European Journal of Internal Medicine 49 (2018) 37–43

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer

Lihi Bar-Lev Schleider[a,b], Raphael Mechoulam[c], Violeta Lederman[b], Mario Hilou[b], Ori Lencovsky[a], Oded Betzalel[b], Liat Shbiro[a], Victor Novack[a,*]

[a] Clinical Cannabis Research Institute, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er-Sheva, Israel
[b] Research Department, Tikun Olam LTD, Israel
[c] Institute for Drug Research, School of Pharmacy, the Hebrew University of Jerusalem, Israel

ARTICLE INFO

Keywords:
Cancer
Medical cannabis
Pain

ABSTRACT

Background: Cancer is a major public health problem as the leading cause of death. Palliative treatment aimed to alleviate pain and nausea in patients with advanced disease is a cornerstone of oncology. In 2007, the Israeli Ministry of Health began providing approvals for medical cannabis for the palliation of cancer symptoms. The aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe the safety and efficacy of this therapy.

Methods: We analyzed the data routinely collected as part of the treatment program of 2970 cancer patients treated with medical cannabis between 2015 and 2017.

Results: The average age was 59.5 ± 16.3 years, 54.6% women and 26.7% of the patients reported previous experience with cannabis. The most frequent types of cancer were: breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%) with 51.2% being at stage 4. The main symptoms requiring therapy were: sleep problems (78.4%), pain (77.7%, median intensity 8/10), weakness (72.7%), nausea (64.6%) and lack of appetite (48.9%). After six months of follow up, 902 patients (24.9%) died and 682 (18.8%) stopped the treatment. Of the remaining, 1211 (60.6%) responded; 95.9% reported an improvement in their condition, 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition.

Conclusions: Cannabis as a palliative treatment for cancer patients seems to be well tolerated, effective and safe option to help patients cope with the malignancy related symptoms.

1. Introduction

As the leading cause of death, cancer is a major public health problem with estimates of about 12.7 million new cancer cases a year in USA alone [1]. Palliative treatment in cancer patients is aimed mainly to alleviate pain and nausea. Approximately 70%–90% of patients with advanced cancer experience significant pain [2].

Opioids are currently the cornerstone medication for the treatment of cancer pain, with success rates of 80–90% [3,4]. However, some patients experience inadequate pain relief with opioids and standard adjuvant analgesics and/or experience unacceptable side effects [2,5].

Nausea and vomiting, the most common chemotherapy side effects are considered by patients as the most stressful [6]. Up to three-fourths of all cancer patients experience chemotherapy-related emesis [7]. Despite the advances in antiemetic therapy, nausea and vomiting continue to be a burden for patients undergoing treatment for malignancies.

Cannabis has a long history of medicinal and recreational use that can be dated back thousands of years. Cannabinoids, the active compounds of the cannabis plant, have a potential therapeutic effect on the core symptoms of cancer such as pain and nausea [8], so it is not surprising that cancer patients frequently use cannabis to reduce their symptoms [9].

In 2007, Israeli Ministry of Health began providing approvals for medical cannabis, mainly for the palliation of the cancer symptoms. The most frequent indication for cannabis treatment in Israel is cancer, with about 60% of the Israeli patients reporting cancer as an indication for the treatment. There is a lack of knowledge regarding the characteristics of the patients, their use patterns, adverse effects and efficacy profiles of cannabis use among cancer patients. Therefore, the aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe safety and efficacy of this therapy.

* Corresponding author at: Soroka Clinical Research Center, Rager Av. 151, Beer-Sheva 84101, Israel.
E-mail address: victorno@clalit.org.il (V. Novack).

https://doi.org/10.1016/j.ejim.2018.01.023
Received 28 December 2017; Received in revised form 17 January 2018; Accepted 19 January 2018

2. Methods

2.1. Study population and treatment program

There are currently above 30,000 patients approved for medical cannabis use in Israel and 10,000 (~33%) of them receive treatment at Tikun-Olam Ltd. (TO), the largest national medical cannabis provider which serves annually ~3400 new patients. The study was conducted in the central cannabis clinic and included all cancer patients starting treatment between March 2015 and February 2017.

During the routine treatment process, all willing patients undergo an extensive initial evaluation and their health status is periodically assessed by the treating team. At the intake session, the nurse assesses a complete medical history, educates the patient on the main active ingredients in the cannabis plant, the possible side effects, coping strategies, provides practical training of administration, and gives an explanation of the regulatory process. The patient fills out a medical questionnaire, which includes the following domains: demographics, comorbidities including substance abuse history, habits, concomitant medications, and measurements of quality of life. Furthermore, the detailed symptoms check-list is assessed. Following intake, the nurse advises on 1. suitable cannabis strains out of sixteen strains available that differ in Δ9-THC/CBD concentration, 2. method of administration, and 3. starting dose and titration protocol. The medical cannabis license specifies two ways of administration: oil and inflorescence (which include flowers, capsules and cigarettes); almost half the patients (44%) have a license for the combination of oil and inflorescence.

