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Cannabis treatment in hospitalized patients using the SYQE inhaler: Results of a pilot open-label study

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Abstract

Objective. The objectives were to evaluate the, usability, feasibility of use, satisfaction, and safety of the Syqe Inhaler Exo (Syqe Inhaler), a metered dose, Pharmacokinetics-validated, cannabis inhaler device in a cohort of hospitalized patients that were using medical cannabis under license as a part of their ongoing medical treatment.

Method. Before and after inhaling from the Syqe Inhaler, participants were asked to fill a questionnaire regarding pain reduction on a visual analog scale from 0 to 10 and, if relevant, reduction in chemotherapy-induced nausea and vomiting and/or spasticity. A patient satisfaction questionnaire and a usability questionnaire were filled in following the last use. Prescribed treatment included 4 daily doses of 500 µg tetrahydrocannabinol each delivered from 16 mg cannabis flos per inhalation plus up to an additional four SOS (distress code for more doses of cannabis) doses.

Result. Daily cannabis dose consumed during hospitalization with the Syqe Inhaler was 51 mg (20–96) versus 1,000 mg (660-3,300) consumed prehospitalization. Patients were easily trained and continued to use Syqe Inhaler for the duration of their hospitalization (5 [3–7] days). Pain intensity 30–60 minutes following inhalations was reported to be significantly lower than pre-inhalation 4 [1–5] versus 7 [2–9]). Participants ranked their satisfaction with Syqe Inhaler as 6 (5–7). Three participants reported mild cough, which resolved spontaneously.

Significance of results. Cannabis inhalation by combustion is not feasible for hospitalized patients. The use of Syqe Inhaler during hospitalization yielded high levels of patients and staff satisfaction with no complications.

Introduction

Chronic pain affects approximately one in every five adults in developed countries (Breivik et al., 2006; Harstall & Ospina, 2003; Johannes et al., 2010). It negatively affects patients' physical and emotional status and their quality of life and is associated with substantial societal costs (Simon, 2012). Despite the many available therapies, many patients suffer from uncontrolled pain and poor quality of life (Katz, 2002).

Chronic pain of various etiologies has shown to be responsive to cannabinoid-based treatments (Abrams et al., 2007; Ellis et al., 2009; Poli et al., 2018; Ware et al., 2010). As such, data were analyzed for 178 participants from five randomized clinical trials (RCTs) and demonstrated that inhaled medical cannabis (MC) results in effective short-term analgesia in one of every five to six neuropathic pain patients treated (Andreae et al., 2015). This effect was consistent across neuropathic pain of various etiologies and represents better analgesic efficacy than other common therapies for chronic neuropathic pain (Boychuk et al., 2015). Lynch and Campbell (2011) reviewed 18 RCTs on patients with chronic pain and concluded that cannabinoids hold a modest analgesic effect. Thus, there is considerable evidence to support the potential use of cannabinoids as analgesics (Boychuk et al., 2015).

MC is indicated in Israel for the treatment of chronic pain and spasticity, symptomatic management of inflammatory bowel disease, Parkinson's disease, and the control of pain and other symptoms in patients with cancer such as chemotherapy-induced nausea and vomiting. This use of cannabis-based medications for these indications has also been demonstrated (Notcutt et al., 2012; Notcutt, 2013; Smith et al., 2015).

Administration via the pulmonary route has proven to be the most rapid and efficient method of cannabinoid delivery. Following inhalation, tetrahydrocannabinol (Δ^9-THC) plasma levels increase rapidly: peak plasma concentrations typically occur at two to four minutes after inhalation, resulting in onset of analgesic effects after about five to ten minutes. However, variability in the depth of inhalation, puff duration, breath-holding time, and that about 30% of the Δ^9-THC dose is degraded resulting from pyrolysis during smoking, leads

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to heterogeneous bioavailability that ranges between 2% and 56% (Grotenhermen, 2003; Huestis, 2007). A step forward has been made by developing cannabis vaporization techniques aimed at delivering inhaled cannabinoids while avoiding the respiratory hazards of smoking. However, none of the currently available vaporizer devices can administer cannabis under standard pharmaceutical parameters in precise and constant doses. Because of these limitations, acceptance of the pulmonary route of cannabis administration as a standard medical treatment is deferred and many physicians are reluctant to prescribe cannabis-based therapy.

