MEDICAL CANNABIS

february**2022**

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MEDICAL CANNABIS RESEARCH SYNOPSIS


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ORIGINAL PUBLISHED RESEARCH ARTICLES

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- Adherence, Safety, and Effectiveness of Medical Cannabis and Epidemiological characteristics of the Patient Population: A prospective Study

TIKUN

Tikun is a pharmaceutical company, pioneer in the research, development, and production of medicinal cannabis products worldwide. Its activity began in Israel in 2005 and up to date, it has defined the Medical Cannabis Industry internationally, with verticalized production units across the world: USA, Canada, Australia, Asia (Israel) and Europe (Greece).

With more than 15 years of clinical and laboratory studies, its innovative formulations offer proven support to patients who suffer from serious health issues and diseases affecting their quality of life such as Parkinson's disease, Crohn's disease, Autism, Multiple Sclerosis, Epilepsy, the side effects of chemotherapy, neuropathic pain and more. The company currently has one of the largest patient databases globally and is constantly enriched with new data.

TO LEARN MORE

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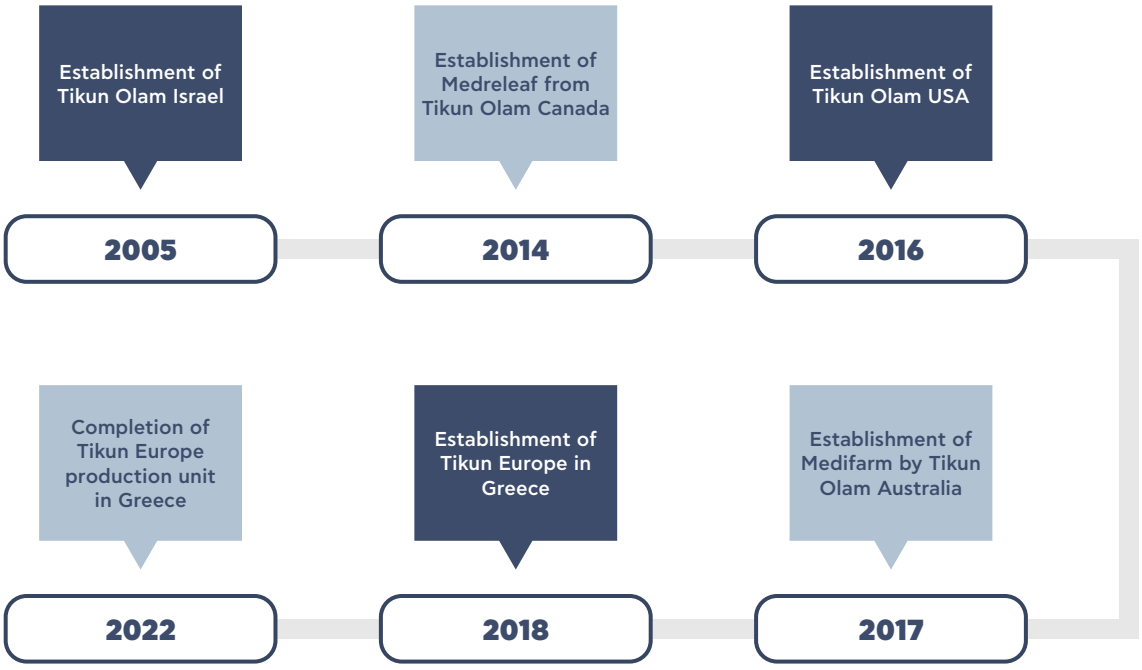
VISION & MISSION

> “Made By Nature and Backed By Science”

Tikun brand name comes from Tikun Olam [tee KOON oh LAHM] which means “Repair the World”. Inspired by this name, the company is dedicated to improving patients’ lives. Its aim is to bring cure and alleviation, by providing evidence based, medical cannabis treatment worldwide. The company’s purpose is to develop and market pharmaceutical formulations created solely by nature, with high efficacy supported by scientific and real data.

Thus, Tikun’s world products, are “Made By Nature and Backed By Science”



TIKUN EUROPE

Tikun Europe at a glance

Tikun Europe is a pharmaceutical company that aims at developing, producing and distributing medical cannabis products, through an R&D department and its vertically integrated production unit in Greece. The production facility is designed to become a state of the art site able to cover the needs of European markets.

Tikun Europe's facility is the largest in Europe, situated at a 56,000 m² designated area in Corinth, Greece. It operates on the basis of strict control and quality standards (GMP – Good Manufacturing Practice), aiming to ensure reliable pharmaceutical formulations. All procedures, from cultivation to harvesting and packaging, are carried out with effective and ecological methods. Greenhouse operation is based on high technology light and temperature control to guarantee limited energy consumption, maximize efficiency, and ensure top quality and safety of the products.

Additionally, to its medical portfolio, Tikun introduces the Tikun CBD (cannabidiol) range. It is a holistic proposal which can be used either complementary to a medical treatment or as stand alone in order to enhance and support homeostasis, helping people to improve quality of life standards.

highlights

- **Founded in Greece in 2018**
- **Member of the Tikun family, an Organization at the forefront of cannabis treatment research with long lasting relationships for over 15 years with major key opinion leaders of the medical cannabis industry**
- **Over 15 years of growing R&D experience from operating facilities in 4 continents through Tikun know-how transfer**
- **Scope to serve 27 countries in the EU**
- **Exclusive, perpetual license agreement with Tikun for all IP (hard IP, soft IP, innovative formulations, clinical studies, 15-year patient database)**
- **Access to Tikun platform through the license agreement (Israel R&D, US specialized new product development team, Tikun research, Tikun patented formulations)**
- **Access to one of the world's largest cannabis treatment patient database**
- **Unique knowledge and experience in training doctors, pharmacists and treating patients**
- **Products created following more than 10 years of clinical trials and laboratory studies**
- **Product development in various pharmaceutical forms and new medical breakthroughs using Tikun proprietary formulations, database and scientific research**
- **CBD portfolio based on Tikun Europe R&D's formulas, meeting all the necessary requirements that assure high quality products**

Tikun Europe production unit

- **The largest GMP facility in Europe – in medical Cannabis - 56,000 m²**
- **Capability to produce several pharmaceutical forms (oil tinctures, vapes, creams, capsules, dry flower etc.)**
- **Climate controlled, hybrid greenhouses 21,000 sqm. with a production capacity of 10 tons p.a. of dry flower**
- **Designed to be expandable**
- **With high security standards**

CHAPTER 1

ENDOCANNABINOID SYSTEM

THE ENDOCANNABINOID SYSTEM • ENDOCANNABINOID SYSTEM RECEPTORS • CANNABINOIDS

CHAPTER 1

ENDOCANNABINOID SYSTEM

THE ENDOCANNABINOID SYSTEM

1. **Wen-Juan Huang, et al. Endocannabinoid system: Role in depression, reward and pain control (Review).**
[Molecular Medicine Reports 2016;14:2899-2903.]

ABSTRACT

Depression and pain co-exist in almost 80% of patients and are associated with impaired health-related quality of life, often contributing to high mortality. However, the majority of patients who suffer from the comorbid depression and pain are not responsive to pharmacological treatments that address either pain or depression, making this comorbidity disorder a heavy burden on patients and society. In ancient times, this depression-pain comorbidity was treated using extracts of the Cannabis sativa plant, known now as marijuana and the mode of action of Δ9-tetrahydrocannabinol, the active cannabinoid ingredient of marijuana, has only recently become known, with the identification of cannabinoid receptor type 1 (CB1) and CB2. Subsequent investigations led to the identification of endocannabinoids, anandamide and 2-arachidonoylglycerol, which exert cannabinomimetic effects through the CB1 and CB2 receptors, which are located on presynaptic membranes in the central nervous system and in peripheral tissues, respectively. These endocannabinoids are produced from membrane lipids and are lipohilic molecules that are synthesized on demand and are eliminated rapidly after their usage by hydrolyzing enzymes. Clinical studies revealed altered endocannabinoid signaling in patients with chronic pain. Considerable evidence suggested the involvement of the endocannabinoid system in eliciting potent effects on neurotransmission, neuroendocrine, and inflammatory processes, which are known to be deranged in depression and chronic pain. Several synthetic cannabinomimetic drugs are being developed to treat pain and depression. However, the precise mode of action of endocannabinoids on different targets in the body and whether their effects on pain and depression follow the same or different pathways, remains to be determined.

ENDOCANNABINOID SYSTEM RECEPTORS

2. **Shenglong Zou and Ujendra Kumar. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System.**
[International Journal of Molecular Sciences 2018;19(833):1-23.]

ABSTRACT

The biological effects of cannabinoids, the major constituents of the ancient medicinal plant Cannabis sativa (marijuana) are mediated by two members of the G-protein coupled receptor family, cannabinoid receptors 1 (CB1R) and 2. The CB1R is the prominent subtype in the central nervous system (CNS) and has drawn great attention as a potential therapeutic avenue in several pathological conditions, including neuropsychological disorders and neurodegenerative diseases. Furthermore, cannabinoids also modulate signal transduction pathways and exert profound effects at peripheral sites. Although cannabinoids have therapeutic potential, their psychoactive effects have largely limited their use in clinical practice. In this review, we briefly summarized our knowledge of cannabinoids and the endocannabinoid system, focusing on the CB1R and the CNS, with emphasis on recent breakthroughs in the field. We aim to define several potential roles of cannabinoid receptors in the modulation of signaling pathways and in association with several pathophysiological conditions. We believe that the therapeutic significance of cannabinoids is masked by the adverse effects and here alternative strategies are discussed to take therapeutic advantage of cannabinoids.

CANNABINOIDS

3. John M McPartland, et al. Are cannabidiol and Δ9 -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review.
[British Journal of Pharmacology 2015;172:737–753]

ABSTRACT

Based upon evidence that the therapeutic properties of Cannabis preparations are not solely dependent upon the presence of Δ9 -tetrahydrocannabinol (THC), pharmacological studies have been recently carried out with other plant cannabinoids (phytocannabinoids), particularly cannabidiol (CBD) and Δ9 -tetrahydrocannabivarin (THCV). Results from some of these studies have fostered the view that CBD and THCV modulate the effects of THC via direct blockade of cannabinoid CB1 receptors, thus behaving like first-generation CB1 receptor inverse agonists, such as rimonabant. Here, we review in vitro and ex vivo mechanistic studies of CBD and THCV and synthesize data from these studies in a meta-analysis. Synthesized data regarding mechanisms are then used to interpret results from recent pre-clinical animal studies and clinical trials. The evidence indicates that CBD and THCV are not rimonabant-like in their action and thus appear very unlikely to produce unwanted CNS effects. They exhibit markedly disparate pharmacological profiles particularly at CB1 receptors: CBD is a very low-affinity CB1 ligand that can nevertheless affect CB1 receptor activity in vivo in an indirect manner, while THCV is a high-affinity CB1 receptor ligand and potent antagonist in vitro and yet only occasionally produces effects in vivo resulting from CB1 receptor antagonism. THCV has also high affinity for CB2 receptors and signals as a partial agonist, differing from both CBD and rimonabant. These cannabinoids illustrate how in vitro mechanistic studies do not always predict in vivo pharmacology and underlie the necessity of testing compounds in vivo before drawing any conclusion on their functional activity at a given target.

4. Ken Mackie. Distribution of Cannabinoid Receptors in the Central and Peripheral Nervous System.
[Handbook of Experimental Pharmacology 2005;168:299-325.]

ABSTRACT

CB1 cannabinoid receptors appear to mediate most, if not all of the psychoactive effects of delta-9-tetrahydrocannabinol and related compounds. This G protein-coupled receptor has a characteristic distribution in the nervous system: It is particularly enriched in cortex, hippocampus, amygdala, basal ganglia outflow tracts, and cerebellum—a distribution that corresponds to the most prominent behavioral effects of cannabis. In addition, this distribution helps to predict neurological and psychological maladies for which manipulation of the endocannabinoid system might be beneficial. CB1 receptors are primarily expressed on neurons, where most of the receptors are found on axons and synaptic terminals, emphasizing the important role of this receptor in modulating neurotransmission at specific synapses. While our knowledge of CB1 localization in the nervous system has advanced tremendously over the past 15 years, there is still more to learn. Particularly pressing is the need for (1) detailed anatomical studies of brain regions important in the therapeutic actions of drugs that modify the endocannabinoid system and (2) the determination of the localization of the enzymes that synthesize, degrade, and transport the endocannabinoids.

5. Ethan B Russo. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects.
[British Journal of Pharmacology 2011;163:1344–1364]

ABSTRACT

Tetrahydrocannabinol (THC) has been the primary focus of cannabis research since 1964, when Raphael Mechoulam isolated and synthesized it. More recently, the synergistic contributions of cannabidiol to cannabis pharmacology and analgesia have been scientifically demonstrated. Other phytocannabinoids, including tetrahydrocannabivarin, cannabigerol and cannabichromene, exert additional effects of therapeutic interest. Innovative conventional plant breeding has yielded cannabis chemotypes expressing high titres of each component for future study. This review will explore another echelon of phototherapeutic agents, the cannabis terpenoids: limonene, myrcene, a-pinene, linalool, b-caryophyllene, caryophyllene oxide, nerolidol and phytol. Terpenoids share a precursor with phytocannabinoids and are all flavor and fragrance components common to human diets that have been designated Generally Recognized as Safe by the US Food and Drug Administration and other regulatory agencies. Terpenoids are quite potent and affect animal and even human behavior when inhaled from ambient air at serum levels in the single digits ng·mL-1. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts.

Particular focus will be placed on phytocannabinoid-terpenoid interactions that could produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections (including methicillin-resistant Staphylococcus aureus). Scientific evidence is presented for non-cannabinoid plant components as putative antidotes to intoxicating effects of THC that could increase its therapeutic index. Methods for investigating entourage effects in future experiments will be proposed. Phytocannabinoid-terpenoid synergy, if proven, increases the likelihood that an extensive pipeline of new therapeutic products is possible from this venerable plant.

6. Robert B Laprairie, et al. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor.

[British Journal of Pharmacology 2015;172:4790–4805]

Background and Purpose:

Cannabidiol has been reported to act as an antagonist at cannabinoid CB1 receptors. We hypothesized that cannabidiol would inhibit cannabinoid agonist activity through negative allosteric modulation of CB1 receptors.

Experimental Approach:

Internalization of CB1 receptors, arrestin2 recruitment, and PLCβ3 and ERK1/2 phosphorylation, were quantified in HEK 293A cells heterologously expressing CB1 receptors and in the STHdhQ7/Q7 cell model of striatal neurons endogenously expressing CB1 receptors. Cells were treated with 2-arachidonylglycerol or Δ9 -tetrahydrocannabinol alone and in combination with different concentrations of cannabidiol.

Key Results:

Cannabidiol reduced the efficacy and potency of 2-arachidonylglycerol and Δ9 -tetrahydrocannabinol on PLCβ3- and ERK1/2-dependent signaling in cells heterologously (HEK 293A) or endogenously (STHdhQ7/Q7) expressing CB1 receptors. By reducing arrestin2 recruitment to CB1 receptors, cannabidiol treatment prevented internalization of these receptors. The allosteric activity of cannabidiol depended upon polar residues being present at positions 98 and 107 in the extracellular amino terminus of the CB1 receptor.

Conclusions and Implications:

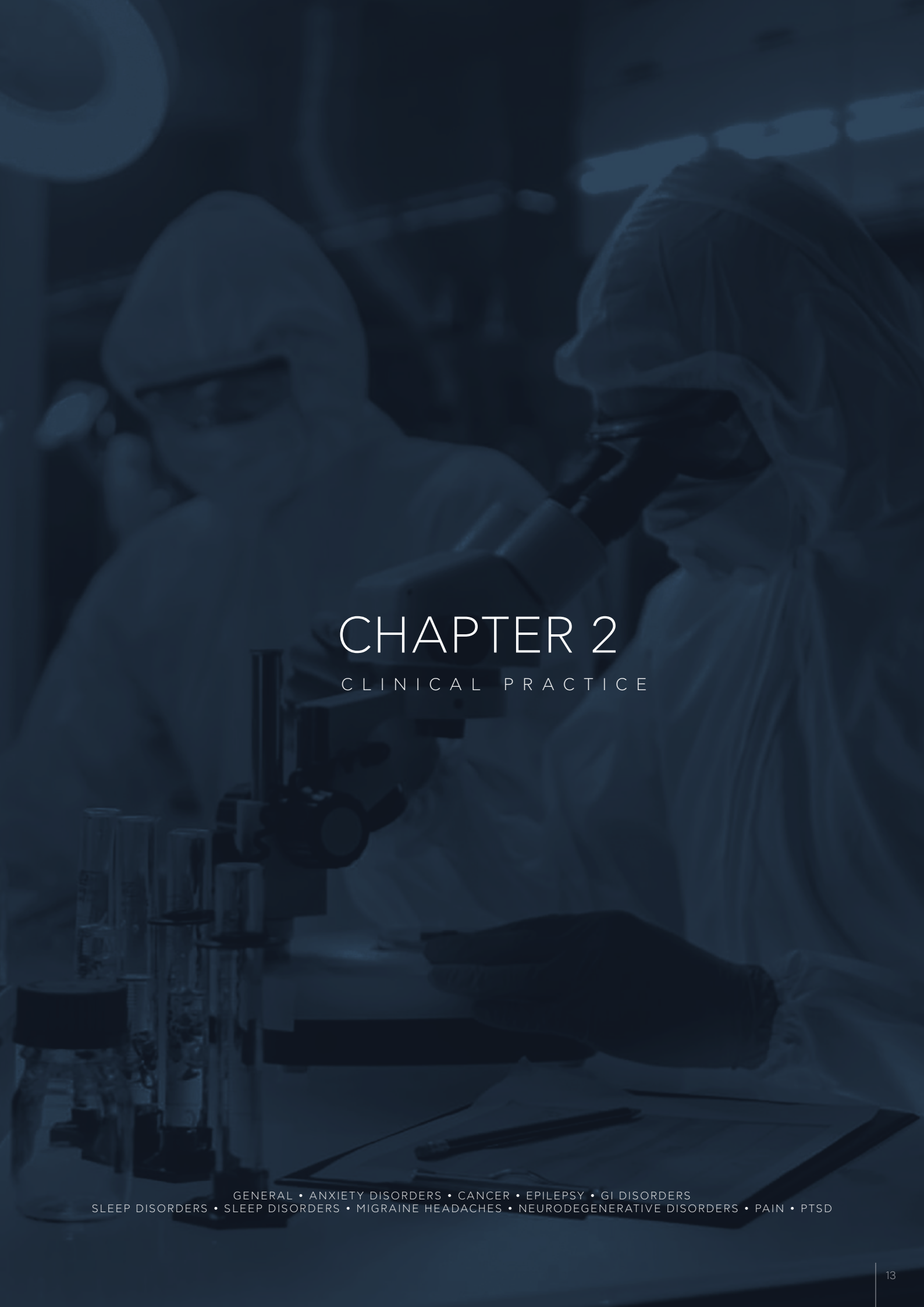
Cannabidiol behaved as a non-competitive negative allosteric modulator of CB1 receptors. Allosteric modulation, in conjunction with effects not mediated by CB1 receptors, may explain the in vivo effects of cannabidiol. Allosteric modulators of CB1 receptors have the potential to treat CNS and peripheral disorders while avoiding the adverse effects associated with orthosteric agonism or antagonism of these receptors.

7. Tamilyn Bakas, et al. The direct actions of cannabidiol and 2-arachidonoyl glycerol at GABAA receptors.

[Pharmacological Research 2017;119:358-370]

ABSTRACT

Cannabidiol (CBD) is a major non-intoxicating component of cannabis and possesses anti-epileptic, anxiolytic and anti-hyperalgesic properties. The mechanism of action of CBD in producing such effects remains unclear. Despite evidence that some endogenous and synthetic cannabinoids interact with GABAA receptors, no-one has yet investigated the effects of CBD. Here we used two-electrode voltage clamp electrophysiology to compare the actions of CBD with those of the major central endocannabinoid, 2-arachidonoyl glycerol (2-AG) on human recombinant GABAA receptors (synaptic α1-6βγ2 and extrasynaptic α4β2δ) expressed on Xenopus oocytes. CBD and 2-AG were positive allosteric modulators at α1-6βγ2 receptors, with low micromolar potencies. The maximal level of enhancement seen with either CBD or 2-AG were on α2-containing GABAA receptor subtypes, with approximately a 4-fold enhancement of the GABA EC5 evoked current, more than twice the potentiation seen with other α-subunit receptor combinations. Further we observed β-subunit selectivity, whereby modulatory activity was higher at β2/β3 over β1 subunits. The β1-subunit homologous mutant β2(V436T) substantially diminished the efficacy of both drugs to a third of that obtained with wild-type β2 subunit combinations, but without changing potency. The potency of CBD increased, and efficacy preserved in binary α1/α2β2 receptors indicating that their effects do not involve the classic benzodiazepine site. Exploration of extra synaptic α4β2δ receptors revealed that both compounds enhanced GABA EC5 evoked currents at concentrations ranging from 0.01–1 μ M. Taken together these results reveal a mode of action of CBD on specifically configured GABAA receptors that may be relevant to the anticonvulsant and anxiolytic effects of the compound.



CHAPTER 2

CLINICAL PRACTICE

GENERAL • ANXIETY DISORDERS • CANCER • EPILEPSY • GI DISORDERS
SLEEP DISORDERS • SLEEP DISORDERS • MIGRAINE HEADACHES • NEURODEGENERATIVE DISORDERS • PAIN • PTSD

CHAPTER 2

CLINICAL PRACTICE

GENERAL

8. Franjo Grotenhermen and Kirsten Muller-Vahl., K. The Therapeutic Potential of Cannabis and Cannabinoids.

[Duetsches Arzteblatt International 2012;109(29-30):495-501]

Background:

Cannabis-based medications have been a topic of intense study since the endogenous cannabinoid system was discovered two decades ago. In 2011, for the first time, a cannabis extract was approved for clinical use in Germany.

Methods:

Selective literature review.

Results:

Cannabis-based medications exert their effects mainly through the activation of cannabinoid receptors (CB1 and CB2). More than 100 controlled clinical trials of cannabinoids or whole-plant preparations for various indications have been conducted since 1975. The findings of these trials have led to the approval of cannabis-based medicines (dronabinol, nabilone, and a cannabis extract [THC:CBD=1:1]) in several countries. In Germany, a cannabis extract was approved in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis. It is commonly used off label for the treatment of anorexia, nausea, and neuropathic pain. Patients can also apply for government permission to buy medicinal cannabis flowers for self-treatment under medical supervision. The most common side effects of cannabinoids are tiredness and dizziness (in more than 10% of patients), psychological effects, and dry mouth. Tolerance to these side effects nearly always develops within a short time. Withdrawal symptoms are hardly ever a problem in the therapeutic setting.