At one and six months after treatment initiation patients undergo a telephone interview to assess the changes in symptom intensity, underlying disease condition, side effects and quality of life. If needed, the nurse can recommend an adjustment of dosage, change of strain or consumption method.

2.2. Study outcomes

For safety analysis we have assessed the frequency of the following side effects at one and at six months: physiological effects – headaches, dizziness, nausea, vomiting, stomach ache, heart palpitation, drop in blood pressure, drop in sugar, sleepiness, weakness, chills, itching, red/irritated eyes, dry mouth, cough, increased appetite, blurred vision, slurred speech; cognitive side effects – restlessness, fear, psycho-active effect, hallucinations, confusion and disorientation, decreased concentration, decreased memory or other. The patients were asked to provide details of the incidence, duration and severity of the reported side effect.

For the efficacy analysis we used the global assessment approach where the patients were asked: “how would you rate the general effect of cannabis on your condition?” At one-month follow-up the response options included the following categories: significant improvement, moderate improvement, serious side effects, no improvement. At six months, the options were: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration, significant deterioration.

Treatment success at six months (primary efficacy outcome) was further defined as at least moderate or significant improvement in the patient's condition and none of the following: cessation of treatment or serious side effects.

We used the numeric rating scale to assess the pain level on an 11-point scale (0 = no pain, 10 = worst pain imaginable) [10] [11]. Quality of life was assessed on Likert scales ranging from very poor, poor, neither poor nor good, good to very good [12]. We asked the patients to report all their prescribed medications (medications they take regularly) before treatment and again after six months. The medications were sorted by drugs family according to the ATC distribution.

One-year and two-year follow-up was done based on the status of the patients on one year and two years of treatment or the most updated status of the patient in November 2017.

This study was approved by the IRB at the Soroka University Medical Center, Beer-Sheva, Israel.

2.3. Statistical analysis

Continuous variables with normal distribution were presented as means with standard deviation. Ordinary variables or continuous variables with non-normal distribution were presented as medians with an interquartile range (IQR). Categorical variables were presented as counts and percent of the total.

We used *t*-test for the analysis of the continuous variables with normal distribution. The non-parametric Wilcoxon test was used whenever parametric assumptions could not be satisfied.

We utilized logistic regression for the multivariate analysis of factors associated with treatment success. We have included the following variables into the models based on clinical considerations: age, gender, pain scale, number of chronic medications, hospitalization in the past six months, employment, car use, previous experience with cannabis, cigarette smoking, quality of life at the baseline, and concerns about cannabis treatment as reflected in the intake form.

Results are displayed as odds ratios with 95% confidence interval. *P* value < 0.05 was considered to be statistically significant. All analyses were performed at the Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel using IBM SPSS version 22 (SPSS, Chicago, IL).

3. Results

3.1. Patient population

During the study period, 3845 subjects received a cannabis license under the cancer indication. Seventy-nine patients (2.1%) died before starting the treatment, 146 (3.7%) received the license but opted not to receive the treatment, one patient (0.2%) switched to a different cannabis supplier, and 3619 patients (94.1%) initiated the treatment. Out of these 2923 (80.7%) responded to the intake questionnaire (Fig. 1). Most of the patients have a license to purchase 30 (57.0%) or 20 (23.2%) grams per month, while 3.9% patients have a license for 100–150 g per month.

Four hundred and eighty-nine (16.7%) patients reported having concerns over the initiation of cannabis treatment. The most common were: possible side effects (162), possible addiction (67), loss of control (56), lack of knowledge regarding the effects (56), assumed lack of effect (43), cannabis being an illicit drug [25], worsening medical condition (20), developing or worsening mental condition (17).

Table 1 shows demographic characteristics of the patients. The mean age was 59.5 ± 16.3 years, with 1261 (43.1%) patients being older than 65 and 37 (1.3%) younger than 18; 17.4% of the patients were employed, 31.8% retired, 46.9% did not work and 3.9 did not answer the question. During the six-month period before commencing cannabis treatment, 1576 (53.9%) were hospitalized with the median number of hospitalization days of 10 (IQR 5–25).

Appendix A shows the distribution of comorbidities with disease duration: 429 (14.4%) patients suffered from hypertension and 326 (11.0%) patients had diabetes. The median time for cancer diagnosis was 0.5 year (range 0.5–21).

At the baseline 2970 patients reported on average of 11.1 ± 7.5 symptoms. Appendix B shows the prevalence of symptoms with the majority of patients (2329, 78.4%) reported sleep problems, 77.7% reported pain with a median pain intensity of 8/10 (IQR 4–9), weakness and fatigue were reported by 72.7% of the patients.