To address this challenge, the Syqe Inhaler was developed. It is a thermal metered-dose cannabis inhaler capable of delivering precise, accurate, and reliable doses of cannabinoids directly from raw cannabis flos while avoiding the respiratory hazards of smoking. A previous phase 1a pharmacokinetic study (Eisenberg et al., 2014) with the Syqe Inhaler demonstrated a pharmacokinetic profile with low interindividual variation that meets the pharmacological standards for inhaled drugs. Adverse effects were minimal and reversible.

Patients face multiple obstacles in continuing treatment with MC during hospitalization and are ultimately "forced" to discontinue their cannabis treatment during such time, causing deviation from a stable treatment regimen and leading to an increase in the use of other analgesic agents, particularly opiates with increased risk of developing adverse effects and a worsening of symptoms. Patients are admitted for various reasons to hospital and they may have different indications for MC therapy.

This open-label, proof-of-concept feasibility study was aimed to assess usability, effectiveness, and satisfaction with the use of the Syqe Inhaler among hospitalized patients holding a valid medical license for the use of MC. Staff satisfaction was also assessed. Specifically, we wished to assess the effectiveness compared with "regular treatment" before hospitalization. This would refer to pain reduction and decrease in spasticity, nausea, and vomiting according to the participants' indication of use.

Study design and setting

The current study was an open-label, proof-of-concept feasibility study conducted at Rambam Heath Care Campus in Haifa, Israel, during between January 2016 and July 2017 and was approved by the local ethics committee. The investigators provided all participants with a detailed explanation of the study aims and design. All participants provided written informed consent. After consenting, a physician documented details about demographics, medical history, and treatment, and conducted a physical examination.

Participants were provided with detailed instructions on the use of the inhaler. Data collection lasted until discharge from the hospital or until termination of participation in the study was requested by a participant (patient) or a staff member.

Materials and methods

Participants

Twenty-two hospitalized patients at the Rambam Health Care Campus (Haifa, Israel) holding a valid license to consume MC from the Israeli Ministry of Health (MoH) as part of their ongoing medical treatment were recruited to participate in the study. MC is officially approved to patients after a request form has been submitted to the Medical Cannabis Unit of the MoH by a specialist physician. The major indications approved by the MoH as a last line of treatment include pain of neuropathic origin, chemotherapy-induced nausea and vomiting, patients in palliative and end-of-life care, inflammatory bowel disease, spasticity, and pain from multiple sclerosis, and cachexia resulting from HIV and other infectious diseases. An approved license is usually given for 1 year and renewed annually as necessary.

Inclusion criteria were hospitalized patients having a valid license to use MC as a part of an ongoing medical treatment and having been prescribed a Syqe Inhaler for use during hospitalization; no medical contraindication for the use of MC; capable of understanding how to use the Syqe Inhaler; and providing written informed consent. Data were collected from participating patients and from staff members (nurses) who treated these patients in different hospital departments (Table 1).

Syqe Inhaler device

The Syqe Inhaler (Syqe Medical Ltd., Tel-Aviv, Israel) is a battery-operated, hand-held, thermal selective-dose inhaler; it is designed to vaporize multiple individual preloaded units (VaporChips) of granulated cannabis flos, resulting in metered-dose pulmonary delivery of the active ingredients. The inhaler comprises a cartridge containing 18 VaporChips, a dose counter, an indication light, and a power switch. In the current study, each VaporChip was preloaded with 16.0 ± 0.5 mg of granulated flos that contained 3.08 ± 0.02 mg Δ^9-THC. During each inhalation, which lasts less than 2.2 seconds, 500 μg Δ^9-THC is administrated (along with other cannabis compounds that are also present in the generated aerosol). The device uses automatic thermal and flow controllers that ensure high-efficiency delivery of cannabinoid aerosol to the lungs, independent of the inhalation pattern of the individual patient. The device further uses a mechanism that causes the inhaling user to generate a chase-air pulse after drug delivery; this drives drug aerosol past the anatomic dead space. This pulmonary event also acts as an indicator to the patient of inhalation completion, enhancing both adherence and bioavailability.

