

## REPORT

# The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study

Elon Eisenberg, Miri Ogintz, and Shlomo Almog

### ABSTRACT

Chronic neuropathic pain is often refractory to standard pharmacological treatments. Although growing evidence supports the use of inhaled cannabis for neuropathic pain, the lack of standard inhaled dosing plays a major obstacle in cannabis becoming a “main stream” pharmacological treatment for neuropathic pain. The objective of this study was to explore the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a novel portable thermal-metered-dose inhaler (tMDI) for cannabis in a cohort of eight patients suffering from chronic neuropathic pain and on a stable analgesic regimen including medicinal cannabis. In a single-dose, open-label study, patients inhaled a single  $15.1 \pm 0.1$  mg dose of cannabis using the Syqe Inhaler device. Blood samples for  $\Delta^9$ -tetrahydrocannabinol (THC) and 11-hydroxy- $\Delta^9$ -THC were taken at baseline and up to 120 minutes. Pain intensity (0–10 VAS), adverse events, and satisfaction score were monitored following the inhalation. A uniform pharmacokinetic profile was exhibited across all participants ( $\Delta^9$ -THC plasma  $C_{max} \pm SD$  was  $38 \pm 10$  ng/mL,  $T_{max} \pm SD$  was  $3 \pm 1$  minutes,  $AUC_{0 \rightarrow \infty} \pm SD$  was  $607 \pm 200$  ng·min/mL). Higher plasma  $C_{max}$  increase per mg  $\Delta^9$ -THC administered (12.3 ng/mL/mg THC) and lower interindividual variability of  $C_{max}$  (25.3%), compared with reported alternative modes of THC delivery, were measured. A significant 45% reduction in pain intensity was noted 20 minutes post inhalation ( $P = .001$ ), turning back to baseline within 90 minutes. Tolerable, light-headedness, lasting 15–30 minutes and requiring no intervention, was the only reported adverse event. This trial suggests the potential use of the Syqe Inhaler device as a smokeless delivery system of medicinal cannabis, producing a  $\Delta^9$ -THC pharmacokinetic profile with low interindividual variation of  $C_{max}$ , achieving pharmaceutical standards for inhaled drugs.

**KEYWORDS** analgesia, inhalation, medicinal cannabis, pain, neuropathic pain, pharmacokinetics,  $\Delta^9$ -THC, vaporization

### INTRODUCTION

The use of cannabinoids for neuropathic pain has drawn medical attention during the last 12 years. At least 10 randomized controlled trials, lasting for

days to months and involving more than 1000 patients, have demonstrated efficacy of different types of cannabinoids for diverse forms of neuropathic pain.<sup>1–11</sup> The most common form of neuropathic pain studied was that associated with multiple sclerosis,<sup>1–4</sup> although pain originating from human immunodeficiency virus (HIV),<sup>5</sup> brachial plexus injuries,<sup>6</sup> and other forms of neuropathic pain<sup>7–11</sup> have also responded to cannabinoids.

Nonetheless, cannabis as a “main stream” medical drug has been a matter of controversy for years due to difficulties with its administration according to a typical medical model of drug prescription. Lack of accurate and precise dosing capabilities is one of the major obstacles for the addition of cannabis

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as a major player in the armamentarium of drugs available for pain management. Moreover, lacking a method to administer cannabis in a pharmaceutical fashion makes it difficult for doctors to prescribe and monitor treatment, further blurring the line between medical use and recreational use. Hence, authorities in many countries refrain from approving cannabis for medical use.

A recent international cross-sectional survey<sup>12</sup> on the patterns and prevalence of the medicinal use of cannabis, completed by 953 participants from 31 countries, conducted by the International Association for Cannabinoid Medicines (IACM) found that pulmonary delivery of cannabis is the most preferred route of administration, used by 86.6% (62.9% for smoking and 23.7% for vaporizing) of the participants. The oral mode of delivery of cannabis in edibles had been used by 10.3% of the participants, whereas only 2.3% participants used either cannabis extracts delivered by oromucosal route (Sativex) or synthetic cannabinoids (Marinol and Nabilone) delivered orally in tablet forms. This can be partially attributed to the slow and erratic absorption of cannabinoids with oral administration,<sup>13</sup> leading to delayed onset and often unsatisfactory magnitude of analgesia. A randomized, controlled, double-blind, double-dummy study on oromucosal administration of cannabis revealed a pharmacokinetic pattern similar to that of oral use.<sup>14</sup>

Smoking proves a rapid and efficient method of cannabinoid delivery. Tetrahydrocannabinol (THC) plasma levels increase rapidly. Peak concentrations typically occur at 1–3 minutes, resulting in first onset of effects after about 7 minutes. However, variability in the depth of inhalation, puff duration, and breath-hold time, and the fact that about 30% of the THC dose is assumed to be destroyed by pyrolysis during smoking, leads to heterogeneous bioavailability following the smoking route that ranges between 2% and 56%.<sup>15,16</sup> Clearly, smoking is not a desirable delivery system for medical cannabis, mainly because of the smoking-related diseases caused by noxious pyrolytic byproducts.

