Dose-dependent Effects of Smoked Cannabis on Capsaicin-Induced Pain and Hyperalgesia in Healthy Volunteers.

Abbreviated Title: Effects of Cannabis on Experimental Pain

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Summary Statement: Smoked cannabis had a delayed effect on capsaicin induced pain in healthy volunteers. The medium dose reduced pain whereas the high dose increased pain.

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ABSTRACT

Background: Although the preclinical literature suggests that cannabinoids produce antinociception and antihyperalgesic effects, efficacy in the human pain state remains unclear. Using a human experimental pain model, we hypothesized that inhaled cannabis would reduce the pain and hyperalgesia induced by intradermal capsaicin.

Methods: In a randomized, double-blinded, placebo controlled, crossover trial in fifteen healthy volunteers, we evaluated concentration-response effects of low, medium, and high dose smoked cannabis (respectively 2%, 4%, and 8% 9-delta-tetrahydrocannibinol by weight) on pain and cutaneous hyperalgesia induced by intradermal capsaicin. Capsaicin was injected into opposite forearms 5 and 45 minutes after drug exposure and pain, hyperalgesia, tetrahydrocannibinol plasma levels, and side effects were assessed.

Results: Five minutes after cannabis exposure, there was no effect on capsaicin-induced pain at any dose. By 45 minutes after cannabis exposure, however, there was a significant decrease in capsaicin-induced pain with the medium dose and a significant increase in capsaicin-induced pain with the high dose. There was no effect seen with the low dose nor was there an effect on the area of hyperalgesia at any dose. Significant negative correlations between pain perception and plasma delta-9-tetrahydrocannibinol levels were found after adjusting for the overall dose effects. There was no significant difference in performance on the neuropsychological tests.

Conclusions: This study suggests that there is a window of modest analgesia for smoked cannabis with lower doses decreasing pain and higher doses increasing pain.

INTRODUCTION

Preclinical studies note that a major cannabinoid receptor, CB1, is expressed in regions involved in dorsal root ganglion [1] dorsal horn of the spinal cord [2], periaquaductal grey and raphe nucleus [3,4] and forebrain [5] suggesting that cannabinoids may modulate nociceptive transmission. Although the preclinical [1,2,6-8] and some early human experimental and clinical pain [9,10] literature suggests that cannabinoids produce antinociception and antihyperalgesic effects, their mechanisms of action and potential therapeutic efficacy and utility remain unclear. One problem in the field is that the complex interaction between the sensory, affective, and cognitive components of clinical pain makes it difficult to study these features in isolation, in terms of identifying potentially responsive components. Using models of experimentally induced pain in human volunteers, however, permits simplified stimulus conditions, crossover designs, and comparisons between human and animal models to define in parallel the physiology and pharmacology of pain states. Thus one is able to investigate the sensory components of pain processing in concert with assessment of analgesic efficacy. Another difficulty in some earlier cannabinoid research lies in the uncertain relationship of traditional experimentally induced human pain models (e.g. pressure, heat, cold) to clinical pain, such that findings may be dependent on the model employed [11]. For example, present models subdivide mechanisms of nociceptive processing into those reflecting acute processing [12], facilitated states [13], and neuropathic pain states [14,15]. Fortunately, several recent human models having evident parallels to these states have been developed [16] which make it possible to study the effects of drugs on components of the systems that sub-serve post injury pain processing [17]. One such model employs the injection of intradermal capsaicin, resulting in the transient (<20-30 minutes) and selective activation of C fibers. This injection results in a brief pain state that is replaced by an enlarged area of tactile allodynia and thermal hyperalgesia that persists for an extended interval [18]. It is thought to represent a facilitated pain state that arises from persistent afferent input.

Finally, in terms of pharmacology, almost all negative studies using either experimentally induced pain [19] or in clinical trials [20,21] have employed fixed dose designs. Most positive studies have reported cannabinoid-related adverse effects on cognitive function and other symptoms [22], although a recent trial of a synthetic cannabinoid agonist in a clinical population reported no significant adverse effects [23]. Results of fixed dose studies are difficult to interpret, since efficacy might be detected and adverse effects limited if dose-response relationships were known.

To address some of these limitations, the present study employed a human experimental pain model and a dose-response design to evaluate the effects of smoked cannabis on acute nociceptive processing (acute thermal stimuli) and the facilitated pain state (intradermal capsaicin). Primary efficacy endpoints included the effect of inhaled cannabis on capsaicin-induced spontaneous and elicited (von Frey and stroking) pain scores. Secondary efficacy endpoints were the effects of inhaled cannabis on capsaicin-induced secondary hyperalgesia and on the affective component of pain as assessed by McGill Pain scores. Based on the results of preclinical studies, we hypothesized that inhaled cannabis would reduce capsaicin-induced pain and hyperalgesia and change the affective quality of pain in a dose-dependent manner.

MATERIALS AND METHODS

Subjects and Study Design

The Institutional Review Board of the University of California at San Diego approved the study. All individuals gave informed, written consent before participating in the research. Recruitment of healthy volunteers was conducted by advertisement in local print media and word-of-mouth. Inclusion criteria were men and women aged 18 years or older and in good health English-speaking, literate, and able to understand the study procedures and communicate with the research team. Exclusion criteria included 1) active acute or chronic medical illness or pain problems, 2) current or past cannabis abuse/dependence, current other psychoactive substance use disorder or major mental disorder (e.g. major depression or psychosis) as determined by DSM IV criteria, 3) pulmonary disease, 4) lack of use of cannabis within the past 6 months, 5) pregnancy, and 6) allergy to the study drug. These criteria were intended to identify persons likely to be able to successfully complete the brief research protocol, based on evidence of having some experience with smoking cannabis within the past 6 months and thus being more likely to tolerate the delivery method of smoking. Subjects were asked to abstain from smoking cannabis for at least 30 days prior to administration of study drug.

A randomized, double-blinded, placebo-controlled crossover design was employed. Prior to the blinded phase, a blood sample was drawn to screen for the absence of THC, then all subjects participated in a high dose training session, using the standardized cued-dosing procedure described below. If subjects were unable to tolerate the highest dose, they were excluded from the study. Eligible subjects participated in four dose-randomized sessions separated by at least one week. At each session, subjects were exposed to placebo, low (2%), medium (4%), or high (8%) dose of cannabis (see below under Cannabis Dosing).

