Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy

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Abstract: A randomized, double-blinded, placebo controlled crossover study was conducted in 16 patients with painful diabetic peripheral neuropathy to assess the short-term efficacy and tolerability of inhaled cannabis. In a crossover design, each participant was exposed to 4 single dosing sessions of placebo or to low (1% tetrahydrocannabinol [THC]), medium (4% THC), or high (7% THC) doses of cannabis. Baseline spontaneous pain, evoked pain, and cognitive testing were performed. Subjects were then administered aerosolized cannabis or placebo and the pain intensity and subjective “highness” score was measured at 5, 15, 30, 45, and 60 minutes and then every 30 minutes for an additional 3 hours. Cognitive testing was performed at 5 and 30 minutes and then every 30 minutes for an additional 3 hours. The primary analysis compared differences in spontaneous pain over time between doses using linear mixed effects models. There was a significant difference in spontaneous pain scores between doses (P < .001). Specific significant comparisons were placebo versus low, medium, and high doses (P = .031, .04, and <.001, respectively) and high versus low and medium doses (both P < .001). There was a significant effect of the high dose on foam brush and von Frey evoked pain (both P < .001). There was a significant negative effect (impaired performance) of the high dose on 2 of the 3 neuropsychological tests (Paced Auditory Serial Addition Test, Trail Making Test Part B.

Perspective: This small, short-term, placebo-controlled trial of inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain. This adds preliminary evidence to support further research on the efficacy of the cannabinoids in neuropathic pain.

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Key words: Diabetic peripheral neuropathy, cannabis, clinical trial.

The prevalence of diabetic peripheral neuropathy (DPN) appears to be increasing so that it now affects an estimated 366 million individuals worldwide. DPN occurs in approximately 50% of patients with diabetes, with about 15% being painful. DPN can present in several forms, ranging from mononeuropathy to distal polyneuropathy. Patients often complain of pain and sensitivity in their feet, usually worse at night. Other symptoms include hyperalgesia, numbness, paresthesia, sensitivity to touch, unsteadiness, and weakness. Multiple studies have demonstrated the adverse impact and high healthcare costs of DPN, with one study showing a 1.5 to 4 times higher expense than for postherpetic neuralgia. There are currently 2 U.S. Food and Drug Administration–approved medications for the treatment of DPN. Many patients do not achieve satisfactory relief with current treatments, which suggests there is a need for research into additional therapeutic approaches to treat this condition.

Preclinical studies show that a major cannabinoid receptor, CB1, is expressed in regions involved in the dorsal root ganglion, dorsal horn of the spinal cord, peri-aqueductal gray and raphe nucleus, and forebrain. In addition, animal models of nerve injury have demonstrated an upregulation of cannabinoid receptors, suggesting a possible role of the cannabinoids in the treatment of neuropathic pain. Animal studies in models of neuropathic pain, including diabetic...
neuropathy, suggest that the cannabinoids may be effective in reducing pain. Although 4 recent studies on the effect of inhaled cannabis on neuropathic pain may be promising, none have focused specifically on painful DPN.

In a randomized, short-term, placebo-controlled, 4-period crossover trial, we studied the effects of low-, medium-, and high-dose inhaled vaporized cannabis on the pain and hyperalgesia of DPN. Our hypothesis was that cannabis would result in a dose-dependent reduction in spontaneous and evoked pain with a concomitant dose-dependent effect on cognitive function.

Methods

Participants

A randomized, double-blinded, placebo-controlled crossover study was conducted in 16 patients with painful DPN to assess the short-term efficacy and tolerability of inhaled cannabis. Subjects participated in 4 sessions, separated by 2 weeks, in which they were exposed to placebo or to a low (1% tetrahydrocannabinol [THC]), medium (4% THC), or high (7% THC) dose of cannabis. Baseline assessments of spontaneous pain, evoked pain, and cognitive testing were performed. Subjects were then administered aerosolized cannabis or placebo, and pain intensity and subjective “highness” scores were measured at 5, 15, 30, 45, and 60 minutes and then every 30 minutes for an additional 3 hours. Cognitive testing was performed at 5 and 30 minutes and then every 30 minutes for an additional 3 hours.

This trial was performed as an outpatient study at the General Clinical Research Center at the University of California, San Diego, Medical Center. The study was approved and monitored by the University of California, San Diego, institutional review board, the Research Advisory Panel of California, the U.S. Food and Drug Administration, the U.S. Drug Enforcement Administration, the U.S. Department of Health and Human Services, and the University of California Center for Medicinal Cannabis Research.