9. Tom P Freeman, et al. Medicinal use of cannabis-based products and cannabinoids.

[British Medical Journal 2019;365:1-7]

ABSTRACT

Cannabis based products for medicinal use contain cannabinoids derived from the cannabis plant, including Δ 9 -tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD. Synthetic cannabinoids for medicinal use typically mimic the effects of specific cannabinoids such as THC. THC is the constituent of cannabis that causes the "high," whereas CBD is not intoxicating at typical doses. THC and CBD have contrasting mechanisms of action and therapeutic indications; THC carries a higher risk of adverse events compared with CBD. Rescheduling on 1 November 2018 permits some unlicensed cannabis-based products to be prescribed for the first time in the UK, but only by doctors on the relevant Specialist Register of the General Medical Council. Indications for treatment, supported by evidence of low to moderate certainty, include chronic pain, some treatment resistant epilepsies, and nausea and vomiting caused by chemotherapy (table 2). Non-medicinal CBD products are legal and widely available on the internet and from health food retailers, but they lack quality standards and should not be used for medicinal purposes.

10. Misty Pratt, et al. Benefits and harms of medical cannabis: a scoping review of systematic reviews.

[Systematic Reviews 2019;8(320):1-35]

Background:

There has been increased interest in the role of cannabis for treating medical conditions. The availability of different cannabis-based products can make the side effects of exposure unpredictable. We sought to conduct a scoping review

of systematic reviews assessing benefits and harms of cannabis-based medicines for any condition.

Methods:

A protocol was followed throughout the conduct of this scoping review. A protocol-guided scoping review conduct. Searches of bibliographic databases (e.g., MEDLINE®, Embase, PsycINFO, the Cochrane Library) and gray literature were performed. Two people selected and charted data from systematic reviews. Categorizations emerged during data synthesis. The reporting of results from systematic reviews was performed at a high level appropriate for a scoping review.

Results:

After screening 1975 citations, 72 systematic reviews were included. The reviews covered many conditions, the most common being pain management. Several reviews focused on management of pain as a symptom of conditions such as multiple sclerosis (MS), injury, and cancer. After pain, the most common symptoms treated were spasticity in MS, movement disturbances, nausea/vomiting, and mental health symptoms. An assessment of review findings lends to the understanding that, although in a small number of reviews results showed a benefit for reducing pain, the analysis approach and reporting in other reviews was sub-optimal, making it difficult to know how consistent findings are when considering pain in general. Adverse effects were reported in most reviews comparing cannabis with placebo (49/59, 83%) and in 20/24 (83%) of the reviews comparing cannabis to active drugs. Minor adverse effects (e.g., drowsiness, dizziness) were common and reported in over half of the reviews. Serious harms were not as common but were reported in 21/59 (36%) reviews that reported on adverse effects. Overall, safety data was generally reported study-by-study, with few reviews synthesizing data. Only one review was rated as high quality, while the remaining were rated of moderate (n = 36) or low/critically low (n = 35) quality.

Conclusions:

Results from the included reviews were mixed, with most reporting an inability to draw conclusions due to inconsistent findings and a lack of rigorous evidence. Mild harms were frequently reported, and it is possible the harms of cannabis-based medicines may outweigh benefits.

11. Harrison J Van Dolah, et al. Clinicians' Guide to Cannabidiol and Hemp Oils.

[Mayo Clinic Proceedings 2019;94(9):1840-1851]

ABSTRACT

Cannabidiol (CBD) oils are low tetrahydrocannabinol products derived from Cannabis sativa that have become very popular over the past few years. Patients report relief for a variety of conditions, particularly pain, without the intoxicating adverse effects of medical marijuana. In June 2018, the first CBD-based drug, Epidiolex, was approved by the US Food and Drug Administration for treatment of rare, severe epilepsy, further putting the spotlight on CBD and hemp oils. There is a growing body of preclinical and clinical evidence to support use of CBD oils for many conditions, suggesting its potential role as another option for treating challenging chronic pain or opioid addiction. Care must be taken when directing patients toward CBD products because there is little regulation, and studies have found inaccurate labeling of CBD and tetrahydrocannabinol quantities. This article provides an overview of the scientific work on cannabinoids, CBD, and hemp oil and the distinction between marijuana, hemp, and the different components of CBD and hemp oil products. We summarize the current legal status of CBD and hemp oils in the United States and provide a guide to identifying higher-quality products so that clinicians can advise their patients on the safest and most evidence-based formulations. This review is based on a PubMed search using the terms CBD, cannabidiol, hemp oil, and medical marijuana. Articles were screened for relevance, and those with the most up-to-date information were selected for inclusion.

12. Gusho CA and Court T. Cannabidiol: A Brief Review of Its Therapeutic and Pharmacologic Efficacy in the Management of Joint Disease.

[Cureus 2020;12(3):e7375]

ABSTRACT

Cannabis use in the management of musculoskeletal diseases has gained advocacy since several states have legalized its recreational use. Cannabidiol (CBD), a commercially available, non- neurotropic marijuana constituent, has shown promise in arthritic animal models by attenuating pro-inflammatory immune responses. Additional research has demonstrated the benefit of CBD in decreasing the endogenous pain response in mice subjected to acute arthritic conditions, and further studies have highlighted improved fracture healing following CBD use in murine mid-femoral fractures. However, there is a lack of high-quality, novel research investigating the use of CBD in human musculoskeletal diseases aside from anecdotal accounts and retrospective reviews, perhaps due to legal ramifications limiting the enrollment of patients. The purpose of this review article is to highlight the extent of current research on CBD and its biochemical and pharmacologic efficacy in the treatment of joint disease, as well as the evidence for use of CBD and cannabis in patients undergoing joint arthroplasty. Based on available literature relying on retrospective data and case reports, it is challenging to propose a recommendation for CBD use in perioperative pain management. Additionally, a number of CBD products currently

available as supplements with different methods of administration, and it is important to remember that these products are non-pharmaceuticals. However, given the increased social relevance of CBD and cannabis-based medicines, future, prospective controlled studies evaluating their efficacy are needed.

13. Sinemyiz Atalay, et al. Antioxidative and Anti-Inflammatory Properties of Cannabidiol.

[Antioxidants 2020;9(21):1-20]

ABSTRACT

Cannabidiol (CBD) is one of the main pharmacologically active phytocannabinoids of Cannabis sativa L. CBD is non-psychoactive but exerts a number of beneficial pharmacological effects, including anti-inflammatory and antioxidant properties. The chemistry and pharmacology of CBD, as well as various molecular targets, including cannabinoid receptors and other components of the endocannabinoid system with which it interacts, have been extensively studied. In addition, preclinical and clinical studies have contributed to our understanding of the therapeutic potential of CBD for many diseases, including diseases associated with oxidative stress. Here, we review the main biological effects of CBD, and its synthetic derivatives, focusing on the cellular, antioxidant, and anti-inflammatory properties of CBD.

14. G. Michael Allan, et al. Systematic review of systematic reviews for medical cannabinoids (Pain, nausea and vomiting, spasticity, and harms).

[Canadian Family Physician 2018;64(2):e78-e94]

ABSTRACT

Objective:

To determine the effects of medical cannabinoids on pain, spasticity, and nausea and vomiting, and to identify adverse events.

Data Sources:

MEDLINE, the Cochrane Database, and the references of included studies were searched.

Study Selection:

Systematic reviews with 2 or more randomized controlled trials (RCTs) that focused on medical cannabinoids for pain, spasticity, or nausea and vomiting were included. For adverse events, any meta-analysis for the conditions listed or of adverse events of cannabinoids was included.

Synthesis:

From 1085 articles, 31 relevant systematic reviews were identified including 23 for pain, 5 for spasticity, 6 for nausea and vomiting, and 12 for adverse events. Meta-analysis of 15 RCTs found more patients taking cannabinoids attained at least a 30% pain reduction: risk ratio (RR) of 1.37 (95% CI 1.14 to 1.64), number needed to treat (NNT) of 11. Sensitivity analysis found study size and duration affected findings (subgroup differences, P≤ .03), with larger and longer RCTs finding no benefit. Meta-analysis of 4 RCTs found a positive global impression of change in spasticity (RR= 1.45, 95% CI 1.08 to 1.95, NNT= 7). Other results were not consistently statistically significant, but when positive, a 30% or more improvement in spasticity had an NNT of 10. Meta-analysis of 7 RCTs for control of nausea and vomiting after chemotherapy found an RR of 3.60 (95% CI 2.55 to 5.09) with an NNT of 3. Adverse effects caused more patients to stop treatment (number needed to harm [NNH] of 8 to 22). Individual adverse events were very common, including dizziness (NNH= 5), sedation (NNH= 5), confusion (NNH= 15), and dissociation (NNH= 20). "Feeling high" was reported in 35% to 70% of users. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) evaluation reduced evidence ratings of benefit to low or very low.

Conclusion:

There is reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy. They might improve spasticity (primarily in multiple sclerosis). There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain, and the benefit is likely small. Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy.

15. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.

[National Academies Press (US) 2017;ISBN-13:978-0-309-45304-2]

ABSTRACT

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days and between 2002 and 2015 the percentage of past month cannabis users in this age range have increased steadily from 6.2 to 8.3 percent (CBHSQ, 2016). Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as adolescents and pregnant women. Unlike other substances, such as alcohol or tobacco, whose use may confer risk, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively. Within this context, in March of 2016, the Health and Medicine Division (formerly the Institute of Medicine [IOM] 1 of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the IOM 1999 report Marijuana and Medicine. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/ National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; The Colorado Health Foundation; The Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

16. G. Michael Allan, et al. CLINICAL PRACTICE GUIDELINES_ Simplified guideline for prescribing medical cannabinoids in primary care

[Canadian Family Physician 2018;64(2):111-120]

ABSTRACT

Objective:

To develop a clinical practice guideline for a simplified approach to medical cannabinoid use in primary care; the focus was on primary care application, with a strong emphasis on best available evidence and a promotion of shared, informed decision making.

Methods:

The Evidence Review Group performed a detailed systematic review of 4 clinical areas with the best evidence around cannabinoids: pain, nausea and vomiting, spasticity, and adverse events. Nine health professionals (2 generalist family physicians, 2 pain management–focused family physicians, 1 inner-city family physician, 1 neurologist, 1 oncologist, 1 nurse practitioner, and 1 pharmacist) and a patient representative comprised the Prescribing Guideline Committee (PGC), along with 2 nonvoting members (pharmacist project managers). Member selection was based on profession, practice setting, location, and lack of financial conflicts of interest. The guideline process was iterative through content distribution, evidence review, and telephone and online meetings. The PGC directed the Evidence Review Group to address and provide evidence for additional questions as needed. The key recommendations were derived through consensus of the PGC. The guideline was drafted, refined, and distributed to a group of clinicians and patients for feedback, then refined again and finalized by the PGC.

Recommendations:

Recommendations include limiting medical cannabinoid use in general, but also outline potential restricted use in a small subset of medical conditions for which there is some evidence (neuropathic pain, palliative and end-of-life pain, chemotherapy-induced nausea and vomiting, and spasticity due to multiple sclerosis or spinal cord injury). Other important considerations regarding prescribing are reviewed in detail, and content is offered to support shared, informed decision making. Conclusion This simplified medical cannabinoid prescribing guideline provides practical recommendations for the use of medical cannabinoids in primary care. All recommendations are intended to assist with, not dictate, decision making in conjunction with patients.

ANXIETY DISORDERS

17. Scott Shannon, et al. Cannabidiol in Anxiety and Sleep: A Large Case Series.

[The Permanente Journal 2019;23:18-041]

ABSTRACT

Context:

Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a "high." A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature.

Objective:

To determine whether CBD helps improve sleep and/or anxiety in a clinical population.

Design:

A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients.

Main Outcome Measures:

Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.

Results:

The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.

Conclusion:

Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.

18. Esther M. Blessing, et al. Cannabidiol as a Potential Treatment for Anxiety Disorders.

[Neurotherapeutics 2015;12:825–836]

ABSTRACT

Cannabidiol (CBD), a Cannabis sativa constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

CANCER

19. Marie Fallon, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines.
[Annals of Oncology 29 (Supplement 4):iv166–iv191, 2018]

ABSTRACT

Pain is common in cancer patients, particularly in the advanced stage of disease when the prevalence is estimated to be more than 70%, contributing to poor physical and emotional well-being. The most comprehensive systematic review indicates pain prevalence ranging from 33% in patients after curative treatment, to 59% in patients on anticancer treatment and to 64% in patients with metastatic, advanced, or terminal disease. Pain has a high prevalence earlier in disease in specific cancer types such as pancreatic (44%) and head and neck cancer (40%). Increased survival with either life-prolonging treatment or curative treatment results in increased numbers of patients experiencing persistent pain due to treatment or disease, or a combination of both. Approximately 5%–10% of cancer survivors have chronic severe pain that interferes significantly with functioning. Despite guidelines and the availability of opioids (the mainstay of moderate to severe cancer pain management), undertreatment is common. European studies confirmed these data from the United States, showing that different types of pain or pain syndromes were present in all stages of cancer and were not adequately treated in a significant percentage of patients, ranging from 56% to 82.3%. According to a systematic review published in 2014 using the Pain Management Index (PMI), approximately one-third of patients do not receive appropriate analgesia proportional to their pain intensity (PI). High prevalence has also been documented in hematology patients at diagnosis, during therapy and in the last month of life. These data reinforce the recommendation that patients with advanced or metastatic cancer require management within an integrated system for palliative care. Cancer-related pain may be presented as a major issue of healthcare systems world-wide: 14.1 million new cancer cases and 8.2 million deaths occurred worldwide in 2012, based on GLOBOCAN estimates and incidence will be > 15 million in 2020, based on projections.

20. Robert A. Swarm, et al. NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY
[NCCN GUIDELINES: ADULT CANCER PAIN_version 2.2021 – June 3, 2021]

The NCCN Guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expressed to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care of treatment. The National Comprehensive Cancer Network (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way.

21. Gil Bar-Sela, et al. The Medical Necessity for Medicinal Cannabis: Prospective, Observational Study Evaluating the Treatment in Cancer Patients on Supportive or Palliative Care.
[Evidence-Based Complementary and Alternative Medicine Volume 2013, Article ID 510392]

ABSTRACT

Background. Cancer patients using cannabis report better influence from the plant extract than from synthetic products. However, almost all the research conducted to date has been performed with synthetic products. We followed patients with a medicinal cannabis license to evaluate the advantages and side effects of using cannabis by cancer patients. Methods. The study included two interviews based on questionnaires regarding symptoms and side effects, the first held on the day the license was issued and the second 6–8 weeks later. Cancer symptoms and cannabis side effects were documented on scales from 0 to 4 following the CTCAE. The distress thermometer was used also. Results. Of the 211 patients who had a first interview, only 131 had the second interview, 25 of whom stopped treatment after less than a week. All cancer or anticancer treatment-related symptoms showed significant improvement ($P < 0.001$). No significant side effects except for memory lessening in patients with prolonged cannabis use ($P = 0.002$) were noted. Conclusion. The positive effects of cannabis on various cancer-related symptoms are tempered by reliance on self-reporting for many of the variables. Although studies with a control group are missing, the improvement in symptoms should push the use of cannabis in palliative treatment of oncology patients.

22. Donald I. Abrams. Integrating cannabis into clinical cancer care.
[Current Oncology 2016;23(S2):S8-S14]

ABSTRACT

Cannabis species have been used as medicine for thousands of years; only since the 1940s has the plant not been widely available for medical use. However, an increasing number of jurisdictions are making it possible for patients to obtain the botanical for medicinal use. For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression. Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy. A pharmacokinetic interaction study of vaporized cannabis in patients with chronic pain on stable doses of sustained-release opioids demonstrated no clinically significant change in plasma opiates, while suggesting the possibility of synergistic analgesia. Aside from symptom management, an increasing body of in vitro and animal-model studies supports a possible direct anticancer effect of cannabinoids by way of a number of different mechanisms involving apoptosis, angiogenesis, and inhibition of metastasis. Despite an absence of clinical trials, abundant anecdotal reports that describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate, are circulating. Human studies should be conducted to address critical questions related to the foregoing effects.

23. Donald I. Abrams. Cannabis in cancer care.
[Clinical Pharmacology & Therapeutics 2015;97(6):575-586]

ABSTRACT

Cannabis has been used in medicine for thousands of years prior to achieving its current illicit substance status. Cannabinoids, the active components of Cannabis sativa, mimic the effects of the endogenous cannabinoids (endocannabinoids), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found predominantly in cells involved with immune function. Delta-9-tetrahydrocannabinol, the main bioactive cannabinoid in the plant, has been available as a prescription medication approved for treatment of cancer chemotherapy-induced nausea and vomiting and anorexia associated with the AIDS wasting syndrome. Cannabinoids may be of benefit in the treatment of cancer-related pain, possibly synergistic with opioid analgesics. Cannabinoids have been shown to be of benefit in the treatment of HIV-related peripheral neuropathy, suggesting that they may be worthy of study in patients with other neuropathic symptoms. Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability.

24. Daniel A. Ladin, et al. Preclinical and clinical assessment of cannabinoids as anti-cancer agents.
[Frontiers in pharmacology 2016;7(361):1-18]

ABSTRACT

Cancer is the second leading cause of death in the United States with 1.7 million new cases estimated to be diagnosed in 2016. This disease remains a formidable clinical challenge and represents a substantial financial burden to the US health care system. Therefore, research and development of novel therapeutics for the treatment of cancer is of high priority. Cannabinoids and their derivatives have been utilized for their medicinal and therapeutic properties throughout history. Cannabinoid activity is regulated by the endocannabinoid system (ECS), which is comprised of cannabinoid receptors, transporters, and enzymes involved in cannabinoid synthesis and breakdown. More recently, cannabinoids have gained special attention for their role in cancer cell proliferation and death. However, many studies investigated these effects using in vitro models which may not adequately mimic tumor growth and metastasis. As such, this article aims to review study results which evaluated effects of cannabinoids from plant, synthetic and endogenous origins on cancer development in preclinical animal models and to examine the current standing of cannabinoids that are being tested in human cancer patients.

25. Paweł Sledzinski, et al. The current state and future perspectives of cannabinoids in cancer biology.
[Cancer Medicine 2018; 7(3):765–775]

ABSTRACT

To date, cannabinoids have been allowed in the palliative medicine due to their analgesic and antiemetic effects, but

increasing number of preclinical studies indicates their anticancer properties. Cannabinoids exhibit their action by a modulation of the signaling pathways crucial in the control of cell proliferation and survival. Many in vitro and in vivo experiments have shown that cannabinoids inhibit proliferation of cancer cells, stimulate autophagy and apoptosis, and have also a potential to inhibit angiogenesis and metastasis. In this review, we present an actual state of knowledge regarding molecular mechanisms of cannabinoids' anticancer action, but we discuss also aspects that are still not fully understood such as the role of the endocannabinoid system in a carcinogenesis, the impact of cannabinoids on the immune system in the context of cancer development, or the cases of a stimulation of cancer cells' proliferation by cannabinoids. The review includes also a summary of currently ongoing clinical trials evaluating the safety and efficacy of cannabinoids as anticancer agents.

26. T. D. Brisbois, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial.
[Annals of Oncology 2011;22: 2086–2093]

ABSTRACT

Background:

A pilot study (NCT00316563) to determine if delta-9-tetrahydrocannabinol (THC) can improve taste and smell (chemosensory) perception as well as appetite, caloric intake, and quality of life (QOL) for cancer patients with chemosensory alterations.

Patients and Methods:

Adult advanced cancer patients, with poor appetite and chemosensory alterations, were recruited from two sites and randomized in a double-blinded manner to receive either THC (2.5 mg, Marinol; Solvay Pharma Inc., n = 24) or placebo oral capsules (n = 22) twice daily for 18 days. Twenty-one patients completed the trial. At baseline and posttreatment, patients completed a panel of patient-reported outcomes: Taste and Smell Survey, 3-day food record, appetite and macronutrient preference assessments, QOL questionnaire, and an interview.

Results:

THC and placebo groups were comparable at baseline. Compared with placebo, THC-treated patients reported improved (P = 0.026) and enhanced (P < 0.001) chemosensory perception and food 'tasted better' (P = 0.04). Premeal appetite (P = 0.05) and proportion of calories consumed as protein increased compared with placebo (P = 0.008). THC-treated patients reported increased quality of sleep (P = 0.025) and relaxation (P = 0.045). QOL scores and total caloric intake were improved in both THC and placebo groups.

Conclusions:

THC may be useful in the palliation of chemosensory alterations and to improve food enjoyment for cancer patients.

27. Mary E. Lynch, et al. A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain.
[Journal of pain and symptom management 2014;47(1):166-173]

ABSTRACT

Context:

Neuropathic pain caused by chemotherapy limits dosing and duration of potentially life-saving anti-cancer treatment and impairs quality of life. Chemotherapeutic neuropathy responds poorly to conventional treatments, and there is an urgent medical need for new treatments. Recent preclinical studies demonstrate that cannabinoid agonists suppress established chemotherapy evoked neuropathy.

Objectives:

This was a pilot trial to begin to investigate a currently available cannabinoid agent, nabiximols (oral mucosal spray containing cannabinoids), in the treatment of chemotherapy-induced neuropathic pain.

Methods:

A randomized, placebo-controlled crossover pilot study was done in 16 patients with established chemotherapy-induced neuropathic pain. A 0e10 point numeric rating scale for pain intensity (NRS-PI) was used as the primary outcome measure.

Results:

When examining the whole group, there was no statistically significant difference between the treatment and the placebo groups on the NRS-PI. A responder analysis demonstrated that there were five participants who reported a two-point or greater reduction in pain that trended toward statistical significance and the number needed to treat was five.

Conclusion:

Chemotherapy-induced neuropathic pain is particularly resistant to currently available treatments. This pilot trial found a number needed to treat of five and an average decrease of 2.6 on an 11-point NRS-PI in five ''responders'' (as compared with a decrease of 0.6 with placebo) and supports that it is worthwhile to study nabiximols in a full randomized, placebo-controlled trial of chemotherapy-induced neuropathic pain.

28. Grant Steele et al. A Comprehensive Review of Cannabis in Patients with Cancer: Availability in the USA, General Efficacy, and Safety.

[Current Oncology Reports 2019;21(1):10]

ABSTRACT

Purpose of Review:

As the legalization of medical cannabis continues across the USA, oncology care providers will be increasingly asked to provide recommendations regarding its use in the cancer setting. In this article, we review recent literature that analyzes cannabis use specifically in patients with cancer and provide an accessible guide for clinicians, researchers, and patients.

Recent Findings:

We aimed to answer questions about the availability of cannabis in the USA, the trials supporting its use in the cancer setting, and the important factors to consider related to safety. Thirty states plus the District of Columbia have established comprehensive medical cannabis programs, each with different regulations and products available. In June 2018, Epidiolex, a cannabis extraction product containing 99% CBD, was approved to treat refractory seizures; however, whole-plant products and non-prescription extraction products dominate the market. Recent randomized, placebo-controlled studies of nabiximols (Sativex) in patients with refractory cancer-pain have largely shown no significant benefits. Conversely, large observational studies suggest patients with cancer using cannabis report significant improvement of many common symptoms. Cannabis use appears well tolerated, with few serious adverse effects reported. Though prospective clinical trials are needed to provide the robust data required to establish the proper role of cannabinoid and cannabis-based therapy in cancer patients, physicians can draw upon the knowledge currently available to have informed discussions with their patients.

