Long-term effectiveness and safety of medical cannabis administered through the metered-dose Syqe Inhaler

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Long-term effectiveness and safety of medical cannabis administered through the metered-dose Syqe Inhaler

Joshua Aviram[a,*], Daniella Atzmony[a], Elon Eisenberg[b,c]

Abstract

Introduction: Preliminary clinical studies on medical cannabis (MC) treatment using the Syqe Inhaler showed short-term effectiveness and safety at very low and precise doses of MC.

Objectives: Here, we retrospectively analyzed "real-life" long-term data collected in real time on the potential effectiveness and safety of MC administered with this device.

Methods: Patients were monitored by Syqe's patient support program. $(-)$-Δ^9-trans-Tetrahydrocannabinol (Δ^9-THC) served as a dosage marker for full-spectrum MC. Pain intensity was evaluated using a numeric pain scale (NPS) from baseline to 120 days after treatment initiation. The change in quality of life (QoL) from baseline was evaluated. Adverse events (AEs) were followed up continuously for 15 months.

Results: Of the 143 patients (mean age 62 ± 17 years; 54% males) included in the analysis, most (72%) were diagnosed with chronic neuropathic pain. The stable daily dose, after a mean 26 ± 10 days of titration was $1,500 \pm 688$ µg aerosolized Δ^9-THC. Significant pain reduction, ranging from 22.8% in the intent-to-treat population to 28.4% in the population that reported baseline pain intensity ≥ 8 points on the NPS ($P < 0.001$), was observed. Ninety-two percent of patients reported improved QoL. Adverse events were reported mostly during the titration phase (34% of patients) and declined to $\leq 4\%$ at 3 to 15 months. Only 7% of patients reported psychoactive AEs (anxiety and restlessness).

Conclusions: Medical cannabis treatment with the Syqe Inhaler demonstrated overall long-term pain reduction, QoL improvement, and a superior AE profile compared with administration of MC by conventional routes. Additional follow-up in a larger population is warranted.

Keywords: Cannabis, Medical use, Metered dose, Chronic pain

1. Introduction

The use of medical cannabis (MC) for treating pain in various medical conditions is on the rise worldwide[9] despite the ongoing debate on whether the low-quality evidence on its effectiveness[10,16] justifies potential harms associated with its use.[14,16] Furthermore, recommended titration regimens and stable effective and safe MC doses are not readily available because of the diverse cultivar selection, which differs in their phytocannabinoid and terpenoid profile,[3] and the multiple administration routes, each with a different bioavailability.[6] Hence, transforming MC into an acceptable medical treatment is a constant challenge.[20]

To achieve a systemic effect, MC is usually delivered orally or sublingually or by inhalation (smoking/vaporization). Both administration routes are characterized by considerable variability in the concentration of $(-)$-Δ^9-trans-tetrahydrocannabinol (Δ^9-THC) in the plasma.[15,17,21] Inhalation of MC is preferred by many patients, possibly because of its fast onset of effects.[17]

The Syqe Inhaler 1.1 (Trade name: SyqeAir, Syqe Medical, Tel Aviv-Yafo, Israel) is a novel metered selective-dose MC inhaler that provides a possible solution for the variability of Δ^9-THC blood levels after inhalation. The inhaler is configured to use a vapor chip (VC) to deliver an aerosol containing 250 or 500 µg Δ^9-THC as an indicator for phytocannabinoids, terpenoids, and other molecules from the whole inflorescence that are aerosolized

concomitantly with Δ^9-THC. The inhaler heats the medical grade cannabis to a temperature below combustion and engages automatic thermal and airflow controls that ensure precise, accurate, and high-efficiency delivery of the produced MC aerosol to the patient's lungs, independent of the inhalation pattern of the individual patient. The inhalation process is similar to shallow breathing (ie, 3–15 L/min): after the user inhales for 1.8 seconds, the inhaler airway becomes blocked and the user experiences resistance. The airway then opens creating a chase-air pulse that flushes the aerosolized MC past anatomic dead space and deep into the lungs, resulting in enhanced bio-availability.[2] An airflow modulation–lung interface reflux serves as an indication for the patient that the inhalation was completed successfully. The entire inhalation process lasts 2 to 5 seconds. For example, the duration of a single inhalation of 500 μg Δ^9-THC is 2.8 seconds.