The device requires minimal training before use and automatically generates logs of the inhalation process.

Treatment

The study medication used was pharmaceutical-grade cannabis flos (Bedrocan, Veendam, The Netherlands) containing 22% Δ^9-THC, 0.1% cannabidiol, and 0.2% cannabinol. Each VaporChip contained 16 ± 0.5 mg cannabis that was pesticide- and heavy metal-free (<0.2 ppm lead, <0.02 ppm mercury, and <0.02 ppm cadmium). Foreign materials such as stalks, insects, and other vermin were absent. Microbiological purity was confirmed (total aerobic microbial count <10 colony-forming units/g, total yeast and mold count of <10 colony-forming units/g, and absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and bile-tolerant gram-negative bacteria). The cannabis flos underwent specialized granulation and preloading into the Syqe Inhaler in a clean room environment, retaining both the microbiological purity and the natural cannabis compounds in their raw form.

The exact treatment regimen (i.e., number of inhalations prescribed) was individualized based on the participants' medical condition and the amount of cannabis used before hospitalization (details on the treatment of each subject are provided in the Results section). A specific predefined number of inhalations was delivered at one or more of the f medication dispensing

Table 1. Patient demographics and baseline clinical characteristics

Number of patients in study	*N* = 21*
Gender, n (%)	
Male, n (%)	10 (45.5)
Age mean ± SD (range), years	44.3 ± 12.5 (25–78)
Cause of chronic neuropathic pain and use of MC in patient cohort, *n* (%)	
Oncologic pain and nausea	9 (42.8)
Neuropathic pain	9 (42.8)
Crohn's disease	1 (4.8)
Multiple sclerosis with spasticity	2 (9.5)
Method of cannabis administration prehospitalization, *n* (%)	
Smoking	17 (81.0)
Vaporization	4 (19.1)
Number of times cannabis consumed per day prehospitalization, *n* (%)	
<9	6 (35.3)
9–15	3 (17.7)
>15	8 (47.1)

*The device was offered to 22 patients, 1 patient preferred not to use it; thus, the analysis was performed on 21 patients.

Table 2. Cannabis consumption during the study

Study population	*N* = 21
Hospital stay, d	4 (3–14)
Prescribed inhalations/d	4 (3–4)
SOS inhalations allowed/d	3 (2–4)
Actual inhalations/d	3 (1–6)
Cannabis dose/d, mg	51 (20–96)
THC dose/d, μg	1,500 (1,000–3,000)
Inhalations during the study	14 (5–25)

All data are presented as *M* (range).
SOS, distress code for more doses of cannabis; THC, tetrahydrocannabinol.

periods in the departments (8 am, 1 pm, 6 pm, and 9 pm). In addition, for each subject, a maximum number of daily SOS inhalations was allowed. The inhalers were stored in the hospital pharmacy and for each enrolled subject a single inhaler was provided to the department and stored in the department medication room. A nurse provided the inhalers to the participants at prespecified hours and in response to SOS requests by the subject. Participants' routine medications were continued throughout the study.

Outcome measures

Outcome measures were obtained using self-completed questionnaires. Before each inhalation, participants provided a score of their pain (as well as nausea and/or spasticity, whenever relevant) on a visual analog scale 0–10 scale (0 = no symptom and 10 = symptom at maximal intensity). A similar questionnaire was completed 30–60 minutes after each inhalation. At the end of participation in the study, each subject completed a satisfaction questionnaire that included items on the ease of use and satisfaction with the treatment, on a scale ranging from 1 to 7 (1 = absolutely do not agree and 7 = absolutely agree). In addition, at the end of the study, medical staff who provided training and monitored participants' use, completed a questionnaire on ease of use and satisfaction, using a 1–5 scale (ranging from 1 = do not agree and 5 = agree). Adverse events were monitored and documented by the study staff.