29. Alexia Blake, et al. A selective review of medical cannabis in cancer pain management.

[Annals of Palliative Medicine 2017;6(Suppl 2):S215-S222]

ABSTRACT

Insufficient management of cancer-associated chronic and neuropathic pain adversely affects patient quality of life. Patients who do not respond well to opioid analgesics or have severe side effects from the use of traditional analgesics are in need of alternative therapeutic options. Anecdotal evidence suggests that medical cannabis has potential to effectively manage pain in this patient population. This review presents a selection of representative clinical studies, from small pilot studies conducted in 1975, to double-blind placebo-controlled trials conducted in 2014 that evaluated the efficacy of cannabinoid-based therapies containing tetrahydrocannabinol (THC) and cannabidiol (CBD) for reducing cancer-associated pain. A review of literature published on Medline between 1975 and 2017 identified five clinical studies that evaluated the effect of THC or CBD on controlling cancer pain, which have been reviewed and summarized. Five studies that evaluated THC oil capsules, THC:CBD oromucosal spray (nabiximols), or THC oromucosal sprays found some evidence of cancer pain reduction associated with these therapies. A variety of doses ranging from 2.7–43.2 mg/day THC and 0–40 mg/day CBD were administered. Higher doses of THC were correlated with increased pain relief in some studies. One study found that significant pain relief was achieved in doses as low as 2.7–10.8 mg THC in combination with 2.5–10.0 mg CBD, but there was conflicting evidence on whether higher doses provide superior pain relief. Some reported side effects include drowsiness, hypotension, mental clouding, and nausea and vomiting. There is evidence suggesting that medical cannabis reduces chronic or neuropathic pain in advanced cancer patients. However, the results of many studies lacked statistical power, in some cases due to limited number of study subjects. Therefore, there is a need for the conduct of further double-blind, placebo-controlled clinical trials with large sample sizes in order to establish the optimal dosage and efficacy of different cannabis-based therapies.

30. Philippa Hawley and Margherita Gobbo. Cannabis use in cancer: a survey of the current state at BC Cancer before recreational legalization in Canada.

[Current Oncology 2019;26(4):e425-e432]

ABSTRACT

Background:

Cancer patients experience multiple symptoms throughout their illness, and some report benefit from the use of cannabis. There are concerns that many patients are accessing products inappropriate for their situation and potentially putting themselves at risk. In the present study, we aimed to capture the prevalence of cannabis use among cancer patients at BC Cancer before recreational legalization in Canada and to identify the reasons that patients take cannabis, the various routes of administration they use, and the reasons that prior users stopped.

Methods:

Patients were eligible if, on the selected study day (15August 2018), they were scheduled for an appointment at any of the 6 BC Cancer sites. Eligible patients were mailed a survey.

Results:

Results of surveys sent to 2998 patients, 821 (27.4%) were returned and included in analysis. Of those respondents, 23% were currently using cannabis-based products, almost exclusively for medical purposes, and an additional 28% had been users in the past (most often recreationally). Of the patients currently using cannabis, 31% had medical authorization. The most common symptoms that the current users were targeting were pain, insomnia, nausea, and anxiety; many were also hoping for anticancer effects.

Conclusions:

More than half the respondents had tried cannabis at some time, and almost one quarter of respondents were currently taking cannabis to help manage their symptoms or treat their cancer, or both. Many more patients would consider use with appropriate guidance from a health care professional. More research is needed to inform physicians and patients about safe uses and doses and about the potential adverse effects of cannabis use.

31. Gil Bar-Sela, et al. Chronic cannabis used by patients with advanced cancer during Immunotherapy initiation: clinical outcomes and endocannabinoid levels evaluation.

[Annals of Oncology 2020;31 (suppl_4): S988-S1017]

ABSTRACT 1852P

Background:

Therapeutic use of medical cannabis among cancer patients has become highly prevalent, while its overall effects on the immune system are unclear. This study aims to determine if cannabis consumption during immunotherapy affects therapy outcome for patients with advanced malignancies.

Methods:

The study was conducted at single Oncology center, in Israel between 01 Sep 2016 and 25 Sep 2018; included 102 [68 immunotherapy alone (I-G) and 34 immunotherapy plus cannabis (IC-G)] consecutive patients with advanced cancers who initiated one of the checkpoint inhibitors. Blood samples were taken before immunotherapy treatment. Endocannabinoid (eCB) levels from various lipid families, were evaluated in a subgroup of 36 patients. Safety and effectivity of cannabis treatment in advanced cancers commencing treatment with immune checkpoint blockers was evaluated with time to tumor progression (TTP) used as a post hoc primary endpoint and overall survival (OS) and eCB concentrations as secondary endpoints with a minimum follow-up time of 7 months.

Results:

Kaplan Maier curve showed a significant difference in TTP [I-G 13.1m (95%CI 6.0- NAm) vs. IC-G 3.4m (95%CI 1.8-6.0m), p=0.0025] and OS [IG 28.5m (95%CI 15.6- NAm) vs. IC-G 6.4m (95%CI 3.2-9.7m), p=0.0009]. After adjusting for the line of treatment, Cox regression analysis showed that cannabis consumption decreases OS (HR= 2.18, 95%CI 1.241-3.819. p=0.007) and TTP (HR= 1.95, 95%CI 1.17-3.26. p=0.011). The use of cannabis reduced grade ≥2 immune-related adverse events (iAE) (I-G 39% vs. IC-G 21%, p=0.057). Further analysis of baseline levels of circulating eCB from various lipid families showed no significant changes in their overall concentrations. However, analyzing a cohort comparing patients with progressive disease to those with complete remission correlates baseline eCB levels and expected OS, suggesting that the eCB system may play a role in immunotherapy outcomes.

Conclusions:

Initiating immunotherapy with cannabis use negatively affects OS and TTP of cancer patients treated with immunotherapy.

32. Amber S. Kleckner, et al. Opportunities for cannabis in supportive care in cancer.

[Therapeutic Advances in Medical Oncology 2019;11:1-29]

ABSTRACT

Cannabis has the potential to modulate some of the most common and debilitating symptoms of cancer and its treatments, including nausea and vomiting, loss of appetite, and pain. However, the dearth of scientific evidence for the effectiveness of cannabis in treating these symptoms in patients with cancer poses a challenge to clinicians in discussing this option with their patients. A review was performed using keywords related to cannabis and important symptoms of cancer and its treatments. Literature was qualitatively reviewed from preclinical models to clinical trials in the fields of cancer, human immunodeficiency virus (HIV), multiple sclerosis, inflammatory bowel disease, post-traumatic stress disorder (PTSD), and others, to prudently inform the use of cannabis in supportive and palliative care in cancer. There is a reasonable amount of evidence to consider cannabis for nausea and vomiting, loss of appetite, and pain as a supplement to first-line treatments. There is promising evidence to treat chemotherapy-induced peripheral neuropathy, gastrointestinal distress, and sleep disorders, but the literature is thus far too limited to recommend cannabis for these symptoms. Scant, yet more controversial, evidence exists in regard to cannabis for cancer- and treatment-related cognitive impairment, anxiety, depression, and fatigue. Adverse effects of cannabis are documented but tend to be mild. Cannabis has multifaceted potential bioactive benefits that appear to outweigh its risks in many situations. Further research is required to elucidate its mechanisms of action and efficacy and to optimize cannabis preparations and doses for specific populations affected by cancer.

33. Jeremy R. Johnson, et al. An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesic.

[Journal of pain and symptom management 2013;46(2):207-218]

ABSTRACT

Context:

Chronic pain in patients with advanced cancer poses a serious clinical challenge. The D9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (U.S. Adopted Name, nabiximols; Sativex) is a novel cannabinoid formulation currently undergoing investigation as an adjuvant therapy for this treatment group.

Objectives:

This follow-up study investigated the long-term safety and tolerability of THC/CBD spray and THC spray in relieving pain in patients with advanced cancer.

Methods:

In total, 43 patients with cancer-related pain experiencing inadequate analgesia despite chronic opioid dosing, who had participated in a previous three-arm (THC/CBD spray, THC spray, or placebo), two-week parent randomized controlled trial, entered this open-label, multicenter, follow-up study. Patients self-titrated THC/CBD spray (n=39) or THC spray (n=4) to symptom relief or maximum dose and were regularly reviewed for safety, tolerability, and evidence of clinical benefit.

Results:

The efficacy end point of change from baseline in mean Brief Pain Inventory-Short Form scores for ''pain severity'' and ''worst pain'' domains showed a decrease (i.e., improvement) at each visit in the THC/CBD spray patients. Similarly, the European Organization for Research and Treatment of Cancer.

34. Kristine A Donovan, et al. Relationship of Cannabis Use to Patient-Reported Symptoms in Cancer Patients Seeking Supportive/Palliative Care.

[Journal of Palliative Medicine 2019;22(10):1191-1195]

ABSTRACT

Background:

The use of cannabis by cancer patients has become increasingly common. With expanding access to medical cannabis, unsanctioned cannabis use is likely to increase. Despite this, the extent to which patients seeking specialized palliative or supportive care for cancer-related symptoms are actively using cannabis has not been well established.

Objective:

We sought to determine the extent to which patients seeking specialized symptom management were using cannabis and to compare the severity of cancer-related symptoms between users and nonusers.

Methods:

We conducted a retrospective review of objectively measured tetrahydrocannabinol (THC) and subjectively reported cannabis use, its demographic and clinical correlates, and patient-reported symptoms in 816 cancer patients in active treatment referred to a supportive/palliative care outpatient clinic for specialized symptom management between January 2014 and May 2017.

Results:

Nearly one-fifth (19.12%) tested positive for THC on urine drug testing. Users were younger, more likely to be men, single, and to have a history of cigarette smoking. Users also were likely to be more recently diagnosed and to have received radiotherapy. Certain moderate-to-severe symptoms, such as lack of appetite, shortness of breath, tiredness, difficulty sleeping, anxiety, and depression, were associated with use after accounting for sociodemographic and clinical differences between cannabis users and nonusers.

Conclusions:

Findings suggest patients seeking specialized symptom management are self-treating with cannabis, despite the lack of high-quality evidence for its use in palliative care. Unsanctioned use is likely to increase in cancer patients. Accurate information is urgently needed to help manage patient expectations for its use and increase understanding of risks and benefits.

35. Steven A Pergam, et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use.

[Cancer 2017;123(22):4488-4497]

ABSTRACT

Background:

Cannabis is purported to alleviate symptoms related to cancer treatment, although the patterns of use among cancer patients are not well known. This study was designed to determine the prevalence and methods of use among cancer patients, the perceived benefits, and the sources of information in a state with legalized cannabis.

Methods:

A cross-sectional, anonymous survey of adult cancer patients was performed at a National Cancer Institute-designated cancer center in Washington State. Random urine samples for tetrahydrocannabinol provided survey validation.

Results:

Nine hundred twenty-six of 2737 eligible patients (34%) completed the survey, and the median age was 58 years (interquartile range [IQR], 46-66 years). Most had a strong interest in learning about cannabis during treatment (6 on a 1-10 scale; IQR, 3-10) and wanted information from cancer providers (677 of 911 [74%]). Previous use was common (607 of 926 [66%]); 24% (222 of 926) used cannabis in the last year, and 21% (192 of 926) used cannabis in the last month. Random urine samples found similar percentages of users who reported weekly use (27 of 193 [14%] vs 164 of 926 [18%]). Active users inhaled (153 of 220 [70%]) or consumed edibles (154 of 220 [70%]); 89 (40%) used both modalities. Cannabis was used primarily for physical (165 of 219 [75%]) and neuropsychiatric symptoms (139 of 219 [63%]). Legalization significantly increased the likelihood of use in more than half of the respondents.

Conclusions:

This study of cancer patients in a state with legalized cannabis found high rates of active use across broad subgroups, and legalization was reported to be important in patients' decision to use. Cancer patients desire but are not receiving information about cannabis use during their treatment from oncology providers.

36. Michaela Aldea, et al. Molecular features of young cannabis smokers with advanced non-small cell lung cancer (aNSCLC).

[Annals of Oncology 2021;32 (suppl_5): S949-S1039]

ABSTRACT 1344P

Background:

Regular cannabis consumption has been reported at a high frequency in young patients (pts) diagnosed with NSCLC.

Their genomic and clinical features may define a unique disease biology. Here, we report molecular characteristics of a cohort of young cannabis smokers with aNSCLC.

Methods:

aNSCLC patients aged < 50 years-old who were genotyped at Gustave Roussy between 2019 and 2020 were included in this study if they had a known cannabis consumption, defined as >10 joints/month for ≥ 1 year. Clinical, molecular and radiological data were collected. The presence of actionable genomic alterations (GA) (defined as ESCAT I and II tier), TMB, PD-L1 expression and STK11 mutations were interrogated. Objective response (OR) and progression-free survival (PFS) were determined for pts treated with immune-checkpoint blocker (ICB) with/without chemotherapy.

Results:

Out of 100 pts with a molecular profile, 67 had a known smoking status: 26 never smokers, 14 tobacco-only and 27 cannabis-smokers. Cannabis smokers were also tobacco smokers (all, median pack-year 30 [12-30]), 25 were men (93%), median age 44 years [39-48], 23 had adenocarcinoma (82%) and 18 were metastatic at diagnosis (67%), with a median of 3 [2-4] metastatic sites. Targetable GA were found in 5/27 (18.5%) patients: 1 ALK fusion (3.7%), 1 ROS1 fusions (3.7%), 1 HER2 mutation (3.7%) and 2 KRAS G12C mutations (7.6%). KRAS mutations (all subtype) were found in 4/26 (15.3%), while STK11 and TP53 mutations were found in 9/18 (50%) and 17/24 (71%) pts, respectively. Median PD-L1 expression was 0 [0 – 70] and median TMB was 10 mut/Mb [4.52-24.69]. Fourteen pts received single agent ICI or chemo-immunotherapy in the front-line setting. OR were obtained in 6/14 (42.8%). Median PFS was 5.75 months [95% CI: 1.68-9.81].

Conclusions:

More than 80% of young cannabis smokers with aNSCLC do not harbor an actionable driver. STK11 mutations have a high prevalence in this population and PD-L1 expression is generally low. Despite high TMB and heavy tobacco smoking, ICB outcomes appear lower than expected in the frontline setting.

37. Jeremy R Johnson, et al. Multicenter, double-blind, randomized, placebocontrolled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain.

[International Journal of Molecular Sciences 2018;19(833):1-23]

ABSTRACT

This study compared the efficacy of a tetrahydrocannabinol:cannabidiol (THC:CBD) extract, a nonopioid analgesic endocannabinoid system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer. In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing, entered a two-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC:CBD extract (n = 60), THC extract (n = 58), or placebo (n = 59). The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC:CBD compared with placebo (improvement of -1.37 vs. -0.69), whereas the THC group showed a nonsignificant change (-1.01 vs. -0.69). Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance. There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. No significant group differences were found in the NRS sleep quality or nausea scores or the pain control assessment. However, the results from the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire showed a worsening in nausea and vomiting with THC:CBD compared with placebo (P = 0.02), whereas THC had no difference (P = 1.0). Most drug-related adverse events were mild/moderate in severity. This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids.

38. Vidya Dusi, et al. Observational study on role of crude cannabis in pain control and quality of life in terminally ill cancer patients: An Indian perspective.

[Annals of Oncology 2019;30 (suppl_9)]

ABSTRACT 356P

Background:

Terminal cancer pain continues to be a significant morbidity. Most of the patients need intervention by pain specialists - and few remain “difficult to treat”. In India, most of these patients do shift to alternative medicine in desperation, with active ingredients, such as steroids/cannabinoids, and few unclassified anti-tumor substances. After listing and analyzing these the two most frequently observed ones are steroids and cannabinoids wherever patients have satisfactory pain control.

Methods:

An interview-based study was conducted as a part of QOL Data collection, which included other symptoms (such as fatigue, cachexia, well-being etc.) in the period of 2016-2018. One of key inclusions was - patients with advanced cancer progressed on multiple lines for which there was no standard of care. After data collection, a subset analysis was conducted with reference to pain control and use of alternative medication. For ease of analysis subjects were grouped into 4 categories based on pain control with opioids and concurrent use of cannabinoids. Subjects whose nature of the medication was not known were excluded. All four groups were analyzed for the pain control with help of visual analogy scale (VAS).

Results:

The baseline demographic characters in all four groups were well balanced and depicted in Table -1. Overall, there were no statistically significant differences in the duration of symptoms, average dose of opioid analgesia, performance status and the stage of disease. Pain relief was better in the cannabis group, when it was used independently or in combination with opioids. No significant additional side effects pertaining to cannabis were reported by the patients. The overall qualities of life, as well as weight gain and nausea control were better in the cannabis group.

Conclusions:

We could infer that Bhang [cannabis crude form], is an effective analgesic independently having synergy with opioids. It also improved overall QOL, especially in cachexia, without adverse effects. If scientifically proven with pharmaceutical grade, it will be a significant addition to the symptomatic care of terminally ill cancer patients. Though available in US, India still does not have regulatory approval for medical cannabis.

39. Aron H Lichtman, et al. Results of a Double-Blind, Randomized, Placebo Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain.

[Journal of pain and symptom management 2018;55(2):179-188.e1]

ABSTRACT

Context:

Prior Phase 2/3 studies found that cannabinoids might provide adjunctive analgesia in advanced cancer patients with uncontrolled pain.

Objectives:

To assess adjunctive nabiximols (Sativex), an extract of Cannabis sativa containing two potentially therapeutic cannabinoids (Δ9-tetrahydrocannabinol [27 mg/mL] and cannabidiol [25 mg/mL]), in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.

Methods:

Phase 3, double-blind, randomized, placebo-controlled trial in patients with advanced cancer and average pain Numerical Rating Scale scores ≥4 and ≤8 despite optimized opioid therapy. Patients randomized to nabiximols (n = 199) or placebo (n = 198) self-titrated study medications over a two-week period, followed by a three-week treatment period at the titrated dose.

Results:

Median percent improvements in average pain Numerical Rating Scale score from baseline to end of treatment in the nabiximols and placebo groups were 10.7% vs. 4.5% (P = 0.0854) in the intention-to-treat population (primary variable) and 15.5% vs. 6.3% (P = 0.0378) in the per-protocol population. Nabiximols was statistically superior to placebo on two of three quality-of-life instruments at Week 3 and on all three at Week 5. In exploratory post hoc analyses, U.S. patients, but not patients from the rest of the world, experienced significant benefits from nabiximols on multiple secondary endpoints. Possible contributing factors to differences in nabiximols efficacy include: 1) the U.S. participants received lower doses of opioids at baseline than the rest of the world and 2) the subgroups had different distribution of cancer pain types, which may have been related to differences in pathophysiology of pain. The safety profile of nabiximols was consistent with earlier studies.

Conclusions:

Although not superior to placebo on the primary efficacy endpoint, nabiximols had benefits on multiple secondary endpoints, particularly in the U.S.

40. Kathryn R Tringale, et al. The role of cancer in marijuana and prescription opioid use in the United States: A population-based analysis from 2005 to 2014.
[Cancer 2019;125(13):2242-2251]

ABSTRACT

Background:

For patients with cancer, marijuana may be an alternative to prescription opioid analgesics. This study analyzed self-reported marijuana and prescription opioid use among people with cancer over a 10-year time-period.

Methods:

Population-based data sets from the US National Health and Nutrition Examination Survey between 2005 and 2014 were compiled for respondents aged 20 to 60 years. Respondents with cancer and respondents without cancer were propensity score-matched (1:2) by demographics to compare substance use. Outcomes included current marijuana and prescription opioid use (ie, within the past 30 days). Pearson chi-square tests and logistic regressions were performed; a 2-tailed P value < .05 was significant.

Results:

There were 19,604 respondents, and 826 people with cancer were matched to 1652 controls. Among the respondents with cancer, 40.3% used marijuana within the past year, and 8.7% used it currently. Respondents with cancer were significantly more likely to use prescription opioids (odds ratio [OR], 2.43; 95% CI, 1.68-3.57; P < .001). Cancer was not associated with current marijuana use in a multivariable conditional logistic regression but was associated with current opioid use (OR, 1.82; 95% CI, 1.17-2.82; P = .008). Among all survey respondents, the odds of marijuana use significantly increased over time (OR, 1.05; 95% CI, 1.01-1.10; P = 0.012), whereas the odds of opioid use did not significantly change. There were no significant differences in the longitudinal odds of marijuana or opioid use over time between respondents with a cancer diagnosis and those without one.

Conclusions:

This population-based analysis revealed a considerable proportion of respondents with cancer self-reporting marijuana use (40.3%) and a significantly higher prevalence of opioid use among respondents with cancer. In the midst of an opioid epidemic, an evolving political landscape, and new ©2019 American Cancer Society. developments in oncology, quantifying the prevalence of opioid and marijuana use in the US population, especially among patients with cancer, is particularly relevant. Although opioid use did not significantly change from 2005 to 2014 among all respondents, marijuana use did increase, likely reflecting increased availability and legislative changes. A cancer diagnosis did not significantly affect longitudinal opioid or marijuana use.

EPILEPSY

41. Guilherme Diogo Silva, et al. CBD in the treatment of epilepsy: a focused review of evidence and gaps.
[Frontiers in Neurology 2020;11: Art 531939]

ABSTRACT

Approximately one third of epilepsy patients do not become seizure free with antiseizure medications. This treatment gap motivates research for new therapeutic options, such as cannabidiol (CBD). CBD differs from other cannabis derivatives because of its consistent efficacy and lack of a psychoactive effect. CBD can be recommended as adjunctive therapy in patients with Dravet and Lennox-Gastaut syndromes. The most common adverse effects (AEs) are drowsiness, reduced appetite, diarrhea, and vomiting. Transaminase elevation is the most common AE that leads to CBD discontinuation. Coadministration with valproate may increase the risk of hepatotoxicity. The combination of CBD and clobazam may increase both the effectiveness and the risk of AEs associated with these drugs. The most striking gaps in knowledge are the efficacy and optimal dose of CBD for adults with focal epilepsies, the long-term safety of CBD use, and strategies to improve access to CBD for people living with epilepsy.

42. Simona Lattanzi, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis.

[Drugs 2018;78(17):1791–1804]

ABSTRACT

Background:

Approximately one-third of patients with epilepsy presents seizures despite adequate treatment. Hence, there is the need to search for new therapeutic options. Cannabidiol (CBD) is a major chemical component of the resin of Cannabis sativa plant, most known as marijuana. The anti-seizure properties of CBD do not relate to the direct action on cannabinoid receptors but are mediated by a multitude of mechanisms that include the agonist and antagonist effects on ionic channels, neurotransmitter transporters, and multiple 7-transmembrane receptors. In contrast to tetra-hydro cannabinol, CBD lacks psychoactive properties, does not produce euphoric or intrusive side effects, and is largely devoid of abuse liability.

Objective:

The aim of the study was to estimate the efficacy and safety of CBD as adjunctive treatment in patients with epilepsy using meta-analytical techniques.

Methods:

Randomized, placebo-controlled, single- or double-blinded add-on trials of oral CBD in patients with uncontrolled epilepsy were identified. Main outcomes included the percentage change and the proportion of patients with ≥ 50% reduction in monthly seizure frequency during the treatment period and the incidence of treatment withdrawal and adverse events (AEs).