At each visit, prior to study drug administration, a blood sample was taken for plasma assay of THC and metabolites (see below for detail plasma assay of THC and other test procedures) and the following data were collected: 1) neurosensory testing (thermal sensation, thermal pain, touch, and mechanical pain) on the volar

aspect of both forearms 2) neurocognitive evaluation and 3) blood pressure, heart rate, respiratory rate and temperature. Subjects were then administered the study drug. At five minutes after the dose, a sample of venous blood was taken to quantify acute cannabis exposure, and the following assessments were performed: 1) neurosensory testing on the right forearm 2) neurocognitive testing and 3) a subjective rating of "highness." After completing the testing, capsaicin (10μl, 10 mg/ml) was injected intradermally on the volar aspect of the right forearm. Pain scores, blood pressure, heart rate and respiratory rate were measured at the time of injection and every 2.5 minutes for 10 minutes. A McGill Pain Questionnaire was administered at the time of capsaicin injection only. Ten minutes after the capsaicin injection, the hyperalgesic area was established to von Frey hair and stroking; the flare response was outlined; and neurosensory testing was performed halfway between the edge of this defined area and the capsaicin injection site. Forty minutes after cannabis dose, a final blood sample was taken from the right antecubital vein for plasma assay of THC and metabolites and the neurosensory testing (left forearm), neurocognitive testing and subjective "highness" ratings were repeated. After completing the testing, capsaicin (10μl, 10 mg/ml) was injected intradermally on the volar aspect of the left forearm and the methods of testing described for the right forearm were repeated. Figure 1 illustrates the schedule of assessments.

Cannabis Assignment and Dosing

Each subject received placebo and three doses of cannabis, given in random order as determined by a computerized random number generator held by the University of California, San Diego Research Pharmacy, who alone had access to the assignment scheme and order. Standardized cannabis and placebo cigarettes were provided by the National Institute on Drug Abuse and were constructed from similar base material using THC concentrations of 0%, 2%, 4%, and 8% by weight. Due to the variable nature of plant material, actual cigarette concentrations varied within nominal dose ranges as follows: low dose (2%): 1.76 – 2.03%; medium dose (4%):

3.3 – 3.96%; and high dose (8%): 6.3 – 7.95%. Placebo cigarettes were prepared from ethanol-extracted cannabis, which reduces the cannabinoid content of the plant material to trace amounts, 0.009% THC in this study. These placebo cigarettes are visually indistinguishable from cigarettes in the experimental arm and maintain the distinctive taste and odor of the active material.

Dosing levels were controlled by utilizing a standardized cued-smoking procedure [24]. Study treatments were administered under direct observation by a study nurse who instructed the participant to light the cigarette and, once lit, inhale for 5 seconds. The subject was then instructed to remove the cigarette from the lips and hold the inhalation for 10 seconds (if possible) before exhaling fully. The process was repeated 3 more times with the subject being given a 40-second resting period between smoking sessions. Smoked cigarettes were collected after each session for weighing, and, to ensure proper custody, were stored under locked conditions in the Research Pharmacy.

Testing paradigm

Pain Measures: Three pain intensities were measured after capsaicin injection: 1) spontaneous pain (visual analog scale of pain intensity, or VASPI), 2) pain resulting from gently stroking the injected area (Brush) and 3) pain resulting from application of a 5.18 von Frey hair to the painful area (von Frey). Pain scores were measured using a visual analog scale consisting of a 100 mm line with "no pain" written at one end and the "worst imaginable pain" written at the other end. Subjects were asked to place a mark along the line in a location corresponding with the intensity of their pain. The distance, in millimeters, from the “no pain” end to the location of the mark yields a measurement of the pain intensity.

McGill Pain Questionnaire Short Form: The McGill Pain Questionnaire Short Form (MPQ-SF) [25] was employed to assess the quality of the pain experience. This instrument consists of 15 pain descriptors, assessing both affective (e.g. tiring, punishing) and sensory (e.g. throbbing, shooting) dimensions of pain. The MPQ is generally used in chronic clinical pain, but it has a long history of application in experimentally induced and

acute post-operative and dental pain research with demonstrated sensitivity to change in loading on sensory-discriminative and motivational-affective dimensions of the pain experience [26,27]. Given the known psychotropic effects of cannabis, we included the MPQ as a secondary outcome measure of the affective dimension of pain reports.

Neurosensory testing: Four neurosensory tests were performed: i) warm and cold sensation, ii) warm and cold pain, iii) touch and iv) mechanical pain. The neurosensory tests were ordered from least noxious to most noxious (warm/cold thresholds, hot/cold pain thresholds, mechanical thresholds and mechanical pain). Warm and cold sensation was measured using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Minneapolis, Minnesota, USA). A 2 cm X 2 cm probe was used with a rate of temperature change of 1°C/second for warm and cool and 1.5°C/second for warm and cold pain. Warm and cold pain measurements used the same instrument to obtain an endpoint of pain rather than temperature change sensation. The subject was given 4 trials with the warm and cold stimulus and 3 trials with the warm and cold pain stimulus. The average of each stimulus was used to determine the threshold. Touch was measured using calibrated von Frey hair filaments of varying size. The filaments were selected at random and 3 successive stimuli were applied for 2 seconds at 5-second intervals per filament, applied in an ascending pattern. The patient was instructed to report if the stimulus was felt. Thresholds are expressed in mN. Mechanical pain was also measured using the von Frey hair filaments but with the endpoint being pain.

Capsaicin-induced pain and secondary hyperalgesia: 100 mg capsaicin (8-methyl N-vanillyl 6-nonamide), dissolved in 10 ml of a 20% cyclodextran vehicle to achieve a concentration of 10 μg/μl, was prepared following aseptic precautions. A volume of 10 μl was then injected intradermally with a sterile tuberculin syringe. The region of secondary hyperalgesia was established with a 5.18 von Frey hair and foam brush gently stroked on the skin. These stimuli began away from the injection site in an area of skin that did not produce pain and were repeated tangentially to the injection site at a progressively closer radius until the subject

reported pain or tenderness. That site was marked on the skin with a felt tip pen and a new series started from the periphery at a different angle until eight determinations of the borders of secondary hyperalgesia were outlined on the skin. These borders, as well as the flare response, were outlined onto a transparency for area determination (cm2).

Cannabinoid Assay: Cannabinoid concentrations in plasma were ascertained by gas chromatography mass spectrometry for 1) Delta-9-tetrahydrocannabinol (delta-9-THC), the principal active compound 2) 11-nor-9-carboxy-tetrahydrocannabinol (11-nor-THC), the principal inactive metabolite of delta-9-THC 3) 11-hydroxyl-tetrahydrocannabinol (11-OH-THC), the principal active metabolite of delta-9-THC 4) cannabinol, a secondary active cannabinoid and 5) cannabidiol, a secondary active cannabinoid.

Safety Assessments: At enrollment, subjects underwent a directed physical examination, vital signs, and an electrocardiogram and/or chest x-ray. They were given information about the subjective effects of cannabis and instructed in relaxation techniques, should those effects become disturbing. Vital signs were monitored throughout the protocol and subjects remained in the laboratory under direct observation by staff for 2 hours after the cannabis procedures were completed. Prior to release from the clinic, a final vital sign and self-report status check was made and the subject was transported from the clinic by taxicab or prearranged transportation.

Measures of cognitive performance were obtained for safety, and to assess for potential confounding of pain reports:

Trail Making Test, Part B: This is a measure of psychomotor speed, attention and cognitive sequencing that requires subjects to connect a series of randomly arranged circles in a designated sequential order, based on alternating numbers and letters (i.e., 1 to A to 2 to B, etc.) Scores are equal to time taken to complete the task in seconds [28]

Paced Auditory Serial Attention Test [29]: In this test, a set of randomized digits was serially presented via tape recording. Subjects were asked to add the current number to the number that preceded it and respond with the sum. Thus, after each new digit was presented, a new total was achieved. Scores were equal to the number of correct responses out of 50 items presented. This test yielded a measure of speed of information processing.