In a study that evaluated the pharmacokinetics of MC using an earlier version of the inhaler, the maximal concentration in plasma (C_{max}) of 1,000 μg of aerosolized Δ^9-THC ranged from 26 to 53 ng/mL.[12] This C_{max} range was much narrower than the reported C_{max} range after cigarette smoking of MC under controlled conditions ($\sim$50–250 ng/mL[17]). In a randomized, double-blind, placebo-controlled trial that evaluated reduction of chronic pain with 500 μg and 1000 μg of aerosolized Δ^9-THC among patients with noncancer pain, average pain was reduced by 1.95 and 2.95 points (on a scale of 0–10), respectively, for 150 minutes. Pharmacokinetics evaluation after administration of 500 μg and 1,000 μg of aerosolized Δ^9-THC through the inhaler showed low variability in plasma concentration among subjects. Δ^9-THC plasma levels after administration of the 1,000-μg dose were twice as high as those after administration of the 500-μg dose, indicating stable dosing. Adverse events (AEs) were mostly mild, reversible, and receded rapidly.[2] Here, we retrospectively analyzed "real-life" long-term data collected in real time on the potential effectiveness of low-dose MC delivered by the Syqe Inhaler in reducing pain and other symptoms and on the safety of this mode of MC delivery.

2. Methods

2.1. Study design and setting

Syqe Medical provides all patients who use its metered-dose inhaler a free patient support program (PSP). On joining this program, the patients provide their informed consent, which allows data collection by Syqe's PSP nurse team. The PSP also includes a call center that archives every AE report.

In this study, we retrospectively analyzed the data of all patients who were enrolled in the program between September 2019 and October 2020. Analysis of the collected data was approved by the Technion - Israel Institute of Technology's Ethics Committee (#125-2021).

2.2. Device

The Syqe Inhaler 1.1 (**Fig. 1**) consists of a cartridge containing 60 preloaded VCs each containing a precise predefined amount of raw ground cannabis, which is free of pesticides, heavy metals (<0.2 ppm lead, <0.02 ppm mercury, and <0.02 ppm cadmium), stalks, and foreign materials, such as insects and other vermin. Microbiological purity is regularly confirmed (total aerobic microbial count of <10 colony forming units [CFU]/g; total yeast and mold count of <10 CFU/g; and absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and

Figure 1. Syqe metered-dose Inhaler. The Syqe Inhaler as used (left image) and its internal components (right image).

bile-tolerant gram-negative bacteria). Each cartridge contains a radiofrequency identification (RFID) label. The device identifies the RFID label both electronically and by distinct mechanical points on the cartridge. Without this authentication, the device will not recognize the cartridge and will not operate. The device requires minimal training before use and automatically generates logs of the inhalation process.

2.3. Medical cannabis treatment

Each patient's treatment regimen (ie, MC dose and the number of inhalations) was individualized using a titration plan provided by Syqe Medical's PSP. Four different titration plans were available. The titration plan was chosen according to the patient's MC use before treatment initiation (when relevant), age, and relevant comorbidities, if any. Each titration plan set a maximum dose limit for the MC regimen (Supplemental Figure 1, available at http://links.lww.com/PR9/A162).

Each VC was preloaded with 13.5 $\pm$ 0.9 mg processed granulated pharmaceutical grade cannabis flowers (Bedrocan, Veendam, The Netherlands). The inhaler is electronically config-ured to deliver an aerosol containing either 250- or 500-μg Δ^9-THC dose from each VC.

Dose titration for naive patients (who had never smoked or vaped MC) began with two 250-μg Δ^9-THC doses per day, and only 1 daily dose of 250 μg Δ^9-THC in patients aged 80 years and older. Experienced patients, who had been smoking or vaping MC before initiating treatment with the metered-dose inhaler, started with four 500-μg Δ^9-THC doses per day. Thereafter, patients could add small incremental doses in accordance with their titration plan, which was subject to the absence of AEs for 3 consecutive days, or to the presence of tolerable AEs, which were defined as AEs perceived by the patient as ones not preventing him or her from continuing the treatment (eg, dry mouth or mild cough). Dose titration was supported and monitored by a PSP nurse, who assisted the patient in reaching a stable treatment regimen with as few AEs as possible. The titration ended once the patient achieved satisfactory symptom relief without any in-tolerable AEs, which were defined as AEs perceived by the patient as ones that prevented him or her from continuing the treatment or defined by the PSP nurse as potentially harmful.

Patients were allowed to use rescue (SOS) doses on top of their scheduled daily dose for breakthrough pain episodes.

2.4. Outcome measures

Average weekly pain intensity was measured by a numerical pain scale (NPS) ranging from 0 (no pain) to 10 (worst imaginable pain intensity).

Adverse events were assessed by an open question: "Have you experienced any AE since the last follow-up?" At each follow-up visit, patients were also asked about changes, if any, to their medication regimens other than MC administered by the inhaler.