Results:

Four trials involving 550 patients with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) were included. The pooled average difference in change in seizure frequency during the treatment period resulted 19.5 [95% confidence interval (CI) 8.1-31.0; p = 0.001] percentage points between the CBD 10 mg and placebo groups and 19.9 (95% CI 11.8-28.1; p < 0.001) percentage points between the CBD 20 mg and placebo arms, in favor of CBD. The reduction in all-types seizure frequency by at least 50% occurred in 37.2% of the patients in the CBD 20 mg group and 21.2% of the placebo-treated participants [risk ratio (RR) 1.76, 95% CI 1.07-2.88; p = 0.025]. Across the trials, drug withdrawal for any reason occurred in 11.1% and 2.6% of participants receiving CBD and placebo, respectively (RR 3.54, 95% CI 1.55-8.12; p = 0.003) [Chi squared = 2.53, degrees of freedom (df) = 3, p = 0.506; I2 = 0.0%]. The RRs to discontinue treatment were 1.45 (95% CI 0.28-7.41; p = 0.657) and 4.20 (95% CI 1.82-9.68; p = 0.001) for CBD at the doses of 10 and 20 mg/kg/day, respectively, in comparison to placebo. Treatment was discontinued due to AEs in 8.9% and 1.8% of patients in the active and control arms, respectively (RR 5.59, 95% CI 1.87-16.73; p = 0.002). The corresponding RRs for CBD at the doses of 10 and 20 mg/kg/day were 1.66 (95% CI 0.22-12.86; p = 0.626) and 6.89 (95% CI 2.28-20.80; p = 0.001). AEs occurred in 87.9% and 72.2% of patients treated with CBD and placebo (RR 1.22, 95% CI 1.11-1.33; p < 0.001). AEs significantly associated with CBD were somnolence, decreased appetite, diarrhea, and increased serum aminotransferases.

Conclusions:

Adjunctive CBD in patients with LGS or DS experiencing seizures uncontrolled by concomitant anti-epileptic treatment regimens is associated with a greater reduction in seizure frequency and a higher rate of AEs than placebo.

43. Orrin Devinsky, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome.

[New England Journal of Medicine 2018;378(20):1888-97]

ABSTRACT

Background:

Cannabidiol has been used for treatment-resistant seizures in patients with severe early-onset epilepsy. We investigated the efficacy and safety of cannabidiol added to a regimen of conventional antiepileptic medication to treat drop seizures in patients with the Lennox–Gastaut syndrome, a severe developmental epileptic encephalopathy.

Methods:

In this double-blind, placebo-controlled trial conducted at 30 clinical centers, we randomly assigned patients with the Lennox–Gastaut syndrome (age range, 2 to 55 years) who had had two or more drop seizures per week during a 28-day baseline period to receive cannabidiol oral solution at a dose of either 20 mg per kilogram of body weight (20-mg cannabidiol group) or 10 mg per kilogram (10-mg cannabidiol group) or matching placebo, administered in two equally divided doses daily for 14 weeks. The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period.

Results:

A total of 225 patients were enrolled; 76 patients were assigned to the 20-mg cannabidiol group, 73 to the 10-mg cannabidiol group, and 76 to the placebo group. During the 28-day baseline period, the median number of drop seizures was 85 in all trial groups combined. The median percent reduction from baseline in drop-seizure frequency during the treatment period was

41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group (P=0.005 for the 20-mg cannabidiol group vs. placebo group, and P=0.002 for the 10-mg cannabidiol group vs. placebo group). The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhea; these events occurred more frequently in the higher-dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial medication because of adverse events and were withdrawn from the trial. Fourteen patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations.

44. Orrin Devinsky, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial.

[The Lancet Neurology 2016; 15(3):270-278]

ABSTRACT

Background:

Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe morbidity and increased mortality. Cannabis-based treatments for epilepsy have generated much interest, but scientific data are scarce. We aimed to establish whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and efficacious in children and young adults with treatment-resistant epilepsy.

Methods:

In this open-label trial, patients (aged 1-30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access program at 11 epilepsy centers across the USA. Patients were given oral cannabidiol at 2-5 mg/kg per day, up titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). The primary objective was to establish the safety and tolerability of cannabidiol, and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The efficacy analysis was by modified intention to treat. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney U test.

Results:

Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, and 137 (64%) patients were included in the efficacy analysis. In the safety group, 33 (20%) patients had Dravet syndrome, and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death-a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30.0 (IQR 11.0-96.0) at baseline and 15.8 (5.6-57.6) over the 12-week treatment period. The median reduction in monthly motor seizures was 36.5% (IQR 0-64.7).

Interpretation:

Our findings suggest that cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomized controlled trials are warranted to characterize the safety profile and true efficacy of this compound.

45. Simona Lattanzi, et al. Efficacy and safety of adjunctive cannabidiol in patients with Lennox–Gastaut syndrome: a systematic review and meta-analysis.

[CNS Drugs 2018;32:905-916]

ABSTRACT

Background:

Lennox–Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy, and available interventions fail to control seizures in most patients. Cannabidiol (CBD) is a major chemical of marijuana, which has anti-seizure properties and different mechanisms of action compared with other approved antiepileptic drugs (AEDs).

Objective:

The aim was to evaluate the efficacy and safety of CBD as adjunctive treatment for seizures in patients with LGS using meta-analytical techniques.

Methods:

Randomized, placebo-controlled, single- or double-blinded trials were identified. Main outcomes included the ≥ 50% reduction in baseline drop and non-drop seizure frequency, and the incidence of treatment withdrawal and adverse events (AEs). Risk ratios (RRs) with 95% confidence intervals (CIs) were estimated through the inverse variance method.

Results:

Two trials were included involving 396 participants. Patients presenting ≥ 50% reduction in drop seizure frequency during the treatment were 40.0% with CBD and 19.3% with placebo [RR 2.12 (95% CI 1.48–3.03); p < 0.001]. The rate of non-drop seizure frequency was reduced by 50% or more in 49.4% of patients in the CBD and 30.4% in the placebo arms [RR 1.62 (95% CI 1.09–2.43); p = 0.018]. The RR for CBD withdrawal was 4.93 (95% CI 1.50–16.22; p = 0.009). The RR to develop any AE during CBD treatment was 1.24 (95% CI 1.11–1.38; p < 0.001). AEs significantly associated with CBD were somnolence, decreased appetite, diarrhea, and increased serum aminotransferases.

Conclusions:

Adjunctive CBD resulted in a greater reduction in seizure frequency and a higher rate of AEs than placebo in patients with LGS presenting seizures uncontrolled by concomitant AEDs.

46. Emily Stockings, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence.

[Journal of Neurology, Neurosurgery, and Psychiatry 2018;89:741–753]

ABSTRACT

Review evidence for cannabinoids as adjunctive treatments for treatment-resistant epilepsy. Systematic search of Medline, Embase and PsycINFO was conducted in October 2017. Outcomes were 50%+ seizure reduction, complete seizure freedom; improved quality of life (QoL). Tolerability/safety were assessed by study withdrawals, adverse events (AEs) and serious adverse events (SAEs). Analyses were conducted in Stata V.15.0. 36 studies were identified: 6 randomized controlled trials (RCTs), 30 observational studies. Mean age of participants was 16.1 years (range 0.5–55 years). Cannabidiol (CBD) 20mg/kg/day was more effective than placebo at reducing seizure frequency by 50%+(relative risk (RR) 1.74, 95% CI 1.24 to 2.43, 2 RCTs, 291 patients, low Grades of Recommendation, Assessment, Development and Evaluation (GRADE) rating). The number needed to treat for one person using CBD to experience 50%+ seizure reduction was 8 (95%CI 6 to 17). CBD was more effective than placebo at achieving complete seizure freedom (RR 6.17, 95%CI 1.50 to 25.32, 3 RCTs, 306 patients, low GRADE rating), and improving QoL (RR 1.73, 95%CI 1.33 to 2.26), however increased risk of AEs (RR 1.24, 95%CI 1.13 to 1.36) and SAEs (RR 2.55, 95%CI 1.48 to 4.38). Pooled across 17 observational studies, 48.5% (95%CI 39.0% to 58.1%) of patients reported 50%+ reductions in seizures; in 14 observational studies 8.5% (95%CI 3.8% to 14.5%) were seizure-free. Twelve observational studies reported improved QoL (55.8%, 95%CI 40.5 to 70.6); 50.6% (95%CI 31.7 to 69.4) AEs and 2.2% (95%CI 0 to 7.9) SAEs. Pharmaceutical-grade CBD as adjuvant treatment in pediatric-onset drug-resistant epilepsy may reduce seizure frequency. Existing RCT evidence is mostly in pediatric samples with rare and severe epilepsy syndromes; RCTs examining other syndromes and cannabinoids are needed.

47. Orrin Devinsky, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome.

[Neurology 2018;90:1204-1211]

ABSTRACT

Objective:

To evaluate the safety and preliminary pharmacokinetics of a pharmaceutical formulation of purified cannabidiol (CBD) in children with Dravet syndrome.

Methods:

Patients aged 4–10 years were randomized 4:1 to CBD (5, 10, or 20 mg/kg/d) or placebo taken twice daily. The double-blind trial comprised 4-week baseline, 3-week treatment (including titration), 10-day taper, and 4-week follow-up periods. Completers could continue in an open-label extension. Multiple pharmacokinetic blood samples were taken on the first day of dosing and at end of treatment for measurement of CBD, its metabolites 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD, and antiepileptic drugs (AEDs; clobazam and metabolite N-desmethylclobazam [N-CLB], valproate, levetiracetam, topiramate, and stiripentol). Safety assessments were clinical laboratory tests, physical examinations, vital signs, ECGs, adverse events (AEs), seizure frequency, and suicidality.

Results:

Thirty-four patients were randomized (10, 8, and 9 to the 5, 10, and 20 mg/kg/d CBD groups, and 7 to placebo); 32 (94%) completed treatment. Exposure to CBD and its metabolites was dose-proportional (AUC0–t). CBD did not affect

concomitant AED levels, apart from an increase in N-CLB (except in patients taking stiripentol). The most common AEs on CBD were pyrexia, somnolence, decreased appetite, sedation, vomiting, ataxia, and abnormal behavior. Six patients taking CBD and valproate developed elevated transaminases; none met criteria for drug-induced liver injury, and all recovered. No other clinically relevant safety signals were observed.

Conclusions:

Exposure to CBD and its metabolites increased proportionally with dose. An interaction with N-CLB was observed, likely related to CBD inhibition of cytochrome P450 subtype 2C19. CBD resulted in more AEs than placebo but was generally well-tolerated.

48. Michael Privitera, et al. Time to onset of cannabidiol (CBD) treatment effect in Lennox–Gastaut syndrome: Analysis from two randomized controlled trials.

[Epilepsia 2021;62:1130–1140]

ABSTRACT

Objective:

To estimate time to onset of cannabidiol (CBD) treatment effect (seizure reduction and adverse events [AEs]), we conducted post hoc analyses of data from two randomized, placebo-controlled, Phase 3 trials, GWPCARE3 (NCT02224560) and GWPCARE4 (NCT02224690), of patients with Lennox–Gastaut syndrome.

Methods:

Patients received plant-derived pharmaceutical formulation of highly purified CBD (Epidiolex, 100 mg/ml oral solution) at 10 mg/kg/day (CBD10; GWPCARE3) or 20 mg/kg/day (CBD20; both trials) or placebo for 14 weeks. Treatment started at 2.5 mg/kg/day for all groups and reached 10 mg/kg/day on Day 7 and 20 mg/kg/day (CBD20 and matching placebo only) on Day 11. Percentage change from baseline in drop seizure frequency was calculated by cumulative day (i.e., including all previous days). Time to onset and resolution of AEs were evaluated.

Results:

Overall, 235 patients received CBD (CBD10 [GWPCARE3 only], n = 67; CBD20 [pooled GWPCARE3&4], n = 168) and 161 received placebo. Mean (range) age was 15.3 years (2.6–48.0). Patients had previously discontinued a median (range) of six (0–28) antiepileptic drugs (AEDs) and were currently taking a median of three (0–5) AEDs. Differences in drop seizure reduction between placebo and CBD emerged during the titration period and became nominally significant by Day 6 ($p = .008$) for pooled CBD treatment groups. Separation between placebo and CBD in ≥50% responder rate emerged by Day 6. Onset of the first reported AE occurred during the titration period in 45% of patients (CBD10, 46%; CBD20, 52%; placebo, 38%). In patients with AEs, resolution occurred within 4 weeks of onset in 53% of placebo and 39% of CBD patients and by end of study in 63% of placebo and 61% of CBD patients.

Significance:

Treatment effect (efficacy and AEs) of CBD may occur within 1 week of starting treatment. Although AEs lasted longer for CBD than placebo, most resolved within the 14-week period.

GI DISORDERS

49. Megan C. Buckley, et al. Inflammatory Bowel Disease and Cannabis: A Practical Approach for Clinicians.

[Advances in Therapy 2021;38:4152–4161]

ABSTRACT

Although still not approved at the federal level for medical or adult recreational use, cannabis has been approved in the United States (USA) by individual states for both of these purposes. A total of 15 states now regulate cannabis for adult use and 36 states for medical use. In more recent years, cannabis has gained popularity for the treatment of chronic conditions, inflammatory bowel disease (IBD) being one of them. However, the exact role of cannabis in the treatment of IBD remains uncertain. While cannabis may help in some instances with symptom management, it has not been proven to help with inflammation or to fundamentally correct underlying disease processes. Additionally, along with the perceived symptom benefits of cannabis come concerning issues like dosing inconsistencies, dependence, and

cannabinoid hyperemesis syndrome. In this review article, we explore the nuanced relationship between cannabis and the treatment of IBD by summarizing the current research. We also use clinical vignettes to discuss the more practical considerations surrounding its use.

50. Angela A Coutts. The gastrointestinal pharmacology of cannabinoids: an update.
[Current Opinion in Pharmacology 2004;4(6):572-9]

ABSTRACT

Recent work in the field of gastrointestinal pharmacology of cannabinoids has focused on enteric endocannabinoid and endovanilloid systems and their modulation in pathophysiological conditions. CB(1) receptor immunoreactivity was detected on enteric cholinergic neurones and vasoactive intestinal peptide-containing submucosal ganglion cells, on discrete nuclei of the dorsovagal complex (involved in emesis) and on central and peripheral vagal terminals, thus controlling gastroesophageal reflux and gastrointestinal motility. CB(1) receptor activation by endocannabinoids inhibited induced fluid secretion and inflammation in animal models and reduced proliferation of cultured colorectal cancer cells. Endocannabinoids also activate cannabinoid CB(2) and vanilloid VR1 receptors in certain inflammatory states. Thus, endocannabinoid metabolism could provide a useful therapeutic target for many gastrointestinal disorders.

51. Waseem Ahmed and Seymour Katz. Therapeutic Use of Cannabis in Inflammatory Bowel Disease.
[Gastroenterology & Hepatology 2016;12(11):668-679]

ABSTRACT

The marijuana plant Cannabis sativa and its derivatives, cannabinoids, have grown increasingly popular as a potential therapy for inflammatory bowel disease (IBD). Studies have shown that modulation of the endocannabinoid system, which regulates various functions in the body and has been shown to play a key role in the pathogenesis of IBD, has a therapeutic effect in mouse colitis. Epidemiologic data and human therapy studies reveal a possible role for cannabinoids in the symptomatic treatment of IBD, although it has yet to be determined in human populations whether cannabinoids have therapeutic anti-inflammatory effects in IBD or are simply masking its many debilitating symptoms. Large, double-blind, randomized, placebo-controlled trials using serial inflammatory markers, biopsy findings, and endoscopic disease severity to demonstrate objective improvement in IBD are necessary before cannabis can be empirically accepted and recommended as an IBD treatment option. Questions concerning its safety profile and adverse effects prompt the need for further research, particularly in regard to dosing and route of administration to maximize benefits and limit potential harms. Cannabis use should be reserved for symptomatic control in patients with severe IBD refractory to the currently available standard-of-care and complementary and alternative medicines.

52. Christel Rousseaux, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors.
[Nature Medicine 2007;13:35–37]

ABSTRACT

Abdominal pain is common in the general population and, in patients with irritable bowel syndrome, is attributed to visceral hypersensitivity. We found that oral administration of specific Lactobacillus strains induced the expression of μ-opioid and cannabinoid receptors in intestinal epithelial cells and mediated analgesic functions in the gut—similar to the effects of morphine. These results suggest that the microbiology of the intestinal tract influences our visceral perception and suggest new approaches for the treatment of abdominal pain and irritable bowel syndrome.

SLEEP DISORDERS

53. Kimberly A Babson, et al. Cannabis, Cannabinoids, and Sleep: a Review of the Literature.
[Current Psychiatry Reports 2017;19(4):23]

ABSTRACT

Purpose of Review:

The current review aims to summarize the state of research on cannabis and sleep up to 2014 and to review in detail the literature on cannabis and specific sleep disorders from 2014 to the time of publication.

Recent Findings:

Preliminary research into cannabis and insomnia suggests that cannabidiol (CBD) may have therapeutic potential for the treatment of insomnia. Delta-9 tetrahydrocannabinol (THC) may decrease sleep latency but could impair sleep quality long-term. Novel studies investigating cannabinoids and obstructive sleep apnea suggest that synthetic cannabinoids such as nabilone and dronabinol may have short-term benefit for sleep apnea due to their modulatory effects on serotonin-mediated apneas. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares associated with PTSD and may improve sleep among patients with chronic pain. Research on cannabis and sleep is in its infancy and has yielded mixed results. Additional controlled and longitudinal research is critical to advance our understanding of research and clinical implications.

54. Eric Murillo-Rodriguez, et al. Potential Effects of Cannabidiol as a Wake-Promoting Agent.
[Current Neuropharmacology 2014;12(3):269-272]

ABSTRACT

Over the last decades, the scientific interest in chemistry and pharmacology of cannabinoids has increased. Most attention has focused on Δ9-tetrahydrocannabinol (Δ9-THC) as it is the psychoactive constituent of Cannabis sativa (C. sativa). However, in previous years, the focus of interest in the second plant constituent with non-psychotropic properties, cannabidiol (CBD) has been enhanced. Recently, several groups have investigated the pharmacological properties of CBD with significant findings; furthermore, this compound has raised promising pharmacological properties as a wake-inducing drug. In the current review, we will provide experimental evidence regarding the potential role of CBD as a wake-inducing drug.

55. Samir Haj-Dahmane and Roh-YuShen. Modulation of the serotonin system by endocannabinoid signaling.
[Neuropharmacology 2011;61(3):414-420]

ABSTRACT

The cannabinoid CB1 receptors and their endogenous agonists, endocannabinoids (eCBs), are ubiquitously distributed throughout the central nervous system (CNS), where they play a key role in the regulation of neuronal excitability. As such, CB signaling has been implicated in the regulation of a myriad of physiological functions ranging from feeding homoeostasis to emotional and motivational processes. Ample evidence from behavioral studies also suggests that eCBs are important regulators of stress responses and a deficit in eCB signaling contributes to stress-related disorders such as anxiety and depression. The eCB-induced modulation of stress-related behaviors appears to be mediated, at least in part, through the regulation of the serotoninergic system. In this article, we review the role of eCB signaling in the regulation of the serotoninergic system with special emphasis on the cellular mechanisms by which cannabinoid CB1 receptors modulate the excitability of dorsal raphe serotonin neurons.

MIGRAINE HEADACHES

56. Ethan Russo. Hemp for Headache An In-Depth Historical and Scientific Review of Cannabis in Migraine Treatment.
[Journal of Cannabis Therapeutics 2001;1(2):21-92]

ABSTRACT

Cannabis, or "marijuana," has been employed in various forms throughout the millennia for both symptomatic and prophylactic treatment of migraine. This document examines its history of medicinal use by smoking and other methods in ancient cultures, including the Chinese, Indian, Egyptian, Assyrian, Greek and Roman, as well as in the Islamic world, and its subsequent adoption by Renaissance and Industrial Age Europeans. The most prominent physicians of the age in the century between 1842 and 1942 preferred cannabis to other preparations in migraine treatment, and it remained part of Western pharmacopoeias for this indication throughout the period. The writings of this era are examined in great detail in an effort to emphasize useful medical documentation that has subsequently been forgotten. In modern times, ethnobotanical and anecdotal references continue to support the efficacy of cannabis for headache treatment, while biochemical studies of THC and anandamide have provided scientific justification for its use via anti-inflammatory, serotonergic and dopa-minergic mechanisms, as well as by interaction with NMD A and endogenous opioid systems. These are examined in detail.

57. Bryson C. Lochte, et al. The Use of Cannabis for Headache Disorders.
[Cannabis and Cannabinoid Research 2017;2(1):61-71]

ABSTRACT

Headache disorders are common, debilitating, and, in many cases, inadequately managed by existing treatments. Although clinical trials of cannabis for neuropathic pain have shown promising results, there has been limited research on its use, specifically for headache disorders. This review considers historical prescription practices, summarizes the existing reports on the use of cannabis for headache, and examines the preclinical literature exploring the role of exogenous and endogenous cannabinoids to alter headache pathophysiology. Currently, there is not enough evidence from well-designed clinical trials to support the use of cannabis for headache, but there are sufficient anecdotal and preliminary results, as well as plausible neurobiological mechanisms, to warrant properly designed clinical trials. Such trials are needed to determine short- and long-term efficacy for specific headache types, compatibility with existing treatments, optimal administration practices, as well as potential risks.

58. Eric P Baron. Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been.
[Headache 2015;55(6):885-916]

ABSTRACT

Background:

The use of cannabis, or marijuana, for medicinal purposes is deeply rooted though history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases, particularly headache and migraine. Through the decades, this plant has taken a fascinating journey from a legal and frequently prescribed status to illegal, driven by political and social factors rather than by science. However, with an abundance of growing support for its multitude of medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis, several states have legalized recreational use, and others have legalized cannabidiol-only use, which is one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients will inevitably inquire about it for many diseases, including chronic pain and headache disorders for which there is some intriguing supportive evidence.

Objective:

To review the history of medicinal cannabis use, discuss the pharmacology and physiology of the endocannabinoid system and cannabis-derived cannabinoids, perform a comprehensive literature review of the clinical uses of medicinal cannabis and cannabinoids with a focus on migraine and other headache disorders, and outline general clinical practice guidelines.

Conclusion:

The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based, anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation.

NEUROLOGICAL DISORDERS

59. Philip McGuire, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial.

[American Journal of Psychiatry 2018;175:225–31]

Objective:

Research in both animals and humans indicates that cannabidiol (CBD) has antipsychotic properties. The authors assessed the safety and effectiveness of CBD in patients with schizophrenia.

Method:

In an exploratory double-blind parallel-group trial, patients with schizophrenia were randomized in a 1:1 ratio to receive CBD (1000 mg/day; N=43) or placebo (N=45) alongside their existing antipsychotic medication. Participants were assessed before and after treatment using the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia (BACS), the Global Assessment of Functioning scale(GAF), and the improvement and severity scales of the Clinical Global Impressions Scale (CGI-I and CGI-S).