Cannabis strains used by the patients include four categories: 1) Twelve [12] Δ9-THC-rich indica strains (22–28% Δ9-THC) without CBD (< 0.5%), consumed by 91.8% of patients. 2) Three sativa strains rich in Δ9-THC without CBD, consumed by 60.5% of patients. 3) One strain

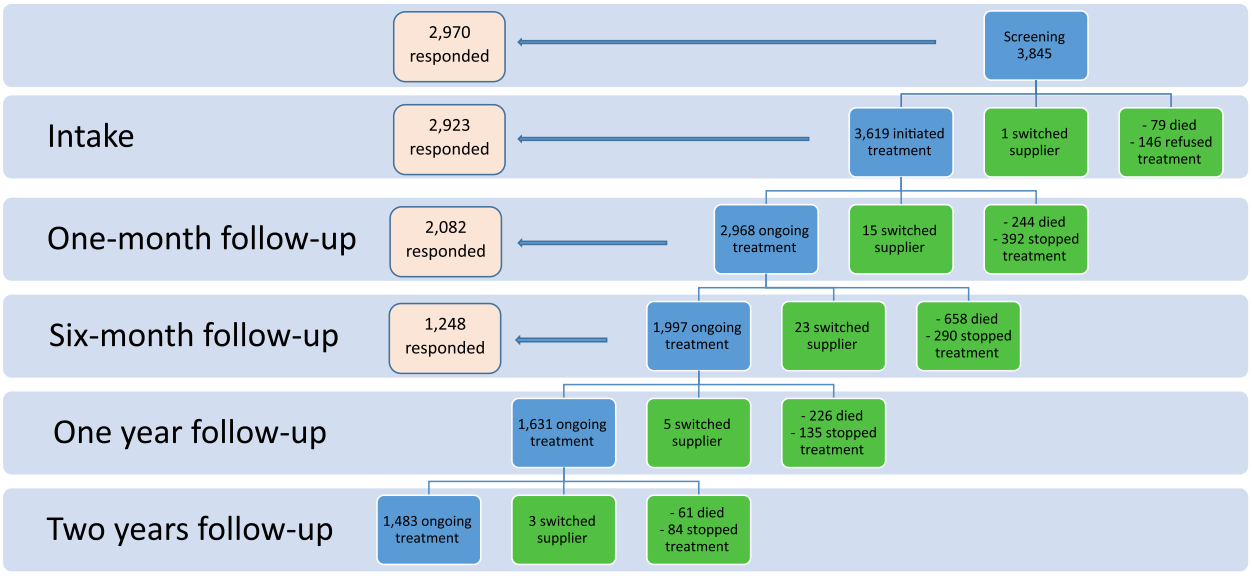


Fig. 1. The study population in the five follow-up periods.

Table 1
Demographic characteristics of cancer patients at intake.

	Total (2970)
Mean age (SD)	59.5 (16.3)
Gender (male), No. (%)	1348 (45.4)
Working (Yes), No. (%)	513 (17.2)
Driving a car (Yes), No. (%)	1474 (49.6)
Median number of hospitalization days in the past six months (IQR)	3 (0–14)
Median number of medications (IQR)	3 (1–6)
Mean body mass index (SD)	24.4 (5.3)
Previous experience with cannabis (Yes), No. (%)	795 (26.7)
Cigarette smoking (Yes), No. (%)	583 (19.6)
Main types of malignancy	
Breast cancer, No. (%)	515 (20.7)
Lung cancer, No. (%)	405 (13.6)
Pancreatic cancer, No. (%)	241 (8.1)
Colorectal cancer, No. (%)	236 (7.9)
Lymphoma, No. (%)	145 (4.9)
Brain/CNS tumors in adults, No. (%)	126 (4.2)
Multiple myeloma, No. (%)	124 (4.2)
Ovarian cancer, No. (%)	118 (4.0)
Prostate cancer, No. (%)	107 (3.6)
Leukemia, No. (%)	77 (2.6)
Liver cancer, No. (%)	67 (2.3)
Bladder cancer, No. (%)	61 (2.1)
Renal cancer, No. (%)	50 (1.7)
Endometrial cancer, No. (%)	44 (1.5)
Hodgkin lymphoma, No. (%)	43 (1.4)
Cervical cancer, No. (%)	41 (1.4)
Melanoma, No. (%)	33 (1.1)

with equal concentrations of Δ9-THC and CBD (~15%), consumed by 23.2% of patients. 4) Two CBD-rich strains (~20%) with a small amount of Δ9-THC (< 1%), consumed by 32.4% of patients. Most patients (72.1%) consume more than one strain.

3.2. Follow-up, one month

At one month, of the 3619 patients who initiated treatment, 244 patients (6.7%) died, 392 (10.8%) stopped treatment, 15 (0.4%) switched to a different cannabis supplier, and 2968 patients (82.0%) continued active treatment. Of the latter group, 2082 (70.1%) responded to the questionnaire with 1380 patients (66.3%) reporting significant improvement, 407 (19.5%) moderate improvement; 123 patients (5.9%) experienced side effects and 172 (8.3%) reported that the cannabis did not help them.

