Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain

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ABSTRACT

We conducted a double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Thirty-nine patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling either medium dose (3.53%), low dose (1.29%), or placebo cannabis with the primary outcome being VAS pain intensity. Psychoactive side-effects, and neuropsychological performance were also evaluated. Mixed effects regression models demonstrated an analgesic response to vaporized cannabis. There was no significant difference between the two active dose groups' results ($p>0.7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo vs. low dose, 2.9 for placebo vs. medium dose, and 25 for medium vs. low dose. As these NNT are comparable to those of traditional neuropathic pain medications, cannabis has analgesic efficacy with the low dose being, for all intents and purposes, as operative as the medium dose. Psychoactive effects were minimal and well-tolerated, and neuropsychological effects were of limited duration and readily reversible within 1-2 hours. Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain.

PERSPECTIVE

As one would expect minimal recreational diversion of low dose medicinal cannabis, the analgesia obtained from 1.29% THC is a meaningful outcome. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning.

INTRODUCTION

Neuropathic pain, a disease of the peripheral or central nervous system, develops when peripheral nerves, spinal cord, or brain are injured or the sensory system simply fails to function in a customary manner. This may be caused by an underlying pathological process (e.g., neuropathy) or catastrophic injury (e.g., stroke or spinal cord injury). Alternatively, the etiology may not be discernable; in such instances the pain should be considered maladaptive "in the sense that the pain neither protects nor supports healing and repair". [15] Unfortunately, pharmacologic management of neuropathic pain can be quite challenging. In randomized clinical trials, no more than half of patients experience clinically meaningful pain relief from pharmacotherapy, where success is defined as partial relief. [19] Given a lack of alternatives, validation of unconventional analgesics such as cannabis may address unmet needs. [49] More than a decade ago, the National Institutes of Health (NIH) Workshop on the Medical Utility of Marijuana concluded that neuropathic pain is a condition in which currently available analgesics are, at best, marginally effective, and suggested that cannabis might hold promise for many sufferers of this malady. [5]

In the last decade, there have been several studies that evaluated the short-term efficacy of smoked cannabis for neuropathic pain. Two trials enrolled patients with painful HIV peripheral neuropathy. [1, 18] A significantly greater proportion of individuals reported at least 30% reduction in pain on cannabis (46%-52%) compared to placebo (18%-24%). [1, 18] Contemporaneously, a human experimental model of neuropathic pain using intradermal injection of capsaicin was conducted in healthy volunteers, [55] and suggested that there may be a therapeutic window for smoked cannabis. Low dose cigarettes (2% delta-9-tetrahydrocannabinol (THC)) had no analgesic value, while high dose (8% THC) cigarettes were associated with reports of an increase in pain. But the medium dose of cannabis cigarettes used in this study (4% THC) provided significant analgesia. A fourth trial enrolled a heterogeneous neuropathic pain patient population (complex regional pain syndrome, peripheral neuropathy, focal nerve or spinal cord injury) and also pointed to a medium dose (3.53%

THC) as being more advantageous than the high dose, but for a different reason. [59] Although medium- and high-dose cannabis were equi-analgesic, negative cognitive effects, particularly with memory, were evident to a much lower extent with the medium-dose (3.53% THC) compared to the high-dose (7% THC). [59]

The purpose of the present study is to compare medium dose (3.53% THC) to low dose (1.29% THC) cannabis. If analgesia were maintained while cognitive and psychomimetic effects were moderated, a case could be made for using low-dose (1.29 % THC) preferentially. In addition to varying the concentration of THC studied, the present study examined vaporization as an alternative to smoking cannabis. The shortcomings of smoking marijuana, such as exposure to tar, have long been recognized as providing an obstacle to the approval of medicinal cannabis. [35] Cannabis vaporization is a technique that avoids the production of irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where toxins are released. [24, 41]

MATERIALS AND METHODS

REGULATORY PROCESS

This study was approved by the Human Subjects Institutional Review Boards at the UC Davis Medical Center (UCDMC) and the Veterans Affairs of Northern California Health Care System (VANCHCS). The endorsement process also included mandated state review for a controlled substance involving the Research Advisory Panel of California. National review followed federal regulatory requirements for cannabis research with submissions to the Food and Drug Administration for an Investigational New Drug Application, the National Institute on Drug Abuse, and the Department of Health and Human Services. [43] The study was registered with Clinical Trials. gov with identification NCT01037088.

The cannabis was harvested at the University of Mississippi under the supervision of the National Institute on Drug Abuse (NIDA). NIDA routinely provides bulk cannabis ranging in strength

from 1.29% to 7% THC, subject to the availability of current crop potency. Placebo cannabis is made from whole plant with extraction of cannabinoids. Following overnight delivery, the cannabis was stored in a freezer at the Sacramento VA Research Pharmacy, located in close proximity to the UC Davis Clinical Translational Science Center Clinical Research Center.

SUBJECTS

Participants were recruited from the UCDMC and VANCHCS Pain Clinics, newspaper advertisements, and newsletter postings. All candidates were initially screened via a telephone interview. Qualified candidates with a requisite neuropathic pain disorder (complex regional pain syndrome (CRPS Type I, formerly known as reflex sympathetic dystrophy) [9, 19, 31], thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy or nerve injury) were interviewed and examined by the principal investigator.

All participants were required to refrain from smoking cannabis or taking oral synthetic delta-9-THC medications (i.e. Marinol®) for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to, as much as feasible, confirm this provision. To further reduce unsystematic variation, subjects were instructed to take all other concurrent medications as per their normal routine during the 3 to 4 week study period.

To reduce the risk of adverse psychoactive effects in naïve individuals,[27] previous cannabis exposure was required of all subjects. To ensure that potential subjects did not have depression profound enough to compromise their ability to tolerate the psychoactive effects of cannabis, the PHQ-9 was administered as a screening tool. [40] Subjects with severe depression were excluded. Individuals whose PHQ-9 score indicated mild or moderate depression were offered referral for psychiatric treatment, if therapy was not already in progress. In addition, the Center for Epidemiological Studies-Depression Scale (CES-D) was administered using the three item subscale measuring suicidal ideation proposed by Garrison et al. [21, 22] and others. [20] If any of the items ("I felt life was not worth living"; "I felt like hurting myself"; "I felt like killing myself") were answered affirmatively, the subject was not enrolled in the study.

Candidates with a history or diagnosis of these serious mental illnesses were also excluded. Medical illnesses were also evaluated, and potential subjects were excluded if they had uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (e.g. asthma, COPD), and/or active substance abuse. Routine laboratory analysis included a hematology screen, blood chemistry panel, and urinalysis. Urine drug toxicologies for opioids, benzolyecgonine (cocaine metabolite), benzodiazepines, cannabinoids, and amphetamines were also performed using urine immunoassay quick tests.

DESIGN

The study used a randomized, double-blind, placebo-controlled, crossover design employing medium dose (3.53% delta-9-THC), low-dose (1.29% delta-9-THC), and placebo cannabis. Two doses of medication and a cumulative dosing scheme[14, 25] were employed to determine dosing relationships for analgesia, psychoactive and cognitive effects.

Our previous cannabis study produced a robust placebo response for the primary outcome, pain intensity. [59] Although overcome by the efficacy of cannabis, we sought a methodology to reduce this effect inasmuch as we were using a lower dose in the present study. Clinical trials involving at least five different medications for neuropathic pain have been associated with unanticipated negative results whereby no significant difference between active study medication and placebo was evident, in the context of at least one positive trial. [16] . Experience from the psychiatric literature suggests that trials with flexible dose designs are almost twice as likely to demonstrate significant differences between antidepressant medications and placebo than fixed dose trials. [36] Higher placebo response rates in the fixed dose trials might be explained by an increase in expectations of receiving a beneficial treatment. In order to reduce this potential confound, we incorporated the use of flexible dosing into the present study and allowed subjects to inhale four to eight puffs of cannabis (or placebo) during the second administration period at 180 minutes (Figure 1). This methodology has been previously accomplished for treatment of neuropathic pain with a cannabinoid (Sativex®)[4] and a GABAergic analogue (Lyrica®)[54] where patients self-titrated their overall dose and pattern of dosing

according to their response to and tolerance of the medicine.

