TIKUN

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Medical Cannabis Research

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Tikun Olam's Research Overview

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Tikun Olam is a proud pioneer and global leader in medical cannabis research. Rooted in Israel's regulatory environment, our team of scientists have conducted cannabis studies and clinical trials for more than a decade, achieving outstanding results and amassing one of the world's largest cannabis treatment databases of currently more than 20,000 patients.

In Hebrew, "Tikun Olam" translates to "Repair the World." This guides our mission to provide science-backed, high-quality medical cannabis that improves the quality of life and overall wellness of our patients. Through extensive research and development, our proprietary strains have been genetically optimized and clinically proven to provide symptomatic relief for a wide variety of ailments, including Crohn's Disease, Parkinson's Disease, epilepsy, autism, cancer, IBD, and more.

Our clinical successes have encouraged us to devote more resources to further improve the safety and efficacy of our products, as well as our understanding of the therapeutic properties of the cannabis plant. We continually conduct laboratory studies (both in vitro and in vivo), retrospective analyses, and clinical trials, and work diligently to follow-up with our patients. We sustain partnerships and collaborative relations with physicians, scientists, and the departmental heads of leading medical institutions across the world. Building on the discoveries and legacy of Dr. Raphael Mechoulam (who mentored our founder, Tzachi Cohen), our research efforts today are led by Dr. Ruth Gallily, Dr. Timna Naftali, Dr. Lihi Bar-Lev Schleider, and Dr. Zvi Bentwich. By sharing our advancements in cannabis treatment research, we aim to inspire and educate the medical community.

Below is a select outline of our research as of July 2019.

COMPLETED & PUBLISHED RESEARCH

1. Treatment of Crohn's Disease with Cannabis: An Observational Study

The Israel Medical Association Journal, 2011

This retrospective study observed cannabis as treatment for Crohn's Disease and found that cannabis use resulted in significant positive effects on the symptoms of the disease (number of bowel movements, quality of bowel activity, abdominal pain, and other complications).

Study Population: 30 patients with Crohn's Disease
Strain Used: *Erez*
Key Results:

- 21 of the 30 patients improved significantly with cannabis treatment
- The average Harvey Bradshaw Index improved from 14 +/- 6.7 to 7 +/- 4.7 (P<.001); the index measures general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and related complications
- The mean number of bowel movements decreased from 8 to 5 per day
- The need for other medication was significantly reduced; most notably, the number of patients needing steroid treatment reduced from 26 to 4
- Only 2 of 15 patients who had surgery prior to cannabis treatment needed additional surgery during treatment

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2. Cannabis Induces a Clinical Response in Patients with Crohn's Disease: A Randomized Placebo-Controlled, Double-Blind Study

Clinical Gastroenterology & Hepatology, 2013

In the world's first randomized, placebo-controlled, double-blinded study of its kind, Dr. Naftali and a team of researchers used Tikun Olam's *Erez* strain to produce dramatic results, with 45% of Crohn's patients achieving "complete remission" and over 90% achieving substantial improvement – with no side effects witnessed.

Study Population: 21 patients with Crohn's Disease Activity Index (CDAI) scores greater than 200, who did not respond to therapy with steroids, immune-modulators, or anti-tumor agents; 11 of the patients were in the cannabis treatment study group, 10 were in the placebo control group
Strain Used: *Erez*
Key Results:

- Complete remission (CDAI score <150) was achieved by 5 of the 11 patients in the cannabis group
- Clinical response (decrease in CDAI score of >100) was observed in 10 of the 11 patients
- 3 of the 11 patients were weaned from steroid dependency
- The cannabis group reported significantly less pain, and improved appetite and quality of life

3. Cannabis for Inflammatory Bowel Disease

Digestive Diseases, 2014

A summary of the research analyzing cannabis as treatment for Inflammatory Bowel Diseases. Evidence suggests that manipulating the endocannabinoid system with cannabinoids may have a positive effect on IBD, but further research is needed to determine the specific cannabinoids, optimal dosage, and mode of administration for maximum benefit.

4. Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol

Pharmacology & Pharmacy, 2015

This laboratory study was conducted on rodents to examine the effect of full-plant cannabis extract on inflammation and pain, in comparison with isolated CBD and commercial anti-inflammatory and anti-nociceptive drugs. Isolated CBD has been shown to have a bell-shaped dose-response, where healing is only observed within a very limited dose range, with no additional beneficial effect achieved at lower or higher doses. This trait of purified CBD poses challenges to clinical use; thus, this study aimed to find a CBD source that eliminates the bell-shaped dose response – and succeeded with *Avidekel*.

Study Population: Lab mice
Strain Used: *Avidekel*
Key Results:

- The full-plant extract of *Avidekel*, which is high in CBD and low in THC, provided a correlative anti-inflammatory and anti-pain dose-response (i.e. as the dose was increased, the pain and inflammation decreased in correlation), superior to the bell-shaped dose-response of isolated CBD, which exhibited less consistent anti-inflammatory and anti-pain properties at lower and higher doses

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- *Avidekel* extract exhibited superior anti-inflammatory effectiveness compared to tramadol (an opioid analgesic) and aspirin (a non-steroid anti-inflammatory)

5. CBD-Enriched Medical Cannabis for Intractable Pediatric Epilepsy

Seizure: European Journal of Epilepsy, 2016

A retrospective study analyzing the effect CBD-enriched cannabis oil had on children and adolescents with refractory epilepsy, being treated at four epilepsy centers in Israel.

Study Population: 74 patients (1 - 18 years old) with intractable epilepsy, resistant to 5-7 antiepileptic drugs
Strains Used: Better and Tikun Olam's CBD-enriched cannabis oil at a 20:1 (CBD:THC) ratio
Key Results:

- 89% of patients reported reduction in seizure frequency
- Improvement in behavior, alertness, language, communication, motor skills, and sleep were reported

6. Medical Cannabis in Parkinson's Disease

Clinical Neuropharmacology, 2017

A retrospective questionnaire-based survey that examined the effects of cannabis on the motor and non-motor symptoms of patients with Parkinson's Disease. The mean age of the patients was 64.2 +/- 10.8 years, the mean disease duration was 10.8 +/- 8.3 years, and the duration of cannabis use was 19.1 +/- 17 months.

Study Population: 47 patients with Parkinson's Disease
Strains Used: Various medical cannabis strains
Key Results:

- 82.2% of patients reported that cannabis improved their overall symptoms
- 81.4% of patients reported that their pain was reduced
- 76.1% of patients reported an improvement in mood
- 73.2% of patients reported tremor reduction
- 72.7% of patients reported reduced muscle stiffness
- 71.1% of patients reported an improvement in sleep quality

7. Epidemiological Characteristics, Safety and Efficacy of Medical Cannabis in The Elderly

European Journal of Internal Medicine, 2018

A prospective study that analyzed the use of cannabis treatment in the elderly, measuring for pain intensity, quality of life, and adverse effects at six months follow-up. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). The study found that the therapeutic use of cannabis is safe and efficacious in the elderly population.

Study Population: 2736 patients aged 65+; at 6 months, 901 patients were eligible for follow-up and completed the survey
Strains Used: *Erez*, *Alaska*, *Avidekel* and other CBD-rich Tikun Olam strains (*Raphael*, *Metatron*, *Michael*)

Key Results:

- Reported pain significantly reduced from a median of 8/10 to 4/10
- Prior to treatment, 66.8% of patients reported high pain-intensity; at six months, this number decreased to only 7.6% of patients
- 93.7% of patients reported that the cannabis treatment improved their condition
- 35.1% of patients reported a decrease in the number of drugs taken or the dosage
- 18.1% of patients stopped using opioid analgesics or reduced their dose
- The most common reported side effects were dizziness (9.7%) and dry mouth (7.1%)

8. Prospective Analysis of Safety and Efficacy of Medical Cannabis in Large Unselected Population of Patients with Cancer

European Journal of Internal Medicine, 2018

This study analyzed the data routinely collected as part of the treatment program of cancer patients treated with medical cannabis between 2015 and 2017. The most frequent types of cancer were breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%), and 51.2% of patients were 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%).

The study concluded that cannabis as a palliative treatment for cancer patients is a well-tolerated, effective and safe option to help patients cope with cancer-related symptoms.

Study Population: 2,970 cancer patients; after six months of treatment, 1,211 patients were eligible for follow-up and responded to the questionnaire
Strains Used: Four categories of Tikun Olam strains - 1) *Midnight*, a 1:1 CBD:THC (~15%) strain, 2) *Avidekel*, a CBD-rich strain with <1% THC, 3) THC-rich indica strains with <.5% CBD, 4) THC-rich sativa strains with <.5% CBD; most patients consumed more than one strain
Key Results:

- 95.9% of patients reported an improvement in their condition
- Prior to treatment, 52.9% of patients reported their pain in the 8-10 interval; after six months, only 4.6% of patients reported this intensity
- Prior to treatment, only 18.7% of patients reported good quality of life; after six months, 69.5% of patients reported good quality of life
- The most improved symptoms were nausea and vomiting (91%), sleep disorders (87.5%), restlessness (87.5%), anxiety and depression (84.2%), pruritus (82.1%) and headaches (81.4%)
- 35.1% of patients decreased their drug consumption, including analgesics, sedatives, corticosteroids, and opioids
- At intake, 344 patients used opioids; after six months, 36% stopped taking opioids and 9.9% reduced their dose
- The most common side effects reported were dizziness (8%) and dry mouth (7.3%)

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9. Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders

Journal of Child Neurology, 2018

A clinical random trial examining the effects of *Avidekel* oil on dystonia and spasticity in children who suffer from cerebral palsy or genetic impairment. Most participants reported significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and quality of life.

Study Population: 20 patients with complex motor disorders (primarily cerebral palsy)
Strain Used: *Avidekel*, tested at 6:1 and 20:1 CBD:THC ratios
Key Results:

- CBD-enriched 5% cannabis oil with CBD:THC ratios of 6:1 and 20:1 are effective in reducing the severity of dystonia and spasticity, and improving motor function ability and quality of life
- All patients demonstrated mood and appetite improvement
- Patients treated with the 6:1 ratio oil demonstrated sleep improvement
- Patients treated with the 20:1 ratio oil demonstrated improvement in constipation

10. Avidekel Cannabis Extracts and Cannabidiol are as Efficient as Copaxone in Suppressing EAE in SJL/J Mice

Inflammopharmacology, 2018

This study compared the efficacy of purified CBD, extracts of CBD-rich *Avidekel*, and Copaxone (glatiramer acetate), an immunosuppressive medication that is used to alleviate the symptoms of multiple sclerosis (MS).

Study Population: Lab mice
Strain Used: *Avidekel*
Key Results:

- CBD and *Avidekel* extracts are as efficient as Copaxone in alleviating the symptoms of EAE (animal model of brain inflammation) in lab mice; thus,
- *Avidekel* may be useful in the treatment of MS symptoms

11. Single Center Experience with Medical Cannabis in Gilles de la Tourette Syndrome

Parkinsonism and Related Disorders, 2018

This study was conducted to assess the response and benefits of using cannabis to treat Tourette Syndrome.

Study Population: 42 patients with Tourette Syndrome
Strain Used: *Erez*
Key Results:

- The mean ranking of efficacy was 3.85 out of 5, indicating a positive response to medical cannabis
- Patients reported reduction in tic severity, better sleep, and improved mood

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12. Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems

Journal of Autism and Developmental Disorders, 2018

A retrospective study assessing the tolerability and efficacy of CBD-rich cannabis in children with ASD.

Study Population: 60 children with ASD and severe behavioral problems
Strain Used: *Avidekel* and other CBD-rich cannabis oil at a 20:1 (CBD:THC) ratio
Key Results:

- Considerable improvement was reported in behavior (61%), communication (47%), and anxiety (39%), after at least 3 months of cannabis treatment
- 33% of children reduced their other medication doses and 24% stopped taking medications altogether

13. Real Life Experience of Medical Cannabis with Autism: Analysis of Safety and Efficacy

Scientific Reports, 2019

This observational study assessed the safety and efficacy of medical cannabis for the treatment of autism spectrum disorders (ASD), analyzing the change in symptoms after six months of using our CBD-rich cannabis oil.

Study Population: 188 children with ASD; 93 completed the follow-up survey at six months
Strain Used: *Avidekel*, at a 20:1 CBD:THC ratio
Key Results:

- 90.2% of patients reported an improvement in symptoms after six months treatment
- Symptoms improved included depression (100%), restlessness (89.8%), rage attacks (89%), anxiety (88.8%), seizures (84.6%), agitation (83.8%), tics (80%), digestion problems (62.5%), constipation (62.5%), sleep problems (58.6%), and more
- Good quality of life was indicated by 31.1% of patients at intake; by 66.8% at six months
- Patients reported improvement in sleep, positive mood, and ability to dress and shower independently
- 34.3% of patients decreased medication consumption, including antipsychotics, antiepileptics, antidepressants, hypnotics, and sedatives
- 20% of patients stopped taking antipsychotics
- Cannabis appears to be a well-tolerated, safe and effective option to relieve ASD symptoms

14. Safety and Efficacy of Medical Cannabis in Fibromyalgia

Journal of Clinical Medicine, 2019

This observational study investigated the characteristics, safety, and effectiveness of medical cannabis therapy for fibromyalgia. Patients studied were referred to cannabis after receiving traditional treatment for at least a year without improvement. The change in symptoms and quality of life was measured after six months of treatment.

Study Population: 367 patients with fibromyalgia; 211 completed the follow-up survey at six months
Strains Used: *Avidekel*, *Alaska*, and other Tikun Olam strains
Key Results:

- 81.1% of patients reported overall treatment success - defined as experiencing at least moderate improvement in their condition without serious adverse effects
- 73.4% of patients reported improved sleep; 13.2% reported their sleep problems were fully relieved

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- 80.8% of patients reported improved depression-related symptoms
- 61.9% of patients reported their quality of life (QOL) to be "good or very good," whereas only 2.7% of patients rated their QOL at this level prior to beginning treatment; QOL components include appetite, sleep quality, and sexual activity
- Overall pain intensity reduced from a median of 9.0 at baseline to 5.0 after six months
- 22.2% of patients stopped or reduced their dosage of opioids; 20.3% reduced their dosage of benzodiazepines

INTERNAL DATABASE STUDIES

1. The Effects of Cannabis on Appetite and Blood Indices of Geriatric Patients

A long-term observational follow-up was conducted from 2009 to 2013, to collect data from elderly nursing home patients who regularly used medical cannabis. The study measured parameters such as nutritional blood work, caloric intake, weight, prescription drug usage, sepsis, trembling, spasticity, and quality of life measurements (mood, sleeping habits, etc.).

This study showed that cannabis can improve the quality of life of geriatric patients in their final years of life.

Study Population: 21 patients aged 70 - 103
Strains Used: Various Tikun Olam strains with 23 -30% THC
Key Results:

- All patients maintained normal weight, protein, and albumin levels
- No patients needed feeding tube insertion due to lack of appetite
- Patients reported pain relief, mood improvement, and increase in sleeping hours
- 76.1% of the patients reduced their medication intake

2. Symptoms Relief Among Tikun Olam Patients Treated with Medical Cannabis

A retrospective cohort study investigating the effect of cannabis on specific symptoms, such as pain, insomnia, lack of appetite, fatigue, and spasticity, in patients who commenced treatment with medical cannabis at Tikun Olam between 2009 – 2016.

Study Population: 1,338 medical cannabis patients who completed a survey before and after six months of treatment
Strains Used: Various Tikun Olam strains
Key Results:

- After at least six months of cannabis treatment, 94% of patients reported improvement in their condition
- Most patients experienced pain reduction and many reported improved sleep, mood, and appetite
- Bowel activity, concentration, and sexual function were improved by some
- 62% of patients reduced their medication consumption
- Most patients did not experience side effects from the treatment, and of those who did, dizziness and dry mouth were the most common reported

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CLINICAL STUDIES IN PROGRESS

1. The Effects of Cannabis on Colitis

Clinical research comparing a group of Colitis patients who will be given *Erez* strain cannabis cigarettes (0.5 grams per cigarette) and a group who will be given placebo cigarettes (a total of two cigarettes per day) for a period of eight weeks, during which the effect of cannabis on blood inflammation indices, life quality, medicine consumption, and adverse side effects, etc., will be monitored.

2. The Effects of Cannabis on Crohn's Disease

Clinical research comparing a test group, receiving the *Avidekel* strain, and a control group (placebo), to examine the effect of cannabis oil administered as treatment for inflammatory intestinal disease. The oil contains a high concentration of CBD (200 mg) and a low concentration of THC (59 mg) and is administered twice a day.

3. Cannabis and IBD Data Collection

Large-scale long-term data collection study on patients using medical cannabis that suffer from inflammatory bowel disease (IBD), to determine the effect of cannabis use on the symptoms and adverse side effects of the disease.

LABORATORY RESEARCH IN PROGRESS

1. The Effects of Cannabis on Immune Response

A study analyzing the effect of extracts of *Avidekel*, *Erez* and *Midnight* on immune response in blood samples in which infection was induced. Preliminary results show a verification of a suppressing effect of natural cannabinoids on the release of inflammation triggering cytokines; indication of a possible inflammation preventing effect of CBD on the immune system.

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Crohn's Disease I

Treatment of Crohn's Disease with Cannabis: An Observational Study

The Israel Medical Association Journal, 2011

This retrospective study observed cannabis as treatment for Crohn's Disease and found that cannabis use resulted in significant positive effects on the symptoms of the disease (number of bowel movements, quality of bowel activity, abdominal pain, and other complications).

Study Population: 30 patients with Crohn's Disease
Strain Used: *Erez*
Key Results:

- 21 of the 30 patients improved significantly with cannabis treatment
- The average Harvey Bradshaw Index improved from 14 +/- 6.7 to 7 +/- 4.7 (P<.001); the index measures general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and related complications
- The mean number of bowel movements decreased from 8 to 5 per day
- The need for other medication was significantly reduced; most notably, the number of patients needing steroid treatment reduced from 26 to 4
- Only 2 of 15 patients who had surgery prior to cannabis treatment needed additional surgery during treatment

Treatment of Crohn's Disease with Cannabis: An Observational Study

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ABSTRACT: **Background:** The marijuana plant cannabis is known to have therapeutic effects, including improvement of inflammatory processes. However, no report of patients using cannabis for Crohn's disease (CD) was ever published.

Objectives: To describe the effects of cannabis use in patients suffering from CD.

Methods: In this retrospective observational study we examined disease activity, use of medication, need for surgery, and hospitalization before and after cannabis use in 30 patients (26 males) with CD. Disease activity was assessed by the Harvey Bradshaw index for Crohn's disease.

Results: Of the 30 patients 21 improved significantly after treatment with cannabis. The average Harvey Bradshaw index improved from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$). The need for other medication was significantly reduced. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgery during an average period of 3 years of cannabis use.

Conclusions: This is the first report of cannabis use in Crohn's disease in humans. The results indicate that cannabis may have a positive effect on disease activity, as reflected by reduction in disease activity index and in the need for other drugs and surgery. Prospective placebo-controlled studies are warranted to fully evaluate the efficacy and side effects of cannabis in CD.

IMAJ 2011; 13: 455–458

KEY WORDS: Crohn's disease, inflammatory bowel disease, cannabis, marijuana

The marijuana plant, *Cannabis sativa*, has been used as a medicinal treatment for a variety of diseases [1]. Cannabinoids have been reported to alleviate neurological conditions including multiple sclerosis-related symptoms such as spasticity, pain, tremor and bladder dysfunction [2]. Other neurological conditions, such as chronic intractable pain, dystonic movement disorders, and Tourette's syndrome were also reported to be alleviated by cannabis use [3]. Cannabis has been used to treat anorexia in AIDS and cancer patients [2,3]. In gastroenterology, cannabis has been used to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation, and diabetic gastroparesis [4].

The cannabis plant contains over 60 different compounds, which are collectively referred to as cannabinoids [5]; of them Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) seem to be the most active. Cannabinoids have a profound anti-inflammatory effect, mainly through the CB2 receptor [2]. Cell-mediated immunity was found to be impaired in chronic marijuana users [6]. A potent anti-inflammatory effect of cannabis was observed in rodents [7]. Studying the functional roles of the endocannabinoid system in immune modulation reveals that it is involved in almost all major immune events. Cannabinoids shift the balance of pro-inflammatory cytokines and anti-inflammatory cytokines towards the T helper cell type 2 profiles (Th2 phenotype) and suppress cell-mediated immunity, whereas humoral immunity may be enhanced [8]. Therefore, cannabinoids may be used to treat various inflammatory conditions including rheumatoid arthritis. In a mouse model of colitis, cannabinoids were found to ameliorate inflammation [9]. Consequently, the non-conventional medical community has recommended cannabis for patients with inflammatory bowel disease. However, there are no systematic reports of the effects of cannabis on IBD. The aim of this study was to describe the response of patients with Crohn's disease who have used cannabis to ameliorate their symptoms.

PATIENTS AND METHODS

This was a retrospective observational study. A voluntary organization that distributes cannabis for legally authorized medical use in Israel was contacted. We interviewed patients with CD who had permission from the Ministry of Health to receive cannabis for their symptoms. Patients were questioned about the details of their disease, previous medical and surgical treatments, and the reason for using cannabis. Disease activity before and after cannabis use was estimated by the Harvey Bradshaw index. All patients assessed their general

IBD = inflammatory bowel disease
CD = Crohn's disease

well-being before and after cannabis use on a Visual Analog Scale. The scale ranged from 0, which represented "very poor general well-being" to 10, indicating "excellent well-being." Whenever possible, medical documents were reviewed for objective signs of disease severity, such as number of hospital admissions and use of other drugs, particularly steroids. The dose and form of administration of cannabis were documented. The study was approved by the institutional ethics committee of our hospital.

RESULTS

Thirty patients with CD who were using cannabis were interviewed. The average age was 36 years (range 21–65 years) and four were female. One patient with CD had a history of partial pancreatectomy for serous cystadenoma, one had asthma and two had hypertension. All other patients were generally healthy apart from their CD. Before the use of cannabis, five patients had undergone right hemicolectomy, three had resection of the terminal ileum, two had resection of a proximal section of the ileum, and three had drainage of a perianal fistula. One patient with severe colitis had a total proctocolectomy with ileoanal anastomosis. After the operation she developed perianal disease and the diagnosis was changed from ulcerative colitis to Crohn's disease. Of the 15 patients who had an operation before using cannabis, 2 (13%) required another surgery during an average time of 2 years while on cannabis. The average duration of disease was 11.3 years (range 1–41 years). Twenty patients with CD had inflammation of the terminal ileum, 5 had inflammation of the more proximal ileum and 8 had Crohn's disease of the colon. One patient had pouchitis. Crohn's disease was fistulizing in 10 patients, fibrostenotic in 5, and luminal in 15. Before cannabis use, 27 patients had received 5-ASA (5-aminosalicylic acid), 26 received corticosteroids, 20 took thiopurines, 6 took methotrexate, and 12 took anti-tumor necrosis factor antibodies. Of 30 patients, 16 smoked tobacco regularly, 3 smoked tobacco before using cannabis but stopped when they started cannabis use, and 14 never smoked tobacco. Of the three patients who stopped tobacco smoking, one did not improve (Harvey Bradshaw score of 4 both before and after cannabis use), one improved significantly (from 11 to 2), and one improved slightly (from 9 to 7), Although tobacco smoking is known to have a negative effect on Crohn's disease, these results do not indicate that smoking cessation in itself had any effect on disease severity in our patients.

The indication for cannabis use was lack of response to conventional treatment in 21 patients and chronic intractable pain in 6. Another four patients smoked cannabis for recreation and continued as they observed an improvement in their medical condition. Most patients smoked cannabis in the form of hand-rolled cigarettes ("joints"). Four patients inhaled the smoke through water ("bong"), and one patient preferred to consume it orally. Most smoked between one and three "joints" a day, but one patient with chronic pain smoked seven joints a day. Since one cigarette contains about 0.5 mg of THC, patients were using 0.5–1.5 mg/day THC, with the exception of one patient who was using 3.5 mg. The average duration of cannabis use was 2.14 years (range 3 months to 9 years). In 14 patients the duration of cannabis use was less than a year.

All patients stated that consuming cannabis had a positive effect on their disease activity. This is also reflected in the Visual Analog Scale, which increased from 3.1 to 7.3. The Harvey Bradshaw index decreased from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$) [Figure 1]. The mean number of bowel movements decreased from eight to five a day and the need for other drugs was significantly reduced [Table 1]. Of particular interest is the observation that cannabis may have a steroid-sparing effect, since the number of patients requiring steroid treatment was reduced from 26 to 4. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgery during an average period of 3 years of cannabis use. In nine patients cannabis treatment did not induce a significant improvement, as reflected by a change of less than 4 points in the Harvey Bradshaw index. Three of these patients did not respond to

THC = Δ9-tetrahydrocannabinol

Figure 1. Harvey Bradshow index before and after cannabis use

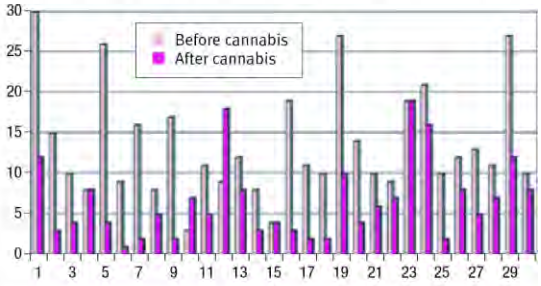

Table 1. Patient characteristics

	Average	Range
Age (yrs)	36	21–65
Male/Female	26/4	
Disease duration (yrs)	11.3	1–41
Disease phenotype	15 luminal, 10 fistulizing, 5 fibrostenotic	
Duration of cannabis consumption	2.1 yrs	3 mos–9 yrs
Amount consumed ("joints"/day)	2.4	0.5–7

Joint = cigarette

any other medical therapy, including TNF antagonists, and are now awaiting surgery.

DISCUSSION

In this study, we describe 30 patients with CD for whom the use of cannabis ameliorated disease activity and reduced the need for other conventional medications. This is the largest and, to the best of our knowledge, the first reported series of CD patients treated with cannabis. It is a retrospective observational study and as such is not a replacement for a prospective placebo-controlled study. There may be a population bias in the sense that some people may be more attracted to the possibility of smoking cannabis than others. This may explain the over-representation of young males in our study population. Also, there may be patients who tried cannabis and whose condition did not improve; they would be lost to follow-up and are not represented in our study. However, the benefit reported by most of the patients in our study suggests a possible significant therapeutic potential. Due to the retrospective nature of our study there may be a bias in recalling disease activity. However, several facts point to an objective benefit of cannabis use. The observed reduced use of steroids (from 26 to 4 patients) [Table 2] and other drugs may point to an objective beneficial effect of cannabis. Whereas 25% to 38% of operated Crohn's disease patients are expected to require a second operation within 5 years of the first [11], only 2 of 15 patients (13%) who had surgery before cannabis consumption required surgery while consuming cannabis. Larger numbers and longer follow-up are needed to verify whether use of cannabis reduces the need for surgery.

The effects of cannabinoids on the immune system are diverse and include modulating proliferation of B cells, T cells, and natural killer cells, modulating production of antibodies and cytokines, and regulating functions of NK cells, macrophages, T helper cells, mast cells and dendritic cells [10]. Although anti-inflammatory effects of cannabis have been described previously, there are no systematic descriptions of the efficacy of cannabis in Crohn's disease. The restraint from the use of an illegal drug may have played a role.

The observed beneficial effect in this study may be due to the anti-inflammatory properties of cannabis, but additional effects of cannabinoids may also play a role. Cannabinoids influence gastrointestinal motility and, in particular, have an anti-diarrheal effect, as observed in mice injected with cholera toxin [12]. The central effect of cannabinoids may induce a sensation of general well-being, which could contribute to the feeling that cannabis use is beneficial. However, this general effect wears off with time as tolerance develops, while the positive effect of cannabis on disease activity in our patients was maintained for an average period of 3.1 years.

One of the reasons that cannabis is unappealing to many patients is that it is administered by smoking. Smoking in general is unacceptable to both medical professionals and many patients. The negative effect of tobacco smoking on Crohn's disease is also well known. Several studies demonstrated a dose-related adverse effect of cannabis on large airway function, but not on small airway function, which is compromised by tobacco smoking [13,14]. Smoking cannabis is the preferred mode of consumption because upon smoking, blood levels of cannabinoids rise rapidly and a central effect is achieved quickly. However, an anti-inflammatory effect, especially in the gut, may be achieved equally well by consuming cannabis orally.

Although many side effects were connected with cannabis use, most of them were in people who consumed other drugs and alcohol together with cannabis. When consumed alone, the safety profile of cannabis is very good [15]. Wang et al. [16] reviewed 31 studies of medical cannabis use and found that 96% of 4779 adverse events were minor. The relative risk for serious adverse events was 1.04, which was not different between the placebo and study groups. Cannabinoids may therefore be a potential addition to the currently limited arsenal of medications used to treat IBD. On the other hand, because the use of medical cannabis may be exploited by drug abusers, extra caution is necessary before cannabis can be recommended to patients. A placebo-controlled study is needed to fully investigate the therapeutic value of cannabis for the treatment of Crohn's disease.

TNF = tumor necrosis factor
NK = natural killer

Table 2. Medical treatment before and after cannabis use (n=30)

Drug	Before	After
No treatment	None	9
5-ASA	27	5
Corticosteroids	26	4
Thiopurine	20	10
Methotrexate	6	0
TNF antagonist	12	4

5-ASA = 5-aminosalicylic acid

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Crohn's Disease II

Cannabis Induces a Clinical Response in Patients with Crohn's Disease: A Randomized Placebo-Controlled, Double-Blind Study

Clinical Gastroenterology & Hepatology, 2013

In the world's first randomized, placebo-controlled, double-blinded study of its kind, Dr. Naftali and a team of researchers used Tikun Olam's *Erez* strain to produce dramatic results, with 45% of Crohn's patients achieving "complete remission" and over 90% achieving substantial improvement – with no side effects witnessed.

Study Population: 21 patients with Crohn's Disease Activity Index (CDAI) scores greater than 200, who did not respond to therapy with steroids, immune-modulators, or anti-tumor agents; 11 of the patients were in the cannabis treatment study group, 10 were in the placebo control group
Strain Used: *Erez*
Key Results:

- Complete remission (CDAI score <150) was achieved by 5 of the 11 patients in the cannabis group
- Clinical response (decrease in CDAI score of >100) was observed in 10 of the 11 patients
- 3 of the 11 patients were weaned from steroid dependency
- The cannabis group reported significantly less pain, and improved appetite and quality of life

Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study

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BACKGROUND & AIMS: **The marijuana plant *Cannabis sativa* has been reported to produce beneficial effects for patients with inflammatory bowel diseases, but this has not been investigated in controlled trials. We performed a prospective trial to determine whether cannabis can induce remission in patients with Crohn's disease.**

METHODS: **We studied 21 patients (mean age, 40 ± 14 y; 13 men) with Crohn's Disease Activity Index (CDAI) scores greater than 200 who did not respond to therapy with steroids, immunomodulators, or anti–tumor necrosis factor-α agents. Patients were assigned randomly to groups given cannabis, twice daily, in the form of cigarettes containing 115 mg of Δ9-tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and 2 weeks thereafter.**

RESULTS: **Complete remission (CDAI score, <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; $P = .43$). A clinical response (decrease in CDAI score of >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; $P = .028$). Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.**

CONCLUSIONS: **Although the primary end point of the study (induction of remission) was not achieved, a short course (8 weeks) of THC-rich cannabis produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn's disease, compared with placebo, without side effects. Further studies, with larger patient groups and a nonsmoking mode of intake, are warranted. ClinicalTrials.gov, NCT01040910.**

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Cannabinoids; Endocannabinoid; Inflammation.

Apart from its recreational properties, the marijuana plant cannabis has been used for centuries as a medicinal treatment for a variety of ailments. The cannabis plant contains more than 60 different compounds, collectively referred to as *cannabinoids*.[1] Although Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) seem to be most active, other as yet unknown ingredients also may have beneficial effects.

Cannabinoids have a profound anti-inflammatory effect, mainly through the cannabinoid 2 receptor, although cell-mediated immunity was found to be decreased in chronic marijuana users.[2] A potent anti-inflammatory effect of cannabis was observed in rats.[3] Almost all major immune modulation events involve the endocannabinoid system. Cannabinoids shift the balance of proinflammatory cytokines and anti-inflammatory cytokines toward a T-helper cell type 2 profile (Th2 phenotype), and suppress cell-mediated immunity, whereas humoral immunity may be enhanced.[4] Cannabinoid exposure antagonizes release of prostaglandins, histamine, and the matrix-active proteases from mast cells.[5] The phagocytic function of macrophages is suppressed by cannabinoid exposure. Cannabinoids also suppress inflammation at a secondary, chronic level by down-regulating the production of cytokines such as tumor necrosis factor (TNF)-α, interferon-γ, and interleukin-1.[6] They therefore may be beneficial in inflammatory conditions.

Within gastroenterology, cannabis has been used to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation, and diabetic gastroparesis.[7] Cannabinoids were found to ameliorate inflammation in a mouse model of colitis.[8] In 2,4,6-trinitrobenzene sulfonic acid–induced colitis, cannabinoids decreased macroscopic inflammation,

Abbreviations used in this paper: CBD, cannabidiol; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; SF-36, Short-Form 36; THC, Δ9-tetrahydrocannabinol; TNF, tumor necrosis factor.

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myeloperoxidase activity, and peristalsis.[9] The combination of THC and CBD was more effective than either substance alone.[10]

In a retrospective observational study, we recently reported that cannabis had beneficial effects in Crohn's disease.[11] However, to date, no placebo-controlled trials have been published on the use of cannabis in inflammatory bowel disease (IBD). We conducted a double-blind, placebo-controlled study to investigate the effects of cannabis on patients with active Crohn's disease.

Materials and Methods

The primary objective of the study was the induction of remission, defined as a Crohn's Disease Activity Index (CDAI) score of 150 or less after 8 weeks of cannabis treatment. Secondary objectives were response rate, determined as a 100-point reduction of CDAI, a reduction of at least 0.5 mg in C-reactive protein (CRP), or improvement in quality of life of at least 50 points, as measured by the Short-Form 36 (SF-36) health survey.

Patients with an established diagnosis of Crohn's disease who were referred to the Gastroenterology Institute at Meir Medical Center, a tertiary-care facility, between September 2010 and September 2011 were screened for eligibility. Eligible patients were at least 20 years of age and had active Crohn's disease, with a calculated CDAI score between 200 and 450 points. All patients had failed at least one form of medical treatment for the disease, including mesalamine, corticosteroids, thiopurines, methotrexate, or anti–TNF-α. Patients receiving corticosteroids were on a stable dose for at least 1 month, and those receiving thiopurines were on a stable dose for at least 3 months. Anti–TNF-α failure was declared after at least 4 doses. Patients with short-bowel syndrome, symptomatic stricture, abscess, abdominal surgery within the previous 3 months, pregnancy or intention to become pregnant within 6 months, a history of mental illness, drug abuse, or previous cannabis consumption were excluded. Patients also were excluded if in their physician's judgment they might be vulnerable to drug addiction or mental instability. The study protocol was approved by the institutional ethics committee. All patients provided written informed consent before enrollment. All co-authors had access to the study data and reviewed and approved the final manuscript.

By using the block method[12] in a 1:1 ratio, patients were assigned randomly to receive either medical cannabis or placebo in the form of cigarettes. Both patients and investigators were blinded to the treatment group assignment. Each cigarette contained 0.5 g of dried cannabis flowers (flowers have a higher THC content than leaves), corresponding to 115 mg THC. The active cannabis was made from dried flowers of genetically identical plants of *Cannabis sativa* Variety Indica Erez (courtesy of Tikun Olam, Ltd, Tel Aviv, Israel), known to contain 23% THC and less than 0.5% CBD. The placebo was made of cannabis flowers from which THC had been extracted. Dried flowers of Cannabis were mixed with 95% ethanol (food grade) and sat in a clean glass jar for 2 weeks. The alcohol then was decanted and fresh 95% ethanol was added to the jar. This procedure was repeated 3 times. After this, the flowers were covered with a mixture of spirits comprising the first distillate head fraction from a proprietary mixture of organically grown pomegranate (*Punica granatum*) juice, pericarps, leaves, and flowers that had been allowed to ferment to completion (~2 wk) in the presence of 0.025% *Saccharomyces cerevisiae* Var. 18 (courtesy of Rimonest, Ltd, Haifa, Israel). After 3 more days, the spirits were decanted and the flowers were allowed to dry in ambient air with ventilation for 72 hours. The final product was tested for cannabinoids and shown to contain less than 0.4% THC and undetectable amounts of all other cannabinoids including CBD. The process was repeated and shown to be reproducible. All cigarettes were machine made to ensure they were identical.

Patients were followed up for 8 weeks of treatment and 2 additional weeks of a wash-out period. Concomitant medications remained constant throughout the study except for corticosteroids, which were tapered when possible. Patients were evaluated at weeks 0, 2, 8, and 10 including medical interview, physical examination, assessment of disease activity (CDAI), and blood tests (complete blood count, liver and kidney function, and CRP). Quality of life (SF-36) and side-effect questionnaires were completed at weeks 0 and 8. The side-effect questionnaire included questions about changes in ability to concentrate, work, sleep, abdominal pain, appetite, general well being, and general satisfaction with the treatment. Relevant symptoms of drug addiction as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition,[13] included cravings for a larger dose and ability to continue regular activities, such as work and studies. Answers were graded by severity from 1 to 7.

Statistical Analyses

Numeric results are presented as mean ± standard deviation, and categoric results are shown in percentages. The difference in CDAI between the 2 groups (study vs control) was examined. The change (delta) in CDAI between the baseline measurement and after 8 weeks of study was calculated and the mean delta was compared between the 2 groups using the *t* test for independent groups. In addition, the performance of each group (ie, the change per group) also was examined by applying the *t* test for paired groups for the study and control groups separately. For categoric measurements, the chi-square and the Fisher exact tests were used to compare the groups at each time point. The delta SF-36 between the baseline measurement and after 8 weeks of study was calculated and the mean delta was

Table 1. Demographic Data

Variable	Study group (N = 11)	Placebo group (N = 10)	*P* value
Age	46 ± 17	37 ± 11	.02
Male	6 (54%)	6 (60%)	.57
Family history of IBD	5 (45%)	5 (50%)	1
Current tobacco smoking	2 (18%)	3 (30%)	.65
Time since diagnosis of Crohn's disease, *y*	18 ± 14	15 ± 8	.797
Involved segment of intestine[a]			
Terminal ileum	8 (72%)	5 (50%)	.38
Colon	4 (36%)	4 (40%)	.6
Other part of small intestine	3 (27%)	2 (20%)	1
Disease phenotype			
Luminal	36% (4)	60% (6)	.39
Fistulizing	45% (5)	20% (2)	.36
Stricturing	18% (2)	20% (2)	1
Past surgery			
Resection of terminal ileum	45% (5)	60% (6)	.66
Partial colectomy	9% (1)	10% (1)	.7
Adhesiolysis	9% (1)	0% (0)	1

NOTE. Mean ± standard deviation, n (%) shown.
[a]One patient might have had involvement of more than 1 segment.

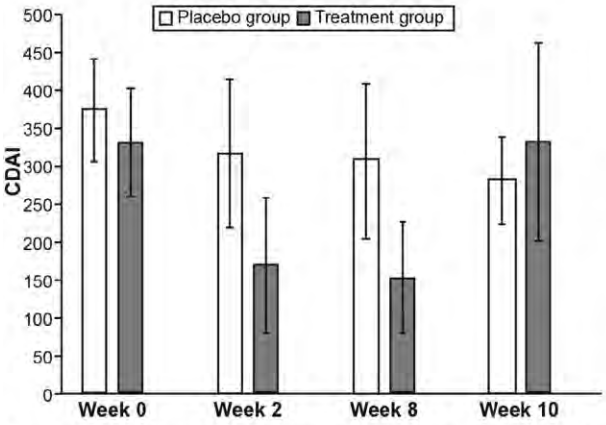

Figure 1. CDAI scores in study and placebo groups before and after treatment.

compared between the 2 groups using the *t* test for independent groups. In addition, the difference in side effects between the 2 subgroups was examined. Because the measurements were ordered, the Mann–Whitney nonparametric test for independent groups was used. All statistical analyses were performed using the statistical software package SPSS, version 20 (SPSS Inc, Chicago, IL).

Results

Of 51 patients screened, 29 did not meet the inclusion criteria: 15 patients had a CDAI less then 200, 7 patients did not consent, 1 patient was diagnosed with ulcerative colitis, 3 patients were designated for surgery (1 because of stricture of the small bowel and 2 because of an intra-abdominal abscess), and 3 patients already were receiving medical cannabis. Twenty-two eligible patients were recruited. One patient withdrew consent before consumption of the study drug and another patient withdrew after 2 weeks of treatment. The second patient was included in the analysis. Thus, 21 patients, 11 in the study group and 10 in the placebo group, completed the study (Supplementary Figure 1). Demographic details of the patients are listed in Table 1. In the study group, 1 patient had a permanent pacemaker, 1 patient had type 2 diabetes, and 1 patient had thalassemia minor. One patient in the placebo group had glaucoma. All other patients were healthy, except for Crohn's disease.

Twenty patients had been treated with thiopurines and 18 patients had been treated with anti-TNF-α in the past. Of the 18 patients treated with anti-TNF-α, 5 patients had to stop treatment because of a severe allergic reaction, 4 patients were still receiving anti-TNF-α, 7 patients did not respond or lost response after at least a full induction dose, 1 patient stopped treatment despite it being effective, and 1 patients stopped treatment owing to pneumonia. At the time of the study, 4 patients (3 in the study group and 1 in the placebo group) were steroid dependent (Table 2). One patient received prednisone 20 mg for 2 years, 1 patient received prednisone 35 mg for 6 months, and 2 patients received budesonide 9 mg for 2 and 3 years each. They all relapsed as soon as they tried to stop the steroids. In patients who had undergone surgery, time from previous surgery to the study was on average 6 years (range, 1–30 y).

Five patients (45%) in the study group and 1 patient (10%) in the placebo group achieved full remission, with a CDAI of 150 or less (Figure 1). This difference did not reach statistical significance ($P = .43$), possibly because of the small sample size. Before treatment, the mean CDAI was 330 ± 105 and 373 ± 94 in the study and placebo groups, respectively ($P = .3$). After 8 weeks of treatment, the CDAI decreased to 152 ± 109 in the study group, and 306 ± 143 in the placebo group (P between groups $< .05$). The response rate (ie, CDAI reduction of >100 points) was 90% (10 of 11) in the study group, whereas in the placebo group the CDAI increased in 3 (30%) patients, decreased by less than 100 points in 3 (30%) patients, and decreased by more than 100 points in 4 (40%) patients (Figure 2). The mean reduction in CDAI was 177 ± 80 in the study group and 66 ± 98 in the placebo group ($P = .005$). Two weeks after cannabis treatment was stopped, the mean CDAI in the study and placebo groups was 331 ± 155 and 280 ± 61, respectively ($P = .43$; Figure 1).

Four patients in the placebo group (but none in the cannabis group) deteriorated and needed rescue intervention during the study period. Three of these 4 patients stopped taking their assigned study treatment (ie, stopped smoking the placebo cigarettes) because they believed it was not helping them. Three steroid-dependent patients in the cannabis group stopped steroids during the study. Thus, at the end of the study no patient in the cannabis group required steroids. Two patients in the study group, who were treated with opiates owing to severe chronic abdominal pain, stopped opiates during the study.

A significant increase in quality of life as assessed by SF-36 was observed in the cannabis group (from 68 at week 0 to 86 after 8 weeks of treatment; $P = .05$), although no effect was observed in the placebo group (SF-36, 71 vs 79; $P = .5$). The delta of SF-36 between the baseline measurement and after 8 weeks was +28 and +5 in the study and placebo groups, respectively ($P = .04$). There were no significant changes in blood count, CRP, or liver and kidney function during the study (Table 3). CRP before treatment was 1.4 ± 2 mg/dL and 2.6 ± 2.5 mg/dL (normal, <0.5 mg/dL) in the cannabis and placebo groups, respectively ($P = .1$). A decrease in CRP of more than 0.5 mg/dL from week 0 to week 8 was observed in 3 patients in the study group and 2 patients in the placebo group ($P = .43$).

Table 2. Past and Current Medical Treatment

	Past medication, n (%)			Concomitant medication, n (%)		
Medication	Study (N = 11)	Placebo (N = 10)	*P* value	Study (N = 11)	Placebo (N = 10)	*P* value
Mesalamine	11 (100)	10 (100)	NS	2 (218)	2 (20)	.7
Steroids	11 (100)	9 (90)	.4	4 (36) (3 steroid dependent)	2 (20) (1 steroid dependent)	.9
Purine analog	10 (90)	10 (100)	NS	2 (27)	6 (60)	.9
Methotrexate	3 (27)	1 (10)	.9	1 (9)	0	1
Anti-TNF-α	9 (81)	8 (80)	.7	1 (9)	4 (40)	.9

NS, not significant.

Table 3. Laboratory Tests

Test	Study (N = 11)			Placebo (N = 10)		
	Start	End	*P* value	Start	End	*P* value
Hemoglobin level, *g/dL*	12.8 ± 1	13.0 ± 1.3	.3	12 ± 1	12 ± 2	.6
Hematocrit, %	39.4 ± 3	35.1 ± 4	.3	38 ± 5	37 ± 6	.6
White blood cell count, *K/μL*	8 ± 3	8.2 ± 3	.9	6.1 ± 2	5.7 ± 2	.7
CRP, *mg/dL*	1.44 ± 2	0.99 ± 0.9	.4	2.6 ± 2.5	1.7 ± 0.7	.2

There was no difference between study and placebo groups in side effects, including sleepiness, nausea, and confusion. However, the study group reported significantly less pain, improved appetite, and a higher satisfaction from the treatment (Table 4). Patients denied any withdrawal symptoms when stopping cannabis use at the end of the study. Blinding assessment was performed at the end of the study for each patient. Except for 2 patients in the placebo group, all other patients were able to tell correctly whether they were receiving cannabis or placebo.

Discussion

Although a significant body of work suggests that cannabinoids suppress inflammation[14] and many patients with IBD self-medicate with cannabis, there are no placebo-controlled trials assessing its efficacy in inflammatory disease. This might be owing to reluctance to use an illegal drug. This was a placebo-controlled trial to critically assess cannabis use for treating Crohn's disease.

The primary end point of this study was induction of remission. Although 5 patients in the study group and 1 patient in the placebo group entered clinical remission, the difference did not reach statistical significance, possibly because of the small sample size. However, our data showed that 8 weeks of treatment with THC-rich cannabis, but not placebo, was associated with a significant decrease of 100 points in CDAI scores.

In this trial, cannabis induced clinical remission in 50% of patients. Taking into account that our participants had long-standing Crohn's disease, with 80% nonresponse or intolerance to anti-TNF-α, this result is impressive. In this trial, the observed improvement was solely symptomatic, with no objective evidence of reduction in inflammatory activity. In addition, patients relapsed 2 weeks after cannabis treatment was stopped. Therefore, based on the available data, one cannot argue that cannabis is a successful treatment for the inflammatory process in Crohn's disease. Thus, until further studies are conducted, cannabis should be reserved for compassionate use only in patients who have exhausted all other medical and surgical options.

Because this was a pilot study, probable efficacy data were unavailable, therefore power calculation could be based on estimation only. With a significance level of 5% and a power of 80% to detect a significant difference of 100 points in CDAI, we would need a sample size of 12 patients in each group, or a total of 24 patients.

Herbal preparations present problems in measuring the contribution of each constituent of a mixture. Thus, mistakes can be made in using nonstandardized extracts for clinical testing. We dealt with this problem by using cannabis made from genetically identical plants grown from twigs of the same mother plant and in equal conditions. Plants were tested to verify an equal content of active ingredients. We also standardized the machine-made cigarettes to contain equal weights of cannabis flowers.

Table 4. Side Effects

	Placebo median (minimum–maximum)	Cannabis median (minimum–maximum)	*P* value
Negative side effects[a]			
Sleepiness	4 (3–4)	3 (1–6)	.5
Nausea	4 (3–4)	4 (1–4)	.3
Concentration	4 (4–5)	4 (4–7)	.3
Memory loss	4 (4–4)	4 (4–6)	.4
Confusion	2 (2–2)	2 (1–2)	.4
Dizziness	2 (1–2)	2 (1–2)	.9
Positive side effects[b]			
Pain	4 (3–4)	1 (1–2)	.001
Appetite	4 (4–4)	2 (1–4)	.008
Satisfaction	7 (3–7)	1 (1–4)	.002

[a]On a scale from 1 to 7, where 1 = no effect; 7 = very strong effect.
[b]On a scale from 1 to 7, where 1 = very satisfied; 7 = very dissatisfied.

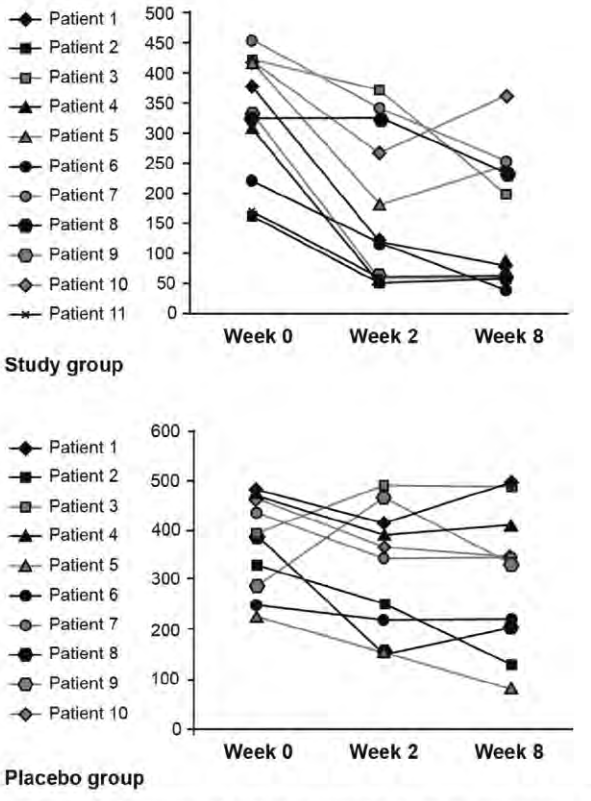

Figure 2. CDAI scores of individual patients in study and placebo groups before and after treatment.

Although this was a placebo-controlled trial, complete blinding of patients was not easy to achieve because of possible psychotropic effects. We tried to minimize this limitation by recruiting only patients naive to cannabinoids. However, at the end of the study period, most of the subjects were able to tell correctly whether they were receiving the study drug or placebo. Future studies with oral administration may overcome this problem due to slower absorption.

In this study, we chose to administer cannabis by smoking because this route induces a rapid increase in blood cannabinoid levels.[15] During smoking, the acids are decarboxylated to the active free cannabinoids, which may explain why ingesting cannabis orally is less effective than smoking.[16] Nevertheless, because of the known harmful effects of smoking on the lungs, the efficacy and safety of oral cannabis should be investigated further.