The most common reported side effects at one month were: dizziness (0.6%), cough due to smoking (0.3%), tiredness (0.3%), nausea (0.3%), confusion and disorientation (0.3%).

3.3. Follow-up, six months

At six months, of the 2968 patients that were assessed in the one-month follow-up, 658 patients (22.1%) died, 290 (9.8%) stopped treatment, 23 (0.8%) switched to a different cannabis supplier and 1997 patients (67.3%) continued treatment. Of the latter group, 1211 (60.6%) responded to the questionnaire with 615 patients (50.8%) reporting at least a significant improvement, 547 patients (45.1%) reported moderate or slight improvement and 49 (4.0%) did not experience a positive effect.

Pain intensity and quality of life were assessed at six months in 1144 and 1165 patients respectively. Prior to treatment initiation 52.9% of patients reported their pain to be in the interval of 8 to 10, while only 4.6% reported this intensity after six months of treatment ($p < 0.001$, Fig. 2). Similarly, only 18.7% of patients reported good quality of life prior to treatment initiation while 69.5% reported good quality of life at 6 months ($p < 0.001$, S3).

The most improved symptoms were nausea and vomiting (91.0%), sleep disorders (87.5%), restlessness (87.5%), anxiety and depression (84.2%), pruritus (82.1%) and headaches (81.4%, Appendix B).

A total of 1013 patients responded to the medication chapter before and during treatment. At intake these patients took together 3982 regularly used drugs (medications they take regularly). 35.1% reported a decreased in their drugs consumption, mainly in the following families: other analgesics and antipyretics, hypnotics and sedatives, corticosteroids and opioids (Table 2). Opioids, for example, was the most prevalent drug consumed by 344 patients (33.9%) at intake, 36% of them stopped taking opioids, 9.9% decreased dose, 51.1% continue to take the same dose, 1.1 increased the dose and 32 patients that did not consumed opioids but started treatment with opioids during the six months of follow-up.

The most common side effects reported at six months by 362 patients (30.1%, with at least one side effect) were: dizziness (96, 8.0%), dry mouth (88, 7.3%), increased appetite (43, 3.6%), sleepiness (40, 3.3%) and psychoactive effect (34, 2.8%).

Out of 290 patients who discontinued the treatment 249 had

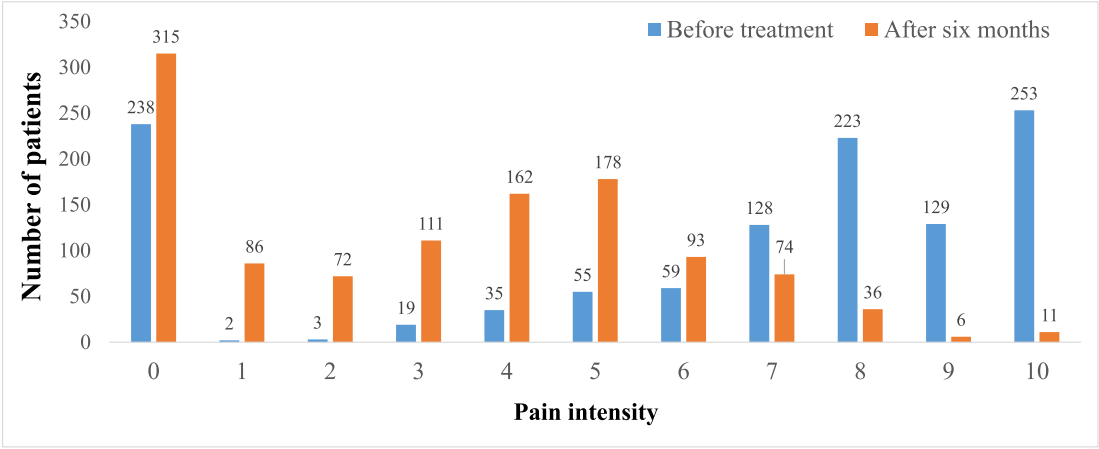


Fig. 2. Assessment of pain intensity. Pain intensity was assessed on 0–10 scale, before and after six months of cannabis therapy. $p < 0.001$.

responded to the follow-up questionnaire at six months. The most common reported reasons for the treatment discontinuation were: there was no longer a need for the cannabis treatment (28.9%), no therapeutic effect (22.5%), and side effects (19.3%). Furthermore, 52.2% of the patients who discontinued the treatment had reported at least moderate improvement in their symptoms.

3.4. Primary efficacy outcome

Overall, 1046 (60%) patients out of 1742 had treatment success at six months (denominator includes all responders to the intake questionnaire except for deceased patients, patients switching to other providers and active patients who did not responded to the follow-up questionnaire). Multivariate analysis revealed that the following factors at intake were associated with treatment success: previous experience with cannabis, pain scale, young age and lack of concerns regarding negative effects of cannabis treatment (Table 3).

Subgroup analysis revealed similar success rates in groups stratified by gender, age, prior experience with cannabis and concerns regarding negative effects of cannabis treatment (Fig. 3).