Results:

After 6 weeks of treatment, compared with the placebo group, the CBD group had lower levels of positive psychotic symptoms (PANSS: treatment difference=21.4, 95% CI=22.5, 20.2) and were more likely to have been rated as improved (CGI-I: treatment difference=20.5, 95% CI= 20.8, 20.1) and as not severely unwell (CGI-S: treatment difference=20.3, 95% CI=20.5, 0.0) by the treating clinician. Patients who received CBD also showed greater improvements that fell short of statistical significance in cognitive performance (BACS: treatment difference=1.31, 95% CI=20.10, 2.72) and in overall functioning (GAF: treatment difference=3.0, 95% CI=20.4, 6.4). CBD was well tolerated, and rates of adverse events were similar between the CBD and placebo groups.

Conclusions:

These findings suggest that CBD has beneficial effects in patients with schizophrenia. As CBD's effects do not appear to depend on dopamine receptor antagonism, this agent may represent a new class of treatment for the disorder.

60. Tamara Pringsheim, et al. Practice Guideline Recommendations Summary: The treatment of tics in people with Tourette syndrome and chronic tic disorders.

[Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology 2019;92(19):896-906]

Objective:

To systematically evaluate the efficacy of treatments for tics and the risks associated with their use, and to make recommendations on when clinicians and patients should treat tics and how clinicians and patients should choose between evidence-based treatment options.

Methods:

In May 2016, a multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives was

recruited to develop this guideline. This guideline follows the methodologies outlined in the 2011 edition of the AAN's guideline development process manual.

Results:

There was high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinum toxin A injections, 5-ling granule, Ningdong granule and deep brain stimulation of the globus pallidus were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. Evidence of harm associated with various treatments was also demonstrated.

Recommendations:

Forty-six recommendations were made regarding the assessment and management of tics in individuals with TS and chronic tic disorders. These include counseling recommendations on the natural history of tic disorders, psychoeducation for teachers and peers, assessment for comorbid disorders, and periodic reassessment of the need for ongoing therapy. Treatment options should be individualized, and the choice should be the result of a collaborative decision between patient, caregiver, and clinician, during which the benefits and harms of individual treatments as well as the presence of comorbid disorders are considered.

61. Éamon Jones and Styliani Vlachou. A Critical Review of the Role of the Cannabinoid Compounds Δ 9-Tetrahydrocannabinol (Δ9 -THC) and Cannabidiol (CBD) and their Combination in Multiple Sclerosis Treatment.

[Molecules 2020;25(4930):1-20]

ABSTRACT

Many people with MS (pwMS) use unregulated cannabis or cannabis products to treat the symptoms associated with the disease. In line with this, Sativex, a synthetic combination of cannabidiol (CBD) and Δ 9 -tetrahydrocannabinol (Δ 9 -THC) has been approved to treat symptoms of spasticity. In animals, CBD is effective in reducing the amounts of T-cell infiltrates in the spinal cord, suggesting CBD has anti-inflammatory properties. By doing this, CBD has shown to delay symptom onset in animal models of multiple sclerosis and slow disease progression. Importantly, combinations of CBD and Δ 9 -THC appear more effective in treating animal models of multiple sclerosis. While CBD reduces the amounts of cell infiltrates in the spinal cord, Δ 9 -THC reduces scores of spasticity. In human studies, the results are less encouraging and conflict with the findings in animals. Drugs which deliver a combination of Δ 9 -THC and CBD in a 1:1 ratio appear to be only moderately effective in reducing spasticity scores but appear to be almost as effective as current front-line treatments and cause less severe side effects than other treatments, such as baclofen (a GABA-B receptor agonist) and tizanidine (an α2 adrenergic receptor agonist). The findings of the studies reviewed suggest that cannabinoids may help treat neuropathic pain in pwMS as an add-on therapy to already established pain treatments. It is important to note that treatment with cannabinoid compounds may cause significant cognitive dysfunction. Long term double-blind placebo studies are greatly needed to further our understanding of the role of cannabinoids in multiple sclerosis treatment.

62. Lucio Marinelli, et al. A randomised controlled cross-over double-blind pilot study protocol on THC:CBD oromucosal spray efficacy as an add-on therapy for post-stroke spasticity.

[British Medical Journal Open 2017;7(9):e016843]

ABSTRACT

Introduction:

Stroke is the most disabling neurological disorder and often causes spasticity. Transmucosal cannabinoids (tetrahydrocannabinol and cannabidiol (THC:CBD), Sativex) is currently available to treat spasticity-associated symptoms in patients with multiple sclerosis. Cannabinoids are being considered useful also in the treatment of pain, nausea, and epilepsy, but may bear and increased risk for cardiovascular events. Spasticity is often assessed with subjective and clinical rating scales, which are unable to measure the increased excitability of the monosynaptic reflex, considered the hallmark of spasticity. The neurophysiological assessment of the stretch reflex provides a precise and objective method to measure spasticity. We propose a novel study to understand if Sativex could be useful in reducing spasticity in stroke survivors and investigating tolerability and safety by accurate cardiovascular monitoring.

Methods and Analysis:

We will recruit 50 patients with spasticity following stroke to take THC:CBD in a double-blind placebo-controlled cross-over study. Spasticity will be assessed with a numeric rating scale for spasticity, the modified Ashworth scale and with the electromyographical recording of the stretch reflex. The cardiovascular risk will be assessed prior to inclusion. Blood pressure, heart rate, number of daily spasms, bladder function, sleep disruption and adverse events will be monitored throughout the study. A mixed-model analysis of variance will be used to compare the stretch reflex amplitude

between the time points; semiquantitative measures will be compared using the Mann-Whitney test (THC:CBD vs placebo) and Wilcoxon test (baseline vs treatment).

63. Barth Wilsey, et al. An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain from Spinal Cord Injury and Disease.

[Journal of Pain 2016;17(9):982–1000]

ABSTRACT

Using eight-hour human laboratory experiments, we evaluated the analgesic efficacy of vaporized cannabis in patients with neuropathic pain related to injury or disease of the spinal cord, the majority of whom were experiencing pain despite traditional treatment. After obtaining baseline data, 42 participants underwent a standardized procedure for inhaling 4 puffs of vaporized cannabis containing either placebo, 2.9%, or 6.7% delta-9-tetrahydrocannabinol on three separate occasions. A second dosing occurred 3 hours later; participants chose to inhale 4 to 8 puffs. This flexible dosing was utilized to attempt to reduce the placebo effect. Using an 11-point numerical pain intensity rating scale as the primary outcome, a mixed effects linear regression model demonstrated a significant analgesic response for vaporized cannabis. When subjective and psychoactive side effects (e.g., good drug effect, feeling high, etc.) were added as covariates to the model, the reduction in pain intensity remained significant above and beyond any effect of these measures (all $p<0.0004$). Psychoactive and subjective effects were dose dependent. Measurement of neuropsychological performance proved challenging because of various disabilities in the population studied. As the two active doses did not significantly differ from each other in terms of analgesic potency, the lower dose appears to offer the best risk-benefit ratio in patients with neuropathic pain associated with injury or disease of the spinal cord.

64. Michael Stillman, et al. Attitudes toward and knowledge of medical cannabis among individuals with spinal cord injury.

[Spinal Cord Series and Cases 2019;5:6]

ABSTRACT

Study Design:

An observational study based on an online survey addressing attitudes toward and knowledge of cannabis among people living with spinal cord injury (SCI).

Objectives:

To characterize attitudes toward and knowledge of cannabis among a nationwide sample (n = 353) of people with SCI. To determine if knowledge and attitudes are influenced by socio-demographic and injury-specific factors.

Setting:

Three academic medical centers in the US.

Methods:

Distribution of an online survey through email lists maintained by 3 SCI centers.

Results:

Participants largely believed that cannabis use is safe, has potential therapeutic benefits, and ought to be legal. Substantial pluralities felt that cannabis use is attended by moderate to great health-related and social risks (15.5% and 25.5%, respectively), and a majority (55.9%) felt it is attended by moderate to great legal risks. Subjects' duration of injury, employment status, and personal history of controlled or illicit substances influenced certain beliefs and attitudes.

Conclusions:

This study is the first to assess beliefs about and attitudes toward cannabis use among a nationwide sample of people with SCI. While limited, it provides a roadmap for future research. It also offers medical providers an initial understanding of which factors may encourage or dissuade their patients with SCI from seeking medical cannabis treatment.

65. Epifanio Mondello, et al. Cannabinoids and spinal cord stimulation for the treatment of failed back surgery syndrome refractory pain.

[Journal of Pain Research 2018:11 1761–1767]

ABSTRACT

Objective:

This study aimed to evaluate pain and its symptoms in patients with failed back surgery syndrome (FBSS) refractory to other therapies, treated with a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), in association with spinal cord stimulation (SCS).

Settings:

Outpatients referred at Pain Unit of San Vincenzo Hospital in Taormina (Italy), between September 2014 and January 2016.

Subjects:

Eleven FBSS patients diagnosed with neuropathic pain using the Douleur Neuropathique 4 questionnaire and suffering from moderate to severe chronic refractory pain and undergoing treatment with SCS and a combination of THC/CBD for 12 consecutive months.

Materials and Methods:

All the included patients discontinued previous unsuccessful therapy at least 2 months before the beginning of the cannabinoid therapy, with the exception of the SCS that was continued. Patients received a fixed dosage of cannabinoid agonists (THC/CBD) that could be increased subjective to pain control response. A Brief Pain Inventory questionnaire was administered to measure pain and its interference with characteristic dimensions of feelings and functions. The duration of treatment with SCS and THC/CBD combination was 12 months.p

Results:

Effective pain management as compared to baseline result was achieved in all the cases studied. The positive effect of cannabinoid agonists on refractory pain was maintained during the entire duration of treatment with minimal dosage titration. Pain perception, evaluated through numeric rating scale, decreased from a baseline mean value of 8.18±1.07–4.72±0.9 by the end of the study duration (12 months) ($P<0.001$).

Conclusion:

The results indicate that cannabinoid agonists (THC/CBD) can have remarkable analgesic capabilities, as adjuvant of SCS, for the treatment of chronic refractory pain of FBSS patients.

66. Uwe K. Zettl, et al. Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis.

[Therapeutic Advances in neurological disorders 2016;9(1) 9–30]

ABSTRACT

Spasticity, one of the main symptoms of multiple sclerosis (MS), can affect more than 80% of MS patients during the course of their disease and is often not treated adequately. δ-9-Tetrahydrocannabinol-cannabidiol (THC-CBD) oromucosal spray is a plantderived, standardized cannabinoid-based oromucosal spray medicine for add-on treatment of moderate to severe, resistant multiple sclerosis-induced spasticity. This article reviews the current evidence for the efficacy and safety, with dizziness and fatigue as the most common treatment-related adverse events, being mostly mild to moderate in severity. Results from both randomized controlled phase III studies involving about,1600 MS patients or 1500 patient-years and recently published studies on everyday clinical practice involving more than 1000 patients or more than, 1000 patient-years are presented.

67. Thomas Meyer, et al. Real world experience of patients with amyotrophic lateral sclerosis (ALS) in the treatment of spasticity using tetrahydrocannabinol:cannabidiol (THC:CBD).

[BMC Neurology 2019;19(1):222]

ABSTRACT

Background:

Treatment of spasticity poses a major challenge in amyotrophic lateral sclerosis (ALS) patient management. Delta-9-tetrahydrocannabinol (THC):cannabidiol (CBD) oromucosal spray (THC:CBD), approved for the treatment of spasticity in multiple sclerosis, serves as a complementary off-label treatment option in ALS-related spasticity. However,

few structured data are available on THC:CBD in the treatment of spasticity in ALS.

Method:

A retrospective mono-centric cohort study was realized in 32 patients that meet the following criteria: 1) diagnosis of ALS, 2) ALS-related spasticity; 3) treatment with THC:CBD. Spasticity was rated using the Numeric Rating Scale (NRS). Patient's experience with THC:CBD was assessed using the net promoter score (NPS) and treatment satisfaction questionnaire for medication (TSMQ-9) as captured through telephone survey or online assessment.

Results:

The mean dose THC:CBD were 5.5 daily actuations (range < 1 to 20). Three subgroups of patients were identified: 1) high-dose daily use (≥ 7 daily actuations, 34%, n = 11), 2) low-dose daily use (< 7 daily actuations, 50%, n = 16), 3) infrequent use (< 1 daily actuation, 16%, n = 5). Overall NPS was + 4.9 (values above 0 express a positive recommendation to fellow patients). Remarkably, patients with moderate to severe spasticity (NRS ≥ 4) reported a high recommendation rate (NPS: + 29) in contrast to patients with mild spasticity (NRS < 4; NPS: − 44). For the three main domains of TSQM-9 high mean satisfaction levels were found (maximum value 100): effectiveness 70.5 (±22.3), convenience 76.6 (±23.3) and global satisfaction 75.0 (±24.7).p

Conclusion:

THC:CBD is used in a wide dose range suggesting that the drug was applied on the basis of individual patients' needs and preferences. Contributing to this notion, moderate to severe spasticity was associated with an elevated number of daily THC:CBD actuations and stronger recommendation rate (NPS) as compared to patients with mild spasticity. Overall, treatment satisfaction (TSQM-9) was high. The results suggest that THC:CBD may serve as a valuable addition in the spectrum of symptomatic therapy in ALS. However, prospective studies and head-to-head comparisons to other spasticity medications are of interest to further explore the effectiveness of THC:CBD in the management of spasticity, and other ALS-related symptoms.

68. Elisabeth G. Celius and Carlos Vila. The influence of THC:CBD oromucosal spray on driving ability in patients with multiple sclerosis-related spasticity.

[Brain and Behavior 2018;8:e00962]

ABSTRACT

Background:

Driving ability is a key function for the majority of patients with multiple sclerosis (MS) to help maintain daily interactions. Both physical and cognitive disability, as well as treatments, may affect the ability to drive. Spasticity is a common symptom associated with MS, and it may affect driving performance either directly or via the medications used to treat it. In this article, we review the evidence relating the antispasticity medicine, Δ9 -tetrahydrocannabinol:cannabidiol (THC:CBD) oromucosal spray (Sativex®), and its potential impact on driving performance.

Methods:

Articles were identified by searching PubMed from 1/1/2000 to 30/6/2017 using a specified list of search terms. The articles identified using these search terms were augmented with relevant references from these papers and other articles known to the authors.

Results:

The results from THC:CBD oromucosal spray driving studies and real-world registries did not show any evidence of an increase in motor vehicle accidents associated with THC:CBD oromucosal spray. The majority of patients reported an improvement in driving ability after starting THC:CBD oromucosal spray, and it was speculated that this may be related to reduced spasticity and/or better cognitive function. It should be noted that THC blood levels are significantly lower than the levels associated with recreational use of herbal cannabis.

Conclusions:

THC:CBD oromucosal spray was shown not to impair driving performance. However, periodic assessment of patients with MS driving ability is recommended, especially after relapses and changes in treatment. Blood THC measurements might be above authorized thresholds for some countries following administration of THC:CBD oromucosal spray, thus specific knowledge of each country's driving regulations and a medical certificate are recommended.

69. Michael Stillman, et al. Utilization of medicinal cannabis for pain by individuals with spinal cord injury.
[Spinal Cord Series and Cases 2019;5:66]

ABSTRACT

Study Design:

A cross-sectional multi-center study using an on-line survey addressing utilization, knowledge, and perceptions of medicinal cannabis (MC) by people with spinal cord injury (SCI).

Objective:

To characterize differences between current (CU), past (PU), and never users (NU) of MC with SCI; to determine why people with SCI use MC; to examine reports of MCs' efficacy and tolerability by individuals with SCI.

Setting:

Three academic medical centers in the United States.

Methods:

Comparison of demographic and attitudinal differences between CU, PU, and NU and differences in the groups' reports of pain, health, and quality of life (QOL). Evaluation of utilization patterns and perceived efficacy of MC among CU and PU and reports of side effects of MC versus prescription medications. Data were analyzed using either Chi Square, distribution-free exact statistics, or t-tests for continuous data.

Results:

Among a nationwide sample (n = 353) of individuals with SCI, NU were less likely than CU and PU to believe that cannabis ought to be legalized and more likely to endorse risks of use. Current users and PU reported greater pain interference in daily life than did NU, but there were no between group differences in QOL or physical or emotional health. Current users and PU took MC to address pain (65.30%), spasms (63.30%), sleeplessness (32.70%), and anxiety (24.00%), and 63.30% reported it offered "great relief" from symptoms. Participants reported that MC is more effective and carries fewer side effects than prescription medications.

Conclusions:

Medicinal cannabis is an effective and well-tolerated treatment for a number of SCI-related symptom

PAIN

70. Jakub Mlost, et al. Cannabidiol for Pain Treatment: Focus on Pharmacology and Mechanism of Action.
[International Journal of Molecular Science 2020;21(8870):1-21]

ABSTRACT

Cannabis has a long history of medical use. Although there are many cannabinoids present in cannabis, Δ 9tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) are the two components found in the highest concentrations. CBD itself does not produce typical behavioral cannabimimetic effects and was thought not to be responsible for psychotropic effects of cannabis. Numerous anecdotal findings testify to the therapeutic effects of CBD, which in some cases were further supported by research findings. However, data regarding CBD's mechanism of action and therapeutic potential are abundant and omnifarious. Therefore, we review the basic research regarding molecular mechanism of CBD's action with particular focus on its analgesic potential. Moreover, this article describes the detailed analgesic and anti-inflammatory effects of CBD in various models, including neuropathic pain, inflammatory pain, osteoarthritis and others. The dose and route of the administration-dependent effect of CBD, on the reduction in pain, hyperalgesia or allodynia, as well as the production of pro and anti-inflammatory cytokines, were described depending on the disease model. The clinical applications of CBD-containing drugs are also mentioned. The data presented herein unravel what is known about CBD's pharmacodynamics and analgesic effects to provide the reader with current state-of-art knowledge regarding CBD's action and future perspectives for research.

71. Aaron Sihota, et al. Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control.

[International Journal of Clinical Practice 2021;75:e13871]

ABSTRACT

Aims:

Opioid misuse and overuse have contributed to a widespread overdose crisis and many patients and physicians are considering medical cannabis to support opioid tapering and chronic pain control. Using a five-step modified Delphi process, we aimed to develop consensus-based recommendations on: 1) when and how to safely initiate and titrate cannabinoids in the presence of opioids, 2) when and how to safely taper opioids in the presence of cannabinoids and 3) how to monitor patients and evaluate outcomes when treating with opioids and cannabinoids.

Results:

In patients with chronic pain taking opioids not reaching treatment goals, there was consensus that cannabinoids may be considered for patients experiencing or displaying opioid-related complications, despite psychological or physical interventions. There was consensus observed to initiate with a cannabidiol (CBD)-predominant oral extract in the daytime and consider adding tetrahydrocannabinol (THC). When adding THC, start with 0.5-3 mg, and increase by 1-2 mg once or twice weekly up to 30-40 mg/day. Initiate opioid tapering when the patient reports a minor/major improvement in function, seeks less as-needed medication to control pain and/or the cannabis dose has been optimised. The opioid tapering schedule may be 5%–10% of the morphine equivalent dose (MED) every 1 to 4 weeks. Clinical success could be defined by an improvement in function/quality of life, a ≥30% reduction in pain intensity, a ≥25% reduction in opioid dose, a reduction in opioid dose to <90mg MED and/ or reduction in opiod-related adverse events.

Conclusions:

This five-stage modified Delphi process led to the development of consensus-based recommendations surrounding the safe introduction and titration of cannabinoids in concert woth tapering opioids.

72. Reham Haleema and Robert Wright. A Scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults.

[Journal of Clinical Medicine Research 2020;12(6):344-351]

ABSTRACT

Indications of cannabis use are numerous although the indication to relief pain remains a major research interest and clinical application. Studies investigating the effect of herbal cannabis and cannabis-based medicine on neuropathic, non-neuropathic pain, acute pain and experimentally induced pain were reviewed. A search was performed in PubMed and Cochrane library for articles published in English between January 1, 2000 and May 8, 2020. The search terms used were related to cannabis and pain in adults. We identified 34 studies, of which 30 were randomized controlled clinical trials (RCTs). Varying effects were identified from the RCTs, and as expected more promising effects from non-RCTs. Cannabis-based medications were found most effective as an adjuvant therapy in refractory multiple sclerosis, and weak evidence was found to support the treatment of cancer pain especially in advanced stages. Chronic rheumatic pain showed promising results. Adverse events of cannabis-based treatment were found to be more frequent with tetrahydrocannabinol herbal strains compared to other cannabis-derived products.

73. Barbara Stella, et al. Cannabinoid Formulations and Delivery Systems: Current and Future Options to Treat Pain.

[Drugs 2021;81(13):1513-1557]

ABSTRACT

The field of Cannabis sativa L. research for medical purposes has been rapidly advancing in recent decades and a growing body of evidence suggests that phytocannabinoids are beneficial for a range of conditions. At the same time impressing development has been observed for formulations and delivery systems expanding the potential use of cannabinoids as an effective medical therapy. The objective of this review is to present the most recent results from pharmaceutical companies and research groups investigating methods to improve cannabinoid bioavailability and to clearly establish its therapeutic efficacy, dose ranges, safety and also improve the patient compliance. Particular focus is the application of cannabinoids in pain treatment, describing the principal cannabinoids employed, the most promising delivery systems for each administration routes and updating the clinical evaluations. To offer the reader a wider view, this review discusses the formulation starting from galenic preparation up to nanotechnology approaches, showing advantages, limits, requirements needed. Furthermore, the most recent clinical data and meta-analysis for cannabinoids used in different

pain management are summarized, evaluating their real effectiveness, in order also to spare opioids and improve patients' quality of life. Promising evidence for pain treatments and for other important pathologies are also reviewed as likely future directions for cannabinoids formulations.

74. Howard Meng, et al. Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis.

[International Anesthesia Research Society 2017;125(5):1638-1652]

ABSTRACT

Background:

There is a lack of consensus on the role of selective cannabinoids for the treatment of neuropathic pain (NP). Guidelines from national and international pain societies have provided contradictory recommendations. The primary objective of this systematic review and meta-analysis (SR-MA) was to determine the analgesic efficacy and safety of selective cannabinoids compared to conventional management or placebo for chronic NP.

Methods:

We reviewed randomized controlled trials that compared selective cannabinoids (dronabinol, nabilone, nabiximols) with conventional treatments (eg, pharmacotherapy, physical therapy, or a combination of these) or placebo in patients with chronic NP because patients with NP may be on any of these therapies or none if all standard treatments have failed to provide analgesia and or if these treatments have been associated with adverse effects. MEDLINE, EMBASE, and other major databases up to March 11, 2016, were searched. Data on scores of numerical rating scale for NP and its subtypes, central and peripheral, were meta-analyzed. The certainty of evidence was classified using the Grade of Recommendations Assessment, Development, and Evaluation approach.

Results:

Eleven randomized controlled trials including 1219 patients (614 in selective cannabinoid and 605 in comparator groups) were included in this SR-MA. There was variability in the studies in quality of reporting, etiology of NP, type and dose of selective cannabinoids. Patients who received selective cannabinoids reported a significant, but clinically small, reduction in mean numerical rating scale pain scores (0–10 scale) compared with comparator groups (−0.65 points; 95% confidence interval, −1.06 to −0.23 points; P = .002, I 2 = 60%; Grade of Recommendations Assessment, Development, and Evaluation: weak recommendation and moderate-quality evidence). Use of selective cannabinoids was also associated with improvements in quality of life and sleep with no major adverse effects.