There is an understandable restraint in the medical community regarding the use of cannabis, which is an illegal drug in most countries. Yet, cannabis has a remarkably good safety profile.[17,18] In this study, during short-term use of 8 weeks, we did not observe any significant side effects. All patients continued normal function and did not report significant differences in behavioral parameters such as concentration, memory, or confusion. Indeed, it is known that tolerance to the central effect of cannabis develops after 12 days of use.[19] When requested to stop cannabis after 8 weeks, none of the patients experienced difficulty or withdrawal symptoms. All patients in the study group expressed strong satisfaction with their treatment and improvement in their daily function. It should be noted, however, that our patients were treated for only a short period. It is well known that cannabis dependence exists and patients might have difficulty weaning after prolonged cannabis use, even when the IBD is in complete remission. Therefore, until further data are available, long-term medical cannabis cannot be recommended. Although the long-term side effects of cannabis are not negligible, other treatments for Crohn's disease, such as steroids, purine analogs, or anti-TNF-α, also carry the risk of significant side effects, some even life-threatening. Additional studies will be needed before the exact effect of cannabis in IBD, whether anti-inflammatory or only symptomatic, can be determined. However, the potential benefits should not be ignored only because of concern for possible side effects. Taking into account that Crohn's disease is a chronic debilitating disease that sometimes severely may compromise patients' quality of life, the ability to provide symptomatic relief judicially, in carefully selected patients, should not be overlooked.

In summary, in this controlled pilot study, cannabis treatment was not superior to placebo in induction of remission. However, cannabis provided a significantly higher rate of clinical response without any alarming side effects. The strain of cannabis used was specifically rich in THC, but other cannabinoids may be beneficial as well. Future larger controlled studies should look into the role of cannabinoids in controlling inflammation and symptoms in IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.04.034.

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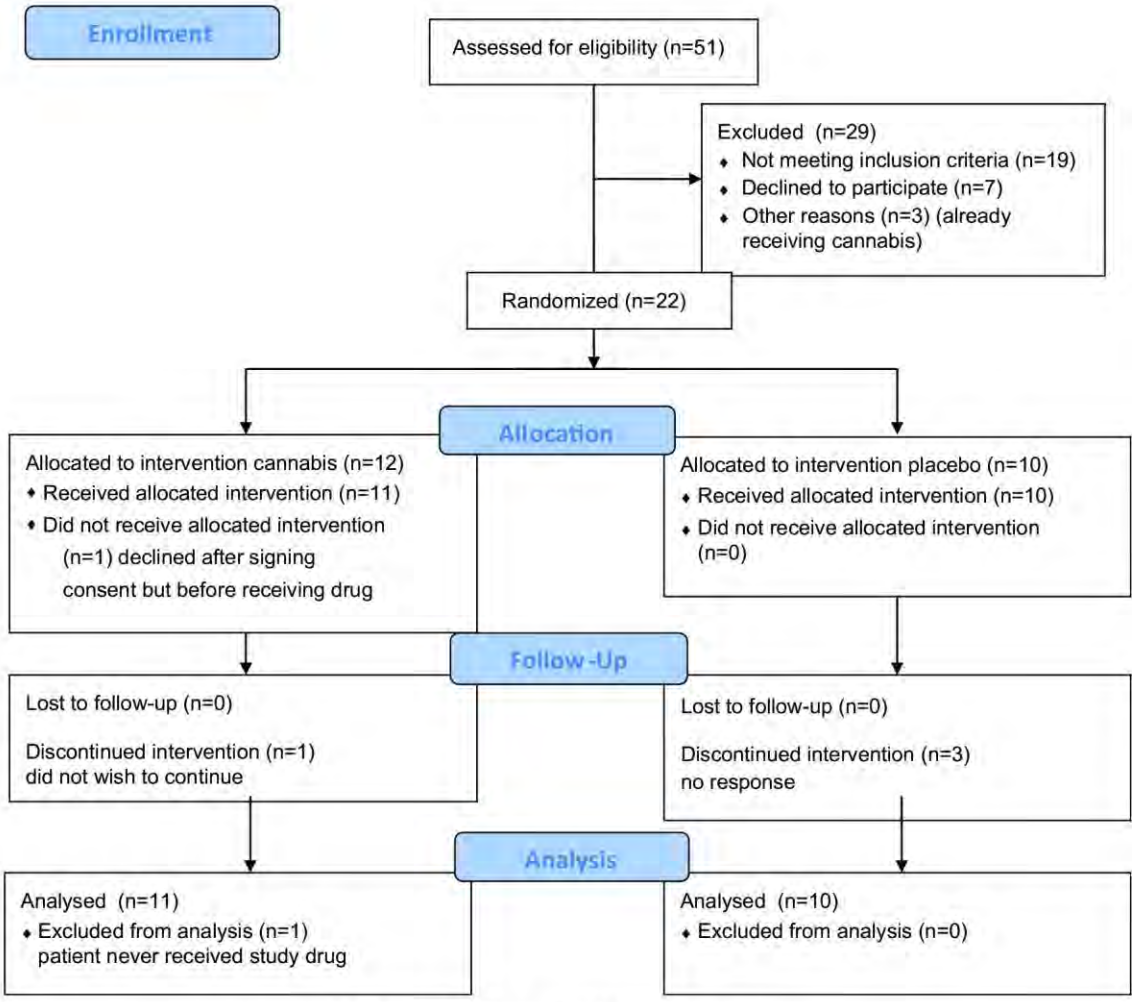
Conflicts of interest

This author discloses the following: Lihi Bar-Lev Schleider is an employee of Tikun Olam organization, which supplied the cannabis and placebo for the research. The remaining authors disclose no conflicts.



Supplementary Figure 1. CONSORT flow diagram.

Inflammatory Bowel Disease

Cannabis for Inflammatory Bowel Disease

Digestive Diseases, 2014

A summary of the research analyzing cannabis as treatment for Inflammatory Bowel Diseases. Evidence suggests that manipulating the endocannabinoid system with cannabinoids may have a positive effect on IBD, but further research is needed to determine the specific cannabinoids, optimal dosage, and mode of administration for maximum benefit.

Digestive Diseases

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Cannabis for Inflammatory Bowel Disease

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Key Words
Cannabidiol · Cannabis · Inflammatory bowel disease · Crohn's disease · Δ9-Tetrahydrocannabinol · Ulcerative colitis

Abstract
The marijuana plant *Cannabis sativa* has been used for centuries as a treatment for a variety of ailments. It contains over 60 different cannabinoid compounds. Studies have revealed that the endocannabinoid system is involved in almost all major immune events. Cannabinoids may, therefore, be beneficial in inflammatory disorders. In murine colitis, cannabinoids decrease histologic and microscopic inflammation. In humans, cannabis has been used to treat a plethora of gastrointestinal problems, including anorexia, emesis, abdominal pain, diarrhea, and diabetic gastroparesis. Despite anecdotal reports on medical cannabis in inflammatory bowel disease (IBD), there are few controlled studies. In an observational study in 30 patients with Crohn's disease (CD), we found that medical cannabis was associated with improvement in disease activity and reduction in the use of other medications. In a more recent placebo-controlled study in 21 chronic CD patients, we showed a decrease in the CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo. Complete remission was achieved in 5 of 11 subjects in the cannabis group and 1 of 10 in the placebo group. Yet, in an additional study, low-dose cannabidiol did not have an effect on CD activity. In summary, evidence is gathering that manipulating the endocannabinoid system can have beneficial effects in IBD, but further research is required to declare cannabinoids a medicine. We need to establish the specific cannabinoids, as well as appropriate medical conditions, optimal dose, and mode of administration, to maximize the beneficial effects while avoiding any potential harmful effects of cannabinoid use.

Introduction

The plant *Cannabis sativa* contains at least 70 different cannabinoids. Of these, the most important psychoactive compound is Δ9-tetrahydrocannabinol (THC). Other important compounds include cannabidiol (CBD), cannabigerol, and cannabichromene. Cannabinol is an oxidation product of THC and an indication that the herb has deteriorated. Olivetol is the biosynthetic precursor.

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These phytocannabinoids exert their effects through binding to specific membrane receptors and manipulating the endocannabinoid system.

The Endocannabinoid System

The endocannabinoid system is an important regulatory lipid signaling system found in all vertebrates and throughout the human body [1]. It consists of cannabinoid receptors, their endogenous ligands, collectively known as endocannabinoids, and the enzymes that synthesize and degrade the ligands.

Two major cannabinoid receptors are currently known, CB1 and CB2. Both are G protein-coupled receptors. CB1 is expressed mainly by neurons in the brain, spinal cord, peripheral nervous system, and enteric nervous system. To a lesser extent, it is also expressed in other organs and tissues including the spleen, heart, lung, intestine, kidney, reproductive organs, skeletal muscle, and skin. CB2 receptors appear to be expressed mainly by cells of the immune system. It has recently been shown that endocannabinoids are also agonists for TRPV1 (transient receptor potential vanilloid subtype 1; also called VR1) receptor, the receptor for the plant compound capsaicin and also for the peroxisome proliferator-activated receptor family [1]. Moreover, GPR55, an orphan G-protein coupled receptor, was suggested to be involved in non-CB1-, non-CB2-mediated actions of cannabinoids, but additional characterization is still required [1].

The endogenous ligands for the cannabinoid receptors include the endocannabinoids anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG). Endocannabinoids are derivatives of arachidonic acid conjugated with ethanolamine or glycerol. They have been found in the brain and plasma as well as in peripheral tissues. Anandamide is a partial agonist of cannabinoid receptors and binds with slightly higher affinity to CB1 than to CB2, while 2-AG appears to bind equally well to both CB receptors with a greater potency and efficacy than anandamide [2].

The in vivo biosynthesis of anandamide is believed to occur through the enzymatic hydrolysis catalyzed by phospholipase D of a membrane lipid precursor, N-arachidonoyl phosphatidylethanolamide [3]. The endocannabinoid 2-AG is generated from diacylglycerol by its lipase, which is selective for the sn-1 position [4]. The endocannabinoids are degraded by the enzymes fatty acid amide hydrolase and monoacylglycerol lipase [1].

Actions of Endocannabinoids

The endocannabinoid system modulates several physiological processes, mainly in the brain, including effects on nociception, memory processes, plasticity, and cell proliferation [5]. Endocannabinoids also play a peripheral modulatory role affecting the immune and cardiovascular systems, as well as reproductive endocrine processes and control of energy metabolism [6]. Anandamide is able to produce analgesia, control motor activity, reduce emesis, stimulate appetite, and induce hypothermia. It also presents antiproliferative effects [7]. 2-AG acts as a messenger molecule in various biological systems, such as the endocrine and immune systems. However, the exact physiological roles of 2-AG remain poorly understood [8]. In the gastrointestinal (GI) tract, activation of prejunctional CB1 receptors reduces excitatory enteric transmission (mainly cholinergic), thereby leading to inhibition of motility [9]. CB1 activation has an inhibitory effect on gastric transit, and also a well-known anti-emetic effect, including inhibition of the apomorphine-induced emetic response [10]. CB2 activation efficaciously counteracts alterations in intestinal motility during inflammatory conditions, but not in healthy animals. It also participates in the control of gut inflammation, as evidenced in mouse models of colitis induced by trinitrobenzene sulfonic acid [11] and in CB2–/– mice [12].

Phytocannabinoid Effects

Much of the pharmacodynamic information on phytocannabinoids refers to the effects of the major constituent of cannabis, Δ9-THC. It acts as a partial agonist of both cannabinoid receptors. However, it also activates non-CB receptors and other targets [13]. It is responsible for the psychoactive effects of cannabis mainly through its actions on the CB1 receptor [14].

CBD is the other important natural cannabinoid, and in fact one of the few which have been investigated pharmacologically. It does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations, but it affects the activity of a significant number of other targets, including ion channels, receptors and enzymes [15].

Pharmacological evidence in animal models suggests that not all the observed therapeutic effects of the cannabis herb can be ascribed to the THC content, or indeed to any single cannabinoid. For example, CBD, which is not psychotropic in itself, has been demonstrated to be anx-

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iolytic in animals and humans, and to reduce the anxiety reaction occasionally induced by THC [16]. CBD elevates THC levels and those of other drugs in the mouse brain [17]. Therefore, it is possible that a standardized extract of the herb, containing predetermined amounts of THC and CBD, and possibly some of the other components, may be more beneficial in practice than any single compound.

Dose and Route of Administration

The bioavailability of cannabis preparations has not been well investigated. The quickest and most reproducible method of obtaining an effect of cannabis is by smoking. Where subjective assessment of the effect is needed, smoking enables some form of self-titration of dose. Smoking carries its own dangers, although for some these may be tolerable if relief of severe chronic pain is achieved. The respiratory side effects of cannabis have not been well studied, but there is strong evidence that cannabis causes bronchial inflammation and respiratory symptoms, and affects lung function [18]. During smoking, the acids are decarboxylated to the active free cannabinoids. This may explain why giving cannabis orally is less effective than smoking it. Recreational cannabis users are well aware of this fact, which has also been demonstrated clinically [19].

The safety of cannabis and the cannabinoids is surprisingly good, but for therapeutic use most patients prefer to remain alert, requiring a fairly narrow dosage range that will reduce pain and nociception without adverse effects such as drowsiness and lack of concentration. A study from the Netherlands tracking data obtained from the Dutch medical cannabis program during the years 2003–2010 reported that in a population of over 5,000 patients using cannabis for medical purposes, the average daily dose of dried cannabis (various potencies) was 0.68 g per day (range: 0.65–0.82 g per day) [20].

Metabolism

THC enters the bloodstream rapidly after smoking. Because of its lipophilicity, it is absorbed into fat tissue, where it may be detected for over 4 weeks. It is gradually released back into the blood stream. THC is fairly quickly converted to 11-hydroxy-THC, a metabolite which is equipotent with THC itself, to 11-nor-9-carboxy-Δ9-THC, which is inactive, and to other cannabinoids, primarily by cytochrome P_{450} enzymes [21]. The relatively slow elimination from the body has implications regarding safety for cognitive tasks, especially relating to driving and operating machinery. This is of major importance if therapeutic use of cannabinoids is to be considered [22].

Clinical Effects of Cannabinoids

Most of the available information regarding the acute effects of smoking cannabis comes from studies conducted on recreational users, with much less information available from patients using cannabis for medical purposes. Since recreational users are more likely to combine cannabis use with alcohol and other drugs, the information should be interpreted with caution. The acute effects of smoking or eating cannabis include euphoria, relaxation, time distortion, intensification of ordinary sensory experiences, and loss of inhibitions. These effects are attributed mostly to THC. Other effects include cardiovascular, ocular, bronchopulmonary, psychological, and psychomotor effects.

Results from preclinical studies suggest that CBD has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptic effects [23]. It has a modulating effect on brain THC levels, but also intrinsic activity by itself. Although not psychoactive, it has a potent analgesic and anti-inflammatory effect mediated by dual cyclooxygenase and lipoxygenase inhibition. This anti-inflammatory effect is several hundred times more potent than that of aspirin (acetylsalicylic acid), when measured in standard animal tests and isolated cell assays [24]. However, after oral administration, it appears to act mainly as a lipoxygenase inhibitor. CBD, like THC, also stimulates the release of prostaglandin E_2 from synovial cells and, like THC, inhibits leukotriene B_4 synthesis in human polymorphonuclear cells in vitro [5, 24].

Adverse Effects and Interactions

Cannabis itself has a remarkably good safety profile, with a therapeutic index estimated at 1:40,000. Adverse reactions to cannabis include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. They are mainly due to THC and are lessened by the presence of CBD [25].

Psychiatric disorders, if already present, may be exacerbated but are rarely induced de novo. The amotivational syndrome (a psychological condition associated with

Table 1. Cannabinoids in various murine models of experimental colitis

Ref.	Model	Treatment	Results
33	Cholera toxin-induced diarrhea in mice	Anandamide	Inhibition of fluid accumulation in the small intestine
34	DNBS mouse colitis	CB1-knockout mice	More severe and extensive colitis
34	DNBS mouse colitis	Pharmacological blockade of the CB1 receptor	More severe and extensive colitis
34	DNBS mouse colitis	CB receptor agonist HU-210	Ameliorated colitis
35	TNBS colitis	Genetic deletion of either CB1, CB2 or both CB receptors	More severe and extensive colitis
36	DNBS mouse colitis	Injection of cannabidiol (5–10 mg/kg i.p.)	Reduced colonic inflammation and weight loss
37	TNBS mouse colitis	Cannabidiol (10 mg/kg i.p.)	Significant improvement in colitis
37	TNBS rat colitis	Intrarectal cannabidiol (20 mg/kg)	Significant improvement in colitis
37	TNBS rat colitis	Cannabidiol (20 mg/kg p.o.)	No improvement in colitis
38	TNBS rat colitis	CBD, THC, or both THC and CBD vs. sulfasalazine	Decrease in macroscopic colitis and myeloperoxidase activity
39	Oil of mustard and DSS-induced colitis	ACEA (a CB1 receptor agonist) and JWH-133 (a CB2 receptor agonist)	Significant improvement in colitis
40	TNBS colitis	Inhibition of the 2-AG-degrading enzyme MAGL	Reduction in both microscopic and histological inflammation
40	TNBS colitis and MAGL inhibitor	CB1 or CB2 receptor antagonists	Effect of MAGL inhibition abolished

DNBS = Dinitrobenzene sulfonic acid; TNBS = trinitrobenzene sulfonic acid; DSS = dextran sulfate sodium; MAGL = monoacylglycerol lipase.

diminished inspiration to participate in social situations and activities) was described among long-term cannabis users [26]. The problem of driving while taking cannabinoids is a cause for concern, and although driving impairment has been shown to be only moderate, the interaction with alcohol, which impairs driving ability significantly, is particularly worrying. The 'hangover' effect seems to be reasonably weak. Other problems attributed to cannabis include gynecomastia, impairment of fetal growth, and a reduction in fertility and immune function. It has been estimated that around 1 in 10 persons who ever use cannabis will become dependent [27]. An interaction with opioids has been postulated, in that cannabinoids may increase the synthesis or release of endogenous opioids, and may upregulate opioid gene expression in brain and spinal cord areas and regions which regulate pain sensation, motor activity, and pituitary secretion [11]. In a systematic review of safety studies of medical cannabinoids evaluating 23 randomized controlled trials and 8 observational studies, 4,779 adverse events were reported, of which 4,615 (96.6%) were not serious. The serious events included relapse of multiple sclerosis (21 events, 12.8%), vomiting (16 events, 9.8%), and urinary tract infection (15 events, 9.1%) [28]. In a study of brain neuroimaging, 59 long-term heavy cannabis users who started use before age 18 were compared to 33 matched controls. Participants underwent diffusion-weighted magnetic resonance imaging and brain connectivity mapping. Axonal connectivity was found to be impaired in chronic users. The authors concluded that delaying the age at which regular use begins may protect from brain damage [29]. In the Dunedin Study, a cohort of 1,037 individuals was followed from birth (1972/1973) to age 38 years. Cannabis use was ascertained in interviews at ages of 18, 21, 26, 32,

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and 38 years. Neuropsychological testing was conducted at age 13, before initiation of cannabis use, and again at age 38. The study demonstrated that persistent cannabis use was associated with neuropsychological decline, and the impairment was concentrated among adolescent-onset cannabis users [30]. On the other hand, a meta-analysis of the effect of cannabis use on global neurocognitive performance showed no significant effect after 25 days of abstinence, concluding that any negative effects of cannabis on neurocognitive performance are attributable to either cannabis residue in the body or withdrawal symptoms, and not to irreversible brain damage [31].

Effects on the GI Tract

Cannabinoid receptors are present throughout the GI tract, including liver, pancreas, stomach, and the small and large intestines. Both CB1 and CB2 receptors are found on enteric neurons, nerve fibers, and terminals throughout the enteric nervous system. CB1 receptors were found on the normal and inflamed human colonic epithelium. Both CB1 and CB2 receptors were found in macrophages and plasma cells in the human colon [29]. General pharmacological action of cannabis consumption on the GI tract includes decreased motility, secretion, and gastric/colonic emptying as well as anti-inflammatory actions [32]. These properties can well explain why cannabinoids seem to have a beneficial effect on inflammatory bowel disease (IBD).

Experimental Animal Models

Cannabinoids were shown to be beneficial in many trials on different models of IBD, some of which are summarized in table 1. The studies have consistently shown that treatment with cannabinoids or cannabinoid agonists reduced inflammation whereas cannabinoid antagonists or cannabinoid receptor knockout increased inflammation.

Human Data

Despite many anecdotal reports on cannabis use in human IBD, there are very few controlled trials. In a survey of 291 patients with IBD who used cannabis, most patients reported using cannabis to ameliorate pain, although ulcerative colitis patients used it also to improve diarrhea. This study, however, was directed to the observation of side effects rather than disease activity. Severe side effects were observed in approximately one third of patients. These included paranoia (32%), anxiety (30%), and palpitations (30%) [41]. It is noteworthy that this study reported an exceptionally high rate of side effects that was not described in any other study, including a meta-analysis of side effects in 1,700 patients using medical cannabis [28]. This high occurrence of side effects may be attributable to the fact that 50% of the patients used cannabis not for their IBD, but for recreation.

In a small study of 13 patients using inhaled cannabis for IBD over a 3-month period, a statistically significant increase in the subject's weight was observed. This was accompanied by an improvement in the disease activity index, perception of general health status, and ability to perform daily activities [42].

We have conducted an observational, retrospective study of 30 Crohn's disease (CD) patients who had a license to use medical cannabis in Israel. Most patients smoked cannabis as 'joints' (0.5 g cannabis/joint) and used between 1–3 joints/day. The Harvey-Bradshaw index decreased from an average of 14 ± 6.7 before cannabis consumption to 7 ± 4.7 ($p < 0.001$). The use of other medications, including 5-aminosalicylic acid, corticosteroids, thiopurine, methotrexate, and TNF antagonists, was also significantly reduced following the use of cannabis [43].

However, in a prospective placebo-controlled study of 19 CD patients, low-dose CBD alone did not show a beneficial effect. The average CD activity index (CDAI) before CBD consumption was 337 ± 108 and 308 ± 96 (p = NS) in the CBD and placebo groups, respectively. After 8 weeks of treatment, CDAI decreased to 220 ± 122 in the CBD group and 216 ± 121 in the placebo group (nonsignificant). No side effects were observed [44]. It should be noted that this study used a very small dose (10 mg/day), whereas several CBD studies have used a dose range between 200 and 800 mg/day in a variety of human diseases [45].

We have recently conducted the first double-blind, placebo-controlled study of THC-rich cannabis inhalation in CD. The study included 21 active CD patients. Complete remission (CDAI score <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; $p = 0.43$). A clinical response (a decrease in the CDAI score >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; $p = 0.028$). Three patients in the cannabis group were weaned from steroid dependency.

Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects. This study, however, is limited by its size and also by the lack of objective measures of disease improvement, such as inflammatory markers [46]. We have, therefore, initiated a larger study which will look into these parameters.

Conclusion

The cannabinoid system has important regulatory functions throughout the human body, including the GI tract, and a major role in the regulation of inflammatory reactions. Despite the importance of the cannabinoid system, it has stayed 'below the radar' of medical research and we are only beginning to discover its implications. Evidence is accumulating showing that manipulation of the endocannabinoid system could have beneficial effects on IBD. However, further research is required before cannabinoids can be declared a medicine. We need to establish the appropriate cannabinoids, as well as medical conditions, dose, and mode of administration for cannabinoid use in IBD.

Disclosure Statement

Lihi Bar Lev is an employee of Tikun Olam organization of medical cannabis. The other authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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Pain & Inflammation

Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol

Pharmacology & Pharmacy, 2015

This laboratory study was conducted on rodents to examine the effect of full-plant cannabis extract on inflammation and pain, in comparison with isolated CBD and commercial anti-inflammatory and anti-nociceptive drugs. Isolated CBD has been shown to have a bell-shaped dose-response, where healing is only observed within a very limited dose range, with no additional beneficial effect achieved at lower or higher doses. This trait of purified CBD poses challenges to clinical use; thus, this study aimed to find a CBD source that eliminates the bell-shaped dose response – and succeeded with *Avidekel*.

Study Population: Lab mice
Strain Used: *Avidekel*
Key Results:

- The full-plant extract of *Avidekel*, which is high in CBD and low in THC, provided a correlative anti-inflammatory and anti-pain dose-response (i.e. as the dose was increased, the pain and inflammation decreased in correlation), superior to the bell-shaped dose-response of isolated CBD, which exhibited less consistent anti-inflammatory and anti-pain properties at lower and higher doses
- *Avidekel* extract exhibited superior anti-inflammatory effectiveness compared to tramadol (an opioid analgesic) and aspirin (a non-steroid anti-inflammatory)

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Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using *Cannabis* Extract Enriched in Cannabidiol

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Abstract

Cannabidiol (CBD), a major constituent of *Cannabis*, has been shown to be a powerful anti-inflammatory and anti-anxiety drug, without exerting a psychotropic effect. However, when given either intraperitoneally or orally as a purified product, a bell-shaped dose-response was observed, which limits its clinical use. In the present study, we have studied in mice the anti-inflammatory and anti-nociceptive activities of standardized plant extracts derived from the *Cannabis sativa* L., clone 202, which is highly enriched in CBD and hardly contains any psychoactive ingredients. In stark contrast to purified CBD, the clone 202 extract, when given either intraperitoneally or orally, provided a clear correlation between the anti-inflammatory and anti-nociceptive responses and the dose, with increasing responses upon increasing doses, which makes this plant medicine ideal for clinical uses. The clone 202 extract reduced zymosan-induced paw swelling and pain in mice, and prevented TNFα production *in vivo*. It is likely that other components in the extract synergize with CBD to achieve the desired anti-inflammatory action that may contribute to overcoming the bell-shaped dose-response of purified CBD. We therefore propose that *Cannabis* clone 202 (Avidekel) extract is superior over CBD for the treatment of inflammatory conditions.

Keywords

***Cannabis sativa* L. Clone 202, Cannabidiol, Anti-Inflammation, Anti-Nociceptive, TNFα**

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1. Introduction

Inflammation and pain have accompanied human life for ages. Many anti-inflammation and anti-pain medications and various approaches have been employed through the centuries and in recent time. Many of used drugs, however, impose severe side effects. *Cannabis* from various origins and species has been employed in various forms as anti-pain agents for thousands of years [1]-[3]. One example is the legitimated drug Sativex® (Nabiximols) that is used in the treatment of severe spasticity in patients with multiple sclerosis [4]. Two other drugs, Marinol (Dronabinol) and Cesamet, have been approved for use in cancer-related anorexia-cachexia syndrome as well as for nausea and vomiting [3]. But a major disadvantage of *Cannabis* phytomedicine is its psychoactive effects due to the presence of Δ^9-Tetrahydrocannabinol (THC).

Recently, a science-based approach is being conducted to specify the benefits of *Cannabis* and its many constituents. A *Cannabis* plant contains hundreds of different chemicals with about 60 - 80 chemicals known as cannabinoids [5]. The major *Cannabis* psychoactive molecule is the Δ^9-tetrahydrocannabinol, known as THC, which binds with high affinity (K_i = 3 - 5 nM) [6] to both the cannabinoid CB1 receptor expressed in the brain and the CB2 receptor expressed on cells of the immune system [7]. Another major constituent is Cannabidiol (CBD) which is devoid of psychotropic effects and binds only with very low affinity (K_i > 10 μM) [6] to the CB1/CB2 receptors. The other cannabinoids are present in minute amounts. Stimulation of CB1 receptor is responsible for the *Cannabis* psychoactivity, while activation of the CB2 receptor leads to attenuated inflammation, decreased injury and accelerated regeneration in many disease states [7]. CBD has been shown to activate central nervous system's limbic and paralimbic regions, which can reduce autonomic arousal and feeling of anxiety [3]. This is in contrast to THC which can be anxiogenic [3]. CBD has also been shown to have anti-emetic, anti-inflammatory and anti-psychotic effects [3]. Studies are looking for potential benefits of phytocannabinoids in management of neuropathic pain, hypertension, post-stroke neuroprotection, multiple sclerosis, epilepsy and cancer [3]. Doses up to 1500 mg per day as well as chronic use of CBD have been reported as being well tolerated by humans [3].

During the last 10 - 15 years, many studies have focused on the anti-inflammatory effects of purified CBD in various animal models, including rheumatoid arthritis, diabetes type 1, inflammatory bowel disease and multiple sclerosis [8]-[13]. These studies showed that purified CBD gives a bell-shaped dose-response curve. Healing was only observed when CBD was given within a very limited dose range, whereas no beneficial effect was achieved at either lower or higher doses. This trait of purified CBD imposes serious obstacles in planning human and animal studies. The aim of the present study was to find a CBD source that could eliminate the bell-shaped dose-response of purified CBD. We found that by using standardized plant extracts from the *Cannabis* clone 202 obtained from Tikun Olam, Israel, which is highly enriched in CBD and barely contains THC, a correlative anti-inflammatory and anti-pain dose-response could be achieved when applied either intraperitoneally or orally in an inflammatory mouse model.

2. Material and Methods

2.1. CBD and *Cannabis* Clone 202 (Avidekel) Extract

Purified CBD was purchased from THC Pharm. GmbH, Frankfurt, Germany. *Cannabis sativa* L. flowers from the clone 202 (Avidekel) rich in CBD while low in any psychotropic constituents was supplied by Tikun Olam Company (a government-approved farm growing medicinal *Cannabis*), Israel. CBD-enriched extract was prepared from the flowers of *Cannabis* clone 202 grown under controlled temperature and light conditions. 100% ethanol (20 ml) was added to the chopped *Cannabis* dry flowers (200 mg) for 24 - 48 hrs, with occasional shaking at room temperature. Following filtration, samples were taken for analysis. Ethanol solutions of *Cannabis* clone 202 extracts (10 mg/ml - 20 mg/ml) were kept at −20˚C in the dark. The extract was evaporated on Rotavapor (BÜCHI Labortechnik AG, Switzerland). For intraperitoneal injection, the dried *Cannabis* clone 202 extract was emulsified in a vehicle composed of ethanol:Cremophor:saline at a 1:1:18 ratio. Purified CBD was emulsified in the same vehicle. For oral administration, the dried *Cannabis* clone 202 extract and the purified CBD were dissolved in olive oil.

2.2. Analysis of the *Cannabis* Clone 202 Extract by Thin-Layer Chromatography (TLC)

Cannabis clone 202 extract (1 μl) was separated on TLC Silica Gel 60 F254 aluminium sheets (Merck, Darm-

stadt, Germany) using hexane:dioxane (4:1) as a solvent in a chamber of 13 × 9 × 12 cm. The separated components were detected by spraying the plates with a freshly prepared solution of 0.5 g Fast Blue B (D9805, Sigma) in acetone/water (9:1; v/v). Cannabinoids in the dried plant material predominately appeared as cannabinoid acids. The TLC analysis shows two major spots corresponding to the acid and neutral form of CBD, respectively, with only a minor spot corresponding to the acid form of THC (**Figure 1(a)**).

2.3. Analysis of the *Cannabis* Clone 202 Extract by Gas Chromatography and Mass Spectrophotometry (GC/MS)

For analysis of the composition of the ethanol extracts of medicinal *Cannabis* clone 202, the ethanol was evaporated and the resin dissolved in 20 ml of methanol and filtered through cotton in a capillary. The concentration of the extract was adjusted to 1 mg/ml to which 50 µg internal standard (Tetracosane, Acros Organics, USA) was added. One µl of this sample was applied for the GC/MS analysis. The quantitative analysis of the samples by GC/MS was performed in a Hewlett Packard G 1800B GCD system with a HP-5971 gas chromatograph with electron ionization detector. The software used was GCD Plus ChemStation. The column used was SPB-5 (30 m × 0.25 mm × 0.25 µm film thickness). Experimental conditions were: inlet, 250˚C; detector, 280˚C; splitless injection/purge time, 1.0 min; initial temperature, 100˚C; initial time, 2.0 min; rate, 10˚C/min; final temperature, 280˚C. The helium flow rate was 1 ml/min. Calibration curve was made from 25.0 to 100 µg/ml Cannabidiol (CBD), Δ^9-Tetetrahydrocannabinol (THC) or Cannabinol (CBN) together with 50.0 µg/ml tetracosane as internal standard. The cannabinoid composition of *Cannabis* clone 202 extract is presented in **Figure 1(b)**, **Figure 1(c)** and **Table 1**.

2.4. Commercial Anti-Nociceptive and Anti-Inflammatory Drugs

The non-steroid anti-inflammatory drug (NSAID) aspirin (acetylsalicylic acid) was purchased from Sigma and dissolved in olive oil. Fifty mg of aspirin was given per os per kg in a volume of 40 µl. The opioid anti-nociceptive Tramadol hydrochloride was obtained from Grunenthal and dissolved in saline. Five mg of Tramadol was given per os per kg.

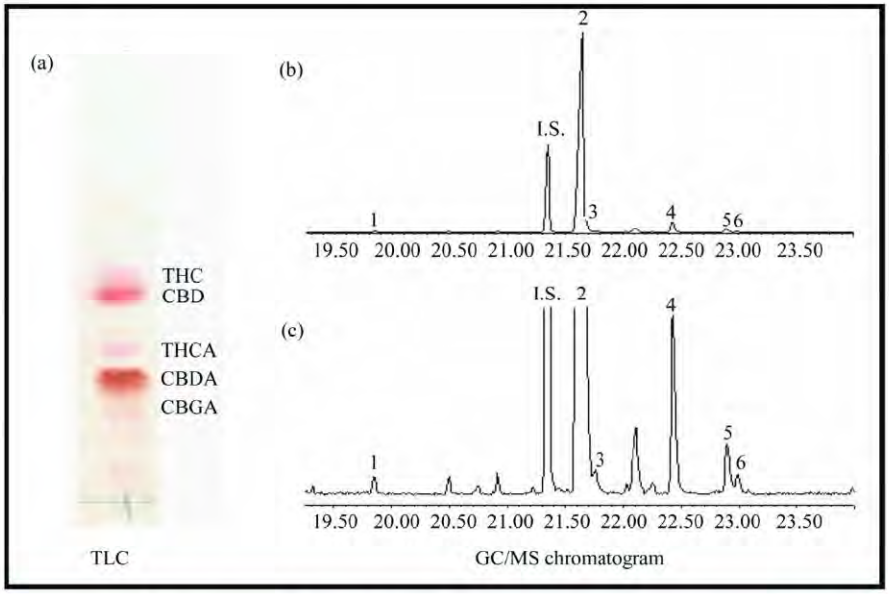

Figure 1. (a) TLC analysis of clone 202 extract. 1 µl of the extract was run on TLC as described in the Method section. CBD = Cannabidiol. CBDA = Cannabidiolic acid; (b) (c) GC/MS chromatograms of an extract from *Cannabis* clone 202. (b) The full chromatogram. (c) Magnification of weaker signals. Number keys: 1: Cannabidivarol (CBDV); 2: Cannabidiol (CBD); 3: Cannabichromene (CBC); 4: Δ^9-Tetrahydrocannabinol (Δ^9-THC); 5: Cannabigerol (CBG); 6: Cannabinol (CBN); I.S.-Internal Standard (Tetracosane).

Table 1. The percentage of main phytocannabinoids found in clone 202 extract according to GC/MS analysis (see Figures 1(b)-(c)).

Phytocannabinoid	Content
Cannabidiol (CBD)	17.9%
Δ^9-Tetrahydrocannabinol (Δ^9-THC)	1.1%
Cannabichromene (CBC)	1.1%
Cannabigerol (CBG)	0.2%
Cannabinol (CBN)	Traces
Cannabidivarol (CBDV)	Traces

As cannabinoid acids during injection to the GC/MS decarboxylate, the results are a total sum of neutral cannabinoids and cannabinoid acids that have decarboxylated into neutral cannabinoids. The content is the mass fraction (% w/w) of the given constituent in the extract.

2.5. Animals

Six to eight week old female Sabra mice (Israel) were maintained in the SPF unit of the Hebrew University-Hadassah Medical School, Jerusalem, Israel. The experimental protocols were approved by the Animal Care Ethical Committee of the Hebrew University-Hadassah Medical School, Jerusalem, Israel. The animals were maintained on standard pellet diet and water ad libitum. The animals were maintained at a constant temperature (20˚C - 21˚C) and a 12 h light/dark cycle.

2.6. Induction of Paw Inflammation in Mice and Treatment with Purified CBD or Clone 202 Extract

To induce inflammation, 40 µl of 1.5% (w/v) zymosan A (Sigma) suspended in 0.9% saline was injected into the sub-planter surface of the right hind paw of the mice. Immediately after zymosan injection, CBD or *Cannabis* clone 202 extract was injected intraperitoneally (i.p.) or given orally. For intraperitoneal injection, these agents were dissolved in 0.1 ml vehicle containing ethanol:Cremophore:saline at a ratio of 1:1:18. Control mice were injected with the vehicle only. For per os administration, the agents were dissolved in olive oil, each mouse receiving 40 µl. Control mice got 40 µl olive oil. After 2, 6 and 24 hrs, paw swelling and pain perception were measured. Serum TNFα titers were determined after 24 hrs. The effects of CBD and *Cannabis* clone 202 extract were compared to those of aspirin (50 mg/kg per os) and tramadol (5 mg/kg, i.p.).

2.7. Measurement of Oedema Formation

The paw swelling (thickness) was measured by calibrated calipers (0.01 mm), 2, 6 and 24 hrs following injections of zymosan alone or with CBD or *Cannabis* clone 202 extracts.

2.8. Pain Assay

The hyperalgesia was evaluated by the paw withdrawal von Frey test at 2, 6, and 24 hrs following injections of zymosan and/or the test compounds. In the von Frey nociceptive filament assay, von Frey calibrated monofilament hairs of logarithmically incremental stiffness (0.008 - 300 g corresponding to 1.65 - 6.65 log of force). In our study, only 1.4 - 60 g corresponding to 4.17 to 5.88 log of force was used, to test the mouse sensitivity to a mechanical stimulus on the swollen paw. The measurements were performed in a quiet room. Before paw pain measurements, the animals were held for 10 sec. The trained investigator applied the filament to the central area of the hind paw with gradual increasing size. The test consisted of poking the middle of the hind paw to provoke a flexion reflex followed by a clear flinch response after paw withdrawal. Each one of the von Frey filaments was applied for approximately 3 - 4 s to induce the end-point reflex. The first testing was done by using the force filament of 1.4 g. If there was no withdrawal response, the next higher stimulus was tried. The mechanical threshold force (in grams (g)) was defined as the lowest force imposed by two von Frey monofilaments of various sizes, required to produce a paw retraction. The untreated left hind paw served as a control.

2.9. Tumor Necrosis Factor α (TNFα) Plasma Levels

Plasma levels of TNFα were measured using a mouse TNFα ELISA kit (R&D System), according to the manufacturer's instructions.

2.10. Statistical Analysis

The results are presented as average ± standard error. Mice treated with CBD or *Cannabis* clone 202 extracts were compared with control mice receiving the vehicle only. Statistical significance was calculated using the ANOVA analysis of variance and Wilcoxon signed-rank test. Differences between the various doses of CBD and clone 202 extracts were analyzed for significance using the repeated measures ANOVA procedure with Post-Hoc test. All tests were 2-tailed and a p-value below 0.05 was considered statistically significant. A minimum of three to four animals was used in each treatment group for each experiment unless otherwise stated. Each experiment was performed at least three times. The graphs represent the average of all mice from the three different experiments. Thus, each bar corresponds to the average of 10 - 12 mice for each treatment group, for each time point, unless otherwise stated.

3. Results

3.1. Effect of CBD and CBD-Enriched Clone 202 Extract on Inflammation and Hyperalgesia (Pain Sensation)

In this study we have used the well-accepted mouse model of zymosan-induced inflammation [14] to investigate the anti-inflammatory and anti-nociceptive activities of *Cannabis* clone 202 extract versus purified CBD. The extent of hind paw swelling was determined 2, 6 and 24 hrs following paw injection of 60 µg zymosan together with either intraperitoneal injection or per os administration of various amounts of either purified CBD or *Cannabis* clone 202 extract, as indicated in the graphs (**Figure 2**, **Figure 3**). Following intraperitoneal injection of 1, 5, 25 and 50 mg/kg of purified CBD, a bell-shaped dose-response is observed (**Figure 2(a)**). The maximum inhibition of inflammation occurred after an injection of 5 mg/kg CBD with 50% and 57% inhibition after 6 and 24 hrs, respectively ($p < 0.001$), while a lower dose (1 mg/kg) being ineffective and higher doses (25 and 50 mg/kg) being less effective with 20% - 25% and 14% - 28% inhibition only, after 6 and 24 hrs, respectively (**Figure 2(a)**). In accordance with these findings, the anti-nociceptive effect, as determined by the von Frey monofilament assay, peaked at 5 mg/kg CBD ($p < 0.001$) (**Figure 2(c)**). The anti-nociceptive effect occurred prior (2 hrs) to inhibition of swelling (6 hrs), and peaked at 6 hrs. Higher concentrations of CBD had less anti-nociceptive effects (**Figure 2(c)**), again getting a bell-shaped dose-response. However, when clone 202 extract was used, a correlative dose-response was observed with increased inhibition of inflammation upon increased doses of the extract, reaching 43% and 64% inhibition at 25 mg and 50 mg, respectively, after 24 hrs ($p < 0.001$) (**Figure 2(b)**). These two dosages of clone 202 extract also showed strong anti-nociceptive effects after 6 and 24 hrs ($p < 0.001$) (**Figure 2(d)**). Although the anti-inflammatory effect of clone 202 extract was higher at 50 mg/kg than at 25 mg/kg with a $p = 0.001$, the anti-nociceptive effect was only slightly higher ($p = 0.01$), suggesting that a plateau has been reached. The clone 202 extract was more efficient for alleviating the pain than CBD ($p = 0.01$) (**Figure 2(d)** versus **Figure 2(c)**).

When CBD or *Cannabis* clone 202 extract was given orally, a similar response was observed. Namely, CBD gives a bell-shaped dose-response with an optimal inhibitory effect at 25 mg/kg ($p < 0.001$) (**Figure 3(a)** and **Figure 3(c)**), whereas *Cannabis* clone 202 extract provides a correlative dose-response curve with a maximum effect on swelling and pain relief at 50 and 150 mg/kg, respectively ($p < 0.001$) (**Figure 3(b)** and **Figure 3(d)**). Significant pain relief was already obtained with an oral clone 202 extract dose of 50 mg/kg (**Figure 3(d)**) that corresponds to about 10 mg/kg CBD (**Table 1**), while 25 mg/kg of purified CBD was needed to achieve the same effect (**Figure 3(c)**). This suggests for a better usage of clone 202 extract.

It should be noted that agents taken per os need to go through the enterohepatic route prior to exerting their effects, where the absorption rate and first-pass liver metabolism affect the blood drug level [15]. This may explain the higher doses required and the delayed response in comparison with the parenteral route, where the agents are immediately available for the blood circulation. The anti-inflammatory and anti-nociceptive effects peak at 6 hrs, which accords with the pharmacokinetics and pharmacodynamics of cannabinoids described by Grotenhermen [15].

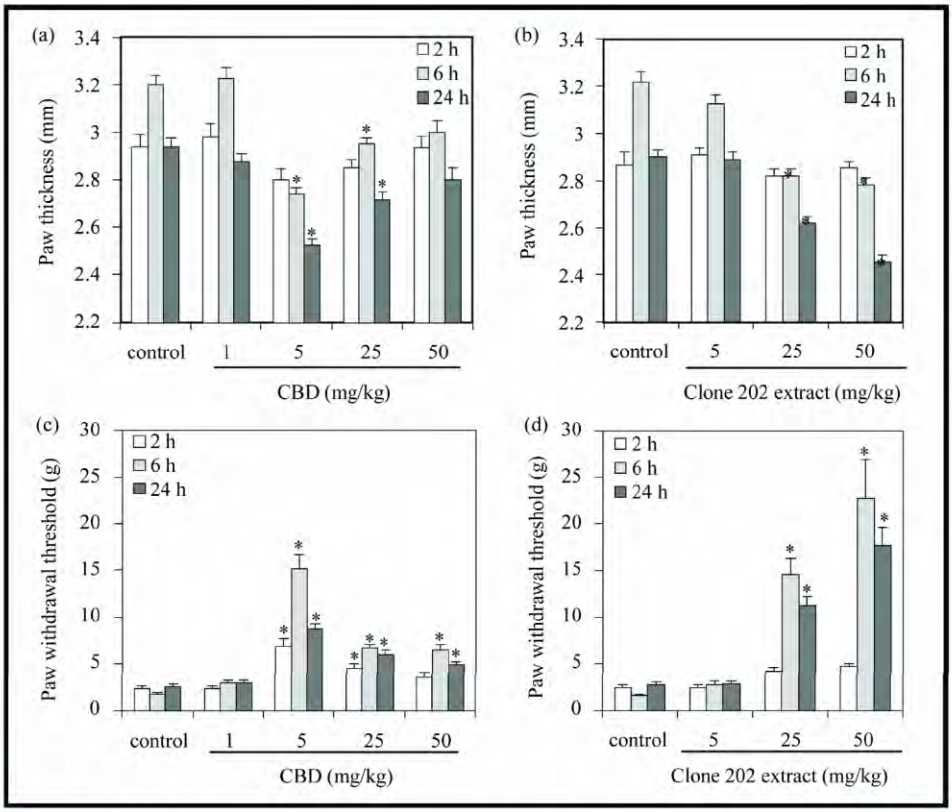

Figure 2. Anti-inflammatory and anti-nociceptive effects of intraperitoneally injected CBD and CBD-enriched clone 202 extract. (a) (b) Prevention of zymosan-induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. Immediately thereafter, CBD (a) or *Cannabis* clone 202 extract (b) was injected intraperitoneally. The paw thickness indicative for paw swelling was measured 2, 6 and 24 hrs thereafter. The paw thickness of untreated mice was 2.0 - 2.2 mm, which made the baseline of the graph. N = 12 for each time point. $^{*}p < 0.001$ compared to control mice. $p < 0.001$ for 50 mg/kg vs 25 mg/kg of clone 202 extract at 24 hrs; (c) (d) Anti-pain effect of CBD (c) and *Cannabis* clone 202 extract (d). The hyperalgesia was measured by using the von Frey nociceptive filament assay. The higher the paw withdrawal threshold, the higher is the anti-nociceptive effect of the drug. The experiments were repeated three times, each experiment with 4 mice in each treatment group. The graphs presents the average of all mice in the three experiments, meaning that the N = 12 for each time point. The bars represent standard error. $^{*}p < 0.001$ compared to control mice. $p < 0.01$ for 50 mg/kg vs 25 mg/kg of clone 202 extract at 24 hrs. $p < 0.01$ for clone 202 extract vs CBD.

3.2. Suppression of TNFα Production by CBD and Clone 202 Extract

TNFα is a well-known pro-inflammatory cytokine secreted by activated macrophages upon inflammation that has been shown to be involved in initiation and amplification of inflammatory processes that ultimately leads to oedema [16]. Therefore, it was important to analyze the effect of CBD and clone 202 extracts on TNFα production. To this end, mice sera were analyzed for TNFα concentration by ELISA 24 hrs after treatment with zymosan in the absence or presence of CBD or clone 202 extract. When comparing the TNFα sera level in mice 24 hrs after injection of increasing doses of purified CBD, a bell-shaped dose-response curve of TNFα production was observed, with a maximum inhibitory effect (43%) achieved at 5 mg/kg ($p < 0.001$), while no inhibition was observed at either lower (1 mg/kg) or higher (25 and 50 mg/kg) doses (**Figure 4(a)**). In contrast, following injection of CBD-enriched clone 202 extract to mice, a clear dose dependent response was apparent. Increased inhibition of TNFα production (39%; 46% and 57%, respectively) was observed following injections with increasing amounts of extract (5 mg/kg, 25 mg/kg and 50 mg/ml, respectively) with a p value less than 0.001 (**Figure 4(b)**). Already at 5 mg/kg did clone 202 extract lead to a strong reduction in TNFα production (**Figure 4(b)**),

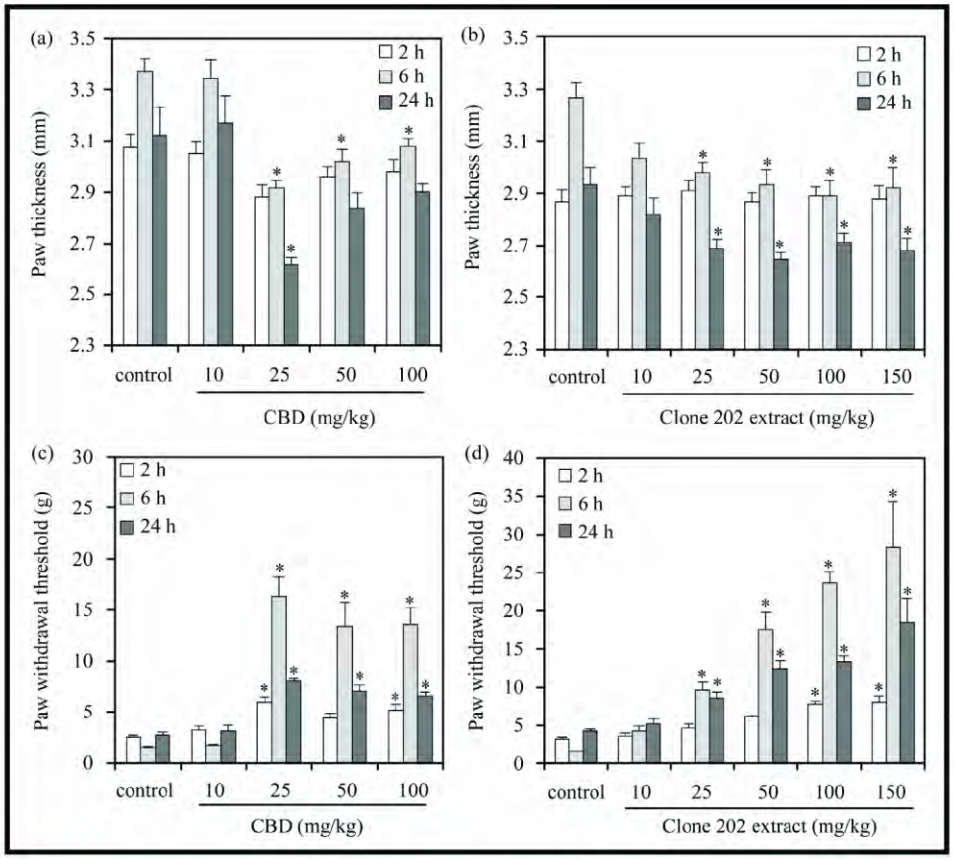

Figure 3. Anti-inflammatory and anti-nociceptive effects of CBD and CBD-enriched clone 202 extract administrated per os. (a) (b) Prevention of zymosan-induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. Immediately thereafter, CBD (a) or *Cannabis* clone 202 extract (b) was given per os dissolved in olive oil (40 µl). The paw thickness indicative for paw swelling was measured 2, 6 and 24 hrs thereafter. The paw thickness of untreated mice was 2.0 - 2.2 mm, which made the baseline of the graph. N = 12 for each time point. $^{*}p < 0.001$ in comparison to control mice. The anti-inflammatory effects of 25, 50, 100 and 150 mg/kg of clone 202 extract were similar; (c) (d) Anti-pain effect of CBD (c) and *Cannabis* clone 202 extract (d) when given orally. The hyperalgesia was measured by using the von Frey nociceptive filament assay. The higher the paw withdrawal threshold, the higher is the anti-nociceptive effect of the drug. The experiments were repeated three times, each experiment with 4 mice in each treatment group. The graphs presents the average of all mice in the three experiments, meaning that the N = 12 for each time point. The bars represent standard error. $^{*}p < 0.001$ in comparison to control mice. $p < 0.001$ for 50 mg/kg clone 202 extract (containing 8.9 mg/kg CBD) vs 10 mg/kg purified CBD. $p < 0.05$ of 100 mg/kg and 150 mg/kg vs 50 mg/kg of clone 202 extract at 6 hrs, indicating a dose-dependent effect.

even though this dose was insufficient in reducing paw swelling (**Figure 2(b)**) or relieve pain (**Figure 2(d)**). At least 25 mg/kg extract, which corresponds to about 5 mg CBD, was required to achieve the anti-inflammatory effect. These data show that TNFα secretion is more sensitive to inhibition by clone 202 extract, than paw swelling and pain.