Analyzing success rates at six months for main types of malignancy revealed similar results of 69.2% success for some types of cancer (renal cancer and Hodgkin lymphoma) and low success rate for other types of cancer (such as 31.2% for melanoma) (Table 4).

4. Discussion

Cannabis as a palliative treatment for cancer patients appears to be well-tolerated, effective and a safe option to help patients cope with the malignancy related symptoms. As can be expected in this population, < 20% of patients reported good quality of life prior to treatment initiation. Impressively, approximately 70% reported good quality of life after 6 months of treatment, indicating a significant improvement.

Table 3
Logistic regression to predict treatment success after six months. Success is defined as at least moderate or significant improvement in the patient's condition and no cessation of treatment or serious side effects.

	Odds ratio	95% Confidence interval	P value
Age	0.98	0.98–0.99	< 0.001
Pain scale	1.06	1.03–1.09	< 0.001
Concerns about cannabis treatment	0.57	0.44–0.73	< 0.001
Previous experience with cannabis	1.32	1.05–1.66	< 0.05

Our analysis revealed that 60% of patients reported therapeutic success and factors that were associated with success included previous experience with cannabis, high levels of pain, young age and lack of concerns regarding negative effects of cannabis treatment.

4.1. Pain

Most patients medicating with cannabis, do so to reduce pain [13,14]. Results of this study demonstrate that pain intensity levels were initially reported as very high (8–10 out of 10 in the VAS scale) in over 50% of the population while after 6 months of treatment < 5% of patients reported such high levels. In a study on cancer patients who did not respond to opioids, Δ9-THC and CBD induced pain reduction, both in an open label study [15] and in a placebo randomized trial [16]. Opioids still constitute a central role in the management of moderate-to-severe cancer pain [17], despite the fact that the rate of discontinuation due to side effects reaches 22% [18]. The success of opioid therapy requires individualization of the dose by using a process of dose titration, creating a long arborous path to pain relief. In a survey of

Table 2
Concomitant medications use at the baseline and six month follow up.

	Intake	Change at six month follow-up					
Medication family	Total	I stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	Other	New medication
Opioids, n (%)	344	124 (36.0)	34 (9.9)	176 (51.1)	4 (1.1)	6 (1.7)	32
Other analgesics and antipyretics, n (%)	177	56 (31.6)	15 (8.4)	102 (57.6)	~	4 (2.2)	2
Anxiolytics, n (%)	155	37 (23.8)	3 (1.9)	113 (72.9)	1 (0.6)	1 (0.6)	5
Hypnotics and sedatives, n (%)	114	29 (25.4)	7 (6.1)	76 (66.6)	~	2 (1.7)	3
Corticosteroids for systemic use, plain, n (%)	85	27 (31.7)	6 (7.0)	49 (57.6)	~	3 (3.5)	7
Antiemetics and antinauseants, n (%)	49	33 (67.3)	1 (2.0)	15 (30.6)	~	~	~
Laxatives, n (%)	38	12 (31.5)	2 (5.2)	23 (60.5)	~	1 (2.6)	2