PROCEDURES

After informed consent was obtained, participants were scheduled for three, 6-hour experimental sessions at the UC Davis Clinical Translational Science Center Clinical Research Center. The sessions were separated by at least 3 days to permit the metabolic breakdown of THC metabolites. [26] The intervals between sessions ranged from 3 to 14 days with a mean (SD) of 7.0 (1.8) days. Participants received either low dose, medium dose, or placebo cannabis at each visit in a crossover design, with each patient receiving each treatment once, in random order (using a web-based random number-generating program, "Research Randomizer" (http://www.randomizer.org/)). The allocation schedule was kept in the pharmacy and concealed from other study personnel. Patients were assigned to treatment after they signed a consent form. Patients and assessors were blinded to group assignments.

The cannabis was stored in a freezer at -20°C until the day before use. At least 12 hours before each session, 0.8 g of cannabis was thawed and humidified by placing the medication above a saturated NaCl solution in a closed humidifier at room temperature. The cannabis was vaporized using the Volcano® vaporizer (Storz & Bickel America, Inc., Oakland, CA). The vapor was collected in a vaporizer bag with a specially designed mouthpiece that allowed one to willfully interrupt inhalation repeatedly without loss of vaporized cannabis to the atmosphere. As a matter of precaution to prevent contamination of the breathing space of observers, this procedure was conducted under a standard laboratory fume hood with constant ventilation in a room with an ambient temperature of 22°C and a humidity of 40% to 60%.

A cued-puff procedure known as the “Foltin Puff Procedure” standardized the administration of the cannabis. [26] Participants were verbally signaled to “hold the vaporizer bag with one hand and put the vaporizer mouthpiece in their mouth” (30 seconds), “get ready” (5 seconds), “inhale” (5 seconds), “hold vapor in lungs” (10 seconds), “exhale and wait” before repeating puff cycle (40 seconds). Subjects inhaled four puffs at 60 minutes. At 180 minutes, the balloon was refilled and deploying the

flexible dose design described previously, subjects inhaled four to eight puffs. Thus, the minimum and maximum cumulative doses for each visit were eight and twelve puffs, respectively. Participants were observed constantly and could signal that they wanted to stop inhalation for whatever reason by raising their hand.

An assessment was performed before the administration of vaporized cannabis or placebo and hourly thereafter (Figure 1) for six hours. Vital signs (blood pressure, respiratory rate, and heart rate) were recorded at baseline and at every hour to ensure well-being of subjects.

Participants were allowed to engage in normal activities, such as reading, watching television, or listening to music, between puff cycles and assessment periods. After each session, participants were accompanied home by a responsible adult. Upon completion of study sessions, participants were compensated with a modest stipend for their participation (prorated at $25 per hour).

OUTCOME MEASUREMENTS

Spontaneous pain relief, the primary outcome variable, was assessed by asking participants to indicate the intensity of their current pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (worst possible pain). As a secondary measure of pain relief, we used the Patient Global Impression of Change. [38]

The Neuropathic Pain Scale[20], an 11-point box ordinal scale with several pain descriptors, was another secondary outcome. When present, allodynia (the sensation of unpleasantness, discomfort, or pain when the skin in a painful area of the subject's body was lightly stroked with a foam paint brush), was measured using a 100-mm VAS. Heat-pain threshold was determined by applying mild-to-moderately painful heat to the most painful area of the subjects' body using the commercially available Medoc TSA 2001 Peltier thermode. [30] This device applied a constant 1-degree Centigrade per second increasing thermal stimulus until the patient pressed the response button, indicating that the temperature change was considered painful; the heat pain threshold (mean of three attempts) was recorded in degrees Centigrade. Separate subjective intensities for "any drug effect," "good drug effect," and "bad drug effect," were measured using a 100-mm VAS anchored by

"not at all" at 0 and "extremely" at 100 . In addition, psychoactive effects, including "high," "drunk," "impaired," "stoned," "like the drug effect," "sedated," "confused," "nauseated," "desire more of the drug," "anxious," "down," and "hungry" were measured similarly. Mood was measured using 6, 100-mm VAS ratings for feeling: sad vs. happy; anxious vs. relaxed; jittery vs. calm; bad vs. good; paranoid vs. self-assured; and fearful vs. unafraid. Subjects were prompted to provide their current rating for the foregoing items at each measurement of these subjective states.

Neurocognitive assessments focused on several domains: attention and concentration, learning and memory, and fine motor speed. Subjects completed the Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol Test, [58] a test of concentration, psychomotor speed, and graphomotor abilities. This pen and paper test involved having subjects substitute a series of symbols with numbers as quickly and accurately as possible during a 120-second period. The results were expressed as the number of correct substitutions. The Hopkins Verbal Learning Test Revised (HVLT) provided information on the ability to learn and immediately recall verbal information, as well as the ability to retain, reproduce, and recognize this information after a delay. [7] Alternate forms (A through F) were used to minimize practice effects. [6, 8] A list of 12 words (four words from each of three semantic categories) were presented, and the subject was asked to recall as many words as possible in any order. After a 20-minute delay, the subject was asked to recall the words once again (i.e., delayed recall). The Grooved Pegboard Test[39] , a test of fine motor coordination and speed, was also administered. In this test, subjects were required to place 25 small metal pegs into holes on a 3" x 3" metal board as quickly as possible. All pegs were alike, and have a ridge on one side, which corresponds to a randomly oriented notch in each hole on the metal board. First the dominant hand was tested, the task was subsequently repeated with the non-dominant hand, and the total time for each test was recorded. A five-minute limit was employed for those unable to complete the task.

Performance on neuropsychological tests often improves as a result of practice effects. [33] This can be somewhat ameliorated by the use of alternate forms.[8] For this study, we used 6 separate versions of the Hopkins Verbal Learning Test and incorporated a practice testing session at the time

of the screening interview in order to lessen early practice effects. Despite our attempts to limit practice effects (using alternate forms, conducting a pre-baseline practice session), these effects cannot be completely eliminated when subjects are tested repeatedly over a brief period. However, this is likely to result in increased variance, thus attenuating the treatment effect. In addition, practice effects were also mitigated by the use of a placebo arm.

STATISTICAL METHODOLOGY

Linear mixed models with subjects treated as a random effect were used to model the primary and secondary pain and neuropsychological response measures. This methodology takes into account the repeated measures aspect of the within-subjects cross-over study design, incorporating information from observations for each subject at different treatment doses and multiple timepoints within each dose. For initial modeling, terms were included for dose (placebo cannabis vs. low-dose (1.29% delta-9-THC) vs. medium dose (3.53% delta-9-THC) treated as a categorical variable), time (0 vs 60 vs 120 vs 180 vs 240 vs 300 minutes treated as a continuous variable), and dose x time interaction. Additional terms were also included for the sequence in which the treatments were administered (e.g., low-placebo-medium vs. low-medium-placebo, etc.) and for second-order time ($time^2$). The quadratic term is intended to model a U-shaped response curve if responses initially increase (decrease), reach a maximum (minimum), then decrease (increase) back to baseline levels or thereabouts. For each outcome measure, each of these last two terms were omitted from subsequent models and not reported if non-significant.

Dose effects at each timepoint were tested with mixed modeling after re-coding time as a categorical factor and including dose and dose x time terms (plus a term for sequence if significant in the initial model). The direction of disparity among the doses was accomplished using Tukey Honestly Significant Difference (HSD) comparison tests for differences of effects over all timepoints and contrasts within each timepoint. No other adjustments for multiple statistical comparisons were made. Models were fitted using residual maximum likelihood methods. Effect sizes for the neuropsychological testing results were calculated as Z-scores relative to the mean and standard

deviation for placebo. All response observations, including information from subjects who did not complete all experimental sessions, were included in the analyses. The proportions of subjects with a 30% pain reduction rate were estimated with 95% score confidence intervals (CI) and compared between each of the active doses and placebo with Chi-square tests. A 5% significance level was used for all testing.

RESULTS

RECRUITMENT AND WITHDRAWALS

Between December 2009 and March 2011, 59 patients were consented to enroll in the study. Twenty subjects did not receive study medication: 9 withdrew for various reasons and 11 were disqualified following a medical evaluation with subsequent disclosure of exclusionary criteria on a physical exam or laboratory finding. Thirty-nine subjects participated in 111 six-hour study sessions (Figure 2 Consort Flow Chart). No participant dropped out due to an experimental intervention. Furthermore, there were no study related serious adverse events.

