannabis users	54 (29.7%)	16 (47.1%)	
Naïve users	128 (70.3%)	18 (52.9%)	
Cannabis group	N=148	N=67	<0.001
Current cannabis users	109 (73.6%)	32 (47.8%)	
Ex cannabis users	32 (21.6%)	26 (38.8%)	
Naïve users	7 (4.7%)	9 (13.4%)	
Average pain intensity [2]	6.4 (1.9)	6.3 (1.9)	0.72
Duration of pain (years)[5]	8 (0.5-82)	7 (1-51)	0.53
Type of pain			0.76
Nociceptive	55 (16.7%)	19 (18.8%)	
Neuropathic	120 (36.4%)	33 (32.7%)	
Both	154 (46.8%)	49 (48.5%)	

[1]Data are presented as number (percentage) unless otherwise indicated.
[2]Mean (SD)
[3]Completed subjects=321; discontinued subjects=98

[4]"Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported having used cannabis but were not using at baseline interview; "naïve users" were those who reported never using cannabis prior to baseline interview.

[5]Median (range), the Wilcoxon Rank Sum Test

Dosing patterns and characteristics

Table S-3. Mode of cannabis administration during the study

Mode of administration	**Number of patients**	**Percentage**
Smoking cannabis at least once	*188*	*88.7%*
Smoking only	58	27.4%
Smoking and oral	93	43.9%
Smoking, oral and vaporized	29	13.7%
Smoking and vaporized	8	3.8%
Never smoking	*24*	*11.3%*
Oral only	17	8.0%
Vaporized only	1	0.5%
Oral and vaporized	6	2.8%
Total	212 [1]	100.0%

1. Three patients did not provide information about mode of administration.

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Table S-4. Daily dosage of cannabis during the study

By category	Number of patients	Percentage
<1 gram/day	29	13.6%
>=1 and <2 grams/day	53	24.8%
>=2 and <3 grams/day	73	34.1%
>=3 grams/day	59	27.6%

Table S-4a Median daily dose of cannabis used, shown by participating clinic

Clinic centers	Median (grams/day)	Range (grams/day)	Interquartile range (grams/day)
Halifax (n=42)	2.97	0.49-3.67	1.93-3.00
Toronto (n=33)	2.71	0.53-3.59	2.14-3.14
Hotel Dieu (n=17)	3.01	0.71-4.43	1.02-3.68
London (n=30)	2.50	0.56-3.51	1.97-2.89
Fredericton (n=31)	2.46	1.02-3.95	1.66-3.01
Vancouver (n=19)	1.55	0.51-3.25	0.98-2.23
Montreal General Hospital (n=42)	1.30	0.09-13.40	0.89-2.49
Entire study (N=214) [1]	2.46	0.09-13.40	1.52-3.00

1. One patient did not have information on the consumption of study cannabis.

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Table S-5: Detailed listing of serious adverse events by cannabis exposure status

Serious adverse event[1]	**Cannabis**		**Control**	
	Number of events	**Rate[2]**	**Number of events**	**Rate[2]**
Surgical and medical procedures	*10*	*5.65*	*11*	*5.39*
Knee arthroplasty	2		1	
Surgery	1		3	
Hysterectomy	1		1	
Amputation	1		0	
Bilateral orchidectomy	1		0	
Cholecystectomy	1		0	
Elective procedure	1		0	
Joint arthroplasty	1		0	
Oophorectomy	1		0	
Colostomy	0		1	
Hip arthroplasty	0		1	
Mastectomy	0		1	
Medical device implantation	0		1	
Oesophagogastric fundoplasty	0		1	
Vaginal operation	0		1	
Gastrointestinal disorders	*10*	*5.65*	*7*	*3.43*
Abdominal pain	3		3 (1 died)	
Intestinal obstruction	3		0	
Rectal haemorrhage	1		1	
Gastrointestinal haemorrhage	1		0	

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Nausea	1		0	
Vomiting	1		0	
Diarrhoea	0		2	
Pancreatitis	0		1	
Musculoskeletal and connective tissue disorders	*5*	*2.82*	*6*	*2.94*
Back pain	2		0	
Arthralgia	1		2	
Musculoskeletal pain	1		1	
Musculoskeletal chest pain	1		0	
Neck pain	0		2	
Fistula	0		1	

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

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Table S-5 (cont'd)

Serious adverse event[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Injury, poisoning and procedural complications	*4*	*2.26*	*1*	*0.49*
Rib fracture	2		0	
Limb injury	1		0	
Patella fracture	1		0	
Pelvic fracture	0		1	
Renal and urinary disorders	*3*	*1.69*	*1*	*0.49*
Nephrolithiasis	3		0	
Urinary tract infection	0		1	
Nervous system disorders	*2*	*1.13*	*4*	*1.96*
Convulsion	1		0	
Multiple sclerosis	1		0	
Dizziness	0		2	
Headache	0		1	
Hypoaesthesia	0		1	
Respiratory, thoracic and mediastinal disorders	*1*	*0.56*	*7*	*3.43*
Pulmonary embolism	1		1	
Bronchospasm	0		3	
Pneumonia	0		3	

Infections and infestations	*1*	*0.56*	*5*	*2.45*
Post procedural infection	1		1	
Abscess	0		1	
Infection	0		1	
Joint abscess	0		1	
Sepsis	0		1	
Vascular disorders	*1*	*0.56*	*3*	*1.47*
Aneurysm arteriovenous	1		0	
Hypertension	0		1	
Hypovolaemic shock	0		1	
Syncope	0		1	

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

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Table S-5 (cont'd)

Serious adverse event[1]	Cannabis		Control	
	Number of events	Rate[2]	Number of events	Rate[2]
Metabolism and nutrition disorders	*1*	*0.56*	*2*	*0.98*
Dehydration	1		1	
Diabetic coma	0		1	
Psychiatric disorders	*1*	*0.56*	*2*	*0.98*
Alcohol problem	1		0	
Completed suicide	0		1 (died)	
Suicide attempt	0		1	
Investigations	*1*	*0.56*	*0*	*0.00*
Biopsy skin	1		0	
General disorders and administration site conditions	*0*	*0.00*	*3*	*1.47*
Pain	0		2	
Chest pain	0		1	
Blood and lymphatic system disorders	*0*	*0.00*	*1*	*0.49*
Lymphadenopathy	0		1	
Eye disorders	*0*	*0.00*	*1*	*0.49*
Vision blurred	0		1	

Hepatobiliary disorders	*0*	*0.00*	*1*	*0.49*
Liver abscess	0		1	
Immune system disorders	*0*	*0.00*	*1*	*0.49*
Hypersensitivity	0		1	
Total	40	22.61	56	27.45

1. Ordered by the rate of serious adverse events in the cannabis group
2. Incidence rate=events/ 100 person-years

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Table S-6: Most frequently reported non-serious adverse events[1]