Similar to the results obtained with intraperitoneal injection, orally administrated CBD gave a bell-shape response, with an optimal response using 25 mg/kg ($p < 0.001$), while higher or lower doses had less effect (**Figure 4(c)**). In contrast, orally delivered clone 202 extract showed an increased inhibitory effect on TNFα production with increased doses (**Figure 4(d)**). Already at 25 mg/kg an inhibition of 48% was achieved that increased further to 66% when given 150 mg/kg clone 202 extract (**Figure 4(d)**). The inhibition of TNFα production was much stronger than the inhibitory effect on paw swelling of 27% - 35%.

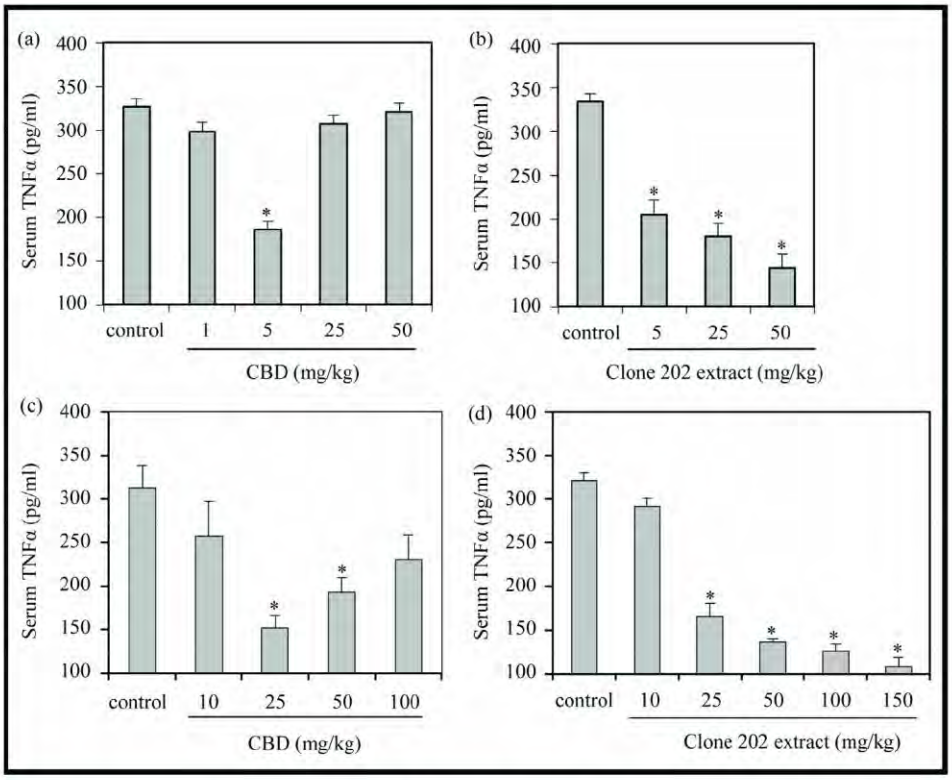

Figure 4. Prevention of zymosan-induced TNFα production by purified CBD and clone 202 extract. (a) (b) Twenty four hours after injecting zymosan and an intraperitoneal dose of CBD (a) or clone 202 extract (b), or a per os dose of CBD (c) or clone 202 extract (d), the TNFα concentration in the serum was determined by ELISA. The experiments were repeated three times, each experiment with 4 mice in each treatment group. The graphs presents the average of all mice in the three experiments, meaning an N = 12 for each treatment. TNFα serum level of untreated mice was 15 pg/ml. The bars represent standard error. $^{*}p < 0.001$ in comparison to control mice. $p < 0.01$ when comparing clone 202 extract with purified CBD. $p < 0.01$ when comparing an increasing doses of clone 202 extract, emphasizing a dose-dependent effect.

3.3. Comparison of CBD and *Cannabis* Clone 202 Extract with Commercial Anti-Nociceptive and Anti-Inflammatory Drugs

Since *Cannabis* clone 202 extract has profound anti-inflammatory and anti-nociceptive effects as described above, it was important to compare its potency with commercial anti-nociceptive and anti-inflammatory drugs. We chose to use tramadol, a strong atypical opioid analgesic drug, and aspirin, a well-known non-steroid anti-inflammatory drug (NSAID) that is also a pain reliever. Immediately after zymosan injection, mice were treated with aspirin (50 mg/kg per os), tramadol (5 mg/kg i.p.), CBD (5 mg/kg i.p.) or clone 202 extract (50 mg/kg i.p.). While aspirin had a moderate effect on paw swelling ($p < 0.001$ at 6 h), tramadol barely had any effect (**Figure 5(a)**). Both CBD and clone 202 extract markedly prevented paw swelling to a much larger extent than aspirin ($p < 0.005$) (**Figure 5(a)**). As expected, aspirin and tramadol had a strong anti-nociceptive effect that exceeded that of CBD and clone 202 extract ($p < 0.01$) (**Figure 5(b)**). Aspirin, but not tramadol, showed a slight inhibitory effect on TNFα production, that was negligible in comparison to the strong inhibitory effect of CBD and clone 202 extract ($p < 0.01$) (**Figure 5(c)**). Thus, CBD and clone 202 extract are endowed with different traits than aspirin and tramadol, making them superior with respect to anti-inflammatory properties.

4. Discussion

In this manuscript we have observed different dose-response patterns when using purified CBD or plant extract

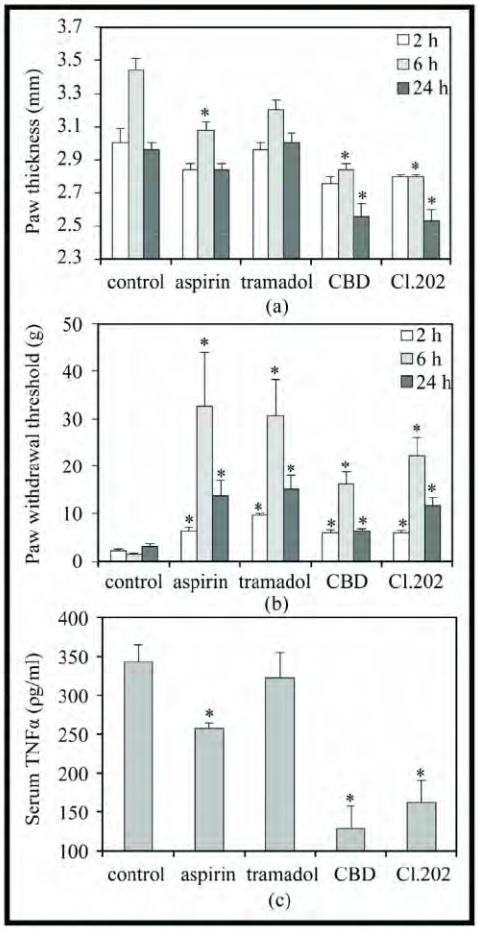

Figure 5. Comparison of anti-inflammatory and anti-nociceptive effects of CBD and *Cannabis* clone 202 extract with the commercial drugs aspirin and tramadol. (a) Prevention of zymosan-induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. Immediately thereafter, aspirin (50 mg/kg per os), tramadol (5 mg/kg i.p.), CBD (5 mg/kg i.p.) or *Cannabis* clone 202 extract (50 mg/kg i.p.) was given. The paw thickness indicative for paw swelling was measured 2, 6 and 24 hrs later. The paw thickness of untreated mice was 2.0 - 2.2 mm, which made the baseline of the graph. N = 5 for each time point of each treatment group. $^{*}p < 0.001$ in comparison to control mice. $p < 0.005$ when comparing CBD and clone 202 extract with aspirin and tramadol; (b) Anti-pain effect of aspirin, tramadol, CBD and *Cannabis* clone 202 extract in mice treated as described in paragraph A. The hyperalgesia was measured by using the von Frey nociceptive filament assay. The higher the paw withdrawal threshold, the higher is the anti-nociceptive effect of the drug. N = 5 for each time point of each treatment group. The bars represent standard error. $^{*}p < 0.001$ in comparison to control mice. $p < 0.05$ when comparing CBD and clone 202 extract with aspirin and tramadol; (c) The TNFα serum concentration at 24 hrs in mice that were treated as described in paragraph A. N = 5 for each treatment. The bars represent standard error. $^{*}p < 0.001$ in comparison to control mice. $p < 0.01$ when comparing CBD and clone 202 extract with aspirin and tramadol.

of the *Cannabis sativa* L. clone 202, which is highly enriched in CBD. Purified CBD showed a bell-shaped dose-response, where a therapeutic response could only be achieved at a certain concentration. This narrow therapeutic window makes it difficult to use CBD in the clinics as a single agent. Therefore, we sought for a better preparation that can utilize the favorable therapeutic effects of CBD. We observed that plant extracts of the non-psychotropic clone 202 could fit this aim. A dose-dependent response was observed on all three parameters tested: namely, the extract prevented zymosan-induced paw oedema, zymosan-induced pain and zymosan-induced TNFα production in mice, with an improved therapeutic effect upon increased dosages. Thus, the limi-

tation with purified CBD could be overcome when presented together with other natural components of the plant. Of note, TNFα secretion was more sensitive to clone 202 extract inhibition than paw swelling and pain.

Our finding that it is possible to get a correlative dose-response using *Cannabis* clone 202 extracts, makes it possible to use it in many pathological conditions. We suggest that clone 202 extracts may be a suitable substitute for the current used *Cannabis* strain in the clinics, especially taking into account that it does not have any psychotropic adverse effects. Following the clinical improvement by the clone 202 extracts, more tedious experiments with CBD might be planned.

Our findings that CBD in the presence of other plant constituents improve the dose-response are supported by some recent reports showing that CBD in a standardized *Cannabis sativa* extract is more potent or efficacious than pure CBD [17]-[19]. These research groups studied the anti-proliferative effect of CBD on tumor cells [17] [19] and the inhibitory effect of CBD on bladder contractility [18]. The higher efficiency of plant extract might be explained by additive or synergistic interactions between CBD and minor phytocannabinoids or non-cannabinoids presented in the extracts. Other phytocannabinoids, including Tetrahydrocannabivarin, Cannabigerol and Cannabichromene, exert additional effects of therapeutic interest [20]. A lot of research has been made to isolate and characterize isolated single constituents of traditional herbal medicine to find their rationale for therapeutic uses. However, our data together with those of others [21] provide legitimation to introduce a new generation of phytopharmaceuticals to treat diseases that have hitherto been treated using synthetic drugs alone. The therapeutic synergy observed with plant extracts results in the requirement for a lower amount of active components, with consequent reduced adverse effects.

5. Conclusion

In conclusion, we recommend standardized plant extract of the *Cannabis* clone 202 for treatment of various inflammatory conditions.

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Conflict of Interest

Prof. Ruth Gallily has been a consultant for Tikun Olam since 2013, and has received a research grant during the years 2012-2014 from Tikun Olam, Israel. There is no conflict of interest.

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Epilepsy

CBD-Enriched Medical Cannabis for Intractable Pediatric Epilepsy

Seizure: European Journal of Epilepsy, 2016

A retrospective study analyzing the effect CBD-enriched cannabis oil had on children and adolescents with refractory epilepsy, being treated at four epilepsy centers in Israel.

Study Population: 74 patients (1 - 18 years old) with intractable epilepsy, resistant to 5-7 antiepileptic drugs
Strains Used: Better and Tikun Olam's CBD-enriched cannabis oil at a 20:1 (CBD:THC) ratio
Key Results:

- 89% of patients reported reduction in seizure frequency
- Improvement in behavior, alertness, language, communication, motor skills, and sleep were reported

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CBD-enriched medical cannabis for intractable pediatric epilepsy The current Israeli experience

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ABSTRACT

Purpose: To describe the experience of five Israeli pediatric epilepsy clinics treating children and adolescents diagnosed as having intractable epilepsy with a regimen of medical cannabis oil.
Methods: A retrospective study describing the effect of cannabidiol (CBD)-enriched medical cannabis on children with epilepsy. The cohort included 74 patients (age range 1–18 years) with intractable epilepsy resistant to >7 antiepileptic drugs. Forty-nine (66%) also failed a ketogenic diet, vagal nerve stimulator implantation, or both. They all started medical cannabis oil treatment between 2–11/2014 and were treated for at least 3 months (average 6 months). The selected formula contained CBD and tetrahydrocannabinol at a ratio of 20:1 dissolved in olive oil. The CBD dose ranged from 1 to 20 mg/kg/d. Seizure frequency was assessed by parental report during clinical visits.
Results: CBD treatment yielded a significant positive effect on seizure load. Most of the children (66/74, 89%) reported reduction in seizure frequency: 13 (18%) reported 75–100% reduction, 25 (34%) reported 50–75% reduction, 9 (12%) reported 25–50% reduction, and 19 (26%) reported <25% reduction. Five (7%) patients reported aggravation of seizures which led to CBD withdrawal. In addition, we observed improvement in behavior and alertness, language, communication, motor skills and sleep. Adverse reactions included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients.
Conclusions: The results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted.

1. Introduction

About one-third of patients with epilepsy suffer from drug-resistant disease defined as failure to stop all seizures after an adequate trial of at least two appropriate medications. The efficacy of current medications in these cases is limited [1–3]. There is great interest in the development of new medications which may have antiepileptic properties, particularly those agents that affect novel receptors.

The two main cannabis ingredients with central nervous system (CNS) activity are psychoactive Δ9-tetrahydro-cannibinol (THC) and the non-psychoactive cannabidiol (CBD). THC directly activates the brain endocannabinoid system, which has a role in synaptic communication [4]. CBD is a cannabinoid receptor antagonist that modulates the endogenous cannabinoid system by potentiating intrinsic anandamide-mediated neurotransmission. In addition, CBD is involved in the regulation of other cerebral neurotransmitters and receptors, as well as having an anti-inflammatory and

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antioxidant properties [5,6]. The mechanism of action of CBD is not well understood, but it has become clear that its anticonvulsant properties do not involve a cannabinoid receptor (CBR)-dependent mechanism [7]. Because of its multiple targets and high toxicity threshold, it is currently being investigated as a potentially useful therapeutic drug in several CNS and extra-CNS disorders, including epilepsy, in both experimental models and in humans [8,9]. The effects of cannabis on epilepsy were described by detailed case reports in the medical literature from as early as the 19th century [10,11]. Those articles were followed by several epidemiological studies that claimed a protective effect of marihuana smoking against seizures [12–14]. CBD was also found to have positive effects on seizure threshold, severity and lethality in several epilepsy mouse and rat models [15–18]. Several small controlled studies on the effect of purified CBD (200–300 mg/d) on epilepsy in adults were conducted in the 1970s [19–22]. While the first two claimed a significant effect of CBD on seizure frequency, the last two did not show any benefit for CBD use over placebo. These reported studies were analyzed in a Cochrane review [23] that concluded that because of the quality of the studies, the only answered question was the secondary outcome measure related to adverse effects and concluded that 200–300 mg/d cannabidiol had been safely administered to small numbers of patients for short time periods.

The last three years have witnessed growing interest among the medical community, parent groups and media in the use of enriched CBD medical cannabis and pure CBD in intractable pediatric epilepsy. Based on anecdotal reports and parental pressure, marijuana is currently licensed for seizures or epilepsy in 14 states in the US [24].

Medical cannabis in various ratios of CBD and THC and in different preparations (modes of administration) is licensed by the Israeli Ministry of Health (MOH) for a number of indications, including oncology-related pain and side effects of chemotherapy, phantom pain, and pain related to multiple sclerosis, diabetic neuropathy, spinal cord injury, post-traumatic stress disorder. severe intractable Gille de la Tourette syndrome, intractable epilepsy in pediatric and adult patients, intractable Crohn's disease and selected cases of severe fibromyalgia. Contraindications for its administration include a history of drug abuse, significant psychiatric background and congestive heart failure. Only experts in each specific field are allowed to apply for a license to access a special unit in the MOH by means of computer-based application forms. Each application is reviewed, and approval is given for a period of 6 months to 1 year if considered appropriate by a group of 30 key leaders in these fields of expertise nominated by the MOH and signed by one designated MOH expert physician. There are currently 23,500 active licenses in the MOH registry (200 for children with epilepsy). The cannabis preparations (oil, cigarettes, inhalation extract or flowers) are produced by 8 MOH-certified growers and distributed by them to the licensed patients through specific distribution points and accompanied by personal guidance for their proper use. Treatment follow-up is performed by the applying physician.

Our objective in this paper is to present the experience of four pediatric epilepsy units in Israel that treat children and adolescents diagnosed as having intractable epilepsy with enriched CBD medical cannabis.

2. Materials and methods

2.1. Subjects

We conducted a retrospective study based on clinical records of clinic and phone call visits of children and adolescents with refractory epilepsy who were being treated in four pediatric epilepsy centres in Israel. The participating clinics are all tertiary referral centers for pediatric epilepsy in Israel, and each treats thousands of patients with epilepsy, including many with intractable disease. All the patients that received CBD-enriched cannabis oil (CECO) were followed by each of the clinics for at least 12 months before receiving CECO. It was offered to them by the physician after they had been resistant to 5–7 drugs, or treatment by a ketogenic diet or vagal nerve stimulation (VNS). The possibility of CECO was also raised by the child's parents who learned about that treatment option via information made available by the media. One pediatric neurologist followed the patients in each clinic.

The cohort included children who were treated with cannabis oil for more than 3 months throughout 2014. Patients aged 1–18 years with refractory epilepsy that was characterized by daily seizures refractory to >7 appropriate antiepileptic drugs (AEDs) and other treatment modes, i.e., VNS 35/74 (47%), epilepsy surgery 3 (4%), and ketogenic diet 29/74 (39%) were included. Patients with severe behavioral disorders and significant family psychopathology were excluded.

The study patients were divided into six groups based on seizure etiology:

1. Acquired
2. Early epileptic encephalopathy with a known genetic etiology
3. Epileptic encephalopathy without a known genetic etiology
4. Congenital brain malformations
5. Hypoxic ischemic encephalopathy
6. Other (etiology not defined)

2.2. Study medication

CBD-enriched cannabis oil was supplied by two licensed growers (Better and Tikun Olam, Tel-Aviv, Israel), and the preparation of the oil was made by two methods. In the first method, the cannabis plant material was extracted in PhEur absolute ethanol, followed by evaporation and decarboxylation. The concentrate was diluted in PhEur canola oil to the required concentration of 20% CBD and 1% THC. Preservatives and antioxidants were added to ensure stability of the active ingredients. The ingredient concentration and quality analysis was done four times by high performance liquid chromatography (HPLC) during the different stages of the preparation process. In the second method, the cannabis oils were extracted from two CBD-rich cannabis strains using ethanol as an extracting solvent. The preparation at the crude extract level, the purified CBD and the final solution level were analyzed by both HPLC and gas chromatography-mass spectrometry. The ratio between THC and CBD was standardized and corrected to 20:1 by the addition of pure CBD. At the final stage, the preparations were assayed to ensure the absence of fungi and molds (based on the Israeli Standard 885 for preparation sterility). The CBD and THC analyses were performed in two independent labs which supply services for the growers. One is a university lab and the other is a GMP-approved lab.

The CBD dosage ranged from 1 to 20 mg/kg/d, and it was divided into two groups, 1–10 mg/kg/d and 10–20 mg/kg/d. The final dose used for each patient was defined according to seizure response and side effects. The THC dosage did not exceed 0.5 mg/kg/d, which is considered far below the safety margin of THC. In some cases, the patient's other medications were reduced if there was decrease in seizure frequency and adjusted according to side effects, in addition to drug level adjustments while on CECO. Seizure reduction was rated according to four levels (0%, <25%, 25–50%, 50–75%, and 75–100%) as reported by parents and older patients. Parents were asked to report the number of seizures per period and we did the percentage calculations. Side effects were also reviewed.

The study was approved by the IRB committee of the four participating centers.

3. Results

A total of 74 patients met the study inclusion criteria. One-half of them (37/74, 50%) were younger than 10 years of age. Sixty-five (88%) of the patients were cognitively impaired as follows: mild 16/74 (22%), moderate 14/74 (19%), and severe 34/74 (46%), with only 10 of them (13%) having normal cognition. The CECO treatment duration was between 3 and 12 months. The median duration of exposure was 5.5 months and the duration of follow-up was 10 months. The CBD dosage ranged from 1 to 20 mg/kg/d: 60 (81%) patients were treated with <10 mg/kg/d of CBD and 14 (19%) treated with >10 mg/kg/d of CBD, with the highest CBD dose reaching 270 mg/day.

Most of the patients (66/74, 89%) reported some reduction in seizure frequency: 13 (18%) had 75–100% reduction, 25 (34%) had 50–75% reduction, 9 (12%) had 25–50% reduction, and 19 (26%) had <25% reduction. Five (7%) patients reported aggravation of seizures which led to withdrawal of the cannabis oil.

One patient, a 7-month-old with severe acquired hypoxic ischemic damage, intractable spasms and partial complex seizures, became seizure-free on CECO at a dosage of 2 mg/kg/d. The improvement demonstrated on his electroencephalogram (EEG) enabled a gradual decrease in the dosages of his other antiepileptic drugs (AEDs).

The results of cannabis oil treatment according to seizure etiology are displayed in Table 1. In the first two groups (epileptic encephalopathies with or without known genetic mutations), 66% (30/45) of the children showed more than a 25% reduction in seizure frequency, with 23/45 (51%) reporting between 50 and 100% reduction in seizure frequency. Table 2 lists the results of cannabis oil treatment according to dosage. Positive effects not related to seizure frequency were reported by 44/74 patients, and they included improved behavior and alertness in 25/44, improved language, communication and motor skills in 11/44, and improved sleep in 8/44.

Adverse events were reported by 34/74 patients (Table 3). The side effects led to the withdrawal of medical cannabis in five patients.

4. Discussion

The use of enriched CBD oil in the treatment for intractable pediatric epilepsy patients is becoming increasingly popular. Three publications on retrospective studies appeared between 2013 and 2015 describing parental surveys or the experience of epilepsy clinics with enriched CBD oil among various pediatric epilepsy populations [25–27]. Although they showed a favorable effect of CBD-enriched cannabis in the pediatric epilepsy population, those reports lacked objectivity as well as crucial data on the study population and on the compounds used according to varying considerations. The first was a retrospective study that described a telephone/Internet survey of 19 parents whose children had various childhood epileptic encephalopathies for which they received CBD-enriched medical marijuana: 16 (84%) had a reduction in seizure frequency and two became seizure-free [25]. The second report was a retrospective chart review from a single tertiary epilepsy center, and it included 75 children and adolescents with various epileptic encephalopathies who were given medical cannabis [26]. Thirty-three percent reported a >50% reduction in seizures, while 57% reported some improvement in seizure control. The response rate was syndrome-dependant: Dravet syndrome had a rate of 23%, Doose syndrome 0%, and Lennox–Gastaut syndrome 88.9%. No benefit was demonstrated in the available EEGs. The third report was an online parental survey that focused on perceived efficacy, dosage, and tolerability of CBD-enriched cannabis preparations for children with infantile spasms and Lennox–Gastaut syndrome and other intractable epilepsies. A total of 117 parents responded to the survey. The perceived efficacy and tolerability were similar across etiologic subgroups, with 85% reporting some reduction in seizure frequency and 14% reporting complete seizure freedom. The median duration and the median dosage of CBD exposure were 6.8 months and 4.3 mg/kg/day, respectively [27]. The few side effects reported in these three studies included increased appetite, somnolence/fatigue, and an increase in seizure frequency [25–27]. Rare adverse events were developmental regression, abnormal movements, status epilepticus requiring intubation, and death. The beneficial effects other than seizure control that were reported in all three studies by parents included sleep quality improvement, increased alertness, and better mood during CBD therapy. Improvements in language and motor skills were reported in 10% of patients in a study by Hussain et al. [27].

Our current investigation is a large retrospective study. It differs from the previously reported studies [25–27] in a number of aspects. The patients and their epilepsy course were well known to the treating physicians in all four participating centers. Only two CBD-enriched cannabis solutions with known and well-controlled compositions were used, and the titration of dosage was done regularly by the treating physician according to seizure response and side effects during clinic visits. The follow-up was done mainly in person with additional in-between phone calls and not by printed questionnaires, which may strengthen the reliability of the data. Because of the novelty of using medical cannabis in pediatric epilepsy, the physicians were very selective in their inclusion criteria and chose only patients with severe refractory epilepsy

Table 1
Results according to seizure etiology.

	Seizure reduction				
	0% no. of cases	<25% no. of cases	25–50% no. of cases	50–75% no. of cases	>75% no. of cases
Known genetic mutation	2	9	2	8	4
Unknown genetic mutation	0	4	5	8	3
Acquired	1	1	1	2	3
Brain malformation	0	1	0	1	1
Hypoxic ischemic	4	1	1	5	0
Others	1	3	0	1	2
Total	8 (11%)	19 (26%)	9 (12%)	25 (34%)	13 (17%)

Table 2
Seizure reduction according to dosage.

Dosage	0% no. of cases	<25% no. of cases	25–50% no. of cases	50–75% no. of cases	>75% no. of cases	Total no. of cases
<10 mg/kg/d	4	14	8	24	10	60 (81%)
>10 mg/kg/d	4	5	1	1	3	14 (19%)

Table 3
Adverse events reported in 34/74 patients.

Adverse events	No. of cases
Seizure aggravation	13 (18%)
Somnolence/fatigue	16 (22%)
Gastrointestinal problems and irritability	5 (7%)

(i.e., all had failed at least 7 AEDs and most had also failed the ketogenic diet, VNS or epileptic surgery or both).

We divided the patients into six groups according to etiology. The largest was the group that had epileptic encephalopathy with or without a known genetic etiology (59%). While 66% of the epileptic encephalopathy group (30/45) showed more than a 25% reduction in seizure frequency, only 45% (14/31) of the other children showed a similar response rate. Importantly, there was no difference in the baseline severity of epilepsy between the groups by the physicians' clinical assessment.

Because of no previous experience and no available data on the effect and safety of CBD and the limitations related to THC dosage, three out of the four participating centres chose to titrate the cannabis oil slowly and kept the patients on a relatively low CBD dose (<10 mg/kg/d), with only 13 patients (17%) reaching a CECO dosage higher than 10 mg/kg/d. The small size of the high dose group precludes our reaching any conclusions regarding dosage-related efficacy.

Side effects of substance use were inevitable, but their rate and severity were not different from most known AEDs. There were no allergic responses. Somnolence and fatigue were relatively common but they were mostly temporary. It is also important to mention that CECO was added to at least 2 other AEDs in all patients, and that drug–drug interactions may have been the underlying cause for the fatigue and somnolence. There were no major systemic side effects, and the reported gastrointestinal problems were of minor significance. The seizure aggravation reported in 7% of the patients can be partly related to the disease's natural history. Most of our study patients were cognitively impaired, thus preventing the option to assess the effect of CECO on cognition.

Our study has several imitations, including the lack of a control group, no consistent rate of dosage elevation, reliance upon parental report on seizure frequency, short duration of the study and lack of long-term outcome, no EEG results and no measurement of other drug levels. Since it is a retrospective study, there was no planned baseline period before commencing CECO. However, because all the patients were well-known and continuously followed-up in the participating clinics, the natural history of their epilepsy was well known and served as baseline.

5. Conclusions

The results of this multicenter study on CBD enriched cannabis oil treatment for intractable epilepsy in a population of children and adolescents are highly promising. Further prospective, well-designed clinical trials using enriched CBD medical cannabis are warranted to validate our findings.

Disclosures

All authors have no commercial, financial or other associations to disclose that pose a conflict of interests I connection with the article.

Author contribution/roles

Michal Tzadok and Bruria Ben Zeev were responsible for the concept and design of the study, for the collection of data, interpretation of the data, and for the drafting and editing of the document. Shimrit Uliel-Siboni, Ilan Linder, Uri Kramer, Orna Epstein, Andrea Nissenkorn, Omer Bar Yosef, Eli Hyman, Shay Menascu, and Michal Dor were responsible for the collection of data. Dorit Granot was responsible for the drafting of the document. Tali Lerman-Sagi and Uri Kramer were responsible for editing of the document. All authors have read and have approved the manuscript as submitted. All authors are responsible for the reported research.

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Parkinson's Disease

Medical Cannabis in Parkinson's Disease

Clinical Neuropharmacology, 2017

A retrospective questionnaire-based survey that examined the effects of cannabis on the motor and non-motor symptoms of patients with Parkinson's Disease. The mean age of the patients was 64.2 +/- 10.8 years, the mean disease duration was 10.8 +/- 8.3 years, and the duration of cannabis use was 19.1 +/- 17 months.

Study Population: 47 patients with Parkinson's Disease
Strains Used: Various medical cannabis strains
Key Results:

- 82.2% of patients reported that cannabis improved their overall symptoms
- 81.4% of patients reported that their pain was reduced
- 76.1% of patients reported an improvement in mood
- 73.2% of patients reported tremor reduction
- 72.7% of patients reported reduced muscle stiffness
- 71.1% of patients reported an improvement in sleep quality

Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience

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Background: The use of medical cannabis (MC) is controversial. Support for its benefits is based on small clinical series.

Objective: The aim of this study was to report the results of a standardized interview study that retrospectively assessed the effects of MC on symptoms of Parkinson disease (PD) and its adverse effects in patients treated for at least 3 months.

Methods: The survey used telephone interviews using a structured questionnaire based on subjective global impressions of change for various parkinsonian symptoms and yes/no questions on adverse effects.

Results: Forty-seven nondemented patients with PD (40 men) participated. Their mean age was 64.2 ± 10.8 years, mean disease duration was 10.8 ± 8.3 years, median Hoehn and Yahr (H&Y) was stage III. The duration of MC use was 19.1 ± 17.0 months, and the mean daily dose was 0.9 ± 0.5 g. The delivery of MC was mainly by smoking cigarettes (38 cases, 80.9%). Effect size (r^2) improvement for falls was 0.89, 0.73 for pain relief, 0.64 for depression, 0.64 for tremor, 0.62 for muscle stiffness, and 0.60 for sleep. The most frequently reported adverse effects from MC were cough (34.9%) in those who used MC by smoking and confusion and hallucinations (reported by 17% each) causing 5 patients (10.6%) to stop treatment.

Conclusions: Medical cannabis was found to improve symptoms of PD in the initial stages of treatment and did not cause major adverse effects in this pilot, 2-center, retrospective survey. The extent of use and the reported effects lend support to further development of safer and more effective drugs derived from *Cannabis sativa*.

Key Words: Parkinson disease, medical cannabis, adverse effects, motor symptoms, nonmotor symptoms, therapeutics

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Current treatments of Parkinson disease (PD) and parkinsonism still provide suboptimal effects, especially regarding the patients' quality of life. This has led to the search for alternative and often unconventional therapies. There is a wealth and steadily growing body of information in the nonmedical literature on the positive effects of cannabis products on motor symptoms (tremor, rigidity, bradykinesia) as well as on nonmotor symptoms (pain, sleep, depression, anxiety, nausea, and vomiting) and quality of life. The widely discussed adverse effects of standard PD medications encourage patients with PD and physicians to try "alternative natural treatments," including the attractive option of medical cannabis (MC). We were able to find only a few small clinical trials of the effects of MC in PD, one of which reported improvement of motor (tremor, rigidity, and bradykinesia) and nonmotor (sleep and pain) symptoms, with no significant adverse effects in 22 patients with PD.[1] In contrast, the results of 2 other studies were negative: there was no improvement of tremor after smoking cannabis among 5 patients,[2] and there were no effects of oral cannabis extract on dyskinesias in a randomized, 4-week, double-blinded, crossover study on 17 patients with PD who tolerated the treatment well.[3]

The use of *Cannabis sativa* for medical purposes had been permitted in Israel since 1991, and it has expanded significantly over the past 5 to 7 years, most likely because of the increased awareness and demand of patients who are exposed to it through social media and the internet, and whose doctors recommend it. However, it is strictly regulated by the Israeli Ministry of Health (MoH), and each patient requires personal permission to use MC after the inspection of each individual case. Selected growers are allowed to produce *Cannabis sativa* for medical use. The costs of MC are not reimbursed by health providers or insurers, and they total approximately 370 NIS (approximately $100 US) per month. Given the expanding request and interest of the patients and insufficient verification from controlled clinical trials, the aim of this report was to assess the effect of MC as adjuvant symptomatic treatment for various PD symptoms, (tremor, muscle stiffness, sleep disorders, depression, pain, weight) and its adverse effects in patients who were granted a license for MC use by the MoH in response to a formal request submitted by the patients' neurologists.

METHODS

A retrospective observational telephone survey was conducted to collect data from patients with PD being treated at the Movement Disorders Clinics of the Tel Aviv Sourasky Medical Center and the Rabin Medical Center. The license for MC use was granted by the MoH for each participant.

The study was approved by the institutional review boards, and all the participating patients agreed to answer questions by telephone. The design of the structured questionnaire was based on the published MC surveys in multiple sclerosis[4] and PD.[5] It consists of 66 questions divided into 3 parts: (1) demographic data and comorbidities; (2) clinical characteristics of the patients, including motor and nonmotor features; and (3) details of MC use and subjective assessment of its effects on different symptoms, including adverse effects.

The effect of MC on motor and nonmotor symptoms and on the activities of daily living was evaluated according to the

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Both Movement Disorders Units were responsible for patient with PD selection and providing the patient's telephone numbers. Tikun Olam Co was responsible for designing and administering the questionnaire, setting up the datasheet, and entering the data. The extraction and analysis of data and the report were performed by the first author (Y.B.). This article represents a final report on these data with the collaboration of all the authors.

Conflicts of Interest and Source of Funding: Lihi Bar-Lev Schleider is an employee of Tikun Olam Co, an Israel pharmaceutical company, which is developing cannabis-based medicinal extracts. Yehuda Baruch was a head of the Israeli Ministry of Health program for Medical Use of Cannabis in 2003 to 2012; at present, Yehuda Baruch is CSO of One World Cannabis Israel, which is a company dedicated to the research of cannabis and cannabinoids and their medical properties. All the other authors have nothing to declare.

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modified 5-point Clinical Global Impressions Scale as follows: 1 = significant improvement, 2 = moderate improvement, 3 = mild improvement, 4 = no change, and 5 = any worsening.[6] Falls before and after MC treatment were registered as yes/no. The telephone interviews were conducted (by L.B.S., J.K., and H.S.) at a prearranged date and time convenient for examinees. The interview lasted around 30 minutes, and a second call was needed to complete data collection in 9/47 cases (19.1 %).

Patients with PD who did not want to participate in the study or were not eligible according to the clinical judgment of the physicians or investigators were excluded from the study. If patients were unable to answer a question, or the question seemed inappropriate, then their response was recorded as irrelevant. All the included patients with PD answered all the questions independently. The responses were accepted as reported by the patient without any modifications, and no attempt to interpret this information was made.

Statistical Analysis

Data were analyzed using a Microsoft Excel 2007 spreadsheet. Results were expressed as means with standard deviations (SDs) or as median with interquartile range (IQR). Irrelevant answers were excluded from the statistical analysis. All the included patients with PD answered all the questions independently without any help. The data on the responses of patients with PD before and after MC were compared according to Student paired *t* test for dependent samples.[7] The effect size for the dependent samples *t* test (r^2) was calculated according to the method proposed by Morris,[8] and interpreted according to Cohen's guidelines: ≤0.5 = small; 0.5 to 0.8 = moderate; and ≥0.8 = large.[9] A higher r^2 value means stronger positive effect of MC in comparison with the period before MC was used. The level of significance was 95% for all tests.

RESULTS

Between 2013 to 2015, 98 patients with PD were suitable for study enrollment: 13 patients refused to participate, 20 could not be reached by telephone, and 4 patients had passed away. Fourteen patients were excluded from the analysis because they used MC for less than 3 months. Among them, 7 patients have not reached the necessary duration of MC treatment, and the other 7 patients interrupted treatment within 1 to 2 months because of MC inefficiency (4) or adverse effects such as loss of consciousness (1), hallucinations (1), and fatigue (1). A total of 47 patients with PD were included in the study.

Demographic Information

The mean age of the 47 subjects was 64.2 years (SD = 10.8; median = 65; IQR, [56.8–70]), of whom 40 (85.1%) were male patients. Thirty (63.8%) were retired, and the other 17 were employed. The PD duration ranged from 2 to 39 years (average, 10.8 years) (SD = 8; median = 8; IQR, [5–15]), and their H&Y stages ranged from I to IV, median = III, IQR of II to III (Table 1). Unclear answers were excluded from the statistical analysis, leading to variations in the total number of the responses.

PD Status Before MC Treatment

The major PD symptoms were reported as follows: 29/45 had rest tremor (64.4%), 24/45 had muscle stiffness (53.3%), 24/45 had freezing of gait (53.3%), 24/45 had gait disorders (53.3%), and 22/47 (46.8%) had recurrent falls (Table 2). Motor fluctuations were reported by 36/46 patients (78.73%): 25/47 (53.2%) complained of "off" times lasting from 0.5 to 24 hours a day, mean of 9.3 hours (SD = 5.8; median = 8; IQR, 4.0–12).

TABLE 1. Demographic Characteristics of 47 Parkinsonian Patients Treated by MC

Variable	Number	%
Age y		
39–55	9	19.1
56–65	15	31.9
66–75	16	34.1
76–87	7	14.9
Sex		
Male	40	85.1
Female	7	14.9
PD duration, y		
2–5	11	23.4
5–9	15	31.9
10–15	10	21.3
16–39	11	23.4
Employed (n = 47)		
Yes	17	36.2
No	30	63.8
H&Y stages (n = 40)		
I	2	5
II	17	42.5
III	12	30
IV	9	22.5

Total "on" times lasted for an average of 11.8 hours (SD = 6.9; median = 12 hours; IQR, 6–16) in 32/47 patients (68.1%). Peak of dose dyskinesias were reported by 21/45 individuals (46.7%).

The emotional condition of the patients was self defined as depression by 43/47 patients (91.5%): it was mild in 10 patients (21.3%), moderate in 20 (42.5%), and severe in 13 (27.7%). Memory impairment was reported by 33/44 patients (71.7%): it was mild in 8 (17.4%), moderate in 18 (39.1%), and severe in 7 (15.2%). Thirty-three of the 47 patients (70.2%) reported having problems in concentration: 8 considered them as being mild (17.0%), 17 as being moderate (36.2%), and 8 as being severe (17%). Thirty-one (67.4%) patients reported experiencing chronic pain, and 31 (66%) patients reported having sleep disorders (Table 2).

Delivery of MC

Most (38/45, 84.4%) of the patients preferred smoking *Cannabis sativa* flowers and leaves (5/45, 11.1%), or oil ingestion (4/46, 8.7%). Cigarettes or "joints" was the most common means of administration, reported by 42/46 (91.3%) of the MC users. The other modes of administration were oil (6/46, 13 %), vaporizer (2/46, 4.3%), and bong (a bong is a filtration device generally used for smoking cannabis, tobacco, or other herbal substances) (1/46, 2.2%). Four patients (4/46, 8.7%) reported using a combination of means of delivery, and 46/47 subjects (97.9%) reported using MC for medical purposes only. Only 1 subject (2.2%) reported that, in addition to medical reasons related to PD, he used MC for recreation.

The daily dose of MC ranged from 0.2 to 2.25 g/d, mean of 0.9 g (SD = 0.5; median = 0.75; IQR, 0.5–1.0) among the 43 subjects who responded to this item in the questionnaire. The duration of MC treatment in the entire study group of 47 persons ranged from 3 to 84 months, average of 19.1 months (SD = 17.0; median = 12; IQR, 6–24). Ten patients reported a need to increase the MC dose for better effects (21.3%). Five patients (5/47, 10.6%)

TABLE 2. The Motor and Nonmotor Symptoms at Baseline of Parkinson's Disease Reported by 47 Patients Treated by MC

Variable	Number	%
Rest tremor	29/45	64.4
Muscle stiffness	24/45	53.3
Gait disorders	29/45	64.4
Freezing of gait	24/45	53.3
Falls	22/47	46.8
Motor fluctuations	36/46	78.3
Depression	43/47	91.5
Memory impairment	33/46	71.7
Mental concentration complaints	33/47	70.2
Chronic pain	31/47	66
Sleep disorder	31/47	66

decided to stop MC treatment 3 to 12 months after initiating it (average, 7 months [SD = 3.9; median = 6; IQR, 4–10]). The reasons that were given for stopping the use of the MC were lack of desirable effect in 2 patients (4.3%), hallucinations in 2 (4.3%), and postural instability in 1 (2.2%).

Effects of MC on PD Symptoms

General Satisfaction and Overall Effectiveness

Most of the patients (37/45, 82.2%) reported that MC improved their overall symptoms, 2 reported no difference (4.4%), and 6 (13.3%) reported feeling worse (Table 3).

Main Effects of MC on Motor and Nonmotor Symptoms of PD

The MC treatment led to a reduction in complaints of falling (from 22/47 [46.8%] to 6/18 [33.3%]) ($P < 0.05$, $r^2 = 0.89$). Reduced general stiffness of the muscles and tremor were reported by 32/44 and 30/41 individuals (72.7% and 73.2%, respectively), whereas 12 persons with stiffness and 11 those with tremor reported no change, and none reported worsening ($P < 0.001$, for both; $r^2 = 0.62$ and 0.64, respectively). Pain reduction was reported by 35/43 individuals (81.4%), and 8 others reported no change (18.6%) ($P < 0.001$, $r^2 = 0.73$). Three quarters of the subjects (35/46, 76.1%) reported an improvement in mood, 10 reported no change (21.7%), and 1 (2.2%) reported a worsening of mood ($P < 0.001$, $r^2 = 0.64$). Most of the patients reported an improvement in sleep quality (33/46, 71.7%), 13 reported no change (28.3%), and 1 (2.2%) reported worsening of sleep ($P < 0.001$, $r^2 = 0.60$). The MC treatment had no subjective effects on memory in 23/40 patients (57.5%), it improved in 10 (25%), and worsened in 7 (17.5%). Urinary symptoms were not changed in most patients (24/33, 72.7%), were improved in 6 (18.2%), and worsened in 3 (9.1%) ($P > 0.05$ for both, $r^2 = 0.03$) (Table 3).

Duration of the MC treatment in the group of 47 persons ranged from 3 to 84 months, average of 19.1 months (SD = 17; median = 12; IQR, 6–24). Ten patients reported the need to increase MC dose after starting for better effects (21.3%).

A total of 5/46 patients (10.9%) spontaneously stopped MC treatment in the interval from 3 to 12 months, on average after 7 months, (SD = 3.9; median = 6; IQR, 4–10). Reasons given for no longer using MC were lack of desirable effect in 2 subjects (4.3%), hallucinations in 2 subjects (4.3%), and postural instability in 1 subject (2.2%).

Adverse Effects of MC

Twenty-eight patients (28/47, 59.6%) noted undesirable effects of MC, among them are mental problems (18/47, 38.3%) like confusion (8/47, 17%), anxiety (8/47, 17%), hallucinations (8/47, 17%), and short-term amnesia (3/46, 6.5%), and 1 patient (1/47, 2.1%) claimed to have developed psychosis (2.1%). Cough associated with MC smoking was reported by 15/43 patients (34.9%), 2/43 (4.7%) experienced dyspnea, 6/47 experienced dizziness (12.8%), and 7/45 experienced unsteadiness (15.6%) (Table 4).

DISCUSSION

This is a real-life survey based on reports of the patients under observation in 2 large movement disorder clinics in Israel. It was performed in the form of a standardized telephone interview. As expected, improvement in pain, sleep, and mood were reported by a significant percentage of patients. In the context of PD, the report of significant reduction of falls is an important finding, along with significant subjective improvement in muscle stiffness and tremor. We propose that this improvement is either an indirect effect of MC for example through its positive effect on fear of falling, as well as relaxation effect on mood and attention, which may improve executive function and decrease falls. This effect may also be associated with the euphoric, analgesic, and sedating effects of MC,[10] which may be different in different strains of the *Cannabis sativa* plant or, alternatively, be related to a placebo effect.[11]

The use of MC in clinical practice is controversial because of its psychotropic and antimotivational effects,[12,13] as well as the risk of addiction, reaching 9%,[14] and possible posttreatment abstinence phenomena.[15,16] Another concern with the use of the herbal form of MC relates to various concentrations of the main active ingredients (Δ-9-tetrahydrocannabinol and cannabidiol) in different strains of *Cannabis sativa* and/or *indica*.[17]

The MC treatment was accompanied by numerous adverse effects, as reported by 60.4% of our study participants, with negative psychotropic effects reported by 39.6% of them. However, no hospitalizations or severe adverse effects were reported. Treatment with MC was continued for a year or more in most cases, which may indicate a preponderance of benefits and satisfaction from this therapy. Importantly, the large percentage of subjects (10/47, 21.3%) who spontaneously increased the dose of MC might indicate a potential for addiction and abuse. In total, 12/61 patients (7/14 excluded and 5/47 included individuals, 19.7%) stopped using MC because of ineffectiveness or intolerable adverse effects.

Although a pathogenetic rationale for treating PD with MC is currently lacking, animal data support a role for cannabinoids in motor control, because of the high density of cannabinoid receptors in the basal ganglia.[18] The highest density of CB1 receptors was found in the globus pallidus and substantia nigra pars reticulata,[19] where the endocannabinoid anandamide concentration is 3 times higher in comparison with other brain regions.[20] There is colocalization of CB1 and D1/D2 receptors in striatal neurons,[21] and locomotor activity was found to be reduced by CB1 inhibition.[22] Controlled clinical studies on the therapeutic potential of MC are few and small, whereas pressure for expanding cannabis use spread by media and patients' communities and families is increasing. Currently, until further controlled studies are performed, and until the long-term results are known, the use of MC should remain limited to patients who failed the best possible established medical treatment.[23]

We acknowledge potential limitations of this study. The sample of patients was not selected through any systematic procedure or by random recruitment. The questionnaire was administered by telephone, and the rate of agreement to participate (61/98 patients,

TABLE 3. The Effects of at Least 3 Months of MC Treatment on Motor and Nonmotor Symptoms of Parkinson's Disease Reported by 47 Patients

Symptom	Considered As Relevant Item (n)	Reported As Not Relevant* (n)	Reported Improvement (n)				Reported As No Change** (n)	Reported Worsening** (n)	P	Effect Size (r^2)
			High	Moderate	Mild	Total**				
Motor symptoms										
Falls (yes/no)	18	2 (10%)	-	-	-	12 (66.7%)	6 (33.3%)	0	<0.001	0.89
Tremor	41	5 (10.9%)	10	9	11	30 (73.2%)	11 (26.8%)	0	<0.001	0.64
Muscle stiffness	44	3 (6.4%)	8	10	14	32 (72.7%)	12 (27.3%)	0	<0.001	0.62
OFF time	29	12 (29.3%)	2	7	9	18 (62.1%)	10 (34.5%)	1(3.4%)	<0.001	0.49
ON time	32	6 (15.8%)	1	9	7	17 (53.1%)	14 (43.8%)	1(3.1%)	<0.001	0.45
Dyskinesias	29	15 (34.1%)	3	4	7	14 (48.3%)	15 (51.4%)	0	<0.001	0.40
Freezing of gait	28	15 (34.9%)	4	6	3	13 (46.4%)	14 (50%)	1(3.6%)	<0.001	0.39
Gait disorder	40	7 (14.9%)	3	8	12	23 (57.5%)	14 (35%)	3(7.5%)	<0.001	0.34
Nonmotor symptoms										
Pain	43	3 (6.5%)	11	16	8	35 (81.8%)	8 (18.6%)	0	<0.001	0.73
Depressed mood	46	1 (2.1%)	15	13	7	35 (76.6%)	10 (21.7%)	1 (2.2%)	<0.001	0.64
Insomnia	46	1 (2.1%)	20	11	1	32 (69.6%)	13 (28.2%)	1 (2.2%)	<0.001	0.60
Appetite	31	1 (3.1%)	5	3	3	11 (35.5%)	20 (64.5%)	0	<0.001	0.31
Libido	36	2 (5.3%)	4	4	4	12 (33.3%)	24 (66.7%)	0	<0.001	0.28
Sexual life	34	3 (8.1%)	3	1	5	9 (26.5%)	25 (73.5%)	0	<0.01	0.21
Nausea	28	18 (39.1%)	1	3	2	6 (24.1%)	22 (78.6%)	0	<0.05 > 0.01	0.18
Constipation	33	12 (26.7%)	2	2	2	6 (18.2%)	26 (78.8%)	1 (3.0%)	<0.01	0.12
Attention	42	3 (6.7%)	3	5	6	14 (33.3%)	21 (50%)	7 (16.7%)	0.01	0.11
Memory	40	4 (9.1%)	2	2	6	10 (25%)	23 (57.5%)	7 (17.5%)	>0.05	0.04
Urination	33	9 (21.4%)	1	2	3	7 (18.2%)	24 (72.7%)	3 (9.1%)	>0.05	0.03

r^2 = effect size for the dependent samples *t* test: ≥0.2 small, ≥0.5 moderate, and ≥0.8 large.

*Proportion (%) from total number of responses (considered as relevant and not relevant together).

**Proportion (%) from considered as relevant only.

62.2%) suggests that this was a highly motivated population. Therefore, there is a potential for a bias to inflate the reports of effectiveness and to minimize adverse effects. Other limitations were the retrospective self-evaluations of the examinees regarding their status over time, given the memory and concentration problems of the elderly patients with PD. We did not take into consideration the time of the interview regarding "off" and "on," or the impact of the euphoric effect after MC. Formal neurocognitive assessment of the interviewed patients was not performed. There could also be possible errors in the interviewer-patient communications because of the difficulty to verify full comprehension of the questions during a telephone conversation. All subjects were chronically ill patients with PD with a range of related conditions, and the need for additional symptom relief may explain the reported positive MC effect.

In conclusion, the results of our study demonstrate that most of the users had found MC to improve their condition, and that MC treatment was safe, without major adverse effects. This pilot, 2-center survey reflects in part the current state of MC treatment for PD in Israel. The extent of use and the reported effects lend support to further development of safer and more effective drugs derived from the now intensively bred and widely cultivated *Cannabis sativa*.

TABLE 4. Adverse Effects Reported by 47 Parkinsonian Patients Treated by MC

Variable	Number	%
Confusion	8/47	17
Anxiety	8/47	17
Hallucinations	8/47	17
Amnesia	3/46	6.5
Psychosis	1/47	2.1
Any kind of psychotropic adverse effects	18/47	38.3
Cough	15/43	34.9
Dizziness	6/47	12.8
Unsteadiness	7/45	15.6
Breathlessness	2/43	4.7
Any physical adverse effects	21/47	44.7
Any adverse effects	28/47	59.6

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Geriatric Safety & Efficacy

Epidemiological Characteristics, Safety and Efficacy of Medical Cannabis in The Elderly
European Journal of Internal Medicine, 2018

A prospective study that analyzed the use of cannabis treatment in the elderly, measuring for pain intensity, quality of life, and adverse effects at six months follow-up. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). The study found that the therapeutic use of cannabis is safe and efficacious in the elderly population.