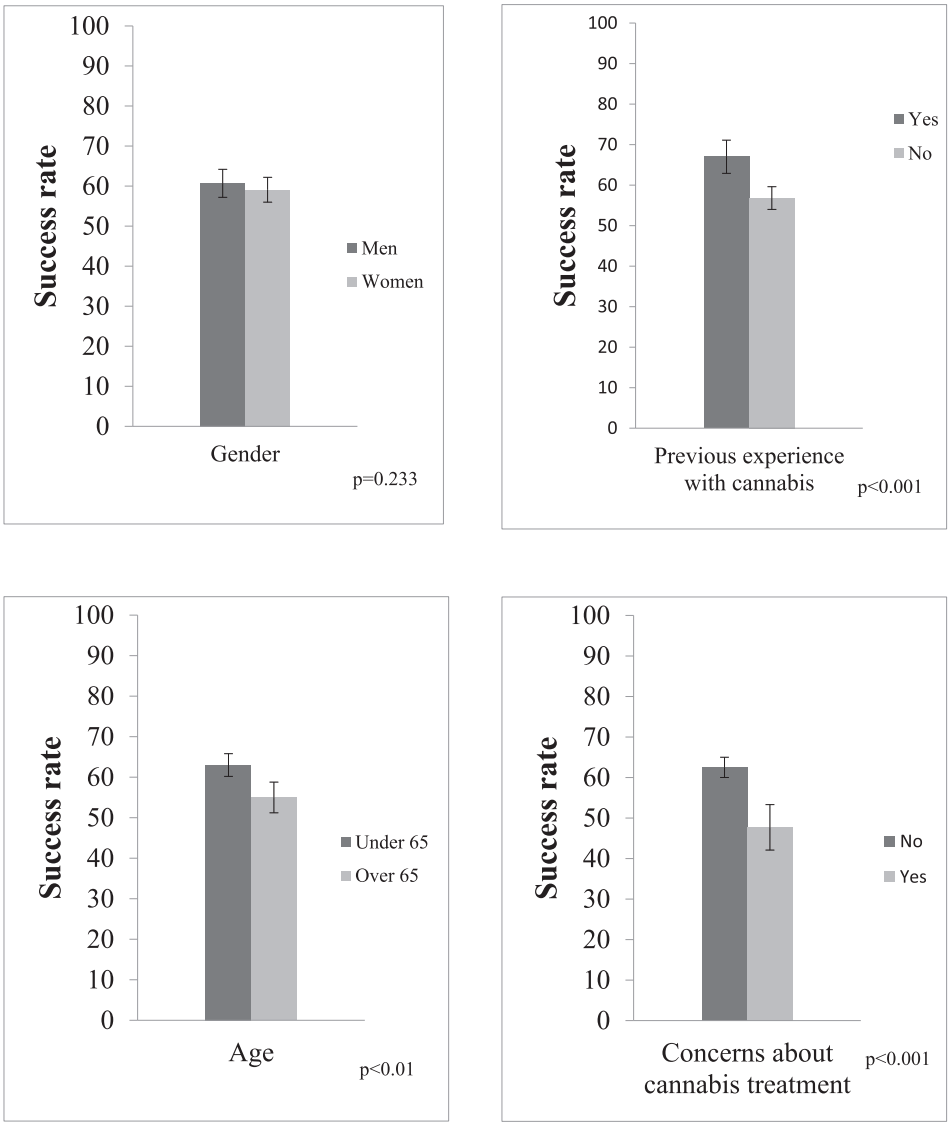


Fig. 3. Subgroup analysis of treatment success. Success is defined as at least moderate or significant improvement in the patient's condition and no cessation of treatment or serious side effects.

ambulatory patients with cancer pain, 31% did not respond to the first opioid treatment option and underwent rotation and nearly a third of them did not respond to the second treatment option either [19]. We believe, that in view of our results demonstrating significant efficacy, cannabis should be considered when attempting to find the treatment to reduce pain in cancer patients.

In addition to pain relief, similar to findings in other prospective studies, the most improved symptoms reported by patients in our cohort were nausea and vomiting, sleep disorders, restlessness, anxiety and depression, pruritus and headaches [20].

4.2. Drugs consumption

Patients using cannabis report a decrease in the consumption of pain medication in general [21] and a reduction of opioids intake in particular [22,23]. In the current sample, 1013 patients took together 3982 regularly used drugs and over a third of the patients reported a decreased in the drugs consumed mainly in the following medications families: other analgesics and antipyretics, hypnotics and sedatives, corticosteroids and opioids.

4.3. Safety

In accordance with other studies evaluating the safety of cannabis treatment over all indications [24], cannabis was found to be safe and well tolerated. Thirty percent of patients in the present study reported at least one side effect at six months, but the side effects were relatively minor and easy to cope with: dizziness, dry mouth, increased appetite, sleepiness and psychoactive effect.

In studies where patients were asked to compare the side effects of cannabis to the side effects of prescribed medications, 79% [25] and 57% [26] said cannabis had fewer side effects than concurrent treatment. In general, patients said that prescription drugs have more side effects than cannabis [27], and that the side effects are more severe [28].

The relatively tolerable adverse events associated with cannabis therapy should be compared to opioid induced side effects such as constipation, mental clouding, somnolence, nausea or pyrosis, dry mouth, urinary retention, itch, and myoclonus [29–31]. In addition, the incidence of serious side effects with opioid medications is between 4.3 and 8.7% [18] and users are risk of developing physical dependence and addiction [32]. In light of the potential complications, development of dependence and increased risk for adverse events it seems that cannabis may be a suitable alternative to medication with opioids.

Table 4
Success rates at six months for main types of malignancy. Success is defined as at least moderate or significant improvement in the patient's condition and no cessation of treatment or serious side effects.

	Success rate, % (95% confidence interval)	Stopped the treatment, No. (%)
Renal cancer (*N* = 26)	69.2 (50.2–80.2)	4 (15.3)
Hodgkin lymphoma (*N* = 39)	69.2 (54.0–84.3)	10 (25.6)
Brain/CNS tumors in adults (*N* = 59)	67.8 (55.5–80.0)	10 (16.9)
Multiple myeloma (*N* = 91)	67.0 (57.1–76.8)	4 (26.3)2
Cervical cancer (*N* = 21)	66.6 (44.6–88.6)	6 (28.5)
Breast cancer (*N* = 392)	61.9 57.1–66.8 ()	120 (30.6)
Lung cancer (*N* = 189)	59.2 (52.1–66.3)	55 (29.1)
Lymphoma (*N* = 105)	59.0 (49.4–68.6)	37 (35.2)
Pancreatic cancer (*N* = 90)	58.8 (48.5–69.2)	27 (30.0)
Colorectal cancer (*N* = 137)	58.3 (50.0–66.7)	46 (33.5)
Leukemia (*N* = 54)	57.4 (43.7–71.0)	14 (25.9)
Liver cancer (*N* = 28)	57.1 (37.6–76.6)	8 (28.5)
Endometrial cancer (*N* = 25)	56.0 (35.0–76.9)	7 (28.0)
Ovarian cancer (*N* = 62)	54.8 (42.1–67.5)	22 (35.4)
Bladder cancer (N = 28)	53.5 (33.8–73.2)	8 (28.5)
Prostate cancer (*N* = 58)	53.4 (40.2–66.6)	18 (31.0)
Melanoma (*N* = 16)	31.2 (5.7–56.7)	7 (43.7)