Statistical analysis

Analyses were conducted by using SPSS for Windows, version 19 (Chicago, IL). Given the low number of participants, the nonparametric Wilcoxon signed-ranked test was used to assess the effects of treatment.

Results

Treatment

Cannabis consumption

Study treatment prescribed and actual consumption per day are detailed in Table 2.

The median number of inhalations prescribed per day was 4 (3–4), and median actual number of inhalations per day was 3 (2–4). This reflects a median prescribed daily dose of Δ^9-THC of 2,000 μg (1,500–2,000) and median amount of Δ^9-THC actually inhaled per day of 1,500 μg (1,000–2,000).

Efficacy

Pain reduction (analgesia). Median pain intensity 7 (2–9) immediately prior to inhalation was statistically significantly higher (Wilcoxon signed-ranked test, Z = –3.059) than the median pain intensity 30–60 minutes following inhalation 4 (1–5) (Figure 1). No within-subject differences were found in the magnitude of the effects following repeated use (i.e., no significant changes between the response to the first and later inhalations were seen; Freidman test, not significant).

Antiemetic. A substantial reduction in nausea intensity was demonstrated in seven patients suffering from nausea. The median nausea intensity 30–60 minutes following inhalation was significantly lower compared with nausea intensity before the inhalation, 2 (1–3) vs 3 (2–4) (Wilcoxon signed-ranked test, Z = –2.197).

Spasticity

Four patients reported spasticity, which was attenuated following inhalation. The median spasticity intensity before inhalation was 8 (7–9) and 30–60 minutes following inhalation the intensity was 7 (6–8) (no statistical test was conducted because of the low number of patients with spasticity).

Participants and healthcare providers' perspective and satisfaction from the Syqe Inhaler

All participants were easily trained to use the inhaler and no device malfunctions were noted. Participants' satisfaction with

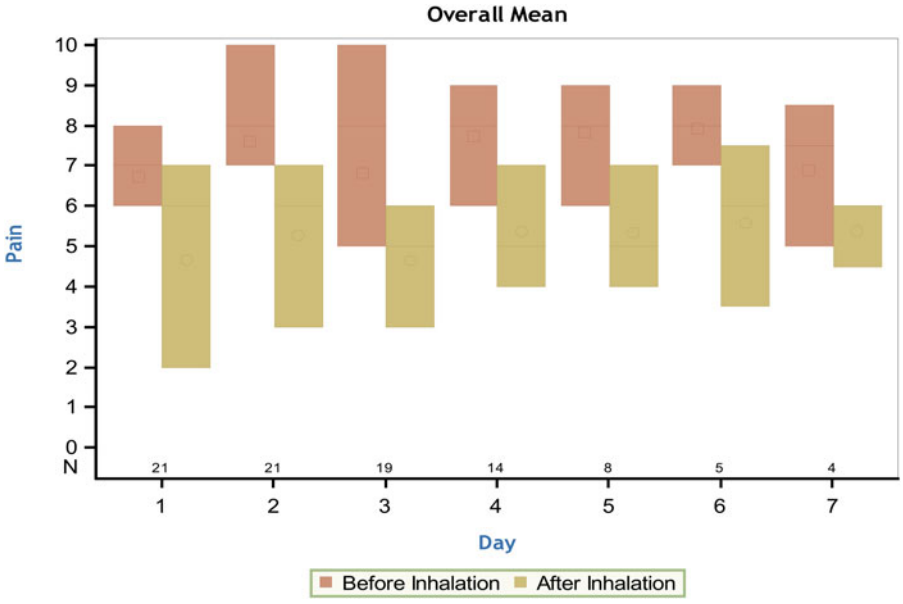

Fig. 1. Pain reduction as reported prior to and 30-60 minutes following Inhalation. Self-reported data is depicted for each patient from the first day of inhaler use (X-axis), and for each day the number of subjects is shown above the X axis. Pain intensity (before inhalation and 30-60 minutes post inhalation) is depicted on a VAS pain scale (Y-axis).