The demographic make-up of the 39 subjects is presented in Table 1. The mean (standard deviation) age was 50 (11) years. The majority were males (28 of 39 subjects). Most patients had peripheral neuropathic pain; 8 met the IASP diagnostic criteria for complex regional pain syndrome (CRPS) type I, [9, 19, 31] 6 had diabetic neuropathy; 3 had idiopathic peripheral neuropathy, 3 had post-herpetic neuralgia, 3 had brachial plexopathy, and 3 had lumbosacral radiculopathy. Twelve subjects had central neuropathic pain; 9 had pain related to spinal cord injury, 3 had involvement of the central neuroaxis by multiple sclerosis and 1 had thalamic pain.

Median (range) time from the diagnosis of neuropathic pain to study enrollment was 9 years (6 months to 43 years). All patients had used cannabis before, as required by inclusion criteria. The median (range) time from most recent exposure to cannabis prior to the screening visit was 9.6 years (1 day to 45 years). Of the 39 patients who completed at least one study visit, 16 were current marijuana users and 23 were ex-users. The use of cannabis varied considerably between current

marijuana users and ex-users. Current users and ex-users were similar in terms of the number of patients who smoked daily (6 current users versus 5 ex-users [when they had used]) and had used approximately once every two weeks (8 users versus 6 ex-users). On the other hand, there were only 2 users versus 12 ex-users who used cannabis rarely (once every four weeks or less).

PRIMARY EFFICACY MEASUREMENT: PAIN INTENSITY

The primary analysis compared patients' mean VAS pain intensities before and after consuming vaporized marijuana. The mean (SD) pain intensity at baseline was 58 (23) prior to administration of placebo, and 53 (23) and 57 (24) for the lower (1.29%) and medium (3.53%) doses of cannabis, respectively, on a 0-100 mm VAS, which were not significantly different (Table 2). A treatment effect was noted with cumulative dosing, with the magnitude of differences between the doses changing over time (treatment by time interaction: $p=0.0133$, Table 2). Although separation of the active agents from placebo is visible by time 60 min (Figure 3), significant separation occurred for the first time at 120 min ($p=0.0002$). Increasing analgesia was apparent after the second inhalation of vaporized cannabis at time 180 min ($p<0.0001$). A significant separation was still evident at times 240 min ($p=0.0004$) and 300 min ($p=0.0018$); the analgesic benefits remained stable at these timepoints (Figure 3). Tukey's HSD test revealed that both active doses of cannabis produced equianalgesic responses that were significantly better than placebo.

Ten of the 38 (26%) subjects who were exposed to placebo had a 30% reduction in pain intensity (95% CI: 15-42%) as compared to 21 of the 37 (57%) exposed to the low dose (95% CI: 41-71%) and 22 of the 36 (61%) receiving the medium dose of cannabis (95% CI: 45-75%). These differences are statistically significant (placebo vs. low: $p=0.0069$; placebo vs medium: $p=0.0023$). There was no significant difference between the two active dose groups' results ($p>0.7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo vs. low dose, 2.9 for placebo vs. medium dose and 25 for medium vs. low dose.

Order of treatment administration (placebo, 1.29%, 3.53%) in this cross-over study was not a significant factor effecting the primary outcome variable ($p>0.9$). Generous spacing of patient visits

was designed to alleviate this potential concern.

SECONDARY OUTCOMES

Global Impression of Change

In addition to VAS ratings for pain intensity, the degree of relief was monitored by a seven-point scale of patient global impression of change. As with the VAS ratings, cannabis provided a greater degree of relief than placebo at every time point (Table 2). Once again, the low and medium dose groups showed virtually identical results which were significantly beyond the placebo effect (Figure 4). Pain relief appears to be maximal after the second dosing at 180 minutes post-baseline, but the peak effect drops off 1-2 hours later ($time^2$: $p=0.0050$).

Neuropathic Pain Scale

Measurements from the Neuropathic Pain Scale (NPS) indicate that smoking cannabis positively affected several of the multidimensional pain descriptors associated with neuropathic pain (Table 3). Modeling of intensity, unpleasantness, and deep pain resulted in significant dose effects (all $p<0.0001$), and these effects changed over time (all dose x time interactions $p<0.03$), with significance reached starting one hour after the first set of dosing and continuing for the duration of observation (all $p<0.045$). Taking all timepoints into consideration, the Tukey HSD tests showed that for each of these pain outcomes, the two active drug doses had the same overall effects, which were significantly better than the placebo's effect. Sharpness, burning, and aching pain levels were significantly different among the doses (all $p<0.001$). Both active doses had equal effects on sharpness which were both significantly stronger than the placebo's effect; both the medium dose and placebo were less effective for burning pain than the low dose but equal to each other; and the low dose significantly reduced aching more than the medium dose which, in turn, significantly reduced aching more than placebo. Levels relating to cold, sensitivity, and superficial pain show complex interactions and effects not easily interpretable in a general way. Itching presents no significant dose or dose x time interactions. With the exception of the baseline dose effect on sensitivity, for all four of these outcomes there were no significant dose effects when considering

each timepoint separately, and Tukey HSD tests did not identify any significantly different overall dose effect (Table 3).

Allodynia

Levels of baseline allodynia were unexplainably significantly lower for the placebo treatment arm. Once the placebo treatment was administered, levels increased slightly or remained constant, while after being treated with cannabis, levels generally decreased over time. This differential response is reflected in the significant dose x time interaction term ($p = 0.0093$), but overall dose responses did not differ at any post-baseline times (See Table 2).

Heat Pain Threshold

Mild to moderately painful heat stimuli delivered to the most painful area of the participant's body produced no significant change in response to treatment over time ($p>0.05$) as well as no indication of treatment differences ($p>0.05$) at any time point (data not shown).

Subjective and Psychoactive Effects

Using several variables to explore side effects, the categorical main effect of treatment (low dose vs. medium dose vs. placebo) as well as treatment by time interaction effects were considered in the modeling.

Subjective Effects

In the medium dose group, the VAS for "any drug effect" and "good drug effect" reached pinnacles at 180 minutes at means of 46 and 48 out of 100 mm, respectively, after the second cumulative dose. There was a significant main effect of treatment ($p<0.0001$ at all time points) with the low dose being below that of the medium dose and the placebo values being lower than both. An interaction with time was not apparent ($p>0.05$) as the effects for all doses were similarly influenced by cumulative dosing after the initial administration and consistently receded slowly during the recovery phase when testing occurred at 240 and 300 minutes. Significant quadratic effects reflect the recovery after the second dosing (both $p<0.02$, Figures 5A and 5B).

Although there was an overall significant dose effect on a "bad drug effect" (Figure 5C,

p=0.0031), this difference was not evident for the active groups when compared to placebo except at 240 minutes. (p=0.0025). However, this effect was very minimal at a mean of 14 out of 100 mm and thus, unlikely to be clinically important.

Psychoactive Effects

There was a significant effect of treatment ($p<0.003$ at all time points) for the VAS "feeling high" with the low dose again being below that of the medium dose and the placebo values being lower than both (Figure 6A). "Feeling stoned" was also scored greater for the medium dose group ($p<0.004$ at all time points); again, the VAS "feeling stoned" revealed that the low dose was below that of the medium dose and the placebo values were equal or lower than the former (Figure 6B). Considering the entire time course, both treatment groups differed from placebo but not from each other on "feeling drunk" ($p<0.0001$), but significance occurred only at 180 minutes with administration of the second dose ($p=0.0174$). However, this was of questionable clinical relevance as the mean VAS measures varied between 6 and 13 out of 100 mm for the three groups at this time point (data not shown). The treatment groups differed from placebo on "feeling impaired" at 180 minutes ($p\leq0.0001$) and 240 minutes ($p=0.0027$). As with the other side-effects mentioned above, this was not meaningful clinically given the low values encountered (Figure 6C).