A step forward has been made by developing cannabis vaporization techniques aimed to deliver inhaled cannabinoids while avoiding the respiratory hazards of smoking. The temperature at the center of a burning cigarette is 750–800°C. The vaporization of cannabis is performed usually at 170–190°C where active cannabinoid as well as flavonoid and terpenoid vapors are formed, but below the point of combustion (230–235°C) where pyrolytic toxic compounds are made. It has been shown that a vaporization technique, implemented in the Volcano vaporizing device, reduces formation of carbon monoxide

and highly carcinogenic compounds such as polynuclear aromatic hydrocarbons (PAHs), benzene, and tar.<sup>17–19</sup> However, none of these devices can administer cannabis under standard pharmaceutical parameters. The pulmonary delivery of cannabinoids in the vapor phase varies within and between doses due to the subjective visual estimation of the dose amount loaded by the user, repeated asynchronous inhalations from the same loaded dose, inconsistent inhalation dynamics, and a time-dependent condensation of vapors onto the inner surfaces of the device. Subsequently, vaporizers in use today make proper medical monitoring unrealistic.

For cannabis to be used as a “main stream” medical drug, it needs to follow customary pharmaceutical standards in terms of dosing. In this study, a novel high-precision hand-held thermal-metered-dose inhaler for the delivery of cannabis, as well as other raw natural substances under pharmaceutical standards—the Syqe Inhaler Exo (Syqe Inhaler) is investigated.

## MATERIALS AND METHODS

### Patients

The study was conducted at the Pain Research Unit of Rambam Health Care Campus in Haifa, Israel. Following its approval by Rambam Health Center Research Ethics Committee and by the Israeli Ministry of Health, all participants gave written informed consents. Patients were enrolled in the study after meeting the following criteria: (a) aged 18 years or older; (b) suffering from neuropathic pain of any type for at least 3 months; (c) stable analgesic regimen for at least 60 days that included medicinal cannabis; (d) normal liver function (defined as aspartate aminotransferase less than 3 times normal), normal renal function (defined as a serum creatinine level <1.50 mg/dL), and normal hematocrit (37–52%); (e) negative pregnancy test ( $\beta$  human chorionic gonadotropin pregnancy test), when applicable; and (f) possessed a valid license from the Israeli Ministry of Health to receive medicinal cannabis.

Exclusion criteria were presence of significant cardiac or pulmonary disease, history of a psychotic disorder, pregnancy or breastfeeding, or presence of a non-neuropathic pain.

### Study Protocol

The study had a single-dose, open-label design. All participants received a detailed explanation of the study design by the principle investigator. After

providing their written informed consent, the study physician obtained a medical history and conducted a physical examination. Routine medications were continued throughout the trial. Patients were required to abstain from using cannabis for 12 hours prior to the trial. Detailed instructions on the use of the Syqe Inhaler were then provided. Following three successful demonstrative inhalations, the participants inhaled a single dose of  $15.1 \pm 0.1$  mg of cannabis flos for 3 seconds. Blood samples were drawn immediately before and at 1, 2, 3, 4, 5, 10, 15, 30, 60, 90, and 120 minutes after inhalation for monitoring plasma levels of THC and its active metabolite 11-hydroxy- $\Delta^9$ -THC (11-OH-THC). The whole blood was collected in  $13 \times 75$  mm purple-top Vacutainer tubes containing EDTA. Samples were kept on ice and centrifuged within 30 minutes. Plasma samples were aliquoted into 3.6-mL polypropylene Nunc cryotubes (Thomas Scientific, NJ, USA), stored frozen at  $-20^\circ\text{C}$ , and analyzed within 6 weeks. The cannabinoid analysis was performed at NMS Labs (Willow Grove, PA, USA) by multidimensional gas chromatography/mass spectrometry method.

Pain intensity was assessed by asking participants to indicate the intensity of their current pain on a 10.0-cm visual analog scale (VAS) between 0 (no pain) and 10.0 (worst possible pain) at baseline (prior to the inhalation) and at 20 and 90 minutes following the inhalation. Adverse events were recorded at 5, 15, 30, 60, and 120 minutes post inhalation, along with those spontaneously reported by the participants. They were evaluated according to standardized criteria in terms of severity, frequency, duration, and relationship to study drug. Adverse events were graded using the NIH Division of AIDS table for scoring severity of adult adverse experiences. Blood pressure and pulse rate were also recorded at baseline and 30 and 90 minutes post inhalation. Satisfaction from the Syqe Inhaler experience compared with the current method of use (smoking) was assessed by using a 10.0-cm VAS anchored by “not at all” at 0 and “very much” at 10.0 cm, 120 minutes following inhalation.

### Study Medication

The study medication employed was pharmaceutical-grade cannabis flos (Bedrocan, Veendam, The Netherlands) containing 19.9% dronabinol (THC), 0.1% cannabidiol (CBD), and 0.2% cannabinol (CBN). The product was free of pesticides and heavy metal ( $<0.2$  ppp lead,  $<0.02$  ppm mercury, and  $<0.02$  ppm cadmium). Foreign materials (stalks, insects, and other vermin) were absent. Microbiological purity was confirmed (total aerobic microbial count

of  $<10$  colony-forming units (CFU)/g, total yeast and mould count of  $<10$  CFU/g, and absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and bile-tolerant gram-negative bacteria).