Adverse Event (Preferred term)	**Cannabis**	**Control**
Headache	40 (4.9%)	24 (4.2%)
Nasopharyngitis	37 (4.5%)	22 (3.8%)
Nausea	36 (4.4%)	21 (3.7%)
Somnolence	29 (3.6%)	10 (1.7%)
Dizziness	27 (3.3%)	21 (3.7%)
Upper respiratory tract infection	21 (2.6%)	21 (3.7%)
Influenza	19 (2.3%)	24 (4.2%)
Pharyngolaryngeal pain	19 (2.3%)	8 (1.4%)
Vomiting	17 (2.1%)	14 (2.4%)
Cough	16 (2.0%)	3 (0.5%)
Rash	14 (1.7%)	9 (1.6%)
Diarrhea	13 (1.6%)	10 (1.9%)
Urinary tract infection	13 (1.6%)	11 (1.9%)
Back pain	12 (1.5%)	9 (1.6%)
Muscle spasms	11 (1.3%)	4 (0.7%)
Depression	10 (1.2%)	10 (1.7%)
Anxiety	10 (1.2%)	2 (0.3%)

1. Data are presented as occurrences of events (percentage).

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Table S-7. Causality of non-serious adverse events (cannabis group only) [1]

System Organ Class (MedDRA)	Certain	Probable/ likely	Possible	Unlikely
Nervous system disorders	16 (40%)	51 (44%)	35 (23%)	60 (12%)
Gastrointestinal disorders	6 (15%)	13 (11%)	25 (17%)	61 (12%)
Respiratory, thoracic and mediastinal disorders	4 (10%)	16 (14%)	32 (21%)	51 (10%)
Infections and infestations	0	0	1 (1%)	86 (17%)
Musculoskeletal and connective tissue disorders	0	2 (2%)	3 (2%)	72 (14%)
Psychiatric disorders	8 (20%)	16 (14%)	18 (12%)	15 (3%)
General disorders and administration site conditions	2 (5%)	3 (3%)	6 (4%)	24 (5%)
Injury, poisoning and procedural complications	0	0	2 (1%)	29 (6%)
Renal and urinary disorders	0	0	2 (1%)	27 (5%)
Skin and subcutaneous tissue disorders	1 (3%)	0	2 (1%)	17 (3%)
Investigations	0	3 (3%)	7 (5%)	11 (2%)
Eye disorders	1 (3%)	4 (3%)	4 (3%)	11 (2%)
Reproductive system and breast disorders	0	1 (<1%)	4 (3%)	10 (2%)
Metabolism and nutrition disorders	2 (5%)	3 (3%)	4 (3%)	5 (1%)
Vascular disorders	0	1 (<1%)	1 (<1%)	6 (1%)
Surgical and medical procedures	0	0	0	6 (1%)
Cardiac disorders	0	1 (<1%)	3 (2%)	0
Blood and lymphatic system disorders	0	0	0	4 (<1%)
Ear and labyrinth disorders	0	2 (2%)	0	2 (<1%)
Immune system disorders	0	0	1 (<1%)	3 (<1%)
Hepatobiliary disorders	0	0	0	2 (<1%)
Endocrine disorders	0	0	0	1 (<1%)
Total[2]	40	116	150	503

[1]Data are presented as occurrences of events (percentage)
[2]Causality of 7 adverse events was "unclassifiable".

Table S-8. Detailed listing of non-serious AEs

System organ class **Preferred Terms**	**Cannabis group**		**Control group**	
Nervous system disorders	*164*	*20.0%*	*93*	*16.0%*
Headache	41		24	
Somnolence	29		10	
Dizziness	27		21	
Amnesia	9		1	
Migraine	7		2	
Paraesthesia	6		2	
Cognitive disorder	6		0	
Sedation	5		1	
Hypoaesthesia	4		5	
Lethargy	4		1	
Memory impairment	4		0	
Syncope	3		4	
Tremor	3		4	
Insomnia	2		4	
Multiple sclerosis	2		3	
Sensory disturbance	2		0	
Balance disorder	1		2	
Burning sensation	1		2	
Vertigo	1		2	
Convulsion	1		1	
Facial palsy	1		1	
Speech disorder	1		1	
Gait disturbance	1		0	

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Motor dysfunction	1		0	
Movement disorder	1		0	
Sinus headache	1		0	
Blindness	0		1	
Neuropathy peripheral	0		1	
Gastrointestinal disorders	*109*	*13.3%*	*101*	*17.4%*
Nausea	36		21	
Vomiting	17		14	
Diarrhoea	13		11	
Dry mouth	7		2	
Abdominal pain	5		12	
Constipation	5		7	
Stomach discomfort	3		5	
Dyspepsia	3		3	
Gastroenteritis viral	3		1	
Dysphagia	2		2	
Dental caries	2		1	
Abdominal distension	2		0	
Diverticulitis	2		0	
Gastroenteritis	1		6	
Toothache	1		3	
Abdominal pain upper	1		2	
Melaena	1		1	
Oral discomfort	1		1	
Gingival recession	1		0	
Haematemesis	1		0	
Hiatus hernia	1		0	
Rectal haemorrhage	1		0	

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Gingivitis	0		2	
Abdominal discomfort	0		1	
Diverticulum	0		1	
Faecal incontinence	0		1	
Gastrooesophageal reflux disease	0		1	
Gingival bleeding	0		1	
Hiccups	0		1	
Mouth ulceration	0		1	
Respiratory, thoracic and mediastinal disorders	*103*	*12.6%*	*67*	*11.5%*
Upper respiratory tract infection	21		22	
Pharyngolaryngeal pain	19		8	
Cough	16		3	
Sinusitis	8		10	
Bronchitis	6		5	
Pneumonia	6		4	
Throat irritation	6		1	
Dyspnoea	4		3	
Lower respiratory tract infection	3		3	
Respiratory tract congestion	2		1	
Respiratory tract infection	2		1	
Sinus congestion	2		0	
Wheezing	1		1	
Dry throat	1		0	
Haemoptysis	1		0	
Nasal congestion	1		0	
Pharyngeal oedema	1		0	
Pulmonary bulla	1		0	

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Rhinitis	1		0	
Rhinorrhoea	1		0	
Laryngitis	0		1	
Pharyngitis	0		1	
Productive cough	0		1	
Pulmonary embolism	0		1	
Throat tightness	0		1	
Infections and infestations	*89*	*10.9%*	*68*	*11.7%*
Nasopharyngitis	37		22	
Influenza	19		24	
Oral herpes	6		2	
Tooth infection	4		0	
Tooth abscess	3		6	
Cellulitis	3		5	
Fungal infection	3		0	
Gingival infection	2		1	
Abscess	1		0	
Abscess jaw	1		0	
Abscess oral	1		0	
Body tinea	1		0	
Herpes simplex	1		0	
Herpes zoster	1		0	
Infected cyst	1		0	
Oral candidiasis	1		0	
Prostate infection	1		0	
Skin infection	1		0	
Staphylococcal infection	1		0	
Viral infection	1		0	

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Infection	0		2	
Abscess limb	0		1	
Genital herpes	0		1	
Gingival abscess	0		1	
Localised infection	0		1	
Nail infection	0		1	
Tinea pedis	0		1	
Musculoskeletal and connective tissue disorders	*77*	*9.4%*	*67*	*11.5%*
Back pain	12		10	
Muscle spasms	11		4	
Arthralgia	8		10	
Pain in extremity	7		14	
Joint sprain	6		6	
Musculoskeletal chest pain	5		1	
Musculoskeletal pain	5		0	
Neck pain	3		4	
Muscular weakness	3		1	
Joint swelling	2		2	
Gout	2		1	
Arthritis	2		0	
Bursitis	2		0	
Sciatica	2		0	
Musculoskeletal stiffness	1		3	
Muscle strain	1		1	
Bone pain	1		0	
Muscle fatigue	1		0	
Muscle twitching	1		0	