Somewhat more suggestive of an agreeable effect was the sensation of "like the drug effect", with means by timepoint that varied between 27 and 43 out of 100 mm for the two active dose groups (data not shown). There was a significant main effect of treatment ($p<0.0001$), with significance reached at all time points, (all $p<0.002$), once again with the low dose being below that of the medium dose and the placebo values being lower than both. While the main effect of treatment for "desire more of the drug" was significant ($p=0.0312$), over the entire time course, the low dose scores were higher than those for placebo, but the medium dose results were no different from either of the other two. Significance was not seen at any single timepoint (data not shown).

"Feeling sedated" was endorsed during every dose session with a significant main effect of treatment ($p<0.0001$) and at all time points ($p<0.05$), but there was no interaction with time ($p>0.05$).

As with other side effects, the effect was highest with the medium dose, moderate with the low dose and lowest with the placebo (data not shown). But the clinical significance was fairly small as the highest mean sedation was 21 out of 100 mm (anchored by “not at all” at 0 and “extremely” at 100) one hour after the second vaporization session at 240 minutes with the medium dose (3.53% THC) and the highest mean sedation for the low dose (1.29%) and placebo were 17 at time 180 and 10 at time 60, respectively. Likewise, “feel confused” had an overall significant main effect of treatment ($p<0.0001$) and time point-specific significance ($p<0.05$) at times 120, 180 and 240 minutes. Again, the ordering of effect strength was as expected: 3.53>1.29>0; however, this was not a clinically meaningful issue with a maximum level of 16 out of 100 mm among all doses at all timepoints (data not shown). Effects on “feeling nauseated” were also not likely to be clinically relevant as these values never exceeded 8 out of 100 mm. The main dose effect ($p=0.0255$) revealed more nausea for the medium dose than for placebo, but in fact, active study medication only separated from placebo at one time point, 240 minutes (data not shown). “Feeling hunger” differed between doses ($p=0.0008$) but showed a recovery effect by the end of the observation period ($dose^2$ $p<0.0001$). Although Tukey’s HSD test shows the higher dose resulted in significantly more hungry feelings than for the medium dose and placebo which were equal to each other, no one time point showed a significant dose difference (data not shown). “Feeling anxiety” and “feeling down” were not prominently affected by cannabis in this study. All the VAS values at the six different time points did not differ significantly between groups ($p>0.05$) and there were no significant main effects (data not shown).

For all of the above subjective and psychoactive side effects, no interaction with time occurred ($p>0.05$) implying that whatever differences existed between and among the active and placebo cannabis doses, fluctuations of responses were in similar directions for all doses over the six time points.

Mood

Mood was measured using VAS for feeling: sad vs. happy; anxious vs. relaxed; jittery vs. calm; bad vs. good; paranoid vs. self-assured; and fearful vs. unafraid. Any mood measure with

significant dose effects over the entire time period either had no treatment effect at any specific timepoint or if there was one, the effect sizes (mean differences between timepoint-significant doses) were all less than 10 out of 100 mm for these locally developed mood scales and, thus, probably not important considerations (data not shown).

Neuropsychological Testing

Results of the five neuropsychological tests are presented in Figures 7A-E. The main effects of dose and time model the cognitive effects over time associated with the given dose of cannabis. The pre-treatment scores (time 0) had non-significant differences at time 0 ($p>0.05$). This was predictable as participants did not have residual effects from previous treatments and had been instructed not to use marijuana for 30 days prior to study entry or during the intervals between study sessions.

The Dominant Hand Grooved Pegboard Test demonstrated significant dose effect differences at 60 minutes ($p=0.0007$) and 240 minutes ($p=0.0023$; Figure 7A) with participants taking a maximum of 10 seconds longer at these timepoints to complete this psychomotor task with the low dose cannabis than with the medium or placebo doses. Although the results do not appear to reflect a typical dose-response relationship, statistically significant differences occur only between placebo and each of the two active study doses according to the Tukey test. Significant dose effect differences were also seen on the Non-Dominant Hand Grooved Pegboard Test at two time points; 120 minutes ($p=0.0035$) and 180 minutes ($p=0.0325$), although in this case both low and medium doses of cannabis increased the completion time. Similar to that seen with the dominant hand, participants on cannabis took a maximum of 10 seconds longer than under placebo conditions (Figure 7B).

The Digit Symbol Test also demonstrated significant dose effect differences at 60 minutes ($p=0.0415$) and 180 minutes ($p=0.0006$), corresponding to study drug administration). Participants were completed fewer items on both active study drug doses, compared to placebo (Figure 7C). Interestingly, some recovery was seen one hour after each administration of medication at times 120

minutes and 240 minutes, in that there were no significant differences in performance.

The Hopkins Verbal Learning Test (HVLT) demonstrated significant dose effect differences at 60 minutes ($p=0.0256$), 180 minutes ($p<0.0001$) and 240 minutes ($p=0.0002$). The effects tracked with study drug administration and both active study drugs resulted in worse performance than placebo (Figure 7D). Based on the Tukey HSD test, the medium dose performance was worse than the low dose, and the low dose was worse than placebo. The differences in the number of words recalled between sessions with active study medication and the placebo session was less than 2 out of a maximum number of 36 words (3 trials of 12 words each).

The HVLT - delayed recall demonstrated significant dose effect differences at 120 minutes ($p=0.0273$), 180 minutes ($p=0.0013$) and 240 minutes ($p=0.0060$). The medium dose resulted in fewer words retained than the other doses (Figure 7E). Although the absolute differences were small (1-2 words out of a maximum of 12), Tukey's HSD test confirmed that the low dose did not differ from the placebo condition (Figure 7E) whereas the medium dose did separate from placebo not only at three time points, but after considering all times together as well.

As expected, cannabis produced a general cognitive decline, as indicated by the difference of scores between treatment groups on all tests over time. Most effect sizes were small, with the greatest dose effects seen on learning and memory, where effect sizes were in the small to medium range (Table 4).

DISCUSSION

In the present study, we substituted low dose (1.29% THC) for the high dose (7% THC) previously utilized in our first study, [59] and compared this measured quantity to medium dose (3.53% THC) cannabis. In addition, we discarded smoking as a delivery technique in favor of vaporizing cannabis to reduce exposure to harmful pyrolytic compounds. [2, 23] Both the low and medium doses proved to be salutary analgesics for the heterogeneous collection of neuropathic pain conditions studied. Both active study medications provided statistically significant 30% reductions in pain

intensity when compared to placebo. The low dose vs. placebo NNT was 3.2; that for the medium dose vs. placebo was 2.9. Both values are similar in magnitude to previous HIV-associated painful sensory neuropathies studies evaluating smoked cannabis, [1, 18] and are in the range of two commonly deployed anticonvulsants used to treat neuropathic pain (lamotrigine, NNT = 5.4; gabapentin, NNT = 3.8). [3, 53] Furthermore, as pointed out by Ellis et. al. [6], cannabis is superior to the null results obtained for amitriptyline [37, 52] and mexiletine. [37]

Both the 1.29% and 3.53% vaporized THC study medications produced equal antinociception at every time point. Of note, the side-effect profiles of the low and medium doses were negligible with minimal psychomimetic effects, as measured by locally-developed mood scales. Likewise, neuropsychological differences were nominally different between the two active doses and placebo. Participants on 3.53% cannabis had worse performance than those on 1.29% for learning and memory, while delayed memory was not different between 1.29% cannabis and placebo. Both doses had equivalent effects on the attention measure, with participants doing worse when on cannabis. Participants on 1.29% cannabis had a slightly worse performance than when on 3.53% cannabis during testing of psychomotor skills with the dominant hand. Both doses had equivalent effects on non-dominant hand performance, which in turn was better than testing under placebo conditions.

In general, the effect sizes on cognitive testing were consistent with the minimal doses of THC employed, with the greatest dose effects seen on learning and memory, where effect sizes were in the small to medium range and unlikely to have significant impact on daily functioning. In support of this viewpoint, evidence has accumulated that frequent recreational users become tolerant to many cannabis-related performance-impairing effects. [28, 29, 32, 34, 44, 56] In recent comparisons of cannabis-related effects on cognitive performance of frequent and infrequent users, cannabis significantly reduced performance on tasks assessing perceptual motor control, motor inhibition, and divided attention among occasional cannabis users. [46, 47] In contrast, among frequent users, cognitive performance was largely unaffected.