The cannabis flos underwent unique processing and loading by Syqe Medical, retaining the natural cannabis compounds in their raw form. The processed cannabis flos was tested for THC by modified gas-chromatography method without derivatization,<sup>20</sup> resulting in a  $\Delta^9$ -THC content of 20.4%. The study drug was provided in preloaded  $15.1 \pm 0.1$  mg doses.

### Study Device

The study device developed by Syqe Medical is a battery-operated, palm-sized, hand-held thermal-metered-dose inhaler, designed to vaporize multiple doses of processed cannabis flos, resulting in pulmonary delivery of active ingredients (Figure 1). The Syqe Inhaler consists of a multidose cartridge, dose counter, indication light, and power switch. The cartridge is preloaded with multiple preweighed  $15.1 \pm 0.1$  mg doses of processed cannabis flos, containing  $3.08 \pm 0.02$  mg  $\Delta^9$ -THC. The vaporization process is instantaneously triggered by the inhalation force of the patient and lasts 3 seconds. The transition to the next dose/inhalation is performed by using a mechanical control. Each dose is heated to  $190^\circ\text{C}$  in 470 ms. The efficiency of the THC vaporization process is  $52.7 \pm 2.7\%$  (data not shown), indicating a low variability between doses inhaled. The device engages automatic thermal and flow controllers that ensure a complete, high-efficiency delivery of cannabinoid vapors to the lungs, independent of the inhalation pattern of the individual patient. Subsequently, the



FIGURE 1. The Syqe Inhaler Exo—a thermal-metered-dose cannabis inhaler.

device requires minimal inhalation training. The device electronically controls and logs the entire inhalation process, allowing for storing and uploading of treatment data logs. The Syqe Inhaler can be programmed to accurately deliver specific doses, enabling individualization of THC regimen in the future. The device allows for “single inhalation” dose resolution, instantaneous administration, and requires no preprocessing or any user intervention other than the inhalation.

## Outcome Measures

The primary outcome of the study was to characterize the interindividual variability of  $\Delta^9$ -THC during the absorption phase. Secondary outcomes included (a) pain reduction from baseline using a 10.0 cm VAS pain scale (0 = no pain; 10 = worst imaginable pain); (b) monitoring adverse effects, blood pressure, and heart rate; and (c) self-estimating the degree of satisfaction with the use of the study device on a 0–10 scale.

## Pharmacokinetic and Statistical Analyses

The peak THC concentration ( $C_{\max}$ ) and time to attain  $C_{\max}$  ( $T_{\max}$ ) were derived directly from the experimental data. Area under the plasma THC concentration time curve (AUC) was determined by linear trapezoidal noncompartmental analysis (WinNonlin Pro version 2.0; Pharsight, Mountain View, CA, USA). The AUC was extrapolated to infinity ( $AUC_{0 \rightarrow \infty}$ ) by the addition of  $C_{\text{last}}/\lambda_Z$ , where  $C_{\text{last}}$  and  $\lambda_Z$  are the last measured THC concentration and the terminal slope on the ln scale, respectively. For those participants who demonstrated a residual plasma THC level at time zero ( $C_0 > 0$ ), the  $AUC_{0 \rightarrow \infty}$  was obtained from the equation:  $AUC_{0 \rightarrow \infty} = AUC_{0 \rightarrow \text{Clast}} + C_{\text{last}}/\lambda_Z - C_0/\lambda_Z$  where  $C_0/\lambda_Z$  is the residual AUC contributed from previous doses.<sup>21</sup>

Results are reported as mean values  $\pm$  SD. For each one of the measured effects (VAS pain intensity, systolic and diastolic blood pressures, heart rate, and satisfaction score), we plotted the mean and 95% confidence interval (CI) at different time points. Differences between VAS pain intensity values and satisfaction scores, before and after inhalation, were tested by two-tailed paired Student *t* test. Blood pressure and heart rate values were compared among different time points by one-way analysis of variance (ANOVA). *P* values  $< .05$  were accepted as significant. All statistical analyses were performed using Minitab Statistical Software, version 16, PN, USA.

## Regulatory Considerations

In conducting the study, we followed the Good Clinical Practice guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, concerning medical research in humans (“Ethical Principles for Medical Research”) and any local (Israeli) regulations.

A clinical site monitoring was performed by GCP-Clinical Studies Ltd., Rosh Ha’Ayin, Israel.

## RESULTS

We screened 30 patients between November and December 2013, of whom 10 were eligible. All 10 patients completed the study. Prior to receipt of pharmacokinetic results, two devices failed posttrial quality control tests, subsequently excluding two patients from all analyses. Patient demographic and baseline characteristic data are presented in Table 1. Participants were predominately men (62.5%), ranging in age from 25 to 69 years (mean age  $\pm$  SD: 42  $\pm$  14). Mean weight  $\pm$  SD and body mass index  $\pm$  SD were 79  $\pm$  21 kg and 27  $\pm$  6 kg/m<sup>2</sup>, respectively. All participants suffered from neuropathic pain: 4 had complex regional pain syndrome (CRPS), 2 had lumbosacral radiculopathy, 1 had pelvic neuropathic pain, and 1 had pain related to spinal cord injury. Median time from the diagnosis of neuropathic pain to study enrollment was 48 months (range: 30–147). All patients were treated routinely with cannabis flos, inhaled by smoking two to three times a day. The median monthly dose was 20–30 g (range: 2–5 up to 30–40).