Study Population: 2736 patients aged 65+; at 6 months, 901 patients were eligible for follow-up and completed the survey
Strains Used: *Erez*, *Alaska*, *Avidekel* and other CBD-rich Tikun Olam strains (*Raphael*, *Metatron*, *Michael*)
Key Results:

- Reported pain significantly reduced from a median of 8/10 to 4/10
- Prior to treatment, 66.8% of patients reported high pain-intensity; at six months, this number decreased to only 7.6% of patients
- 93.7% of patients reported that the cannabis treatment improved their condition
- 35.1% of patients reported a decrease in the number of drugs taken or the dosage
- 18.1% of patients stopped using opioid analgesics or reduced their dose
- The most common reported side effects were dizziness (9.7%) and dry mouth (7.1%)

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Original Article

Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly

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ABSTRACT

Introduction: There is a substantial growth in the use of medical cannabis in recent years and with the aging of the population, medical cannabis is increasingly used by the elderly. We aimed to assess the characteristics of elderly people using medical cannabis and to evaluate the safety and efficacy of the treatment.

Methods: A prospective study that included all patients above 65 years of age who received medical cannabis from January 2015 to October 2017 in a specialized medical cannabis clinic and were willing to answer the initial questionnaire. Outcomes were pain intensity, quality of life and adverse events at six months.

Results: During the study period, 2736 patients above 65 years of age began cannabis treatment and answered the initial questionnaire. The mean age was 74.5 ± 7.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0–10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose.

Conclusion: Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative.

1. Introduction

The use of medical cannabis in recent years is growing substantially [1–3], with varied indications such as: chronic pain, chemotherapy-induced nausea and vomiting, multiple sclerosis, Alzheimer's disease, anorexia nervosa, anxiety, dementia, dystonia, Huntington's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), psychosis, Tourette syndrome, epilepsy and more [4–6]. The number of people aged 60 years and over is expected to double by 2025 worldwide and by 2050 in the United States [7–9]. Epidemiological data show that the older population constitutes a growing segment of medical cannabis users, ranging from approximately 7% to more than one third, depending on the country [10–12].

It is well known that aging is associated with substantial changes in pharmacokinetics and pharmacodynamics; for instance, hepatic drug clearance as well as renal elimination are both decreased in the elderly. Furthermore, aging is associated with increased body fat and decreased lean body mass [13,14], which increase the volume of distribution for lipophilic drugs, such as cannabis. Only a small number of studies have evaluated the pharmacokinetics of cannabis and cannabinoids in the elderly population [15–17]. Interaction of cannabis and other drugs is also largely unknown, as the current evidence is scarce. Concomitant administration of cannabis with other drugs that influence the hepatic CYP family enzymes may greatly alter the metabolism of the cannabinoids. This issue is especially important in the elderly population, where polypharmacy is common [18,19]. Common adverse events patients experience due to cannabis use include dizziness, euphoria, drowsiness, confusion and disorientation [4,20]. These events are particularly important in the elderly population, which may suffer from conditions such as dementia, frequent falls, mobility problems, hearing or vision impairments [21,22]. Thus, studies conducted on younger adults cannot be simply extrapolated to the elderly population.

Despite the significant rise in use, the current evidence on the efficacy and safety of medical cannabis in elderly is scarce. Only a small

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number of studies included elderly patients or analyzed them separately [20]. The aim of this study was to assess the characteristics of the older population receiving medical cannabis for a wide variety of diseases as well as evaluate the safety and efficacy of short and medium-term use.

2. Materials and methods

2.1. Study design and population

In Israel, most physicians who wish to prescribe medical cannabis for their patients send an authorization request to the Israel Medical Cannabis Agency (IMCA), a unit within the Israeli Ministry of Health (IMOH) [42]. Following the authorization for use patients are asked to contact one of the eight specified medical cannabis suppliers in Israel. To date, over 32,000 medical cannabis licenses were given in Israel, and approximately 33% of the patients receive their cannabis from "Tikun Olam Ltd.", the largest medical cannabis supplier in Israel.

The study included all the patients who initiated treatment with medical cannabis at "Tikun Olam" from January 20, 2015 to October 30, 2017, that were willing to answer the initial questionnaire and were 65 years of age or older at the initiation of treatment. The study was approved by the "Soroka University Medical Center" institutional review board (IRB) Committee. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All the patients gave informed consent to participate in the study.

2.2. Data sources and collection

As part of the routine treatment process, every patient who begins treatment with medical cannabis from "Tikun Olam" receives thorough instructions from a certified nurse on the use of the drug, possible side effects, route of administration and the regulatory process that the use of medical cannabis entails. The medical cannabis license specifies two possible routes of administration: oil and inflorescence, delivered as flowers, capsules and cigarettes. During this intake session, following the patient's consent, the patient's medical history, medication use, habits, detailed symptoms list, quality of life assessment, indication for cannabis treatment and demographic data are evaluated by the nurse. At the end of the intake session the nurse recommends, out of the 15 available cannabis strains, specific strains suitable to the patient's condition. Every patient is eligible for either a single strain or several strains.

All the patients were followed up at one month and at six months from treatment initiation by a telephone interview. The interview after six months is extensive and includes an assessment of adverse events, treatment satisfaction, changes in symptoms and in drug regimens.

2.3. Study outcomes

For safety analysis, at six months of treatment, we assessed the occurrence and frequency of any adverse events and specifically the following: headache, dizziness, nausea, vomiting, stomach ache, dry mouth, somnolence, weakness, confusion and disorientation, restlessness, hallucinations, red eyes, palpitations, drop in sugar levels and cough. The patients were asked to provide details of the incidence, duration and severity of the reported adverse event.

For efficacy analysis, after six months of treatment, we assessed the following parameters:

- Quality of life – global assessment by the patient using the Likert scale with five options: very good, good, not good nor bad, bad or very bad.
- Pain intensity – assessment by the numeric visual analog scale with an 11-point scale (0 = no pain, 10 = worst pain imaginable).
- Perception of the general effect of cannabis – global assessment by using the Likert scale with seven options: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration or significant deterioration.
- Treatment success – treatment success was defined as moderate or significant improvement in the patient's condition and compliance with the treatment.

2.4. Statistical analysis

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

When appropriate, univariate comparisons were made using χ^2-test or Fisher's exact test for categorical variables, and using Student's *t*-test or Mann–Whitney test for quantitative variables. Paired Wilcoxon test was used to compare ordinal variables.

A p-value of 0.05 or less (two-sided) was considered statistically significant. IBM SPSS software, version 24.0, was used for statistical analysis.

3. Results

3.1. Characteristics of the cohort

We identified 2736 patients over the age of 65 who initiated treatment with medical cannabis from "Tikun Olam" during the study period and were willing to answer the initial questionnaire. During the six months follow-up period, 564 patients died, 661 had been treated for less than six months, 297 stopped the treatment within six months and 28 patients switched to a different cannabis supplier. Thus, of the entire cohort, 1186 (43.3%) were eligible to answer the follow-up questionnaire after six months of treatment. Of the eligible patients, 901 (76.0%) responded to the questionnaire (Fig. 1). Of the entire population, 334 patients (12.2%) used medical cannabis from a different supplier prior to the initiation of treatment with "Tikun Olam". The elderly population comprises 34.2% of all the patients who initiated cannabis treatment with "Tikun Olam" in the study period (data not shown).

Table 1 shows demographic characteristics of the cohort. The mean age was 74.5 ± 7.5 years, with a slight female predominance (1463, 53.5%). The most common route of administration was oil (1022, 37.3%), followed by smoking (669, 24.4%) and vaporization (176, 6.4%).

Table 2 shows the indications for the medical cannabis. The most common indications were pain (1822, 66.6%) and cancer (1482, 60.8%), with a significant overlap between the two groups (cancer associated pain). All other indications comprise < 10% of the indications in the cohort. Cancer was also the most prevalent diagnosis at treatment initiation, followed by cardiovascular diseases (Supplementary data Table 1).

3.2. Strains of cannabis

Out of the 901 respondents at six months, 264 (29.3%) used one strain, 482 (53.5%) used two strains and 141 (15.6%) used between three to six strains. Most of the patients were using THC (tetrahydrocannabinol) rich strains of cannabis, whether the origin is from a *sativa* dominant species ("Erez" was used by 54.6% of the patients) or an *indica* dominant species ("Alaska" was used by 27.4% of the patients), regardless of the indication for cannabis use (Supplementary data Table 2). CBD (cannabidiol) rich strains were used by patients who suffer from pain (23.3%), chemotherapy side effects (30.9%), Parkinson's disease (45.7%) and inflammatory bowel disease (40%).

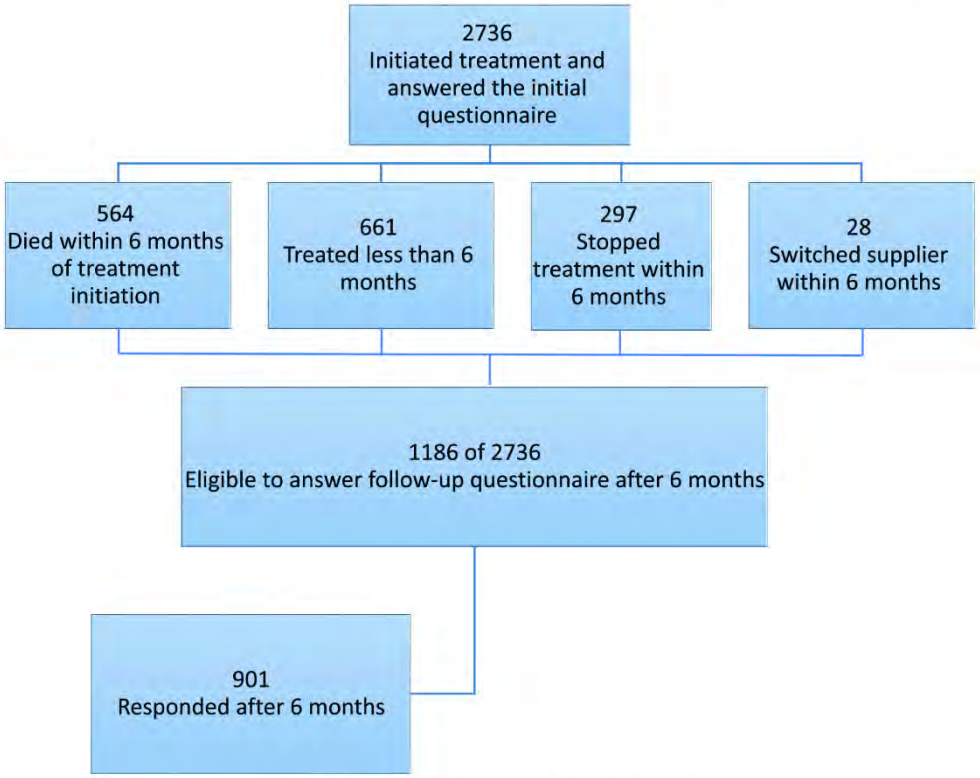

Fig. 1. Flow chart for the selection of the study population.

Table 1
Baseline characteristics of the patients at treatment initiation.

Variable	Number of patients (N = 2736)
Age (years)	65–74 – 1525 (55.7%) 75–84 – 885 (32.3%) ≥85 – 326 (11.9%)
Male	1273 (46.5%)
BMI	25.2 ± 5.0
Driving a car	986 (36.0%)
Approved monthly dosage of cannabis (grams)	28.8 ± 14.9
Approved route of administration	Oil - 737 (26.9%) Inflorescence - 640 (23.4%) Oil + Inflorescence – 1331 (48.6%)
Previous experience with cannabis	694 (25.4%)
Cigarettes smokers	424 (15.5%)
Number of regularly used medications	6 (3,9)
Number of days hospitalized in the past six months	0 (0,9)

Table 2
Indications for receiving cannabis prescription.

Indication	Number of patients (N = 2736)
Cancer associated pain	1001 (36.6%)
Nonspecific pain	821 (30.0%)
Cancer – chemotherapy treatment	661 (24.2%)
Parkinson's disease	146 (5.3%)
Others	49 (1.8%)
Post-traumatic stress disorder	21 (0.8%)
Crohn's disease	10 (0.4%)
Amyotrophic lateral sclerosis	9 (0.3%)
Compassion treatment	7 (0.3%)
Ulcerative colitis	5 (0.2%)
Alzheimer's disease	4 (0.1%)
Multiple sclerosis	2 (0.1%)

The following indications were aggregated into the category 'Others': epilepsy, tic disorder, multiple system atrophy, essential tremor, dementia, tension headache, cluster headache, peripheral vascular disease, myelodysplastic syndrome, fibromyalgia and rheumatoid arthritis.

3.3. Outcomes of cannabis treatment

The treatment with cannabis induced a significant reduction in the intensity of the reported pain, from a median of 8 on a scale of 0–10 to a median of 4 after six months of treatment (Fig. 2). Moreover, prior to the treatment, 573 (66.8% of the respondents) reported high pain intensity of 8–10 and at six months of treatment only 65 (7.6%) reported high pain intensity ($p < .001$).

The general assessment of quality of life was improved with the treatment. At baseline, 540 (79.3% of respondents) defined their quality of life as either bad or very bad, while after the treatment, 505 (58.6%) defined their quality of life as either good or very good ($p < .001$, Fig. 3).

In addition to the general improvement in the quality of life, the patients perceived the treatment as effective for their condition. When asked to globally assess the effects of the treatment on their condition, 844 patients (93.7% of the respondents) reported improvement and 378 of them (41.9% of the total respondents) defined it as a significant improvement (Fig. 4).

Overall, in 708 out of 1198 patients (59.1%), the treatment was considered successful (identified by at least a moderate improvement in their condition while still receiving treatment). The denominator included all the patients who answered the follow-up questionnaire and the patients who stopped treatment, for any cause.

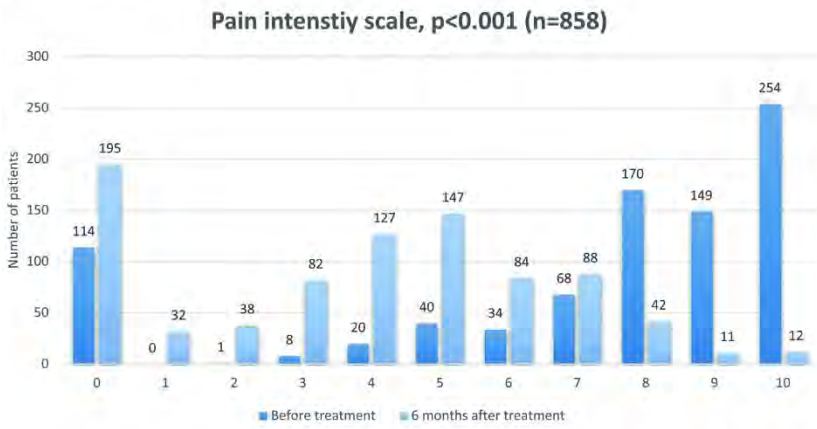

Fig. 2. Assessment of the pain intensity on a 0–10 scale before and after six months of cannabis therapy.

3.4. Cannabis safety and treatment adherence

Of the 297 that stopped the treatment (10.8% of the entire group, Fig. 1), 162 provided a reason for their discontinuation: 44 (1.6%) stopped the treatment because of ineffectiveness; 38 (1.4%) stopped due to adverse effects; 22 (0.8%) because of the bureaucracy that the treatment continuation entails; 25 (0.9%) because their indication for cannabis was temporary, such as chemotherapy treatments; 33 (1.2%) for other various reasons.

Of the 901 patients who responded to the follow-up questionnaire (still receiving the treatment at six months), 286 (31.7%) reported at least one adverse event due to the treatment after six months (Table 3). The most common adverse events were dizziness (9.7%) and dry mouth (7.1%). Of the 286 patients that reported adverse events, 33 (11.5%) rated their severity as 7–10 on a scale of 1–10).

Of the 515 patients that responded to the question regarding falls, 275 (53.4%) reported falling once or more in the six months preceding treatment initiation (median number of falls – 1, interquartile range [0–2]) and 113 (21.9%) reported falling once or more within the six months after treatment initiation (median number of falls – 0, interquartile range [0–0], $p < .001$).

3.5. Effect on medications regimen

Of the patients who responded to the questionnaire, 791 of the patients (87.8%) answered the questions regarding changes in medication regimen at six months: 463 patients (58.5%) reported no change in the total number of chronic medications they use, and 104 (13.1%) began treatment with a new chronic drug (Table 4). 278 patients (35.1%) reported a decrease in the number of drugs or their dosage, and 47 patients (5.9%) reported an increase in the number of drugs or their dosage. Moreover, 143 patients (18.1%) stopped using opioid analgesics or reduced their dose, while only 32 (4.0%) increased the dose of opioids or began using them after the initiation of cannabis treatment.

4. Discussion

In this study of elderly patients treated with medical cannabis, we have shown that the treatment is effective in improving pain and quality of life, was not associated with serious adverse events and was characterized by a low discontinuation rate.

4.1. Cohort characteristics

The characteristics of our cohort are different from those of previous studies. Several studies conducted in California found that most medical cannabis users were males and that the older population constitute a small minority [23–25]. Studies conducted in Canada and in an international survey showed similar results [12,26]. It should be noted that these studies were held between 2006 and 2012, and more recent data from six states in the United States showed a substantial increase in the

Fig. 3. Quality of life prior and six months after the initiation of cannabis treatment.

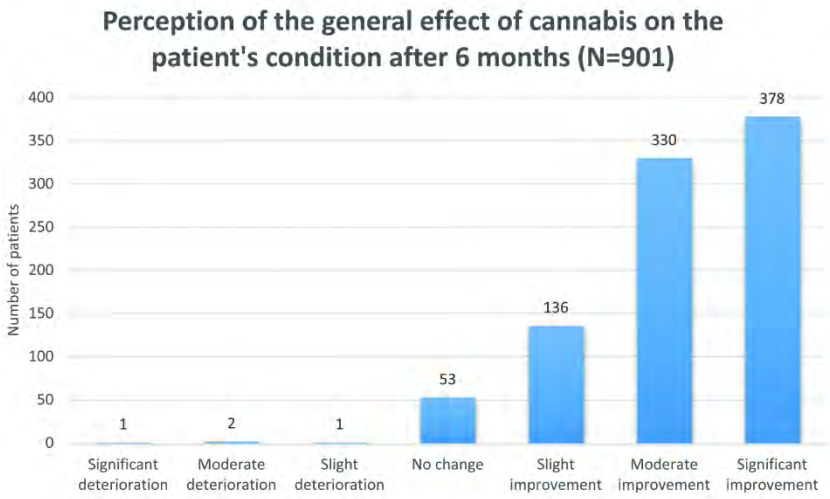

Fig. 4. Perception of the general effect of cannabis on the patient's condition after six months of treatment.

Table 3
Adverse events after six months of treatment with cannabis.

Adverse event	Number of patients (N = 901)
Dizziness	87 (9.7%)
Dry mouth	64 (7.1%)
Somnolence	35 (3.9%)
Weakness	21 (2.3%)
Nausea	20 (2.2%)
Confusion and disorientation	17 (1.9%)
Drop in sugar levels	16 (1.8%)
Cough	13 (1.4%)
Headache	10 (1.1%)
Vomiting	10 (1.1%)
Sore throat	9 (1.0%)
Restlessness	8 (0.9%)
Hallucinations	7 (0.8%)

use of cannabis by the elderly population [11]. Hazekamp et al. [10] reported that in the Netherlands between 2003 and 2010, a third of the medical cannabis population was the elderly. None of these studies analyzed the elderly population separately, or focused on its unique characteristics.

In the majority of the previous studies the main indications for using medical cannabis were chronic pain, anxiety, sleep disturbances and arthritis whereas cancer was the indication for only a small percent of the patients. In our cohort, pain was the most common indication, but cancer was almost as common; all other indications comprised only a small part of the cohort. The noted differences in study populations may be attributed to variable definitions of medical cannabis users. While we included only patients who received an authorization for cannabis from a physician, some of the other studies include patients who self-treated their conditions with cannabis [24,26]. Furthermore, we should emphasize that the nature of our cohort is largely determined by the indications and restrictions that the Israeli Ministry of Health sets to prescribing medical cannabis [27]. For example, sleep disturbances, arthritis and depression, also very common in the elderly population, are not authorized indications for medical cannabis use in Israel. The high death rate in our study might reflect the severity of the patients' condition and the fact that cannabis in Israel is mainly prescribed as a palliation treatment.

4.2. Cannabis efficacy

The rates of treatment satisfaction were high, with a significant relief of pain (most common indication) for most patients and a significant improvement in the overall quality of life. Clinically meaningful pain reduction is defined as a decrease of 2 points on a 0-to-10 numerical pain rating or a 30% improvement in pain intensity [28,29].

Table 4
Changes in drug regimens after six months of treatment with cannabis (n = 791).

Drug class	Number of patients who stopped using a certain drug	Number of patients who reduced the dose of a certain drug	Number of patients who increased the dose of a certain drug	Number of patients who added a new drug
Opioid analgesics[a]	114 (14.4%)	29 (3.7%)	6 (0.8%)	26 (3.3%)
Other analgesic drugs[b]	58 (7.3%)	17 (2.1%)	0 (0%)	6 (0.8%)
Benzodiazepines	59 (7.5%)	14 (1.8%)	1 (0.1%)	5 (0.6%)
Neuropathic pain drugs[c]	32 (4%)	14 (1.8%)	0 (0%)	6 (0.8%)
SSRI or SNRI	17 (2.1%)	2 (0.3%)	2 (0.3%)	7 (0.9%)
Antihypertensive drugs	90 (11.4%)	13 (1.6%)	4 (0.5%)	9 (1.1%)
Antidiabetic drug	23 (2.9%)	6 (0.8%)	0 (0%)	4 (0.5%)
Anti-psychotics	15 (1.9%)	1 (0.1%)	0 (0%)	9 (1.1%)
Anti-emetics	15 (1.9%)	2 (0.3%)	0 (0%)	0 (0%)
All other drugs	242 (30.6%)	36 (4.6%)	19 (2.4%)	76 (9.6%)
Total	665 (84.1%)	134 (16.9%)	32 (4%)	148 (18.7%)

SSRI – Selective Serotonin Reuptake Inhibitor; SNRI – Serotonin–Norepinephrine Reuptake Inhibitor.

[a] Includes: Morphine, Tramadol, Fentanyl, Oxycodone, Buprenorphine, Oxycodone-naloxone (Targin), Acetaminophen-Oxycodone (Percocet), Codeine-Caffeine-Paracetamol (Rokacet).

[b] Includes: NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), Paracetamol, Dipyrone.

[c] Includes: Pregabalin, Gabapentin, Amitriptyline.

Our study shows a median decrease of 4 points, which represents a substantial improvement. These findings are consistent with other similar studies [30–32]. A recent systematic review and meta-analysis found limited evidence for the use of cannabis as a treatment for chronic pain, but it should be noted that many of the reviewed studies used cannabinoid-based medicines and not herbal cannabis [33]. Nevertheless, large randomized trials are still needed to determine the utility of cannabis in chronic pain management. The significant improvement in the quality of life and the broad perception that cannabis is helpful for the patients' illnesses as found in our study are consistent with other reports [24,30].

4.3. Cannabis safety

Our study showed that cannabis treatment was not associated with a high number of adverse events in the short and medium-term of the follow-up. Only a small number of patients stopped the treatment due to adverse events. Most common adverse events were related to the central nervous system and the gastrointestinal system. These findings are consistent with other studies that showed that medical cannabis adverse events are mostly non-serious [4,31–34]. Dizziness is reported as one of the most common adverse events of cannabis use, as it was in our study. It is especially important in the elderly and frail population since dizziness can increase the risk of falls. Nevertheless, the number of falls in our study was significantly lower after the treatment in comparison to before treatment. Long-term adverse effects of chronic cannabis use should be elucidated in further studies, both in young and elderly populations.

After six months of treatment with cannabis, the vast majority of the patients stopped using a certain chronic medication or reduced the doses of the chronic drugs. The most common medications that were stopped or reduced were analgesics, and specifically opioids. Use of cannabis as a substitute for prescription medication has been shown by a number of studies, with higher rates of reduction and discontinuation than seen in our study [30,31,35–39]. Opioids are known to cause a plethora of serious adverse events especially in chronic use and in the elderly [40]. The adverse effects of opioids appear to be more frequent and severe than those induced by cannabis. However, randomized-controlled trials are still required to determine if cannabis can truly aid in reducing the impact of the opioid epidemic and in which ways [41].

4.4. Strengths and limitations of the study

The strengths of this study include the large cohort of patients and the focus on the elderly population. All the patients were seen by a physician prior to receiving their medical cannabis license, thus eliminating 'self-treating' patients. The study does not exclude specific diagnoses and reflects a large part of elderly medical cannabis users in Israel.

Our study has several limitations. The observational nature of our study can only allow us to determine association and not causality. We did not include elderly patients who began treatment with "Tikun Olam" and refused to answer our initial questionnaire. Our follow-up period is rather short, only six months. We also had a substantial number of patients who did not respond to the follow-up questionnaire (24%). Most of the patients are using a mixture of cannabis strains and we cannot determine the exact dose of active components each patient is receiving. The characteristics of our cohort are limited by the regulations of the Israeli Ministry of Health.

5. Conclusions

The older population is a large and growing part of medical cannabis users. Our study finds that the therapeutic use of cannabis is safe and efficacious in this population. Cannabis use can decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including from double-blind randomized-controlled trials, in this special population is imperative.

Conflict of interest statement

The study was supported by 'Tikun Olam Ltd.', cannabis supplier in Israel. Victor Novack serves in the scientific advisory board of 'Tikun Olam Ltd.' and Lihi Bar-Lev Schleider is an employee of 'Tikun Olam Ltd.'. Ran Abuhasira has no conflicts of interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.01.019.

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Palliative Cancer Care

Prospective Analysis of Safety and Efficacy of Medical Cannabis in Large Unselected Population of Patients with Cancer

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This study analyzed the data routinely collected as part of the treatment program of cancer patients treated with medical cannabis between 2015 and 2017. The most frequent types of cancer were breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%), and 51.2% of patients were 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%).

The study concluded that cannabis as a palliative treatment for cancer patients is a well-tolerated, effective and safe option to help patients cope with cancer-relatedsymptoms.

Study Population: 2,970 cancer patients; after six months of treatment, 1,211 patients were eligible for follow-up and responded to the questionnaire
Strains Used: Four categories of Tikun Olam strains - 1) *Midnight*, a 1:1 CBD:THC (~15%) strain, 2) *Avidekel*, a CBD-rich strain with <1% THC, 3) THC-rich indica strains with <.5% CBD, 4) THC-rich sativa strains with <.5% CBD; most patients consumed more than one strain
Key Results:

- 95.9% of patients reported an improvement in their condition
- Prior to treatment, 52.9% of patients reported their pain in the 8-10 interval; after six months, only 4.6% of patients reported this intensity
- Prior to treatment, only 18.7% of patients reported good quality of life; after six months, 69.5% of patients reported good quality of life
- The most improved symptoms were nausea and vomiting (91%), sleep disorders (87.5%), restlessness (87.5%), anxiety and depression (84.2%), pruritus (82.1%) and headaches (81.4%)
- 35.1% of patients decreased their drug consumption, including analgesics, sedatives, corticosteroids, and opioids
- At intake, 344 patients used opioids; after six months, 36% stopped taking opioids and 9.9% reduced their dose
- The most common side effects reported were dizziness (8%) and dry mouth (7.3%)

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

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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.

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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

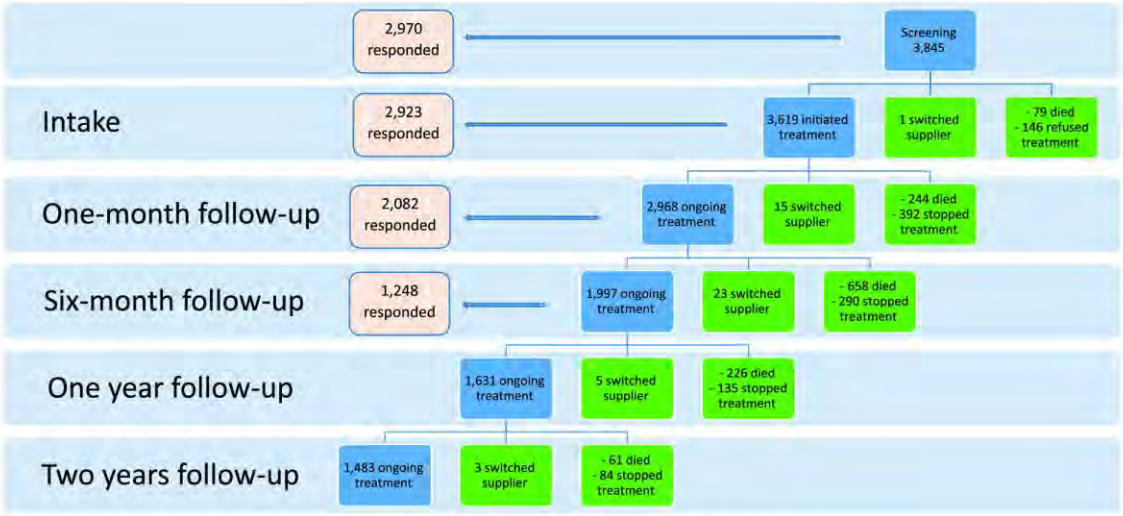


Fig. 1. The study population in the five follow-up periods.

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

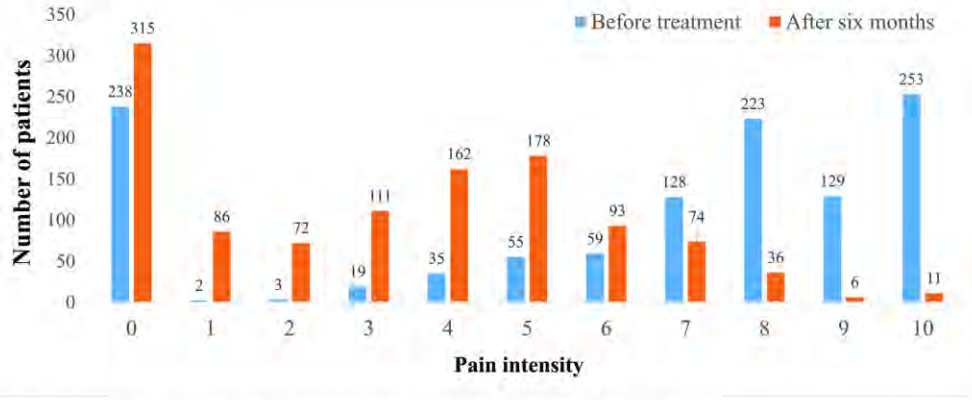


Fig. 2. Assessment of pain intensity. Pain intensity was assessed on 0–10 scale, before and after six months of cannabis therapy. $p < 0.001$.

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

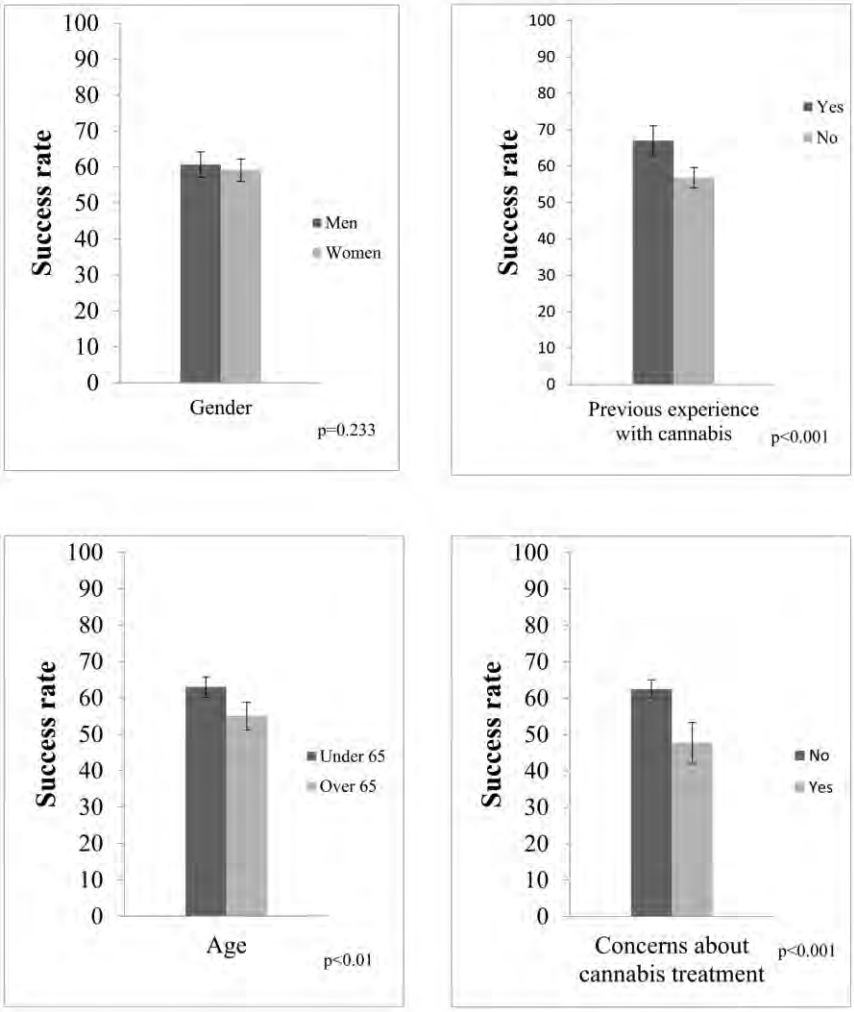


Fig. 3. Subgroup analysis of treatment success. Success is defined as at least moderate or significant improvement in the patient's condition and no cessation of treatment or serious side effects.

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

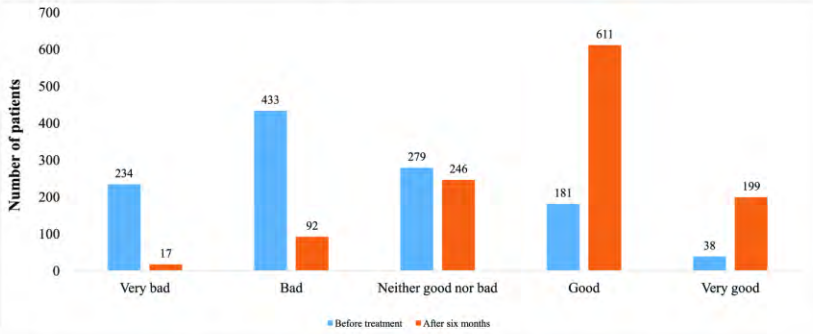
A. Disease prevalence and duration.

	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. $p < 0.001$.

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Complex Motor Disorders

Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders

Journal of Child Neurology, 2018

A clinical random trial examining the effects of *Avidekel* oil on dystonia and spasticity in children who suffer from cerebral palsy or genetic impairment. Most participants reported significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and quality of life.

Study Population: 20 patients with complex motor disorders (primarily cerebral palsy)
Strain Used: *Avidekel*, tested at 6:1 and 20:1 CBD:THC ratios
Key Results:

- CBD-enriched 5% cannabis oil with CBD:THC ratios of 6:1 and 20:1 are effective in reducing the severity of dystonia and spasticity, and improving motor function ability and quality of life
- All patients demonstrated mood and appetite improvement
- Patients treated with the 6:1 ratio oil demonstrated sleep improvement
- Patients treated with the 20:1 ratio oil demonstrated improvement in constipation

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Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders

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Abstract

A complex motor disorder is a combination of various types of abnormal movements that are associated with impaired quality of life (QOL). Current therapeutic options are limited. We studied the efficacy, safety, and tolerability of medical cannabis in children with complex motor disorder. This pilot study was approved by the institutional ethics committee. Two products of cannabidiol (CBD) enriched 5% oil formulation of cannabis were compared: one with 0.25% δ-9-tetrahydrocannabinol (THC) 20:1 group, the other with 0.83% THC 6:1 group. Patients aged 1 to 17 years (n = 25) with complex motor disorder were enrolled. The assigned medication was administered for 5 months. Significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and QOL was observed in the total study cohort, regardless of treatment assignment. Adverse effects were rare and included worsening of seizures in 2 patients, behavioral changes in 2 and somnolence in 1.

Keywords

dystonia, spasticity, movement disorders, cerebral palsy, cannabis, CBD, THC

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Complex motor disorders are a heterogeneous group of neurologic diseases that present with a combination of various types of abnormal movements and postures, including spasticity and dystonia. These abnormal movements and postures are usually associated with serious orthopedic problems, chronic pain, feeding difficulties, constipation, sleep disorder, epilepsy, and impaired quality of life. The etiology of complex motor disorder includes perinatal and postnatal brain injury due to various causes (perinatal hypoxic ischemic injury, stroke, traumatic brain injury, autoimmune diseases, poisoning), and neuro-genetic syndromes. Cerebral palsy is the most common form of childhood-onset complex motor disorder with multiple comorbidities. Prevalence estimates are 2 to 3 per 1000 live births.[1,2]

The goals of complex motor disorder treatment are improvement of quality of life achieved by decreasing abnormal movements and tone; prevention of musculoskeletal complications; pain relief; and resolution of sleep problems. Therapeutic options range from pharmacotherapy to medical and nonmedical invasive procedures, such as botulinum toxin injections, baclofen pump, selective dorsal rhizotomy, and deep brain stimulation.[2] The clinical effects of these therapies are variable and at times poorly sustained. Pharmacologic treatment of these conditions is limited, especially within the pediatric population: some medications may cause serious side effects and some are not approved for children. The mechanism of action of these medications, their dosage and side effects, as well as invasive treatment options have been reviewed by a few authors.[2-7] Cell-based therapy studies have been conducted in small trials using neural progenitor cells, umbilical cord mononuclear cells, and mesenchymal stem cells. Follow-up data have been reported.[8]

Medical cannabis is currently widely used. Cannabinoid-based therapies have been studied for a variety of illnesses, including neurologic diseases, especially drug-resistant epilepsy and movement disorders. The methodology and results of these studies are controversial.[9-20]

Cannabinoid-based medications are phytocannabinoids and synthetic cannabinoids, which have a number of mechanisms of action, including interaction with endocannabinoid receptors.[12] The endocannabinoid system is involved in the

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modulation of many physiological functions, including neurodevelopment, cognition, mood, motor control, feeding behavior, and pain.[15,16] The endocannabinoid system is a complex endogenous signaling system consisting of the 7-transmembrane domain and G protein–coupled receptors, their endogenous ligands, the endocannabinoids, and the enzymes responsible for endocannabinoid biosynthesis and degradation.[21] The most studied endocannabinoid receptors are cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), but endocannabinoids also have other molecular targets. Molecules that are a product of the degrading and biosynthetic pathway of endocannabinoids can interact with other receptors.[21]

Synthetic cannabinoids, such as nabilone, dronabinol, and Sativex, are cannabinoid receptor agonists with effects similar to THC. These have been approved for clinical indications, including spasticity, pain, and intractable epilepsy.[14,16]

Phytocannabinoids are derived from the Cannabis plant (marijuana), which contains more than 80 pharmacologically active cannabinoid compounds.[12,21] The 2 major phytocannabinoids are THC, the main psychoactive constituent of the marijuana plant, and cannabidiol (CBD), a phytocannabinoid that is believed to have no psychoactive properties[22] but more sedating, antiemetic, and analgesic ones.[16] All cannabinoids have the heterocyclic terpeno-phenolic chemical structure and are very lipophilic. They cross the blood-brain barrier, accumulate in lipid-laden tissues, including brain parenchyma and neuronal cell membranes specifically, and are released gradually into the bloodstream over days and weeks.[14,22] The onset of physiological and psychological effects varies depending on the method of treatment administration, with peak effects occurring 30 minutes after inhalation or 1 to 6 hours after ingestion, and lasting for 2 to 4 hours.[12] Cannabinoids are primarily metabolized by the hepatic cytochrome P450 enzyme system.

Acute physiologic effects of cannabis include tachycardia, elevated blood pressure, bronchial relaxation, dry mouth and throat, and conjunctival injection.[12] Psychological effects vary by individual and dose and may be positive (relaxation, euphoria, heightened perception, sociability, sensation of time slowing, increased appetite, and decreased pain) or negative (paranoia, anxiety, irritability, impaired short-term memory, poor attention and judgment, and hindered coordination and balance).[12] Hadland and Harris discussed the physiological and psychological effects of cannabis in chronic users[12] together with changes in cognition, brain structure and brain function, as well as the psychiatric side effects associated with cannabis use.[14]

The therapeutic potential of cannabinoids for movement disorders is based on the current understanding of cannabinoids' pharmacology and mechanism of action.[10,16] CB1 receptors are highly expressed in the central nervous system, especially in the basal ganglia. CB2 receptors are mostly expressed in the immune system, where they modulate inflammation, but they have also been found in the basal ganglia, in neurons within the dorsal vagal motor nucleus, the nucleus ambiguous, the spinal trigeminal nucleus, and microglia.[16]

Animal models suggest that CB1 agonists reduce overactivity of the globus pallidus interna and improve dystonia by reducing γ-aminobutyric acid (GABA) reuptake.[16] THC has been found to bind to CB1 and CB2 receptors. Cannabidiol does not activate CB1 and CB2 receptors, but inhibits endocannabinoid degradation and interacts with many other, non-endocannabinoid-signaling systems.[10] Cannabidiol may also potentiate some of THC's beneficial effects as it reduces the psychoactivity of THC, thus allowing patients to tolerate higher amounts of THC.[10] Cannabidiol may also supplement the antispastic effects of THC (eg, via local potentiation of glycine signaling, inhibition of endocannabinoid degradation, or retardation of demyelination through anti-inflammatory, antioxidant, and antiexcitotoxic mechanisms).[10] Kluger et al have reviewed preclinical and clinical studies regarding the therapeutic potential of cannabinoids for movement disorders.[16] Most of the studies included in the review had been conducted in adults. The efficacy of medical cannabis in pediatric complex motor disorder has not been established yet.

Methods

The present intervention study was approved by the Ethics Committee of the Wolfson Medical Center, Holon. The parents or legal guardian of the patient gave written informed consent before their child was enrolled in the study. The inclusion criteria included children aged 1-18 years, diagnosed with complex motor disorder with predominant dystonia, spasticity, or both; normal electrocardiogram; and a stable medical condition (no cardiorespiratory and renal deterioration). Exclusion criteria were surgical or medical intervention, such as orthopedic surgery or botulinum toxin injections, scheduled during the study period or in the 6 months prior to study entry, and psychiatric illness in a patient or first-degree relative.

Two products of cannabidiol-enriched 5% oil formulation of the cannabis strain Avidekel (Tikun Olam Ltd) were compared: cannabidiol-to-THC ratio 6:1 and cannabidiol-to-THC ratio 20:1. The aim was to check the difference in efficacy between cannabidiol and THC on spasticity, dystonia, sleep, mood, constipation, and appetite. One group of patients received cannabidiol to THC in a ratio of 20:1 (ie, a minimal amount of THC) and the other group received cannabidiol to THC in a ratio of 6:1 (ie, a higher amount of THC).

The analysis and quality assurance followed the high standards of ISO-9001, HACCP–Hazard Analysis, GAP–Good Agricultural Practice, Pesticides & microbiology Control (Tikun Olam Ltd).

Two types of medication were randomly selected. The initial dose was 1 drop 3 times daily (cannabidiol 6 mg and THC 0.99 mg for the 6:1 group and cannabidiol 6 mg and THC 0.3 mg daily for the 20:1 group). The dose was up-titrated gradually at different rates until one of the following was observed: intolerance, serious side effects, maximum THC dose of 15 mg per day, or the end of the study. The medication was administered either orally or by feeding tube 2 to 3 times daily for 5 months. Treatment was started after 2 months of observation at the second visit in order to exclude changes due to disease evolution. All other medications, including antiepileptic drugs and medication for dystonia and spasticity, were continued. To prevent side effects due to the combination of benzodiazepines and medical cannabis, clonazepam was reduced in 5 patients, but was restarted in 3 of them because of severe withdrawal symptoms.

Assessments were performed at baseline and at every monthly visit thereafter. Baseline data collected for each participant included a medical and neurologic history, electroencephalogram (EEG), and blood tests: complete blood count, biochemistry tests, liver function tests, creatinine phosphokinase (CPK). During each visit, the patient was examined by a pediatric neurologist and a physical therapist trained in pediatric movement disorders. Each patient was assessed by the Berry Albright Dystonia scale,[23] Gross Motor Function Measure,[24,25] parents' numeric rating scale (NRS)[26] for spasticity, dystonia, estimation of mood, sleep, appetite, and constipation, visual analog scale (VAS) for pain, Cerebral Palsy Child (CPCHILD) questionnaire[27] (chapter 6), and questionnaires for adverse effects. Electrocardiogram (ECG), EEG, and blood tests were repeated for each patient at baseline and at the end of the study. The neurologist was available 24 hours a day in order to manage any side effects of the medication.

Statistical Analysis

Data were recorded on paper forms and uploaded to Excel spreadsheet. Data analyses were conducted using SPSS version 22 for Windows. As this was a pilot study, a power calculation was not performed. Within the scope of the study, it was estimated that it was feasible to recruit 25 participants into the trial. Continuous data are summarized as mean ± standard deviation values with corresponding 95% confidence intervals. Continuous variables were compared by group using the *t* test or Mann-Whitney *U* as appropriate. Within-group before vs after comparisons were made using the paired *t* test or the Wilcoxon signed ranks test as appropriate. Nominal variables are presented as frequency counts and were compared by group using the chi-square test. All tests were 2-sided and considered significant at $P < .05$.

Results

Twenty-five patients were recruited. A total of 20 patients completed the 5-month study. Five patients were withdrawn by their parents because of various causes. One patient from the 6:1 group developed severe irritability and inappropriate crying and laughing under 60 mg of cannabidiol/10 mg of THC; the titration was 3 drops weekly. Two patients showed lack of improvement after a 2-month treatment period. One patient demonstrated worsening of seizures, and 1 patient did not start the treatment because of emergency orthopedic surgery between visits 1 and 2. These patients were analyzed as intention to treat.

Details of the participants are shown in Tables 1 and 2. The mean age was 6.51 years (range 1-16.8 years), with 16 males and 9 females. Nineteen patients were diagnosed with cerebral palsy, 5 patients had a neurogenetic syndrome and 1 child had complex motor disorder due to traumatic brain injury. The Gross Motor Function Classification System (GMFCS) score was 5 in 17 patients (68%), 4 in 7 (28%), and 3 in 1 (4%). Six patients had epilepsy or a history of seizures prior to the study. An abnormal electroencephalogram was found in 7 patients, and all were treated with antiepileptic medications, including phenobarbital, clonazepam, lamotrigine, topiramate, and valproic acid. Four patients were treated with trihexyphenidyl, 5 with baclofen, 1 with tetrabenazine, and 1 had a baclofen pump. The medication was administered by feeding tube in 6 patients. The maximal dose of cannabidiol and THC was 90 mg/d and 14.85 mg/d relatively in the 6:1 group and 210 mg/d and 10.50 mg/d in the 20:1 group (shown in Table 1).

Table 1. Baseline characteristics of the Study Population.

Measure	6:1 group	20:1 group	*P* value
Age, y	7.15 ± 4.63	5.71 ± 4.97	.46
Mean THC, mg/d (visit 7)	6.27 ± 7.20	3.67 ± 3.61	.32
Mean CBD, mg/d (visit 7)	38 ± 43.67	91.75 ± 69.11	.06
Mean THC, mg/kg/d (visit 7)	0.61 ± 0.69	0.28 ± 0.24	.22
Mean CBD, mg/kg/d (visit 7)	3.73 ± 4.18	5.53 ± 4.85	.42
Absolute THC, mg/d	14.85	10.50	
Absolute CBD, mg/d	90	210	
Maximal THC, mg/kg/d	1.78	0.76	
Maximal CBD, mg/kg/d	10.79	15.22	
Female sex, %	35.7	36.4	.97
Diagnosis, %, CP/G	71.4/28.6	81.8/18.2	.55
GMFCS, %			.51
3	7.10	0.00	
4	21.40	36.40	
5	71.40	63.60	
FT, %	21.4	27.3	.73

Abbreviations: CBD, cannabidiol; CP, cerebral palsy; FT, feeding tube; G, neurogenetic syndrome; GMFCS, Gross Motor Function Classification System; THC, δ-9-tetrahydrocannabinol.

Table 3 presents Berry Albright Dystonia scale; Gross Motor Function Measure; Cerebral Palsy Child questionnaire; numeric rating scale for spasticity, mood, appetite, stool function, and sleep; and visual analog scale scores by visit. Except for numeric rating scale for dystonia, changes in scores were not observed between visit 1 and visit 2. Numeric rating scale for spasticity, Gross Motor Function Measure overall and Dimension A (laying and rolling) and Dimension B (sitting) improved from baseline in the entire study population regardless of treatment assignment. The cohortwide improvement in dimension A appears to be attributable to the improvement in the 6:1 group.

The Cerebral Palsy Child questionnaire for quality of life (QOL) improved in the total study cohort. Additionally, numeric rating scale for mood, stool function, sleep, and appetite statistically improved in the whole group. The overall improvement in constipation appears to be driven by the improvement in the 20:1 group, whereas the overall change in sleep is driven by the improvement in the 6:1 group. Visual analog scale scores improved significantly in the whole group as did pain duration and frequency.

Dystonia and QOL improved in the 20:1 group under a mean dosage of THC 3.67 ± 3.61 mg/d, 0.28 ± 0.24 mg/kg/d, and cannabidiol 91.75 ± 69.11 mg/d, 5.53 ± 4.85 mg/kg/d. In contrast, in the 6:1 group, QOL improved under a mean dosage of THC 6.27 ± 7.20 mg/d, 0.61 ± 0.69 mg/kg/d, and cannabidiol 38 ± 43.67 mg/d, 3.73 ± 4.18 mg/kg/d.

Table 2. Characteristics of the Study Population.

Patients	CPK, start	CPK, end	Medications at the start	Medications at the end	EEG, start	EEG, end	Seizure
6:1 group							
1	NA	117 (20-117)	Clonazepam	Clonazepam	EA	NA	History
2	NA	NA	No	No	N	NA	No
3	NA	NA	Neuleptil	Neuleptil	N	NA	No
4	NA	NA	No	No	N	N	No
5	NA	470	No	No	N	N	No
6	NA	NA	No	No	N	NA	No
7	213 (20-200)	233 (20-200)	Baclofen, clonazepam, trihexyphenidyl	Baclofen, clonazepam, trihexyphenidyl	EA	EA	No
8	NA	NA	Valproic acid	Valproic acid	EA	NA	Current
9	NA	NA	Clonazepam	No	NA	NA	No
10	122 (0-150)	146 (0-150)	Topiramate, lamotrigine	Topiramate, lamotrigine	EA	EA	Current
11	NA	NA	Trihexyphenidyl, baclofen pump	Trihexyphenidyl, baclofen pump	NA	NA	No
12	NA	NA	Adderall, clonidine, melatonin, colchicine	Adderall, clonidine, melatonin, colchicine	NA	NA	No
13	N	NA	Clonazepam, Baclofen, dantrolene, trihexyphenidyl	Clonazepam, baclofen, dantrolene, trihexyphenidyl	N	NA	History
14	NA	N	Clonazepam, baclofen, lamotrigine, Nozinan, omeprazole	Clonazepam, baclofen, lamotrigine, Nozinan, omeprazole	N	N	Current
20:1 group							
15	351 (0-160)	NA	Trihexyphenidyl	Clonazepam, risperidone	NA	NA	No
16	157 (0-157)	NA	Baclofen, clonazepam	Clonazepam	N	NA	No
17	NA	NA	Clonazepam, trihexyphenidyl, tetrabenazine, Scopoderm patch	Clonazepam, trihexyphenidyl, tetrabenazine, Scopoderm patch	NA	NA	No
18	177 (160)	NA	Clonazepam	Trihexyphenidyl	EA	NA	No
19	104	170 (0-145)	Clonazepam, fluoxetine	Clonazepam, fluoxetine	N	NA	No
20	N	NA	Clonazepam	No	NA	NA	No
21	NA	NA	Phenobarbital	Phenobarbital	EA	NA	No
22	N	NA	Levetiracetam, clonazepam	Levetiracetam, valproic acid, clonazepam	EA	EA	Current
23	180 (0-150)	159 (0-150)	Clonazepam	No	N	NA	No
24	NA	NA	Phenobarbital, omeprazole	Phenobarbital, omeprazole	N	NA	Current
25	N	N	No	No	N	N	No

Abbreviations: THC, δ-9-tetrahydrocannabinol; CBD, cannabidiol; EA, epileptic activity; N, normal; NA, not available.