Separate appraisals using the Patient Global Impression of Change and the multidimensional

NPS revealed that both active agents alleviated pain compared with placebo. Interestingly, evoked pain brought about by lightly touching skin using a foam paintbrush or through testing heat pain threshold with the commercially available Medoc TSA 2001 Peltier thermode (Medoc, Ramat Yishai, Israel) did not confirm an analgesic effect of cannabis. These results are similar to those in our first study[59] and that of another study involving the use of smoked cannabis in patients with human immunodeficiency virus (HIV)-associated sensory neuropathy. [1] The lack of an effect on the experimental heat pain threshold suggests that the analgesic effect of cannabis in treating acute pain would be less than optimal; this is consistent with the recommendation that cannabinoids are not suitable for post-operative pain. [10]

Undesirable consequences of smoking cannabis (i.e., psychological and/or cognitive effects) were identifiable but, consistent with a survey showing that these side-effects are acceptable to patients with chronic pain, [57] no participant withdrew because of tolerability issues. Subjects receiving active agent endorsed a "good drug effect" (Fig 5B) more than a "bad drug effect" (Fig 5C), and the latter was at issue only for the higher dose of cannabis. Similarly, feeling "high," "stoned," or "impaired" were less problematic for the lower strength cannabis (Fig 6A–C). In general, side effects and changes in mood were relatively inconsequential, and again similar to a survey of cannabis users, many who reported daily treatment with cannabis for chronic pain to be a satisfactory experience. [48] A reasonable explanation would be that patients self titrate cannabis, balancing analgesia against negative side effects.

Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5–1 g of plant material. [42] The usual THC concentration varies between 10 and 40 mg, but concentrations >100 mg per cigarette have been detected. Several years ago, it was opined that there are too many variables in the published clinical trials with cannabis to use those studies as a basis for deriving doses.[12] In the present study, subjects consumed unknown amounts of cannabis as the residual vaporized cannabis was emptied into the atmosphere after they consumed 4-8 puffs. Thus, we are not able to comment upon the amount of cannabis consumed. A

recent survey of the amount of medicinal cannabis used per week varied from three grams or less (40.1%) to seven or more grams (23.3%). [48] There being no information as to the concentration of cannabis consumed by those surveyed, it is not feasible to provide any insight whether or not those medicinal cannabis patients were or were not receiving low or high concentrations of THC.

Inferences from currently marketed cannabinoids with a dose-specific prescription provide little additional insight into a best practice for dosing of THC. Marinol (dronabinol) is synthetic THC with sesame oil. Most of the active ingredient is metabolized during digestion, however, so that only 10% to 20% of the original dose reaches the bloodstream. Cesamet (nabilone) is a slightly different blend of synthetic THC that is absorbed more completely into the bloodstream. Both are FDA approved and can be prescribed to reduce chemotherapy-induced nausea and vomiting; Marinol can also be prescribed to stimulate appetite. Among the concerns about both these drugs, though, are that they do not work rapidly, and the amount of medication that reaches the bloodstream varies from person to person. [27]. Sativex is another cannabinoid that has been developed. It is an oromucosal spray that allows flexible, individualized dosing according to the patient's response and tolerance of the medicine. [4] This usually results in the administration of approximately 8-12 sprays/day. [4] Each spray delivers THC 2.7 mg and cannabidiol (CBD) 2.5 mg, giving an approximate average dose of THC 22-32 mg/day and CBD 20-30 mg/day. [4]. In clinical trials, intoxication scores have been low and euphoria reported by only 2.2% of patients. [49] But adverse events such as dizziness, diarrhea, fatigue, nausea, headache and somnolence occur quite frequently with Sativex, although they are generally of mild-to-moderate intensity and their incidence can be markedly reduced by gradual upward titration. [51] Marketed by GW Pharmaceuticals in Britain, numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. [50] Eventually, head-to-head randomized, double-blind comparative efficacy studies of cannabinoids, will have to be performed to determine relative advantages and side-effect profiles. These studies should involve comparative efficacy of cannabinoids with each

other and with other medications, as well as with herbal cannabis. Cannabis sativa contains >400 compounds in addition to the psychoactive substance, THC. It may be that unknown ingredients in the whole plant are more efficacious than THC alone or a mixture of just two constituents (THC and CBD). As previously opined, longitudinal, case control, and double-blind studies are required to rigorously assess marijuana's therapeutic efficacy for specific patient groups, conditions, and diseases. [48]

Not being well standardized, medicinal cannabis has no mandatory labeling for concentration or purity.[64] Eventually, the production of cannabis may undergo quality control measures and standardization through regulation and licensure of producers. Otherwise, purity, concentration and product labeling will not be dependable and quantitative prescribing will not be feasible. Labeling standards may eventually include warning labels and restrictions,[11] similar to those on tobacco and alcohol products as well as dosages and timing directions. In this manner, the use of low doses could potentially be prescribed by physicians interested in helping patients use cannabis effectively while minimizing cognitive and psychological side-effects. Viewed with this in mind, the present study adds to a growing body of literature supporting the use of cannabis for the treatment of neuropathic pain. It provides additional evidence of the efficacy of vaporized cannabis as well as establishes low dose cannabis (1.29%) as having a favorable risk-benefit ratio.

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Disclosures

The authors have no conflicts of interest to report.

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Figure Legends

Figure 1. Experimental procedures and timing of cannabis vaporization sessions

Figure 2. Consort Flow Chart

Figure 3. VAS Pain Intensity

Figure 4. Global Impression of Change

Figure 5. Subjective Side Effects

Figure 6. Psychoactive Side Effects

Figure 7. Neuropsychological Test Scores

Figure 1

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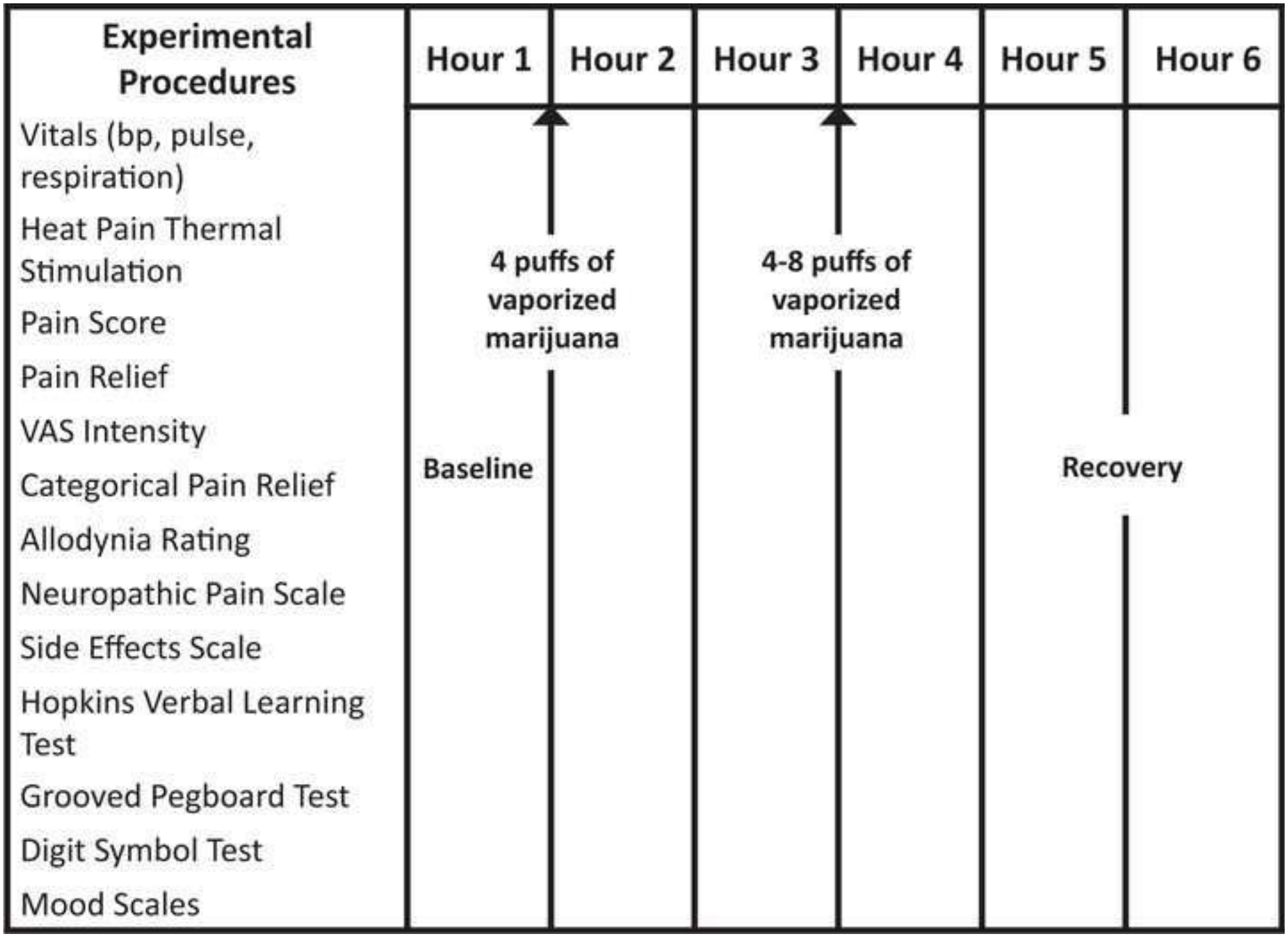