Before conducting the analysis of the study's data (October 2020), all patients who had reached the stable-dose phase were contacted by the PSP nurses and were requested to report any perceived change from baseline, in their quality of life (QoL), using a 5-point Likert scale ("much worse," "worse," "no change," "better," or "much better").

2.5. Data collection

Data were collected by Syqe's PSP nurses based on outcomes that were reported by the patients. A baseline meeting, during which the nurse instructed the patient on using the inhaler, was held in person at the patient's home. In this meeting, the nurse asked the patient about previous MC treatments, comorbidities, medication history, and concomitant medications. Women were asked whether they were pregnant or breastfeeding. Pain intensity and patient demographics (age and sex) were also recorded.

Inasmuch as possible, the same PSP nurse collected data on pain intensity and AEs by phone at predefined times: 7, 14, 21, 30, 60, 90, and 120 days after treatment initiation. Additional scheduled calls were made by the PSP team for safety monitoring at 180 and 360 days after treatment initiation. At each call, women were also asked whether they were pregnant or breastfeeding. Patients were instructed to call the PSP support service at any time of the day or night if needed.

2.6. Statistical analysis

The intention-to-treat (ITT) population included all patients who were treated with the inhaler and had data for any time point. The per-protocol (PP) population included all patients who had data for all time points. Categorical variables are presented as number and percentage. Distribution was assessed by the Shapiro–Wilk test of normality. Data with nonnormal distribution is presented as median and interquartile range (IQR), and normally distributed data are presented as mean $\pm$ SD. R software (V.1.1.463) with lme4[7] and tidyverse[23] packages was used to analyze changes in outcome measures by generalized linear mixed-effect regression models[13] for the ITT analyses. Repeated measures analysis of variance (ANOVA) was used for the PP analysis. Differences were considered significant if the P value was lower than 0.05.

3. Results

3.1. Patient characteristics

At the time of data analysis (October 2020), 215 patients were enrolled and initiated treatment with MC using the Syqe Inhaler. Of them, 143 patients (54% male) with a mean age of 62 $\pm$ 17 years completed the titration and were eligible for the ITT analysis. Most patients (n = 103, 72%) were prescribed MC treatment using the metered-dose inhaler because of chronic neuropathic pain. Other diagnoses included chronic musculoskeletal pain (n = 14, 10%), cancer pain (n = 9, 6%), chronic nociplastic pain (n = 4, 3%), chronic visceral pain (n = 2, 1%), and medical conditions with concomitant chronic pain (n = 6, 4%). Five

additional patients (3%) received MC with the inhaler for diagnoses other than chronic pain (symptomatic cancer, essential tremor, Parkinson disease, obsessive compulsive disorder, and multiple sclerosis). All etiologies for the indications are presented in Supplemental Table 1 (available at http://links.lww.com/PR9/A162). None of the female patients were pregnant or breastfeeding at enrollment.

Thirty-eight patients (27%) had comorbidities as follows: 23 (16%) had hypertension; 12 (8%) had diabetes; 3 (2%) had congestive heart failure; and 1 patient each had Meniere disease, emphysema, asthma, or Addison disease.

During the follow-up period, 28 patients (19.5%) dropped out from the PSP for the following reasons: 3 patients (2%) died because of causes unrelated to the treatment (2 from cancer and 1 patient with myasthenia gravis complicated by severe pneumonia), 7 patients (5%) withdrew because of financial reasons, 3 patients (2%) no longer needed MC treatment for their chronic pain (2 were cured by surgical interventions and a third patient was cured spontaneously), 8 patients (6%) reported worsening of their medical condition (eg, severe cardiac in-sufficiency, brain metastases, and severe muscle dystrophy affecting respiratory function), 5 patients (3%; all men) stopped treatment because of ineffectiveness, 1 patient (<1%) withdrew because of AEs, and 1 patient (<1%) because of regulatory reasons (**Fig. 2**).
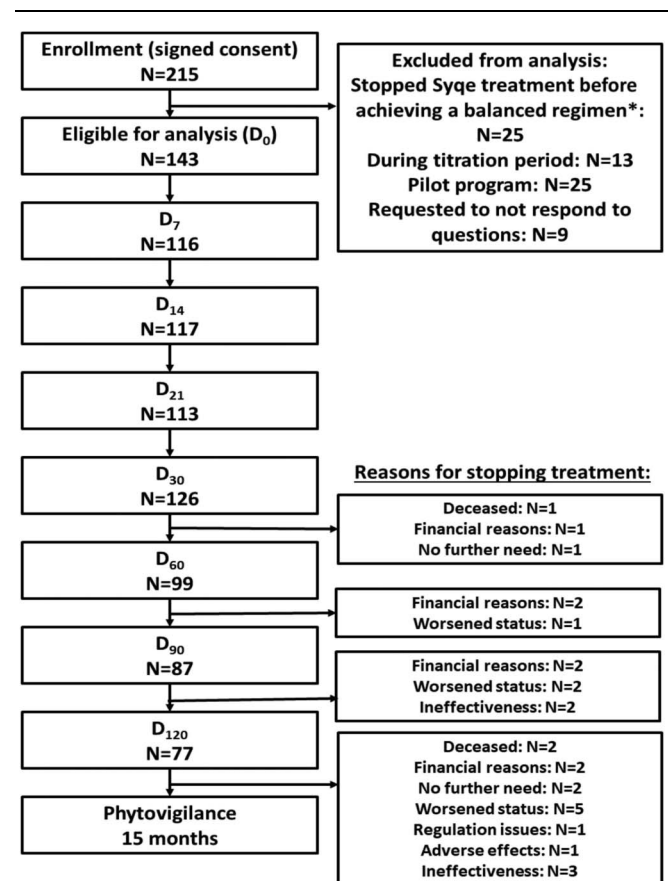