Subjective "Highness" Score: Subjects were asked to rate their feeling of "high" on a 10-point scale from 0 "not high at all" to 10 "the highest you've ever been".

The Beck Depression Inventory II was administered once at each visit prior to exposure to cannabis. The Beck Depression Inventory II [30] consists of 21 questions, each graded on a four-point scale ranging from 0 to 3. Statements are ordered to show increasing severity of the cognitive and somatic dimension of depressed mood. We used the Beck primarily to exclude smoking for subjects who might be depressed or suicidal-- and thus vulnerable to the known adverse psychotropic effects of cannabis.

Statistical Methods

The software used for the analysis was R: Version 2.3.1 (2006-06-01). Mixed effect, repeated measure linear regression was used to address the main question about the relationship of pain and cannabis. Pain scores were modeled as a function of cannabis dose and time. The pain score (Brush, VASPI or Von Frey, considered separately) was the dependent variable in regression, while cannabis dose was the main predictor of interest. The decrease of pain over time was expected to be nonlinear so a quadratic time component was modeled, as well as a random (subject-specific) intercept. The early and late capsaicin injections were modeled separately.

The assumption that the dose curves were parallel over time was checked by modeling the interaction between time and dose. In addition, an analysis as described above was performed using a linear combination of the three pain scores (first principal component) instead of a single pain score as the outcome. Additionally, the first pain score (Brush, VASPI or Von Frey) obtained after each of the two (early and late) capsaicin injections was modeled as the function of the amount of each of cannabinoids/metabolites measured during the blood draw closest to the time of the cannabis dose. This model was as similar as possible to the model used to assess the main pain/cannabis dose relationship, although there were some design-imposed departures. In addition to the subject-specific intercept, binary indicators of the medium and high doses were included as a conservative measure. The question became "Over and above the gross dose effects established in the main analysis, was there further explanatory power in the assayed plasma concentration?" The difference in time between blood draw and capsaicin injection was also included as a covariate. The effect of cannabis on heart rate, respiratory rate and blood pressure was examined in a repeated measures model similar to the one described above, where heart rate and blood pressure were modeled as functions of cannabis dose and time since smoking. Beck scores were examined over the four visits. The difference in the baseline and post-cannabis neurocognitive test performance (at 5 and 40 minutes past smoking) was assessed in a series of paired Wilcoxon rank-sum tests.

RESULTS

Of twenty-nine subjects screened, four were ineligible because one or more exclusion criteria were met. Twenty-five subjects entered the high-dose training session, of which two dropped out due to time constraints, two were lost to follow-up, one dropped out due to fear of the blood draws, and one was excluded due to anxiety after cannabis exposure. Nineteen subjects were randomized in the blinded phase of the study. Participants in the study had a mean age of 28.9 years (SD=10.9) and were 58% male (n=11), 95% unmarried (n=18), and 37% Caucasian (n=7). After randomization, two subjects dropped out due to time constraints, one was lost to follow-up and one dropped out due to dizziness. Fifteen subjects completed the protocol.

Subjective Pain Scores

Intradermal capsaicin injections induced spontaneous pain and elicited pain (stroking and von Frey stimulation) in all subjects. Repeated measures analysis of subjective pain scores showed no difference in pain perception between any of the cannabis doses and placebo during the early time course (right arm) on any measure, (TABLE 1) and low dose did not differ from placebo at any time point (TABLES 1 AND 2). However, during the late time course (left arm), both medium and high doses differed significantly from placebo, albeit in opposite directions (TABLE 2). At the medium dose, subjects reported decreased pain sensation, above and beyond the decrease to be expected as a function of time elapsed after capsaicin (p-values of the medium dose coefficients for the subjective pain scores ranged between 0.011 and 0.027, overall drop in pain score between medium dose and placebo range between 6.2 and 6.7 points). At the high dose, subjects reported increased perception of pain (p-values of the high dose coefficients for the subjective pain scores ranged between 0.009 and 0.002, overall rise in pain score between medium dose and placebo ranged between 7.1 and 8.7 points).

The results were similar for all three pain measures: Brush, VASPI and von Frey. On further examination, these tests were found to be very highly correlated (Pearson r = .985 between Brush & VASPI and VASPI & von Frey. Pearson r = .974 between Brush & von Frey) and were subsequently combined in a first principal component analysis. The plots of raw and fitted data for all pain measures and the resultant composite pain scores are presented in Figures 2 and 3. The assumption of the parallel dose-curves present in the random effects model was tested by modeling time-dose interactions. The interactions were not significant, which supports the parallel dose curves assumption.

There was no effect of cannabis on the pain quality as measured by the MPQ-SF. Total MPQ-SF scores for the early and late time period were placebo - 8.3$\pm$3.0 and 8.8$\pm$3.0, low dose - 9.9$\pm$3.1 and 8.3$\pm$2.5, medium dose - 9.7$\pm$3.7 and 11$\pm$3.9, and high dose - 9.6$\pm$3.1 and 8.6$\pm$2.7. Neither sensory nor affective dimensions were affected.

Secondary Hyperalgesia

Capsaicin produced a secondary hyperalgesia to stroking and von Frey hair stimulation in 14 of 15 subjects and a flare response in all subjects. Twelve of 15 subjects had heat hyperalgesia as evident by decrease in the hot pain thresholds after capsaicin injection. Cannabis did not attenuate the heat hyperalgesia at any dose (figure 4). Furthermore, there was no effect of any dose of inhaled cannabis on the secondary hyperalgesia or flare response in either the early or late time course (figure 5). Baseline neurosensory thresholds did not differ significantly for any of the measures recorded across the placebo and cannabis test days. There was no significant effect of cannabis on any neurosensory threshold, painful or non-painful (TABLE 3).

Plasma Cannabinoid Concentrations

The percent weight (±SD) of the cannabis cigarette smoked for the low, medium and high dose was 49±11, 44±9, and 41±13 respectively. Mixed effect regression analysis of the assayed concentration of cannabinoids/metabolites in the blood as predictors of pain perception showed that delta-9-THC and 11-OH-THC were significantly negatively associated with subjective pain scores both at the early and the late capsaicin injection (p-values of corresponding regression coefficients ranging from 0.009 to 0.05, partial correlations ranging from -0.52 to -0.43). At the late injection, the high dose indicator showed borderline significance in increasing pain perception. 11-nor-THC was significantly negatively correlated with estimated amount of pain at the early capsaicin injection but not at the late injection (p-values of early injection regression coefficient ranging from 0.007 to 0.07, partial correlations ranging from-0.52 to -0.36). Cannabinol and cannabidiol did not show any association with the pain scores obtained at early or late capsaicin injection, although this was expected, given that neither cannabinol nor cannabidiol were present at levels above 0.25% in the cannabis used in this study. Table 4 summarizes the assayed plasma levels of the THC and other cannabinoids and metabolites.