Figure 2
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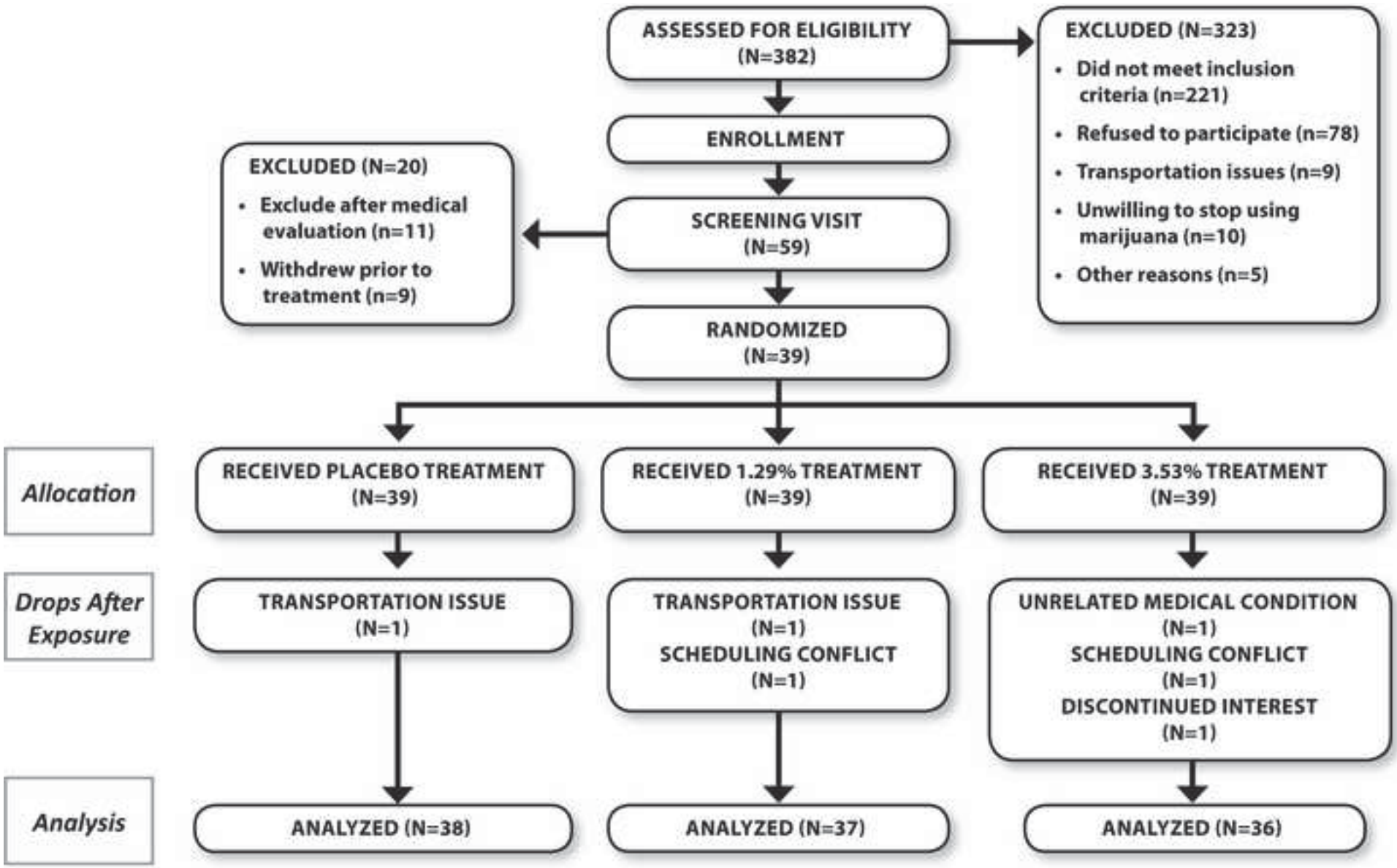

Figure 3

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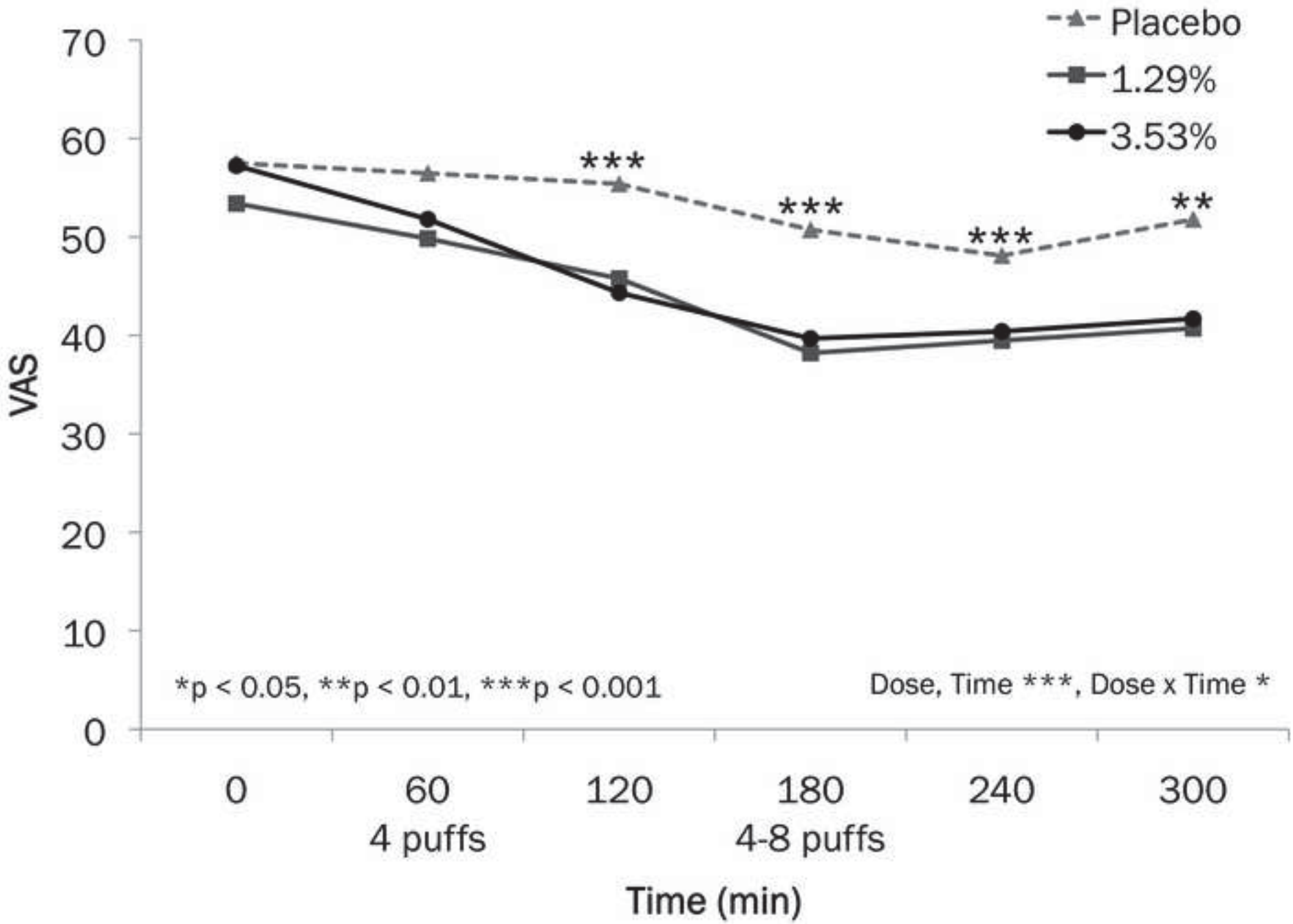