Musculoskeletal disorder	1		0	
Pain in jaw	1		0	
Myalgia	0		2	
Bone cyst	0		1	
Bone development abnormal	0		1	
Chest wall cyst	0		1	
Coccydynia	0		1	
Fasciitis	0		1	
Joint stiffness	0		1	
Muscle spasticity	0		1	
Osteoarthritis	0		1	
Psychiatric disorders	*57*	*7.0%*	*24*	*4.1%*
Depression	10		10	
Anxiety	10		2	
Euphoric mood	9		0	
Disturbance in attention	5		2	
Confusional state	3		4	
Panic attack	2		1	
Paranoia	2		0	
Irritability	1		1	
Mood altered	1		1	
Abnormal behaviour	1		0	
Agitation	1		0	
Apathy	1		0	
Dissociation	1		0	
Exaggerated startle response	1		0	
Flat affect	1		0	
Flight of ideas	1		0	

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Hallucination	1		0	
Mania	1		0	
Nicotine dependence	1		0	
Restlessness	1		0	
Self esteem decreased	1		0	
Suicidal behaviour	1		0	
Withdrawal syndrome	1		0	
Delusion	0		1	
Mental disorder	0		1	
Stress	0		1	
General disorders and administration site conditions	*35*	*4.3%*	*23*	*4.0%*
Fatigue	8		3	
Asthenia	6		1	
Oedema peripheral	4		6	
Hyperhidrosis	4		1	
Chest pain	3		5	
Pain	2		0	
Inflammation	1		1	
Chest discomfort	1		0	
Cyst	1		0	
Feeling jittery	1		0	
Local reaction	1		0	
Local swelling	1		0	
Nodule	1		0	
Ulcer	1		0	
Oedema	0		3	
Chills	0		1	

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Malaise	0		1	
Pyrexia	0		1	
Injury, poisoning and procedural complications	*31*	*3.8%*	*23*	*4.0%*
Contusion	7		6	
Fall	5		5	
Limb injury	2		1	
Neck injury	2		1	
Soft tissue injury	2		0	
Wound	2		0	
Concussion	1		1	
Arthropod bite	1		0	
Back injury	1		0	
Blister	1		0	
Head injury	1		0	
Injection site haemorrhage	1		0	
Muscle injury	1		0	
Road traffic accident	1		0	
Skeletal injury	1		0	
Skin injury	1		0	
Thermal burn	1		0	
Skin laceration	0		2	
Ankle fracture	0		1	
Blood blister	0		1	
Foot fracture	0		1	
Infusion site haemorrhage	0		1	
Joint dislocation	0		1	
Rib fracture	0		1	

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Tooth fracture	0		1	
Renal and urinary disorders	*29*	*3.5%*	*22*	*3.8%*
Urinary tract infection	13		11	
Cystitis	4		3	
Urinary incontinence	3		1	
Dysuria	3		0	
Bladder pain	1		0	
Bladder transitional cell carcinoma	1		0	
Calculus bladder	1		0	
Renal cyst	1		0	
Stress urinary incontinence	1		0	
Urine odour abnormal	1		0	
Flank pain	0		2	
Kidney infection	0		2	
Haematuria	0		1	
Nephrolithiasis	0		1	
Pollakiuria	0		1	
Skin and subcutaneous tissue disorders	*20*	*2.4%*	*16*	*2.8%*
Rash	14		9	
Pruritus	2		0	
Dry skin	1		0	
Psoriasis	1		0	
Rash pruritic	1		0	
Skin lesion	1		0	
Ingrowing nail	0		2	
Alopecia	0		1	
Erythema	0		1	
Rash maculo-papular	0		1	

Skin irritation	0		1	
Skin reaction	0		1	
Investigations	*21*	*2.6%*	*8*	*1.4%*
Weight increased	6		3	
Weight decreased	5		2	
Blood pressure increased	2		1	
Biopsy liver	2		0	
Blood urine present	2		0	
Electrocardiogram abnormal	1		0	
Electroencephalogram abnormal	1		0	
Heart rate increased	1		0	
X-ray abnormal	1		0	
Hepatic enzyme increased	0		1	
Urethroscopy	0		1	
Eye disorders	*20*	*2.4%*	*14*	*2.4%*
Vision blurred	6		6	
Dry eye	3		0	
Conjunctivitis	2		1	
Eye infection	1		2	
Visual disturbance	1		1	
Asthenopia	1		0	
Conjunctival hyperaemia	1		0	
Corneal erosion	1		0	
Eye irritation	1		0	
Eye pain	1		0	
Eyes sunken	1		0	
Photophobia	1		0	
Cataract	0		1	

Eye inflammation	0		1	
Uveitis	0		1	
Visual field defect	0		1	
Reproductive system and breast disorders	*15*	*1.8%*	*6*	*1.0%*
Vaginal haemorrhage	3		1	
Vaginal infection	3		0	
Vulvovaginal mycotic infection	2		1	
Menorrhagia	2		0	
Breast mass	1		1	
Breast cyst	1		0	
Lactation disorder	1		0	
Vaginal pain	1		0	
Vulvovaginal discomfort	1		0	
Ovarian cyst	0		1	
Testicular swelling	0		1	
Vaginal candidiasis	0		1	
Metabolism and nutrition disorders	*14*	*1.7%*	*7*	*1.2%*
Increased appetite	7		0	
Decreased appetite	3		1	
Anorexia	2		2	
Hypercholesterolaemia	1		2	
Hypocalcaemia	1		0	
Hyperglycaemia	0		1	
Hypothyroidism	0		1	
Vascular disorders	*8*	*1.0%*	*9*	*1.5%*
Hypertension	1		5	
Haematoma	1		1	
Accelerated hypertension	1		0	

Aneurysm	1		0	
Circulatory collapse	1		0	
Haemangioma	1		0	
Skin ulcer	1		0	
Venous thrombosis	1		0	
Epistaxis	0		2	
Phlebitis	0		1	
Surgical and medical procedures	*7*	*0.9%*	*12*	*2.1%*
Tooth extraction	2		2	
Dental operation	2		0	
Elective surgery	1		2	
Arthroscopic surgery	1		0	
Joint arthroplasty	1		0	
Cyst removal	0		2	
Gingival graft	0		2	
Foot operation	0		1	
Mole excision	0		1	
Nail operation	0		1	
Wisdom teeth removal	0		1	
Cardiac disorders	*4*	*0.5%*	*7*	*1.2%*
Palpitations	3		2	
Tachycardia	1		0	
Atrial fibrillation	0		1	
Bradycardia	0		1	
Cardiovascular disorder	0		1	
Sinus arrhythmia	0		1	
Ventricular extrasystoles	0		1	
Ear and labyrinth disorders	*4*	*0.5%*	*5*	*0.9%*

Cerumen impaction	1		0	
Deafness	1		0	
Tinnitus	2		1	
Ear infection	0		3	
Ear pain	0		1	
Immune system disorders	*4*	*0.5%*	*5*	*0.9%*
Hypersensitivity	1		1	
Urticaria	3		3	
Systemic lupus erythematosus	0		1	
Blood and lymphatic system disorders	*4*	*0.5%*	*0*	*0*
Anaemia	3		0	
Neutrophilia	1		0	
Hepatobiliary disorders	*2*	*0.2%*	*1*	*0.2%*
Cholecystitis	1		0	
Cholelithiasis	1		0	
Hepatic cyst	0		1	
Endocrine disorders	*1*	*0.1%*	*0*	*0*
Adrenal adenoma	1		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*0*	*0*	*3*	*0.5%*
Breast cancer	0		1	
Gingival cyst	0		1	
Uterine polyp	0		1	
Total	**818**		**581**	