Side Effects

Adverse events are summarized in Table 5. Mild to moderate side effects occurred in 7 of 19 randomized subjects, primarily at the highest dose of cannabis. No serious adverse events occurred. Repeated measures analysis of the vital signs data showed that all doses of cannabis increased heart rate compared to placebo. Specifically, the low, medium, and high doses resulted in heart rate increases of 7.9, 7.5, and 12.0 beats per minute respectively, consistent with previous reports of the cardiovascular effects of cannabis. In the case of respiratory rate, only the high dose of cannabis was significantly different from placebo (+0.79 respirations), while other cannabis doses showed no effect. Low dose cannabis resulted in lower systolic blood

pressure (-3.0 mmHg), although other doses did not replicate this effect. None of the cannabis strengths tested showed any effect on diastolic blood pressure. There was no difference in Beck scores at the four visits and the summary of scores was at the low end of the Beck scale (Kruskal-Wallis test p-value = 0.82). On measures of neuropsychological functioning, there was no significant difference in performance in Paced Auditory Serial Attention Test total correct, Trails B time to complete before and after cannabis exposure. There was a slight (not reaching significance) worsening on medium and high doses between baseline and 5 minutes post-exposure, which stabilized at 40 minutes post-exposure (Figure 6). However, subjects did report a dose-dependent increase in their sensation of "high", as ascertained by their rating of "highness" on a scale from 1 to 10 (Figure 7). This effect persisted into the late time course.

DISCUSSION

This study demonstrated different effects of three doses of smoked cannabis on spontaneous and elicited pain secondary to intradermal capsaicin injection. The medium cannabis dose, 4% THC by weight, produced delayed analgesia while the high dose, 8% THC cannabis, produced a delayed increase in pain. The low dose had no analgesic effect. There was a significant correlation between plasma levels of THC and metabolites with decrease in pain; however, there was no correlation between the high dose plasma levels and increase in pain. This suggests that there may be another compound within the cannabis leaf that we did not measure that may be leading to the increased pain at the high dose. It is known that the cannabis leaf contains over 400 compounds of which 60 are called the cannabinoids[31]. We only measured plasma levels of three compounds.

The delayed onset of analgesia is surprising considering that the subjective ratings of "high" peaked early, suggesting early central nervous system penetration. However, there may be a dissociation between analgesia and side effects, a phenomenon seen with other analgesics such as the opioids. The increase in pain observed with the high dose is consistent with earlier analgesic studies with cannabinoids. For example, chronic delivery of cannabinoids has been shown to cause thermal hyperalgesia [32], although the mechanism of this pronociception is unclear. Another possible explanation for the increased pain at the high dose seen in our study may be that the emotional effects produced by cannabinoids, e.g. dysphoria could counteract the analgesic effect. However, there was no effect observed in the affective score on the McGill Pain Questionnaire to support this hypothesis.

In contrast to the effects on spontaneous and elicited pain, we found no effect of inhaled cannabis on acute painful and non-painful heat, cold and mechanical thresholds. This finding is in conflict with preclinical studies on the effects of cannabinoids on acute nociceptive processing, demonstrating that administration of cannabinoids to normal animals produces both thermal [1,6,7,33] and mechanical [34-36] antinociception via the CB_1 receptor. Two previous studies have demonstrated that acute delivery of oral THC [22] and smoked cannabis [37]

resulted in a decreased pain response to radiant noxious heat. Both studies resulted in significant psychomotor side effects that suggest that the dose of cannabis required to affect acute nociception may lead to psychomotor side effects. Likewise, our study showed no effects on acute nociceptive processing at doses that had minimal psychomotor effects.

It has been noted that CB_1 receptors are located on the periaquaductal grey, raphe nucleus, and forebrain, which are known to process nociceptive input [3,5,7]. However, the site of analgesic action of the cannabinoids is unknown. It has been suggested that human experimental pain can be used to evaluate analgesic site of action. Although far from conclusive, there are components of the intradermal capsaicin response that may be used to evaluate site of action. Intradermal capsaicin triggers selective and transient (<20-30 minutes) activation of C fibers resulting in a rapid onset of pain, secondary hyperalgesia and a flare response [18]. The spontaneous pain is mediated by both peripheral and central mechanisms, the secondary hyperalgesia is mediated by spinal mechanisms and the flare response represents antidromic invasion of the axon collaterals and the subsequent release of neuropeptides which is a peripheral mechanism [38],[39]. Therefore, a review of the effects of analgesics with known mechanisms may suggest the site of action of the cannabinoids. For instance, previous studies with systemically mediated opioids and N-Methyl-D-Aspartate antagonists show an effect on capsaicin induced pain and secondary hyperalgesia but no effect on the flare response [40,41]. In addition, intravenous lidocaine has been shown to block the flare response of intradermal capsaicin whereas the opioids have no effect [42].

It is difficult to draw firm conclusions on the predictive value of human experimental pain for drug efficacy in clinical pain because studies involving experimental pain 1) often test drug efficacy with a single dose of drug and 2) often administer the drug prior to the initiating stimulus. Nonetheless, it has been suggested that such models may provide a link between preclinical animal pain models and clinical trials in patients with chronic neuropathic pain [41,43,44]. Comparing our results to the human experimental pain literature on agents with known clinical efficacy has yielded two comparisons of interest. First, cannabinoids behave similarly to opioids

in models of facilitated pain (i.e. intradermal capsaicin, heat-capsaicin sensitization, first-degree burn). These protocols result in a brief report of intense pain followed by a longer lasting area of secondary hyperalgesia. Both the pain and hyperalgesia of these models have shown consistent responses to the opioids [40,41] and inconsistent responses to non-opioids [44-46]. Our results indicate that inhaled cannabis decreases the pain of intradermal capsaicin (within a therapeutic window) but has no antihyperalgesic effects. Second, effects of cannabinoids resemble the actions of non-opioids in acute pain models (i.e., thermal and mechanical) involving a brief report of pain that quickly resolves when the stimulus is removed. These models are consistently sensitive to opioids and resistant to non-opioids [41-43,47]. Our results suggest that the cannabinoids act more like the non-opioids on acute nociception.

Limitations on the generalizability of the present study for human experimental or clinical research include the small sample size and use of only healthy volunteers. Additionally, only subjects who were experienced cannabis users and who were able to tolerate the highest study dose of cannabis were randomized. It is possible that clinically ill samples, especially cannabis- naïve subjects, would have a different analgesic response and incidence of side effects when exposed to the effective dose found in this study (4% THC).

Results of this study may, however, raise interesting questions of relevance to the design of human experimental pain models—or perhaps of clinical trials assessing the potential therapeutic use of cannabinoids. We identified. a potential narrow "therapeutic window" for analgesic efficacy. Future studies might include a more comprehensive pharmacokinetic assessment, with the goal of elaborating the time course of analgesia. Analgesic effects were delayed, modest, and may or may not be translated into the clinical arena. The bi-phasic response (analgesia at medium dose and hyperalgesia at high dose) is of concern. It is unknown if this is a property unique to cannabis or unique to the cannabinoids as a class.