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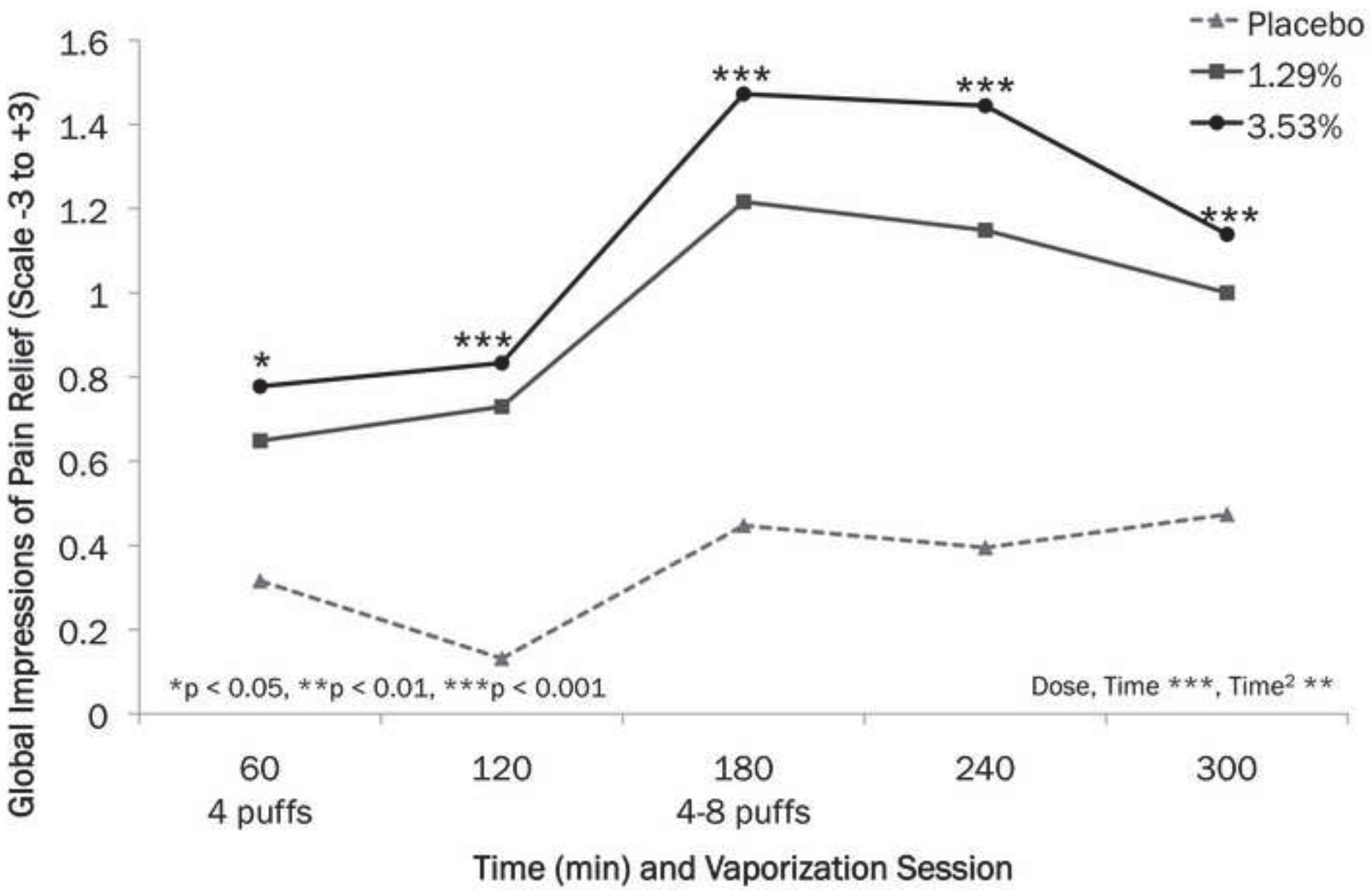

Figure 5

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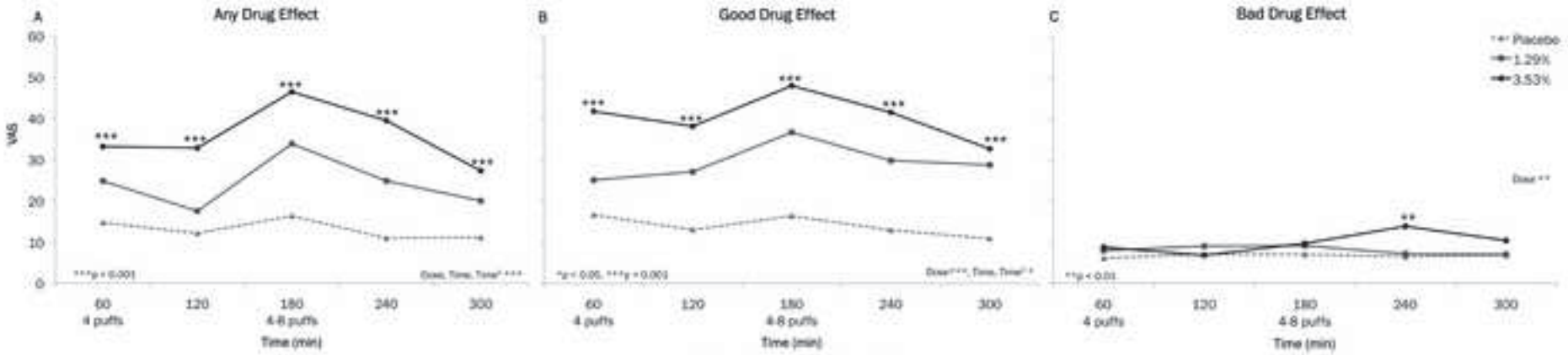

Figure 5. Subjective side effects.

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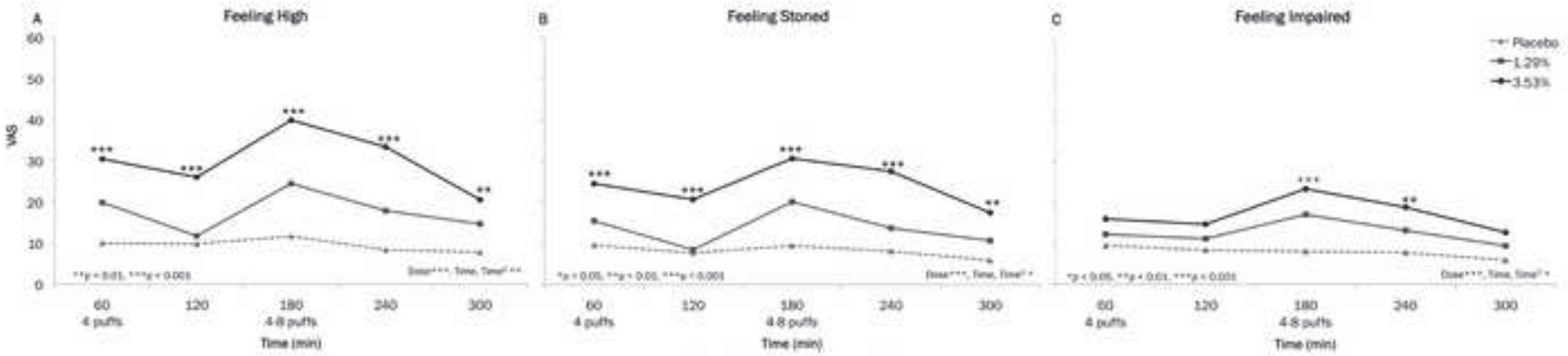

Figure 6. Psychoactive side effects.