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Table S-9. Incidence rate of adverse events, by past cannabis use[1]

	Group	Current cannabis users		Ex cannabis users		Naïve users	
		Number	Incidence rate[2] (95% CI)	Number	Incidence rate[2] (95% CI)	Number	Incidence rate [2] (95% CI)
All SAE	Cannabis	20	0.16(0.09-0.23)	13	0.31(0.14-0.48)	7	0.65 (0.17-1.13)
	Controls			12	0.19(0.08-0.30)	44	0.31(0.22-0.41)
All Non-serious adverse events	Cannabis	501	4.02(3.67-4.37)	256	6.18(5.43-6.94)	61	5.65(4.23-7.07)
	Controls			186	2.93(2.50-3.35)	395	2.81(2.53-3.09)
System Organ Class (MedDRA)							
Nervous system disorders	Cannabis	83	0.67(0.52-0.81)	67	1.62(1.23-2.01)	14	1.30(0.62-1.98)
	Controls			23	0.36(0.21-0.51)	70	0.50(0.38-0.62)
Gastrointestinal disorders	Cannabis	62	0.50(0.37-0.62)	33	0.80(0.52-1.07)	14	1.30(0.62-1.98)
	Controls			25	0.39(0.24-0.55)	76	0.54(0.42-0.66)
Respiratory, thoracic and mediastinal disorders	Cannabis	67	0.54(0.41-0.66)	31	0.75(0.49-1.01)	5	0.46(0.06-0.87)
	Controls			24	0.38(0.23-0.53)	43	0.31(0.21-0.40)
Infections and infestations	Cannabis	55	0.44(0.32-0.56)	28	0.68(0.43-0.93)	6	0.56(0.11-1.00)
	Controls			26	0.41(0.25-0.57)	42	0.30(0.21-0.39)
Musculoskeletal and connective tissue disorders	Cannabis	57	0.46(0.34-0.58)	15	0.36(0.18-0.55)	5	0.46(0.06-0.87)
	Controls			23	0.36(0.21-0.51)	44	0.31(0.22-0.41)
Psychiatric disorders	Cannabis	32	0.26(0.14-0.35)	21	0.51(0.29-0.72)	4	0.37 (0.01-0.74)]
	Controls			8	0.13(0.04-0.21)	16	0.11(0.06-0.17)
General disorders and administration site conditions	Cannabis	16	0.13(0.07-0.19)	15	0.36(0.18-0.55)	4	0.37(0.01-0.74)
	Controls			9	0.14(0.05-0.23)	14	0.10(0.05-0.15)

[1]"Current cannabis users" were those who reported using cannabis and were still using at baseline interview; "Ex cannabis users" were those who reported having used cannabis but were not using at baseline interview; "naïve user" were those who reported never using cannabis prior to baseline interview.

[2]Unit: events/person-year

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Table S-10: Unadjusted and adjusted rate ratios of SAEs for medical cannabis, by daily dose

Average daily dose	Number of patients[1]	Cumulative person-years	Number of Events	Incidence rate [2]	Unadjusted IRR (95% CI)	Adjusted IRR [3] (95%CI)
Serious adverse event (SAE)						
0	216	204.1	56	0.27	1.00	1.00
<1 grams/day	29	20.6	1	0.05	0.18 (0.01-2.81)	0.34 (0.03-4.16)
1-1.99 grams/day	53	40.6	7	0.17	0.63 (0.21-1.89)	1.31 (0.41-4.15)
2-2.99 grams/day	73	61.1	18	0.29	1.07 (0.51-2.26)	1.51 (0.62-3.73)
>= 3 grams/day	59	54.7	14	0.26	0.93 (0.41-2.11)	1.34 (0.50-3.63)
Non-serious adverse event (AE)						
0	216	204.1	574	2.81	1.00	1.00
<1 grams/day	29	20.6	157	7.62	2.71 (1.99-3.70)	2.34 (1.69-3.25)
1-1.99 grams/day	53	40.6	182	4.48	1.59 (1.19-2.14)	1.72 (1.25-2.38)
2-2.99 grams/day	73	61.1	294	4.81	1.71 (1.34-2.19)	1.63 (1.21-2.19)
>= 3 grams/day	59	54.7	183	3.35	1.19 (0.89-1.59)	1.40 (0.67-1.95)

IRR=Incidence rate ratio; 95% CI=95% confidence interval

1. One patient in the cannabis group did no have information on daily dosage.
2. Incidence rate=events/person-year
3. 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 vs. never), and study sites.

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Table S-11: Incidence rates of adverse events, by past cannabis use [1]

Adverse events	Group	Current cannabis users		Ex cannabis users		Naïve users	
		N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]	N [2]	Incidence rate (95% CI) [3]
All SAE	Cannabis	20	0.16 (0.09-0.23)	13	0.31 (0.14-0.48)	7	0.65 (0.17-1.13)
	Control	--	----	12	0.19 (0.08-0.30)	44	0.31 (0.22-0.41)
All Non-serious adverse events	Cannabis	500	4.01 (3.66-4.36)	255	6.16 (5.40-6.92)	61	5.65 (4.25-7.09)
	Control	--	----	184	2.89 (2.48-3.31)	390	2.78 (2.50-3.05)
Nervous system disorders	Cannabis	83	0.67 (0.52-0.81)	66	1.59 (1.21-1.98)	14	1.30 (0.62-1.98)
	Control	--	----	23	0.36 (0.21-0.51)	70	0.50 (0.38-0.62)
Gastro-intestinal disorders	Cannabis	62	0.50 (0.37-0.62)	33	0.80 (0.52-1.07)	14	1.30 (0.62-1.98)
	Control	--	----	25	0.39 (0.24-0.55)	74	0.53 (0.41-0.65)
Respiratory, thoracic and mediastinal disorders	Cannabis	67	0.54 (0.41-0.66)	31	0.75 (0.49-1.01)	5	0.46 (0.06-0.87)
	Control	--	----	24	0.38 (0.23-0.53)	42	0.30 (0.21-0.39)
Infections and infestations	Cannabis	55	0.44 (0.32-0.56)	28	0.68 (0.43-0.93)	6	0.56 (0.11-1.00)
	Control	--	----	26	0.41 (0.25-0.57)	41	0.29 (0.20-0.38)
Musculoskeletal and connective tissue disorders	Cannabis	57	0.46 (0.34-0.58)	15	0.36 (0.18-0.55)	5	0.46 (0.06-0.87)
	Control	--	----	22	0.35 (0.20-0.49)	43	0.31 (0.21-0.40)
Psychiatric disorders	Cannabis	32	0.26 (0.14-0.35)	21	0.51 (0.29-0.72)	4	0.37 (0.01-0.74)
	Control	--	----	8	0.13 (0.04-0.21)	16	0.11 (0.06-0.17)
General disorders and administration site conditions	Cannabis	16	0.13 (0.07-0.19)	15	0.36 (0.18-0.55)	4	0.37 (0.01-0.74)
	Control	--	----	9	0.14 (0.05-0.23)	14	0.10 (0.05-0.15)