Finally, because more information is needed regarding abuse potential, tolerance, efficacy in neuropathic pain, and safety issues of inhaled cannabis, we cannot advocate a place for using cannabis in the

treatment armamentarium at this time. A concern over the clinical use of inhaled cannabis is health related issues that result from the delivery method. Long-term use of inhaled cannabis has been shown to be associated with increased respiratory symptoms suggestive of obstructive lung disease; however, short-term use of inhaled cannabis does not appear to be associated with respiratory complications[48]. Long-term use of inhaled cannabis has not been associated with increased aerodigestive cancers as is seen with tobacco use [49]. Another safety issue with cannabis relates to the psychotropic effects of cannabis, and its known "paradoxical" effects (e.g., dysphoria, dejection, and depressed mood). Such effects must be carefully considered in work addressing the future clinical application of cannabinoids. As for neurocognitive effects of long term cannabis use, a large meta-analysis showed no effects on memory, recall, speeded information processing, and executive function.[50]

In summary, in this model of human experimental pain, smoked cannabis was demonstrated to have a delayed biphasic effect on pain scores induced by intradermal capsaicin. The low dose had no effect, the medium dose significantly reduced the pain and the high dose significantly increased the pain. There was no effect on capsaicin induced secondary hyperalgesia, acute sensory thresholds, or neurocognitive assessments. There was a significant correlation between plasma levels of THC and metabolites with decrease in pain; however, there was no correlation between the high dose plasma levels and increase in pain. No conclusions on the analgesic efficacy of smoked cannabis on clinical pain states can be made from this study as the relationship between analgesic effects in experimental pain and clinical pain states is unknown.

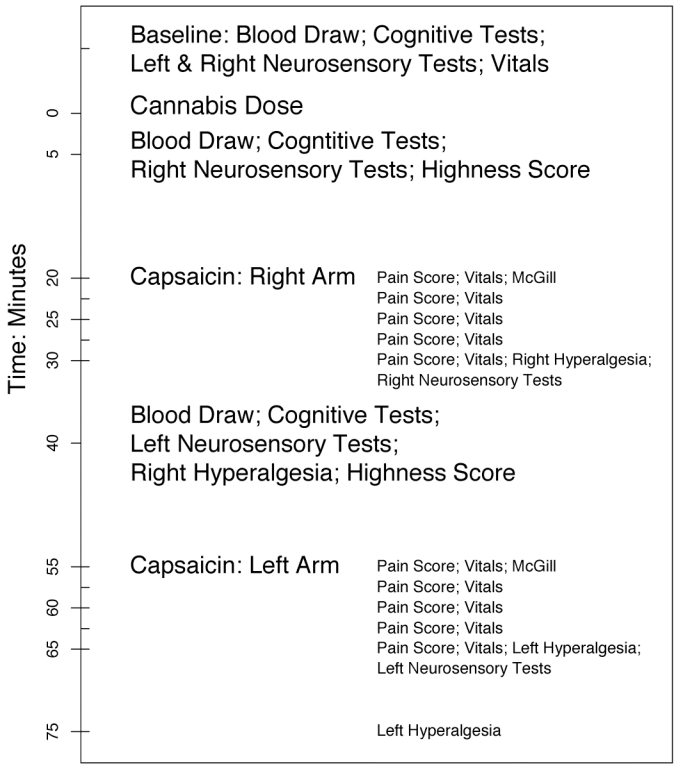

Figure 1. Schedule of Assessments

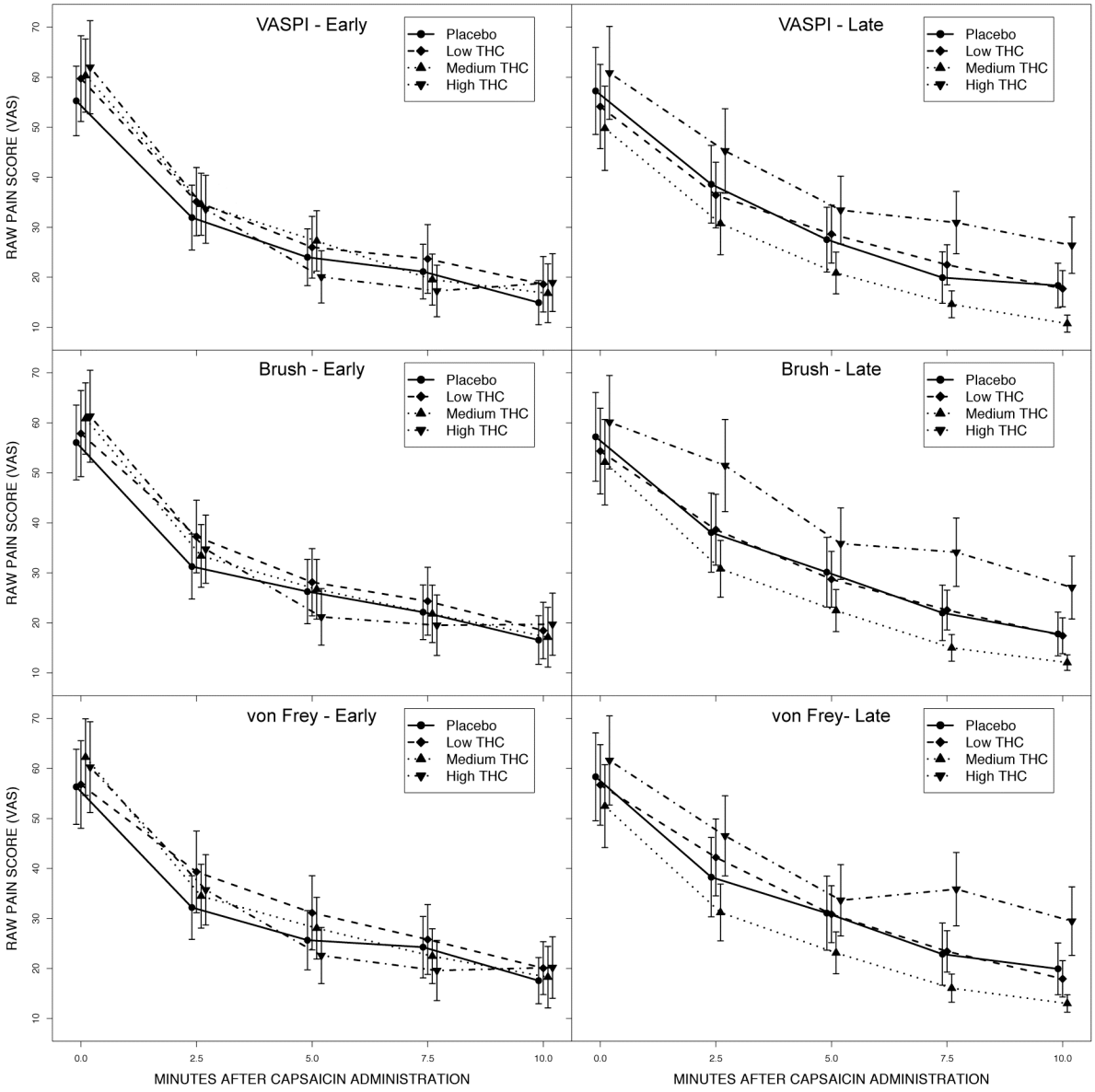

Figure 2. The effects of smoked cannabis on the spontaneous pain (VASPI), and elicited pain to brush and von Frey hair stimulation after injection of capsaicin 20 minutes (early) and 55 minutes (late) after cannabis administration. Results are presented using the raw data from 100mm visual analog scale ratings for each outcome measurement (VASPI, Brush, von Frey). Data represent the mean $\pm$ SEM.