Participants were men and women age 18 or older with 2) diabetes mellitus type 1 or type 2, who had stable glycemia (HbA1c ≤ 11%) and were maintained by diet or a stable regimen of diabetic therapy for at least 12 weeks before the evaluation, 3) presence of both spontaneous and evoked pain in the feet, 4) at least a 6-month history of painful DPN diagnosed according to research diagnostic criteria (using the Michigan Neuropathy Screening Instrument), which included the presence of abnormal bilateral physical findings (reduced distal tendon reflexes, distal sensory loss) or electrophysiological abnormalities (distal leg sensory nerve conduction studies), plus paresthesia and a spontaneous pain of intensity ≥4 on the 11-point numeric rating scale. Exclusion criteria were 1) current Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), substance use disorders; 2) lifetime history of dependence on cannabis; 3) lifetime history of DSM-IV schizophrenia, bipolar disorder, generalized anxiety or panic disorder, or previous psychosis with or intolerance to cannabinoids; 4) current use of cannabis within the past 30 days; 5) positive urine toxicology screen for cannabinoids during the wash-in week before initiating study treatment; 6) pregnant or planning pregnancy, or positive urine pregnancy test at baseline; 7) serious medical conditions that might affect participant safety or the conduct of the trial (eg, cardiac or pulmonary disease); 8) other medical conditions that are associated with peripheral neuropathy or pain of vascular origin that might confound the assessment of painful DPN; and 9) lower extremity amputations other than toes; and 10) documented unstable blood glucose (fasting <70 mg/dL or random blood glucose >250 mg/dL). If subjects were taking medications to treat the DPN pain, they were required to maintain a stable dose for 30 days prior and for the duration of the study.

Subjects passing a brief telephone screening directed toward painful diabetic neuropathy were invited to in-person interviews that included the following areas. 1) medical history: a systematic semistructured interview was conducted, and as above, individuals with cardiovascular disease, uncontrolled hypertension, and chronic pulmonary disease (eg, asthma, chronic obstructive pulmonary disorder) were excluded; 2) substance abuse history: the Substance Abuse Module of the Diagnostic Interview Schedule for DSM-IV was administered to exclude individuals with current substance use disorders or a past history of dependence on cannabis; and 3) psychiatric screen: the Screening Module of the Structured Clinical Interview for DSM-IV was used to identify individuals reporting potential histories of anxiety or psychotic disorders using the appropriate module of the Structured Clinical Interview for DSM-IV, and subjects were excluded if these disorders were diagnosed. All subjects were provided information about the range of subjective effects they may experience from inhaling marijuana and were instructed in relaxation techniques, should those effects become disturbing. None of the subjects required these relaxation techniques. Vital signs were monitored throughout the protocol, and subjects remained in the laboratory under direct observation by staff for 2 hours after the cannabis dosing was completed. Before the participant was released 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.

Baseline depression was assessed using the Beck Depression Inventory-II (BDI-II). The BDI-II consists of 21 questions, each graded on a 4-point scale ranging from 0 to 3; statements are ordered to show increasing severity of the cognitive and somatic dimensions of depressed mood. Scores range from 0 to 63, with higher scores indicating more depressed mood. Scores from 0 to 13 indicate minimal depressive symptoms; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression. The items of the BDI were clinically derived and have undergone extensive testing for reliability and internal consistency.

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Cannabis Source and Preparation

All active and placebo cannabis was provided by the National Institute on Drug Abuse (NIDA) and was constructed of the same base material. Active strengths ranged from 1 to 7% Δ-9-THC concentration by weight. Cannabidiol concentration was <1%. Placebo cannabis was whole plant material from which the cannabinoids had been extracted and was identical in appearance to active cannabis. Cannabis was placed in an airtight container and stored in a locked, alarmed freezer at the University of California, San Diego, Medical Center Investigational Drug Service Pharmacy. Cannabis was humidified at room temperature within a desiccator using a saturated sodium chloride solution for 12 to 24 hours before use. The potency of the cannabis was provided by the Research Triangle Institute, a subcontractor to the NIDA Drug Supply Program and the University of Mississippi. Under the contract arrangement, the Research Triangle Institute prepares, analyzes, stores, and ships marijuana to recipients designated by NIDA. Confirmatory testing for the potency of cannabis used in this study was not done. However, prior Center for Medicinal Cannabis Research studies conducted initial periodic testing to confirm the potency and stability of each batch of cannabis material provided by NIDA. Cannabis cigarettes were selected from each batch, and the entire content of each cannabis cigarette was extracted into Folch’s reagent (chloroform/methanol, 2:1) for analysis by gas chromatography. This internal testing demonstrated adequate agreement between the labeled potency and actual potency and confirmed the stability of stored cannabis material over the life of the study. Nurses weighed material before and after vaporization and returned all used and unused medication to the pharmacy Investigational Drug Service for appropriate disposal. Randomization was performed by a research pharmacist using a random number permutations, and the key to study assignment was withheld from investigators until completion of statistical analyses.