A total of 15 patients continued medical cannabis therapy. All available EEGs indicated neither benefit nor worsening. There were no changes in ECG or blood tests. Of the 4 patients with elevated CPK before the onset of treatment and available CPK titers, 1 patient's CPK level decreased and the 3 others increased by the end of the study (Table 2). Abnormalities of hepatic aminotransferase levels were found in 1 patient, before the study. There was no worsening during the study period. Reported side effects included a worsening of seizures in 2 patients who had partially controlled seizures before the intervention. This was not accompanied by a worsening of epileptic activity on EEG. Two patients, 1 from each group, developed behavioral changes: the first child from the 6:1 group manifested excitation due to rapid titration of the medication, with complete normalization after tapering. The second patient developed mood fluctuations under a combination of a morning dose of Ritalin LA 20 mg and cannabidiol-THC 20:1. Termination of methylphenidate was effective in controlling the behavioral changes. Additionally, 1 patient from the 6:1 group developed somnolence at a cannabidiol dose of 18 mg/d (1.8 mg/kg/d) and THC dose of 2.97 mg/d (0.3 mg/kg/d). Dose reduction improved the patient's alertness, and the patient was maintained on the lower dose.

Discussion

There are only 2 studies regarding the efficacy and safety of cannabinoids in pediatric movement disorders. In 2004 Lorenz demonstrated the efficacy of dronabinol (synthetic pure δ-9-tetrahydrocannabinol [THC] in an oil-filled soft gelatin capsule) in 8 patients with neurologic diseases of different etiology (neurodegenerative, mitochondrial diseases, post-hypoxic state, epilepsy, posttraumatic reaction).[9] He reported that dronabinol reduced spasticity and dystonia, increased patient interest in his/her surroundings, and had an anticonvulsive effect.

Kuhlen et al reported positive effects of dronabinol in 16 patients, aged 1.3-26.6 years, in specialized pediatric palliative care, with complex neurologic conditions and resistant

Table 3. Outcome Measures Scores.[a]

	Visit 1	Visit 2	Visit 4	Visit 7	*P* value
All patients					
BADS	15.68 ± 6.23	15.52 ± 5.92	14.90 ± 5.66	12.69 ± 4.62	.009
NRS for dystonia	7.36 ± 2.63	8.32 ± 1.35	6.83 ± 2.40	6.40 ± 2.68	.002
NRS for spasticity	8.29 ± 1.16	8.08 ± 1.55	6.83 ± 2.35	6.60 ± 2.43	.002
GMFM total	11.49 ± 16.20	12.16 ± 15.39	11.16 ± 10.23	14.71 ± 15.06	.001
GMFM lay	34.82 ± 3.42	36.63 ± 29.63	38.40 ± 28.44	44.39 ± 29.88	.001
GMFM sit	13.13 ± 21.44	15.60 ± 22.21	14.10 ± 17.32	19.72 ± 23.27	.009
QOL	40 (0-80)	40 (0-80)	60 (20-80)	60 (20-80)	.036
VAS	5.68 ± 3.14	5.98 ± 2.88	4.70 ± 3.09	4.27 ± 2.65	.022
Mood	4.56 ± 1.64	4.68 ± 1.65	4.96 ± 1.57	5.32 ± 1.35	.018
Appetite	5.00 ± 1.67	4.68 ± 2.00	5.00 ± 1.91	5.32 ± 1.80	.027
Stool	4.44 ± 2.02	4.60 ± 1.98	5.04 ± 2.01	5.74 ± 1.69	.021
Sleep	3.48 ± 2.00	3.80 ± 1.80	4.54 ± 1.56	5.08 ± 1.19	.002
6:1 group					
BADS	14.64 ± 7.58	14.93 ± 6.56	13.97 ± 6.89	11.97 ± 5.39	.951
Dystonia NRS	6.64 ± 3.18	7.86 ± 1.23	6.33 ± 2.64	6.57 ± 2.17	.087
NRS spasticity	8.21 ± 1.18	7.86 ± 1.56	6.62 ± 2.06	6.93 ± 1.86	.011
GMFM total	12.57 ± 20.38	12.91 ± 19.21	10.16 ± 10.08	15.33 ± 17.69	.284
GMFM lay	32.92 ± 21.8	34.18 ± 31.5	34.54 ± 27.67	41.87 ± 31.50	.047
GMFM sit	14.88 ± 26.05	16.67 ± 26.47	12.18 ± 15.59	22.42 ± 27.07	.695
QOL	46.67 ± 21.46	43.08 ± 21.36	60.00 ± 19.07	55.38 ± 20.56	.011
VAS	6.22 ± 2.87	6.24 ± 3.18	4.78 ± 3.36	4.74 ± 2.63	.426
Mood	4.43 ± 1.60	4.36 ± 1.44	4.92 ± 1.61	5.29 ± 1.50	.057
Appetite	4.82 ± 1.83	4.72 ± 1.85	5.30 ± 1.57	5.36 ± 1.57	.098
Stool	5.42 ± 1.87	5.14 ± 1.79	5.38 ± 2.02	5.69 ± 1.80	.751
Sleep	3.43 ± 1.87	3.71 ± 1.73	5.08 ± 0.95	5.36 ± 0.63	.011
20:1 group					
BADS	17.00 ± 3.87	16.27 ± 5.13	16.00 ± 3.80	13.55 ± 3.56	.021
Dystonia NRS	8.27 ± 1.35	8.91 ± 1.30	7.36 ± 2.11	6.18 ± 3.31	.036
NRS spasticity	8.40 ± 1.17	8.36 ± 1.57	7.09 ± 2.74	6.18 ± 2.06	.048
GMFM total	10.12 ± 9.28	11.21 ± 9.29	12.33 ± 10.76	13.93 ± 11.69	.054
GMFM lay	37.25 ± 29.91	39.75 ± 28.25	42.96 ± 29.99	47.59 ± 28.85	.079
GMFM sit	11.36 ± 14.60	14.24 ± 16.44	16.36 ± 19.69	16.51 ± 18.60	.277
QOL	30.91 ± 20.71	34.55 ± 28.41	49.09 ± 16.40	57.78 ± 12.02	.023
VAS	4.91 ± 3.49	5.61 ± 2.52	4.58 ± 2.89	3.62 ± 2.67	1
Mood	4.73 ± 1.74	5.09 ± 1.87	5.00 ± 1.61	5.36 ± 1.21	.185
Appetite	5.25 ± 1.49	4.63 ± 2.33	4.63 ± 2.33	5.25 ± 2.19	.891
Stool	3.18 ± 1.47	3.91 ± 2.07	4.64 ± 2.01	5.80 ± 1.62	.011
Sleep	3.55 ± 2.25	2.91 ± 1.92	3.91 ± 1.92	4.73 ± 1.62	.107

Abbreviations: BADS, Barry Albright Dystonia Scale; GMFM, Gross Motor Function Measure; NRS, numeric rating scale; QOL, quality of life; VAS, visual analog scale.
[a]Results for all measurements are presented as mean ± SD.

spasticity.[15] The dosages necessary to achieve a therapeutic effect varied from 0.08 to 1.0 mg/kg/d with a median of 0.33 mg/kg/d. Side effects were rare and consisted only of vomiting and restlessness. Though the study was prospective and side effects were closely monitored, the efficacy of dronabinol was assessed by the parents, nurses, and physiotherapists, without standardized testing.

Our pilot study indicates that cannabidiol-enriched 5% oil formulation of cannabis with ratios of cannabidiol to THC of 6:1 and 20:1 is effective in children with complex motor disorder by reducing the severity of dystonia and spasticity, and improving motor function ability and quality of life. All participants demonstrated mood and appetite improvement, patients who received a product with cannabidiol-to-THC ratio of 20:1 demonstrated improved constipation, whereas subjects treated with higher amount of THC (cannabidiol-to-THC ratio of 6:1) demonstrated sleep improvement.

We did not find a difference between the 2 medications in the antispastic effect. Spasticity reduction in our patients was achieved by a median dosage of THC of 0.44 mg/kg/d compared to 0.33 mg/kg/d in the Kuhlen et al study.

Our findings demonstrate that medical cannabis can be administered over at least a 5-month period without severe side effects or aggravating existing symptoms. The worsening of seizures in 1 patient may be related to the reduction of the dose of clonazepam, or to the natural history of the disease. We did not find any interaction of cannabis with the underlying medications, including clonazepam. We observed mood changes in

1 patient treated with methylphenidate. Mood deterioration has not been previously reported in patients treated with a combination of THC and methylphenidate.[28]

Limitations of our study include the small sample size, which makes rejection of the null hypotheses difficult. Additionally, titration of the medication was slow, so that the total time on the optimal dose was limited. This may lead to an underestimation of treatment efficacy. Most importantly, there was no concurrent control group, making it impossible to rule out time as a cause of symptom improvement. Moreover, the placebo effect is a well-known phenomenon in pharmacologic treatment including cannabis[15,29] and could not be excluded in our patients. Lack of verbal contact with most of our patients made the assessment of cognitive impact and psychological side effects difficult. It remains questionable whether tolerance would have developed in these patients. On the other hand, overall improvement in several outcome measures was observed despite the small sample size in the total study cohort. Additional studies using concurrent, non-cannabis-treated controls are needed to more comprehensively assess the efficacy of medical cannabis in children with complex motor disorder.

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Author Contributions

SL made a substantial contribution to the design of the work, as well as acquisition, analysis and interpretation of data. Drafted the article. Approved the version to be published. LBLS made a substantial contribution to the concept and design of the work. NS, LL, YT and IL made a substantial contribution to the acquisition of data. TLS revised the article critically for important intellectual content. LB made a substantial contribution to the concept and design of the work; acquisition, analysis and interpretation of data. Drafted the article and approved the version to be published.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was conducted in accordance with all ICH-GCP guidelines 0101-14 wome.

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Multiple Sclerosis

Avidekel Cannabis Extracts and Cannabidiol are as Efficient as Copaxone in Suppressing EAE in SJL/J Mice

Inflammopharmacology, 2018

This study compared the efficacy of purified CBD, extracts of CBD-rich *Avidekel*, and Copaxone (glatiramer acetate), an immunosuppressive medication that is used to alleviate the symptoms of multiple sclerosis (MS).

Study Population: Lab mice
Strain Used: *Avidekel*
Key Results:

- CBD and *Avidekel* extracts are as efficient as Copaxone in alleviating the symptoms of EAE (animal model of brain inflammation) in lab mice; thus,
- *Avidekel* may be useful in the treatment of MS symptoms

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Inflammopharmacology

ORIGINAL ARTICLE

Avidekel Cannabis extracts and cannabidiol are as efficient as Copaxone in suppressing EAE in SJL/J mice

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Abstract
Multiple sclerosis (MS) is an autoimmune disease leading to the destruction of myelin with consequent axonal degeneration and severe physical debilitation. The disease can be treated with immunosuppressive drugs that alleviate the symptoms and retard disease aggravation. One such drug in clinical use is glatiramer acetate (Copaxone). The non-psychotropic immunosuppressive cannabinoid compound cannabidiol (CBD) has recently been shown to have beneficial effects on experimental autoimmune encephalomyelitis (EAE). The aim of our study was to compare the efficacy of CBD and standardized extracts from a CBD-rich, Δ^9-THC^{low} *Cannabis indica* subspecies (Avidekel) with that of Copaxone. Our data show that CBD and purified Avidekel extracts are as efficient as Copaxone to alleviate the symptoms of proteolipid protein (PLP)-induced EAE in SJL/J mice. No synergistic effect was observed by combining CBD or Avidekel extracts with Copaxone. Our data support the use of Avidekel extracts in the treatment of MS symptoms.

Keywords Avidekel extracts · Cannabidiol (CBD) · Cannabis · Experimental autoimmune encephalomyelitis (EAE) · Immunosuppression

Abbreviations

CBD	Cannabidiol
CNS	Central nervous system
EAE	Experimental autoimmune encephalomyelitis
MS	Multiple sclerosis
PLP	Proteolipid protein

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). The early phase of MS is characterized by relapses, while the later phase by progressive disability. Findings from animal models and immunological studies of patients with MS suggest that a peripheral immune response targeting various myelin components drives the disease process during the early phase, whereas immune reactions within the CNS dominate the progressive phase (Hemmer et al. 2015). Accordingly, treatment protocols have been developed based on immunosuppressive drugs, the aim of which is to alleviate the clinical symptoms and slow down disease progression (Reich et al. 2018). One outstanding drug in MS therapy is glatiramer acetate (Copaxone) that was accidently discovered by the research group of Prof. Ruth Arnon (Teitelbaum et al. 1971) when they tried to produce a synthetic antigen capable of inducing experimental autoimmune encephalomyelitis (EAE), an animal model of autoimmune inflammatory CNS disorders, including MS. Instead, they observed that Copaxone was protective in EAE models. Subsequent clinical evaluation resulted in FDA approval for the use of Copaxone in relapsing–remitting MS in 1996 (Arnon 1996).

Cannabidiol (CBD), the major non-psychotropic component of Cannabis, has long been known to have strong anti-inflammatory activities and has been shown in animal models to have beneficial effects on various autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease (Burstein 2015; Gallily et al. 2015; Malfait et al. 2000; Weiss et al. 2008). CBD has also been shown to alleviate the clinical symptoms of myelin oligodendrocyte glycoprotein (MOG_{35-55})-induced EAE in C57BL/6 mice (Rahimi et al. 2015). A major disadvantage of CBD is its bell-shaped dose–response curve resulting in a limited therapeutic dose range (Gallily et al. 2015;

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Malfait et al. 2000; Weiss et al. 2008). In contrast to purified CBD, standardized plant extracts of the *Cannabis indica* subspecies Avidekel (formerly known as Clone 202), which is highly enriched in CBD (18%) and barely contains the psychotropic Δ^9-tetrahydrocannabinol (THC) (1%), provide a correlative anti-inflammatory and anti-nociceptive dose–response when applied intraperitoneally or orally in an inflammatory mouse model (Gallily et al. 2015). The Avidekel extracts also contain trace amounts of other cannabinoids that might act in synergy with CBD (Gallily et al. 2015). Since Avidekel does not have psychotropic effects and also exhibit pain relieving activities (Gallily et al. 2015), it was worth studying the effects of Avidekel extracts on clinical symptoms of a mouse EAE animal model. Indeed, we found that Avidekel extracts had similar suppressive activity as purified CBD and Copaxone. No further suppression was observed when combining CBD or Avidekel extracts with Copaxone, suggesting for maximum suppressive effects using either drug alone.

Materials and methods

Materials

Purified CBD was purchased from THC Pharm. GmbH, Frankfurt, Germany. Flowers from the Avidekel *Cannabis indica* subspecies (formerly clone 202), which are rich in CBD (18%) while low in Δ^9-THC (1%) (Gallily et al. 2015), were supplied by Tikun Olam Company (A government-approved farm growing Medicinal Cannabis), Israel. CBD-enriched extract was prepared from the flowers of Avidekel grown under controlled temperature and light conditions. 100% ethanol (10 ml) was added to the chopped Avidekel dry flowers (100 mg) for 24 h with occasional shaking at room temperature. Following filtration, samples were taken for analysis as previously described (Gallily et al. 2015). Ethanol solutions of Avidekel extracts (10 mg/ml–20 mg/ml) were kept at − 20 °C in the dark. The extract was evaporated on Rotavapor (BÜCHI Labortechnik AG, Switzerland). For intraperitoneal injection, the dried Avidekel extract was emulsified in a vehicle composed of ethanol:Cremophor:saline at a 1:1:18 ratio. Purified CBD was emulsified in the same vehicle. Copaxone solution (20 mg/ml, Teva Pharmaceutical Industries Ltd, Israel) was diluted in PBS just before subcutaneous (s.c) administration.

Mice

Female SJL/J mice (Harlan Laboratories) were 6–7 weeks old at the beginning of the experiments. The mice were maintained at a constant temperature (20–21 °C) and a 12-h light/dark cycle in the SPF unit of the Hebrew University-Hadassah Medical School, Jerusalem, Israel. The animals were maintained on standard pellet diet and water ad libitum. The experimental protocols were approved by the Animal Care Ethical Committee of the Hebrew University-Hadassah Medical School, Jerusalem, Israel (Ethical Approval Number MD-16-14765-5).

PLP-induced EAE

Mice were immunized with proteolipid protein $PLP_{139-151}$ emulsified in Complete Freund's Adjuvant (CFA) together with pertussis toxin to induce relapsing–remitting EAE as described (McCarthy et al. 2012). In brief, 6–7-week-old female SJL/J were subcutaneously injected with an emulsion of 200 µg $PLP_{139-151}$ (GL Biochem., Shanghai, China) in 0.1 ml CFA (Sigma, Israel) on day 0, followed by intraperitoneal (i.p.) administration of 250 ng pertussis toxin (Sigma, Israel) in 0.2 ml PBS on day 0 and day 2. Upon signs of paralysis (usually after 9–11 days), the EAE mice were randomized into 4–6 groups depending on the experiment, with 6–8 mice per group. The mice (average weight of 20 ± 2 g at the beginning of the experiment) were then injected intraperitoneally with 0.1 ml vehicle (ethanol:Cremophor:saline at a ratio of 1:1:18) containing purified CBD (5 mg/kg) or Avidekel extract (50 mg/kg) 5 days a week for up to 60 days. Copaxone (50 mg/kg) was injected s.c. in 0.1 ml PBS. Control mice were injected i.p. with 0.1 ml vehicle only. In most of the experiments, PLP induced 3 phases of paralysis.

Neurological assessment

The mice were observed daily for the appearance of neurological paralytic symptoms and scored in a scale from 0 to 5 (McCarthy et al. 2012) according to the following signs: Grade 0: No neurological signs; Grade 0.5: Half paralyzed tail; Grade 1: Fully paralyzed tail; Grade 1.5: Fully paralyzed tail and weak or altered gait; Grade 2: Fully paralyzed tail and hind limb weakness; Grade 2.5: Unilateral hind limb paralysis; Grade 3: Complete hind limb paralysis; Grade 3.5: Complete hind limb paralysis and forelimb weakness; Grade 4: Full paralysis of all limbs (quadriplegia); Grade 5: Moribund state or death. Mice with clinical scores of 4–5 were euthanized.

Statistical Analysis

The results are presented as average ± standard error. Mice treated with CBD or Avidekel extracts were compared with control mice receiving the vehicle only or with mice receiving Copaxone. Mice treated with CBD and Copaxone or Avidekel extracts together with Copaxone were compared with mice treated with only one of the compounds. Raw p values were obtained from two-tail Mann–Whitney tests and

adjusted for multiple comparisons within each experiment using the Holm modification of the Bonferroni correction (Holm 1979). A p value equal to or below 0.05 was considered statistically significant. Six–eight animals were used in each treatment group for each experiment.

Results

Purified CBD and Avidekel extracts alleviate EAE symptoms

Experimental autoimmune encephalomyelitis (EAE) was induced in SJL/J mice by subcutaneous injection of $PLP_{139-151}$ emulsified in CFA followed by two intraperitoneal injections of pertussis toxin at days 0 and 2. The PLP-induced EAE model caused three distinct disease phases (I,

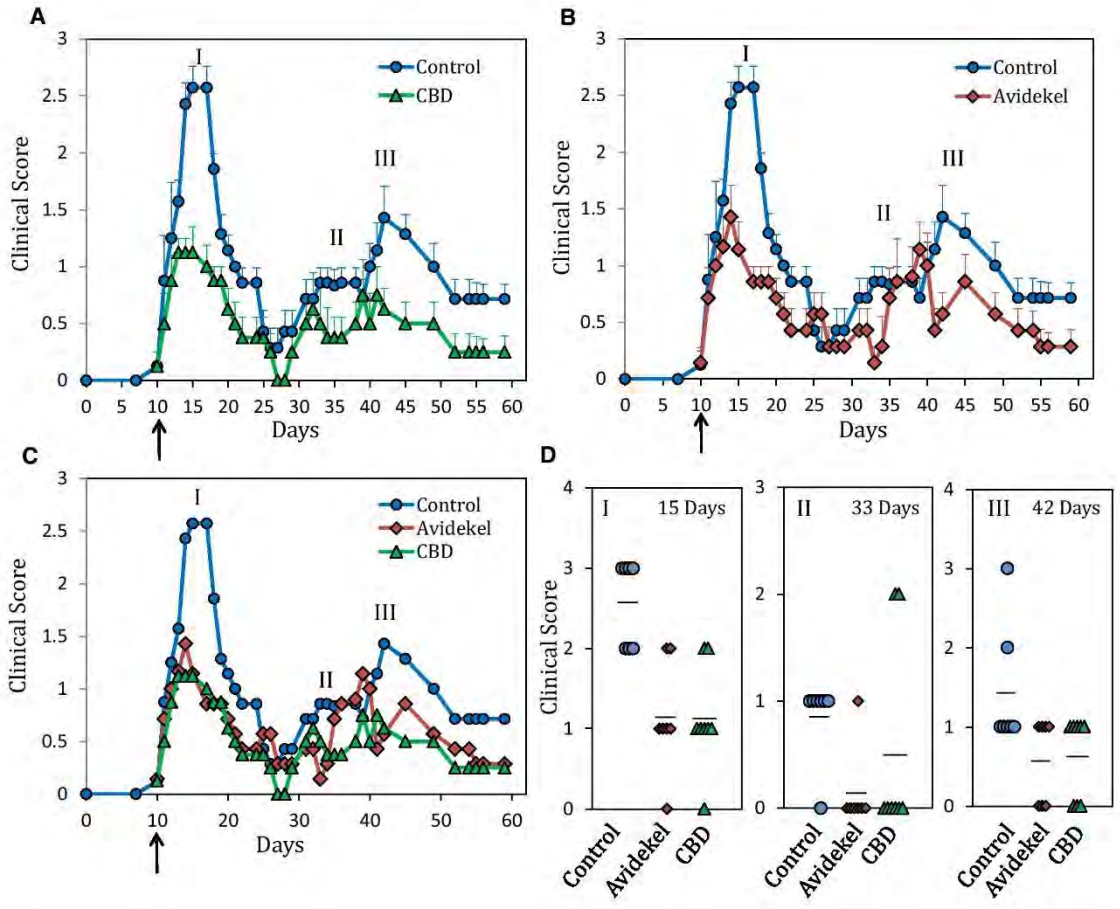

Fig. 1 Suppression of EAE symptoms by CBD and Avidekel extracts. EAE was induced by $PLP_{139-151}$ and at day 10 (indicated by an arrow), when the first neurological signs (Score 1) were observed, the mice were daily treated with CBD, Avidekel extracts or vehicle alone (Control) 5 days a week for 50 days. The clinical scores were monitored daily. Three relapse phases were observed as indicated (I, II, and III). Each group comprised 8 mice. **a–c** The graphs represent the average of data obtained from a representative experiment using 8 mice per treatment group. **a** Comparison of CBD with control mice. **b** Comparison of Avidekel with control mice. **c** The three treatment groups (Control, CBD or Avidekel) are presented together. Days 14–18 of phase I: $p<0.001$ for CBD vs control and Avidekel vs control. Days 31–35 of phase II: $p<0.005$ for CBD vs control and $p<0.01$ for Avidekel vs control. Days 41–49 of phase III: $p<0.001$ for CBD vs control and $p<0.03$ for Avidekel vs control. **d** The graphs present the clinical score of individual mice in each group at the peak of each relapse phase (I, II and III). The lines represent the average

II, III) (Fig. 1), which is in contrary to the MOG-induced EAE model where only one prolonged disease phase is observed (Rahimi et al. 2015). The first neurological symptoms (Score 1) were usually observed around day 10. From that day, the mice were daily injected intraperitoneally with purified cannabidiol (CBD; 5 mg/kg) or Avidekel Cannabis extracts (50 mg/kg), and the clinical scores were followed up daily. One of the 8 mice died in the control group in Phase I, while none died in the treated groups. Both CBD and Avidekel extracts efficiently inhibited the clinical symptoms appearing during all three relapse phases (Fig. 1). During days 14–18 of phase I, CBD suppressed the symptoms by $56.0 \pm 1.8\%$ ($p < 0.001$) and Avidekel extracts by $54.3 \pm 5.2\%$ ($p < 0.001$) at the average. During days 31–35 of phase II, CBD suppressed the symptoms by $39.1 \pm 8.1\%$ ($p < 0.005$) and Avidekel extracts by $48.9 \pm 11.9\%$ ($p < 0.01$) at the average. During days 41–49 of phase III, CBD suppressed the symptoms by $50.4 \pm 5.8\%$ ($p < 0.001$) and Avidekel extracts by $49.7 \pm 6.9\%$ ($p < 0.03$) at the average (Fig. 1). These data clearly show that Avidekel extracts are as efficient as CBD in suppressing EAE symptoms. Also, it is important to note the rapid onset of the therapeutic effects exerted by CBD and Avidekel extracts.

CBD and Avidekel extracts are at least as efficient as Copaxone in suppressing EAE symptoms

We next compared the efficacy of CBD and Avidekel extracts with that of Copaxone to suppress EAE symptoms. We observed that CBD at 5 mg/kg and Avidekel at 50 mg/kg were more efficient than the standard Copaxone dosage of 50 mg/kg during relapse phases I and II ($p < 0.05$), but showed similar suppression during relapse phase III (Figs. 2, 3, 4, 5). During days 11–13 of phase I, CBD suppressed the

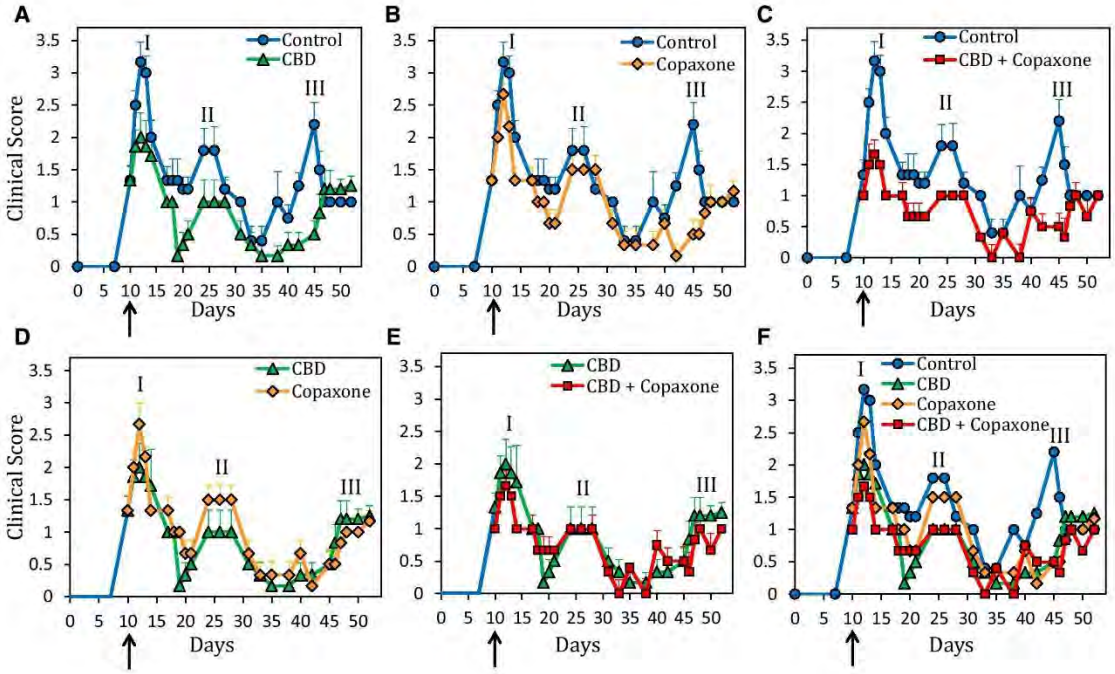

Fig. 2 CBD was at least as efficient as Copaxone to relieve EAE symptoms. EAE was induced by $PLP_{139-151}$ and at day 10 (indicated by an arrow), when the first neurological signs (Score 1) were observed, the mice were treated daily five times a week with CBD, Copaxone alone or in combination. Each treatment group comprised 6–8 mice. The graphs represent the average of data obtained from a representative experiment. **a** Comparison of CBD with Control mice. **b** Comparison of Copaxone with Control mice. **c** Comparison of CBD + Copaxone with control mice. **d** Comparison of Copaxone with CBD-treated mice. **e** Comparison of CBD + Copaxone with CBD-treated mice. **f** The four treatment groups (Control, CBD, Copaxone and CBD + Copaxone) are presented together. During days 11–13 of phase I: $p < 0.002$ for CBD vs control; $p < 0.006$ for Copaxone vs control; $p < 0.05$ for CBD vs Copaxone; $p < 0.05$ for CBD + Copaxone vs CBD; $p < 0.001$ for CBD + Copaxone vs Copaxone. During days 24–26 of phase II: $p < 0.01$ for CBD vs control; $p < 0.17$ for Copaxone vs control; $p < 0.05$ for CBD vs Copaxone; $p < 0.003$ for CBD + Copaxone vs Copaxone. During days 42–46 of phase III: $p < 0.0001$ for CBD, Copaxone and CBD + Copaxone vs control. In phase III there was no difference between the three treatment groups

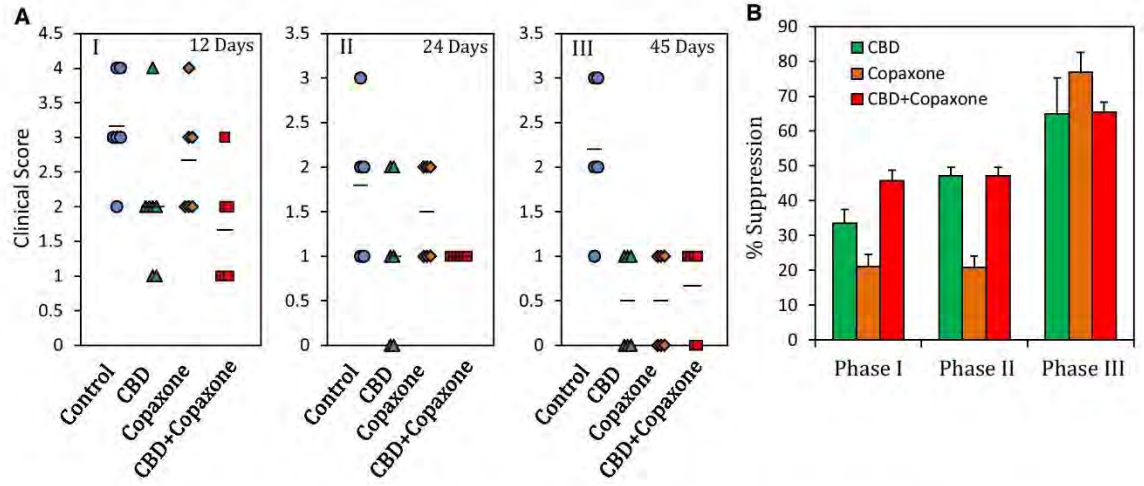

Fig. 3 **a** The graphs present the clinical scores of individual mice from the experiment presented in Fig. 2. The results from the peak of each relapse phase (I, II and III) are given. The lines represent the average. **b** The % of suppression achieved by each drug in the three relapse phases is given. The data are calculated from days 11–13 of phase I, days 24–26 of phase II and days 42–46 of phase III. In phase I, $p<0.05$ for CBD vs Copaxone and $p<0.05$ for CBD + Copaxone vs CBD, and in phase II, $p<0.03$ for CBD vs Copaxone. No differences were observed between the three treatment groups in phase III

symptoms by 33.5 ± 3.9% ($p<0.002$), Avidekel extracts by 40.3 ± 2.7% ($p<0.001$) while Copaxone only by 21.1 ± 3.5% ($p<0.006$) at the average. During days 24–26 of phase II, CBD suppressed the symptoms by 47.2 ± 2.2% ($p<0.01$), Avidekel extracts by 39.7 ± 2.6% ($p<0.03$), while Copaxone still only by 20.8 ± 3.4% ($p<0.05$) at the average. During days 42–46 of phase III, all three drugs showed strong suppression. During this phase, CBD suppressed the symptoms by 65.0 ± 10.3% ($p<0.0001$), Avidekel extracts by 80.0 ± 8.0% ($p<0.0001$), and Copaxone by 76.8 ± 5.7% ($p<0.0001$) at the average (Figs. 2, 3, 4, 5). Concurrent administration of CBD with Copaxone provided in general similar suppressive effects as CBD alone, with a slightly higher suppression during phase I ($p<0.05$) (Figs. 2, 3, 4, 5). Also, combined treatment of Avidekel extracts with Copaxone had in general similar suppressive effects as Avidekel alone, with a slightly higher suppression during phase II ($p<0.05$) (Figs. 4, 5). One of the 8 mice in the control group died in phase I, and three other control mice died in phase III. One of the 8 mice in the CBD-treated group died in phase I; all other mice survived. Altogether, our data show that CBD and Avidekel extracts are efficient in relieving EAE symptoms, and may, thus, be potential drugs in combined MS therapy.

Discussion

There are still no treatments that can cure MS patients. Since the main mechanism of injury appears to be inflammation, the drugs used for relapsing forms of MS usually target various parts of the immune system that aim to dampen the inflammation. Current drugs approved for relapsing forms of MS include interferon-β, Copaxone, mitoxantrone, natalizumab and fingolimod (Reich et al. 2018). Sativex, an oromucosal spray containing Δ^9-THC and CBD at a ratio of approximately 1:1, has been used to treat MS-related spasticity with improved quality of life (Giacoppo et al. 2017). The drawback of Δ^9-THC is its euphoric effects. CBD does not have psychotropic effects, but as a single agent, it usually gives a bell-shaped dose–response (Gallily et al. 2015), which makes it difficult to reach an optimal dose. Therefore, many attempts have been made to develop medical Cannabis subspecies with low Δ^9-THC content, while retaining the therapeutic benefits of Cannabis. One such species is Avidekel which contains high levels of CBD (18%), while very low levels of Δ^9-THC (1%) (Gallily et al. 2015). In contrast to

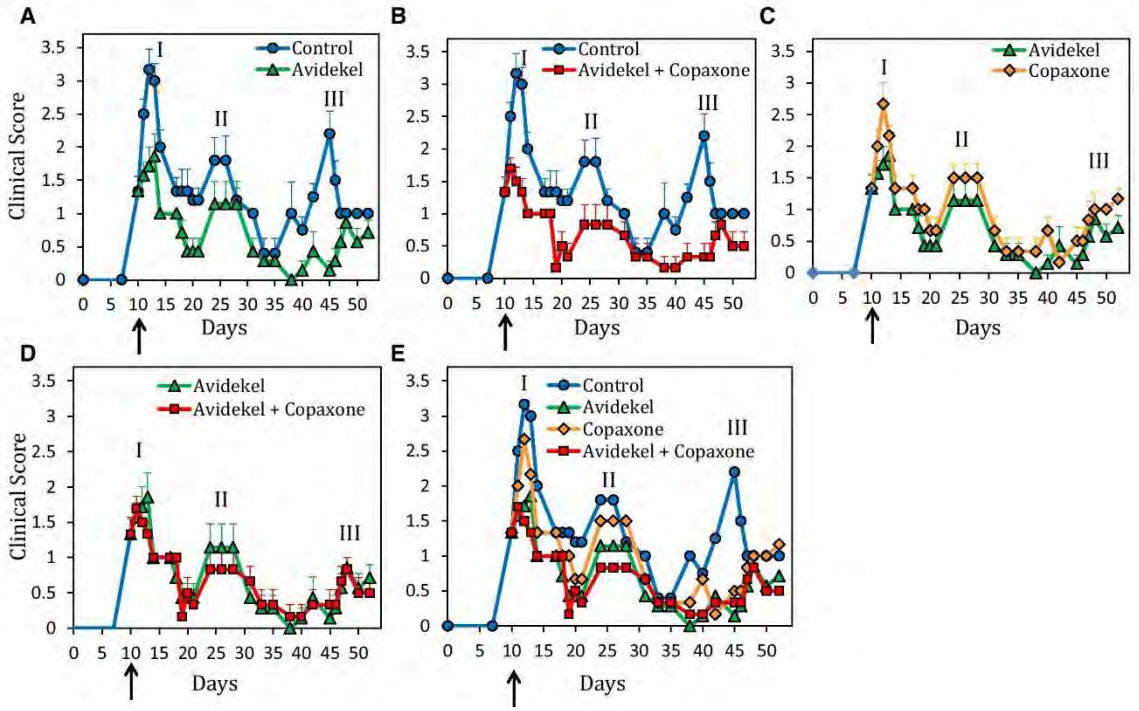

Fig. 4 Avidekel extract was at least as efficient as Copaxone to relieve EAE symptoms. EAE was induced by $PLP_{139-151}$ and at day 10 (indicated by an arrow), when the first neurological signs (Score 1) were observed, the mice were treated daily five times a week with Avidekel extracts, Copaxone alone or in combination. Each treatment group comprised 6–8 mice. The graphs represent the average of data obtained from a representative experiment. **a** Comparison of Avidekel with Control mice. **b** Comparison of Avidekel + Copaxone with control mice. **c** Comparison of Copaxone with Avidekel-treated mice. **d** Comparison of Avidekel + Copaxone with Avidekel-treated mice. **e** The four treatment groups (Control, Avidekel, Copaxone and Avidekel + Copaxone) are presented together. During days 11–13 of phase I: $p < 0.001$ for Avidekel vs control; $p < 0.006$ for Copaxone vs control; $p < 0.05$ for Avidekel vs Copaxone; $p < 0.001$ for Avidekel + Copaxone vs Copaxone. During days 24–26 of phase II: $p < 0.03$ for Avidekel vs control; $p < 0.17$ for Copaxone vs control; $p < 0.05$ for Avidekel vs Copaxone; $p < 0.002$ for Avidekel + Copaxone vs Copaxone and $p < 0.05$ for Avidekel + Copaxone vs Avidekel. During days 42–46 of phase III: $p < 0.0001$ for Avidekel, Copaxone, Avidekel + Copaxone vs control. In phase III there was no difference between the three treatment groups

purified CBD, Avidekel extracts provide a correlative dose response, with stronger effects upon increasing dosages. In addition to its anti-inflammatory properties, Avidekel also exerts anti-pain activity and causes relaxation. Both effects are beneficial for many severe disease conditions.

CBD is known for its strong anti-inflammatory effects (Burstein 2015; Gallily et al. 2015; Malfait et al. 2000; Weiss et al. 2008), and has recently been shown to have beneficial effects on EAE (Rahimi et al. 2015). Avidekel was shown to have strong anti-inflammatory as well as anti-nociceptive activities in an inflammatory mouse model (Gallily et al. 2015). Therefore, it was of high interest to study its ability to suppress EAE clinical symptoms. Both CBD and Avidekel extracts at the dosages given were more efficient than Copaxone during relapse phases I and II, while having similar strong suppressive effects during relapse phase III. This suggests for different therapeutic kinetics of these drugs. The immunosuppressive effect of Copaxone was achieved at a relative late time-point, while CBD and Avidekel extracts caused immediate relief. Upon prolonged treatment, the suppressive effects were more pronounced for all three drugs as seen by higher suppression in phase III in comparison to phases I and II. The combined treatment of CBD or Avidekel extracts with Copaxone in general did not increase the suppression above the one achieved with CBD or Avidekel alone, except for some periods were the suppression was slightly enhanced. Importantly, there were no antagonistic effects between CBD/Avidekel extracts and Copaxone, as was observed by Rahimi et al. for the combined treatment of CBD with palmitoylethanolamide (PEA)

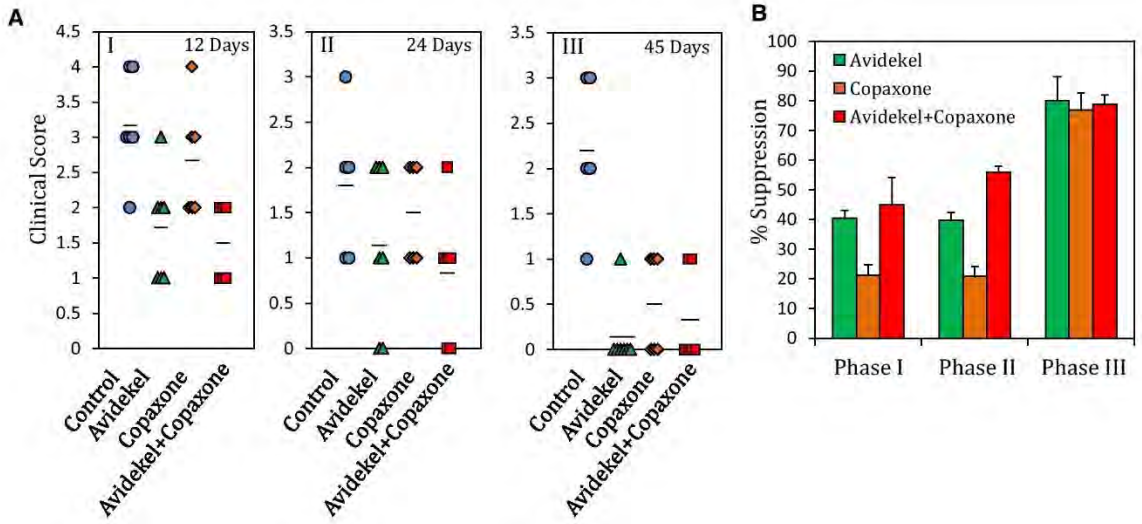

Fig. 5 **a** The graphs present the clinical scores of individual mice from the experiment presented in Fig. 4. The results from the peak of each relapse phase (I, II and III) are given. The lines represent the average. **b** The % of suppression achieved by each drug in the three relapse phases is given. The data are calculated from days 11–13 of phase I, days 24–26 of phase II and days 42–46 of phase III. In phase I, $p<0.05$ for Avidekel vs Copaxone; and in phase II, $p<0.05$ for Avidekel vs Copaxone and $p<0.05$ for Avidekel + Copaxone vs Avidekel. No differences were observed between the three treatment groups in phase III

(Rahimi et al. 2015). Altogether, our study demonstrates strong immunosuppressive activities of CBD and Avidekel extracts that might be beneficial for MS patients. We, therefore, propose to combine Avidekel extracts with current treatment protocols.

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Tourette Syndrome

Single Center Experience with Medical Cannabis in Gilles de la Tourette Syndrome
Parkinsonism and Related Disorders, 2018

This study was conducted to assess the response and benefits of using cannabis to treat Tourette Syndrome.

Study Population: 42 patients with Tourette Syndrome
Strain Used: *Erez*
Key Results:

- The mean ranking of efficacy was 3.85 out of 5, indicating a positive response to medical cannabis
- Patients reported reduction in tic severity, better sleep, and improved mood

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Short communication

Single center experience with medical cannabis in Gilles de la Tourette syndrome

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ABSTRACT

Introduction: Patients with Gilles de la Tourette syndrome (GTS) experience reduced function and impaired quality of life. The current medical treatments for this syndrome can cause significant side effects and offer partial symptomatic relief. In a few small trials medical cannabis (MC) has been suggested to offer symptomatic relief with a relatively benign side effect profile. We conducted a real-life assessment of clinical benefit and adverse effects of chronic MC treatment among patients with GTS.

Methods: GTS patients treated with MC were interviewed via phone regarding treatment efficacy and side effect profile from chronic MC consumption. Global efficacy was rated on a Likert scale of 1–5 and side effects of treatment were recorded.

Results: Forty-Two GTS patients (33 males, mean age 34.5) were interviewed for this study. The total global impression score of efficacy was 3.85 out of a total 5 possible points. Patients reported during the free discussion part of the interview about reduction in tic severity, better sleep and improved mood as positive effects of MC. Thirty-eight patients reported any kind of benefit from treatment while 10 patients with more than one year of consumption elected to stop treatment with MC for various reasons including severe side effects as psychosis in one patient.

Conclusion: MC seems to hold promise in the treatment of GTS as it demonstrated high subjective satisfaction by most patients however not without side effects and should be further investigated as a treatment option for this syndrome.

1. Introduction

Gilles de la Tourette syndrome (GTS) is diagnosed based on core features of multiple motor and at least one phonic tic lasting more than one year [1]. When tics are severe and debilitating, behavioral therapy is the first-line of treatment but if this fails, different drugs can be used to treat symptoms including dopamine receptor blockers, monoamine depleting agents and α2-adrenergic agonists, however these do not always provide satisfactory symptomatic relief and have disturbing side effects [1]. Generally, GTS attenuates with age in at least half of those who suffer from the condition. However, some individuals have persistently severe symptoms throughout adulthood.

Patients with GTS can experience reduced function and impaired quality of life compared with the general population [2]. These include musculoskeletal pain, social isolation, occupational restrictions and social withdrawal. GTS is associated with significant comorbidities which also affect quality of life such as obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), anxiety and depression [1]. Because of this, psychological distress and frustration are common among patients with GTS, with the syndrome having negative effect on employment, income and education status in adults [3].

Cannabis is a natural substance that contains more than 60 different cannabinoids. The two main components, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) differ in concentrations in formulations and exert the different effects. Two distinct cannabinoid receptors have been described; CB-1 receptors are located in areas of the brain that are

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related to reward, appetite and nociception (hippocampus, association cortex, basal ganglia, cerebellum and spinal cord), while CB-2 receptors are located in the striatum, ventral tegmentum, hippocampus and thalamus [4]. Activation of CB-2 receptors has been reported to induce feeling of well-being, impaired memory, slowed locomotor functions and sleep promoting effects [5]. The medical use of cannabis (MC) has been proposed for several conditions and regulated in some western countries.

A 2009 Chochrane review on cannabinoids for GTS detected 2 small trials that assessed THC as either monotherapy or adjuvant therapy with placebo. The first was a double blind single dose crossover trial and the other a six-week parallel group study with a total of 28 participants. Both trials reported a positive effect on the frequency and severity of tics on subjective report, yet objective endpoints were not affected by treatment, thus impairing any definitive conclusion [6].

The Israeli ministry of health approved the use of MC for several indications in 2013, including patients suffering from GTS with significant impairments in daily living who failed to respond favorably to common medications. This treatment is contraindicated in cases of active psychosis. Patients are issued a license and can initially consume 20 g of MC either as oil or for inhalation with increased doses available through a biannual evaluation by a neurologist and psychiatrist who are together required to recommend the continuation of treatment. Upon obtaining a license, patients chose a distributor and acquire the recommended MC formulation with varying concentrations of THC and CBD and the option of monthly change in distributor and MC formulations.

We conducted a real-life efficacy study in order to assess the response, benefits and side effects of use of MC for the treatment of GTS.

2. Methods

A telephoned survey of GTS patients from the Movement Disorders Unit (MDU) of the Tel-Aviv Medical Center (TLVMC) who received MC after individual approval from the Israeli Ministry of Health was performed throughout May–July 2018 after receiving approval from our institutions' IRB. GTS patients that were processed for MC licensing through the MDU since 2013 were contacted at least one year after receiving their MC license. Patients' were approached by either JK or TT, research coordinators in the MDU, indicated consent through the telephone and answered a structured questionnaire which assessed subjective clinical global impression of efficacy of MC on the clinical syndrome on a Likert scale of 1–5. The prevalence of ever suffering from various GTS symptoms was assessed as well. In addition, adverse effects, mode of consumption, current occupation and demographic data were collected, as well a free discussion about the patient's experience (Supplemental Table 1).

3. Results

We identified 63 potential subjects with the diagnosis of GTS who were processed for MC through the MDU of TLVMC since 2013, 5 were excluded from the study as they were subsequently found to suffer from other hyperkinetic movement disorder (tardive dyskinesia and dystonic tics), an additional 10 patients were excluded for consuming MC for less than one year and 6 were lost to follow-up. A total of 42 patients with GTS participated in this study (33 males, mean age 34.45), group characteristics are presented in Table 1. The global impression of efficacy was 3.85 (SD 1.41) out of a total 5 possible points, indicating positive response to MC. In a free text report, patients reported reduction in tic severity, better sleep and improved mood as positive effects of MC.

Seventeen of the participants were taking GTS related medications together with MC, while all participants had previous experience with at least one GTS related therapy. Two patients were taking atypical antipsychotics, typical antipsychotic was used by one patient, SSRI's were used by 8 patients, benzodiazepines by 5, methylphenidate by 3, tricyclic antidepressant by one and tetrabenazine by 2 patients when surveyed for this study. Thus, over half of our cohort was using MC as the only treatment for their disease.

Table 1
Group characteristics.

Age	34.45 (11.84) (20–73)
Gender m/f	33/9
Years of education	13.29 (2.32) (8–18)
Age of diagnosis	15.07 (10.29) (6–41)
Years of cannabis consumption	2.35 (1.25) (1–5)
Mode of consumption (oil/inhalation/both)	4/28/10
Current dosage (grams)	29.37 (9.48) (20–50)
Mean response	3.85 (1.41)
Currently occupied n (%)	31 (73.81)
Stopped treatment n (%)	10 (23.81)
OCD n (%)	27 (64.28)
ADHD n (%)	26 (61.91)
Depression n (%)	15 (35.71)
Anxiety n (%)	20 (47.62)

Results are presented as mean and std with range in relevant categories displayed as well.
m/f – male/female, n-number, OCD-obsessive-compulsive disorder, ADHD – Attention-deficit hyperactivity disorder.

A little less than one quarter of our cohort (10/42) elected to stop treatment with MC after at least a year of treatment, however only 4 patients reported no effect of MC on their symptoms, even though they renewed their license at least once. The other 6 patients stopped consumption for various reasons including side effects. Four patients reported hallucinations, 6 reported irritability and confusion while 7 reported subjective cognitive decline. One patient detailed an acute psychotic episode. Other side effects that were noted but did not affect consumption were increased appetite, dry eyes and fatigue. Aside from the patient with the psychotic episode, all other GTS patients received renewed licenses through the MDU.

4. Discussion

Our cohort of patients seems representative of the GTS population at large in general characteristics which include male predominance [7] and occurrence of comorbidities such as OCD, ADHD and affective disorders [8]. Impressively, the average years of education indicate above basic high school education, with 3/4 of our cohort currently employed, suggesting adequate coping mechanisms.

The mean ranking of MC response was 3.85/5 among our cohort with a slightly over 75% of participants electing to continue use of cannabis to alleviate symptoms. Those who stopped treatment did so for either lack of efficacy or due to side effects. While symptoms of GTS tend to abate with time and are variable across seasons and months [9], the choice of contacting GTC patients with over one years' treatment with MC was in part intended to overcome this.