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1. “Current cannabis users” were those who reported using cannabis and were still using at baseline interview; “Ex cannabis users” were those who reported having used cannabis but were not using at baseline interview; “naïve users” were those who reported never using cannabis prior to baseline interview.
2. N=Number of events reported.
3. Incidence rate=events/person-year; 95%CI=95% confidence interval

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Table S-12: Change in neurocognitive function by cannabis exposure and time

Neurocognitive function tests	Independent variables	ß[2]	SE[3]	P
Verbal paired associates I - Recall	Cannabis vs. controls	-1.458	1.515	0.337
	6 month vs. baseline	*1.791*	*0.853*	*0.037*
	12 months vs. baseline	*5.367*	*0.848*	*<0.001*
Verbal paired associates II- Recall	Cannabis vs. controls	0.043	0.423	0.919
	6 month vs. baseline	*0.600*	*0.241*	*0.013*
	12 months vs. baseline	*1.231*	*0.239*	*<0.001*
Digit-symbol coding	Cannabis vs. controls	-2.479	3.786	0.513
	6 month vs. baseline	*4.468*	*2.198*	*0.043*
	12 months vs. baseline	*4.597*	*2.187*	*0.037*
Picture arrangement	Cannabis vs. controls	-1.120	0.928	0.228
	6 month vs. baseline	*1.976*	*0.476*	*<0.001*
	12 months vs. baseline	*3.103*	*0.473*	*<0.001*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, education (college/university vs. high school/elementary), disability status (yes/no), alcohol use (current vs. former or never users), past cannabis use (ever/never), average pain intensity and quality of life (evaluated by Physical Component Summary and Mental Component Summary) at each time point, and study sites
2. ß=fixed regression coefficient for cannabis use
3. SE=standard error

Table S-13: Pulmonary function measures in cannabis-smoking subjects by tobacco smoking status

Pulmonary function tests	Current tobacco users			Former or never tobacco users		
	Number of patients	Before cannabis (baseline)	1-year after Cannabis	Number of patients	Before cannabis (baseline)	1-year after Cannabis
SVC, L	63	4.24 (1.05)	4.21 (1.06)	72	4.24 (1.01)	4.23 (1.01)
FRC, L	54	3.33 (1.09)	3.55 (1.28)	64	3.08 (0.77)	3.00 (0.72)
RV, L	62	2.19 (0.77)	1.99 (0.89)	72	1.82 (0.65)	1.73 (0.61)
TLC, L	60	6.38 (1.63)	6.34 (1.63)	68	6.11 (1.15)	6.05 (1.11)
DL_{CO}	59	21.23 (5.21)	19.37 (6.53)	69	23.30 (7.82)	22.90 (7.61)
FEV_1,L	63	3.15 (0.76)	3.08 (0.75)	72	3.28 (0.79)	3.24 (0.84)
FVC, L	63	4.25 (1.03)	4.21 (1.04)	72	4.25 (0.99)	4.19 (1.03)
FEV_1/FVC (%)	63	74.51 (8.15)	73.40 (8.69)	71	77.51 (7.46)	77.01 (7.50)
$FEF_{25-75\%}$	63	2.70 (1.17)	2.37 (1.08)	72	2.93 (1.52)	2.84 (1.32)

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Table S-14: Change in pulmonary function over time in cannabis users

Pulmonary function tests	**ß[2]**	**SE[3]**	**P**
SVC, L	-0.021	0.031	0.507
FRC, L	0.054	0.066	0.414
RV, L	*-0.142*	*0.061*	*0.021*
TLC, L	-0.040	0.071	0.575
DL_{CO}	*-1.086*	*0.446*	*0.016*
FEV_1,L	*-0.054*	*0.021*	*0.010*
FVC, L	-0.053	0.028	0.061
FEV_1/FVC (%)	*-0.780*	*0.386*	*0.045*
$FEF_{25-75\%}$	*-0.200*	*0.078*	*0.011*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, tobacco (current vs. former or never users), past cannabis use (current cannabis users vs. ex or naïve users), and study sites.
2. ß=fixed regression coefficient for cannabis use.
3. SE=standard error

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Table S-15. Blood test results in cannabis-exposed subjects over 12 months (shown by gender where available)

Parameters	Number of patients	Normal range	Unit	Mean (SD)		Δ=Before-After	
				Before cannabis	1-year after cannabis	Mean (SD)	P-value
WBC	78	3.7-10.8	$\times 10^9$/L	7.29 (1.82)	7.34 (1.97)	0.05 (1.78)	0.80
RBC	34	3.5-5.1 (F)	$\times 10^9$/L	4.44 (0.35)	4.40 (0.40)	-0.04 (0.27)	0.43
	44	*4.2-5.8 (M)*	*$\times 10^9$/L*	*4.83 (0.45)*	*4.71 (0.45)*	*-0.12 (0.23)*	*<0.001*
Hb	34	112-155 (F)	g/L	137.35 (9.28)	136.59 (11.21)	-0.76 (7.99)	0.58
	44	*132-172 (M)*	*g/L*	*150.30 (12.31)*	*146.98 (12.57)*	*-3.32 (7.82)*	*0.01*
HCT	34	0.32-0.46 (F)	L/L	0.41 (0.03)	0.40 (0.03)	-0.00 (0.02)	0.30
	44	*0.37-0.51 (M)*	*L/L*	*0.44 (0.04)*	*0.43 (0.04)*	*-0.01 (0.02)*	*<0.001*
MCV	78	80-101	fL	91.89 (4.43)	91.79 (4.44)	-0.09 (1.85)	0.65
MCH	78	26.5-34.5	pg	31.12 (1.55)	31.22 (1.47)	0.10 (0.73)	0.24
MCHC	*78*	*323-356*	*g/L*	*338.42 (6.25)*	*339.86 (6.03)*	*1.44 (6.17)*	*0.04*
RDW	78	11.6-15.5	%	13.22 (0.78)	13.17 (0.69)	-0.05 (0.55)	0.42
PLT	78	125-420	$\times 10^9$/L	268.03 (61.98)	262.13 (56.35)	-5.90 (37.77)	0.17
MPV	78	7.0-11.5	fL	9.02 (0.98)	8.92 (1.03)	-0.10 (0.49)	0.08
Neutrophils	78	0.45-0.77		0.64 (0.09)	0.63 (0.08)	-0.01 (0.10)	0.25
Lymphocytes	*78*	*0.14-0.42*		*0.26 (0.07)*	*0.28 (0.07)*	*0.02 (0.08)*	*0.04*
Monocytes	78	0.02-0.12		0.07 (0.02)	0.06 (0.02)	-0.00 (0.02)	0.29
Eosinophils	78	0-0.07		0.03 (0.02)	0.02 (0.02)	-0.00 (0.02)	0.48
Basophils	78	0-0.02		0.01 (0.01)	0.00 (0.00)	-0.00 (0.01)	0.04
WBC diff manual-Neutrophils	78	1.9-7.1	$\times 10^9$/L	4.70 (0.54)	4.64 (1.59)	-0.06 (1.69)	0.74
WBC diff manual-Lymphocytes	*78*	*0.9-3*	*$\times 10^9$/L*	*1.88 (0.54)*	*2.04 (0.58)*	*0.16 (0.48)*	*0.01*
WBC diff manual-Monocytes	78	0.20-0.95	$\times 10^9$/L	0.47 (0.18)	0.46 (0.18)	-0.02 (0.16)	0.36
WBC diff manual-Eosinophils	78	0-0.45	$\times 10^9$/L	0.19 (0.19)	0.18 (0.13)	-0.01 (0.13)	0.67
WBC diff manual-Basophils	78	0-0.15	$\times 10^9$/L	0.03 (0.04)	0.01 (0.04)	-0.01 (0.05)	0.09