Figure 2. CONSORT 2010 flow diagram (numbers of patients). D, day from the first use of the inhaler; only patients who reported their NPS score were included in each visit's analysis; *, 25 patients (17%) did not achieve a balanced regimen because 1 patient (<1%) did not intend to use the inhaler a priori, 6 (4%) for financial reasons, 6 (4%) deceased (causes unrelated to treatment with the inhaler), 1 (<1%) improved health, 3 (2%) worsened health (causes unrelated to treatment with the inhaler), 3 (2%) stopped treatment because of adverse events, and 5 (3%) stopped treatment because of ineffectiveness.

3.2. Previous medical cannabis treatment

Seventy-five patients (52%) used MC before using the inhaler. The most common form of MC was oil extract (n = 38, 51%), followed by inhalation of inflorescence (n = 16, 21%). Twenty-one patients (28%) used both administration methods concomitantly. The most common cannabis dose was 20 grams per month (n = 54, 38%). A lower dose of 10 grams per month was used by 4 patients (3%), whereas higher doses of 30, 40, 50, and 60 grams per month were used by 8, 5, 3, and 1 patients, respectively.

Of the 75 patients who had previously used MC, 57 (76%) retrospectively reported experiencing MC-related AEs before using the inhaler, 34 of these 57 patients (60%) used oil extracts of MC, 7 (12%) smoked or vaporized and 16 (28%) used both concomitantly.

3.3. Inhaler treatment characteristics

At the time of data analysis, the patients were using the inhaler for an average of 9.0 ± 4.1 months. The duration of the titration phase was 26 ± 10 days. After titration, the average daily aerosolized Δ^9-THC dose was 1,500 ± 688 µg. After achievement of a stable dose, only a minority of the patients (n = 13, 9%) required rescue inhalations.

Of the 75 patients who had used MC before initiating treatment with the inhaler, 12 (16%) concomitantly continued their non-inhaler MC treatment. Nine of these 12 patients (75%) reduced their monthly MC doses.

3.4. Treatment effectiveness

The 5 patients who were not treated for chronic pain were not included in the effectiveness analysis.

At the end of the titration phase, 105 patients (76%) reported a reduction in pain intensity of at least 1 NPS point, 24 patients (17%) reported no change, and 9 patients (7%) reported an increase in pain intensity of at least 1 point. Comparison of the 33 patients who reported increased pain intensity or no change in pain intensity at the end of the titration period revealed no unique demographic or pain etiology characterization that could distinguish them from patients who responded to the treatment. Forty-eight patients (34%) and 16 patients (12%) reported a reduction of ≥30% and ≥50%, respectively, in pain intensity.

Among the 138 patients who had chronic pain, pain intensity measured by the NPS decreased by 1.62 points (95% CI, −1.99 to −1.24; P < 0.001)—from 7.3 ± 1.5 at baseline to 5.5 ± 1.6 at 120 days after treatment initiation (22.8% pain reduction). In the PP population, pain intensity significantly decreased by 2.6 points (95%CI, −2.9 to −2.2; P < 0.001)—from 7.3 ± 2.2 points at baseline to 5.1 ± 1.3 points at 120 days (25.4% pain reduction).

Among 67 patients with severe pain intensity at baseline (≥8 points), pain intensity significantly decreased by 2.1 points (95% CI, −2.6 to −1.7; P < 0.001)—from 8.4 ± 0.6 points at baseline to 6.0 ± 1.2 points at 120 days after treatment initiation (28.4% pain reduction **Fig. 3**). Of 43 patients who reported opioid use at baseline, 25 patients (58%) reported reduced opioid doses at 120 days after initiating treatment with the inhaler.