Less than half of the cohort were taking any form of GTS related medications when assessed for this study even though in order to be eligible for MC, patients were required to have previous use of at least one disease related medication. Recent studies have indicated benefit from use of MC among patients with GTS albeit in small number of participants. Muller-Vahl et al. reported significant clinical improvement among 14/17 GTS patients who were using cannabis in both tic severity, OCD and ADHD with no serious adverse effects [1]. These findings were later replicated in two small randomized double-blind studies [10,11] incorporating a total of 36 participants with 7 dropouts. However, one of these trials was a single dose study while the other being a short six-week follow up study. Interestingly, one of these studies indicated deterioration in OCD symptoms under cannabis treatment. This was not detected in our study as none of the participant described worsening of obsessive or compulsive symptoms, even

though this was not directly questioned.

Common side effects of cannabis include tiredness and dizziness, relaxation, euphoria and reduction in cognitive capabilities. In our cohort, such symptoms caused the termination of use of cannabis in 1/6 of the patients. As we did not control for the type of MC or frequency of treatment, the severity and potential modification of side effects of MC remains to be detailed. Slow titration and habituation might address some of these side effects as attested by the majority of GTC patients that elected to continue treatment. A recent study analyzing side effects of MC that were prescribed for various reasons, detected 6.9% of use cessation due to adverse events within 6 months of initiation, within one year 15% stopped medication [12]. The fact that relatively high percent of our patients chose to stop treatment may indicate that the use of MC among GTS is not based solely on a strong pleasure effect.

5. Limitation

In this retrospective descriptive study, without randomization, some of the effects could be attributed to placebo. In addition, the many formulations and doses of MC make comparative analysis difficult. Even though to the best of our knowledge, this is the largest natural history study addressing GTS treatment with MC, the absolute number of participants remains relatively low. In addition, 6 GTS patients were lost to follow up. However, this was compensated by a relevant long treatment period as we contacted patients at least one year after initiating MC treatment. We did not assess concurrent use of other illicit substances which could affect response to treatment and could shed light on the "gateway drug" theory regarding use of MC. In addition, possible weight gain as a side effect of MC was not addressed. Despite all this, the positive subjective report on the benefit of cannabis on GTS should encourage further studies in this direction.

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Disclosure

Lihi Bar-Lev Schleider is an employee of Tikun Olam Ltd., an Israeli pharmaceutical company which is developing cannabis-based medicinal extracts. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.004.

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Autism Spectrum Disorder I

Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems

Journal of Autism and Developmental Disorders, 2018

A retrospective study assessing the tolerability and efficacy of CBD-rich cannabis in children with ASD.

Study Population: 60 children with ASD and severe behavioral problems
Strain Used: *Avidekel* and other CBD-rich cannabis oil at a 20:1 (CBD:THC) ratio
Key Results:

- Considerable improvement was reported in behavior (61%), communication (47%), and anxiety (39%), after at least 3 months of cannabis treatment
- 33% of children reduced their other medication doses and 24% stopped taking medications altogether

Journal of Autism and Developmental Disorders
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BRIEF REPORT

Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study

Adi Aran[1] · Hanoch Cassuto[2] · Asael Lubotzky[1] · Nadia Wattad[1] · Esther Hazan[1]

Abstract
Anecdotal evidence of successful cannabis treatment in autism spectrum disorder (ASD) are accumulating but clinical studies are lacking. This retrospective study assessed tolerability and efficacy of cannabidiol-rich cannabis, in 60 children with ASD and severe behavioral problems (age = 11.8 ± 3.5, range 5.0–17.5; 77% low functioning; 83% boys). Efficacy was assessed using the Caregiver Global Impression of Change scale. Adverse events included sleep disturbances (14%) irritability (9%) and loss of appetite (9%). One girl who used higher tetrahydrocannabinol had a transient serious psychotic event which required treatment with an antipsychotic. Following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients. This preliminary study supports feasibility of CBD-based cannabis trials in children with ASD.

Keywords Cannabidiol · Medical cannabis · Medical marijuana · Autism spectrum disorder · Disruptive behavior

Introduction

About 50% of children with autism spectrum disorder (ASD) suffer from behavioral problems such as tantrums, self-injury and violence (Maskey et al. 2013). These behavioral difficulties increase their social isolation, limit their ability to benefit from intervention efforts and often cause more distress to caregivers than the core autistic symptoms. Unfortunately, about 40% of children with ASD and disruptive behavior do not respond well to standard behavioral and medical treatment (Adler et al. 2015). Consequently, an exceptionally high percentage of parents are seeking help through unproven methods (Hofer et al. 2017), including the use of compounds made of the cannabis plant.

The cannabis plant contains two main cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is psychoactive and can cause anxiety and psychosis. CBD is not psychoactive and has potential anxiolytic, antipsychotic, anti-inflammatory and antioxidant properties with a relatively high toxicity threshold (Campos et al. 2017). Recently, CBD is emerging as a therapeutic option for refractory epilepsy (Devinsky et al. 2017, 2018; Thiele et al. 2018) and a CBD compound (Epidiolex, GW pahrmaceuticals) was approved by the U.S. Food and Drug Administration to treat severe forms of epilepsy (Lennox Gastaut and Dravet syndromes). These findings are of specific importance for people with ASD, as 10–30% of people with ASD have comorbid epilepsy (Ballaban-Gil and Tuchman 2000) and several synaptic plasticity pathways appear to be involved in both disease processes (Lee et al. 2015).

Moreover, alerted activation of the endocannabinoid system (ECS) was found in various animal models of epilepsy (Rosenberg et al. 2017) and ASD (Zamberletti et al. 2017). In some of these models, activating of the ECS or administrating CBD (Kaplan et al. 2017; Gururajan et al. 2012) ameliorated the social deficits.

A recent study demonstrated reduced concentration of the endocannabinoid anandamide in children with ASD (Karhson et al. 2018). However, to our knowledge, there

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is no previous report on the impact of medical cannabis in children with ASD.

Methods

Patients

All children with ASD and refractory disruptive behaviors, in a single national referral center (Shaare Zedek Medical Center, Jerusalem, Israel), to whom medical approval to use cannabis was issued for this indication, between 4/2016 and 1/2017, were systematically investigated after 7–13 months of treatment (August 2017). Prior to the retrospective collection of data, written informed consent was obtained from parents of all children.

Treatment

The cannabis was given as an adjuvant therapy, upon parental request, following specific individual approval of the Israeli Ministry of Health. All children were prescribed whole plant extracts that contain CBD and THC in a 20:1 ratio, dissolved in olive oil (CHP, ™Better, Israel; Avidekel, Tikun Olam Ltd, Israel, Topaz BOL Pharma, Israel). The cannabis oil was given sublingual two to three times a day with doses up-titrated over 2–4 weeks, to effect and tolerability (starting CBD dose was 1 mg/kg/day, maximal CBD dose was 10 mg/kg/day).

Outcome Measures

Patients were assessed using the following questionnaires: a modified Liverpool Adverse Events Profile, the Caregiver Global Impression of Change (CGIC) scale, the Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD) and the Autism Parenting Stress Index (APSI). More details on the instruments and statistical analysis are described in the Supplementary Material.

Results

Patients

The sample consisted of 60 children, 5–18 years old. Mean age was 11.8 ± 3.5 years; 77% had low cognitive functioning based on preexisting psychological evaluations [Autism Diagnostic Observation Schedule (ADOS) or Childhood Autism Rating Scale (CARS)]; 83% were boys. Clinical characteristics of the group are summarized in Table S1, available online.

All children attended special education programs for children with ASD and at the time of the treatment met DSM-5 criteria for ASD. All had severe behavioral problems, based on a Clinical Global Impression Scale—Severity (CGI-S) score of 6 or 7.

Treatment

The initial treatment for all patients was a whole plant extract that contains CBD and THC in a 20:1 ratio. In 29 patients with an insufficient response (CGI-S scores ≥ 5 despite treatment), strains with lower CBD:THC ratios were tried (up to a 6:1; maximal CBD dose was 5 mg/kg/day). The lower CBD:THC ratio was reported to be much better by parents of 13 patients, slightly better in 7 patients, no change in 6 and worse in 3. The mean total daily dose was 3.8 ± 2.6 mg/kg/day CBD and 0.29 ± 0.22 mg/kg/day THC for children who received three daily doses (n = 44) and 1.8 ± 1.6 mg/kg/day CBD and 0.22 ± 0.14 mg/kg/day THC for children who received two daily doses (n = 16).

Retention Rates

By the end of this study, forty-four children (73%) were still on cannabis treatment (mean treatment duration: 10.9 ± 2.3 months). Sixteen children (27%) stopped the cannabis treatment after 4.1 ± 2.6 months due to the following reasons: Three were treated for less than 2 weeks due to marked irritability in two and unsuccessful attempts to give the oil in the third. These 3 were excluded from the efficacy assessments below. Five children stopped the treatment (after 6 ± 2 months) due to low efficacy, seven (after 4.0 ± 2.1 months) due to a combination of low efficacy and side effects and one adolescent girl stopped the treatment after 6 months due to a transient psychotic event.

Adverse Events

Adverse events were reported by parents (n = 57) throughout the treatment period and were systematically assessed at each patient visit and at the end of the study (Table 1). Hypervigilance leading to aggravation of sleep problems was reported in 14% of the patients but usually resolved by omitting or adjusting the evening dose. Other common side effects included restlessness, irritability and loss of appetite. Three children (5%) stopped the treatment due to side effects that included marked irritability after treatment onset in 2 cases and a psychotic event in one adolescent girl. This 13 years old girl received 6.5 mg/kg/day CBD and no other

Table 1 Adverse events reported by parents during the treatment with cannabis

Adverse event	No of patients (%)
Any adverse event	29 (51%)
Sleep disturbances	8 (14%)
Restlessness	5 (9%)
Nervousness	5 (9%)
Loss of appetite	5 (9%)
Gastrointestinal symptoms	4 (7%)
Unexplained laugh	4 (7%)
Mood changes	3 (5%)
Fatigue	3 (5%)
Nocturnal enuresis	2 (3.5%)
Gain of appetite	2 (3.5%)
Weight loss	2 (3.5%)
Weight gain	2 (3.5%)
Dry mouth	2 (3.5%)
Tremor	2 (3.5%)
Sleepiness	1 (2%)
Anxiety	1 (2%)
Confusion	1 (2%)
Cough	1 (2%)
Serious adverse event	**No of patients (%)**
Psychotic event	1 (2%)

medications. She gradually increased the THC dose and when she reached 0.72 mg/kg/day, she developed an abrupt behavioral change that included unusual vocalization and refusal to eat and sleep for 48 h. She stopped the CBD and THC and started Ziprasidone 1.4 mg/kg/day. The symptoms resolved after 9 days.

Global Impression of Change in Behavior, Anxiety and Communication Following Cannabis Treatment

Figure 1 demonstrates the overall improvement in behavior, anxiety and communication as rated by parents on the CGIC scale. Considerable improvement in behavior problems ('much improved' or 'very much improved') was reported in 61% of the children. Considerable improvement in anxiety and communication problems was reported in 39% and 47% of the children respectively. CGIC ratings were not correlated with age, functional level, severity of behavioral problems at baseline and comorbidity with epilepsy.

Improvement in Disruptive Behavior Assessed by the HSQ-ASD and APSI

HSQ scores improved by 29% from 4.74 ± 1.82 at baseline to 3.36 ± 1.56 following the cannabis treatment. The mean improvement was 1.38 ± 1.79 (median = 0.81).

APSI scores improved by 33%, from 2.04 ± 0.77 at baseline to 1.37 ± 0.59 following the cannabis treatment. The mean improvement was 0.66 ± 0.74 (median = 0.53).

Concomitant Use of Medications

Forty nine children (82%) were treated with medications and cannabis concomitantly: 43 children (72%) used antipsychotics 10 (17%) received mood stabilizers, 7 (12%) received benzodiazepines, 4 (7%)—SSRIs and 4 (7%) received stimulants (details appear in the Supplementary Material, online). Following the cannabis treatment, 16 (33%) received fewer medications or lower dosage, 12 (24%) stopped taking medications and 4 (8%) received more medications or higher dose.

Discussion

To our knowledge, this is the first report on the impact of CBD-rich medical cannabis in children with ASD. Specifically, following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients. Moreover, 16 children (33%) received less medications or lower dosage and 12 (24%) stopped taking medications (all received at least 1 antipsychotic), while 4 children (8%) received more medications or higher dose. However, strains with a relatively high THC concentration (6:1-CBD to THC ratio) might lead to a serious psychotic episode that would require treatment with an antipsychotic.

Based on these promising results, we have launched a placebo controlled cross-over trial that will assess CBD-rich cannabis in 150 children with ASD and disruptive behavior (NCT02956226). Another large placebo controlled study (NCT03202303) will assess Cannabidivarin (CBDV), a homolog of CBD, in 100 children with ASD.

CBD-rich cannabis might help children with ASD via several possible mechanisms including its anxiolytic and antipsychotic properties (Campos et al. 2017) as well as its immunomodulatory effect and its impact on the endocannabinoid system (ECS). Several human studies revealed associations between polymorphisms in the gene encoding CB1 endocannabinoid receptor and social reward processing (Chakrabarti and Baron-Cohen 2011).

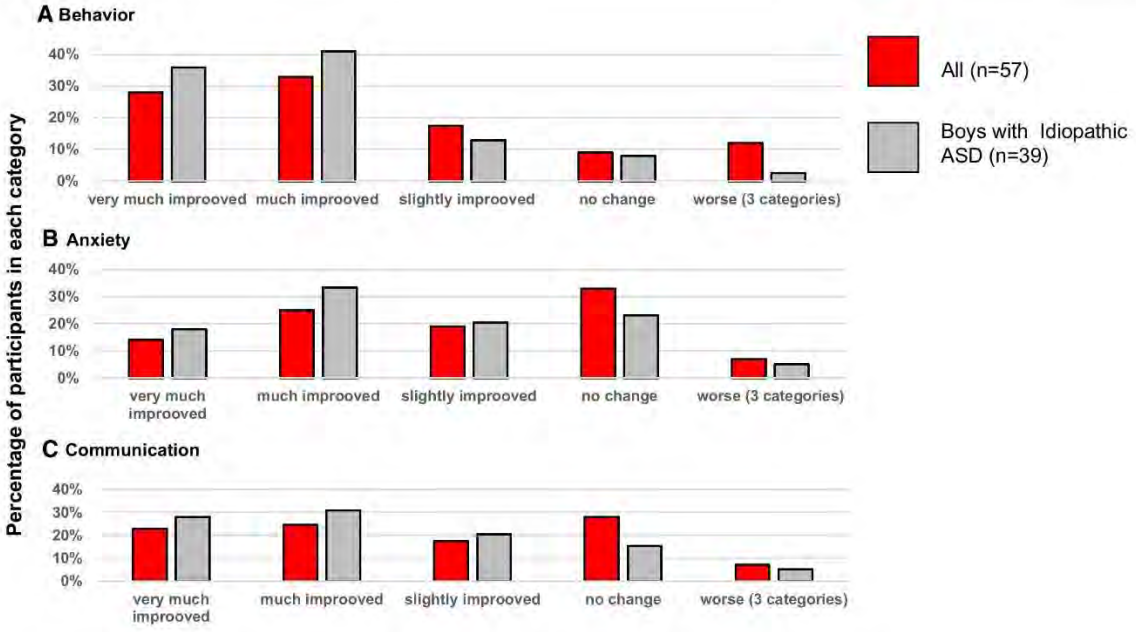

Fig. 1 Caregivers global impression of change in behavior anxiety and communication following cannabis treatment

These preclinical data and the results of the current study render worthwhile further exploration of this treatment avenue in controlled studies. Until such evidence is available, physicians should be cautious in the use of medical cannabis in children with ASD since initial reports of promising treatment in children with ASD are often found, in controlled studies, to result from a pure placebo response (King et al. 2013). Furthermore, the use of recreational cannabis in adolescents is associated with several risks including decreased motivation, addiction, mild cognitive decline, and schizophrenia. However, these complications are all attributed to THC, while we used CBD-rich compounds. Nevertheless, as safety data in children are sparse, it is recommended that clinical use be withheld until ongoing randomized trials are published.

Finally, this study has several limitations. It is an uncontrolled retrospective study of a subgroup of children with severe and refractory behavioral problems. The participants used various cannabis strains from different growers and a broad range of CBD and THC dose, and the number of participants was not large enough to evaluate the impact on different ASD subgroups.

Author Contributions AA: Study conception and design; acquisition, analysis and interpretation of data; drafted manuscript; critically revised manuscript and gave final approval. CH and LA: Study conception; interpretation of data; critically revised manuscript and gave final approval. WN: Study design; acquisition of data; critically revised manuscript and gave final approval. EH: Study design; acquisition, analysis and interpretation of data; drafted manuscript; critically revised manuscript and gave final approval.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Autism Spectrum Disorder II

Real Life Experience of Medical Cannabis with Autism: Analysis of Safety and Efficacy
Scientific Reports, 2019

This observational study assessed the safety and efficacy of medical cannabis for the treatment of autism spectrum disorders (ASD), analyzing the change in symptoms after six months of using our CBD-rich cannabis oil.

Study Population: 188 children with ASD; 93 completed the follow-up survey at six months
Strain Used: *Avidekel*, at a 20:1 (CBD:THC) ratio
Key Results:

- 90.2% of patients reported an improvement in symptoms after six months treatment
- Symptoms improved included depression (100%), restlessness (89.8%), rage attacks (89%), anxiety (88.8%), seizures (84.6%), agitation (83.8%), tics (80%), digestion problems (62.5%), constipation (62.5%), sleep problems (58.6%), and more
- Good quality of life was indicated by 31.1% of patients at intake; by 66.8% at six months
- Patients reported improvement in sleep, positive mood, and ability to dress and shower independently
- 34.3% of patients decreased medication consumption, including antipsychotics, antiepileptics, antidepressants, hypnotics, and sedatives
- 20% of patients stopped taking antipsychotics
- Cannabis appears to be a well-tolerated, safe and effective option to relieve ASD symptoms

SCIENTIFIC REPORTS

OPEN

Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy

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There has been a dramatic increase in the number of children diagnosed with autism spectrum disorders (ASD) worldwide. Recently anecdotal evidence of possible therapeutic effects of cannabis products has emerged. The aim of this study is to characterize the epidemiology of ASD patients receiving medical cannabis treatment and to describe its safety and efficacy. We analysed the data prospectively collected as part of the treatment program of 188 ASD patients treated with medical cannabis between 2015 and 2017. The treatment in majority of the patients was based on cannabis oil containing 30% CBD and 1.5% THC. Symptoms inventory, patient global assessment and side effects at 6 months were primary outcomes of interest and were assessed by structured questionnaires. After six months of treatment 82.4% of patients (155) were in active treatment and 60.0% (93) have been assessed; 28 patients (30.1%) reported a significant improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their condition. Twenty-three patients (25.2%) experienced at least one side effect; the most common was restlessness (6.6%). Cannabis in ASD patients appears to be well tolerated, safe and effective option to relieve symptoms associated with ASD.

There has been a 3-fold increase during the last 3 decades in the number of children diagnosed with autism spectrum disorders worldwide[1–5]. No specific treatments are currently available and interventions are focussing on lessening of the disruptive behaviors, training and teaching self-help skills for a greater independence[6].

Recently, CBD enriched cannabis has been shown to be beneficial for children with autism[7]. In this retrospective study on 60 children, behavioural outbreaks were improved in 61% of patients, communication problems in 47%, anxiety in 39%, stress in 33% and disruptive behaviour in 33% of the patients. The rationale for this treatment is based on the previous observations and theory that cannabidiol effects might include alleviation of psychosis, anxiety, facilitation of REM sleep and suppressing seizure activity[8]. A prospective single-case-study of Dronabinol (a THC-based drug) showed significant improvements in hyperactivity, lethargy, irritability, stereotypy and inappropriate speech at 6 month follow-up[9]. Furthermore, Dronabinol treatment of 10 adolescent patients with intellectual disability resulted in 8 patients showing improvement in the management of treatment-resistant self-injurious behaviour[10].

In 2007, The Israel Ministry of Health began providing approvals for medical cannabis, mainly for symptoms palliation. In 2014, The Ministry of Health began providing licenses for the treatment of children with epilepsy. After seeing the results of cannabis treatment on symptoms like anxiety, aggression, panic, tantrums and self-injurious behaviour, in children with epilepsy, parents of severely autistic children turned to medical cannabis for relief.

Although many with autism are being treated today with medical cannabis, there is a significant lack of knowledge regarding the safety profile and the specific symptoms that are most likely to improve under cannabis treatment. Therefore, the aim of this study was to characterize the patient population receiving medical cannabis treatment for autism and to evaluate the safety and efficacy of this therapy.

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	Total (188)
Mean age (SD)	12.9 (7.0)
Gender (male), No. (%)	154 (81.9)
Mean body mass index (SD)	29.0 (5.3)
Previous experience with cannabis (Yes), No. (%)	19 (10.1)
Comorbidities:	
Epilepsy, No. (%)	27 (14.4)
Attention Deficit Hyperactivity Disorder, No. (%)	7 (3.7)
Tourette syndrome, No. (%)	4 (2.1)
Celiac Disease, No. (%)	3 (1.6)
Anxiety Disorder, No. (%)	3 (1.6)

Table 1. Demographic and clinical characteristics of patients at intake.

		Change at six months		
	Intake prevalence Total (188)	Symptom disappeared	Improvement	No change or deterioration
Restlessness, No. (%)	170 (90.4)	1 (1.2)	71 (89.8)	7 (8.8)
Rage attacks, No. (%)	150 (79.8)	1 (1.3)	65 (89.0)	7 (9.5)
Agitation, No. (%)	148 (78.7)	1 (1.4)	57 (83.8)	10 (14.7)
Sleep problems, No. (%)	113 (60.1)	9 (19.5)	27 (58.6)	10 (21.7)
Speech Impairment, No. (%)	113 (60.1)	—	15 (30)	35 (70)
Cognitive impairment, No. (%)	91 (48.4)	—	15 (27.2)	40 (72.7)
Anxiety, No. (%)	69 (36.7)	—	24 (88.8)	3 (11.1)
Incontinence, No. (%)	51 (27.1)	2 (9.0)	7 (31.8)	13 (59.0)
Seizures, No. (%)	23 (12.2)	2 (15.3)	11 (84.6)	—
Limited Mobility, No. (%)	17 (9.0)	2 (18.1)	—	9 (81.8)
Constipation, No. (%)	15 (8.0)	1 (12.5)	6 (62.5)	2 (25)
Tics, No. (%)	15 (8.0)	1 (20.0)	4 (80.0)	—
Digestion Problems, No. (%)	14 (7.4)	1 (12.5)	5 (62.5)	2 (25.0)
Increased Appetite, No. (%)	14 (7.4)	1 (33.3)	1 (33.3)	1 (33.3)
Lack of Appetite, No. (%)	14 (7.4)	2 (40.0)	1 (20.0)	2 (40.0)
Depression, No. (%)	10 (5.3)	—	5 (100.0)	—

Table 2. Symptom prevalence and change. Symptom prevalence at intake in 188 patients assessed at intake and change at six months in patients responding to the six-month questionnaire.

Results

Patient population. During the study period, 188 ASD patients initiated the treatment. Diagnosis of ASD was established in accordance with the accepted practice in Israel; six board certified paediatric psychiatrists and neurologists were responsible for treatment of 125 patients (80.6%), the remaining 30 children were referred by 22 other physicians. Table 1 shows demographic characteristics of the patient population. The mean age was 12.9 ± 7.0 years, with 14 (7.4%) patients being younger than the age of 5, 70 patients (37.2%) between 6 to 10 years and 72 (38.2%) aged 11 to 18. Most of the patients were males (81.9%). Twenty-seven patients (14.4%) suffered from epilepsy and 7 patients (3.7%) from Attention Deficit Hyperactivity Disorder (ADHD).

At baseline parents of 188 patients reported on average of 6.3 ± 3.2 symptoms. Table 2 shows the prevalence of symptoms with most common being restlessness (90.4%), rage attacks (79.8%) and agitation 78.7%.

Cannabis products recommended to the patients were mainly oil applied under the tong (94.7%). Seven patients (3.7%) received a license to purchase oil and inflorescence and three patients (1.5%) received a license to purchase only inflorescence. Most patients consumed oil with 30% CBD and 1.5% THC, on average 79.5 ± 61.5 mg CBD and 4.0 ± 3.0 mg THC, three times a day (for a more detailed distribution of CBD/THC consumptions see Supplementary Fig. S1). Insomnia recorded in 46 patients (24.4%) was treated with an evening does of 3% THC oil with on average additional 5.0 ± 4.5 mg THC daily. All the products content was validated by HPLC (High Performance Liquid Chromatography) in each production cycle. The cannabis dose was not significantly associated with weight (r correlation coefficient $= -0.13$, $p = 0.30$), age (r correlation coefficient $= -0.10$, $p = 0.38$), or gender ($p = 0.38$).

Follow-up, one month. After one month, out of 188 patients, 8 (4.2%) stopped treatment, 1 (0.5%) switched to a different cannabis supplier, and 179 patients (94.6%) continued active treatment (Fig. 1). Of the latter group, 119 (66.4%) responded to the questionnaire with 58 patients (48.7%) reporting significant improvement, 37

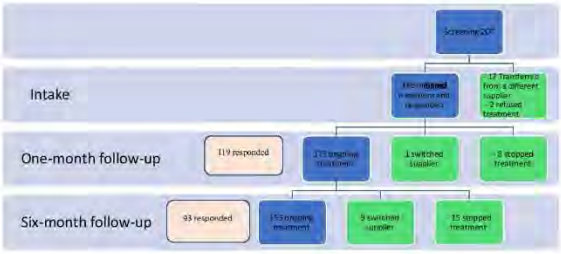

Figure 1. The study population in the three follow-up periods, at intake, after one month and after six months of medical cannabis treatment.

(31.1%) moderate improvement; 7 patients (5.9%) experienced side effects and 17 (14.3%) reported that the cannabis did not help them.

The reported side effects at one month were: sleepiness (1.6%), bad taste and smell of the oil (1.6%), restlessness (0.8%), reflux (0.8%) and lack of appetite (0.8%).

Follow-up, six months. After six months, of the 179 patients assessed in the one-month follow-up, 15 patients (8.3%) stopped treatment, 9 (4.9%) switched to a different cannabis supplier and 155 patients (86.6%) continued treatment (Fig. 1). Of the latter group, 93 (60.0%) responded to the questionnaire with 28 patients (30.1%) reporting a significant improvement, 50 patients (53.7%) moderate improvement, 6 patients (6.4%) slight improvement and 8 (8.6%) having no change in their condition. None of the variables entered to the multivariate analysis to predict treatment success was statistically significant.

To assess the potential response bias, we have compared baseline characteristics between 93 respondents and 62 non-respondents to the 6-month questionnaire. The former group was slightly older (13.7 ± 0.8 vs. 10.8 ± 0.5, $p = 0.004$).

Quality of Life. Quality of life, mood and ability to perform activities of daily living were assessed before the treatment and at six months. Good quality of life was reported by 31.3% of patients prior to treatment initiation while at 6 months good quality of life was reported by 66.8% ($p < 0.001$, Supplementary Fig. S2). Positive mood was reported by the parents on 42% before treatment and 63.5% after 6 months of treatment ($p < 0.001$). The ability to dress and shower independently was significantly improved from 26.4% reported no difficulty in these activities prior to the treatment to 42.9% at six months ($p < 0.001$). Similarly, good sleep and good concentration were reported by 3.3% and 0.0% (respectively) before the treatment and on 24.7% ($p < 0.001$) and 14.0% ($p < 0.001$) during an active treatment (Table 3).

The improved symptoms at 6 months included seizures, of the 13 patients on an active treatment at six months 11 patients (84.6%) reported disappearances of the symptoms and two patients reported improvement; restlessness and rage attacks were improved in 72 patients (91.0%) and 66 (90.3%) respectively (Table 2).

Medications Use. The most common concomitant chronic medications on the intake were antipsychotics (56.9%), antiepileptics (26.0%), hypnotics and sedatives (14.9%) and antidepressants (10.6%). Out of 93 patients responding to the follow-up questionnaire, 67 reported use of chronic medications at intake. Overall, six patients (8.9%) reported an increase in their drugs consumption, in 38 patients (56.7%) drugs consumption remained the same and 23 patients (34.3%) reported a decrease, mainly of the following families: antipsychotics, antiepileptics antidepressants and hypnotics and sedatives (Table 4). Antipsychotics, the most prevalent class of medications taken at intake (55 patients, 33.9%); at 6 months it was taken at the same dosage by 41 of them (75%), 3 patients (5.4%) decreased dosage and 11 patients (20%) stopped taking this medication (Table 4).

Side Effects. The most common side effects, reported at six months by 23 patients (25.2%, with at least one side effect) were: restlessness (6 patients, 6.6%), sleepiness (3, 3.2%), psychoactive effect (3, 3.2%), increased appetite (3, 3.2%), digestion problems (3, 3.2%), dry mouth (2, 2.2%) and lack of appetite (2, 2.2%).

Out of 23 patients who discontinued the treatment, 17 (73.9%) had responded to the follow-up questionnaire at six months. The reasons for the treatment discontinuation were: no therapeutic effect (70.6%, twelve patients) and side effects (29.4%, five patients). However, 41.2% (seven patients) of the patients who discontinued the treatment had reported on intentions to return to the treatment.

Discussion

Cannabis as a treatment for autism spectrum disorders patients appears to be well-tolerated, safe and seemingly effective option to relieve symptoms, mainly: seizures, tics, depression, restlessness and rage attacks. The compliance with the treatment regimen appears to be high with less than 15% stopping the treatment at six months follow-up. Overall, more than 80% of the parents reported at significant or moderate improvement in the child global assessment.

	Sleep			Eating with Appetite			Concentration on daily tasks			Bowel Activity		
	Before	During	p value	Before	During	p value	Before	During	p value	Before	During	p value
Severe difficulty	44 (47.3)	2 (2.2)		2 (2.2)	1 (1.1)		75 (80.6)	21 (22.6)		3 (3.2)	2 (2.2)	
Moderate difficulty	18 (19.4)	27 (29.0)		6 (6.5)	13 (14.0)		11 (11.8)	41 (44.1)		13 (14.0)	17 (18.3)	
No difficulty	28 (30.1)	39 (41.9)	<0.001	59 (63.4)	47 (50.5)	0.751	2 (2.2)	11 (11.8)	<0.001	71 (76.3)	54 (58.1)	0.242
Good	2 (2.2)	15 (16.1)		10 (10.8)	16 (17.2)		0	10 (10.8)		5 (5.4)	13 (14.0)	
Very Good	1 (1.1)	8 (8.6)		16 (17.2)	14 (15.1)		0	3 (3.2)		1 (1.1)	4 (4.3)	

Table 3. Assessment of daily activities. Ability to perform activities of daily living was assessed prior to and six months after initiation of cannabis treatment. Numbers in parenthesis represent the % of patients.

	Intake	Change at six months follow-up				
Medication family	Total	Stopped taking this medication	Dosage decreased	Has not changed	Dosage increased	New medication
Antipsychotics, n (%)	55	11 (20)	3 (5)	41 (75)	0	0
Antiepileptics, n (%)	46	6 (13)	0	35 (76)	2 (4.5)	3 (6.5)
Antidepressants, n (%)	10	3 (30)	0	4 (40)	1 (10)	2 (20)
Hypnotics and sedatives, n (%)	10	2 (20)	1 (10)	7 (70)	0	0
Anxiolytics, n (%)	7	2 (28)	0	5 (72)	0	0

Table 4. Concomitant medications. Concomitant medications use at the baseline and six months follow up in patients responding to the six-month questionnaire.

The exact mechanism of the cannabis effects in patients with ASD is not fully elucidated. Findings from ASD animal models indicate a possible dysregulation of the endocannabinoid (EC) system[11–16] signalling behaviours, a dysregulation that was suggested to be also present in ASD patients[17]. Mechanism of action for the effect of cannabis on ASD may possibly involve GABA and glutamate transmission regulation. ASD is characterized by an excitation and inhibition imbalance of GABAergic and glutamatergic signalling in different brain structures[18]. The EC system is involved in modulating imbalanced GABAergic[19] and glutamatergic transmission[20].

Other mechanism of action can be through oxytocin and vasopressin, neurotransmitters that act as important modulators of social behaviours[21]. Administration of oxytocin to patients with ASD has been shown to facilitate processing of social information, improve emotional recognition, strengthen social interactions, reduce repetitive behaviours[22] and increase eye gaze[23]. Cannabidiol was found to enhance oxytocin and vasopressin release during activities involving social interaction[16].

Two main active ingredients (THC and CBD) can have different psychoactive action mechanisms. THC was previously shown to improve symptoms characteristic to ASD patients in other treated populations. For example, patients reported lower frequency of anxiety, distress and depression[24], following THC administration, as well as improved mood and better quality of life in general[25]. In patients suffering from anxiety, THC led to improved anxiety levels compared to placebo[26] and in dementia patients, it led to reduction in nocturnal motor activity,violence[27,28] behavioural and severity of behavioural disorders[29]. Moreover, cannabis was shown to enhances interpersonal communication[30] and decrease hostile feelings within small social groups[31].

In our study we have shown that a CBD enriched treatment of ASD patients can potentially lead to an improvement of behavioural symptoms. These findings are consistent with the findings of two double-blind, placebo-controlled crossover studies demonstrating the anxiolytics properties of CBD in patients with anxiety disorder[32,33]. In one, CBD had a significant effect on increased brain activity in the right posterior cingulate cortex, which is thought to be involved in the processing of emotional information[32], and in the other, simulated public speaking test was evaluated in 24 patients with social anxiety disorder. The CBD treated group had significantly lower anxiety scores than the placebo group during simulated speech, indicating reduction in anxiety, cognitive impairment, and discomfort factors[33].

The cannabis treatment appears to be safe and side effects reported by the patients and parents were moderate and relatively easy to cope with. The most prevalent side effects reported at six months was restlessness, appearing in less than 6.6% of patients. Moreover, the compliance with the treatment was high and only less than 5% have stopped the treatment due to the side effects. We believe that the careful titration schedule especially in the ASD paediatric population is important for maintaining a low side effects rate and increase of the success rate. Furthermore, we believe that a professional instruction and detailed parents' training sessions are highly important for the increasing of effect to adverse events ratio.

The present findings should be interpreted with caution for several reasons. Firstly, this is an observational study with no control group and therefore no causality between cannabis therapy and improvement in patients' wellbeing can be established. Children of parents seeking cannabis therapy might not constitute a representative sample of the patient with the specific disease (self-selection bias). We have not formally confirmed the ASD diagnosis, however all the children included in the study were previously diagnosed with ASD by certified neurologist or psychiatrist, as required by Ministry of Health prior to the initiation of the cannabis-based treatment.

This study was based on a subjective self-report of the patient's parent's observation and not by the patients themselves. These reports, with subjective variables such as quality of life, mood, and general effects, may be

biased by the parent's opinion of the treatment. Moreover, even though the effect was assessed at six months, the possibility of the inflated expectations of the novel treatment "miracle" effect cannot be excluded. The questionnaire response rate at 6 months was 60%, thus the estimates of the efficacy and safety of the treatment can be biased. However, high compliance (above 80%) with the treatment provides a good evidence of the patients and parents satisfaction with the treatment.

While this study suggest that cannabis treatment is safe and can improve ASD symptoms and improve ASD patient's quality of life, we believe that double blind placebo-controlled trials are crucial for a better understanding of the cannabis effect on ASD patients.

Methods

Study Population. There are currently over 35,000 patients approved for medical cannabis use in Israel and 15,000 (~42.8%) of them receive treatment at Tikun-Olam Ltd. (TO), the largest national provider of medical cannabis. This study included all patients receiving cannabis license at TO with the diagnosis of autism in the years 2015–2017.

During the routine treatment process at the cannabis clinic, all willing patients underwent an extensive initial evaluation and their health status was periodically assessed by the treating team. At the intake session, the nurse assessed a complete medical history. The patient's parents were interviewed by the nurse and filled a medical questionnaire, which included the following domains: demographics, comorbidities, habits, concomitant medications, measurements of quality of life and a detailed symptoms check-list. Following intake, the nurse advised on the treatment plan.

Treatment Regiment. The treatment in majority of the patients was based on cannabis oil (an extract of a high CBD strain dissolve in olive oil in a ratio THC:CBD of 1:20, 30% CBD and 1.5% THC), and underwent an individualized titration. The starting dose was one sublingual drop three times a day with one oil drop (0.05 ml) containing 15 mg CBD and 0.75 mg Δ9-THC. Oil contained 45% olive oil, 30% CBD, 1.5% THC, <1.5% CBC, 0.5% CBG, <0.5% CBDV and <0.1% CBN. The remaining ingredients were terpenes, flavonoids, waxes and chlorophyll

In patients who reported high sensitivity to previously used medications, the treatment started with oil containing 1:20 15% CBD and 0.75% THC. In patients with severe sleep disturbances, following the initial treatment phase, 3% THC oil was added to the evening dose. In cases with a significant aggressive or violent behaviour, 3% THC oil was added.

The dose was increased gradually for each patient depending on the effect of the cannabis oil on the targeted symptoms according to the treatment plan and the tolerability of each patient. Finding of the optimal dose could take up to two months and dosage range is wide: from one drop three times a day to up to 20 drops three times a day of the same product.

After one month, the treating team contacted the parents to follow-up on the treatment progression. At six months patients underwent an additional assessment of the symptom intensity, side effects and quality of life.

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 patient parents 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 patient parents were asked: "How would you rate the general effect of cannabis on your child condition?" the options were: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration and significant deterioration. Autism symptoms severity assessment included the following items: restlessness, rage attacks, agitation, speech impairment, cognitive impairment, anxiety, incontinence, depression and more. Quality of life was assessed on a Likert scale ranging from very poor to poor, neither poor nor good and good to very good[34].

The study was approved by Soroka University Medical Centre Ethics Committee and due to the nature of the data analysis based on the routinely obtained clinical data, it was determined that no informed consent is required. All methods were performed in accordance with the relevant institutional and international research guidelines and regulations.

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 and paired t-test for the analysis of the continuous variables with normal distribution. The non-parametric Mann-Whitney U test and paired 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, number of chronic medications, number of total symptoms, and the three most prevalent symptoms: restlessness, rage attacks and agitation (as a dichotomous variable- yes/no), as reflected in the intake form.

P value < 0.05 was considered to be statistically significant. All analyses were performed at the Clinical Research Centre, Soroka University Medical Centre, Beer-Sheva, Israel using IBM SPSS version 22 (SPSS, Chicago, IL).

Declarations. The study was approved by Soroka University Medical Center Ethics Committee (study number: SCRC-0415-15) and the need for informed consent was waived due to the retrospective nature of the data analysis.

Availability of Data

The data set generated and/or analysed during the current study are not publicly available due to medical confidentiality but are available from the first author on reasonable request summarized form pending the approval of the IRB.

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Author Contributions

L.B.L.S., V.N. and R.M. planned the study; N.S. collected the data, L.B.L.S. and V.N. analysed the data, L.B.L.S. wrote the manuscript, V.N. and G.M. reviewed and approved the manuscript.

Additional Information

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Competing Interests: L.B.L.S. and N.S. are employees of Tikun-Olam Ltd. V.N. is a paid member of the Tikun Olam Ltd. scientific advisory board. R.M. and G.M. have no conflicts of interest pertaining to the current manuscript.

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Fibromyalgia

Safety and Efficacy of Medical Cannabis in Fibromyalgia

Journal of Clinical Medicine, 2019

This observational study investigated the characteristics, safety, and effectiveness of medical cannabis therapy for fibromyalgia. Patients studied were referred to cannabis after receiving traditional treatment for at least a year without improvement. The change in symptoms and quality of life was measured after six months of treatment.

Study Population: 367 patients with fibromyalgia; 211 completed the follow-up survey at six months
Strains Used: *Avidekel*, *Alaska*, and other Tikun Olam strains
Key Results:

- 81.1% of patients reported overall treatment success - defined as experiencing at least moderate improvement in their condition without serious adverse effects
- 73.4% of patients reported improved sleep; 13.2% reported their sleep problems were fully relieved
- 80.8% of patients reported improved depression-related symptoms
- 61.9% of patients reported their quality of life (QOL) to be "good or very good," whereas only 2.7% of patients rated their QOL at this level prior to beginning treatment; QOL components include appetite, sleep quality, and sexual activity
- Overall pain intensity reduced from a median of 9.0 at baseline to 5.0 after six months
- 22.2% of patients stopped or reduced their dosage of opioids; 20.3% reduced their dosage of benzodiazepines

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Safety and Efficacy of Medical Cannabis in Fibromyalgia

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Abstract: Background: Chronic pain may be treated by medical cannabis. Yet, there is scarce evidence to support the role of medical cannabis in the treatment of fibromyalgia. The aim of the study was to investigate the characteristics, safety, and effectiveness of medical cannabis therapy for fibromyalgia. Methods: A prospective observational study with six months follow-up period based on fibromyalgia patients who were willing to answer questionnaire in a specialized medical cannabis clinic between 2015 and 2017. Results: Among the 367 fibromyalgia patients, the mean age was 52.9 ± 15.1, of whom 301 (82.0%) were women. Twenty eight patients (7.6%) stopped the treatment prior to the six months follow-up. The six months response rate was 70.8%. Pain intensity (scale 0–10) reduced from a median of 9.0 at baseline to 5.0 ($p < 0.001$), and 194 patients (81.1%) achieved treatment response. In a multivariate analysis, age above 60 years (odds ratio [OR] 0.34, 95% C.I 0.16–0.72), concerns about cannabis treatment (OR 0.36, 95% C.I 0.16–0.80), spasticity (OR 2.26, 95% C.I 1.08–4.72), and previous use of cannabis (OR 2.46 95% C.I 1.06–5.74) were associated with treatment outcome. The most common adverse effects were mild and included dizziness (7.9%), dry mouth (6.7%), and gastrointestinal symptoms (5.4%). Conclusion: Medical cannabis appears to be a safe and effective alternative for the treatment of fibromyalgia symptoms. Standardization of treatment compounds and regimens are required.

Keywords: medical cannabis; fibromyalgia; quality of life; chronic pain

1. Introduction

Fibromyalgia is a common syndrome of chronic pain, often accompanied by sleeping disturbances, cognitive impairment, and psychiatric and somatic symptoms [1,2]. The prevalence of fibromyalgia is 2%–8% of the entire population, and it is the most common reason for generalized pain among working age women worldwide [3,4].

Therapy for fibromyalgia is challenging and based on a multidisciplinary approach. Patients with fibromyalgia may respond to a combination of pharmacological (e.g., tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, and anticonvulsants) and non-pharmacological interventions (e.g., aerobic exercise, cognitive-behavioral therapy, and rehabilitation programs) [5]. On the other hand, utilization of opioids was found to be associated with poorer symptoms and poorer functional and occupational status compared to nonusers [6].

Medical cannabis represents a promising therapeutic option for fibromyalgia patients due to its effectiveness and relatively low rate of serious adverse effects [7,8]. Although the identification of cannabinoid receptors and their endogenous ligands has triggered a large body of studies, there is a paucity of large-scale and prospective clinical trials regarding their role in fibromyalgia [9]. Only a handful of studies have examined the effect of medical cannabis on fibromyalgia. These studies had rather small sample sizes (31–40 subjects) and a short duration of follow up, which makes the generalizability of the results questionable [10–12]. In the current analysis of the prospective registry, we aim to investigate the safety and effectiveness of fibromyalgia patients receiving medical cannabis.

2. Experimental Section

2.1. Study Population

In Israel, patients prescribed medical cannabis are required to receive an approval from the Israel Medical Cannabis Agency (IMCA), a department within the Israeli Ministry of Health. Currently, there are more than 30,000 patients approved for medical cannabis use in Israel. Following the authorization, patients are asked to contact one of eight specified medical cannabis providers. Patients receive structured guidance by a certified nurse in the cannabis field regarding the available strains and route of administration. The monthly dose is set by the IMCA authorization according to the clinical indication. The patient then starts gradual titration process after choosing a strain according to his/her own decision Tikun-Olam Ltd. (TO) is the largest medical cannabis provider in Israel, which serves annually a third of the entire medical cannabis users in Israel.

This analysis of the prospectively collected data included all patients with diagnosis of fibromyalgia (primary or secondary to other conditions) who initiated treatment with medical cannabis in TO from January 2015 to December 2017. The data were extracted and analyzed retrospectively. The fibromyalgia diagnosis was established by a board-certified rheumatologist according to the American College of Rheumatology preliminary diagnostic criteria for fibromyalgia [13]. Patients were referred to cannabis treatment by ether the family physician, pain physician, or specialized rheumatologist after receiving treatment for at least a year without improvement. The study was approved by the Soroka University Medical Center (SUMC) institutional ethics committee and was conducted by the SUMC Clinical Cannabis Research Institute.

2.2. Data Collection

The intake questionnaire included demographic details, daily habits, substance abuse, medical background, concurrent use of other medications, symptoms checklist, and quality of life (QOL) assessment, stratified by components in 5 points Likert scale (e.g., sleep; appetite; sexual activity; and how a patient would assess their quality of life on a 5 points scale, with 1 being very poor and 5 being very good). Fibromyalgia symptoms after six months were assessed using 8-points Likert scale (1—severe symptomatic deterioration, to 8—maximal symptomatic improvement). A certified nurse educated the patients on the use of medical cannabis; gave instructions on route of administration according to the medical cannabis license (oil vs. inflorescence), delivery methods (drops, flowers, capsules, or cigarettes), and possible adverse effects; and provided an explanation on regulatory issues. The nurse also advised on selecting the cannabis strain (out of 14 strains available) and treatment dose according to titration protocol.

Cannabis products are composed of two major active components: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the psychoactive component, which affects pain, appetite, orientation, and emotions, through CB1 and CB2 receptors. CBD has analgesic, anti-inflammatory, and anti-anxiety effects via a complex mechanism acting as a negative allosteric modulator of CB1 receptor [14]. The relative proportion of THC:CBD determines each strain's type of effect, pharmacokinetics, and adverse events. In addition, more than 60 other cannabinoids have been identified, with a variety of clinical effects (e.g., anti-inflammatory and analgesic effects) and pharmacokinetics.

In this study, we used a gradual titration process rather than a fixed dose. Initially, all patients received a low dose of cannabis below the therapeutic effect (e.g., a drop of 15% THC-rich cannabis TID). Patients then were instructed to increase the dosage gradually in small intervals (e.g., a single drop per day) until they reached a therapeutic effect (e.g., subjective relief of their pain, significant improvement in their quality of life). In case of inflorescence (each cigarette contained 0.75 g of cannabis), patients were instructed to use one breath every 3–4 h, and to increase the amount gradually in this interval until therapeutic effect is reached. Mixing of oil and inflorescence at the same usage was not recommended. In case of adverse events, patients were instructed to use the last dosage that did not cause undesirable symptoms. The titration was similar for both THC- and CBD-rich strains. In addition, the cannabis provider operated a 24/7 call center to address any concerns that might have been raised by the patients. The final dosage depended on the primary indication for cannabis use, age, medical background, parallel use of other analgesic regimes, and previous exposure to cannabis. All patients underwent one and six month follow-up telephonic interviews. The later was extensive and included an assessment of the change in medical cannabis dose and regimen, change in QOL, disease- and medical cannabis-related symptoms, and alteration in the use and dosage of other medications.

2.3. Study Outcomes

For safety analysis, we assessed the frequency of medical cannabis-related side effects, including those of patients who ceased cannabis use before six months had passed. We also assessed patients' perceptions regarding the change in fibromyalgia symptoms in the 6 month follow-up. The following symptoms were included: headaches, dizziness, nausea, vomiting, constipation, drop in sugar, drowsiness, weakness, dry mouth, cough, increased/lack of appetite, hyperactivity, restlessness, cognitive impairment, depression, anxiety, confusion, and disorientation. For disease-related symptoms, patients were asked to report whether each symptom disappeared, improved, deteriorated, or remained unchanged at six months follow up.

For effectiveness analysis, the primary outcome was treatment response, defined as at least moderate or significant improvement in a patient's condition at six months follow-up without the cessation of treatment or serious side effects. Patients lost to follow-up were considered as failures for the purposes of the effectiveness analysis. In addition, we assessed the following secondary outcomes:

- Pain intensity—assessment by the numeric rating scale (NRS) with an 11-point scale (0 = no pain, 10 = worst pain imaginable).
- Quality of life—global assessment by the patient using the Likert scale with five options: very good, good, neither good nor bad, bad, or very bad.
- Perception of the general effect of cannabis—global assessment by using the Likert scale with seven options: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration, or significant deterioration.

2.4. Statistical Analysis

Continuous variables with normal distribution were presented as means with standard deviation. Ordinal 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 to control possible confounders. The final model was selected according to the statistical significance of coefficients, their clinical relevance, and the model discriminatory characteristic, which were evaluated by calculating the c-statistic, in addition to choosing the minimal −2 log likelihood of each model. We considered a p-value of 0.05 or less (two-sided) as statistically significant. IBM SPSS software, version 25.0, was used for statistical analysis.

3. Results

3.1. Cohort Characteristics

We identified 367 patients with fibromyalgia who had started the treatment with medical cannabis. During the study period, 35 received medical cannabis for less than six months and were not eligible for six months follow-up, 28 stopped medical cannabis treatment before six months follow-up, four switched to another medical cannabis supplier, and two died within the first six months (Figure 1). Out of the remaining 298 patients treated for six months, 211 responded with the follow-up questionnaire (70.8% response rate). In addition, out of the 87 patients who did not respond to the six months questionnaire, 76 patients (87.3%) were using cannabis at six months. To minimize selection bias, we compared baseline characteristics among six months respondents and non-respondents. As shown in Table S1, there were no differences in baseline characteristics among those who responded to the six months follow-up questionnaire compared to those who did not.

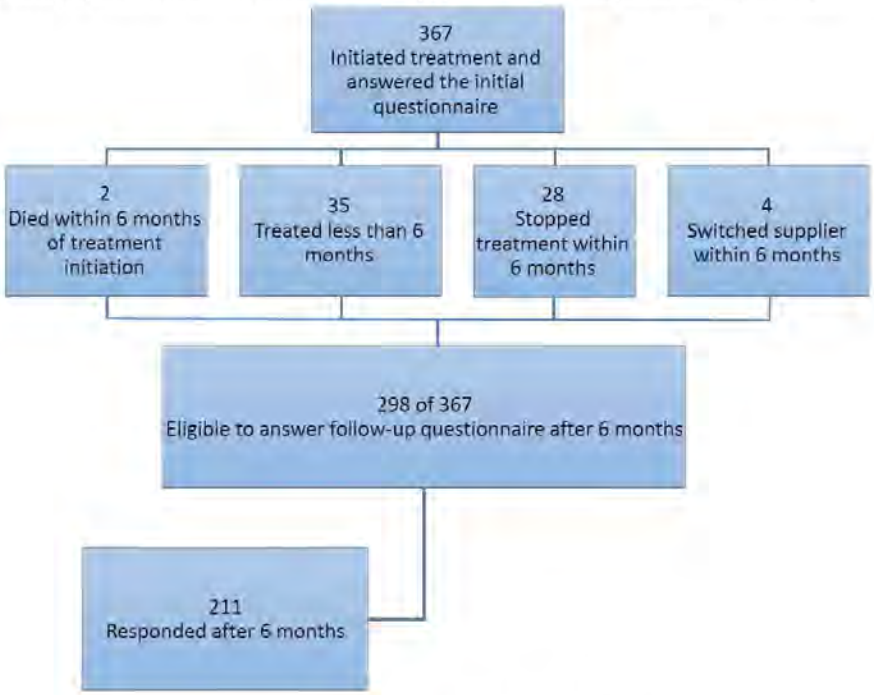

Figure 1. Flow chart of the study population.