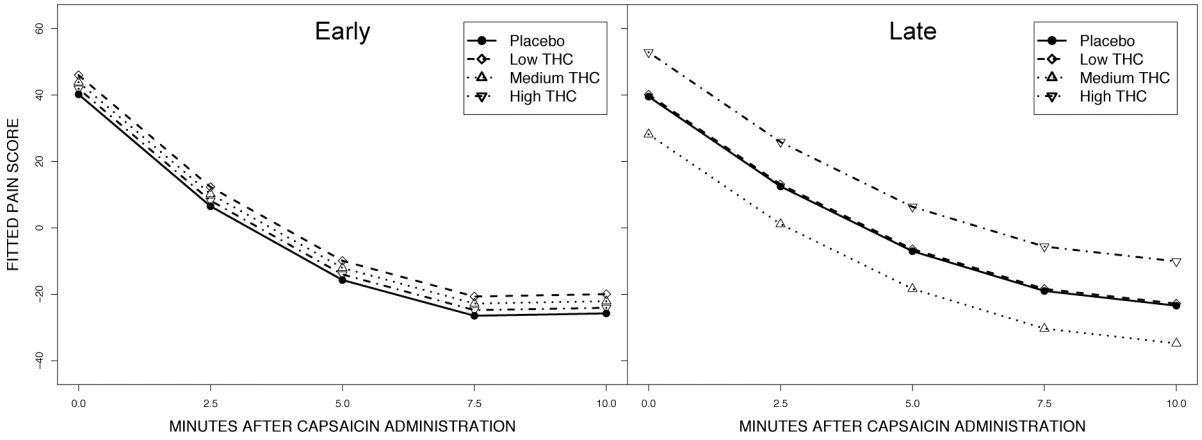

Figure 3. The effects of smoked cannabis on composite scores of pain induced by the injection of capsaicin 20 minutes (early) and 55 minutes (late) after cannabis administration. Results are presented using the fitted data (principle components) of all outcome measurements (VASPI, Brush, von Frey).

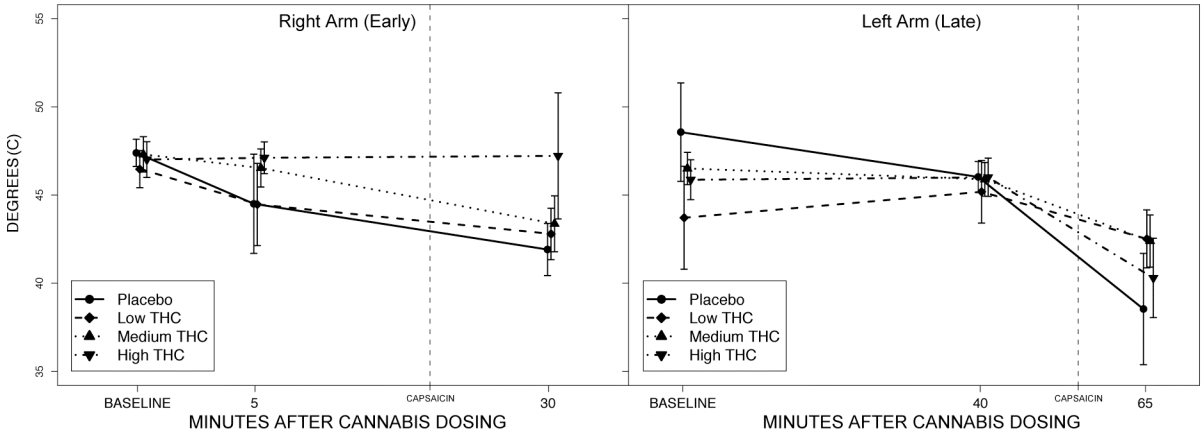

Figure 4. The effects of smoked cannabis on the heat hyperalgesia after injection of capsaicin 20 minutes (early) and 55 minutes (late) after cannabis administration. Results are presented using the degrees centigrade temperature that resulted in the report of pain. Data represent the mean $\pm$ SEM.