The interindividual variability in plasma cannabinoids levels are presented in Figure 2 and Table 2. Two patients had residual plasma THC, above the limit of quantitation, at baseline. In all six others, THC was first detected in the blood sample drawn 1 minute post inhalation. THC mean plasma  $C_{\max}$  for the entire group was 38  $\pm$  10 ng/mL and occurred after 3  $\pm$  1 minutes. Mean THC  $AUC_{0 \rightarrow \infty}$  was 607  $\pm$  200 ng-min/mL. As predicted, no measurable plasma levels of the active metabolite (11-OH-THC) were monitored within the time frame of the blood sampling (0–120 minutes).

The mean baseline VAS pain intensity was 7.5  $\pm$  1.4. A significant analgesic response was noted 20 minutes after inhalation (difference of 3.4 points, 95% CI: [2.1, 4.9]; *P* = .001). The VAS values reported at 90 minutes post dosing showed virtually identical results as at baseline (Figure 3).

TABLE 1. Demographic and Baseline Characteristics of Participants

Characteristic	Participant							
	A	B	C	D	E	F	G	H
Gender	M	M	M	M	F	F	F	M
Age (years)	35	41	44	25	41	53	69	28
Weight (kg)	122	73	80	58	89	56	85	71
BMI	35.6	21.8	26.4	17.9	30.8	23.3	34	23.7
Cause of pain								
Spinal cord injury			✓					
CRPS	✓	✓					✓	✓
Lumbosacral radiculopathy					✓	✓		
Pelvic neuropathic pain				✓				
Duration of pain (months)	32	87	30	36	36	75	147	48
Cannabis use								
Dosing: (g Cannabis/month)	20–30	20–30	20–30	15–20	2–5	20–30	15–20	30–40
Concomitant medications								
Opiates		✓					✓	✓
Antidepressants	✓	✓						✓
Anticonvulsants	✓	✓					✓	✓
Benzodiazepines	✓							
Steroids		✓						
NSAIDs, Beta blockers, Others	✓		✓	✓	✓		✓	

The adverse effects were minimal, reversible, and well tolerated. Seven patients (87.5%) experienced lightheadedness for the first 10 minutes following inhalation, but the effect receded rapidly thereafter. Three patients fully recovered within 15 minutes and all the others within 30 minutes post inhalation.

As depicted in Figure 4, comparing with baseline, a borderline significance decrease in the mean systolic blood pressure was noted 30 minutes following inhalation, which persisted for 90 minutes (from  $133 \pm 13$  to  $122 \pm 10$  and  $121 \pm 11$  mm Hg at 30 and 90

minutes post inhalation, respectively;  $P = .068$ ). No significant differences in mean diastolic blood pressure (BP) and heart rate were measured during the study period (for diastolic BP: from  $82 \pm 9$  to  $75 \pm 10$  and  $81 \pm 12$  mm Hg at 0, 30, and 90 minutes post inhalation, respectively;  $P = .410$ ). For heart rate: from  $71 \pm 12$  to  $72 \pm 11$  and  $69 \pm 13$  bpm at 0, 30, and 90 minutes post inhalation, respectively;  $P = .873$ ).

All patients selected inhalation, using the Syqe Inhaler device as their preferred treatment compared with smoking, their current mode of use (satisfaction score of  $9.37 \pm 0.52$  compared with  $5.37 \pm 2.61$ , 95%

TABLE 2. Pharmacokinetics of  $\Delta^9$ -THC Following a Single-Dose Inhalation of  $15.1 \pm 0.1$  mg Processed Cannabis Flos, Containing  $3.08 \pm 0.02$  mg THC, by Using the Syqe Inhaler

Participant	$C_{max}$ ( $\mu\text{g/L}$ )	$T_{max}$ (min)	AUC ( $\mu\cdot\text{min/L}$ )
A	46	3	495
B	53	2	825
C	29	3	850
D	30	5	491
E	38	2	284
F	46	2	724
G	39	3	712
H	26	4	473
Mean	38	3	607
SD	10	1	200

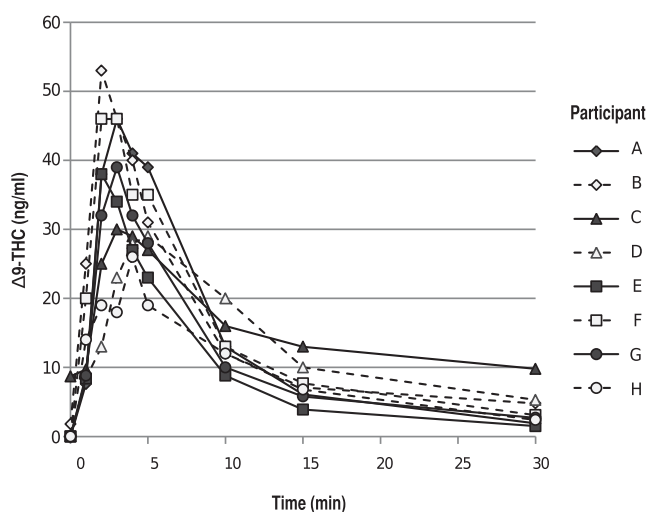


FIGURE 2.  $\Delta^9$ -THC plasma levels following single-dose inhalation of  $15.1 \pm 0.1$  mg processed cannabis flos, containing  $3.08 \pm 0.02$  mg THC, by using the Syqe Inhaler.