Table 1 shows baseline characteristics of the study population. The majority of the patients were 40–60 years old (181 patients, 49.3%) and female (301 patients, 82.0%) with BMI of 28.6 ± 18.2 kg/m^2. Patients had reported previous experience with recreational cannabis in the past in 45.2% of cases. The median length of fibromyalgia symptoms was 7 years, and 320 (87.2%) patients reported constant daily pain. In 283 patients (77.1%), fibromyalgia was the primary pain-related indication to initiate medical cannabis therapy. Fibromyalgia was the secondary indication to initiate cannabis therapy in 35 (9.5%) patients with cancer, 22 (6.0%) patients with post-traumatic stress disorder (PTSD), and in 27 (7.4%) patients with other indications.

Table 1. Baseline characteristics of the patient population.

Variable	Number of Patients (N = 367)
Age (years), mean ± SD	52.9 (15.1)

Age groups, *n* (%)	
40 years and below	75 (20.4)
40–60 years	181 (49.3)
60 years and above	111 (30.2)
Females, *n* (%)	301 (82.0)
BMI (kg/m^2), mean ± SD	28.6 (18.2)
Work status: works regularly	59 (16.1)
Part-time work	53 (14.4)
Unemployed/retired	233 (63.4)
Other	22 (5.9)
Driving a car, *n* (%)	231 (62.9)
Approved monthly dosage of cannabis ≤ 20 g, *n* (%)	328 (89.4%)
Approved route of administration, *n* (%)	Oil 74 (20.2) Inflorescence 247 (67.3) Oil + Inflorescence 44 (12.0)
Previous experience with cannabis, *n* (%)	166 (45.2)
Cigarette smokers, *n* (%)	137 (37.3)
Number of regularly used medications, median (i.q range)	5.0 (3.0–8.0)
Number of regularly used medications for fibromyalgia, median (i.q range)	1.0 (1.0–2.0)
Treatment indication: primary fibromyalgia, *n* (%)	283 (77.1)
Cancer, *n* (%)	35 (9.5)
PTSD, *n* (%)	22 (6.0))
Other, *n* (%)	27 (7.4)
Years of chronic pain, median (i.q. range)	7.0 (3.0–13.0)
Type of pain: Daily, *n* (%)	320 (87.2)
Episodic, *n* (%)	47 (12.8)

BMI—body mass index, SD—standard deviation I.Q range—interquartile range, and PTSD—post traumatic stress disorder.

The median cannabis approved dosage was 670 mg/day (inter-quartile range 670–670 mg) at initiation and 1000 mg/day (inter-quartile range 700–1000 mg) at six months ($p = 0.01$). The median THC and CBD dosages at six months were 140 mg/day (inter-quartile range 90–200 mg) and 39 mg/day (inter-quartile range 10–69 mg), respectively. When comparing dose at six months between patients with fibromyalgia as a primary or secondary indication, the primary fibromyalgia patients utilized lower THC dosages (75 ± 53 vs. 95 ± 63 mg/day, $p = 0.04$) but similar CBD dosages (63 ± 51 vs. 67 ± 71 mg/day, $p = 0.70$).

3.2. *Safety Analysis*

At treatment initiation, 328 (89.4%) patients received 20 g or less of cannabis per month, which was administrated to 247 (67.3%) patients using inflorescence (Table 1). During the study follow-up, a total mean of 3.3 regimens was prescribed per patient, with a total of 952 (56.4%) THC-rich regimens used compared to 129 (21.7%) CBD-rich regimes (Table S2).

Medical cannabis-related adverse events, reported by patients six months after cannabis use, are shown in Table S3. Overall the most common symptoms were dizziness reported by 19 patients (7.9%), dry mouth by 16 patients (6.7%), nausea/vomiting by 13 patients (5.4%), and hyperactivity by 12 patients (5.5%).

3.3. *Effectiveness Analysis*

The overall treatment success was achieved in 194 out of 239 patients (81.1%)—proportion of patients reporting at least moderate improvement in their condition while still receiving medical

cannabis without experiencing serious adverse events out of patients who either responded to the six months questionnaire or stopped the treatment (Figure 2). Comparison of fibromyalgia-related symptoms among patients at intake and at six months follow-up is shown in Table S4. The sleep problems reported by 196 patients (92.9%) at intake improved in 144 patients (73.4%) and disappeared in 26 patients (13.2%, $p < 0.001$). Depression-related symptoms reported by 125 patients (59.2%) at the baseline improved in 101 patients (80.8%, $p < 0.001$).

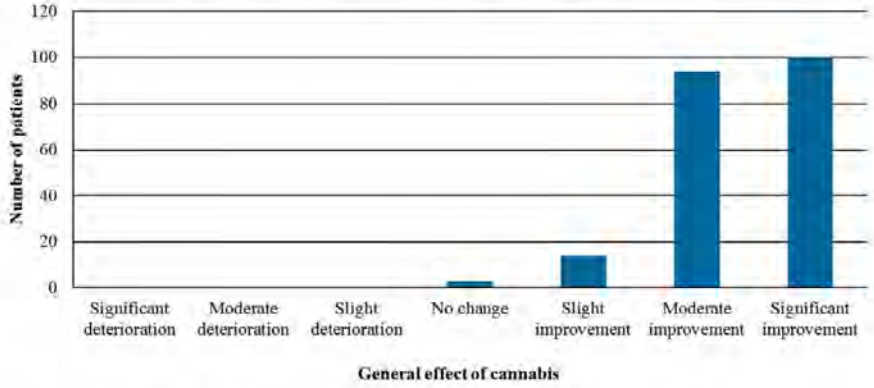

Figure 2. Perception of the general effect of cannabis on the patient's condition after six months of treatment.

In a multivariate logistic regression (Table 2), age above 60 (O.R 0.34, 95% C.I 0.16–0.72) and concerns about cannabis treatment (O.R 0.36, 95% C.I 0.16–0.80) were associated with treatment failure, whereas spasticity at treatment initiation (O.R 2.26, 95% C.I 1.08–4.72) and previous use of cannabis (O.R 2.46 95% C.I 1.06–5.74) were associated with treatment success.

Table 2. Multivariate analysis for treatment response at six months.

Variable	*p* Value	Odds Ratio	95% Confidence Interval
Age > 60 years	0.01	0.34	0.16–0.72
Concerns about cannabis-prior to treatment initiation	0.01	0.36	0.16–0.80
Spasticity	0.03	2.26	1.08–4.72
Previous experience with cannabis	0.04	2.46	1.06–5.74

Figure 3 shows the evaluation of pain intensity (presented in NRS 11 points scale) at baseline and six months follow-up. Prior to treatment initiation, 193 patients (52.5%) reported a high level of pain scale (8–10). However, after six months of follow-up, only 19 patients (7.9%) reported similar pain intensity. Overall pain intensity reduced from a median of 9.0 (inter-quartile range 8.0–10.0) at baseline to 5.0 (inter-quartile range 4.0–6.0) after six months ($p < 0.001$).

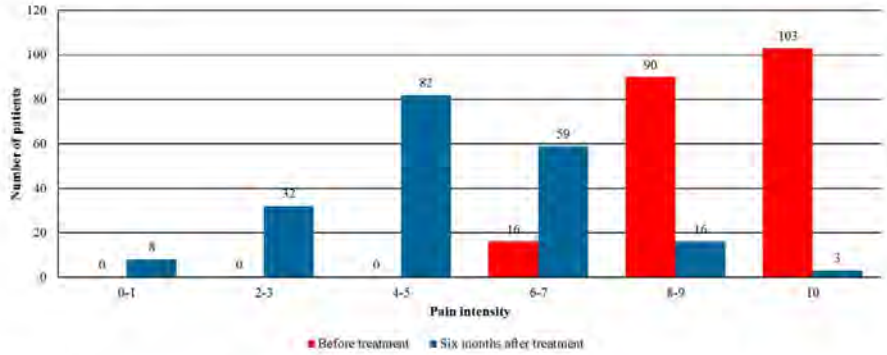

Figure 3. Assessment of the pain intensity on the 0–10 scale before and after six months of cannabis therapy ($p < 0.001$).

The evaluation of QOL (in 5 points Likert scale) prior to and after six months of medical cannabis treatment is shown in Figure 4. Whereas prior to treatment initiation 10 patients (2.7%) reported good or very good QOL, after six months of treatment 148 patients (61.9%) reported their QOL to be good or very good ($p < 0.001$). When analyzing QOL components, sleep quality, appetite, and sexual activity significantly improved at six months ($p < 0.001$, 0.02, and 0.03 respectively, Figure S1). Other components (e.g., mobility, dressing, and concentration) did not improve, and the quality of daily activities deteriorated at six months ($p < 0.001$).

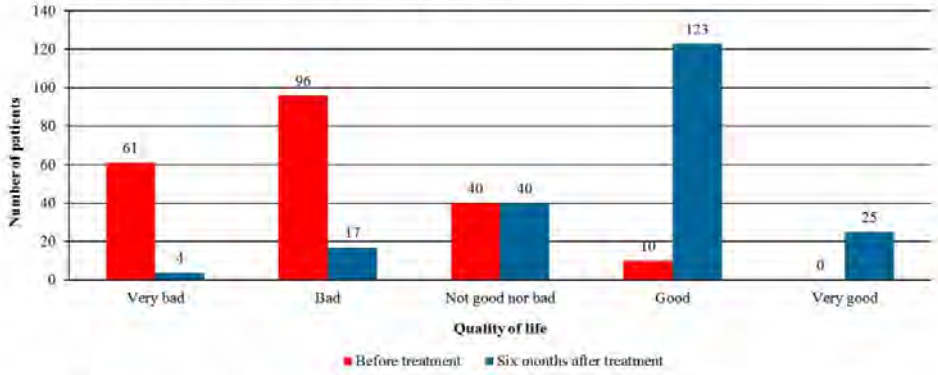

Figure 4. Quality of life prior and six months after the initiation of cannabis treatment ($p < 0.001$).

3.4. Additional Regimens

The change in the utilization of other drugs for the treatment of fibromyalgia after six months is shown in Table S5. Most patients ceased, reduced, or at least did not change the dosage of their chronic drugs for fibromyalgia while receiving medical cannabis. At six months, 28 out of 126 patients (22.2%) stopped or reduced their dosage of opioids (<0.001), and 24 out of 118 (20.3%) reduced their dosage of benzodiazepines ($p < 0.001$). When stratifying the analysis to patients with primary vs. secondary fibromyalgia (Table S6), both groups show the same improvement at six months in terms of pain intensity and overall quality of life.

4. Discussion

In the present study, we demonstrated that medical cannabis is an effective and safe option for the treatment of fibromyalgia patients' symptoms. We found a significant improvement in pain intensity and significant improvement in patients' overall quality of life and fibromyalgia-related symptoms after six months of medical cannabis therapy. In addition, there were relatively minor

adverse effects with a small number of patients who discontinued the use at six months. To the best of our knowledge, this is the first trial to use herbal cannabis in fibromyalgia patients.

A search of the current literature has identified three randomized controlled trials evaluating the effect of medical cannabis on fibromyalgia-related symptoms. Skrabek et al. enrolled 32 patients to receive nabilone, an orally administered cannabinoid, vs. placebo therapy [10]. At four weeks follow-up there was a significant decrease of 2 points of NRS in addition to improvement in anxiety and overall quality of life. Ware et al. enrolled 29 patients in a trial of nabilone vs. amitriptyline to investigate the effect on sleep disorders among fibromyalgia patients over 2 weeks of therapy. The authors found a moderate effect on insomnia, but not on other aspects of sleep, in addition to no improvement in pain and quality of life [11]. Lastly, Fiz et al. enrolled 56 patients to receive either medical cannabis (the type is not mentioned) or standard therapy [15]. The authors reported a significant effect on pain two hours from consumption, with no effect on quality of life or sleep disorders. Data regarding pain intensity longer than 2 h were not available. Compared to the studies mentioned above, our study has several advantages. First, our study represents a real-world experience of herbal cannabis use in the cohort of patient with fibromyalgia. Second, we have assessed a substantially larger cohort of 367 fibromyalgia patients with six months follow-up of 211 patients (vs. 30–56 patients in previous studies). Our data also provided a relatively long follow-up of six months periods (compared to only several weeks follow up), which allowed us to analyze the effect and safety of medical cannabis on fibromyalgia patients over an extended period of time. Lastly, we studied the effect of medical cannabis on every aspect of fibromyalgia: improvement in chronic pain, quality of life, disease perception and specific symptoms, and the incidence of adverse effects.

There are several pharmacological regimes that are recommended to treat fibromyalgia [5]. However, their efficacy is relatively limited. The use of low-dose amitriptyline, a tricyclic antidepressant, was associated with 30% reduction in pain level with minor effect on sleep quality. A similar pain reduction rate was shown in meta-analyses of both anticonvulsants and serotonin–noradrenalin reuptake inhibitors [16,17]. However, withdrawal rates due to side effects in these studies were higher compared with placebo. Our results pointed out that cannabis may be at least equal to these regimes, yet with minor adverse effects that resulted in low dropout rates in our study.

Medical cannabis use was reported to be associated with a change in the utilization of other prescription regimens [18–20]. In our cohort, after six months of medical cannabis therapy, a substantial fraction of patients stopped or decreased the dosage of other medical therapies. Of note, 22.2% of opioids users at the baseline reduced or ceased the use of these medications at six months follow-up. Considering that opioid use is coupled with a complex titration process, higher risk for dependency, and a higher rate of serious adverse effects, medical cannabis may pose a reasonable therapeutic alternative [21–23].

Previous studies have shown that medical cannabis use was more prevalent among young adults and males [24,25]. However, our cohort was composed of a majority of 40–60 years old women, representing the population most affected by fibromyalgia [26,27]. These findings correlate with more recent reports that indicate a substantial increase in the age of medical cannabis users [28,29]. Although patients baseline NRS was considerably high (9/10), it represents patients who failed to respond to the standard therapy during a follow up of at least a year. Thus, our study cohort represents severe and poorly controlled fibromyalgia patients, which explains the higher symptomatic burden. Previous studies reported similar characteristics. For instance, Fiz et al. reported 37 mm VAS decrease two hours after cannabis administration (baseline VAS was 80mm) [15]. Goldenberg et al. reported a mean VAS of 81.5 mm among placebo users compared to fluoxentine- and amitriptyline-treated fibromyalgia patients [30].

Patients in our and other studies are often reporting that medical cannabis is more tolerable and with fewer adverse events compared to other therapies [31]. Similar to previous studies, we found that medical cannabis use is safe among fibromyalgia patients [7,32]. At six months follow-up, there was a relatively low rate of minor adverse events, and only 28 patients (7.6%) stopped using medical

cannabis. In concordance with the literature, we found that dizziness, dry mouth, hyperactivity, drowsiness, and gastrointestinal symptoms are all possible adverse effects of cannabis use [14,33].

In our cohort, we had a relatively low rate of adverse events. For instance, the most commonly reported adverse events after six months were dizziness (7.9%), dry mouth (6.7%), and vomiting/nausea (5.4%). Yet, comparing our findings to other studies using the same titration approach yields similar rates of the adverse events. For instance, among 2736 elderly patients (65 and older) who used medical cannabis, dizziness was reported by 9.7% after six months of use [8]. First, as mentioned above, this may be associated with the gradual titration process, which may lead to the mitigation of most of cannabis' adverse effects. Second, the evaluation of adverse events occurred only after six months of therapy. Since most of the patients developed tolerance to adverse effects in days, this may have led to lower rate of reported adverse events at six months follow-up. These findings further support the previously suggested cannabis titration approach of "start low, go slow, and stay low" to minimize both adverse events and the risk of addiction [14]. Lastly, the majority of our cohort used relatively low dosage (20 g or less per month) of cannabis at baseline and after six months (89.4% and 78.1%, respectively). The mean THC and CBD did not change between the first and last month of follow-up. These findings can also explain the low rate of adverse events, which were mostly dose-dependent. Clinicians should be aware of unjustified dose escalations (e.g., above 3 g/day in non-cancer patients) to prevent misuse or addiction to cannabis [34].

We found that patients' concerns and worries regarding cannabis prior to treatment initiation were associated with lower odds of treatment success, whereas previous experience with cannabis was associated with treatment success. We acknowledge that these findings and the observational nature of our study could constitute evidence for the strong placebo effect associated with cannabis use, and emphasize the importance of double-blinded clinical trials, especially when testing subjective outcomes such as pain and quality of life. Yet, even blinded clinical trials may be biased towards overestimating the effectiveness of medical cannabis due to the lack of the psychoactive effect of placebo substances [35].

Our study has several important limitations. First, this study was of an observational nature and could not establish causality between medical cannabis use and improvement in fibromyalgia outcomes. The improvement at six months may be alternatively explained by regression to the mean phenomenon. Since this was not a randomized controlled trial, we can recommend neither a specific dosage nor specific cannabis product. Second, the close to 30% non-respondent rate in the six months follow-up may have resulted in a non-response bias. Yet, there were no significant differences between respondents to the non-respondents at the baseline characteristics, and more than 85% of the non-respondents were still using medical cannabis at six months. In addition, we cannot evaluate the actual compliance on a monthly basis. In concordance with the vast majority of studies, data on the actual utilization of cannabis were not available. Third, the fibromyalgia diagnosis was established by the referring rheumatologist; therefore ,we could not verify that the American College of Rheumatology preliminary diagnostic criteria for fibromyalgia were fulfilled in every case [13]. Fourth, we had no control group to compare the clinical outcomes of medical cannabis use. Hence, some of the improvement may be attributed to spontaneous improvement in the course of the disease rather than medical cannabis utilization. Moreover, the patients in this study used 14 different strains, which prevented us from conducting a comparison between THC and CBD strains and products in terms of effectiveness and safety. Fifth, the change in the utilization of other drugs (than cannabis) for the treatment of fibromyalgia was based on self-reports and was prone to recall biases. Yet, we showed that most patients ceased, reduced, or at least did not change the dosage of their chronic drugs for fibromyalgia while receiving medical cannabis. Additionally, although we found that cannabis use is relatively safe among fibromyalgia patients, the conclusion should not be made about safety while driving under the influence of cannabis, as it was not a measured outcome of this study. The data of this study was provided by a registry that included cannabis users with several clinical indications. Hence, the questionnaire that was used did not include specific symptoms of fibromyalgia (e.g., fibro fog). Lastly, at this stage of medical cannabis

research, we are not in a position to identify and thus synthesize single or multiple agents that are responsible for the therapeutic effects.

5. Conclusions

Notwithstanding these limitations, the present observational study innovates by showing that medical cannabis may be an effective and safe treatment to fibromyalgia in a large cohort with six months follow up. Our data indicates that medical cannabis could be a promising therapeutic option for the treatment of fibromyalgia, especially for those who failed on standard pharmacological therapies. We show that medical cannabis is effective and safe when titrated slowly and gradually. Considering the low rates of addiction and serious adverse effects (especially compared to opioids), cannabis therapy should be considered to ease the symptom burden among those fibromyalgia patients who are not responding to standard care. Moreover, our results highlight the need for further research to identify the effect of cannabis on other clinical conditions that are associated with fibromyalgia: cognitive impairment, fatigue, and additional chronic pain syndromes. Future studies should aim to compare medical cannabis to the standard therapy of fibromyalgia, to establish the proper place of cannabis in fibromyalgia therapeutic arsenal.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Quality of life components on a 5-points Likert scale at baseline and at six months of follow-up. Table S1: Baseline characteristics of the patients stratified by response at six months follow-up. Table S2: Cannabis used by the patients. Table S3: Medical cannabis related adverse events after six months. Table S4: Symptom prevalence at intake and after six months. Table S5: Changes in other drug regimens after six months of treatment with cannabis. Table S6: Study outcomes stratified by primary vs. secondary fibromyalgia.

Author Contributions: I.S., L.B.-L.S., and V.N. are responsible for study conception and design. L.B.-L.S. extracted the data. I.S. Drafted the manuscript and conducted the statistical analysis. L.B.-L.S., M.A.-S and V.N. gave critical revisions.

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Conflicts of Interest: The authors declare no conflict of interest.

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Symptoms Relief

Symptoms Relief Among Tikun Olam Patients Treated with Medical Cannabis

A retrospective cohort study investigating the effect of cannabis on specific symptoms, such as pain, insomnia, lack of appetite, fatigue, and spasticity, in patients who commenced treatment with medical cannabis at Tikun Olam between 2009 – 2016.

Study Population: 1,338 medical cannabis patients who completed a survey before and after six months of treatment
Strains Used: Various Tikun Olam strains
Key Results:

- After at least six months of cannabis treatment, 94% of patients reported improvement in their condition
- Most patients experienced pain reduction and many reported improved sleep, mood, and appetite
- Bowel activity, concentration, and sexual function were improved by some
- 62% of patients reduced their medication consumption
- Most patients did not experience side effects from the treatment, and of those who did, dizziness and dry mouth were the most common reported

SYMPTOMS RELIEF AMONG TIKUN-OLAM PATIENTS TREATED WITH MEDICAL CANNABIS

Clinical Research Center

Soroka University Medical Center,

Be'er-Sheva, Israel

January 2016

2 Introduction

In recent years, there is an increasing use of medical products based on cannabis. There are more than 30,000 studies or literature reviews that have been published under the search words cannabis, cannabinoids and marijuana, almost half of which have been published in the last five years (PubMed Central). There is a tremendous amount of evidence to support that cannabis that is taken for medical reasons is relatively safe to use, but the evidence on the effectiveness of the medical cannabis are complex, strong for certain indications and weak for others.

In 2007, the Ministry of Health (MOH) began issuing licenses for the use of cannabis for medical treatment in patients with a variety of symptoms. Currently, there are about 23,000 active patients that have received licenses for medical cannabis.

This is a retrospective cohort study aiming to investigate the effect of cannabis on specific symptoms as an indication for the cannabis treatment (pain, insomnia, lack of appetite, fatigue and spasticity), in patients who commenced treatment with medical cannabis at TO between the years 2009-2016, and answered the company's questionnaires.

- We hypothesize that cannabis will be associated with symptoms relief.
- We hypothesize that cannabis will reduce use in antidepressants, painkillers and sleeping pills and improve quality of life measures, such as sleep, appetite and mood.

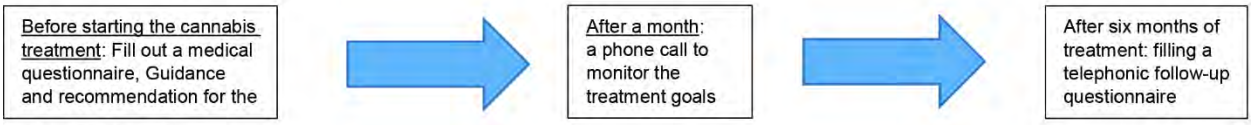
3 Methods

Once the patients receive a license to purchase cannabis products from Tikun-Olam (TO), he/she receives a 45-minute guidance session, conducted by a trained nurse.

In order to determine the treatment plan, the patients are asked to fill in a medical questionnaire, which includes personal details, diseases, symptoms, medications, quality of life measurements, etc.

A month after the training, a pollster from TO calls the patient and Checks if there is an improvement in his/her condition, if there is no relief, partial relief or the patient reported on side effects, the pollster seeks to coordinate a conversation with a nurse to improve the treatment (adjusting dosage, strain or consumption method).

Six months after commencing the cannabis treatment, a pollster from TO are conducted again with a questionnaire on the impact of cannabis on diseases, symptoms, medication, quality of life measurements and adverse events.



4 Objectives

Primary objective:

- To examine the effect of cannabis on symptoms relief (especially the main symptoms- pain, insomnia, lack of appetite, fatigue and spasticity).

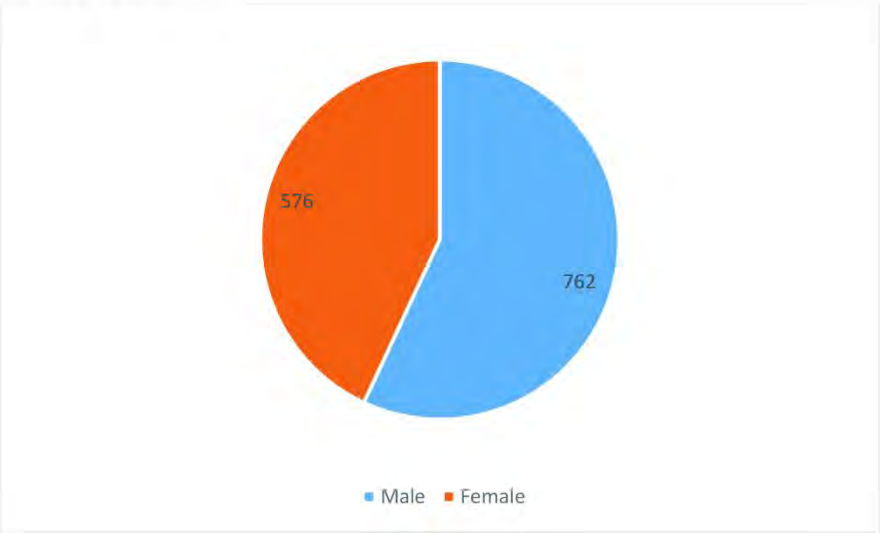
Secondary objectives:

- To examine the effect of cannabis on medications use (especially antidepressants, painkillers and sleeping pills).
- To examine the effect of cannabis on measures of quality of life such as sleep, appetite and mood

5 Population

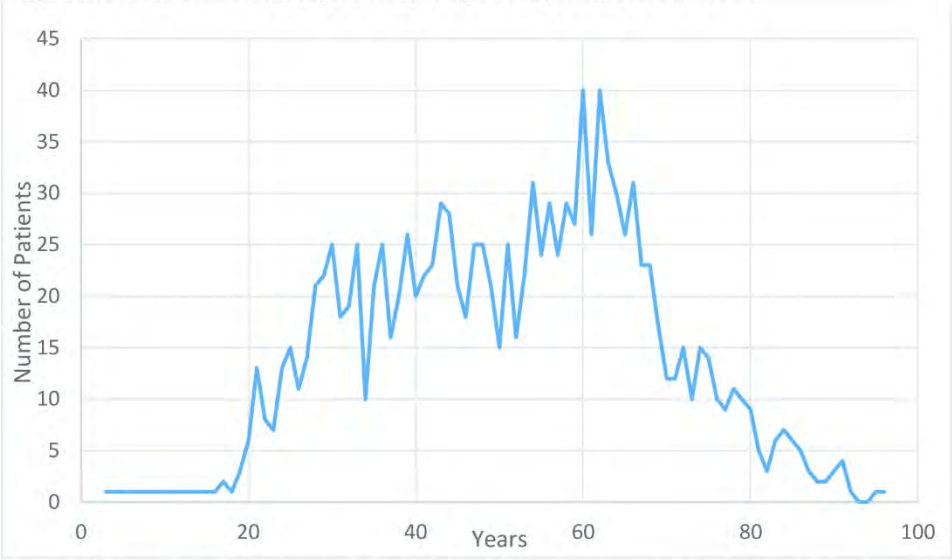
There is a total of 1338 patients who completed a questionnaire before, and after six months of treatment (762 males, see figure 1).

Figure 1. Gender



The average age of the patient in the beginning of the treatment was 51.59 (SD- 16.7) (see figure 2).

Figure 2. The patient's age at the beginning of the treatment

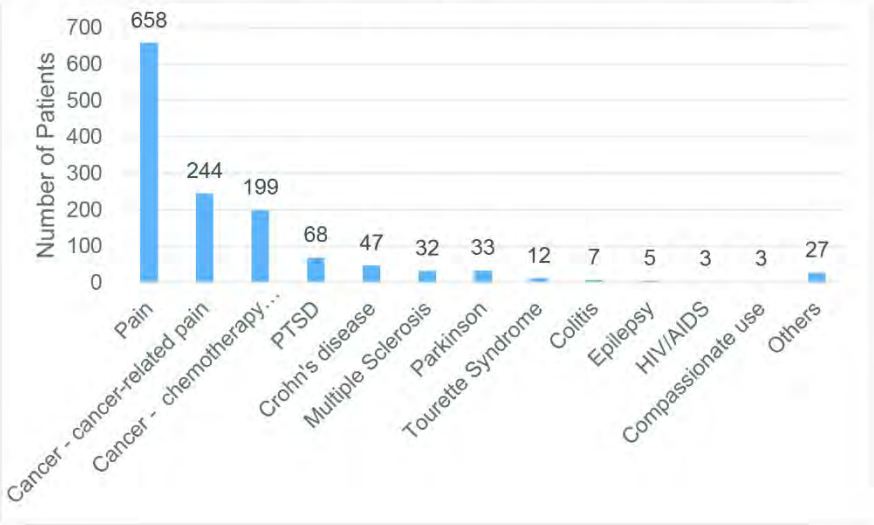


55 patients did not answer to this question.

Currently, only a qualified physician can write a recommendation for medical cannabis for specific medical indications listed in Appendix 1 on page 45.

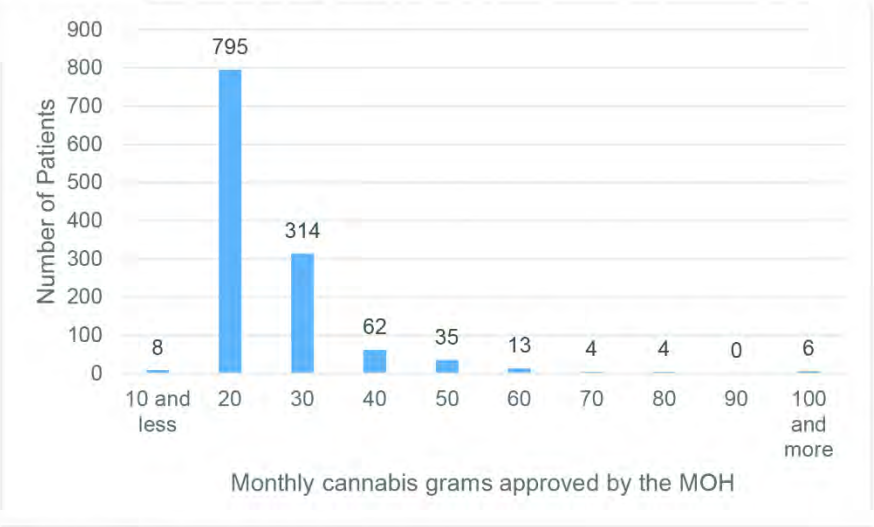
Most of the patients where licensed medical cannabis under the pain and cancer indications (see figure 3).

Figure 3. The indication under which the medical cannabis license was received



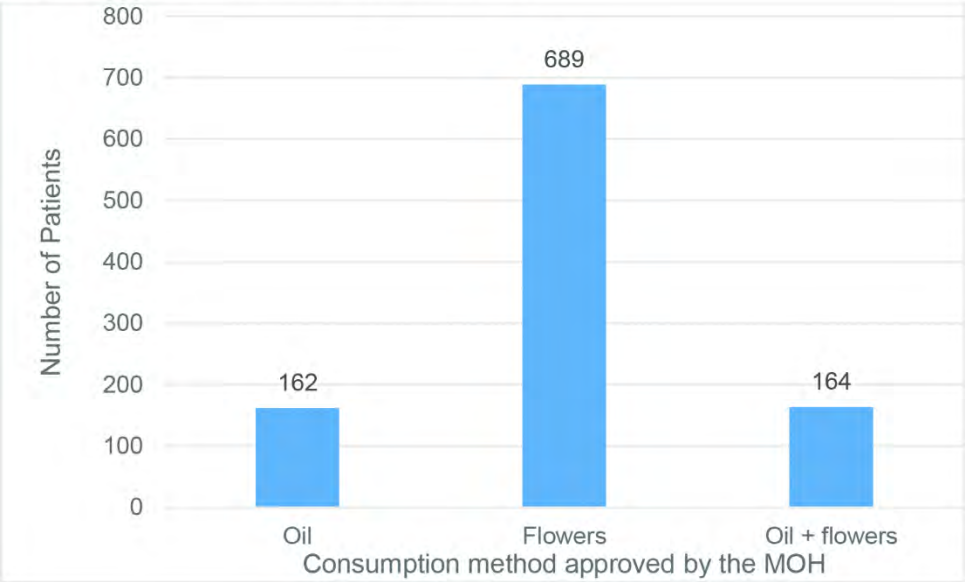
The doctor's recommendation for cannabis is submitted to the medical cannabis unit at the Health Ministry (YAKAR) that issues a medical cannabis license under the patient's name. The license indicates the approved monthly dose (10-120 grams) and the consumption method approved (see figures 4-5).

Figure 4. Approved monthly dose



97 patients did not answer to this question

Figure 5. Approved consumption method



323 patients did not answer to this question (in the past it was not part of the license).

About a third of the patients described that they suffer from more than one medical condition (see figure 6).

Figure 6. Number of diseases per patients

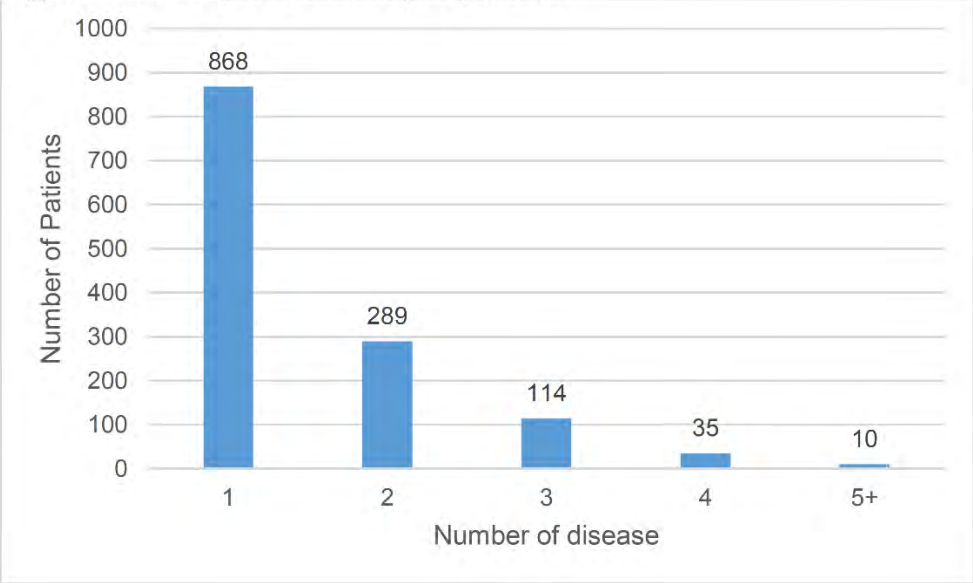


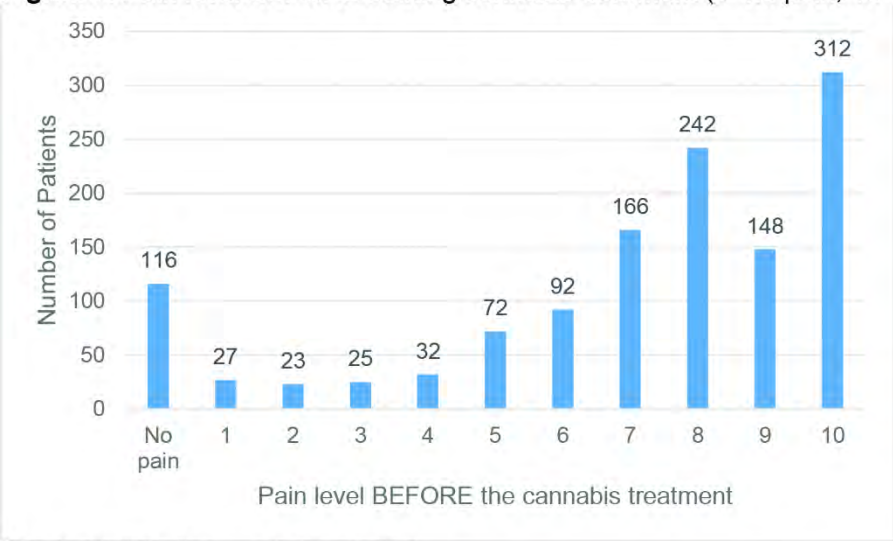
Table 1 showing the number of patients (percentage) who reported on the diseases listed and the mean disease duration (SD). The most common indication is cancer with 27% of the patients.

Table 1. Disease frequency, duration and severity.

	Total Responses (%)	Mean disease duration (SD)
Cancer	454 (27.1%)	2.6 (3.7)
Pain	195 (11.6%)	7.9 (6.2)
Spinal Disk Herniation	184 (11%)	7.8 (6)
Diabetes	117 (7%)	10.7 (7.4)
Hypertension	104 (6.2%)	10 (6.9)
Post-Traumatic Stress Disorder (PTSD)	93 (5.5%)	9.8 (6.3)
Arthritis	79 (4.7%)	9.8 (6.9)
Fibromyalgia	79 (4.7%)	8.5 (5.6)
Crohn's Disease	53 (3.2%)	9.7 (6.8)
Migraines	44 (2.6%)	13 (6.6)
Parkinson's Disease and Parkinsonism	37 (2.2%)	6.9 (4.6)
Multiple Sclerosis	33 (2%)	10 (7.1)
Heart Disease	29 (1.7%)	9.3 (6.9)
Depression	24 (1.4%)	7.6 (6.8)
Degenerative Disc Disease	15 (0.9%)	8.8 (5.8)
Colitis	13 (0.8%)	9.3 (6.7)
Asthma	11 (0.7%)	19.8 (0.5)
Tourette syndrome	10 (0.6%)	10.1 (7)
Dementia	10 (0.6%)	2.7 (4.1)
Stroke	9 (0.5%)	4.7 (4.3)
Epilepsy	8 (0.5%)	13 (7.7)
Chronic Obstructive Pulmonary Disease (COPD)	8 (0.5%)	4.3 (1.5)
Irritable Bowel Syndrome	7 (0.4%)	16 (8)
ALS	7 (0.4%)	11.5 (12)
Obsessive Compulsive Disorder	7 (0.4%)	5.3 (3)
Attention Deficit Hyperactivity Disorder (ADHD)	5 (0.3%)	9.8 (6.3)
Autism	5 (0.3%)	13.5 (9.2)
Anxiety Disorder	4 (0.2%)	8.3 (2.9)
Glaucoma	4 (0.2%)	11 (12.7)
HIV/AIDS	4 (0.2%)	7.8 (10.3)
Hepatitis	4 (0.2%)	7.5 (0.7)
Gastroesophageal Reflux Disease (GERD)	3 (0.2%)	11.7 (7.2)
Anemia	3 (0.2%)	10.3 (9.5)
Seizure Disorder (non epilepsy)	3 (0.2%)	0 (0)
Bipolar Disorder	2 (0.1%)	20 (0)
Diverticulitis	2 (0.1%)	12.5 (10.6)
Schizophrenia	2 (0.1%)	16 (0)
Endometriosis	1 (0.1%)	0 (0)

Before the cannabis treatment each patient is asked to rate his pain level on a scale of 0 (no pain) to 10 (unbearable pain) (see figure 7), the median pain level is 8 (IQR- 7-10).

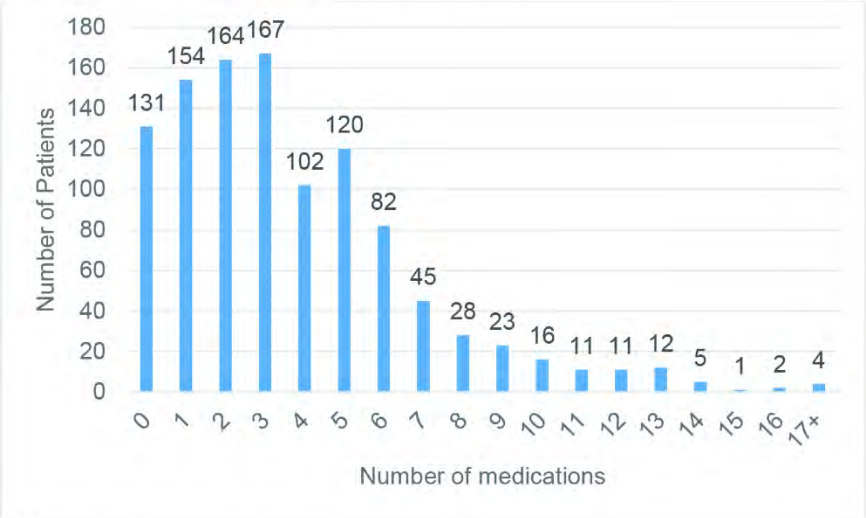
Figure 7. Pain level BEFORE starting cannabis treatment (0- no pain, 10- unbearable pain):



83 patients did not answer to this question

90% of the patient reported taking medications, 58% of them consume more than two different medications every day (see figure 8).

Figure 8. Number of medications per patient



260 patients did not answer to this question

Each patient is asked to go over a list of symptoms and to describe it. The severity of the symptoms is rated by nears (mild, moderate and severe) according to the patient's condition Appendix 2 on pages 46-51, (see table 2).

Table 2. Symptoms frequency and severity

	Total Responses (%)	Mild (%)	Moderate (%)	Severe (%)
Paresthesia (prickling)	635 (47.5%)	141 (22%)	191 (30%)	303 (48%)
Spasticity	578 (43.2%)	154 (27%)	202 (35%)	222 (38%)
Burning Sensation	486 (36.3%)	103 (21%)	117 (24%)	266 (55%)
Sleep Problems	413 (30.9%)	30 (7%)	147 (36%)	236 (57%)
Pruritus (itching)	403 (30.1%)	182 (45%)	124 (31%)	97 (24%)
Weakness	349 (26.1%)	65 (19%)	181 (52%)	103 (30%)
Tremor	348 (26%)	198 (57%)	82 (24%)	68 (20%)
Insomnia	302 (22.6%)	44 (15%)	87 (29%)	171 (57%)
Exhaustion	286 (21.4%)	59 (21%)	159 (56%)	68 (24%)
Limited Mobility	254 (19%)	54 (21%)	105 (41%)	95 (37%)
Vomiting	234 (17.5%)	94 (40%)	93 (40%)	47 (20%)
Anxiety	216 (16.1%)	77 (36%)	92 (43%)	47 (22%)
Dry Mouth	213 (15.9%)	90 (42%)	85 (40%)	38 (18%)
Digestion Problems	208 (15.5%)	34 (16%)	109 (52%)	65 (31%)
Drowsiness	200 (14.9%)	66 (33%)	103 (52%)	31 (16%)
Depression	194 (14.5%)	72 (37%)	78 (40%)	44 (23%)
Headache	194 (14.5%)	64 (33%)	81 (42%)	49 (25%)
Constipation	185 (13.8%)	60 (32%)	77 (42%)	48 (26%)
Dizziness	161 (12%)	82 (51%)	59 (37%)	20 (12%)
Respiratory Problems	128 (9.6%)	48 (38%)	64 (50%)	16 (13%)
Cognitive Impairment	127 (9.5%)	60 (47%)	51 (40%)	16 (13%)
Visual Impairment	118 (8.8%)	70 (59%)	31 (26%)	17 (14%)
Numbness	113 (8.4%)	33 (29%)	42 (37%)	38 (34%)
Hypertension (high blood pressure)	105 (7.8%)	74 (70%)	25 (24%)	6 (6%)
Nausea	95 (7.1%)	42 (44%)	31 (33%)	22 (23%)
Irritated Eyes	93 (7%)	51 (55%)	37 (40%)	5 (5%)
Tinnitus (ringing in the ears)	91 (6.8%)	38 (42%)	29 (32%)	24 (26%)
Increased Appetite	85 (6.4%)	41 (48%)	33 (39%)	11 (13%)
Diarrhea	77 (5.8%)	32 (42%)	30 (39%)	15 (19%)
Tachycardia (rapid heartbeat)	69 (5.2%)	51 (74%)	16 (23%)	2 (3%)
Spasms	66 (4.9%)	24 (36%)	29 (44%)	13 (20%)
Hives	50 (3.7%)	29 (58%)	9 (18%)	12 (24%)
Hypotension (low blood pressure)	33 (2.5%)	25 (76%)	6 (18%)	2 (6%)
Hallucinations	33 (2.5%)	15 (45%)	12 (36%)	6 (18%)
Mucositis	30 (2.2%)	10 (33%)	14 (47%)	6 (20%)
Speech Impairment	23 (1.7%)	11 (48%)	7 (30%)	5 (22%)
Seizures	19 (1.4%)	4 (21%)	8 (42%)	7 (37%)
Bradycardia (slow heart beat)	4 (0.3%)	4 (100%)	0 (0%)	0 (0%)

The patients were asked to rate their quality of life aspects (sleep, appetite, concentration and bowel activity) from very good to severe difficulty (see table 3). As shown in Table 3, 74% of the responders had sleeping problems before the cannabis treatment, 41% suffered from lack of appetite, 38% from concentration difficulties, and 29% suffered from difficulty in their bowel activity before the treatment.

Table 3. Ability to perform the following activities of daily living BEFORE beginning cannabis treatment

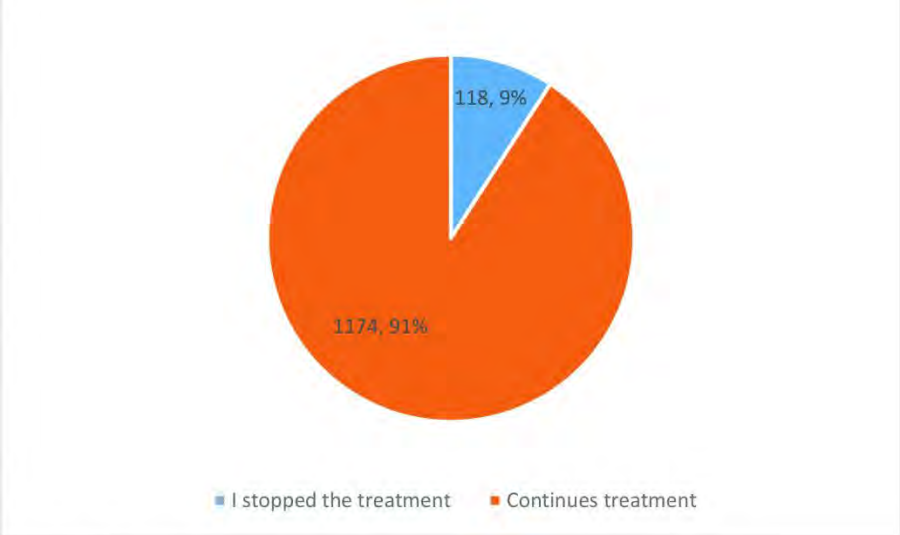
	Very Good	Good	No difficulty	Moderate difficulty	Severe difficulty
Sleep	37	63	157	361	395
Appetite	105	149	322	260	143
Concentration	90	130	362	282	76
Bowel Activity	187	122	266	221	155

6 Results

6.1 Characteristics of consumption

Ninety-one present of the 1292 patients who answered this question were compliant with the treatment (see figure 9).

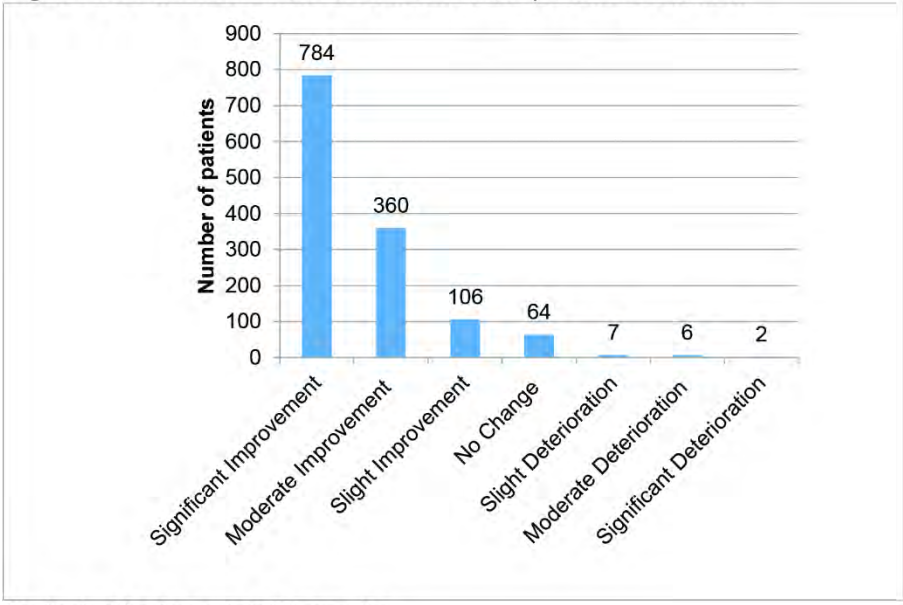
Figure 9. Compliance



46 patients did not answer to this question

At least six month after beginning the treatment the patients were asked to rate the effect of the cannabis on their medical condition from significant improvement – no change – significant deterioration. 94% of the patients reported on improvement, 5% no change and 1% of the 1329 responders reported on deterioration (see figure 10).

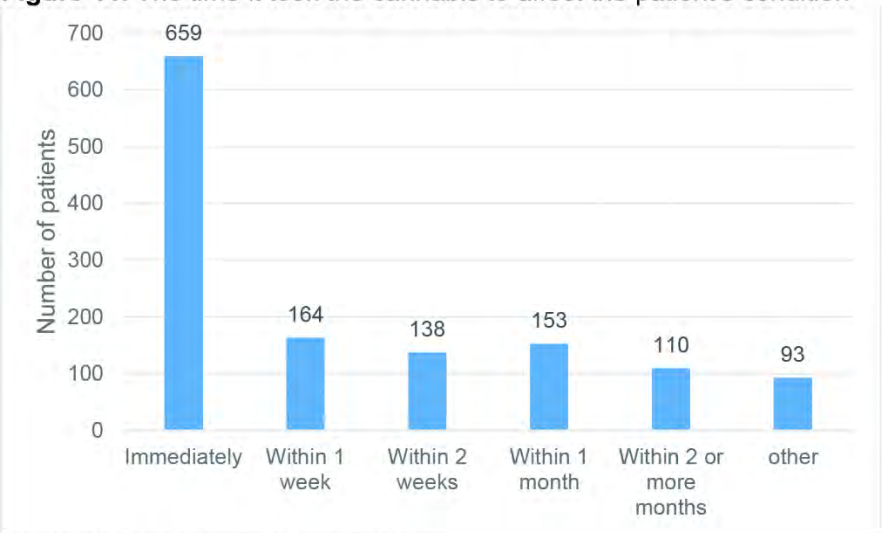
Figure 10. The effect of the treatment on the patient's condition.



9 patients did not answer to this question

We asked the patients to estimate how long it took the cannabis to affect their medical condition, 19% of the patients reported it helped within one month or more to find the suitable strain and dosage (see figure 11).

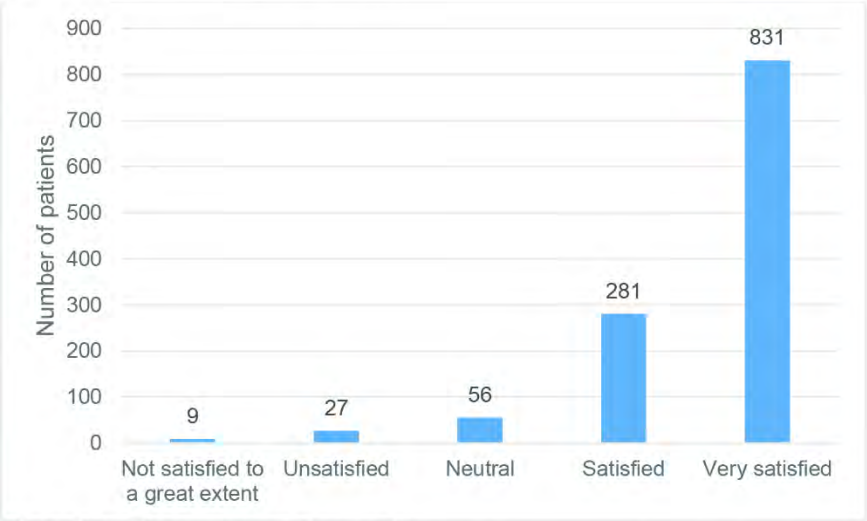
Figure 11. The time it took the cannabis to affect the patient's condition



21 patients did not answer to this question

Ninety- two present of the 1204 patients who answered this question were satisfied with the treatment (see figure 12).