3.4.1. Evaluation of quality of life

Ninety-two of 143 patients (64.3%) rated the change in their QoL from initiation of treatment (**Fig. 4**). None of them reported "much worse" or "worse" QoL. Nine percent reported "no change," 59% reported "better," and 33% reported "much better" QoL.

3.5. Treatment safety

Among the 143 patients, 59 (41%) reported 102 treatment-related AEs (**Table 1**). The most common treatment-related AEs were dizziness (n = 26, 18.1% of patients), headache (n = 15, 10.7%), and sleepiness (n = 11, 7.7%). Most AEs (n = 66, 64%) were reported before the end of the titration phase, and less AEs were reported during the maintenance phase; the median day for AE reporting was −8 (ie, before the end of the titration period). Specifically, of the 143 patients in the ITT population, 48 (34%), 6 (4%), 6 (1%), and 2 (2%) reported at least 1 AE at 1, 3, 6, and 9 months, respectively, from treatment initiation. None of the patients reported AEs at 12 and 15 months. **Figure 5A** demonstrates the distribution of the 102 AEs across time, relative to the end of the titration period ("0" on the x-axis). Most AEs were short-termed, with a median of 15 minutes (IQR, 5–30 minutes) (**Fig. 5B**). All AEs resolved spontaneously without an intervention. None of the reported AEs were caused by malfunction of the inhaler.

Of the 59 patients who reported AEs during treatment with the inhaler, 30 (51%) had used MC before starting treatment with the inhaler and had retrospectively reported AEs from that previous MC use. The rate of AEs reported after MC administration with the
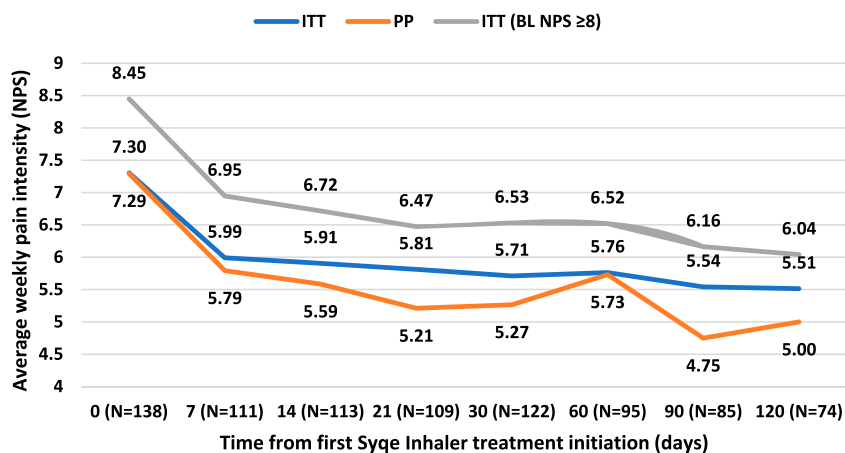

Figure 3. Changes in pain intensity during treatment. For the PP sample, N = 38 at all time points; for the ITT sample, baseline NPS ≥ 8, N = 67 at BL. BL, baseline; ITT, intention-to-treat population; N, number of patients on the x-axis represents the full ITT analysis sample; NPS, numeric pain scale; PP, per-protocol population.
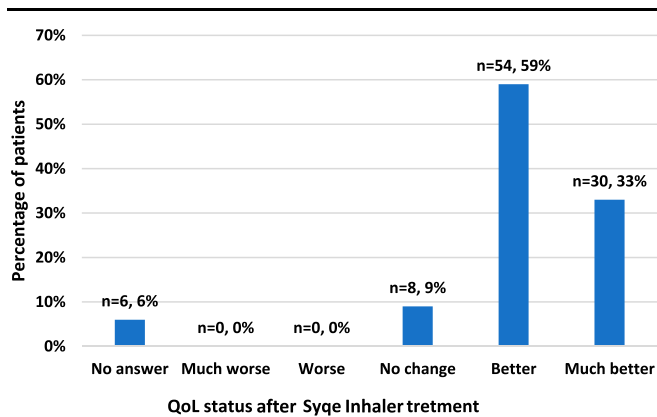
Figure 4. Changes in perceived quality of life after medical cannabis treatment using the Syqe Inhaler. The numbers on the bars indicate the number of patients who responded. N, number of patients; QoL, quality of life.

metered-dose inhaler rate was 35% lower than the rate of AEs reported when using MC by other administration routes (41% vs 76%).