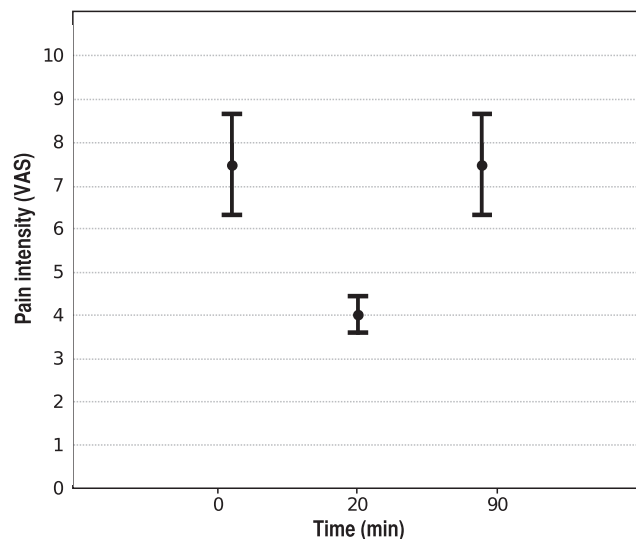


FIGURE 3. VAS pain intensity following single-dose inhalation of  $15.1 \pm 0.1$  mg processed cannabis flos, containing  $3.08 \pm 0.02$  mg THC, by using the Syqe Inhaler.

CI for mean difference: [1.72, 6.28];  $P = .004$ ), as presented in Figure 5.

## DISCUSSION

The present study determined the pharmacokinetic and pharmacodynamic profiles of low  $\Delta^9$ -THC dose inhaled by using the metered-dose Syqe Inhaler, under practical use conditions. Loading the Syqe

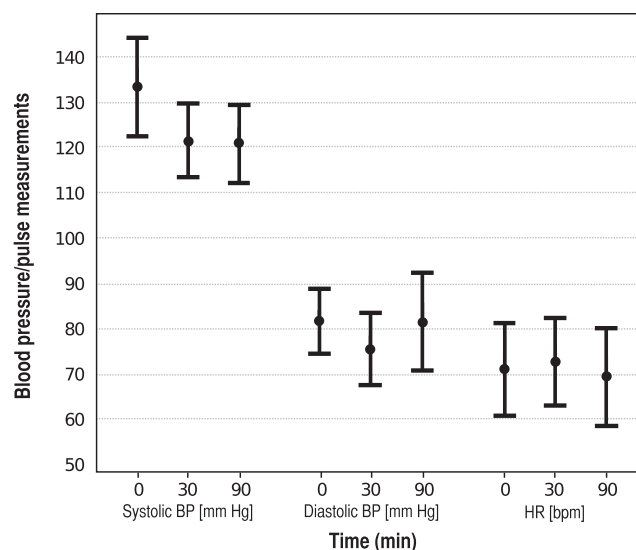


FIGURE 4. Blood pressure and heart rate following single-dose inhalation of  $15.1 \pm 0.1$  mg processed cannabis flos, containing  $3.08 \pm 0.02$  mg THC, by using the Syqe Inhaler.

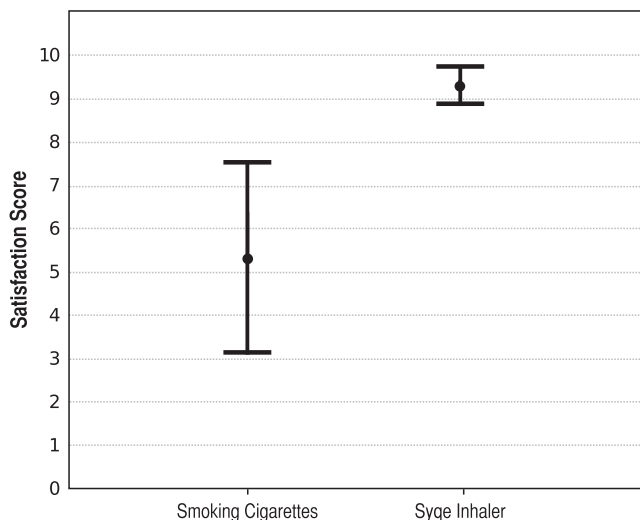


FIGURE 5. Satisfaction with the Syqe Inhaler compared with smoking Cannabis flos.