Conclusions:

Selective cannabinoids provide a small analgesic benefit in patients with chronic NP. There was a high degree of heterogeneity among publications included in this SR-MA. Well-designed, large, randomized studies are required to better evaluate specific dosage, duration of intervention, and the effect of this intervention on physical and psychologic function.

75. Daniela Furrer, et al. Cannabis against chronic musculoskeletal pain: a scoping review on users and their perceptions.

[Journal of Cannabis Research (2021) 3:41]

ABSTRACT

Background:

Chronic musculoskeletal pain (CMP) may lead to reduced physical function and is the most common cause of chronic non-cancer pain. Currently, the pharmacotherapeutic options against CMP are limited and frequently consist of pain management with non-steroidal anti-inflammatories, gabapentinoids, or opioids, which carry major adverse effects. Although the effectiveness of medical cannabis (MC) for CMP still lacks solid evidence, several patients suffering from it are exploring this therapeutic option with their physicians.

Objectives:

Little is known about patients' perceptions of their MC treatment for CMP. We aimed to increase this knowledge, useful for healthcare professionals and patients considering this treatment, by conducting a scoping literature review, following guidance by Arksey and O'Malley, to describe the views and perceptions of adult patients who had consumed MC to relieve chronic CMP.

Methods:

Databases (PUBMED, EMBASE, Web of Science) and websites were searched using combinations of controlled and free vocabulary. All studies and study designs reporting on patients' perceptions regarding MC against CMP were considered. Studies had to include adult patients reporting qualitatively or quantitatively, i.e., through questionnaires, on MC use to treat CMP or other non-cancer pain, since studies reporting exclusively on perceptions regarding CMP were very rare. Study characteristics were extracted and limitations of the study quality were assessed. The review includes patients' demographic characteristics, patterns of MC use, perceived positive and negative effects, use of alcohol or other drugs, reported barriers to CM use, and funding sources of the studies.

Results:

Participants of the 49 included studies reported that MC use helped them to reduce CMP and other chronic non-cancer pain, with only minor adverse effects, and some reported improved psychological well-being. In the included studies, men represent between 18 and 88% of the subjects. The mean age of participants in these studies (42/49) varied between 28.4 and 62.8 years old. The most common route of administration is inhalation.

76. Sonja Vuckovic, et al. Cannabinoids and pain: new insights from old molecules.

[Frontiers in Pharmacology 2018:9(article 1259)]

ABSTRACT

Cannabis has been used for medicinal purposes for thousands of years. The prohibition of cannabis in the middle of the 20th century has arrested cannabis research. In recent years there is a growing debate about the use of cannabis for medical purposes. The term 'medical cannabis' refers to physician-recommended use of the cannabis plant and its components, called cannabinoids, to treat disease or improve symptoms. Chronic pain is the most commonly cited reason for using medical cannabis. Cannabinoids act via cannabinoid receptors, but they also affect the activities of many other receptors, ion channels and enzymes. Preclinical studies in animals using both pharmacological and genetic approaches have increased our understanding of the mechanisms of cannabinoid-induced analgesia and provided therapeutical strategies for treating pain in humans. The mechanisms of the analgesic effect of cannabinoids include inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve endings, modulation of postsynaptic neuron excitability, activation of descending inhibitory pain pathways, and reduction of neural inflammation. Recent meta-analyses of clinical trials that have examined the use of medical cannabis in chronic pain present a moderate amount of evidence that cannabis/cannabinoids exhibit analgesic activity, especially in neuropathic pain. The main limitations of these studies are short treatment duration, small numbers of patients, heterogeneous patient populations, examination of different cannabinoids, different doses, the use of different efficacy endpoints, as well as modest observable effects. Adverse effects in the short-term medical use of cannabis are generally mild to moderate, well tolerated and transient. However, there are scant data regarding the long-term safety of medical cannabis use. Larger well-designed studies of longer duration are mandatory to determine the long-term efficacy and longterm safety of cannabis/cannabinoids and to provide definitive answers to physicians and patients regarding the risk and benefits of its use in the treatment of pain. In conclusion, the evidence from current research supports the use of medical cannabis in the treatment of chronic pain in adults. Careful follow-up and monitoring of patients using cannabis/cannabinoids are mandatory.

77. Pilar Goya, et al. Cannabinoids and neuropathic pain.

[Mini Reviews in Medicinal Chemistry 2003;3(7):765-72]

ABSTRACT

The therapeutic and psychotropic properties of the hemp plant Cannabis sativa, have been known for centuries. The compounds responsible for these actions are the cannabinoids, tricyclic structures derived from the benzopyran ring of which the most representative is (-)-Δ9- tetrahydrocannabinol, Δ9-THC, main component of the plant isolated and characterized in 1964 [1]. These compounds interact with the cannabinoid receptors of which up to now two have been characterized. The endogenous cannabinoids and other compounds, mainly heterocycles, also bind to these receptors, so that the term cannabinoid has now been extended to include all these substances. Many recent publications have dealt with general aspects of the cannabinoid system, cannabinergic ligands and potential therapeutical applications [2-4]. Nevertheless, in this review concerning cannabinoids and neuropathic pain a small introduction to the subject follows.

78. John A. Sturgeon, et al. Clinical Profiles of Concurrent Cannabis Use in Chronic Pain: A CHOIR Study.

[Pain Medicine 2020;21(11):3172–3179]

ABSTRACT

Objective:

Despite evidence of the analgesic benefits of cannabis, there remains a relative scarcity of research on the short- and long-term effects of cannabis use in individuals with chronic pain.

Design:

The current study is a secondary analysis of clinical data from the Collaborative Health Outcomes Information Registry (CHOIR).

Setting:

Data were drawn from a cohort of patients of a multidisciplinary tertiary care pain clinic.

Subjects:

The study sample consisted of data from 7,026 new patient visits from CHOIR; of these, 1,668 patients with a follow-up time point within 180 days were included in a longitudinal analysis.

Methods:

Clinical data were analyzed to characterize crosssectional differences in pain and indicators of psychological and physical function according to self-reported, concurrent cannabis use. Additionally, a propensity score–weighted longitudinal analysis was conducted, examining cannabis use as a predictor of changes in clinical variables across time.

Results:

Cross-sectional analyses suggested significantly poorer sleep and significantly higher intensities of pain, emotional distress, and physical and social dysfunction in patients reporting ongoing cannabis use; however, these differences were relatively small in magnitude. However, no differences between cannabis users and nonusers in terms of longitudinal changes in clinical variables were noted.

Discussion:

Our results are among the first to examine concurrent cannabis use as a prognostic variable regarding trajectories of pain-related variables in tertiary care. Future studies may benefit from examining the effect of cannabis initiation, concurrent medication use, and specific aspects of cannabis use (dose, duration of use, or cannabis type) on clinical outcomes.

79. Ethan B Russo. Cannabinoids in the management of difficult to treat pain.

[Therapeutics and Clinical Risk Management 2008:4(1) 245–259]

ABSTRACT

This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol®) and nabilone (Cesamet®) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex®, a cannabis derived oromucosal spray containing equal proportions of THC (partial CB1 receptor agonist) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with CB1 receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

80. Srabani Banerjee and Suzanne McCormack. Medical Cannabis for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Guidelines.

[Canadian Agency for Drugs and Technologies in Health 2019;ISSN:1922-8147]

ABSTRACT

Chronic pain is defined as pain that persists for more than three months. It may present as headache, musculoskeletal pain, visceral pain, neuropathic pain, pain arising from rheumatic disease, and cancer pain. Chronic pain is a global problem. In Canada, approximately 25% adults have a chronic pain condition. The prevalence estimates of chronic pain are likely to vary depending on the sample population surveyed, and the assessment method. Costs associated with chronic pain include both direct and indirect costs. It is estimated that in Canada the annual direct cost to the healthcare system is over six billion dollars and the annual indirect cost due to job loss and sick days is over 37 billion dollars. Chronic pain is a problem for the individual suffering, and also a societal burden. Therapies for management for chronic pain include several pharmacological agents (such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioid analgesics). However, these medications offer limited pain relief and are associated with adverse effects. There is increasing interest in the use of cannabis-based medicines. Cannabis-based medicines contain cannabinoids derived from the cannabis plant, including delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD. There is, however, uncertainty and controversy regarding the use of cannabis-based medicines for the management of chronic pain. The purpose of this report is to review the clinical effectiveness of medical cannabis for the treatment of chronic pain. Additionally, this report aims to review the evidence-based guidelines regarding associated with the use of medical cannabis for the treatment of chronic pain.

81. Atefeh Noori, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies.

[British Medical Journal Open 2021;11(7):e047717]

ABSTRACT

Objective:

To assess the efficacy and harms of adding medical cannabis to prescription opioids among people living with chronic pain.

Design:

Systematic review.

Data Sources:

CENTRAL, EMBASE and MEDLINE.

Main Outcomes and Measures:

Opioid dose reduction, pain relief, sleep disturbance, physical and emotional functioning and adverse events.

Study Selection Criteria and Methods:

We included studies that enrolled patients with chronic pain receiving prescription opioids and explored the impact of adding medical cannabis. We used Grading of Recommendations Assessment, Development and Evaluation to assess the certainty of evidence for each outcome.

Results:

Eligible studies included five randomised trials (all enrolling chronic cancer-pain patients) and 12 observational studies. All randomised trials instructed participants to maintain their opioid dose, which resulted in a very low certainty evidence that adding cannabis has little or no impact on opioid use (weighted mean difference (WMD) −3.4 milligram morphine equivalent (MME); 95% CI (CI) −12.7 to 5.8). Randomised trials provided high certainty evidence that cannabis addition had little or no effect on pain relief (WMD −0.18 cm; 95%CI −0.38 to 0.02; on a 10 cm Visual Analogue Scale (VAS) for pain) or sleep disturbance (WMD −0.22 cm; 95%CI −0.4 to −0.06; on a 10 cm VAS for sleep disturbance; minimally important difference is 1 cm) among chronic cancer pain patients. Addition of cannabis likely increases nausea (relative risk (RR) 1.43; 95%CI 1.04 to 1.96; risk difference (RD) 4%, 95%CI 0% to 7%) and vomiting (RR 1.5; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%) (both moderate certainty) and may have no effect on constipation (RR 0.85; 95%CI 0.54 to 1.35; RD −1%; 95%CI −4% to 2%) (low certainty). Eight observational studies provided very low certainty evidence that adding cannabis reduced opioid use (WMD −22.5 MME; 95%CI −43.06 to −1.97).

Conclusion:

Opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to very low certainty evidence.

82. Karma Rabgay, et al. The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis.

[Journal of American Pharmaceutical Association 2020;60(1):225-234.]

ABSTRACT

Objectives:

To determine the effects of cannabis, cannabinoids, and their administration routes on pain and adverse euphoria events.

Data Sources:

A systematic search was performed in PubMed, ScienceDirect, ClincalTrials.gov, Scopus, Cochrane Library, and Embase from inception until June 2017.

Study Selection:

Randomized controlled trials investigating the effects of cannabis or cannabinoids on pain reduction.

Data Extraction:

Two reviewers extracted and assessed the quality of studies by means of Cochrane risk of bias. Standardized mean difference (SMD) was calculated. Random-effects model was undertaken to pool the treatment effects.

Results:

A total of 25 studies involving 2270 patients were included. We found that delta-9- tetrahydrocannabinol/cannabidiol (THC/CBD) (oromucosal route), THC (oromucosal route), and standardized dried cannabis (with THC; SCT; inhalation route) could reduce neuropathic pain score (SMD -0.41, 95% CI -0.7 to -0.1; -0.61, 95% CI -1.2 to -0.02; and -0.77, 95% CI -1.4 to -0.2; respectively). For nociceptive pain, only standardized cannabis extract (with THC; SCET) via oral route could reduce pain score (SMD -1.8, 95% C; -2.4 to -1.2). In cancer pain, THC/CBD via oromucosal route and THC via oral or oromucosal route could reduce pain score (SMD -0.7, 95% CI -1.2 to -0.2; and -2.1, 95% CI -2.8 to -1.4; respectively). No study was observed for THC/CBD via oral route or inhalation or THC via inhalation for cancer and nociceptive pain, SCET via oromucosal route or inhalation for neuropathic and cancer pain, THC via oromucosal route for nociceptive pain, and SCT via oromucosal or oral route for neuropathic, cancer, and nociceptive pain. Statistically significant increased risks of euphoria were observed in THC/CBD (oromucosal), THC (oromucosal), and SCT (inhalation).p

Conclusion:

The use of cannabis and cannabinoids via certain administration routes could reduce different types of pain. Product developers could consider our findings as part of their product design so that the effective route of cannabis and cannabinoids for pain control can be achieved.

83. Russell K Portenoy, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial.

[Journal of Pain 2012;13(5):438-49]

ABSTRACT

Patients with advanced cancer who have pain that responds poorly to opioid therapy pose a clinical challenge. Nabiximols (Nabiximols is the U.S. Adopted Name [USAN] for Sativex [GW Pharma Ltd, Wiltshire, U.K.], which does not yet have an INN), a novel cannabinoid formulation, is undergoing investigation as add-on therapy for this population. In a randomized, double-blind, placebo-controlled, graded-dose study, patients with advanced cancer and opioid-refractory pain received placebo or nabiximols at a low dose (1-4 sprays/day), medium dose (6-10 sprays/day), or high dose (11-16 sprays/day). Average pain, worst pain and sleep disruption were measured daily during 5 weeks of treatment; other questionnaires measured quality of life and mood. A total of 360 patients were randomized; 263 completed. There were no baseline differences across groups. The 30% responder rate primary analysis was not significant for nabiximols versus placebo (overall P = .59). A secondary continuous responder analysis of average daily pain from baseline to end of study demonstrated that the proportion of patients reporting analgesia was greater for nabiximols than placebo overall (P = .035), and specifically in the low-dose (P = .008) and medium-dose (P = .039) groups. In the low-dose group, results were similar for mean average pain (P = .006), mean worst pain (P = .011), and mean sleep disruption (P = .003). Other questionnaires showed no significant group differences. Adverse events were dose-related and only the high-dose group compared unfavorably with placebo. This study supports the efficacy and safety of nabiximols at the 2 lower-dose levels and provides important dose information for future trials. Perspective: Nabiximols, a novel cannabinoid formulation, may be a useful add-on analgesic for patients with opioid-refractory cancer pain. A randomized, double-blind, placebo-controlled, graded-dose study demonstrated efficacy and safety at low and medium doses.

84. Laura Orsolini, et al. Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review.

[Medicina 2019;55(9):525]

ABSTRACT

Background and Objectives: Post-traumatic stress disorder (PTSD) is a common psychiatric disorder resulting from a traumatic event, is manifested through hyperarousal, anxiety, depressive symptoms, and sleep disturbances. Despite several therapeutic approaches being available, both pharmacological and psychological, recently a growing interest has developed in using cannabis and synthetic cannabinoids stems from their consideration as more efficient and better tolerated alternatives for the treatment of this condition. The present paper aims to evaluate the clinical and therapeutic potentials of medical cannabis and synthetic cannabinoids in treating PTSD patients. Methods: A systematic electronic search was performed, including all papers published up to May 2019, using the following keywords (((cannabis[Title/Abstract]) OR (synthetic cannabinoids [Title/Abstract])) AND ((PTSD[Title/Abstract]) OR (Posttraumatic stress disorder[Title/Abstract])))) for the topics 'Cannabis', 'Synthetic Cannabinoids', 'PTSD', and MESH terms, on the PubMed, Cochrane Library, and Web of Science online databases. For data gathering purposes, PRISMA guidelines were followed. Results were organized into two groups, considering cannabis and synthetic cannabinoids as different therapeutic approaches for PTSD. Results: Present data show that cannabis and synthetic cannabinoids, both acting on the endocannabinoids system, may have a potential therapeutic use for improving PTSD symptoms, e.g., reducing anxiety, modulating memory-related processes, and improving sleep. Conclusions: Even though the current literature suggests that cannabis and synthetic cannabinoids may have a role in the treatment of PTSD, there is currently limited evidence regarding their safety and efficacy. Therefore, additional research is needed in order to better understand the effectiveness and therapeutic usage of these drug classes and monitor their safety.

85. Alexander Neumeister, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study.

[Molecular Psychiatry 2013;18:1034–1040]

ABSTRACT

Endocannabinoids and their attending cannabinoid type 1 (CB1) receptor have been implicated in animal models of post-traumatic stress disorder (PTSD). However, their specific role has not been studied in people with PTSD. Herein, we present an in vivo imaging study using positron emission tomography (PET) and the CB1-selective radioligand [11C]OMAR in individuals with PTSD, and healthy controls with lifetime histories of trauma (trauma-exposed controls (TC)) and those without such histories (healthy controls (HC)). Untreated individuals with PTSD (N=25) with non-combat trauma histories, and TC (N=12) and HC (N=23) participated in a magnetic resonance imaging scan and a resting PET scan with the CB1 receptor antagonist radiotracer [11C]OMAR, which measures the volume of distribution (VT) linearly related to CB1 receptor availability. Peripheral levels of anandamide, 2-arachidonoylglycerol, oleoylethanolamide, palmitoylethanolamide and cortisol were also assessed. In the PTSD group, relative to the HC and TC groups, we found elevated brain-wide [11C]OMAR VT values ($F(2,53)=7.96$, $P=0.001$; 19.5% and 14.5% higher, respectively), which were most pronounced in women ($F(1,53)=5.52$, $P=0.023$). Anandamide concentrations were reduced in the PTSD relative to the TC (53.1% lower) and HC (58.2% lower) groups. Cortisol levels were lower in the PTSD and TC groups relative to the HC group. Three biomarkers examined collectively—OMAR VT, anandamide and cortisol—correctly classified nearly 85% of PTSD cases. These results suggest that abnormal CB1 receptor-mediated anandamide signaling is implicated in the etiology of PTSD, and provide a promising neurobiological model to develop novel, evidence-based pharmacotherapies for this disorder.

86. Mizrachi Zer-Aviv T, et al. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention.
[Behavioral Pharmacology 2016;27(7):561-9]

ABSTRACT

There is substantial evidence from studies in humans and animal models for a role of the endocannabinoid system in the control of emotional states. Several studies have shown an association between exposure to trauma and substance use. Specifically, it has been shown that there is increased prevalence of cannabis use in post-traumatic stress disorder (PTSD) patients and vice versa. Clinical studies suggest that PTSD patients may cope with their symptoms by using cannabis. This treatment-seeking strategy may explain the high prevalence of cannabis use among individuals with PTSD. Preliminary studies in humans also suggest that treatment with cannabinoids may decrease PTSD symptoms including sleep quality, frequency of nightmares, and hyperarousal. However, there are no large-scale, randomized, controlled studies investigating this specifically. Studies in animal models have shown that cannabinoids can prevent the effects of stress on emotional function and memory processes, facilitate fear extinction, and have an anti-anxiety-like effect in a variety of tasks. Moreover, cannabinoids administered shortly after exposure to a traumatic event were found to prevent the development of PTSD-like phenotype. In this article, we review the existing literature on the use of cannabinoids for treating and preventing PTSD in humans and animal models. There is a need for large-scale clinical trials examining the potential decrease in PTSD symptomatology with the use of cannabis. In animal models, there is a need for a better understanding of the mechanism of action and efficacy of cannabis. Nevertheless, the end result of the current clinical and preclinical data is that cannabinoid agents may offer therapeutic benefits for PTSD.

87. Edward Chesney, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials.
[Neuropsychopharmacology 2020;45:1799–1806]

ABSTRACT

Cannabidiol (CBD) is being investigated as a treatment for several medical disorders but there is uncertainty about its safety. We conducted the first systematic review and meta-analysis of the adverse effects of CBD across all medical indications. Double-blind randomized placebo-controlled clinical trials lasting ≥7 days were included. Twelve trials contributed data from 803 participants to the meta-analysis. Compared with placebo, CBD was associated with an increased likelihood of withdrawal for any reason (OR 2.61, 95% CI: 1.38–4.96) or due to adverse events (OR 2.65, 95% CI: 1.04–6.80), any serious adverse event (OR 2.30, 95% CI: 1.18–4.48), serious adverse events related to abnormal liver function tests (OR 11.19, 95% CI: 2.09–60.02) or pneumonia (OR 5.37, 95% CI: 1.17–24.65), any adverse event (OR 1.55, 95% CI: 1.03–2.33), adverse events due to decreased appetite (OR 3.56, 95% CI: 1.94–6.53), diarrhoea (OR 2.61, 95% CI: 1.46–4.67), somnolence (OR 2.23, 95% CI: 1.07–4.64) and sedation (OR 4.21, 95% CI: 1.18–15.01). Associations with abnormal liver function tests, somnolence, sedation and pneumonia were limited to childhood epilepsy studies, where CBD may have interacted with other medications such as clobazam and/or sodium valproate. After excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhoea (OR 5.03, 95% CI: 1.44–17.61). In summary, the available data from clinical trials suggest that CBD is well tolerated and has relatively few serious adverse effects, however interactions with other medications should be monitored carefully. Additional safety data from clinical trials outside of childhood epilepsy syndromes and from studies of over-the-counter CBD products are needed to assess whether the conclusions drawn from clinical trials can be applied more broadly.

88. Wayne Hall. A summary of reviews of evidence on the efficacy and safety of medical use of cannabis and cannabinoids.
[European Monitoring Centre for Drugs and Drug Addiction 2018]

ABSTRACT

This paper accompanies the report Medical use of cannabis and cannabinoids — questions and answers for policymaking and summarises the findings of major systematic reviews of the evidence on the effectiveness and safety of cannabis and cannabinoids when used to treat symptoms of various medical conditions. It provides more detail on topics summarised in the main report, in particular on the sections on the available evidence on the effectiveness of medical use of cannabis and cannabinoids and those on the health risks and potential unintended consequences associated with the medical use of cannabis and cannabinoids. The first section of this paper summarises in detail the conclusions of three influential peer-reviewed publications (Koppel et al., 2014; NASEM, 2017; Whiting et al., 2015). These reviews evaluated all the published evidence on the efficacy and safety of cannabis for multiple medical uses. They used a clearly specified search strategy to identify studies, clear rules for deciding which studies to include and exclude, standardised criteria for evaluating the degree of bias in the studies and explicit criteria for synthesising the overall evidence. The paper then

summarises the findings of systematic reviews and meta-analyses of the evidence on the effectiveness of cannabinoids in treating chronic pain; chemotherapy induced nausea and vomiting in cancer patients; appetite stimulation in HIV/AIDS; intractable epilepsy; and palliative care for cancer. All these reviews used explicit search criteria, standardised tools for assessing study bias and explicit methods of synthesising the overall findings. Their degree of agreement is also summarised in a table. A third section summarises reviews of the adverse effects of medical use of cannabis as indicated in randomised controlled clinical trials. The section includes the results of a meta-analysis of adverse effects reported in clinical trials conducted by Whiting et al. (2015). The section also considers long-term harms reported among recreational cannabis users that may be potential adverse effects of long-term medical use of cannabis and cannabinoids. Finally, the paper includes an overview of studies, primarily conducted in the US, that explore the potential unintended consequences of the medical use of cannabis and cannabinoids. Cannabis and cannabinoids have been made available in a wide range of forms, and the various products and preparations tended to be described in different ways in different publications. While the main report uses a new typology in describing the different forms in which cannabis and cannabinoids are made available, we have chosen in the background paper to use the original terminology from the studies under consideration.