4. Discussion

In the current study, we assessed the long-term effectiveness and safety of low and precise MC doses administered through the metered-dose Syqe Inhaler on patients with chronic pain due to various etiologies. Our analysis shows that after a structured titration phase, which was guided by professional nurses, patients reported significant pain reduction ranging from 22.8% in the ITT population to 28.4% in the population that reported high pain intensity at baseline of $\geq$8 points on the NPS. The percentage of reduction in pain intensity was comparable with the rate of 22.3% seen after 90 days of sublingual or smoked or vaped MC use.[4]

Table 1

Treatment-related adverse events.

Adverse events	Study population N = 143 n (%)
Total	59 (41)
Nervous system disorders	**33 (23)**
Dizziness	25 (17)
Confusion	3 (2)
Sleepiness	11 (8)
Concentration impairment	3 (1)
Memory impairment	2 (3)
Headache	15 (10)
Gastrointestinal disorders	**14 (10)**
Nausea	4 (3)
Heartburn	3 (2)
Dry mouth	6 (4)
Vomiting	1 (<1)
Psychiatric disorders	**15 (10)**
Anxiety	8 (6)
Restlessness	2 (1)
Cardiovascular disorders	**2 (1)**
Palpitations	2 (1)
Miscellaneous disorders	**18 (13)**
Cough	4 (3)
Tinnitus	1 (<1)
Muscle pain	1 (<1)

N do not add up to 100% because of concomitant adverse events. Bold values represent adverse effects rates by a systemic grouping.

Although 17% of the patients in the current study reported no decrease in pain intensity at the end of the titration phase and 7% reported worsening of pain, these patients elected to continue using the inhaler. It is possible that these patients have found other treatment benefits for using the inhaler, such as improved sleep or mood, which are often reported by patients treated with MC.[4]

The rate of AEs during the study was low, and most of them were reported during the titration phase, essentially disappearing after attainment of a stable treatment regimen. These results are in line with our previous clinical studies, in which significantly lower Δ^9-THC plasma levels were associated with similar analgesic effects and superior safety profiles compared with that observed with MC cigarette smoking.[4]

Although the AE rates of sublingual or smoked or vaped MC declined from 40% after a month of treatment to 30% a year later,[4] in the current study, AEs declined from 34% during the titration phase to almost none during the maintenance phase, which ranged from 3 to 15 months. In a study on patients with fibromyalgia treated by a single vaporizer session of MC from the Bedrocan cultivar, which is the cultivar used for the VCs of the inhaler, 80% of the treated patients reported psychoactive effects,[11] whereas in our study, only 10% reported psychoactive AEs, such as anxiety and restlessness. Hence, MC treatment using the inhaler seems similar to traditional MC for effectiveness, but superior regarding safety, while exposing the patients to very low doses of aerosolized Δ^9-THC.

The mean daily stable dose used by patients in the study was 1,500 μg (1.5 mg) of aerosolized Δ^9-THC, which is much lower compared with other administration routes of MC.[19] Two recent guideline articles recommended a maximal daily dose of 40 to 50 mg of Δ^9-THC through the oral or sublingual route.[8,18] Furthermore, the mean monthly amount of MC prescribed per patient in Israel (as of mid-2021) was about 30 gr, which equals about 1 gram per day. As the concentration of Δ^9-THC in MC supplied in Israel can vary between 1% and 20%, patients consume approximately 10 to 200 mg of Δ^9-THC daily.

The high Δ^9-THC doses of conventional MC use[19] produce high Δ^9-THC plasma levels (C_{max} range of ~50–250 ng/mL[17]), which are much higher than those required for achieving pain relief, and result in a higher rate of AEs.[1] Wallace et al.[22] showed that the therapeutic window for optimal pain reduction is 16 to 31 ng/mL of plasma Δ^9-THC.[22] Congruently, in a 3-arm randomized clinical trial using the Syqe Inhaler, administration of 500 μg and 1000 μg of aerosolized Δ^9-THC produced average C_{max} plasma Δ^9-THC levels of 14.3 $\pm$ 7.7 ng/mL and 33.8 $\pm$ 25.7 ng/mL, respectively. The range of this therapeutic window is further supported by the pharmacokinetics study on nabiximols oromucosal spray, where after the administration of 8 consecutive sprays, the maximal Δ^9-THC plasma concentration was 5.4 $\pm$ 2.41 ng/mL[21]—too low to show a clinically meaningful analgesic effect of this administration mode.[5] Furthermore, the inhaler enables repeatable dosing and structured titration of MC, which allow achieving a stable and consistent steady-state dosage compared with smoking or vaporizing. The latter shows considerable variability in plasma Δ^9-THC levels among patients and within each patient.[17] Hence, administration of MC with conventional administration routes may result in overdosing or AEs even after a prolonged duration of treatment.[3]