Inhaler with  $15.1 \pm 0.1$  mg cannabis doses and heating to  $190^{\circ}\text{C}$  for 3 seconds yielded  $52.7 \pm 2.7\%$  of the total  $\Delta^9$ -THC available for inhalation. In comparison, by using different types of smoking procedures, the actual amount of THC delivered in the smoke varies widely and has been estimated at 20–37%, the remainder being lost through combustion (23–30%) and side-stream smoke (40–50%).<sup>22</sup> Furthermore, even by applying the Volcano vaporization technique, heating a dose of 200 mg crude flower tops of cannabis, containing 18% THC, to  $200^{\circ}\text{C}$  resulted in a THC delivery of only 22%.<sup>23</sup> This difference in the extraction efficiency between the Volcano vaporizer and the Syqe Inhaler is probably based on the amount of cannabis loaded, its thickness, and the surface area exposed to the heating source.<sup>24</sup> Whereas smoking marijuana increases levels of noxious smoke compounds, as expected from an inhalation of combusted products, it has been shown that at vaporization temperatures of  $155$ – $218^{\circ}\text{C}$ , polynuclear aromatic hydrocarbons<sup>18</sup> as well as carbon monoxide, benzene, toluene, and particulate tar levels<sup>17</sup> were dramatically reduced in the cannabis vapor phase. Although combustion products were not monitored, the noxious intake from the Syqe Inhaler is expected to be very little, if any, based on the following observations: (1) each dose consists of small amount ( $15.1 \pm 0.1$  mg) of high THC concentration (20%) cannabis; (2) unlike the combusted marijuana, which turned to ash, our residual material, after vaporization, obtained a consistent amber colored appearance; (3) no burning sensation of the upper respiratory track was reported by the participants; (4) no increase of cannabinol (a product of THC oxidation) was

measured in residues; and (5) no transformation of  $\Delta^9$ - to  $\Delta^8$ -THC was detected in residues.

In the present study, we observed a pharmacokinetic profile of THC similar to those previously reported.<sup>13,19,25–31</sup> The pulmonary delivery of THC is characterized by rapid absorption, followed by biphasic decline in plasma concentration over time: a phase of rapid decline corresponding to the distribution of THC to tissues and extensive storage, followed by a phase of prolonged release from adipose tissue to the blood and elimination. Predictably, intravenous administration of THC, as a reference mode of delivery, yields the highest increase of plasma  $C_{\text{max}}$  level per mg of THC administered ( $43.8^{13}$ ,  $32.8^{25}$  and  $23.8^{25}$  ng THC/mL plasma/mg THC), as illustrated in Figure 6. Among the alternative modes of pulmonary delivery, the Syqe Inhaler yielded the highest increase of  $C_{\text{max}}$  per mg of THC available in the cannabinoid material used—mean of  $12.3$  ng/mL/mg THC compared with  $3.9$ – $9.0$  ng/mL/mg for Volcano vaporizer (19, 31) and  $2.9$ – $4.6$  ng/mL/mg for smoking cannabis cigarettes.<sup>26–28</sup> The rapidity of the absorption and distribution processes of THC could lead  $C_{\text{max}}$  to be an artifact of the sampling protocol; that is, random sampling over a large number of individual peaks and valleys after each puff could have produced artificial peak responses. This constraint led Huestis et al.<sup>28</sup> to use a continuous withdrawal pump with adjustable speeds for fast sequential blood sampling in order to fully characterize the absorption phase of marijuana smoking. They reported a mean  $C_{\text{max}}$  increase of  $3.54$  or  $4.28$  ng/mL per mg THC observed after the first puff of a  $1.75\%$  or  $3.55\%$   $\Delta^9$ -THC cigarette, respectively. The smoking protocol consisted of a 2-second inhalation, a 10-second hold period, and a 72-second exhalation and rest period. Our results are higher by a factor of 2.9–3.5 compared with those obtained by Huestis et al., most probable due to a 33% longer inhalation period, the lack of side-stream smoke and the minimal pyrolytic destruction of THC, if any, during the vaporization process in the Syqe Inhaler (Figure 6).

$C_{\text{max}}$  interindividual variability of the Syqe Inhaler is 25.3%. Several studies have reported coefficient of variation (CV) values of 47–85% for vaporizer,<sup>19,31</sup> 32–116% for smoking cigarettes,<sup>13,26,28</sup> 42–115% for oral administration,<sup>13,14,32</sup> and 59–67% for oromucosal route of delivery,<sup>14</sup> as illustrated in Figure 7. Most of the studies were conducted under controlled dosing and experimental conditions. In real life, a higher interindividual variability is expected. One proposed explanation to the relatively low CV reported in the present report is that the Syqe Inhaler is equipped with unique flow and thermal controllers that ensure a complete, high-efficiency delivery of