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Parameters	Number of patients	Normal range	Unit	Mean (SD)		Δ=Before-After	
				Before cannabis	1-year after cannabis	Mean (SD)	P-value
ALP	78	30-118	U/L	66.52 (22.68)	66.31 (19.14)	-0.22 (12.28)	0.88
ALT	34	7-54 (F)	U/L	20.03 (9.53)	18.85 (8.02)	-1.18 (5.71)	0.24
	44	10-63 (M)	U/L	29.88 (33.52)	28.11 (24.78)	-1.78 (12.71)	0.36
AST, SGOT	34	13-32 (F)	U/L	20.94 (5.90)	20.97 (5.59)	0.03 (3.90)	0.97
	44	14-42 (M)	U/L	25.82 (14.52)	24.55 (10.92)	-1.27 (8.11)	0.30
Bilirubin direct serum	78	1.7-8.6	umol/l	1.51 (0.69)	1.69 (0.96)	0.18 (1.14)	0.17
Bilirubin total serum	78	5-30	umol/l	9.99 (3.89)	10.18 (4.01)	0.13 (3.60)	0.75
Chloride serum	78	98-110	mmol/l	104.65 (2.78)	104.82 (2.77)	0.17 (3.02)	0.63
Creatinine serum	34	55-103	umol/l	75.03 (14.96)	74.44 (15.32)	-0.59 (4.92)	0.49
	44	70-124	umol/l	86.07 (13.55)	85.55 (14.55)	-0.52 (8.21)	0.67
GGT	34	7-45 (F)	U/L	22.82 (17.56)	23.53 (21.35)	0.71 (13.13)	0.76
	44	7-60 (M)	U/L	36.68 (37.46)	34.64 (35.65)	-2.05 (17.57)	0.44
Potassium	78	3.5-5.2	mmol/L	4.28 (0.35)	4.31 (0.38)	0.04 (0.40)	0.43
Sodium	78	135-144	mmol/L	139.03 (1.87)	138.90 (2.28)	-0.13 (2.34)	0.63
UREA	34	2.9-8.1 (F)	mmol/L	5.02 (1.61)	5.00 (1.51)	-0.02 (1.23)	0.93
	44	3.0-9.3 (M)	mmol/L	5.59 (1.74)	5.63 (1.45)	0.04 (1.21)	0.83
Prolactin	34	1.39-24.2 (F)	ug/L	12.10 (8.13)	13.69 (16.80)	2.10 (12.73)	0.35
	44	1.61-18.77 (M)	ug/L	9.30 (5.78)	8.12 (3.16)	-1.18 (5.34)	0.15
Testosterone	34	0.20-2.67 (F)	nmol/L	0.65 (0.36)	0.66 (0.34)	0.01 (0.24)	0.83
	44	2.46-21.6 (M)	nmol/L	11.45 (5.77)	11.27 (6.52)	-0.17 (5.62)	0.84
TSH	78	0.49-4.67	mIU/L	1.53 (0.82)	1.58 (1.00)	0.05 (0.77)	0.59

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Table S-16. Numbers of patients with abnormal blood tests, by time

Parameters	N (%) of patients with ABOVE normal results			N (%) of patients with BELOW normal results		
	Baseline: above normal 12 month: above normal	Baseline: above normal 12 month: normal	Baseline: normal 12 month: above normal	Baseline: below normal 12 month: below normal	Baseline: below normal 12 month: normal	Baseline: normal 12 month: below normal
WBC	3	1	3	0	0	0
RBC	0	0	1	4	0	1
Hb	1	0	2	2	0	1
HCT	1	0	2	2	0	0
MCV	0	0	0	0	0	0
MCH	1	1	1	0	0	0
MCHC	0	0	0	0	1	0
RDW	1	1	0	0	0	0
PLT	0	3	0	0	0	1
MPV	0	1	0	0	0	2
Neutrophils	0	3	2	0	0	1
Lymphocytes	1	0	1	0	3	0
Monocytes	0	1	0	0	1	0
Eosinophils	2	1	1	0	0	0
Basophils	0	0	0	0	0	0
WBC diff manual-Neutrophils	3	2	4	0	0	1
WBC diff manual-Lymphocytes	1	1	2	1	1	1
WBC diff manual-Monocytes	0	1	0	0	2	0
WBC diff manual-Eosinophils	3	2	0	0	0	0
WBC diff manual-Basophils	0	1	1	0	0	0

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Parameters	N (%) of patients with ABOVE normal results			N (%) of patients with BELOW normal results		
	Baseline: above normal 12 month: above normal	Baseline: above normal 12 month: normal	Baseline: normal 12 month: above normal	Baseline: below normal 12 month: below normal	Baseline: below normal 12 month: normal	Baseline: normal 12 month: below normal
ALP	0	3	0	0	0	0
ALT	1	1	0	0	0	0
AST, SGOT	2	1	1	0	0	0
Bilirubin direct serum	0	0	0	0	32	0
Bilirubin total serum	0	0	0	0	0	1
Chloride serum	0	3	1	0	1	1
Creatinine serum	1	1	0	4	7	0
GGT	8	1	2	0	0	0
Potassium	0	1	2	0	0	0
Sodium	0	0	0	0	1	1
UREA	2	4	0	1	1	2
Prolactin	3	7	1	0	0	1
Testosterone	0	0	1	3	4	2
TSH	0	0	1	1	5	3

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Table S-17. Pain intensity measures[1] in cannabis-exposed[2] and control patients, by month of follow-up

Group	Number of patients	Before cannabis (baseline)	3 months after cannabis	6 months after cannabis	9 months after cannabis	12 months after cannabis
1. The AVERAGE level of pain over the last 24 hours						
CANNABIS	145	6.78 (1.65)	5.79 (2.14)	5.45 (2.19)	5.94 (2.10)	5.54 (2.11)
CONTROL	157	5.89 (1.98)	5.99 (2.14)	5.88 (2.17)	6.02 (2.21)	6.10 (2.13)
2. The LOWEST level of pain over the last 24 hours						
CANNABIS	145	4.27 (1.99)	4.01 (2.18)	3.53 (2.03)	3.96 (2.14)	3.61 (2.00)
CONTROL	157	3.58 (2.14)	4.20 (2.50)	3.88 (2.26)	4.45 (2.57)	3.96 (2.31)
3. The HIGHEST level of pain over the last 24 hours						
CANNABIS	145	8.19 (1.49)	7.25 (2.08)	7.12 (2.11)	7.47 (1.98)	7.24 (2.14)
CONTROL	157	7.45 (2.12)	7.31 (2.16)	7.19 (2.28)	7.22 (2.18)	7.55 (2.08)
4. CURRENT level of pain right now						
CANNABIS	145	5.65 (2.11)	5.14 (2.36)	4.74 (2.30)	5.20 (2.30)	4.96 (2.29)
CONTROL	157	5.16 (2.43)	5.26 (2.50)	5.18 (2.32)	5.25 (2.62)	5.19 (2.39)

1. Scales of pain intensity are 0 (no pain) to 10 (worst pain possible).
2. Only subjects with complete data obtained at all time points are included in this table.