4.1. Limitations

This study has several limitations. First, the sample is relatively small. Second, because of the ongoing nature of the study design and the
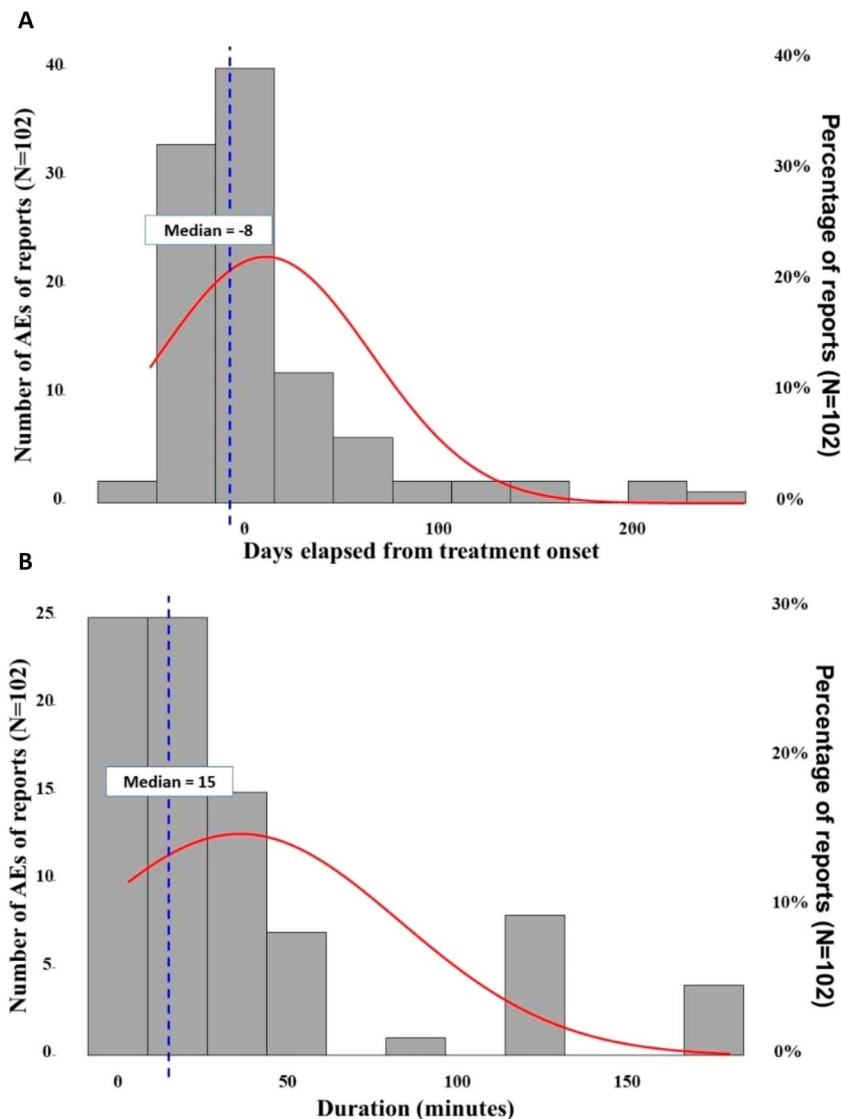
Figure 5. Characteristics of adverse events (AEs) reported after medical cannabis treatment using the Syqe Inhaler by time from treatment initiation and AE duration. (A) The time that elapsed from inhaler treatment onset to the report of AEs; "0" refers to the end of titration for each patient, relative to the time for which the AE was reported. (B) The duration (in minutes) of all reported AEs; red lines demonstrate the nonnormal (skewed) distribution of the measure, with most AEs reported during the titration period and not after stabilization (5A). Most AEs were short-termed (5B).

19.5% attrition rate, the sample size became smaller at each time point; however, the PP analyses controlled for this limitation.

5. Conclusions

Medical cannabis treatment with the Syqe Inhaler demonstrated overall long-term pain reduction, quality of life improvement, and opioid-sparing effect in a cohort of patients with chronic pain, using just a fraction of the amount of MC compared with other modes of delivery by inhalation. These outcomes were accompanied by a lower rate of AEs and almost no AE reports during a long-term steady-state follow-up. Additional follow-up in a larger population is warranted to corroborate our findings.

Disclosures

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A162.