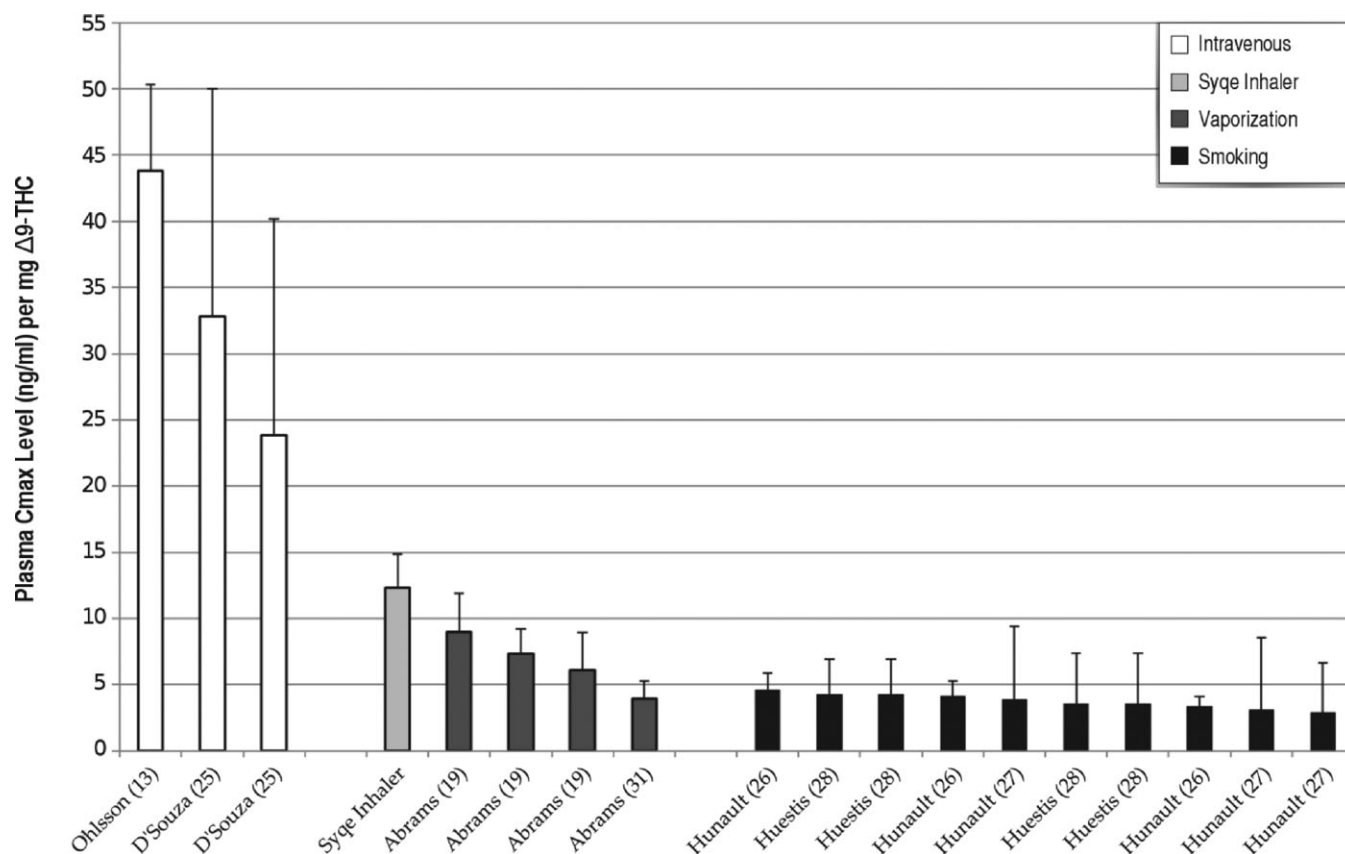


FIGURE 6. Mean and 95% confidence limits of plasma  $C_{max}$  levels per mg  $\Delta^9$ -THC administered by intravenous, the Syqe Inhaler, vaporization, and smoking modes of delivery. Numbers in parentheses represent related references.

cannabinoid vapors to the lungs, independent of the inhalation pattern of the individual patient.

In the present study, low THC dose proved to be salutary analgesics for the heterogeneous collection of neuropathic pain conditions studied. A single inhalation of  $3.08 \pm 0.02$  mg of total available  $\Delta^9$ -THC elevated the  $C_{max}$  plasma level to  $38 \pm 10$  ng/mL and provided a 45% reduction of pain intensity, which reversed within 90 minutes. Undoubtedly, repetitive inhalations over the day are necessary to maintain a significant analgesic effect over time. Our results are consistent with recent clinical trials that enrolled a population of patients suffering from chronic neuropathic pain of various etiologies and pointed to low doses of THC as having a favorable risk-benefit ratio.<sup>9–11</sup> Ware et al.<sup>11</sup> reported that compared with placebo, a single smoked inhalation of low dose, comparable to this consumed in our report ( $25 \pm 1$  mg cannabis, containing 9.4%  $\Delta^9$ -THC; 2.35 mg total available  $\Delta^9$ -THC), given three times a day for 5 days, was associated with mean  $C_{max}$  elevation of 45 ng/mL and 11.4% decrease in average daily pain intensity. In another clinical trial, Wilsey et al.<sup>10</sup> reported that inhalation of vaporized 10.3 mg

total available  $\Delta^9$ -THC, divided into two sessions, separated by interval of 2 hours, is associated with 31% and 25% reduction of pain intensity, at 3 and 5 hours, respectively. Increasing the THC dose to 28.2 mg produced equianalgesic response that remained stable at these time points. Of note, in another clinical trial, Wilsey et al.<sup>9</sup> reported that identical levels of analgesia were produced at each cumulative dose level by smoking either 19 (intermediate dose) or 34 mg of total available  $\Delta^9$ -THC (high dose), divided into three doses, reaching a plateau or “ceiling effect” of 45% reduction of neuropathic pain.