4.4. Limitations

The present findings should be interpreted with caution for several reasons. This is an observational study with no control group and therefore no causality between cannabis therapy and improvement in patients' wellbeing can be established. Patients who seek cannabis therapy might not constitute a representative sample of the patient with a specific disease (self-selection bias). We used data collected routinely as part of the treatment program; therefore, some information like monthly income and use of illicit substances was not available. Finally, some of the improvement in symptoms may be due to the fact that some patients have completed the chemotherapy regimen.

The main advantages of this study are: its large sample size and prospective follow-up with relatively high response rates while most surveys are based on self-reporting data with an inherent exclusion of patients stopping the treatment and high rates of lost to follow-up.

5. Conclusions

Cancer patients are a unique population characterized with multiple symptoms and different medications in use. In an age where a physician often prescribes a different medication for each symptom, cannabis, as a comprehensive treatment that affects several symptoms, becomes a desirable therapeutic option.

Competing interest statement

Lihi Bar-Lev Schleider, Violeta Lederman, Mario Hilou, Oded Betzalel – employees of Tikun-Olam Ltd. without shares or options.

Victor Novack – paid member of the Tikun Olam Ltd. scientific advisory board.

Raphael Mechoulam, Ori Lencovsky, Liat Shbiro – no conflicts of interest pertaining to the current manuscript.

Declaration of interest

Tikun Olam Ltd. supported this study.

Appendix A

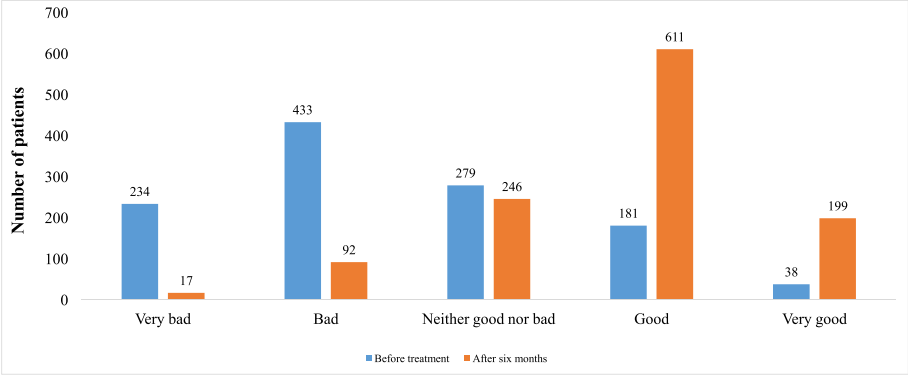
A. Disease prevalence and duration.

	Total responses, No. (%)	Median disease duration (IQR)
Hypertension	429 (14.4)	10 (5–15)
Diabetes	326 (11.0)	8 (4–15)
Ischemic heart disease	215 (7.2)	8 (3–15)
Nonspecific pain	146 (4.9)	3 (1–7)
Osteoporosis	57 (1.9)	5 (3–13.5)
Spinal disk herniation	52 (1.8)	10 (4.5–14)
Hypertriglyceridemia	52 (1.8)	8 (5–10)
Asthma	49 (1.6)	21 (21 − 21)
Depression	45 (1.5)	5.5 (1 − 21)
Arthritis	44 (1.5)	8 (4–21)
Chronic obstructive pulmonary disease (COPD)	43 (1.4)	5 (3 − 10)
Fibromyalgia	37 (1.2)	8 (4.25–10)

B. Symptom prevalence at intake and change at six months.

	Total (2970)	Change at six months		
		Symptom disappeared	Improvement	No change or deterioration
Sleep problems, No. (%)	2329 (78.4)	155 (16.7)	655 (70.8)	114 (12.3)
Weakness and fatigue, No. (%)	2160 (72.7)	84 (10.9)	429 (55.9)	255 (33.2)
Digestion problems, No. (%)	1918 (64.6)	199 (26.7)	375 (50.3)	171 (23.0)
Anxiety and depression, No. (%)	1694 (57.0)	62 (10.1)	455 (74.1)	97 (15.8)
Nausea and vomiting, No. (%)	1662 (56.0)	251 (36.3)	378 (54.7)	62 (9.0)
Lack of appetite, No. (%)	1453 (48.9)	130 (25.8)	313 (62.1)	61 (12.1)