References

[1] Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med 2018;49:44–50.
[2] Almog S, Aharon-Peretz J, Vulfsons S, Ogintz M, Abalia H, Lupo T, Hayon Y, Eisenberg E. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: a randomized, double-blinded, placebo-controlled trial. Eur J Pain 2020; 24:1505–16.
[3] Aviram J, Lewitus GM, Vysotski Y, Yellin B, Berman P, Shapira A, Meiri D. Prolonged medical cannabis treatment is associated with quality of life

improvement and reduction of analgesic medication consumption in chronic pain patients. Front Pharmacol 2021;12:1–14.

[4] Aviram J, Pud D, Gershoni T, Schiff-Keren B, Ogintz M, Vulfsons S, Yashar T, Adahan HM, Brill S, Amital H, Goor-Aryeh I, Robinson D, Green L, Segal R, Fogelman Y, Tsvieli O, Yellin B, Vysotski Y, Morag O, Tashlykov V, Sheinfeld R, Goor R, Meiri D, Eisenberg E. Medical cannabis treatment for chronic pain: outcomes and prediction of response. Eur J Pain 2020;25:359–74.

[5] Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain Physician 2017;20:E755–96.

[6] Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain 2018;19:37.

[7] Bates D, Maechler M, Bolker B, Walker S. lme4: Linear mixed-effects models using Eigen and S4. R Package version 17, 2014. p. 1–23. Available at: https://cran.r-project.org/web/packages/lme4/index.html. Accessed May 9, 2022.

[8] Bhaskar A, Bell A, Boivin M, Briques W, Brown M, Clarke H, Cyr C, Eisenberg E, De Oliveira Silva RF, Frohlich E, Georgius P, Hogg M, Horsted TI, MacCallum CA, Müller-Vahl KR, O'Connell C, Sealey R, Seibolt M, Sihota A, Smith BK, Sulak D, Vigano A, Moulin DE. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified delphi process. Postgrad Med 2021;3:1–12.

[9] Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL. Qualifying conditions of medical cannabis license holders in the United States. Health Aff (Millwood) 2019;38:295–302.

[10] Busse JW, Vankrunkelsven P, Zeng L, Heen AF, Merglen A, Campbell F, Granan L, Aertgeerts B, Buchbinder R, Coen M, Juurlink D, Samer C, Siemieniuk RAC, Kumar N, Cooper L. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ Rapid Recomm 2021; 374:1–10.

[11] van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. PAIN 2019;160:860–9.

[12] Eisenberg E, Ogintz M, Almog S. 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. J Pain Palliat Care Pharmacother 2014;28:216–25.

[13] Gewandter JS, McDermott MP, McKeown A, Smith SM, Williams MR, Hunsinger M, Farrar J, Turk DC, Dworkin RH. Reporting of missing data and methods used to accommodate them in recent analgesic clinical trials: ACTTION systematic review and recommendations. PAIN 2014; 155:1871–7.

[14] Gilron I, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Haroutounian S, Moore A, Rice ASC, Wallace M. Risks of harm with cannabinoids, cannabis, and cannabis-based medicine for pain management relevant to patients receiving pain treatment: protocol for an overview of systematic reviews. Pain Rep 2019;4:e742.

[15] Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing, pharmacodynamic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of cannabis based medicine extracts (CBMEs). J Cannabis Ther 2004;3:35–78.

[16] Haroutounian S, Arendt-Nielsen L, Belton J, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Finn DP, Finnerup NB, Fisher E, Fogarty AE, Gilron I, Hohmann AG, Kalso E, Krane E, Mohiuddin M, Moore RA, Rowbotham M, Soliman N, Wallace M, Zinboonyahgoon N, Rice ASC. International association for the study of pain presidential task force on cannabis and cannabinoid analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. PAIN 2021;162:S117–24.

[17] Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers 2009;4:1770–804.

[18] MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med 2018;49:12–9.

[19] Mehmedic Z, Chandra S, Slade D, Denham H, Foster S, Patel AS, Ross SA, Khan IA, ElSohly MA. Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci 2010;55:1209–17.

[20] Savage SR, Romero-Sandoval A, Schatman M, Wallace M, Fanciullo G, McCarberg B, Ware M. Cannabis in pain treatment: clinical & research considerations. J Pain 2016;17:654–68.

[21] Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase i study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. Eur J Clin Pharmacol 2013;69:1135–47.

[22] Wallace MS, Marcotte TD, Atkinson JH, Padovano HT, Bonn-Miller M. A secondary analysis from a randomized trial on the effect of plasma tetrahydrocannabinol levels on pain reduction in painful diabetic peripheral neuropathy. J Pain 2020;21:1175–86.

[23] Wickham H. Tidyverse: Easily install and load "Tidyverse" packages. Version 1.3.0. Compr R Arch Netw, 2019. Available at: https://cran.r-project.org/web/packages/tidyverse/tidyverse.pdf. Accessed May 9, 2022.