Cannabis Dosing and Measures

At each session prior to study drug delivery, the following were measured in order: 1) a spontaneous and evoked pain score; 2) BDI-II score; 3) cognitive testing; and 4) baseline blood pressure, heart rate, respiratory rate, and temperature. After study drug administration, the following were assessed in order: 1) spontaneous and evoked pain scores at 5, 15, 30, 45, and 60 minutes and every 30 minutes thereafter for 4 hours; 2) subjective “highness” scores, euphoria, and somnolence at 30, 60, 90, 120, and 240 minutes; and 3) cognitive testing at 5 and 30 minutes and 30 minutes thereafter for 4 hours.

Cannabis Dosing

Each subject received placebo and a single dosing session of 3 doses of cannabis (1, 4, and 7% THC). A washout period of 2 weeks between dose administrations was implemented to minimize a carryover effect of the cannabis treatment. Study treatments were administered under direct observation by a study nurse using a cued-
were to add the current number to the number that preceded it and responded with the total. Thus, after each new digit was presented, a new total was achieved. The number of correct responses was the primary outcome variable.

Subjective highness was assessed by asking the participants 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”) at each assessment point. Euphoria and somnolence were assessed using a “yes/no” format. Any other adverse effects (AEs) that the subjects voluntarily reported were recorded.

Data Analysis

Three types of pain were statistically analyzed: spontaneous, evoked foam brush, and evoked von Frey. Mixed effects models with subject-specific random intercepts were used for all analyses, unless stated otherwise. Changes in pain scores over 240 minutes following the inhalation were analyzed using 2 end points. First, pain scores at each time point were regressed on log_{10}-transformed time and drug dose. Time-dose interactions were investigated but excluded from the final models because of nonsignificant P values. A significant interaction term would indicate differences in slopes (a measure of change in pain over time) between different doses. Without the interactions, models assume differences in pain scores between doses to be constant at all time points. Log transformation of time was used because the observed pain scores exhibited a steep initial decrease in their values (Fig 1), followed by a more gradual change. Such patterns are consistent with logarithmic functions. To evaluate a potential unblinding effect of the order of the placebo dose (first visit vs other) on mean pain scores, it was added as a covariate, but it did not have a significant effect on the outcomes; thus, it was not kept in the models. Separately, an indicator for previous study treatment condition (5 levels: none, placebo, low, medium, and high) was added to the models as a covariate to assess a potential carryover effect. The secondary end points for analyzing change in pain scores over time were individual differences in pain scores between doses to be constant at all time points. Lower values of change in pain correpond to better pain relief. These changes were compared between doses with the repeated measures analysis of covariance (ANCOVA), where pain scores at baseline (time = 0) were used as covariates. This method was also used to compare doses on the average minimum achieved pain level over the span of 240 minutes and the average time it took to achieve the lowest pain. Tukey’s honestly significant difference test for multiple comparisons using the Dunnet method.

Statistical methods described above were also applied to evaluate effects of dose on neurocognitive performance as measured by change in scores of 3 tests: Trail Making Test A, Trail Making Test B, and PASAT-50, for which raw scores were converted to a standardized scale in which a lower score indicates worse performance. Participants showed improvement in test performance over the 4 visits; therefore, visit order was included in these models to control for practice effects. Baseline (time = 0) performance score was also included to account for initial differences between doses. Lower values (ie, larger negative numbers) in the change in scaled scores for neurocognitive testing correspond to worse performance.

Similarly, changes in subjective highness score were evaluated using repeated measures ANCOVA models to regress change in scores on treatment and baseline value as covariate. Larger changes in subjective highness scores correspond to greater feeling of highness measured over time.