CHAPTER 3

MEDICAL CANNABIS RESEARCH BY TIKUN OLAM

TIKUN OLAM MEDICAL STUDIES OVERVIEW • ORIGINAL PUBLISHED RESEARCH ARTICLES

CHAPTER 3

MEDICAL CANNABIS RESEARCH BY TIKUN OLAM

TIKUN OLAM MEDICAL STUDIES OVERVIEW

Medical Research

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.

Through extensive research and development, Tikun's 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, autism, cancer, Inflammatory Bowel Disease, and more.

Clinical successes have encouraged Tikun to devote more resources to further improve the safety and efficacy of it's products, as well as it's understanding of the therapeutic properties of the cannabis plant. Tikun continually conduct laboratory studies (both in vitro and in vivo), retrospective analyses, and clinical trials, and works diligently to follow-up with patients.

Below is an outline of medical cannabis research as of February 2022.

COMPLETED & PUBLISHED RESEARCH

1. Timna Naftali, et al. Treatment of Crohn's Disease with Cannabis: An Observational Study.
[The Israel Medical Association Journal 2011;13(8):455-8]

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 ($p<.00\ 1$); 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
- 18.1% of patients stopped using opioid analgesics or reduced their dose

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

[Clinical Gastroenterology & Hepatology 2013;11(10):1276-80]

In the world's first randomized, placebo-controlled, double-blind 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. Timna Naftali, et al. Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial.

[Journal of Crohn's and Colitis 2021;15(11):1799-1806]

Study participants underwent an eight-week follow-up in which each participant received Avidekel or placebo oil and an additional two weeks of wash-up to see what happens during consumption cessation, a total of ten weeks of follow-up. During the study, patients attended four visits and were evaluated by medical interview, physical examination, blood and stool tests. In addition, a colonoscopy was performed before the start of cannabis treatment and at the end of eight weeks of treatment.

Study Population: 56 patients with Crohn's disease (30 males, mean age 34.5).

Study Product: Avidekel oil with 16% CBD and 4% THC VS placebo (46% of patients received placebo).

Key Results:

- No patient stopped treatment during the 10 weeks of follow-up.
- Improvement in disease symptoms - The CDAI score (Crohn's disease activity index) improved significantly in the cannabis group, compared to the improvement in the placebo group.
- Decrease in abdominal pain - there was a significant relief in the intensity of abdominal pain in the cannabis group (decrease in the CDAI score in the pain section), compared to the placebo group, in which the intensity of pain remained at the same level.
- Improvement in the quality of life - In the cannabis group, a significant improvement in the quality of life was observed (an increase in the SF-36 questionnaire score), compared with the placebo group whose quality of life remained at the same level.
- Positive overall effect of treatment - Patients were asked to rate from 1 to 7, where 1 = great improvement, 7 = severe deterioration, various aspects of life. In the cannabis group, a significant improvement was observed in the various areas.
- Side effects - No significant differences were observed between the cannabis group and the placebo group.

4. Timna Naftali, et al. Cannabis for Inflammatory Bowel Disease.

[Digestive Diseases 2014;32(4):468-74]

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.

5. Timna Naftali, et al. Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects.

[European Journal of Gastroenterology & Hepatology 2019;31(11):1376-1381]

Inflammatory bowel diseases (mainly Crohn's and colitis) are chronic, debilitating, non-infectious, inflammatory diseases of the digestive tract. Conventional treatment consists of anti-inflammatory and immunomodulating drugs. However, the rate of response to currently available treatments is limited to 40–60%, and many patients remain symptomatic despite maximal medical treatment. This study, conducted in collaboration with the Gastroenterology Unit at Meir Medical Center, is a large-scale, long-term study that included data on patients licensed to treat medical cannabis with inflammatory bowel disease to determine the effect of cannabis on disease symptoms on long-term treatment as well as side effects. Most patients reported significant improvement in their symptoms and the use of other medications after 1 year of cannabis consumption was significantly reduced.

Study Population: 127 Crohn's and colitis patients who received a license for use of medical cannabis (86 males, mean age 39.6).

Strain Used: Half of the patients in the study received the company's products regularly.

Key Results:

- During the study period, 127 patients received a license to use medical cannabis and entered the study.
- General improvement - the average Harvey-Bradshaw index, which measures the severity of the disease, improved from 14.0 to 7.0 ($P < 0.001$).
- Weight gain - During follow-up of 3.6 years (median 44 months), there was a slight but statistically significant weight gain of 2 kg.
- Decrease in drug consumption - the need for other medications was significantly reduced.
- Improve in employment rates - employment among patients increased from 65% to 74%.
- From the study it can be concluded that most Crohn's and colitis patients using cannabis are satisfied with a dose of 30 gram per month.
- No negative effects of cannabis use were observed on the patients' social or occupational status.
- The side effects described by the patients were mild. The most common were dry mouth (63%), memory decline (34%), eye irritation (14%), dizziness, (13%) confusion (9%), and restlessness (8%).

6. Ruth Gallily, et al. Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol.

[Pharmacology & Pharmacy 2015;6(2):75-85]

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 antiinflammatory 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 antiinflammatory 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)

7. Michal Tzadok, et al. CBD-enriched Medical Cannabis for Intractable Pediatric Epilepsy.
[Seizure 2016;35:41-44]

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 children with intractable epilepsy (between the ages of 1-18, half of them under the age of 10) with intractable epilepsy, resistant to 5-7 antiepileptic drugs

Strains used: About half of the patients in the study received the company's products regularly (CBD-enriched, mostly Avidekel 30%).

Key Results:

- 5 (6.7%) children discontinued treatment during 10 months of follow-up.
- Overall improvement - CBD treatment had a positive and significant effect on the frequency and intensity of seizures.
- Decrease in seizures - 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.
- Improvement in various aspects - there improvement in behavior and alertness, language, communication, motor skills and sleep.
- Side effects included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients.

8. Yacov Balash, et al. Medical Cannabis in Parkinson's Disease.
[Clinical Pharmacology 2017;40(6):268-272]

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.l ± 17 months.

Study Population: 47 patients with Parkinson's Disease

Strains used: Various medical cannabis strainsp

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 stiff ness
- 71.1% of patients reported an improvement in sleep quality

9. Ran Abuhasira, et al. Epidemiological Characteristics, Safety and Efficacy of Medical Cannabis in The Elderly.
[European Journal of Internal Medicine 2018;49:44-50]

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: 2,736 patients aged 65+; at 6 months, 901 patients were eligible for follow-up and completed the survey

Strains used: Erez. Alaska. Avidekel

Key Results:

- 93.73 of patients reported that the cannabis treatment improved their condition
- 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

- 35.1% of patients reported a decrease in the number of drugs taken or the dosage
- 18.1% stopped using opioid analgesics or reduced their dose
- The most common reported side effects were dizziness (9.7%) and dry mouth (7.1%)

10. Lihi Bar-Lev Schleider, et al. Prospective Analysis of Safety and Efficacy of Medical Cannabis in Large Unselected Population of Patients with Cancer.

[European Journal of Internal Medicine 2018;49:37-43]

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

Study Population: 2,970 cancer patients; after six months of treatment, 1,211 patients were eligible for follow-up and responded to the questionnaire

Strain Used: Midnight, Avidekel, and other THC-rich Tikun Olam strains

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%)

11. Stephanie Libzon, et al. Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders.

[Journal of Child Neurology 2018;33(9):565-571]

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)

Strains used: Avidekel. tested at 6:1 and 20:1 CBD:THC ratiosp

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

12. Ruth Gallily and Zhannah Yekhtin. Avidekel Cannabis Extracts and Cannabidiol are as Efficient as Copaxone in Suppressing EAE in SJL/J Mice.

[Inflammopharmacology 2019;27(1):167-173]

A study comparing 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

Strains 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

13. Avner Thaler, et al. Single Center Experience with Medical Cannabis in Gilles de la Tourette Syndrome.

[Parkinsonism and Related Disorders 2019;61:211-13]

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

Study Population: 42 patients with Tourette Syndrome

Strains 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

14. Adi Aran, et al. Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems - A Retrospective Feasibility Study.

[Journal of Autism and Developmental Disorders 2019;49(3):1284-1288]

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

Strains used: Avidekel, 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

15. Lihi Bar-Lev Schleider, et al. Real Life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy.

[Scientific Reports 2019;9(1):200]

An observational study assessing 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 Avidekel cannabis oil.

Study Population: 188 children with ASD; 93 completed the follow-up survey at six months

Strains 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
- 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

16. Dana Barchel, et al. Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities.

[Frontiers in Pharmacology 2019;9:1521]

Children with autism spectrum disorder (ASD) commonly exhibit comorbid symptoms such as aggression, hyperactivity and anxiety. Several studies are being conducted worldwide on cannabidiol use in ASD; however, these studies are still ongoing, and data on the effects of its use is very limited. After obtaining a license from the Israeli Ministry of Health, parents of children with ASD were instructed by a nurse practitioner how to administer oral drops of cannabidiol oil. The aim of this study, conducted in collaboration with the Clinical Pharmacology and Toxicology Unit at Assaf Harofeh Medical Center, was to examine prospectively the safety characteristics and the changes in symptoms by a bi-weekly questionnaire. Parents' reports suggest that cannabidiol may improve ASD comorbidity symptoms.

Study Population: 53 children diagnosed with ASD (45 boys, mean age 11).

Strain Used: Avidekel 20:1 30% CBD and Erez 3% THC extracts.

Key Results:

- 2 patients (3.7%) discontinued treatment during the study (lasting 66 days on average) and another 2 patients continued cannabis treatment with another provider.
- Overall improvement - An improvement in ASD symptoms was reported in 74.5% of patients.
- Decreased self-injury and rage attacks - Self-injury and rage attacks improved in 67.6% of patients.
- Decreased hyperactivity - Hyperactivity symptoms improved in 68.4%.
- Improved sleep - Sleep problems improved in 71.4%.
- Decreased anxiety - Anxiety improved in 47.1%.
- Side effects included drowsiness, decreased appetite, and increased appetite.

17. Iftach Sagy, et al. Safety and efficacy of Medical Cannabis in Fibromyalgia.

[Journal of Clinical Medicine 2019;8(6):807]

An observational study investigating 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 fibromyalgia patients; 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 events
- 73,4% of patients reported improved sleep; 13.2% reported their sleeps problems were fully relieved
- 80.8% of patients reported improved-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 9/10 at baseline to 5/10 after six months
- 22.2% of patients stopped or reduced their dosage of opioids; 20.3% reduced their dosage of benzodiazepines

18. Timna Naftali, et al. Placebo-controlled study - Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial.

[PLoS One 2021;16(2):e0246871]

Ulcerative colitis is an inflammatory bowel disease characterized by inflammation of the large intestine. The disease poses a significant personal and socioeconomic burden due to its effects on patients' quality of life, daily functioning and use of healthcare system. The most common symptoms in colitis patients are: multiple bowel movements, severe abdominal pain and blood in the stool. The current treatment carries many long-term risks including malignancies, infections, and decreased bone density. Therefore, it is not surprising that many patients with colitis seek alternative treatments for their illnesses. A common such alternative treatment is the use of cannabis. However, clinical studies in the field are lacking.

The aim of this randomized, double-blind, placebo-controlled study, conducted in collaboration with Meir Medical Center, was to evaluate the effect of medical cannabis on the clinical condition of ulcerative colitis patients. Cannabis treatment induced clinical remission and improved quality of life in patients with mild to moderately active ulcerative colitis.

Study Population: 32 patients with ulcerative colitis (18 males, mean age 30).

Study Product: Erez rolls compared to placebo (47% of patients received placebo).

Key Results:

- No patient stopped treatment during the 8 weeks of follow-up. 17 patients (53%) continued treatment for another year after the study ended.
- Overall improvement - a clinical response (considered to be above 3 points in the Lichtiger index score) was observed in the cannabis group more significantly than in the placebo group; Cannabis group patients improved from 10.9 to 5.0. There was also a decrease in the score of the placebo group, due to the placebo effect, but was more moderate from 11.0 to 8.0.
- Decrease in the number of bowel movements per day - In the cannabis group, the number of bowel movements per day decreased from 2.6 to 1.0. In the placebo group, the number of bowel movements decreased from 2.6 to 2.
- Decrease in abdominal pain – of the patients who reported severity of abdominal pain of ≥2 (on a scale of 1 to 10, with 10 being the highest level of pain), in the cannabis group the level of pain decreased from 10 to 1. In the placebo group, the level of pain decreased from 9 to 8.
- Improvement in quality of life - The cannabis group observed a significant improvement in quality of life (from a score of 77 to a score of 98), compared to the placebo group whose quality of life remained at the same level (score of 78 all the way).
- Symptomatic improvement - The cannabis group patients reported a significant improvement compared to the placebo group also in appetite, concentration, libido, pain, general satisfaction with the treatment (on a grade from 1 to 7, 1 = improved, 4 = no change, 7 = deteriorated).
- Side effects - No significant differences were observed between the cannabis group and the placebo group.

19. Lihi Bar-Lev Schleider, et al. Adherence, Safety, and Effectiveness of Medical Cannabis and Epidemiological characteristics of the Patient Population: A prospective Study.

[Frontiers in Medicine 2022;9(Article 827849)]

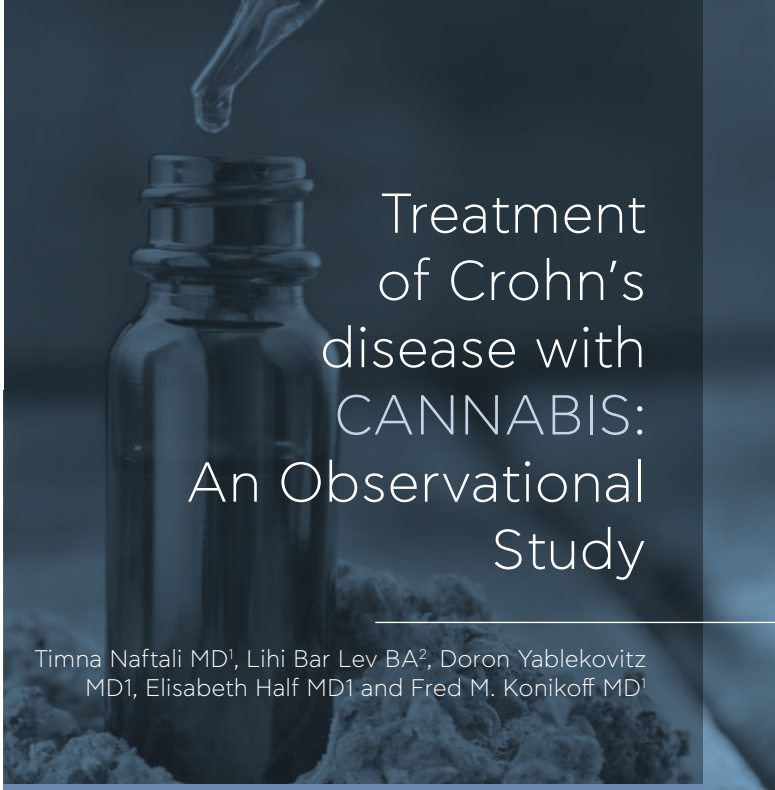
A prospective study investigating the adherence, safety, and effectiveness of patients to medical cannabis.

Study Population: ~10.000 patients with cancer (49.1%), non-specific pain (29.3%) etc

Strains used: Erez, Alaska, Avidekel

Key Results:

- 70.6% of patients experienced treatment success
- 91.5% of patients reported rage attacks decrease
- 89.5% of patients reported restlessness decrease
- 89.1% of patients reported improved sleep
- 88.9% of patients reported nausea improvement
- Supervised medical-cannabis treatment is associated with high adherence, improvement in quality of life, and a decrease in pain level with a low incidence of serious adverse events



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: TTo 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

keywords

- 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.

IBD = inflammatory bowel disease
CD = Crohn's disease

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 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.

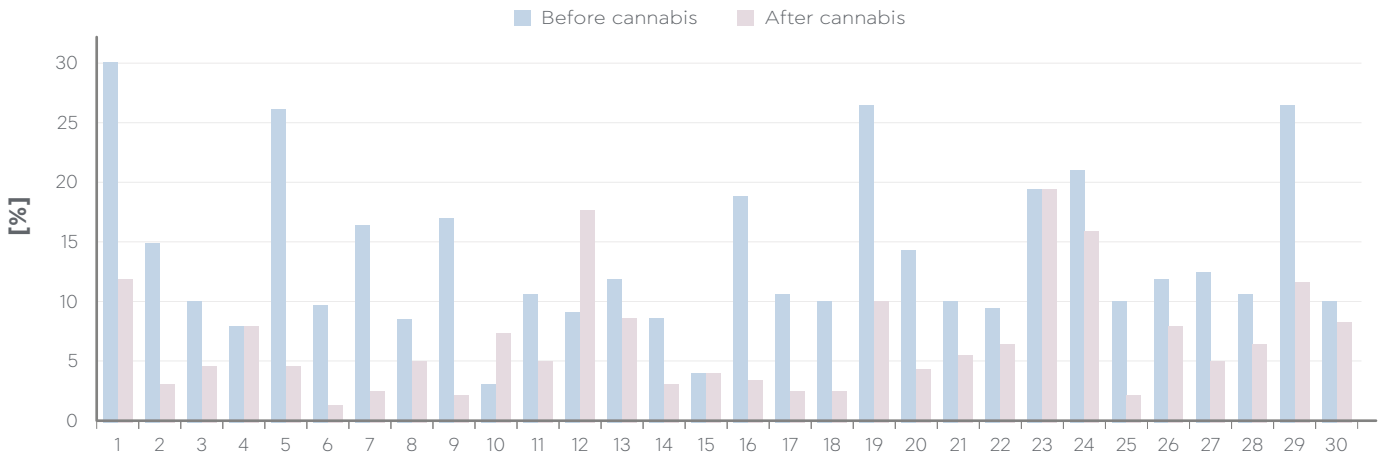
RESULTS

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 fistuliz- ing 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.

Figure 1

Harvey Bradshow index before and after cannabis use



THC = Δ9-tetrahydrocannabinol

Table 1

Patient characteristics

	Average	Range
Age (yrs)	36	21 - 65
Male / Female	26 / 4	Age (yrs)
Disease duration (yrs)	11.3 yrs	1 - 41 yrs
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

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 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, mac- rophages, 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.

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

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 chol- era 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.

TNF = tumor necrosis factor
NK = natural killer

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.

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

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abstract

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, immuno- modulators, or anti–tumor necrosis factor-a 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 treat- ment 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.

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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)-a, interferon-g, 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, in- testinal 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, myeloperoxidase activity, and peristalsis.[9] The combination of THC and CBD was more effective than either substance alone.[10]

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, D9-tetrahydrocannabinol; TNF, tumor necrosis factor.

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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. Sec- ondary 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-a. 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-a 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 (w2 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 venti- lation for 72 hours. The final product was tested for cannabi- noids 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.

Table 1

Demographic Data

Variable	Study group (N 1⁄4 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

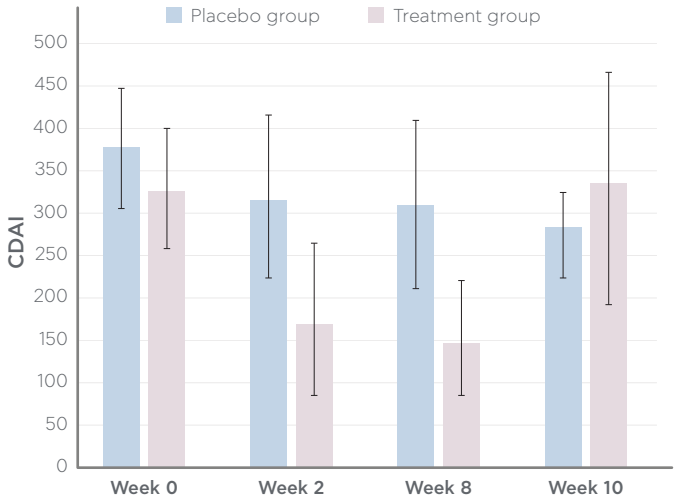
5-ASA = 5-aminosalicylic acid

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 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 or- dered, 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).

Figure 1

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



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-a in the past. Of the 18 patients treated with anti–TNF-a, 5 patients had to stop treatment because of a severe allergic reaction, 4 patients were still receiving anti–TNF-a, 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).

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-a	9 (81)	8 (80)	.7	1 (9)	4 (40)	.9

NS, not significant.

Table 3 Laboratory Tests

	Study (N = 11)			Placebo (N = 10)		
Test	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/mL	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

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 1⁄4 .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).

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 longstanding 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.

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

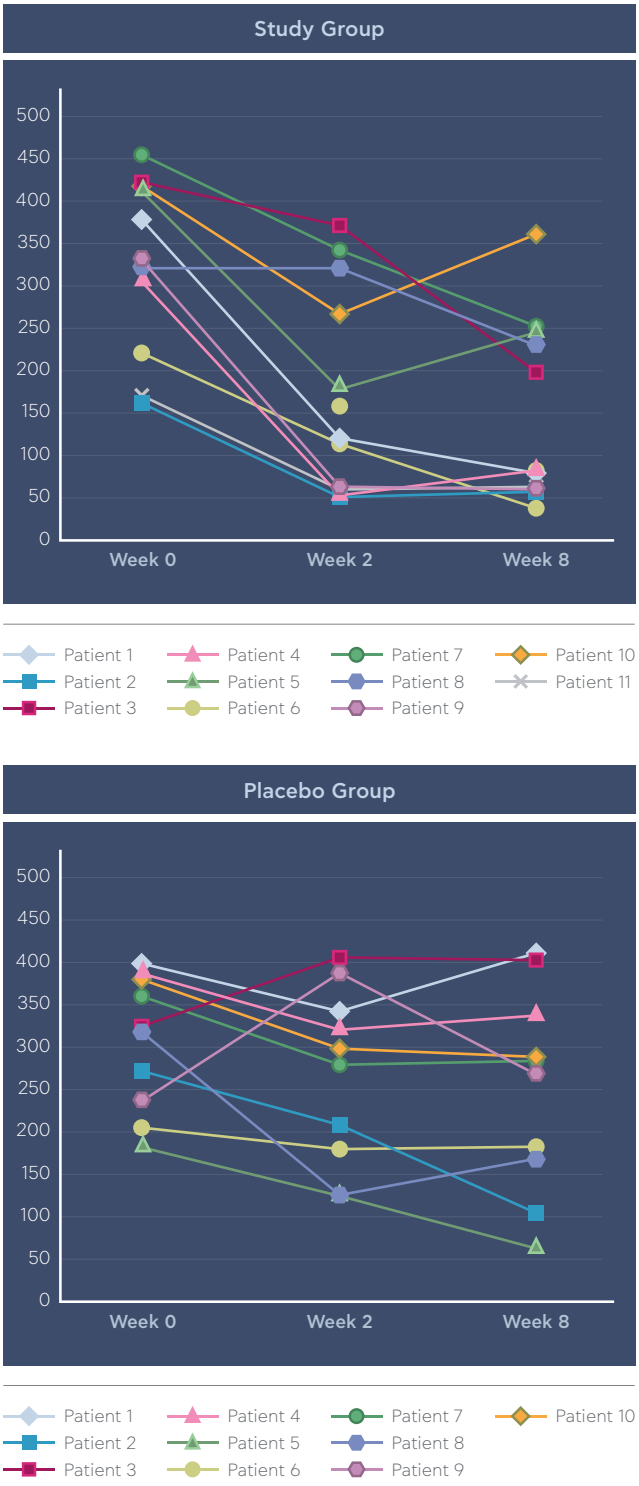
[a]On a scale from 1 to 7, where 1 1⁄4 no effect; 7 1⁄4 very strong effect.
[b]On a scale from 1 to 7, where 1 1⁄4 very satisfied; 7 1⁄4 very dissatisfied.