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Table S-18. Effects[1] of cannabis use on pain intensity over time[2]

	Exp (Cannabis vs. control)	Time [3]	Exp× Time
1. The average level of pain over the last 24 hours	0.5270 (0.0654)	0.0149 (0.2463)	*-0.0923 (<.00001)*
2. The lowest level of pain over the last 24 hours	0.4019 (0.3105)	*0.0336 (0.0078)*	*-0.0788 (<.0001)*
3. The highest level of pain over the last 24 hours	0.4817 (0.0884)	0.0042 (0.7423)	*-0.0599 (0.0013)*
4. Current level of pain right now	0.3151 (0.3330)	0.0015 (0.9113)	*-0.0449 (0.0197)*

1. Data are presented as fixed regression coefficient (P value).

2. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never) and study sites

3. Time is used as a continuous variable, with 0 as baseline, 3 as 3-month telephone interview, 6 as 6-month clinic visit, 9 as 9-month telephone interview, and 12 as 1-year clinic visit.

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Table S-19. McGill Pain Questionnaire (MPQ) scores in cannabis-exposed and control patients, by month of follow-up [1]

	Group	Number of patients [2]	Before cannabis (baseline)	6 months after cannabis	12 months after cannabis
1. Sensory	CANNABIS	140	19.42 (7.60)	15.57 (8.11)	16.48 (8.60)
	CONTROL	126	15.96 (7.96)	14.98 (7.47)	16.32 (8.47)
2. Affective	CANNABIS	93	5.14 (3.37)	4.35 (3.05)	4.75 (3.40)
	CONTROL	78	4.27 (3.24)	4.35 (3.09)	4.60 (3.21)
3. Evaluative	CANNABIS	118	2.84 (1.23)	2.32 (1.22)	2.48 (1.31)
	CONTROL	94	2.65 (1.28)	2.59 (1.16)	2.34 (1.27)
4. Miscellaneous	CANNABIS	119	6.18 (3.47)	5.55 (3.42)	5.87 (3.70)
	CONTROL	105	5.77 (3.43)	5.55 (3.54)	5.82 (3.63)
Total score	CANNABIS	143	32.29 (13.66)	25.32 (14.34)	27.50 (15.75)
	CONTROL	127	26.55 (14.15)	25.80 (13.16)	26.88 (14.73)
Present Pain Intensity (PPI) [3]	CANNABIS	151	2.75 (0.99)	2.25 (1.00)	2.32 (1.07)
	CONTROL	170	2.47 (1.09)	2.46 (1.09)	2.45 (1.09)

1. Data are presented as Mean (SD).

2. Only subjects with complete data obtained at all time points are included in this table.

3. Scales of PPI are 0 (no pain) to 5 (excruciating pain).

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Table S-20. Effects[1] of cannabis on pain quality measured by the McGill Pain Questionnaire (MPQ)[2]

Independent variables	Sensory	Affective	Evaluative	Miscellaneous	Total score	Present Pain Intensity
Exp (Cannabis vs. control)	*2.7932 (0.0201)*	1.1861 (0.0548)	0.2034 (0.33726)	0.5220 (0.3072)	*4.8703 (0.0210)*	*0.2757 (0.0568)*
T_1 (6-month vs. baseline)	-0.9762 (0.1678)	0.0769 (0.8385)	-0.0638 (0.6451)	-0.2190 (0.5463)	-0.7559 (0.5344)	-0.0059 (0.9490)
T_2 (12-month vs. baseline)	0.3571 (0.6136)	0.3333 (0.3774)	*-0.3085 (0.0264)*	0.0476 (0.8956)	0.3307 (0.7858)	-0.0177 (0.8479)
Exp×T_1	*-2.8738 (0.0033)*	-0.8619 (0.0929)	*-0.4531 (0.0150)*	-0.4028 (0.4188)	*-6.2091 (0.0002)*	*-0.4908 (0.0003)*
Exp×T_2	*-3.2929 (0.0008)*	-0.7204 (0.1599)	-0.0474 (0.7985)	-0.3501 (0.4821)	*-5.1209 (0.0023)*	*-0.4062 (0.0026)*

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never) and study sites
2. Data are presented as fixed regression coefficient (P value).

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Table S-21. Modified Edmonton Symptom Assessment Scale (ESAS) scores in cannabis-exposed and control patients, by month of follow-up [1]

	Group	Number of patients [2]	Before cannabis (baseline)	6 months after cannabis	12 months after cannabis
1. Sleep [3]	CANNABIS	154	5.86 (2.88)	4.86 (3.08)	5.38 (2.95)
	CONTROL	168	5.69 (2.82)	5.67 (2.79)	5.85 (2.69)
2. Wellbeing [3]	CANNABIS	154	4.97 (2.49)	4.54 (2.16)	4.82 (2.33)
	CONTROL	168	4.75 (2.53)	4.50 (2.52)	4.75 (2.40)
3. Pain [3]	CANNABIS	154	7.07 (1.76)	5.96 (2.33)	5.99 (2.26)
	CONTROL	168	6.25 (2.18)	6.36 (2.11)	6.32 (2.21)
4. Stength [3]	CANNABIS	154	5.57 (2.52)	5.19 (2.46)	4.95 (2.64)
	CONTROL	168	4.95 (2.52)	5.12 (2.52)	4.89 (2.53)
5. Appetite [3]	CANNABIS	154	4.70 (2.99)	3.96 (2.98)	4.11 (2.87)
	CONTROL	168	3.35 (2.82)	3.74 (2.76)	3.60 (3.05)
6. Nausea [3]	CANNABIS	154	2.73 (2.92)	2.38 (2.75)	2.66 (2.90)
	CONTROL	168	2.22 (2.80)	2.23 (2.65)	2.20 (2.64)
7. Vomiting [3]	CANNABIS	154	1.04 (2.01)	1.00 (1.93)	1.11 (2.09)
	CONTROL	168	0.78 (1.82)	0.66 (1.58)	0.61 (1.36)
8. Constipation [3]	CANNABIS	154	3.17 (3.03)	2.74 (2.95)	2.97 (2.95)
	CONTROL	168	3.19 (3.13)	3.35 (3.17)	3.27 (3.14)
9. Sleepiness [3]	CANNABIS	154	5.24 (2.78)	4.97 (2.82)	5.18 (2.95)
	CONTROL	168	4.92 (2.91)	5.32 (2.97)	5.11 (2.94)
10. Shortness of breath [3]	CANNABIS	154	1.70 (2.08)	2.34 (2.45)	2.39 (2.48)
	CONTROL	168	2.18 (2.67)	2.45 (2.62)	2.81 (2.81)

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	Group	Number of patients	Before cannabis (baseline)	6 months after cannabis	12 months after cannabis
11. Depression [3]	CANNABIS	154	3.31 (2.82)	2.95 (2.66)	3.29 (2.79)
	CONTROL	168	3.12 (2.78)	3.46 (2.98)	3.54 (2.94)
12. Nervouness [3]	CANNABIS	154	2.51 (2.52)	2.64 (2.59)	2.72 (2.61)
	CONTROL	168	2.78 (2.74)	3.21 (2.93)	3.17 (2.74)
Total symptom distress score [4]					
	CANNABIS	154	47.87 (15.68)	43.54 (17.54)	45.59 (17.97)
	CONTROL	168	44.20 (17.20)	46.06 (17.14)	46.11 (17.07)
Total number of symptoms [5]					
	CANNABIS	154	10.47 (1.77)	10.54 (1.83)	10.56 (1.79)
	CONTROL	168	10.40 (1.95)	10.63 (1.58)	10.51 (1.87)
Total number of moderate/severe symptoms [6]					
	CANNABIS	154	6.00 (2.41)	5.47 (2.73)	5.74 (2.79)
	CONTROL	168	5.46 (2.62)	5.83 (2.68)	5.77 (2.58)

1. Data are presented as Mean (SD).

2. Only subjects with complete data obtained at all time points are included in this table.

3. The scale for each symptom is 0 (no) to 10 (worst possible).

4. A total symptom distress score is calculated by summing of the scores of all 12 symptoms on the ESAS (ranges from 0 to 120).