Movement limitation, No. (%)	1051 (35.4)	24 (7.5)	134 (41.6)	164 (50.9)
Paresthesia, No. (%)	1043 (35.1)	60 (16.2)	185 (50.0)	125 (33.8)
Dizziness, No. (%)	939 (31.6)	97 (28.4)	171 (50.1)	73 (21.4)
Dry Mouth, No. (%)	928 (31.2)	89 (27.1)	82 (25.0)	157 (47.9)
Drowsiness, No. (%)	896 (30.2)	40 (12.7)	179 (57.0)	95 (30.3)
Respiratory problems, No. (%)	828 (27.9)	74 (29.7)	92 (36.9)	83 (33.3)
Spasticity, No. (%)	820 (27.6)	53 (18.3)	146 (50.5)	90 (31.1)
Headache, No. (%)	686 (23.1)	78 (30.2)	132 (51.2)	48 (18.6)
Burning sensation, No. (%)	669 (22.5)	52 (21.7)	130 (54.2)	58 (24.2)
Restlessness, No. (%)	602 (20.3)	36 (15.6)	166 (71.9)	29 (12.6)
Pruritus, No. (%)	553 (18.6)	71 (38.6)	80 (43.5)	33 (17.9)
Numbness	489 (16.5)	25 (14.5)	72 (41.9)	75 (43.6)
Cognitive impairment, No. (%)	489 (16.5)	23 (13.6)	54 (32.0)	92 (54.4)
Tremor, No. (%)	466 (15.7)	37 (28.7)	57 (44.2)	35 (27.1)
Visual impairment, No. (%)	461 (15.5)	27 (17.9)	15 (9.9)	109 (72.2)



C. Quality of life assessment. Quality of life was assessed prior to and six months after initiation of cannabis treatment. $p < 0.001$.

References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.

[2] Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010;39:167–79.

[3] Ahmedzai S, Brooks D, Group T-FCT. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manage 1997;13:254–61.

[4] Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012;13:e58–68.

[5] Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004;112:299–306.

[6] Bakowski MT. Advances in anti-emetic therapy. Cancer Treat Rev 1984;11:237–56.

[7] Schwartzberg LS. Chemotherapy-induced nausea and vomiting: clinician and patient perspectives. J Support Oncol 2007;5:5–12.

[8] National Academies of Sciences E, and Medicine. The Health Effects of Cannabis and Cannabinoids: the Current State of Evidence and Recommendations for Research. National Academies Press.

[9] Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs 2011;43:128–35.

[10] Ferraz MB, Quaresma M, Aquino L, Atra E, Tugwell P, Goldsmith C. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990;17:1022–4.

[11] Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

[12] Group W. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998;28:551–8.

[13] Light MK, Orens A, Lewandowski B, Pickton T. Market Size and Demand for Marijuana in Colorado. 209. Denver: Colorado Department of Revenue; 2014. p. 202014. https://www coloradogov/pacific/sites/default/files/Market% 20Size%20and%20Demand%20Study, %20July.

[14] Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert AS, Walton M, et al. Characteristics of adults seeking medical marijuana certification. Drug Alcohol Depend 2013;132:654–9.

[15] Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage 2013;46:207–18.

[16] Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012;13:438–49.

[17] Juneja R. Opioids and cancer recurrence. Curr Opin Support Palliat Care 2014;8:91–101.

[18] Mesgarpour B, Griebler U, Glechner A, Kien C, Strobelberger M, Van Noord M, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. Eur J Pain 2014;18:605–16.

[19] Reddy A, Yennurajalingam S, Pulivarthi K, Palla SL, Wang X, Kwon JH, et al. Frequency, outcome, and predictors of success within 6 weeks of an opioid rotation among outpatients with cancer receiving strong opioids. Oncologist 2013;18:212–20.

[20] Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. Evid Based Complement Alternat Med 2013;2013.

[21] Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in medicare part D. Health Aff 2016;35:1230–6.

[22] Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016;17:739–44.

[23] Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis and Cannabinoid Research. 2. 2017. p. 160–6.

[24] Harris D, Jones RT, Shank R, Nath R, Fernandez E, Goldstein K, et al. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. J Addict Dis 2000;19:89–103.

[25] Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int J Drug Policy 2013;24:511–6.

[26] Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduction Journal 2005;2:18.

[27] Ware M, Adams H, Guy G. The medicinal use of cannabis in the UK: results of a nationwide survey. Int J Clin Pract 2005;59:291–5.

[28] Reiman A. Medical cannabis patients: patient profiles and health care utilization patterns. Complement Health Pract Rev 2007;12:31–50.

[29] Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. J Clin Oncol 2014;32:1662–70.

[30] Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992;7:69–77.

[31] Taylor CB, Zlutnick SI, Corley MJ, Flora J. The effects of detoxification, relaxation, and brief supportive therapy on chronic pain. Pain 1980;8:319–29.

[32] Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. Pain Physician 2008;11:S105–20.