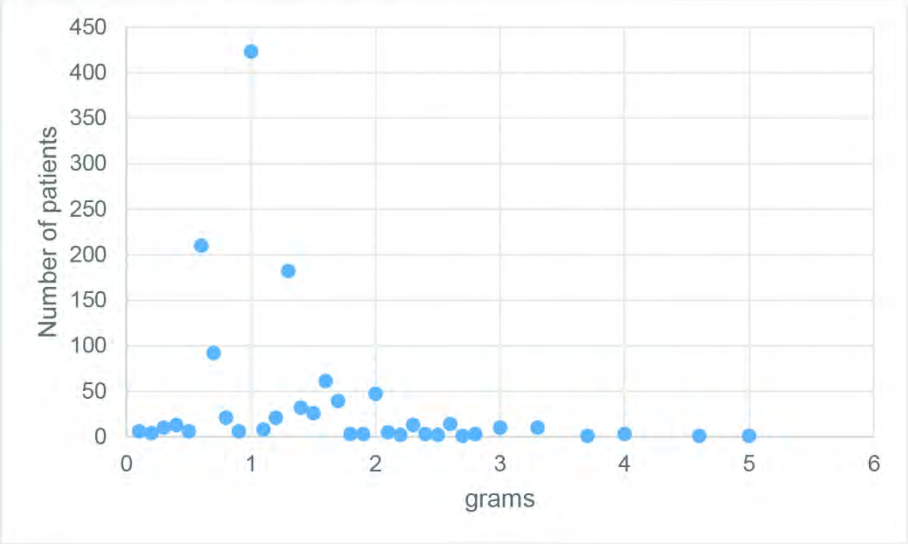
Figure 12. Treatment satisfaction



134 patients did not answer to this question

The average dose consumed is 1.14 grams a day, with standard deviation of 0.5 gram (see figure 13).

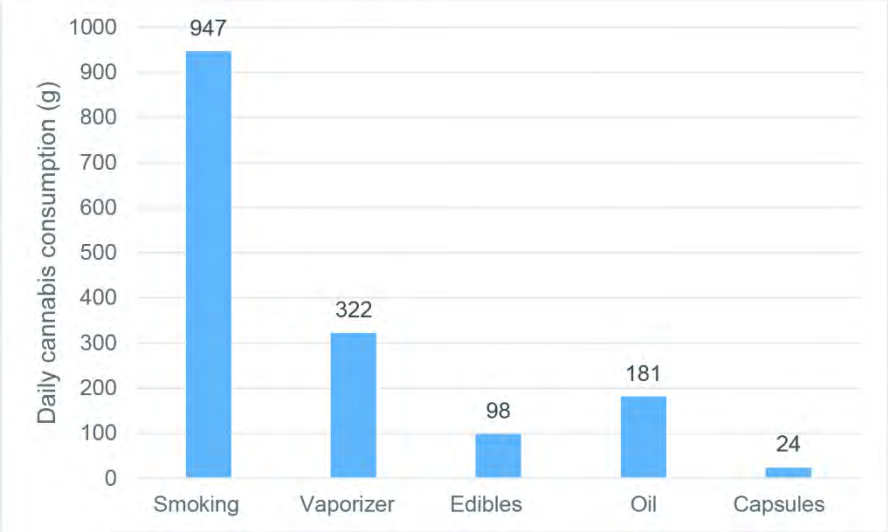
Figure 13. Daily cannabis consumption (g)



56 patients did not answer to this question

234 patient use more than one consumption method. 71% of the patients smoke cannabis and only 29% find an alternative for smoking (see figure 14).

Figure 14. Method of consumption



6.2 Symptoms relief

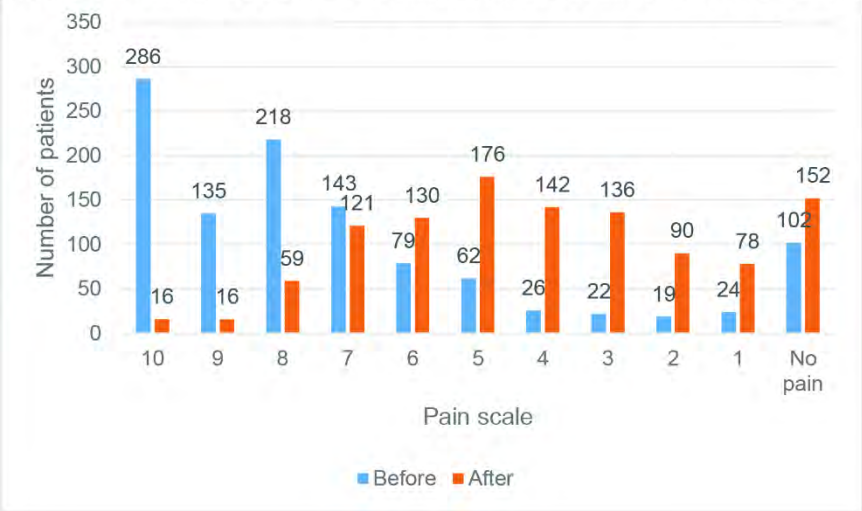
For each symptom that reported by the patient on the beginning of the treatment, we asked the patients to estimate the change in the treatment period, from significant improvement to significant deterioration (see table 4).

Table 4. The effect of six-month cannabis treatment on the symptoms reported at the beginning of the treatment

	Significant Improvement N (%)	Moderate Improvement N (%)	Slight Improvement N (%)	No Change N (%)	Slight Deterioration N (%)	Moderate Deterioration N (%)	Significant Deterioration N (%)
Anxiety	46 (28%)	50 (30%)	32 (19%)	33 (20%)	1 (1%)	1 (1%)	2 (1%)
Burning Sensation	68 (22%)	85 (27%)	72 (23%)	80 (25%)	6 (2%)	2 (1%)	2 (1%)
Constipation	20 (19%)	23 (21%)	16 (15%)	46 (43%)	0 (0%)	2 (2%)	0 (0%)
Depression	49 (34%)	46 (32%)	21 (14%)	26 (18%)	1 (1%)	1 (1%)	1 (1%)
Diarrhea	9 (21%)	9 (21%)	6 (14%)	19 (44%)	0 (0%)	0 (0%)	0 (0%)
Digestion Problems	26 (19%)	30 (22%)	25 (18%)	53 (39%)	1 (1%)	0 (0%)	1 (1%)
Dizziness	20 (20%)	17 (17%)	19 (19%)	42 (41%)	1 (1%)	2 (2%)	1 (1%)
Drowsiness	18 (13%)	27 (20%)	28 (21%)	59 (44%)	2 (1%)	1 (1%)	0 (0%)
Exhaustion	29 (14%)	49 (24%)	39 (19%)	81 (39%)	5 (2%)	4 (2%)	1 (0%)
Headache	24 (20%)	31 (26%)	20 (17%)	39 (33%)	1 (1%)	3 (3%)	1 (1%)
Hypertension (high blood pressure)	13 (18%)	23 (32%)	8 (11%)	28 (38%)	1 (1%)	0 (0%)	0 (0%)
Hives	3 (14%)	1 (5%)	7 (32%)	11 (50%)	0 (0%)	0 (0%)	0 (0%)
Increased Appetite	8 (14%)	7 (12%)	6 (10%)	28 (47%)	6 (10%)	2 (3%)	2 (3%)
Insomnia	63 (30%)	71 (34%)	32 (15%)	36 (17%)	2 (1%)	0 (0%)	3 (1%)
Irritated Eyes	4 (8%)	0 (0%)	7 (14%)	34 (69%)	3 (6%)	1 (2%)	0 (0%)
Limited Mobility	29 (14%)	26 (12%)	29 (14%)	112 (53%)	7 (3%)	5 (2%)	3 (1%)
Hypotension (low blood pressure)	2 (8%)	6 (24%)	2 (8%)	14 (56%)	0 (0%)	1 (4%)	0 (0%)
Numbness	8 (9%)	10 (12%)	10 (12%)	51 (60%)	2 (2%)	2 (2%)	2 (2%)
Paresthesia (prickling)	87 (19%)	97 (21%)	102 (22%)	158 (34%)	12 (3%)	4 (1%)	5 (1%)
Pruritus (itching)	52 (25%)	42 (20%)	50 (24%)	58 (27%)	6 (3%)	2 (1%)	2 (1%)
Tachycardia (rapid heartbeat)	7 (19%)	5 (14%)	1 (3%)	24 (65%)	0 (0%)	0 (0%)	0 (0%)
Bradycardia (slow heart beat)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Seizures	4 (29%)	4 (29%)	3 (21%)	3 (21%)	0 (0%)	0 (0%)	0 (0%)
Sleep Problems	101 (36%)	87 (31%)	39 (14%)	49 (17%)	2 (1%)	1 (0%)	4 (1%)
Spasms	8 (20%)	8 (20%)	7 (18%)	15 (38%)	1 (3%)	0 (0%)	1 (3%)
Spasticity	99 (24%)	99 (24%)	84 (21%)	112 (27%)	8 (2%)	2 (0%)	4 (1%)
Tinnitus (ringing in the ears)	7 (12%)	4 (7%)	6 (10%)	38 (66%)	2 (3%)	1 (2%)	0 (0%)
Tremor	47 (22%)	54 (26%)	50 (24%)	57 (27%)	1 (0%)	0 (0%)	1 (0%)
Vomiting	38 (31%)	26 (21%)	24 (19%)	32 (26%)	3 (2%)	0 (0%)	1 (1%)
Weakness	24 (10%)	50 (21%)	52 (22%)	100 (42%)	10 (4%)	1 (0%)	0 (0%)
Nausea	13 (30%)	8 (19%)	10 (23%)	10 (23%)	2 (5%)	0 (0%)	0 (0%)
Cognitive Impairment	9 (9%)	13 (14%)	11 (12%)	53 (56%)	6 (6%)	2 (2%)	1 (1%)
Respiratory Problems	11 (17%)	6 (9%)	6 (9%)	37 (57%)	4 (6%)	0 (0%)	1 (2%)
Dry Mouth	9 (6%)	9 (6%)	17 (12%)	101 (71%)	5 (3%)	1 (1%)	1 (1%)
Speech Impairment	1 (6%)	4 (22%)	3 (17%)	7 (39%)	3 (17%)	0 (0%)	0 (0%)
Hallucinations	8 (44%)	4 (22%)	2 (11%)	3 (17%)	0 (0%)	1 (6%)	0 (0%)
Mucositis	0 (0%)	2 (25%)	2 (25%)	4 (50%)	0 (0%)	0 (0%)	0 (0%)
Visual Impairment	1 (1%)	3 (4%)	0 (0%)	62 (78%)	11 (14%)	1 (1%)	2 (3%)

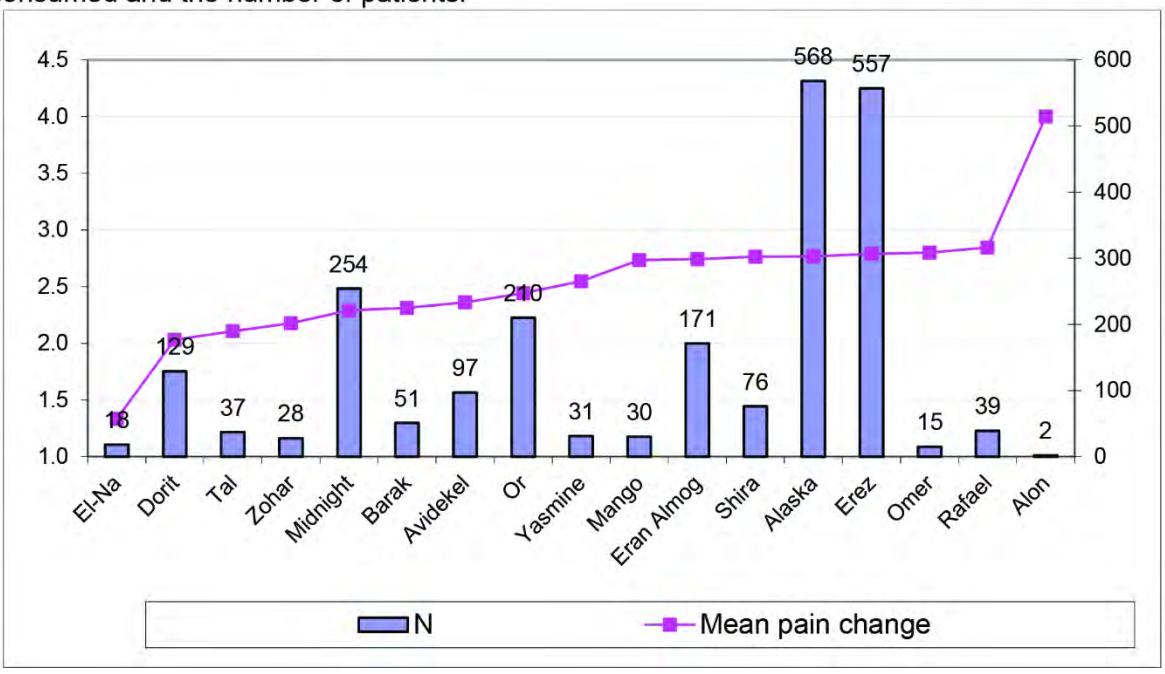
Most of the patients experienced pain reduction (see figure 15). The median pain scale was reduced from 8 (7-10 IQR) to 5 (3-6 IQR).

Figure 15. Pain scale before and after cannabis treatment in 1116 patients who answered both questions.



We checked if the delta in pain scale is high for certain strains and low in others (see figure 16).

Figure 16. The Δ in pain scale before and after at least six month of treatment according to the strain consumed and the number of patients.



The patients how reported on an improvement in a specific symptom, were asked to estimate what strain was responsible for the improvement. The distribution of the strain according to the different symptoms Shown in table 5.

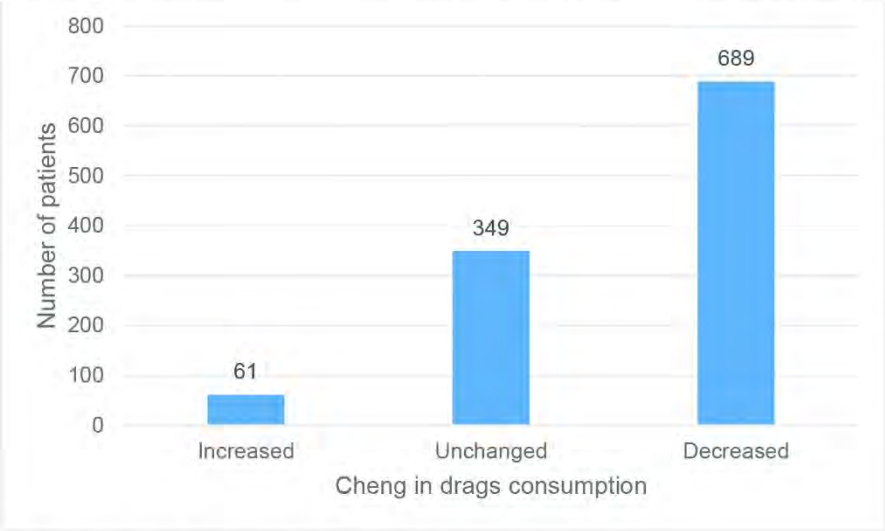
Table 5. The cannabis strain that was responsible for the positive effect for each symptom.

	Barak	Dorit	Avidekel	Shira	Eran Almog	Or	Rafael	Alaska	Midnight	Erez
Anxiety	0% (0)	6% (3)	10% (5)	4% (2)	8% (4)	6% (3)	6% (3)	19% (10)	15% (8)	25% (13)
Burning Sensation	2% (2)	4% (5)	4% (4)	3% (3)	2% (2)	4% (5)	4% (4)	31% (35)	7% (8)	39% (44)
Constipation	0% (0)	5% (1)	0% (0)	11% (2)	0% (0)	5% (1)	0% (0)	37% (7)	16% (3)	26% (5)
Depression	0% (0)	2% (1)	5% (2)	0% (0)	7% (3)	7% (3)	5% (2)	45% (19)	10% (4)	17% (7)
Diarrhea	0% (0)	0% (0)	8% (1)	0% (0)	8% (1)	0% (0)	0% (0)	50% (6)	8% (1)	25% (3)
Digestion Problems	0% (0)	6% (2)	3% (1)	3% (1)	6% (2)	3% (1)	0% (0)	41% (13)	13% (4)	25% (8)
Dizziness	6% (1)	12% (2)	6% (1)	6% (1)	12% (2)	0% (0)	0% (0)	24% (4)	6% (1)	18% (3)
Drowsiness	0% (0)	0% (0)	10% (3)	7% (2)	20% (6)	3% (1)	3% (1)	27% (8)	7% (2)	23% (7)
Exhaustion	0% (0)	2% (1)	2% (1)	7% (3)	10% (4)	2% (1)	7% (3)	40% (17)	7% (3)	19% (8)
Headache	0% (0)	0% (0)	17% (4)	8% (2)	17% (4)	0% (0)	4% (1)	21% (5)	8% (2)	25% (6)
Hypertension (high blood pressure)	0% (0)	13% (1)	13% (1)	0% (0)	0% (0)	0% (0)	0% (0)	38% (3)	13% (1)	25% (2)
Hives	25% (1)	0% (0)	25% (1)	0% (0)	0% (0)	0% (0)	0% (0)	25% (1)	25% (1)	0% (0)
Increased Appetite	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	50% (3)	17% (1)	33% (2)
Insomnia	2% (2)	4% (4)	1% (1)	2% (2)	15% (16)	9% (10)	0% (0)	15% (16)	10% (11)	41% (45)
Irritated Eyes	20% (1)	0% (0)	20% (1)	0% (0)	20% (1)	0% (0)	0% (0)	20% (1)	0% (0)	20% (1)
Limited Mobility	4% (1)	0% (0)	8% (2)	8% (2)	8% (2)	4% (1)	8% (2)	27% (7)	12% (3)	23% (6)
Hypotension (low blood pressure)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)	0% (0)
Numbness	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	17% (1)	0% (0)	33% (2)	0% (0)	50% (3)
Paresthesia (prickling)	1% (1)	1% (1)	3% (4)	4% (5)	5% (6)	7% (8)	3% (4)	32% (38)	7% (8)	36% (42)
Pruritus (itching)	1% (1)	6% (5)	5% (4)	1% (1)	0% (0)	5% (4)	0% (0)	35% (29)	5% (4)	37% (31)
Tachycardia (rapid heartbeat)	0% (0)	0% (0)	0% (0)	0% (0)	25% (1)	0% (0)	0% (0)	50% (2)	0% (0)	25% (1)
Bradycardia (slow heart beat)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Seizures	0% (0)	0% (0)	40% (2)	0% (0)	20% (1)	0% (0)	0% (0)	0% (0)	0% (0)	40% (2)
Sleep Problems	3% (4)	3% (5)	2% (3)	1% (2)	15% (23)	5% (8)	1% (1)	16% (25)	10% (15)	40% (61)
Spasms	0% (0)	0% (0)	0% (0)	0% (0)	9% (1)	9% (1)	0% (0)	45% (5)	9% (1)	27% (3)
Spasticity	1% (1)	3% (4)	4% (5)	3% (3)	3% (4)	6% (7)	2% (2)	34% (40)	8% (10)	32% (38)
Tinnitus (ringing in the ears)	0% (0)	14% (1)	0% (0)	0% (0)	0% (0)	29% (2)	0% (0)	14% (1)	29% (2)	14% (1)
Tremor	0% (0)	1% (1)	5% (4)	0% (0)	7% (5)	10% (7)	3% (2)	33% (24)	8% (6)	29% (21)
Vomiting	2% (1)	0% (0)	2% (1)	6% (3)	12% (6)	2% (1)	6% (3)	32% (16)	16% (8)	20% (10)
Weakness	0% (0)	0% (0)	9% (4)	9% (4)	4% (2)	2% (1)	2% (1)	36% (16)	11% (5)	22% (10)
Nausea	0% (0)	0% (0)	5% (1)	9% (2)	0% (0)	0% (0)	0% (0)	50% (11)	14% (3)	23% (5)
Cognitive Impairment	0% (0)	10% (1)	0% (0)	20% (2)	20% (2)	0% (0)	0% (0)	10% (1)	10% (1)	30% (3)
Respiratory Problems	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	14% (1)	0% (0)	14% (1)	0% (0)	71% (5)
Dry Mouth	0% (0)	0% (0)	0% (0)	0% (0)	13% (1)	0% (0)	0% (0)	63% (5)	13% (1)	13% (1)
Speech Impairment	0% (0)	50% (1)	50% (1)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Hallucinations	0% (0)	13% (1)	13% (1)	13% (1)	0% (0)	13% (1)	0% (0)	25% (2)	13% (1)	13% (1)
Mucositis	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	100% (1)
Visual Impairment	0% (0)	25% (1)	0% (0)	0% (0)	50% (2)	0% (0)	0% (0)	25% (1)	0% (0)	0% (0)

6.3 Medications use

62% of the patients reduced their medication consumption (see figure 17). 1338 patient reduced 1517 medications, an average of 2.5 medications per patient. In addition, there was a dosage decrease in 336 medications.

Figure 17. Change in medication consumption since starting the cannabis treatment

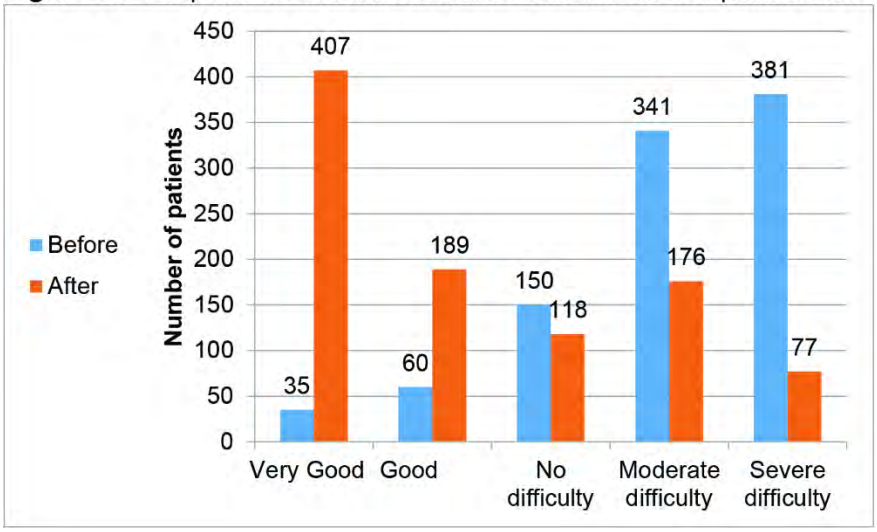


193 patients did not answer to this question

6.4 Quality of life

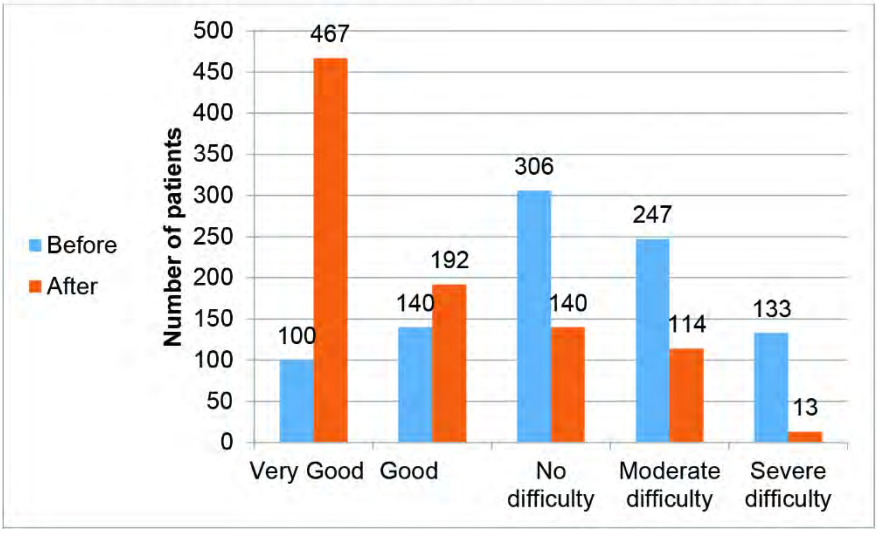
Before the cannabis treatment there were 722 patients who reported sleep difficulty (74%), and after at list six month of treatment this number was reduced to 253 (26%) (see figure 18).

Figure 18. Sleep before and after cannabis treatment in 967 patients who answered both questions.



Before the cannabis treatment there were 380 patients who reported on appetite difficulty (41%), and after at list six month of treatment this number was reduced to 127 (13%) (see figure 19).

Figure 19. Appetite before and after cannabis treatment in 926 patients who answered both questions.



Before the cannabis treatment, there were 342 patients who reported on difficulty in their ability to concentrate (38%), and after at list six month of treatment this number was reduced to 249 (28%) (see figure 20).

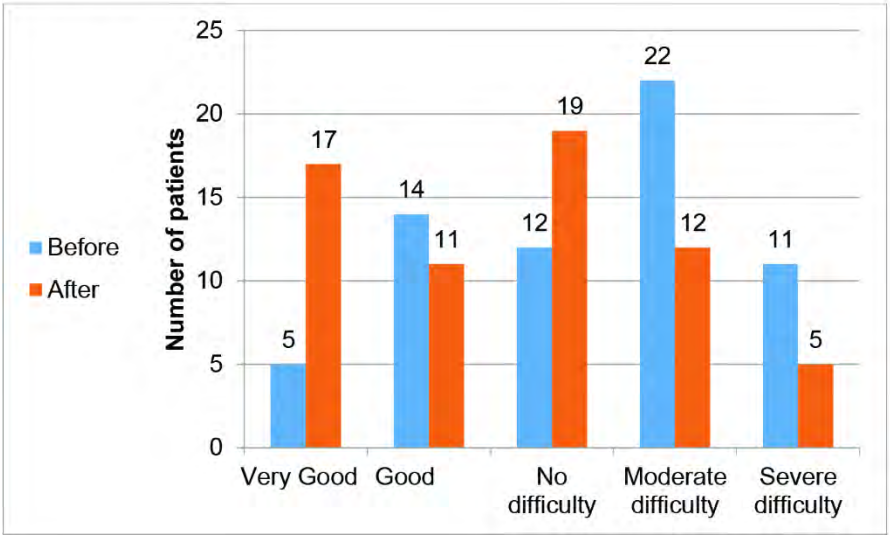
Figure 20. Concentration before and after cannabis treatment in 891 patients who answered both questions.

Before the cannabis treatment, there were 346 patients who reported on difficulty in bowel activity (39%), and after at list six month of treatment this number was reduced to 232 (26%) (see figure 21).

Figure 21. Bowel Activity before and after cannabis treatment in 880 patients who answered both questions.

Before the cannabis treatment, there were 33 patients who reported on difficulty in sexual function (51%) and after at list six month of treatment this number was reduced to 17 (26%) (see figure 22).

Figure 22. Sexual Function before and after cannabis treatment in 64 patients who answered both questions.



Before the cannabis treatment, there were 293 patients who reported on negative mood (28%), and after at list six month of treatment this number was reduced to 74 (7%) (see figure 23).

Figure 23. General mood before and after cannabis treatment in 1032 patients who answered both questions.

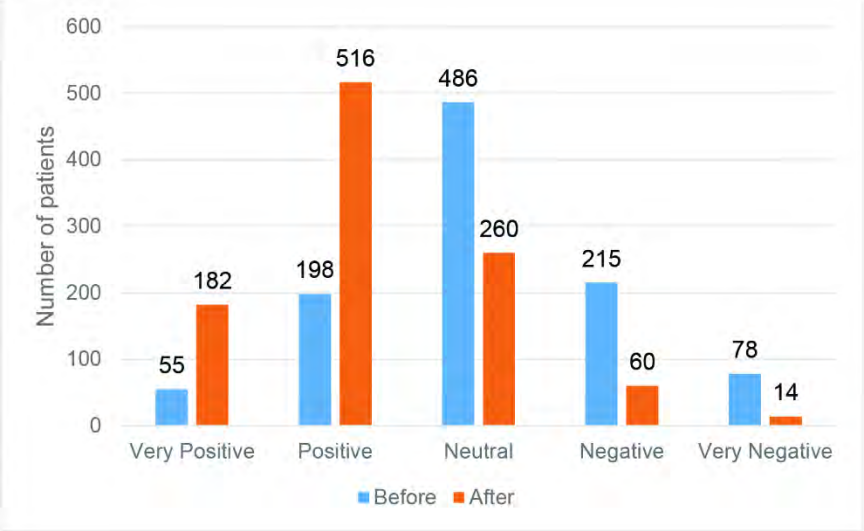


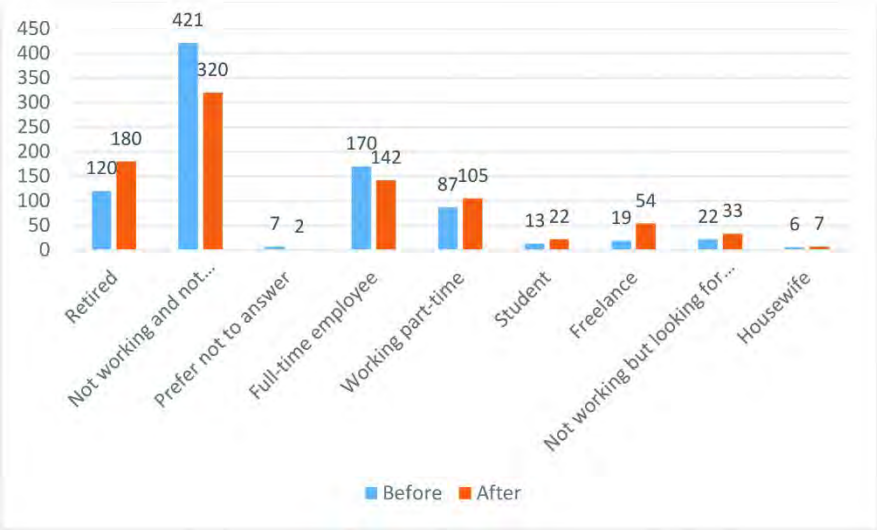
Table 6 shows the number of patients who reported pain before and during the treatment and the median (IQR) pain scale. It also shows the number of patients who reported they were hospitalized in the past six month and the number of hospitalization days. The data reveals that more patients were hospitalized during the treatment but for fewer days (reduces from 9 to 3).

Table 6. Characteristics of pain and hospitalization in the study participants.

	Before	After	T test / Chi-square	p
Pain				
Reported pain [N(%)]	1139 (85%)	1022 (76%)		
Median pain scale 1-10 (IQR)	8 (7-10)	5 (3-6)		
Hospitalization				
Reported hospitalization	129 (9%)	215 (16%)		
Mean number of hospitalization days in the past six months (SD)	8.9 (19.6)	3.17 (14.1)		

Many of those engaged in the field of cannabis hold a belief that patients who consume medical cannabis stop working. Figure 24 shows the employment status of the participants.

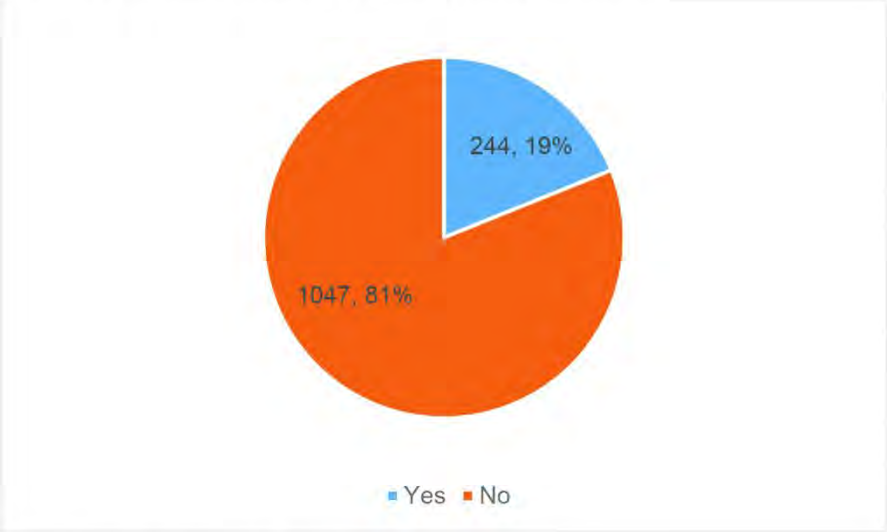
Figure 24. Employment status before and after cannabis treatment in 865 patients who answered both questions.



The majority of the patients did not experience side effects from the treatment. 244 patients reported 351 side effects, the most common were dizziness and dry mouth (see figures 25-26).

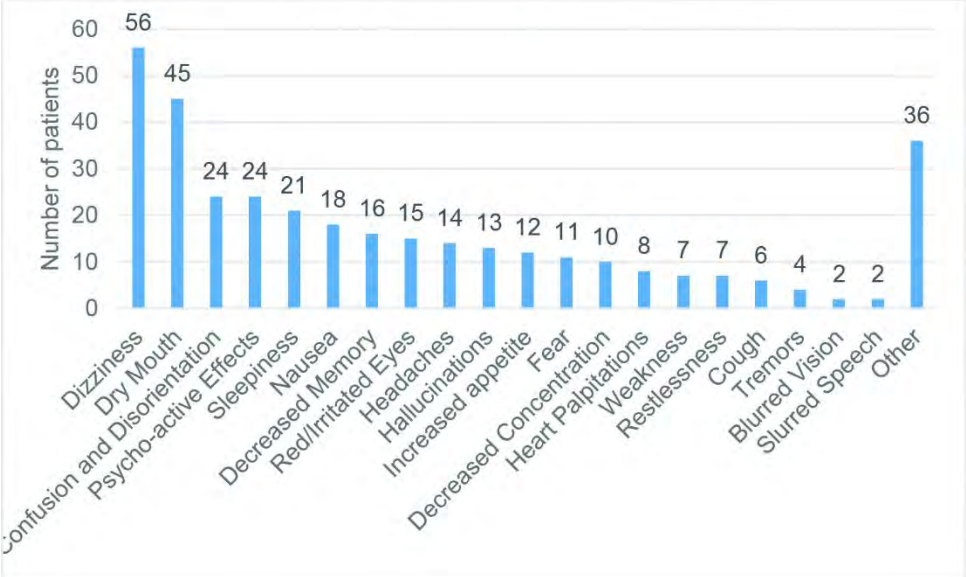
6.5 Side effects

Figure 25. Side effects during the cannabis treatment



46 patients did not answer to this question

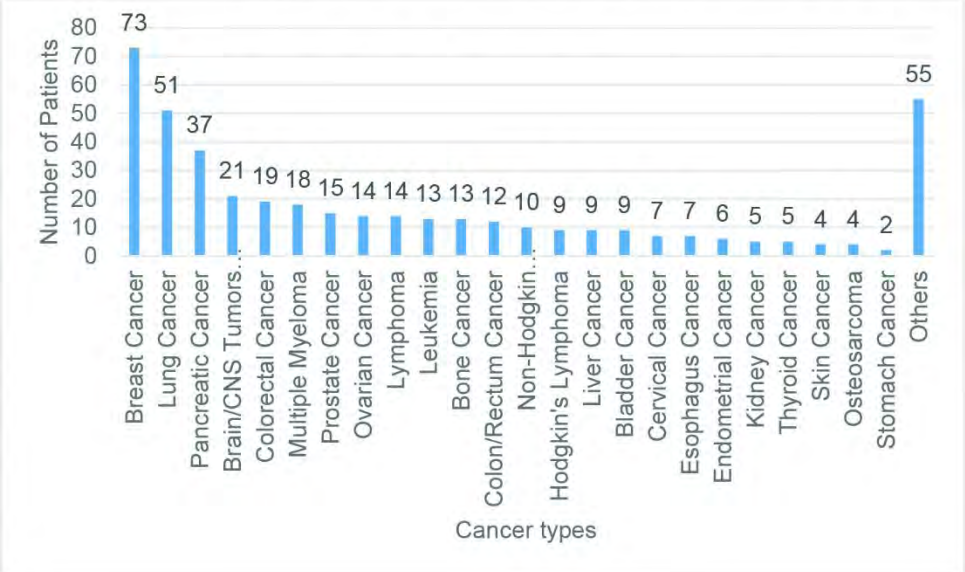
Figure 26. Side effects during the cannabis treatment



7 Analysis of data by disease

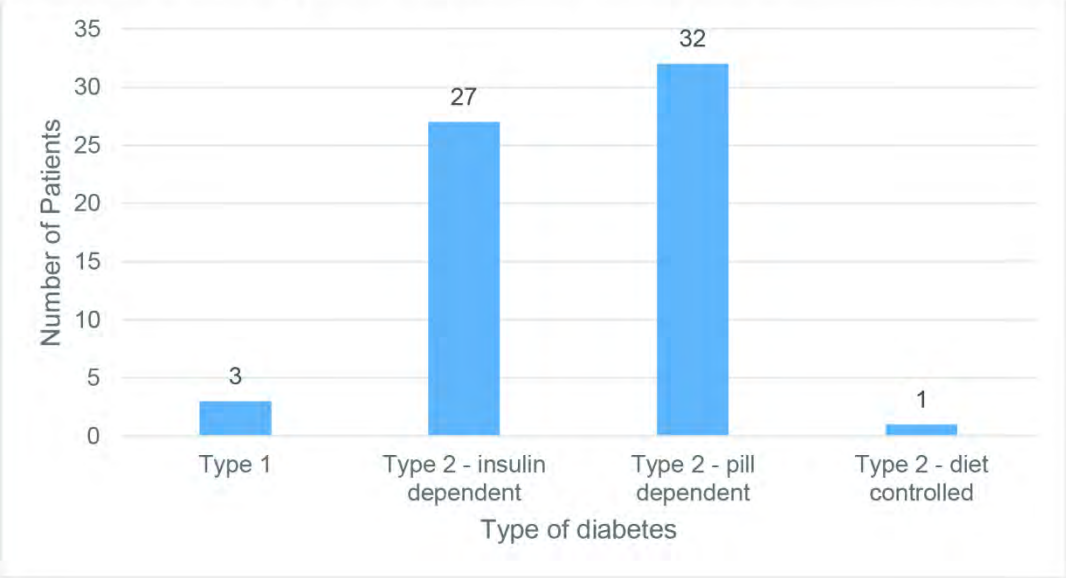
7.1 Cancer

Figure 27. Cancer type of 432 patients who reported cancer and answered this question.



7.2 Diabetes

Figure 28. Diabetes type in the 63 patients who reported diabetes and answered this question.



7.3 Arthritis

Figure 29. Arthritis type of the 34 patients who reported arthritis and answered this question.

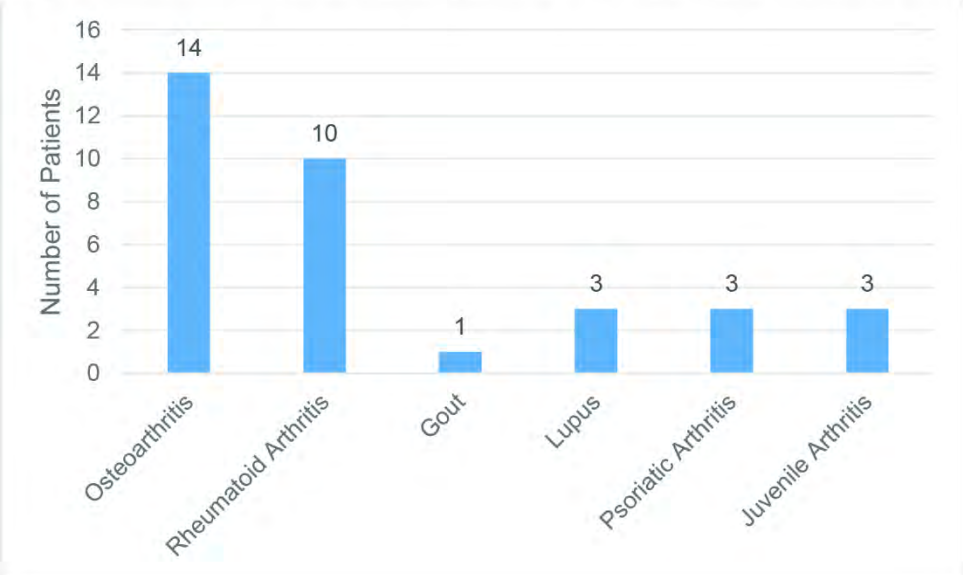


Table 7. Local symptoms related to arthritis in 23 patients who reported arthritis and answered this question.

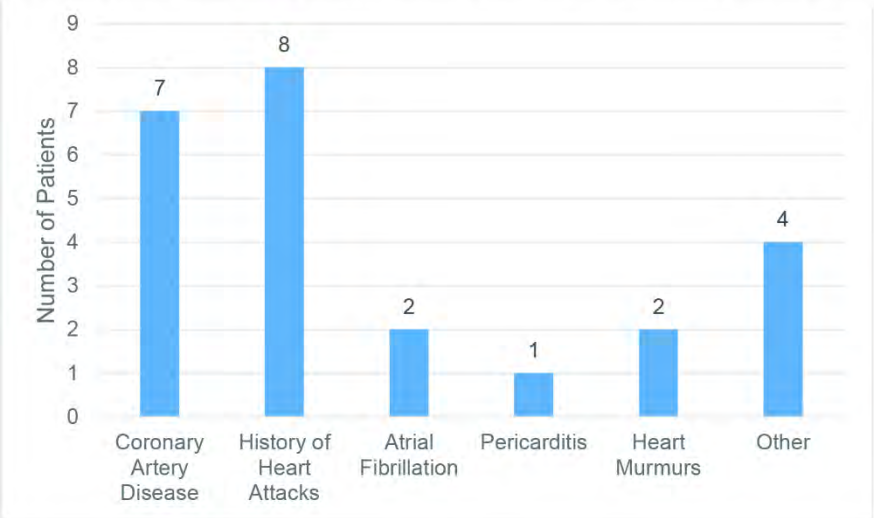
Local symptoms related to Arthritis	None	Mild	Moderate	Severe	Total Responses
Fever	17	2	4	0	23
Swelling	3	5	8	7	23
Redness	13	2	6	1	22

Table 8. Symptoms related to Arthritis before and after the treatment in 23 patients who reported Arthritis and answered this question.

	Significant Deterioration N (%)	Moderate Deterioration N (%)	Slight Deterioration N (%)	No Change N (%)	Slight Improvement N (%)	Moderate Improvement N (%)	Significant Improvement N (%)	I don't suffer from this symptom any more
Fever	0	0	1	8	4	2	4	2
Swelling	0	0	1	6	8	1	4	1
Redness	0	0	1	7	5	1	4	1

7.4 Heart disease

Figure 30. Type of Heart Disease in 24 patients who reported Heart Disease and answered this question.



7.5 Post-Traumatic Stress Disorder

Figure 31. Frequency of aversive memories in PTSD patients before and after the treatment

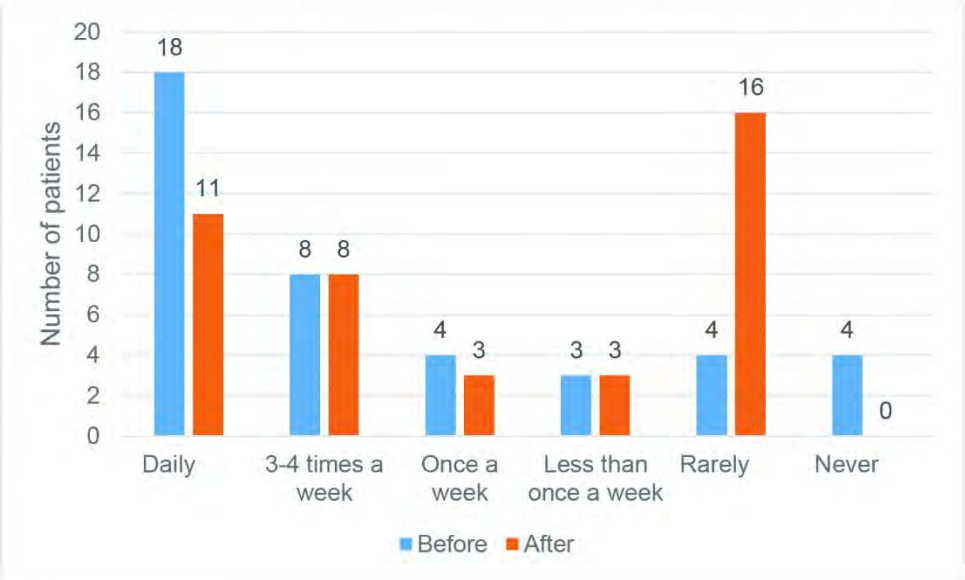
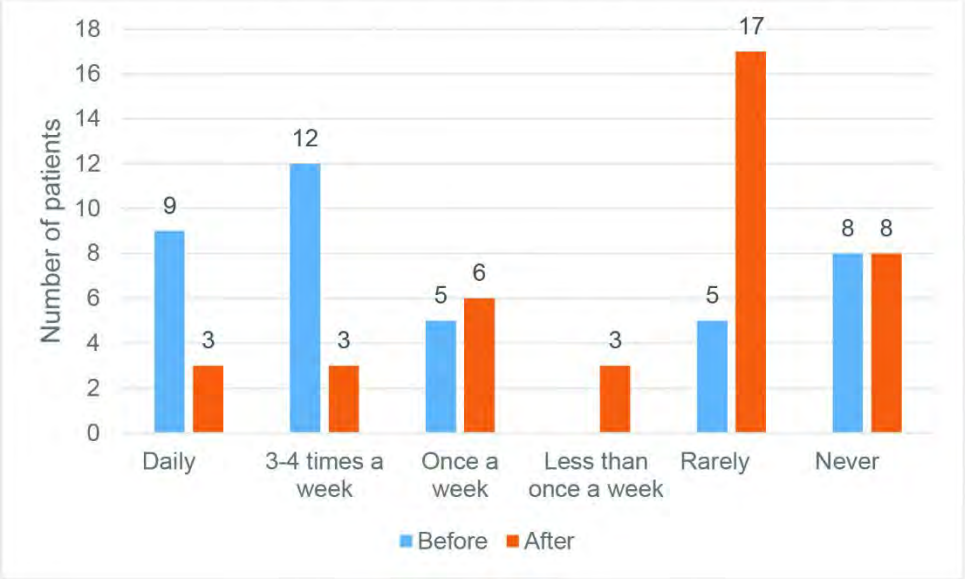


Figure 32. Frequency of rage attacks in PTSD patients before and after the treatment



9. Appendix

Appendix 1. Medical indications recognized by the Ministry of Health:

Oncology Field:

- Patients undergoing chemotherapy or those up to six months after treatment for nausea and pain relief related to their treatment.
- For pain relief for patients with metastatic cancers and after conventional treatment methods are exhausted.

Pain Field:

- For patients suffering from neuropathic pain from a clear organic source, after at least one year of treatment at a recognized pain clinic before requesting cannabis, after exhausting conventional treatment options, and with the recommendation of their pain clinic.

Gastroenterological Field:

- Crohn's Disease- For patients that aren't responding to conventional treatment options well enough.
- Colitis- In special cases, it will be given to patients with ulcerative colitis that aren't responding to conventional treatment options.

Infectious Diseases:

- HIV/AIDS- Patients with Cachexia symptoms (defined as at least 10% loss in body weight).

Neurological Field:

- Multiple Sclerosis- Patients suffering from spasticity that aren't responding to conventional treatment options.
- Parkinson's Disease- Patients undergoing anti-Parkinson's treatment for at least one year and experiencing chronic pain or pain from stiffness, that aren't responding to conventional treatment options.
- Tourette's Syndrome- Adult patients suffering from severe symptoms that impede daily functioning and that aren't responding to conventional treatment options.

Palliative Care Field:

- Terminally ill patients.

Psychiatric Field:

- Post-Traumatic Stress Disorder (PTSD) – Adult patients that have been diagnosed with PTSD and meet the criteria for at least 21% disability by the Bituah Leumi (National Insurance Institute) (NII), that have been suffering from the disorder for at least two years and exhibiting extreme emotional distress. In addition, patients need to have tried three combinations of conventional medicinal interventions for at least two months each and three commonly accepted psychological interventions.

Symptoms Relief Summary

TIKUN
REPAIR THE WORLD

Symptom Relief Summary for Patients Using Tikun Olam Strains

Symptom	Strains That Provided Relief (In Order)	% Patients Experienced Slight to Significant Improvement
Anxiety	Erez, Alaska, Midnight	77%
Burning Sensation	Erez, Alaska, Midnight	72%
Cognitive Impairment	Erez, Eran Almog	35%
Constipation	Alaska, Erez, Midnight	55%
Depression	Alaska, Erez, Midnight	80%
Diarrhea	Alaska, Erez, Eran Almog, Midnight	56%
Digestion Problems	Alaska, Erez, Midnight	59%
Dizziness	Alaska, Erez, Eran Almog, Midnight	56%
Drowsiness	Alaska, Erez, Eran Almog, Midnight	54%
Exhaustion	Alaska, Erez, Eran Almog, Midnight	57%
Headache	Erez, Alaska, Eran Almog, Avidekel	63%
Hives	Avidekel, Alaska, Midnight	51%
Hypertension	Alaska, Erez, Midnight, Avidekel	61%
Hypotension	Alaska	40%
Increased Appetite	Alaska, Erez, Midnight	36%
Insomnia	Erez, Alaska, Eran Almog	79%
Limited Mobility	Alaska, Erez, Midnight	40%
Mucositis	Erez	50%
Nausea	Alaska, Erez, Midnight	72%
Numbness	Erez, Alaska, Or	33%
Paresthesia	Erez, Alaska, Or, Midnight	62%
Pruritus	Erez, Alaska, Or, Midnight, Avidekel	69%
Respiratory Problems	Erez	35%
Seizures	Avidekel, Erez, Eran Almog	79%
Sleep Problems	Erez, Alaska, Eran Almog	81%
Spasms	Alaska, Erez	58%
Spasticity	Alaska, Erez, Midnight	69%
Speech Impairment	Avidekel	45%
Tinnitus	Or, Midnight, Alaska, Erez	29%
Tremor	Alaska, Erez, Or	72%
Vomiting	Alaska, Erez, Midnight	71%
Weakness	Alaska, Erez, Midnight	53%

Meta-Analysis

META-ANALYSIS

A systematic evidence review of medical cannabis studies featuring commercially-available cannabis products, as of February 2019.

6,689 Studies Reviewed

From *PubMed's* database of peer-reviewed literature on medical cannabis

6 Companies Providing Research-Backed Cannabis Products

GW Pharmaceuticals, AbbVie Inc., Cesamet, Greenwich Biosciences, Elixinol, Tikun Olam

4 Prescription Pharmaceuticals

Sativex for MS, Marinol for appetite stimulation, Epidiolex for seizures, Casamet for nausea

2 Non-Prescription Medicines

Tikun Olam's cannabis strains, Elixinol's hemp CBD tincture

1 Tikun Olam

The only *natural* THC-rich medical cannabis brand with commercially available products backed by peer-reviewed research

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