Finally, the proportions of people who experienced euphoria and somnolence during the experiment were compared between doses, using mixed effects logistic regressions with random subject effect. Where appropriate, Firth’s correction was applied.

All tests were 2-sided and deemed significant if P value was less than .05. Assumptions appropriate for parametric methods were checked prior to each analysis and, when necessary, outcome transformations were used. All analyses were performed using statistical software R, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

Prior to the study, power analyses were performed and showed that a sample size of 20 was needed to detect a significant beta coefficient in a repeated measures regression model at alpha level = .05 and 80% power, where the size of the coefficient is equivalent to a partial correlation of .45 between cannabis and pain outcome.

Results

Thirty-one individuals were screened. Of these, 7 were not eligible for medical (n = 2) or psychiatric (n = 1) reasons or because of insufficient pain intensity/type (eg, nighttime pain only). An additional 8 subjects were excluded for other reasons, resulting in 16 consenting
participants who were randomized. One participant completed only 2 treatments (placebo and high-dose); those data were used in analyses as appropriate. Baseline characteristics of the study’s cohort are given in Table 1. In general, the sample consisted of approximately equal numbers of men and women, of African American or white ethnicity, who were middle-aged or older, and who had longstanding, often insulin-requiring, diabetes mellitus. Patients reported chronic neuropathic pain of moderately severe intensity. One third of the group had a body mass index in the obese range. The 8 participants who reported use of analgesic medications did not statistically differ from the rest of the group on most baseline characteristics, including baseline pain score, duration of diabetes, and pain (all $P > .10$; detailed results are not shown), with the exception of height. Users of analgesic medications were on average 3.6 inches taller than nonusers ($P = .027$).

Figure 1. Raw (left panel) and predicted (right panel) mean pain scores ($\pm$ standard error) for (A) spontaneous pain, (B) evoked pain (foam brush), and (C) evoked pain (von Frey) from the randomized, double-blinded, placebo-controlled crossover study on effect of inhaled cannabis on DPN pain ($N = 16$). Raw mean scores are means of actual values recorded during the experiment. Predicted mean scores are estimates obtained from the mixed effects models.
**Effects on Pain**

Mixed effects model shows that with every 1 log10 units of time, spontaneous pain intensity score decreased, on average, by 1.1 points. There was significant difference in spontaneous pain scores between doses (P < .001; Fig 1A). Specifically, average pain intensity score in the placebo dose was .44 points higher than the pain score in the low dose (P = .031), .42 points higher as compared to the medium dose (P = .04), and 1.2 points higher as compared to the high dose (P < .001).

There was no statistical difference between the low and the medium doses (P = .92), but the average pain score in the high dose was .73 and .75 points lower than the average scores in the low and the medium doses, respectively (both P < .001). The overall effect of dose on pain remained significant (P < .001) after controlling for prior dose level, which was also a significant predictor of pain (P < .001). On the dose level, only the differences in pain scores between high dose and other doses remained significant. Specifically, the adjusted mean pain scores for high dose were 1.1 points lower than in placebo, 1.01 points lower than in low dose, and .9 points lower than in medium dose (all P < .001).

For evoked foam brush pain, the average reduction in pain was .86 points for every 1 log10 units of time (Fig 1B), and significant differences (dif.) in mean pain scores were observed between the placebo and the medium doses (dif. = .41, P = .045), between the placebo and the high doses (dif. = 1.06, P < .001), between the low and the high doses (dif. = .75, P < .001), and between the medium and the high doses (dif. = .65, P = .002). After adjusting for prior treatment, significant differences (all P < .001) in mean evoked foam brush pain scores were observed between the placebo and the high doses (dif. = 1.1), the low and the high doses (dif. = .92), and the medium and the high doses (dif. = .73). Similarly, for evoked von Frey pain, the average reduction in pain was .94 points for every 1 log10 units of time (Fig 1C), and significant differences in mean pain scores were observed between the placebo and the high doses (dif. = .70, P < .001), between the low and the high doses (dif. = .54, P = .007), and between the medium and the high doses (dif. = .40, P = .04). These differences remained significant after adjusting for prior treatment (placebo vs high: dif. = .66, P = .001; low vs high: dif. = .69, P = .001; medium vs high: dif. = .52, P = .013).