5. A total number of symptoms is calculated by summing of the number of symptoms whose scale is not 0.

6. Moderate intensity of any symptom is defined as 4-6 and severe as 7-10 on the scale. A total number of moderate/severe symptoms is summing all the moderate and severe symptoms for each patient.

Table S-22. The effect[1] of cannabis on symptom distress, measured by modified Edmonton Symptom Assessment Scale[2]

Independent variables	Total symptom distress score	Total number of symptoms	Total number of moderate/severe symptoms
Exp (Cannabis vs. control)	1.5575 (0.5116)	0.2530 (0.3164)	0.2632 (0.4708)
T_1 (6-month vs. baseline)	1.8565 (0.1286)	0.2262 (0.1296)	0.3690 (0.0632)
T_2 (12-month vs. baseline)	1.9143 (0.1171)	0.1012 (0.4974)	0.3095 (0.1191)
Exp×T_1	*-6.1851 (0.0005)*	-0.1613 (0.4546)	*-0.8950 (0.0019)*
Exp×T_2	*-4.1916 (0.0178)*	-0.0103 (0.9620)	*-0.5693 (0.0475)*

1. Data are presented as fixed regression coefficient (P-value).
2. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never), baseline pain intensity and study sites

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Table S-23. Profile of Mood States (POMS) in cannabis-exposed and control patients, by month of follow-up [1]

	Group	Number of patients [2]	Before cannabis (baseline)	6 months after cannabis	12 months after cannabis
1. Tension-Anxiety	CANNABIS	152	6.43 (3.94)	5.81 (4.16)	5.65 (4.14)
	CONTROL	167	6.04 (4.32)	6.04 (4.33)	6.27 (4.51)
2. Depression-Dejection	CANNABIS	153	5.43 (4.20)	4.60 (4.22)	4.49 (4.25)
	CONTROL	167	5.27 (4.61)	5.34 (5.04)	5.45 (4.76)
3. Anger-Hostility	CANNABIS	154	5.61 (4.55)	5.19 (4.20)	4.54 (3.88)
	CONTROL	167	5.22 (4.40)	5.50 (5.06)	5.27 (4.81)
4. Vigor-Activity	CANNABIS	153	4.60 (3.72)	5.02 (3.95)	4.98 (4.17)
	CONTROL	168	5.36 (4.23)	4.84 (3.54)	5.46 (4.25)
5. Fatigue-Inertia	CANNABIS	153	11.33 (5.01)	9.45 (5.17)	9.58 (5.17)
	CONTROL	167	10.31 (5.05)	10.18 (5.13)	10.35 (5.25)
6. Confusion-Bewilderment	CANNABIS	152	4.94 (3.09)	4.66 (3.14)	4.44 (3.03)
	CONTROL	168	5.36 (3.39)	5.20 (3.34)	5.35 (3.47)
Total Mood Disturbance Score	CANNABIS	149	29.37 (18.28)	24.75 (19.04)	23.92 (19.04)
	CONTROL	164	27.01 (19.18)	27.30 (20.52)	27.09 (21.29)

1. Data are presented as Mean (SD).

2. Only subjects with complete data obtained at all time points are included in this table.

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Table S-24. The effects[1] of cannabis on Profile of Mood Scale measures [2]

Independent variables	Tension-Anxiety	Depression-Dejection	Anger-Hostility	Vigor-Activity	Fatigue-Inertia	Confusion-Bewilderment	Total Mood Disturbance Score
Exposure status (Cannabis vs. control)	-0.3027 (0.6277)	-0.1982 (0.7629)	-0.4098 (0.5254)	-0.4881 (0.3733)	0.1950 (0.7858)	*-1.0375 (0.0325)*	-1.4006 (0.6255)
T_1 (6-month vs. baseline)	-0.0060 (0.9839)	0.0629 (0.8465)	0.2829 (0.3962)	-0.5238 (0.0862)	-0.1272 (0.7478)	-0.1622 (0.4670)	0.2957 (0.8308)
T_2 (12-month vs. baseline)	0.2231 (0.4519)	0.1751 (0.5896)	0.0494 (0.8822)	0.0997 (0.7437)	0.0449 (0.9096)	-0.0164 (0.9415)	0.0793 (0.9543)
Exp×T_1	-0.6108 (0.1553)	*-0.8946 (0.0571)*	-0.6936 (0.1499)	*0.9437 (0.0330)*	*-1.7551 (0.0022)*	-0.1190 (0.7129)	*-4.9132 (0.0145)*
Exp×T_2	*-0.9994 (0.0202)*	*-1.1131 (0.0180)*	*-1.1111 (0.0212)*	0.2843 (0.5199)	*-1.7916 (0.0018)*	-0.4820 (0.1366)	*-5.5239 (0.0060)*

1. Data are presented as fixed regression coefficient (P-value).
2. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never), baseline pain intensity and study sites

Table S-25. Change in quality of life (SF-36v2®) summary scores over one year

	Physical Component Summary		Mental Component Summary	
	Cannabis (N=142)	**Control (N=146)**	**Cannabis (N=142)**	**Control (N=146)**
Clinic visits	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline	27.15 (7.00)	30.89 (8.50)	41.94 (11.72)	42.34 (13.30)
6 months	30.05 (8.03)	31.43 (8.70)	42.55 (11.77)	43.16 (13.60)
12 months	30.25 (8.96)	32.38 (8.76)	42.88 (12.14)	41.70 (13.32)
Comparisons [1]	**ß (SE)[2]**	**P**	**ß (SE) [2]**	**P**
Cannabis vs. control	-3.937 (1.187)	0.001	0.441 (1.853)	0.812
Time difference				
6 months vs. baseline	0.536 (0.546)	0.326	0.821 (0.916)	0.370
12 months vs. baseline	1.484 (0.546)	0.007	-0.640 (0.916)	0.485
Group by time interaction				
Group× (6 months)	2.360 (0.777)	0.003	-0.206 (1.304)	0.875
Group× (12 months)	1.619 (0.777)	0.038	1.584 (1.304)	0.225

1. A random effects model with a random intercept for patient is fitted, adjusting for age at enrollment, gender, disability status (yes/no), baseline concomitant pain medication (yes/no), tobacco use (current vs. former or never users), alcohol use (current vs. former or never users), past cannabis use (ever/never) and study sites
2. ß=fixed regression coefficient for cannabis use; SE=standard error

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