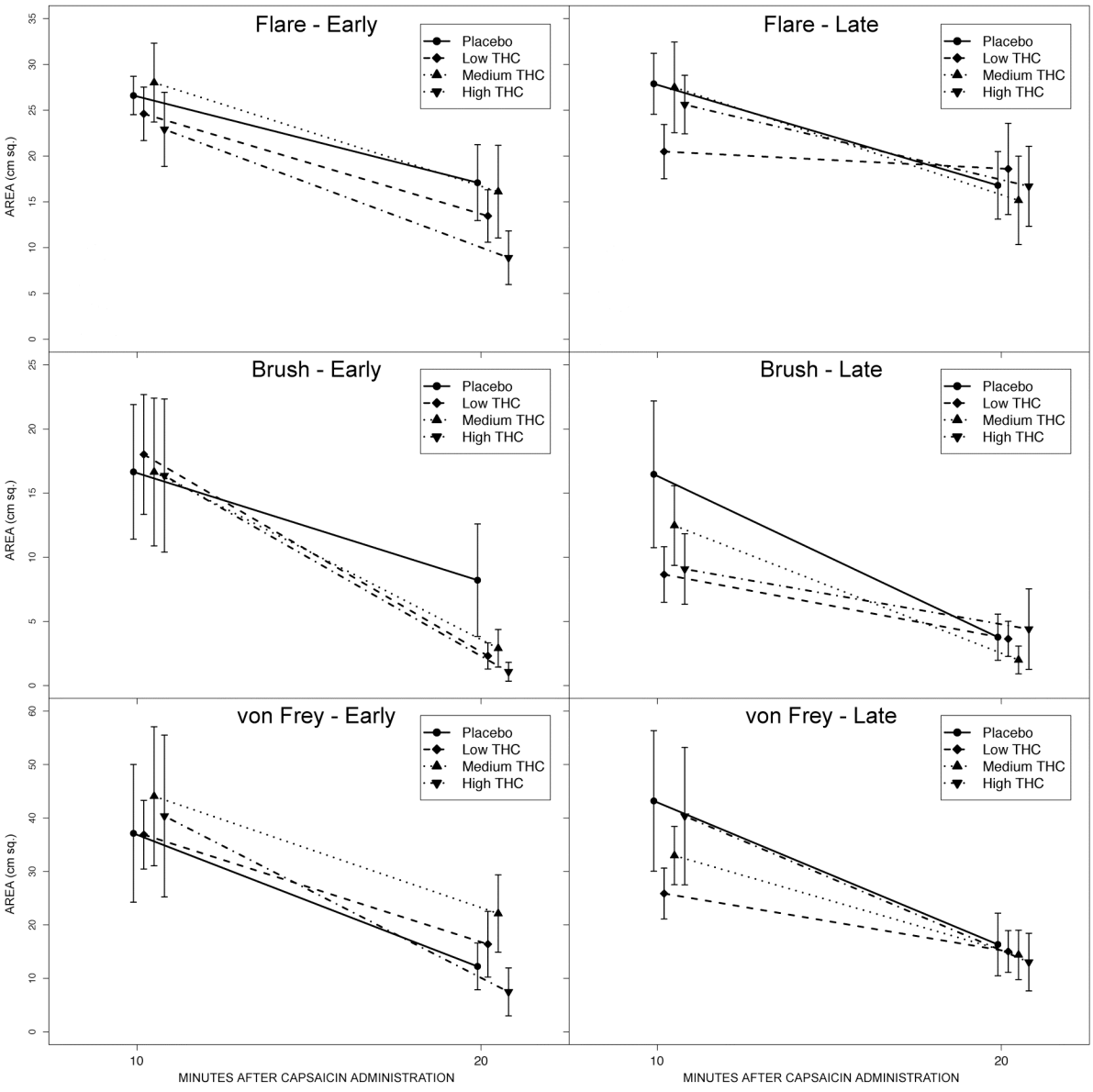

Figure 5. The effects of smoked cannabis on the flare and area of hyperalgesia (in cm^2) elicited to brush and von Frey hair stimulation induced by the injection of capsaicin 20 minutes (early) and 55 minutes (late) after cannabis administration. Data represent the mean $\pm$ SEM.

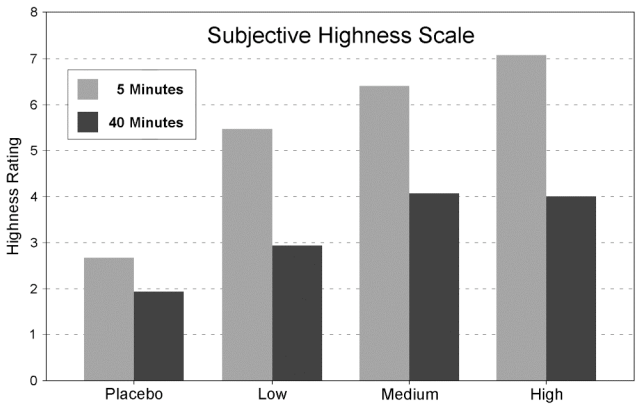

Figure 6. Subjective highness scores reported by subjects 5 minutes and 40 minutes after cannabis exposure.

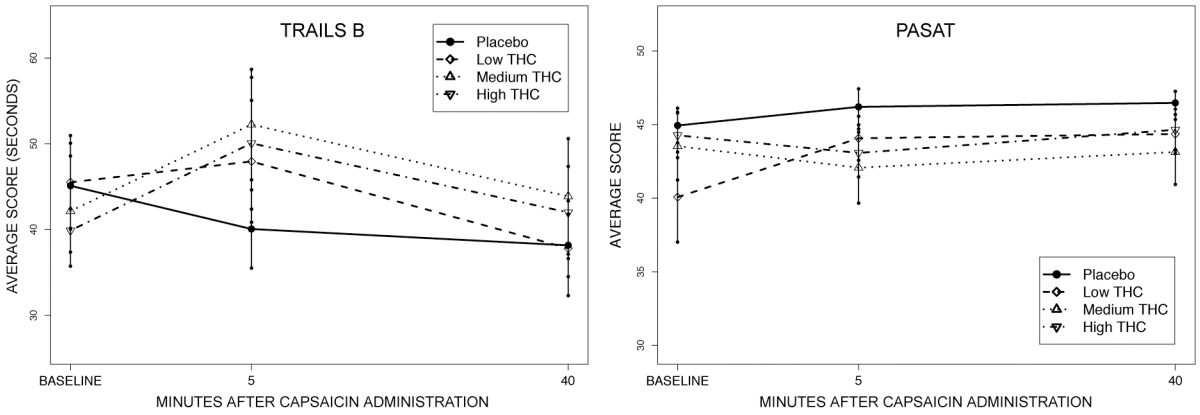

Figure 7. The effects of smoked cannabis on neurocognitive functioning 5 minutes and 45 minutes after cannabis exposure. For the Trail Making Test, a higher number represents more impairment. For the PASAT, a lower number represents more impairment. Data represent the mean $\pm$ SEM.

TABLE 1 – Right Arm/Early Time course

Instrument	Cannabis Dose	Change from Placebo	Std. Error	P-value
Brush	Low	3.0331	3.1928	0.3429
VASPI	Low	3.1733	3.0247	0.2950
von Frey	Low	3.6932	3.2664	0.2592
Brush	Medium	1.8064	3.1928	0.5720
VASPI	Medium	2.2533	3.0247	0.4569
von Frey	Medium	2.1732	3.2664	0.5064
Brush	High	1.1264	3.1928	0.7245
VASPI	High	0.9200	3.0247	0.7612
von Frey	High	0.7465	3.2664	0.8194

Change From Placebo shows the coefficient of the dose indicator in the corresponding mixed effects model (effect size) and corresponds to the overall change from placebo, positive or negative, in the units of the pain instrument. Standard error and p-value for each change are given in the following columns. VASPI = Visual Analog Spontaneous Pain Intensity

TABLE 2 – Left Arm/Late Time course

Instrument	Cannabis Dose	Change From Placebo	Std. Error	P-value
Brush	Low	0.0592	2.8865	0.9837
VASPI	Low	0.3803	2.7138	0.8887
von Frey	Low	0.6486	2.8617	0.8209
Brush	Medium	-6.2604	2.8210	0.0273
VASPI	Medium	-6.7172	2.6521	0.0119
von Frey	Medium	-6.6764	2.7967	0.0177
Brush	High	8.7101	2.8301	0.0023
VASPI	High	7.0519	2.6607	0.0085
von Frey	High	7.3652	2.8058	0.0092

Change From Placebo shows the coefficient of the dose indicator in the corresponding mixed effects model (effect size) and corresponds to the overall change from placebo, positive or negative, in the units of the pain instrument. Standard error and p-value for each change are given in the following columns. VASPI = Visual Analog Spontaneous Pain Intensity

TABLE 3: Summary of sensory thresholds (QST) to thermal stimuli (Cool, Warm, Hot Pain [HP}, Cold Pain [CP]) and mechanical stimuli (von Frey [VF]) at baseline on the right (R) and left (L) arm and at various time points after cannabis exposure. The 5 and 40 minute post cannabis exposure time points represent QST prior to capsaicin injection on the R and L arm respectively. The 30 and 65 minute post cannabis exposure time points represent QST after capsaicin injection on the R and L arm respectively. A visual analog pain score (VAS) on a scale of 0-100 was obtained after each painful stimuli.