Mean change in pain intensity scores was compared between conditions at every time point. Table 2 lists estimated means and standard deviations of change in pain adjusted for baseline pain values, where negative values indicate decrease in pain as compared to baseline. The repeated measures ANCOVA analyses showed that decreases in spontaneous pain for the high-dose cannabis were significantly greater than decreases in the placebo after 30 minutes (d = −1.02, P = .026), 45 minutes (d = −1.15, P = .006), and 60 minutes (d = −1.05, P = .016). For changes in foam brush evoked pain, when comparing high-dose cannabis and placebo, the effect sizes were d = −.089 (P = .06) and d = −.89 (P = .12) at 45 and 60 minutes, respectively. A significantly greater effect of high dose compared to placebo was also seen in analysis of changes in von Frey pain after 15 minutes (d = −.94, P = .04), 45 minutes (d = −.88, P = .06), and 60 minutes (d = −.94, P = .04).

As mentioned above, the mixed effects models for comparing pain change over time between doses also evaluated potential unblinding or carryover effect from a previous dose. Models that included a binary indicator for the order of the placebo dose (first visit vs other) showed that it did not have significant effects on pain outcomes (all P > .37) and it did not alter the effect of dose on pain outcomes. Models that controlled for the previous dose (none, placebo, low, medium, high) showed that although significant differences between the doses remained as outlined above, the previous dose was also significantly associated with the 3 pain outcomes. Specifically, placebo, low, and medium prior doses were significantly associated with higher mean pain scores at the following visit (d = −.41−.81, all P < .01) as compared to a visit with no prior dose (ie, scores at first visit). However, the effect of high prior dose was not statistically different from the effect of no prior dose (d = .11−.3, all P > .08). Additionally, high prior dose was significantly associated with lower mean pain scores at a subsequent visit when compared to placebo and low prior doses for spontaneous and evoked foam brush pain (d = −.65 to −.34, all P < .05) and medium dose for spontaneous pain (d = −.4, P = .03).

The minimum pain score achieved during each 4-hour session was obtained for every participant, as well as the time (in minutes) he or she took to achieve it. The unadjusted average values for these measures are given in Table 3, separately for each dose and pain type. On
average, the lowest minimum pain score was achieved in the high dose, and the highest minimum pain score was in the placebo dose. However, models that adjusted for baseline pain score showed that these differences did not reach statistical significance, although for spontaneous pain, the effect size between the medium and the placebo doses was \( d = -0.61 \), and between the high and the placebo doses, \( d = -0.60 \). There were no statistical differences between doses in the average time it took to reach the lowest pain score.

Table 3 also shows results of the analyses of percent (%) reduction in pain scores from baseline to the time point when the pain was the lowest. Pairwise comparisons showed that the mean percent reduction in spontaneous pain for the high dose was significantly greater compared to the placebo dose (70 vs 53%, \( d = 0.81, P = 0.032 \)), whereas comparison between the medium and the placebo doses approached significance (65 vs 53%, \( d = 0.72, P = 0.06 \)). Comparison of the proportions of participants who achieved at least 30% reduction in spontaneous pain scores did not show statistically significant results.

Analyses of percent reduction in foam brush evoked pain, and, separately, von Frey evoked pain scores did not show statistically significant differences between doses.

### Effects on Neurocognitive Tests

Results for the neurocognitive testing scaled scores at each time point are shown in Figs 2A–2C. The overall tests for differences between doses in mean changes from baseline at each time point were not significant for any of the cognitive tests. However, using a less conservative pairwise analysis and adjusting for visit order and baseline scaled score (time = 0), performance on the PASAT during placebo differed from medium (\( d = -1.03, P = 0.024 \)) and high (\( d = -1.14, P = 0.008 \)) doses at 15 minutes, whereas Trail Making Part B differed between placebo and high dose only at 120 minutes (\( d = -1.15, P = 0.009 \)). There were no significant differences between treatment conditions on Trail Making Part A at any time point. The largest mean scaled score changes with treatment, compared to baseline, were typically <1.5 scaled score.
points. Given the small sample size and limited power, we also examined effect sizes. Effect sizes were greater than .5 on Trail Making Part A at 15 minutes for high versus low (d = −.63) and high versus medium doses (d = −.80); Trail Making Part B at 15 minutes (medium vs low dose [d = −.56]), 60 minutes (high vs placebo [d = −.53]), and 120 minutes (high, medium, and low vs placebo [d = −1.15, −.71, and −.75, respectively]); and on the PASAT at 15 minutes (high, medium, and low vs placebo [d = −1.14, −1.03, and −.72, respectively]) and 60 minutes (high vs placebo [d = −.81], high vs low [d = −.70]).