using the inhaler was 6 (5–7). This includes an absolute agreement of participants with statements such as "I would like to continue use the device" and "Inhalation was easy," both receiving median scores of 7 ("absolutely agree"). Other responses were: "I felt less need to smoke cannabis" (median = 6, i.e., "agree") and "I am satisfied with the device" (median = 6.5). The six healthcare providers who participated in the study also agreed with all statements, regarding their satisfaction with the device, ease of training of the participants, and use by them (Figure 2).

Noteworthy is a patient treated following eye surgery with severely impaired vision who also reported high levels of satisfaction with the device and ease of operation.

Safety

No severe adverse events were reported. Three participants reported a mild cough immediately following inhalation, which resolved spontaneously within a minute. No device failures were recorded as well.

Discussion

The current study aimed to assess ease of use feasibility of use and satisfaction of patients and staff, with MC treatment provided using the Syqe Inhaler, which allows the administration of low, accurate, precise, and reliable cannabis dosages via inhalation.

A recent phase 1a pharmacokinetic and pharmacodynamic study (Grotenhermen, 2003) demonstrated a low between-participants' variability of plasma cannabinoids concentrations following administration of a single inhalation using the Syqe Inhaler. A crucial step before progressing to additional studies is to assess participants' and staff's perceptions and satisfaction with the inhaler. Our main findings were that both patients and staff were highly satisfied with operating and using the device. The study staff found that it was easy to train participants on using the device, and participants subsequently easily used it with no complications. The outcome measures on patient satisfaction were demonstrated with Likert scales, a well-established and validated method for such evaluations (Sullivan & Artino, 2013).

Importantly, participants who were enrolled into our study had previously had on average 30 g cannabis (median) per month (range = 20–100 g) prescribed to them. Based on the results of the current study, if the participants had substituted the inhaler for their usual MC consumption (10 by smoking, 2 via vaporizers), median monthly consumption would have been 1.49 g (3 inhalations per day [1–6] × 0.016 g × 31 days), reflecting about 20-fold reduction of MC than their current monthly consumption.

If this trend translates into typical MC consumption, the marketed and used amount of MC per patient will reduce significantly, which is likely to reduce the amount of cannabis that is diverting to individuals who are unauthorized to use it, a risk that cannot be underestimated. The use of tamper-proof cartridges in the Syqe Inhaler helps reduce this risk even further.

The use of a device that allows the administration of low, accurate, precise, and reliable dosages of cannabis holds another important advantage: that of safety. In the current study, no severe adverse events were recorded, a fact that could be potentially explained by the low dose. The dose investigated in the current study is much smaller than in the case of smoked cannabis, in which daily dosages investigated in prior studies ranged from 19 to 96 mg cannabinoids (Abrams et al., 2007; Ellis et al., 2009; Wilsey et al., 2008). The dose in the current study was also lower than previous studies in which cannabis was administrated via a pipe (1.625–5.85 mg THC per session) (Ware et al., 2010), and a Volcano vaporizer (estimated 10.32 mg cannabinoids per inhalation) (Wilsey et al., 2013).

All participants reported reduction in pain, and 50% (6/12) demonstrated pain reduction of 20% or higher. This high level of patient satisfaction with the current treatment regimen of two to four daily doses of 500 µg Δ^9-THC per inhalation (plus additional SOS dosages) supports the therapeutic efficacy of this current regimen. Positive treatment effects were also seen regarding nausea and spasticity. Another advantage of using the inhaler is that, while hospitalized as well as in other settings, participants can safely use the device in their beds, avoiding smoke and fire hazards.