The adverse effects we observed in our study were minimal, reversible, and receded rapidly, in accordance with clinical studies involving low-dose cannabis delivered by inhalation, as mentioned above. No participant withdrew because of tolerability issues. The preweighed low dose selected in the Syqe Inhaler of  $3.08 \pm 0.02$  mg THC was based on three insights: (1) lowering the risk of occurrence and intensity of adverse effects—increasing the THC dosing does not necessarily enhance the efficacy; (2) providing patients a high resolution flexible tool



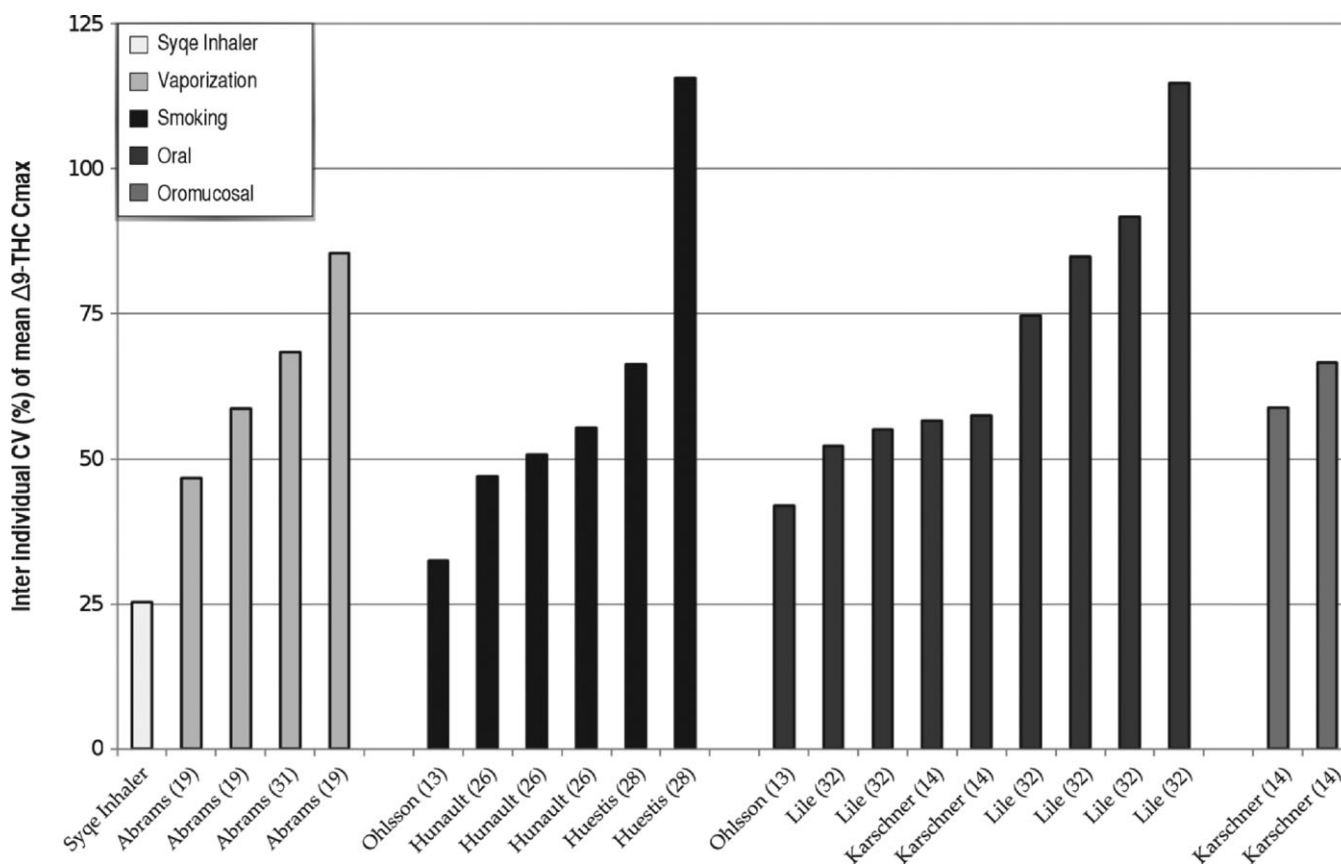


FIGURE 7. Interindividual variability of  $\Delta^9$ -THC plasma  $C_{max}$  obtained by the Syqe Inhaler, vaporization, smoking, oral, and oromucosal methods of delivery. Numbers in parentheses represent related references.

to self-titrate their individual dosing and balance analgesia against negative side effects; and (3) providing, for the first time, a medical device that pharmaceutically complies with the typical medical model of drug prescription.

In conclusion, our trial suggests the potential use of the Syqe Inhaler device as a pharmaceutical method for cannabis dosing, adding a much needed treatment in the limited armamentarium of effective therapies for the management of chronic pain. Additional studies that combine multiple dosing regimens, individualization of treatment by self-titration, monitoring efficacy, and safety parameters are warranted for the complete characterization of the Syqe Inhaler as a medical device.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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