Analyses of changes in subjective highness score showed a stairstep effect of dose that mostly wore off after 4 hours (Table 4). Significant differences in changes (all P < .05) were observed at 30 minutes (medium vs placebo [d = 1.14]), at 60 minutes (medium vs placebo [d = 1.49], high vs placebo [d = 1.64], high vs low [d = 1.01]), at 90 minutes (medium vs placebo [d = .97], high vs placebo [d = 1.21], high vs low [d = 1.13]), and at 120 minutes (medium vs placebo [d = 1.25], high vs placebo [d = 1.47], medium vs low [d = 1.11], high vs low [d = 1.34]) but not at 240 minutes. Additionally, mixed-effects models were used to correlate subjective highness score with spontaneous pain score. The analysis estimated that as the subjective highness score increased by 1 point, the pain score decreased on average by .32 points (P < .001).

Discussion

Our short-term, single-session, crossover study in general found a dose-dependent reduction in pain intensity in response to inhaled cannabis in patients with DPN. Overall, our finding of an analgesic effect of cannabis is consistent with other trials of cannabis in diverse neuropathic pain syndromes.1,2,14,48-50

Nevertheless, there is some uncertainty regarding the dosing range that results in analgesia after administration of cannabis. Some recent studies on the potential effectiveness of cannabis have shown that a medium dose (3.5% THC) is as effective as the high dose (7% THC).1,48 Another dose-finding study examined doses of inhaled cannabis ranging from 0 to 9.4% THC on 23 patients with chronic neuropathic pain. This translated into a daily dose ranging from approximately 2 to 7 mg THC. Only the high dose separated from placebo.46 That high dose is lower than most of those delivered in our protocol (eg, 4, 16, and 28 mg THC). Studies in experimentally induced pain suggest that high doses may increase pain.5,47 In addition, a phase IIb study in cancer pain showed that a sublingual spray of a THC-cannabidiol (CBD) combination was effective only at low and medium doses but not a high dose.30 The uncertainty of dosing from these studies may reflect differences in pain mechanism, small sample size, or psychosocial status of the subjects.20,31,37

There was a significant dose-dependent effect of cannabis on both spontaneous and evoked pain in our study. However, the effect on spontaneous pain was more consistent than the effect on evoked pain. A previous study we performed in healthy volunteers using the

### Table 3. Minimum Pain Score Achieved in 240 Minutes, Time It Took to Achieve the Minimum, Percent Reduction in Pain Associated With the Minimum Pain, and Proportion of Participants Who Have Achieved 30% or More in Pain Reduction

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose (1% THC)</th>
<th>Medium dose (4% THC)</th>
<th>High dose (7% THC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum pain score</td>
<td>3.1 (±2.8)</td>
<td>2.6 (±2.7)</td>
<td>2.6 (±2.8)</td>
<td>2.1 (±2.4)</td>
</tr>
<tr>
<td>Time to minimum pain (min)</td>
<td>76 (±63)</td>
<td>103 (±94)</td>
<td>107 (±81)</td>
<td>95 (±68)</td>
</tr>
<tr>
<td>% reduction in pain</td>
<td>52.8 (±40)</td>
<td>63.8 (±37)</td>
<td>64.8 (±36)*</td>
<td>69.6 (±32)**</td>
</tr>
<tr>
<td>Pain reduction ≥30%</td>
<td>10 (62)</td>
<td>10 (67)</td>
<td>12 (80)</td>
<td>13 (81)</td>
</tr>
<tr>
<td><strong>Evoked pain (foam brush)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum pain score</td>
<td>2.5 (±2.8)</td>
<td>2.0 (±2.3)</td>
<td>2.3 (±2.8)</td>
<td>1.6 (±2.0)</td>
</tr>
<tr>
<td>Time to minimum pain (min)</td>
<td>76 (±65)</td>
<td>103 (±96)</td>
<td>118 (±89)</td>
<td>80 (±59)</td>
</tr>
<tr>
<td>% reduction in pain</td>
<td>60.0 (±39)</td>
<td>63.8 (±39)</td>
<td>66.7 (±36)</td>
<td>68.6 (±33)</td>
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<tr>
<td>Pain reduction ≥30%</td>
<td>10 (62)</td>
<td>11 (73)</td>
<td>12 (80)</td>
<td>14 (88)</td>
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<td><strong>Evoked pain (von Frey)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Minimum pain score</td>
<td>2.5 (±3.0)</td>
<td>2.0 (±2.6)</td>
<td>2.2 (±3.0)</td>
<td>1.9 (±2.4)</td>
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<tr>
<td>Time to minimum pain (min)</td>
<td>74 (±63)</td>
<td>79 (±81)</td>
<td>107 (±94)</td>
<td>65 (±70)</td>
</tr>
<tr>
<td>% reduction in pain</td>
<td>61.2 (±42)</td>
<td>66.7 (±37)</td>
<td>70.3 (±37)</td>
<td>65.5 (±37)</td>
</tr>
<tr>
<td>Pain reduction ≥30%</td>
<td>12 (75)</td>
<td>12 (80)</td>
<td>11 (73)</td>
<td>13 (81)</td>
</tr>
</tbody>
</table>

