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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.*

***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.[44] DPN occurs in approximately 50% of patients with diabetes, with about 15% being painful.[3,13] 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.[21] 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.[6,11,23] 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.[12]

Preclinical studies show that a major cannabinoid receptor, CB1, is expressed in regions involved in the dorsal root ganglion,[29] dorsal horn of the spinal cord,[45] periaqueductal gray and raphe nucleus,[28,34] and forebrain.[33] 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.[32,42,51] Animal studies in models of neuropathic pain, including diabetic

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neuropathy, suggest that the cannabinoids may be effective in reducing pain.[4,8,9,46] Although 4 recent studies on the effect of inhaled cannabis on neuropathic pain may be promising, none have focused specifically on painful DPN.[1,14,48,49]

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 1) age 18 or older with 2) diabetes mellitus type 1 or type 2, who had stable glycemia (HbA1c $\leq$ 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),[35] 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 $\geq$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[40] 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.[10]