Placebo	**Cool**	**Warm**	**Hot Pain**	**HP VAS**	**Cold Pain**	**CP VAS**	**VF sensation**	**VF Pain**	**VF VAS**
Baseline R	29.13±1.57	35.57±2.44	47.39±2.98	24.60±25.96	7.46±10.32	13.80±16.48	2.56±0.85	6.40±.80	0.93±2.71
Baseline L	29.52±1.61	33.92±3.00	48.57±10.80	27.37±26.28	4.80±6.58	11.07±12.92	2.45±0.86	6.65±0.00	1.46±4.69
5 minutes R	28.45±2.15	35.32±1.44	44.51±10.90	25.05±28.50	5.97±8.61	13.01±16.90	2.73±0.94	6.55±0.38	0.60±2.32
30 minutes R	27.78±2.99	36.61±3.20	41.91±5.72	37.00±34.90	3.57±6.29	9.47±20.85	2.75±0.88	5.93±0.98	9.07±12.52
40 minutes L	28.74±2.09	34.11±2.91	46.03±3.38	25.29±23.69	7.23±9.86	12.69±11.43	2.54±0.81	6.45±0.52	3.93±9.77
65 minutes L	28.36±2.27	35.37±0.98	38.54±12.22	36.60±33.05	8.05±11.79	20.93±24.66	2.69±0.96	5.86±0.88	12.27±18.53
Low									
Baseline R	29.23±1.96	35.65±1.55	46.47±4.07	26.53±21.41	8.6±10.23	14.14±12.03	2.45±0.82	6.56±0.24	3.00±7.94
Baseline L	29.55±1.58	34.47±1.26	43.71±11.29	29.00±22.99	7.93±8.75	11.29±12.29	2.36±0.73	6.64±0.05	2.53±7.06
5 minutes R	28.51±2.18	35.72±1.72	44.47±9.03	28.53±25.83	9.55±11.11	13.11±11.91	2.68±.087	6.65±0.00	0.47±1.81
30 minutes R	26.69±7.45	35.73±1.67	42.79±5.64	36.47±32.70	7.56±11.41	12.96±17.86	2.80±0.90	5.50±0.89	16.60±17.91
40 minutes L	28.38±1.87	34.99±3.34	45.19±6.87	25.59±26.12	7.75±10.23	10.45±8.86	2.17±0.81	6.61±0.15	1.43±4.55
65 minutes L	28.17±2.58	35.02±1.32	42.51±6.36	30.25±27.75	7.35±9.94	8.05±10.33	2.46±0.79	5.89±0.886	13.21±12.62
Medium									
Baseline R	29.26±1.87	36.04±2.06	47.31±3.89	19.43±15.05	6.95±10.81	10.50±14.50	2.79±0.75	6.54±0.39	1.07±3.05
Baseline L	29.48±2.06	34.63±0.86	46.51±3.56	19.20±14.05	5.65±8.45	9.87±12.09	2.51±0.87	6.57±0.31	1.67±5.23
5 minutes R	26.40±6.14	35.66±2.48	46.53±4.18	20.34±19.04	7.50±11.37	8.40±9.68	2.68±0.93	6.56±0.31	1.27±3.59
30 minutes R	29.16±2.84	36.84±2.65	43.37±6.13	33.91±21.25	7.05±11.22	13.64±15.30	2.81±0.83	6.04±0.77	11.60±16.52
40 minutes L	27.70±5.83	35.06±1.24	45.89±3.72	23.40±17.76	6.89±10.20	8.73±9.07	2.50±0.75	6.49±0.50	1.00±2.80
65 minutes L	27.81±2.87	35.72±2.25	42.39±5.71	28.80±27.15	7.45±10.91	8.75±10.11	2.71±0.74	6.09±0.73	9.40±10.29
High									
Baseline R	28.98±1.69	35.43±1.71	47.01±3.93	22.67±24.02	7.87±10.23	15.59±16.69	2.73±0.82	6.57±0.31	0.73±2.84
Baseline L	29.24±1.64	35.20±0.99	45.87±4.38	25.80±24.15	8.29±10.35	12.00±16.34	2.65±0.79	6.60±0.20	2.73±7.27
5 minutes R	28.37±2.07	35.79±2.34	47.11±3.48	26.07±23.52	6.61±9.35	14.81±19.63	2.63±0.94	6.64±0.05	0.53±2.07
30 minutes R	26.13±7.38	35.43±2.79	47.22±13.86	34.68±30.91	13.88±18.48	20.06±22.99	2.81±0.92	5.73±0.94	16.50±19.11
40 minutes L	28.02±1.82	35.11±3.37	46.01±4.20	26.21±25.07	8.55±9.92	12.57±17.15	2.56±0.83	6.61±0.15	2.36±5.79
65 minutes L	28.05±1.97	35.78±2.03	40.30±8.71	35.92±29.68	9.05±11.10	19.06±23.47	2.76±0.90	5.76±0.86	21.14±26.79

TABLE 4: Plasma levels of the primary cannabiniod and the active and inactive metabolites

	Delta-9-THC		11OH-THC		11-nor-THCCOOH		CBN		CBD	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Low	26.7(23.2)	6.8(5.6)	1.6(1.3)	1.1(1.7)	8(6.9)	26.1(17.1)	0.1(0.14)	0	0.6(1)	0.1(0.2)
Medium	39.7(43.7)	9.1(11)	2.1(2.1)	1.2(1.9)	11.7(12.9)	36.3(29.5)	0.9(0.9)	0.2(0.2)	0.4(0.7)	0.2(0.5)
High	58.5(49.5)	13.6(12.5)	3.3(2.9)	2.4(2.2)	14.2(13)	49.5(35.4)	1.5(2.2)	0.3(0.5)	0.5(0.9)	0.2(0.4)

Mean Plasma levels (ng/ml) of the primary active cannabinoid Delta-9-tetrahydrocannabinol (delta-9-THC), primary active metabolite 11-hydroxyl-tetrahydrocannabinol(11OH-THC), primary inactive metabolite 11-nor-9-carboxy-tetrahydrocannabinol (11-nor-THCCOOH), as well as two secondary active cannabinoids, cannabinol (CBN) and cannabidiol (CBD) after smoking low, medium, and high doses of cannabis. Plasma levels were collected at 5 minutes and 45 minutes after smoking the cannabis. Values in parentheses are the standard deviation.

TABLE 5 - Side effects

	LOW (n=17)	MEDIUM (n=17)	HIGH (n=16)	PLACEBO (n=15)
Any side effect	2 (11.8)	0 (0)	5 (31.3)	1 (6.7)
Dizziness/Faintness	1 (5.9)		3 (18.8)	
Somnolence			1 (6.0)	
Feeling Cold			1 (6.0)	
Cognitive Impairment			1 (6.0)	
Dyspnea			1 (6.0)	
Dry Mouth			1 (6.0)	
Injection Site Effects (bruising, pain, stiffness)	2 (11.8)		1 (6.0)	
Nausea/Vomiting			1 (6.0)	1 (6.7)

Number of randomized subjects (%) who experienced side effects at any time on study.

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