Figure 7
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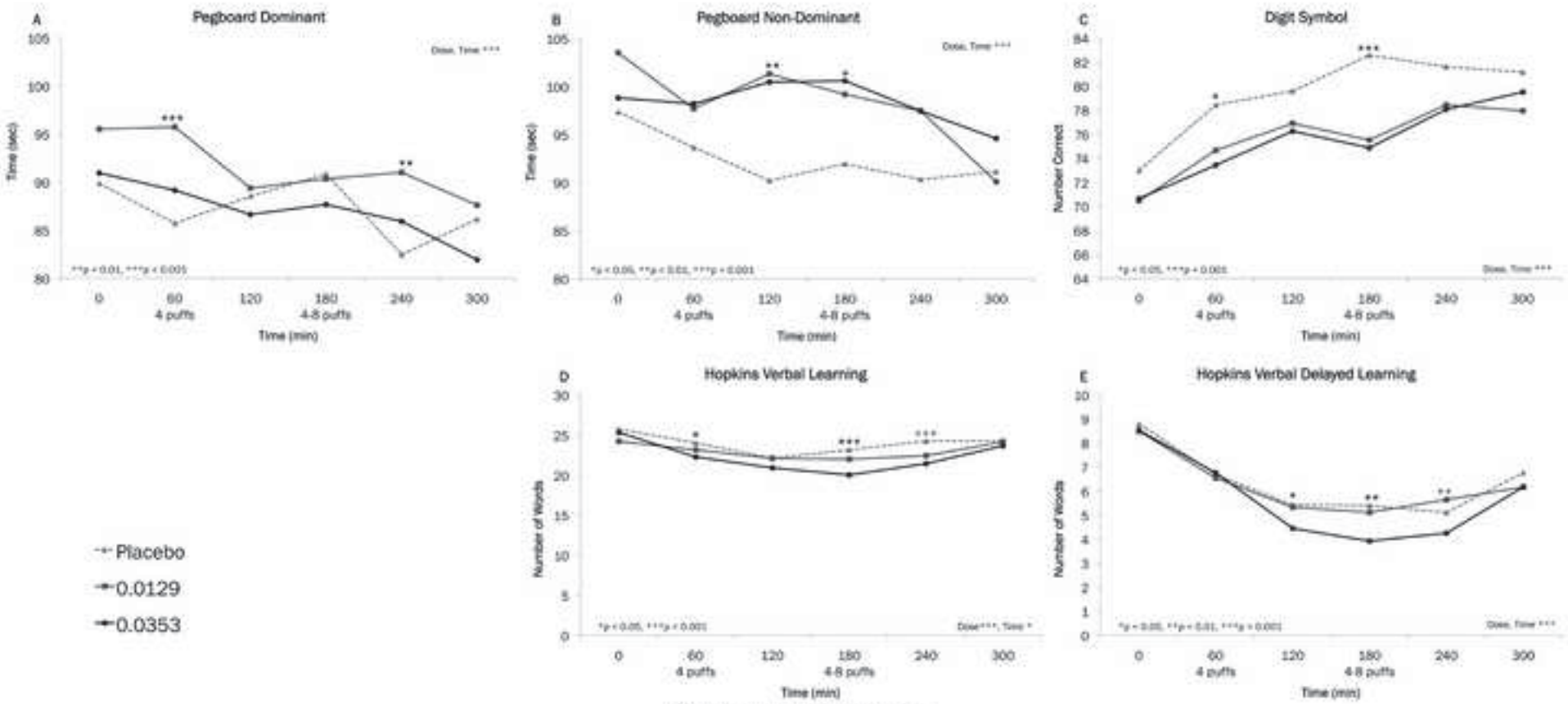

Figure 7. Neuropsychological test scores.

Table 1. Demographics and characteristics of patients (N = 39)	
Sex (no.)	
Male	28
Female	11
Age (yr)	
Mean	50
Standard deviation	11
Education Level (no.)	
Some High School	2
High School Graduate	9
Some College	18
College Graduate	10
Race (no.)	
Caucasian	28
African-American	5
Hispanic	3
Asian American	2
American Indian	1
Other	0
Cause of pain (no.)	
Spinal Cord Injury	9
Complex Regional Pain Syndrome type I	8
Diabetic Neuropathy	6
Multiple Sclerosis	3
Post-herpetic Neuralgia	3
Idiopathic Peripheral Neuropathy	3
Brachial Plexopathy	3
Lumbosacral Radiculopathy	3
Post-Stroke Neuropathy	1
Mean ± SD Baseline VAS (0-100 mm)	
Pain Intensity	
Placebo	57.5 ± 22.8
1.29%	53.4 ± 23.4
3.53%	57.3 ± 24.1
Duration of pain	
Median	9 years
Range	0.5-43.4 years
Concomitant medications (no.)	
Opioids	20
Anticonvulsants	20
Antidepressants	8
NSAIDs	4

Table 2 Significance levels for estimators of **Primary Outcome Pain Intensity and Related Measures** and dose effects at specified timepoints

	Dose	Time	Time2	Dose x Time	0	60	120	180	240	300
Intensity	<0.0001	<0.0001	---	0.0133	ns	ns	0.0002	<0.0001	0.0004	0.0018
Unpleasantness	<0.0001	<0.0001	---	0.0111	ns	0.0155	0.0013	<0.0001	<0.0001	<0.0001
Global Impresssion of Change	<0.0001	0.0003	0.0050	ns	na	0.0128	<0.0001	<0.0001	<0.0001	0.0001
Allodynia	ns	0.0001	---	0.0093	0.0392	ns	ns	ns	ns	ns

ns = not significant; na=not applicable, since there is no baseline measure.

Table 3 Significance levels for estimators of Neuropathic Pain Scale measures and dose effects at specified timepoints.

Measure	Dose	Time	Dose x Time	0	60	120	180	240	300
Intensity	<0.0001	<0.0001	0.0133	ns	ns	0.0002	<0.0001	0.0004	0.0018
Sharpness	0.0006	<0.0001	ns	ns	ns	ns	0.0009	ns	ns
Burning*	0.0001	<0.0001	ns	ns	ns	ns	0.0102	ns	ns
Aching	<0.0001	<0.0001	ns	ns	0.0084	ns	0.0029	ns	0.0444
Cold	0.0463	0.0023	0.0229	ns	ns	ns	ns	ns	ns
Sensitivity*	ns	0.0004	0.0033	0.0194	ns	ns	ns	ns	ns
Itching	ns	0.0124	ns	ns	ns	ns	ns	ns	ns
Unpleasantness	<0.0001	<0.0001	0.0128	ns	ns	0.0162	0.0021	0.0353	0.0157
Deep Pain	<0.0001	<0.0001	0.0257	ns	ns	0.0103	0.0055	0.0036	0.0034
Superficial Pain*	ns	<0.0001	0.0140	ns	ns	ns	ns	ns	ns

ns = not significant *Adjusted for sequence effect

Table 4 Effect Sizes of Neuropsychological Tests

Time (minutes)	Dose (% THC)	Effect size compared to placebo				
		Pegboard Dominant	Pegboard Non-Dominant	WAIS III Digit Symbol	HVLT-Sum of all trials	HVLT-Delay
0	1.29	0.10	0.13	-0.11	-0.27	-0.13
	3.53	0.02	0.03	-0.10	-0.07	-0.11
60	1.29	0.21	0.08	-0.18	-0.13	-0.04
	3.53	0.07	0.09	-0.24	-0.26	0.02
120	1.29	0.02	0.27	-0.11	0.00	-0.02
	3.53	-0.03	0.25	-0.14	-0.17	-0.22
180	1.29	-0.01	0.17	-0.30	-0.17	-0.08
	3.53	-0.05	0.20	-0.33	-0.46	-0.42
240	1.29	0.18	0.20	-0.13	-0.28	0.12
	3.53	0.07	0.20	-0.15	-0.43	-0.20
300	1.29	0.03	-0.02	-0.12	-0.02	-0.15
	3.53	-0.09	0.08	-0.06	-0.09	-0.15