Note: Values are shown as mean (standard deviation) or n (%). Lower minimum pain scores and greater % pain reduction indicate better pain relief. Lower times to minimum pain indicate faster pain relief. Comparing to placebo: *P < .10, **P < .05.
same doses as those used in the current study showed a significant reduction in capsaicin-induced spontaneous and evoked pain but not secondary hyperalgesia.47 Our current findings, taken together with the previous study in healthy volunteers, suggest a supraspinal mechanism of cannabis, as hyperalgesia and allodynia are likely spinally mediated.

Marijuana contains nearly 500 known compounds, of which more than 80 are classified as cannabinoids.7 The most abundant and main psychoactive compound in cannabis is THC.22 Other major cannabinoids found in cannabis are CBD and cannabinol. CBD is the second most abundant compound in the plant.24 CBD is less psychoactive than THC and appears to enhance the effects of THC, although it is unclear whether this is due to a pharmacokinetic or pharmacodynamic interaction.27 Nabiximols is a sublingual spray containing both THC and CBD and is currently in phase III trials for cancer pain. A preliminary study in 177 cancer patients showed that the THC-CBD combination was superior to THC alone.36 Because the CBD concentration in the cannabis used in this study was so low (<1%), the effects observed are most likely due to THC.

With respect to cognition, there were modest effects of treatment. Attention/working memory, as measured by the PASAT, showed the greatest impact at 15 minutes posttreatment with some residual, albeit nonsignificant, differences in high versus low dose and placebo at 60 minutes. Interestingly, the effect on speeded set switching was greatest at 120 minutes, with the high dose versus placebo difference reaching statistical significance, and medium and low dose showing nonsignificant effect sizes of approximately .7 when compared to placebo. Of note, most of the scaled score differences were less than 1.5 points lower than baseline and did not drop below a score of 8 (in normative groups, scaled scores have a mean of 10 and standard deviation of 3), indicating that there were no dramatic declines in cognition and not into the impaired range. However, it is possible

### Table 4. Changes in Subjective Highness Score From Baseline (Time = 0)

<table>
<thead>
<tr>
<th>TIME (Min)</th>
<th>PLACEBO</th>
<th>LOW DOSE (1% THC)</th>
<th>MEDIUM DOSE (4% THC)</th>
<th>HIGH DOSE (7% THC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>2.76 ± .46</td>
<td>3.66 ± .89</td>
<td>5.67 ± .90**</td>
<td>5.08 ± .87*</td>
</tr>
<tr>
<td>60</td>
<td>2.13 ± .34</td>
<td>3.56 ± .65</td>
<td>5.47 ± .68**</td>
<td>5.81 ± .65**</td>
</tr>
<tr>
<td>90</td>
<td>2.24 ± .37</td>
<td>2.43 ± .75</td>
<td>4.60 ± .81**</td>
<td>5.17 ± .81**</td>
</tr>
<tr>
<td>120</td>
<td>1.16 ± .33</td>
<td>1.47 ± .67</td>
<td>4.01 ± .73**</td>
<td>4.52 ± .68**</td>
</tr>
<tr>
<td>240</td>
<td>.91 ± .25</td>
<td>.44 ± .44</td>
<td>1.23 ± .44</td>
<td>2.02 ± .42</td>
</tr>
</tbody>
</table>

NOTE. Values are shown as mean ± standard deviation, where higher values are associated with stronger feeling of high over time.
Comparing to placebo: *P < .10, **P < .05.