Finally, the capability to obtain direct, precise, and accurate data on cannabinoid consumption and daily dosages by

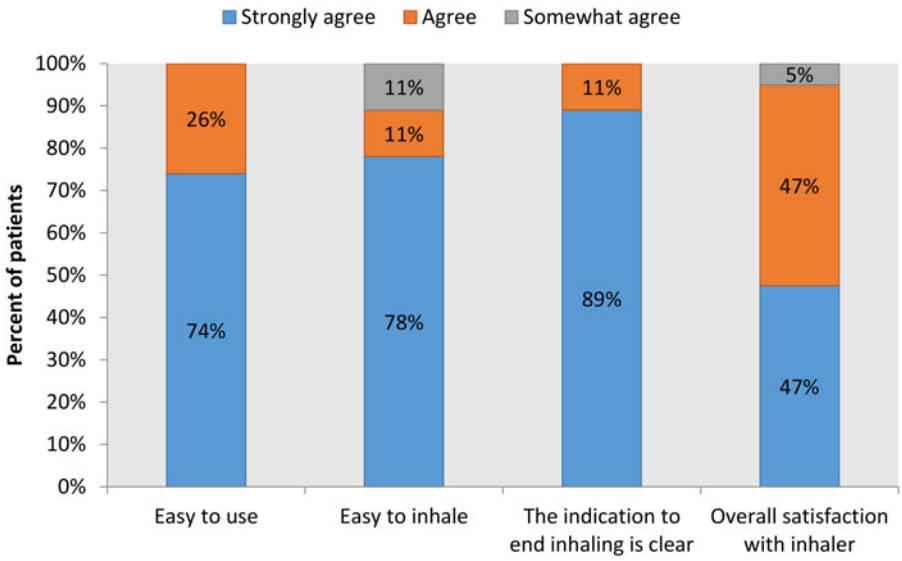

Fig. 2. Subjects' perspective and satisfaction from the Syqe inhaler. The X axis represents statements relating to usability and satisfaction with the Syqe Inhaler. The Y axis depicts a percent of patients that strongly agreed (blue), agreed (orange) or somewhat agreed (gray) with each statement. The data represents self-reported responses filled in by the patients in study questionnaires.

inhalation from raw cannabis flos (in this trial, 500 μgΔ^9-THC per inhalation) provides a tool for research that may generate further sound conclusions on appropriate cannabinoid dosing and treatment regimens for various indications.

Study limitations

RCTs aimed at assessing the efficacy of low cannabis doses are needed. However, efficacy was not a primary aim of this open-label study, and because no placebo was provided, results should be interpreted with caution. In conclusion, the current study results have demonstrated the feasibility of administrating cannabis using the Syqe Inhaler, allowing for the first time, to administer small, safe, accurate, precise, and reliable dosages of cannabinoids.

This is important for it allows patients to use this inhaler quite readily in the hospital setting and replace other forms of use, especially smoking cannabis which unfortunately is still quite prevalent in Israel and in other countries (Andreae et al., 2015; Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010). Although not studied in this trial, a home version of the Syqe inhaler has been authorized by the MoH and is now in use in Israel. Two future studies are now planned: The first comparing patients using cannabis flos for symptom reduction to patients who will switch over to the Syqe Inhaler. The second will involve randomizing new patients recommended cannabis for symptom reduction to receive either flos or the Syqe Inhaler. If the final result will show that the Syqe Inhaler is more accurate, easier to use, efficient, and demonstrates good drug delivery parameters, we believe that this will greatly advance the treatment of patients suffering from chronic pain and other chronic symptoms.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S147895151900021X

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Conflicts of interest. Funding to conduct this study was provided by Syqe Medical Ltd., which developed the Syqe Inhaler device and holds its intellectual property. The Syqe Medical Ltd. team was involved in the study design. The authors were responsible entirely for the conduct of the study, the statistical analyses, results interpretation, and manuscript writing. E.E. serves as a Syqe Medical Ltd. consultant. O.M. is a Syqe Medical Ltd. employee. No other financial interests exist.

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