### Table 5. Adverse Effects (N = 16)

<table>
<thead>
<tr>
<th>Euphoria, % (P value)*</th>
<th>Placebo</th>
<th>Low Dose (1% THC)</th>
<th>Medium Dose (4% THC)</th>
<th>High Dose (7% THC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>56.2</td>
<td>66.7 (.43)</td>
<td>86.7 (.042)</td>
<td>100 (.002)</td>
<td></td>
</tr>
<tr>
<td>Somnolence, % (P value)*</td>
<td>37.5</td>
<td>26.7 (.49)</td>
<td>60.0 (.12)</td>
<td>73.3 (.018)</td>
</tr>
</tbody>
</table>

*Comparing to placebo.
that these changes could impact tasks requiring intact attention and speeded processing (e.g., automobile driving) and as such these activities should be avoided in the hours after treatment, particularly at higher doses. This may limit the clinical usefulness with some patients. However, whether repeated dosing at low, clinically effective levels results in increased tolerance to the psychoactive effects is not known and is an area in need of future research. In addition, this study utilized a very brief battery and thus did not address cognitive functions such as learning and memory, or psychomotor speed (e.g., Grooved Pegboard), which have been impacted in other clinical trials of cannabis for the treatment of pain.49

Our study used vaporization of the cannabis leaf as the delivery method. Heating the cannabis leaves to below combustion temperatures (175–225°C) releases the cannabinoids in a vapor that is easily inhaled and titratable to effect. Vaporization is an attractive delivery method for research because it permits the inhalation of volatilized gases without exposure to hazardous pyroles and the high concentrations of carbon monoxide than occurs with combustion.2 In addition, the pharmacokinetics of inhalation are superior to ingestion,26 as peak effects occur quickly and are more easily titrated. As shown in Fig 1, there is an initial steep drop in pain within the first 15 minutes followed by a slower decrease in pain over time. By comparison, ingestion of cannabinoids results in a delayed and highly variable onset and offset of action across individuals, a reduced ability to titrate dosing, and more side effects. On the other hand, in clinical settings, many individuals may find vaporization to be inconvenient or adverse in its own right. This may further limit the clinical applicability of cannabis. Finally, all patients reported either euphoria or somnolence as AEs, which may limit the acceptability of cannabis for analgesia, as is the case for many patients who are prescribed opioids for pain relief. In any event, this was a single-dose study, and no conclusions can be drawn about long-term tolerability as compared with currently available therapeutics.

Limitations of our study include possible lack of blinding due to the psychoactive effects of THC and crossover design, the brief duration of the trial, a restricted assessment of neuropsychiatric and other AEs, and the small number of subjects in the study. There are 2 crossover trials of cannabis that assessed blinding. Results suggest that with the acute delivery, subjects (whether naive or experienced users) are no more likely than by chance to guess assignment. However, with continued exposure, the chance of guessing correctly increases.48 Another study showed that subjects who received placebo first were less likely to guess correctly as compared to those who received cannabis first.14,20 Studies in healthy volunteers show that even placebo cannabis results in reports of “high feeling” although less than with active cannabis, showing dose-dependent increase in reports of “highness.”47 However, in our study, after adjusting for previous exposures, the results remained significant. The placebo response in our study is greater than most studies of neuropathic pain, suggesting that the anticipation of a “high feeling” may have led to a reduction in pain unrelated to the cannabis. Another limitation is the small number of subjects in the study. Power analysis showed that we would need a total of 20 subjects to detect an effect; however, the study was discontinued at 16 subjects because of difficulties with recruitment within the time frame of funding. We chose to focus on anticipated AEs (subjective highness, euphoria, somnolence, and cognitive impairment) and relied on the subjects to voluntarily report other AEs. Therefore, we may have missed more AEs than reported. In addition, we used the Michigan Neuropathy Screening Instrument. Although this instrument is a validated screening tool, the requirement for either reduced deep tendon reflexes or abnormal electrophysiological abnormalities will push the selection of patients with at least a component of large fiber neuropathy, essentially excluding those with predominant small fiber neuropathy. Furthermore, there may have been an indirect effect on pain through a reduction in anxiety that results from cannabis.38 We tried to control for this by excluding patients with a history of anxiety.

Despite these limitations, these preliminary findings, along with prior studies, suggest that cannabis might have analgesic effects in neuropathic pain syndromes, including in patients with treatment-refractory DPN. Larger randomized trials with longer-term follow-up are warranted to assess the analgesic effectiveness of cannabis.

Acknowledgments

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References