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.

Figure 2

CDAI scores 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.

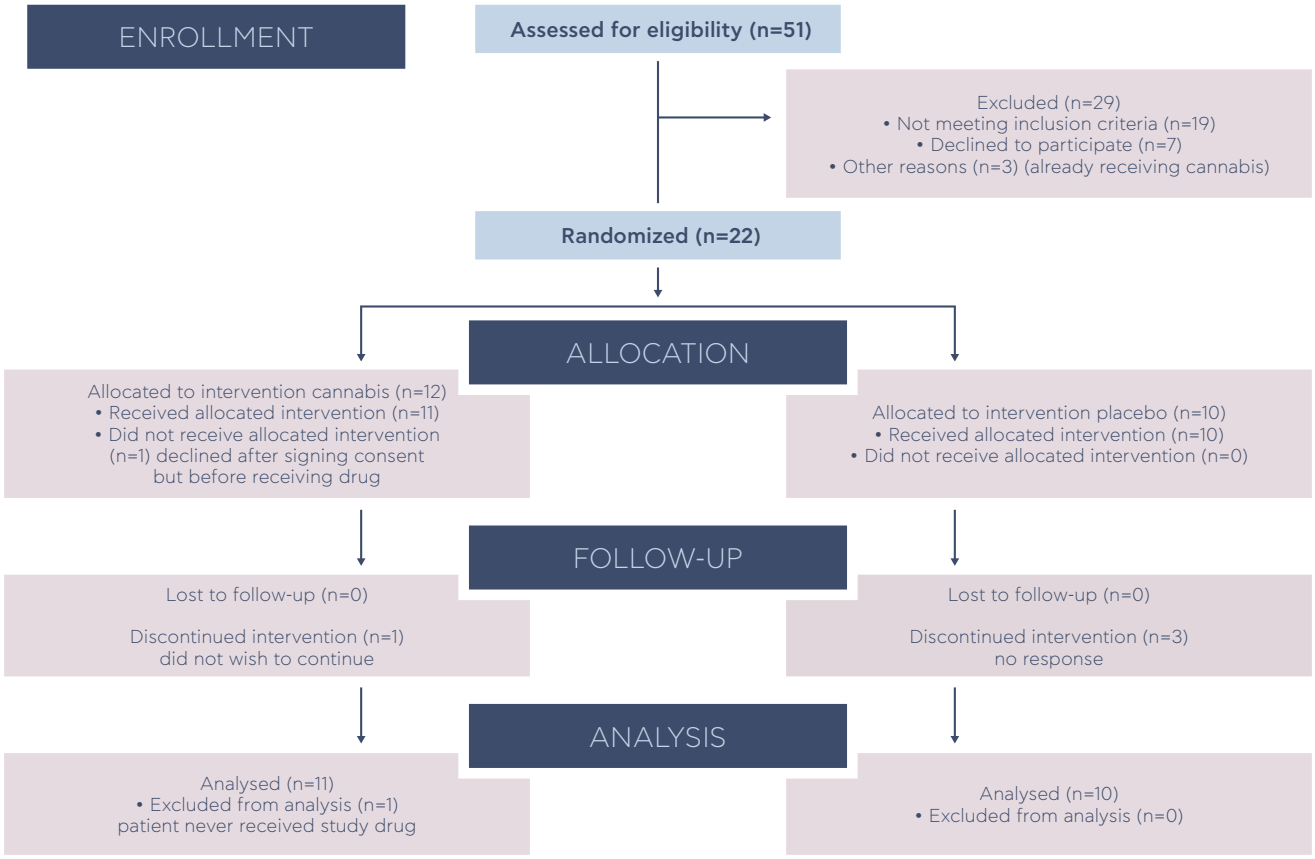
There is an understandable restraint in the medical community regarding the use of cannabis, which is an illegal drug in most countries. Yet, cannabis has a remarkably good safety profile.[17,18] In this study, during short-term use of 8 weeks, we did not observe any significant side effects. All patients 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 cannabi- noids 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.

Supplementary Figure 1 CONSORT flow diagram.



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Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial.

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abstract

Aims: Despite reports that medical cannabis improves symptoms in Crohn's disease [CD], controlled studies evaluating disease response are lacking. This study assessed the effect of cannabidiol [CBD]-rich cannabis oil for induction of remission in CD.

Methods: In a double-blind, randomised, placebo-controlled, single-centre trial, patients received orally either cannabis oil containing160/40 mg/ml cannabidiol/ tetrahydrocannabinol [CBD/THC] or placebo for 8 weeks. Disease parameters, including the CD activity index [CDAI], and simple endoscopic score for CD [SES-CD], were assessed before and after treatment. In a subgroup of patients, blood samples were collected for CBD and THC plasma levels.

Results: The study included 56 patients, age 34.5 ± 11 years, men/women 30/26 [54/46%],30 in cannabis and 26 in placebo groups. CDAI at recruitment and after 8 weeks was 282 (interquartile range [IQR] 243-342) and 166 [IQR 82–226], and 264 [IQR 234–320] and 237 [IQR 121–271] [p <0.05] in the cannabis and placebo groups, respectively. Median quality of life [QOL] score improved from 74 for both groups at baseline to 91 [IQR 85–102] and 75 [IQR 69–88] after 8 weeks in the cannabis and placebo groups, respectively [p = 0.004]. SES-CD was 10 [IQR 7–14] and 11 [IQR7-14], and 7 [4–14] and 8 [IQR 4–12] [p = 0.75] before and after treatment, in the cannabis and placebo groups, respectively. Inflammatory markers (C-reactive protein [CRP], calprotectin) remained unchanged.

Conclusions: Eight weeks of CBD-rich cannabis treatment induced significant clinical and QOL improvement without significant changes in inflammatory parameters or endoscopic scores. The oral CBD-rich cannabis extract was well absorbed. Until further studies are available, cannabis treatment in Crohn's disease should be used only in the context of clinical trials.

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The cannabis plant is known to have therapeutic effects, including improvement in inflammatory processes. However, no controlled studies have been published to date investigating the effect of cannabis as an anti-inflammatory in Crohn's patients. The aim of this double-blind, placebo-controlled randomized study, conducted in collaboration with Meir Medical Center, was to evaluate the effect of Avidekel oil, a CBD-rich and low-THC cannabis extract, on Crohn's disease activity.

Study participants underwent an eight-week follow-up in which each participant received Avidekel or placebo oil and an additional two weeks of wash-up to see what happens during consumption cessation, a total of tenweeks of follow-up. During the study, patients attended four visits and were evaluated by medical interview, physical examination, blood and stool tests. In addition, a colonoscopy was performed before the start of cannabis treatment and at the end of eight weeks of treatment.

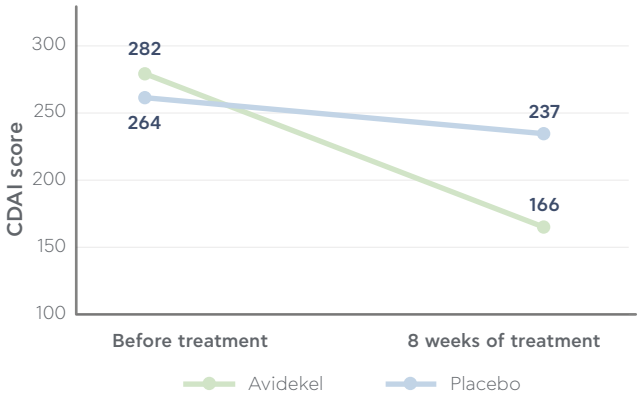
Study Population: 56 patients with Crohn's disease (30 males, mean age 34.5).

Study Product: Avidekel oil with 16% CBD and 4% THC VS placebo (46% of patients received placebo).

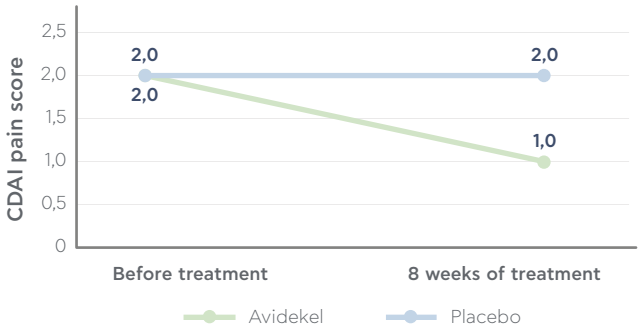
RESULTS

• No patient stopped treatment during the 10 weeks of follow-up.

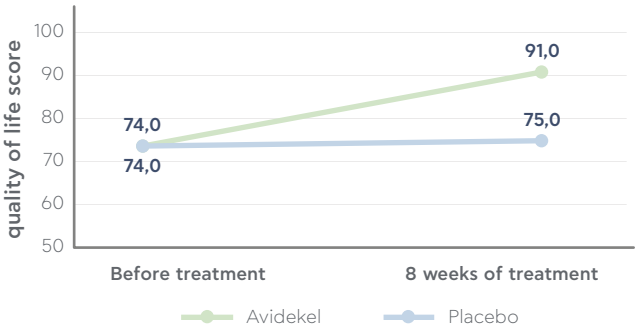
• Improvement in disease symptoms - The CDAI score (Crohn's disease activity index) improved significantly in the cannabis group, compared to the improvement in the placebo group.



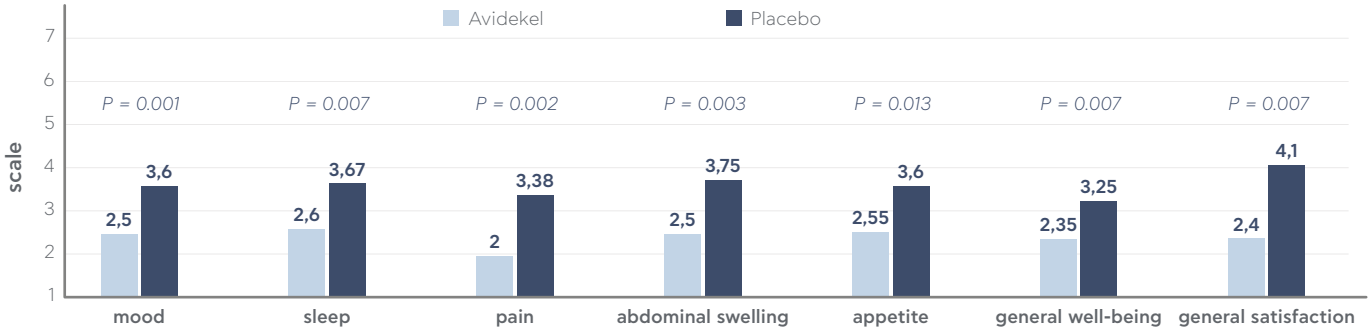
• Decrease in abdominal pain - there was a significant relief in the intensity of abdominal pain in the cannabis group (decrease in the CDAI score in the pain section), compared to the placebo group, in which the intensity of pain remained at the same level.



• Improvement in the quality of life - In the cannabis group, a significant improvement in the quality of life was observed (an increase in the SF-36 questionnaire score), compared with the placebo group whose quality of life remained at the same level.



• Positive overall effect of treatment - Patients were asked to rate from 1 to 7, where 1 = great improvement, 7 = severe deterioration, various aspects of life. In the cannabis group, a significant improvement was observed in the various areas.



• Side effects - No significant differences were observed between the cannabis group and the placebo group.

Eight weeks of CBD-rich cannabis treatment induced significant clinical and QOL improvement without significant changes in inflammatory parameters or endoscopic scores. The oral CBD-rich cannabis extract was well absorbed. Until further studies are available, cannabis treatment in Crohn's disease should be used only in the context of clinical trials.

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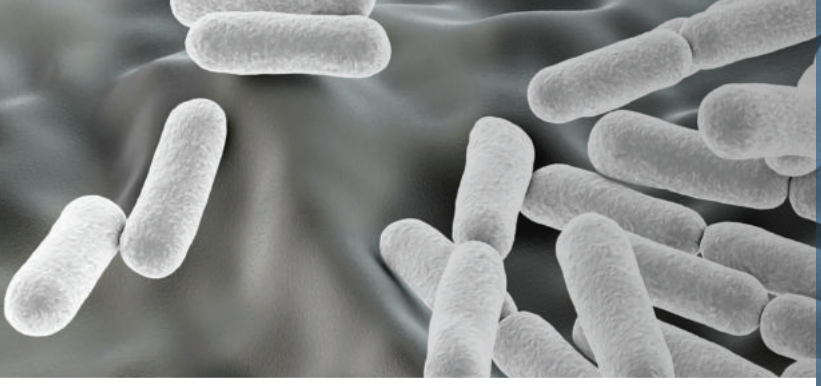

Cannabis for the Treatment of Inflammatory Bowel Disease: A True Medicine or a False Promise?

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abstract

Cannabis is the most widely used recreational drug worldwide and is used by some patients with inflam-matory bowel disease (IBD) to ameliorate their disease. Whereas epidemiological studies indicate that as many as 15% of IBD patients use cannabis, studies inspecting cannabis use in IBD are few and small. We have conducted several studies looking at the use of cannabis in IBD. In Crohn's disease, we demonstrated that cannabis reduces the Crohn's disease activity index (CDAI) by >100 points (on a scale of 0–450). Two small studies in ulcerative colitis showed a marginal benefit. However, no improvement was observed in inflammatory markers or in endoscopic score in either disease. Many questions regarding cannabis use in IBD remain unanswered. For example, cannabis is a complex plant containing many ingredients, and the synergism or antagonism between them likely plays a role in the relative efficacy of various cannabis strains. The optimal doses and mode of consumption are not determined, and the most common form of consump-tion, i.e. smoking, is unacceptable for delivering medical treatment. Cannabis is a psychotropic drug, and the consequences of long-term use are unknown. Despite all these limitations, public opinion regards cannabis as a harmless drug with substantial medical efficacy. In Israel, the number of licenses issued for the medical use of cannabis is rising rapidly, as are the acknowledged indications for such use, but good quality evidence for the effectiveness of cannabis is still lacking. Further studies investigating the medical use of cannabis are urgently needed.

Digestive Diseases 2014;32(4):468-74.

keywords

- Cannabis
- Crohn's disease
- IBD
- Ulcerative colitis

Abbreviations: CBD, cannabidiol; CDAI, Crohn's disease activity index; ECS, endocannabinoid system; IBD, inflammatory bowel disease; RCT(s), randomized controlled trial(s); THC, Δ9-tetrahydrocannabinol.

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BACKGROUND

Cannabis is the most widely used recreational drug worldwide. The cannabis plant contains as many as 100 phytocannabinoids, as well as other ingredients such as terpenes and flavonoids.[1] The phytocanna-binoids exert their effect through the endocan-nabinoid system (ECS), which is an endogenous system with an important role in modulating mood, memory, reward homeostasis, immune regulation, and energy balance.[2] The best-known phytocan-nabinoids are Δ9-tetrahydrocannabinol (THC), responsible for the psychotropic effect of cannabis, and cannabidiol (CBD), which does not have a central effect but was shown to have an anti-inflammatory effect.[3]

REPORTS OF CANNABIS USE IN INFLAMMATORY BOWEL DISEASE

Many animal and laboratory studies demonstrated that cannabis can ameliorate inflammation in inflam-matory bowel disease (IBD).[4] Consequently, there are many epidemiological studies and anecdotal reports about cannabis use in IBD patients. Various studies demonstrated that the prevalence of can-nabis use among IBD patients varies between 12% and 15%, although a much higher percentage of patients (50%–60%) report ever

using cannabis during their lifetime.[5,6] Patients claim that cannabis ameliorates their symptoms, including improvement in diarrhea, abdominal pain, and appetite[7]; however, most studies contain no information about the dose and mode of cannabis consumption. We conducted an observational study of 127 IBD patients who were using cannabis by license from the Ministry of Health in Israel and found that most patients were satisfied with a monthly dose of 30 g and that 70% were consuming cannabis by smoking it, whereas the others were consuming it orally, mostly in the form of oil.[8] Nevertheless, since patients are using many different varieties of cannabis, with different content of cannabinoids, obtaining more accurate information is difficult.

RANDOMIZED CONTROLLED TRIALS OF CANNABIS IN IBD

In view of the many reports about cannabis use in IBD, it is surprising that very few randomized controlled trials (RCTs) have been conducted. Two Cochrane reviews found only three trials performed in Crohn's disease[9] and only two in ulcerative colitis.[10] This can be partly explained by the fact that investigating cannabis use is inherently difficult. The large variations between different cannabis strains and the many different modes of cannabis consumption make properly standardized cannabis treatment hard to achieve.

In the first RCT, 21 Crohn's disease patients were randomized to receive either cannabis flowers or a placebo containing 23% THC. A clinical response, defined as a decrease in the Crohn's disease activity index (CDAI) by >100 points (on a scale of 0–450) was observed in 10/11 (91%) subjects in the cannabis group and 4/10 (40%) in the placebo group (P=0.028).[11] Another trial looking at the use of CBD for Crohn's disease found no significant difference in the CDAI between the study and the placebo groups (220±122 and 216±121, respectively, P=NS).[12]

The first RCT to report cannabis use in ulcerative colitis included 60 patients who received a CBD-rich cannabis botanical extract for 10 weeks. Remission rates were similar for the CBD (28%) and placebo (26%) groups. Although CBD is usually well toler-ated, in this study side effects led to a 40% protocol deviation in the study group.[13] We performed a study of cannabis in ulcerative colitis at the Meir Medical Center, demonstrating that the disease activity index (Lichtiger score) after 8 weeks of cannabis treatment was 4 in cannabis participants compared with 8 in the placebo group (P between groups 0.001).[10]

There are no studies regarding the maintenance of remission with cannabis in either Crohn's disease or ulcerative colitis.

The Israeli Gastroenterological Association issued recommendations for the use of cannabis in IBD. These were adopted by the Israeli Ministry of Health. These recommendations state that since the evidence of cannabis efficacy in IBD is still lacking, cannabis should be used only as a compassionate treatment in patients for whom the established forms of treatment have failed—that is, patients who still suffer from the active disease despite treatment by biologics, and who are not candidates for surgery.

REGULATION OF MEDICAL CANNABIS IN ISRAEL

Despite the lack of scientifically sound evidence, cannabis use is rapidly gaining popularity and legitimacy throughout the world. Medical cannabis treatment was introduced in Israel in 1994, but until 2001 it was approved for only 64 patients. During the last decade, pressure from the media and politicians, together with increasing awareness of physicians and patients, pushed the numbers up. Consequently, the number of permits increased from 12,000 in 2013 to 60,000 in 2019. New instructions published by the Ministry of Health allowed each specialist to recommend the treatment within the limits of his/ her specialization. The recommendations were examined by qualified physicians in the Ministry, and 90% of the requests were granted. A license was sent to the patient specifying the dispensary allocated to them, the amount of cannabis, and the consumption method approved. The dispensary supplied cannabis to the patients and instructed them on how to use it. However, there was no specification of the strain of cannabis to be used or the content of THC allowed. Consequently, the treating physician ended up prescribing a treatment but having no control of the doses of the psychoactive substance the patient would consume. During those years more than 80,000 licenses were issued, and, at the time of writing, more than 50,000 are active.

Regarding the various indications for cannabis use so far, 40% of the patients were oncology patients, 30% suffered from intractable pain after the failure of all conventional treatments, and 2,000 patients (4%) were treated for post-traumatic stress disorder after failure of at least 3 years of all conventional, medical, and psychological treatments. More than 1,000 patients (2%) were treated for Crohn's disease and 150 for ulcerative colitis. More than 1,000 patients (2%) were treated for fibromyalgia (an indication that brought a lot of professional objection). The other patients suffered from neurological disorders, autoimmune diseases, and others (data from M.D., former medical adviser to the Israeli Minister of Health on Cannabis).

THE MINISTRY OF HEALTH CANNABIS REFORM

Lately, in an attempt to define the prescription of cannabis more accurately, the Ministry of Health issued a list of allowed cannabis variations and is removing the dispensing of cannabis from cannabis producers to pharmacies. The allowed variations include flowers or oil, Cannabis sativa or C. indica, and various proportions of THC and CBD, ranging from 3% to 20%. Thus, the physician prescribing cannabis can define the exact dose of THC and CBD.

In parallel, during the last years, the Cannabis Unit of the Israeli Ministry of Health initiated a set of new regulations intended for quality control assurance. The previous system was based on a direct supply of cannabis from the grower to the patients. The new system included strict

quality control, high manufacturing standards, and distribution of cannabis products through pharmacies.

A structured process of introducing new indications was initiated. The process is quite complicated, and the implementation was delayed by a court decision for several months.

In an effort to establish more scientifically sound evidence about the medical role of cannabis, a research committee, chaired by Professor Rafael Mechulam, approved more than 400 research projects, including 60 clinical studies. New research is evaluating the possible use of cannabis in the treatment of opioid addiction and the treatment of other psychiatric disorders. New indications explored in recent years include autism in children and intractable epilepsy of childhood; approximately 1,000 children in each group have been treated, with significant success. New ways of administration are being developed, starting from new inhalation devices,[14] and continuing with topical preparations for psoriasis and atopic dermatitis.[15,16] New manufacturing methods using nanotechnology are also being investigated.

CONCLUSION

The use of medical cannabis is rapidly increasing, and physicians are faced with an increasing demand from patients to prescribe it. Sadly, this is not accompanied by scientifically sound evidence regarding the efficacy, if any, of cannabis treatment. Very little is known about the effect of cannabis, the significance of various cannabinoid combinations, or the mode of cannabis consumption. On the other hand, we cannot afford to ignore the many reports about the positive effect of cannabis. The current treatment for IBD is successful in about 60% of patients, so if indeed there is a potential for another medication this should be explored using rigorous and scientifically sound methods. Only by conducting large well-designed randomized controlled trials will we be able to benefit from the potential of this plant.

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Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects.

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abstract

Objective: Use of medical cannabis for improving symptoms of inflammatory bowel disease is increasing. However, reports on long-term outcomes are lacking. This prospective, observational study assessed the effects of licensed cannabis use among patients with inflammatory bowel disease.

Methods: Dose and mode of consumption, adverse events, use of other medications, and long-term effects were evaluated among 127 patients with inflammatory bowel disease using legalized medical cannabis. Blood count, albumin, and C-reactive protein were assessed before, 1 month, and at least 1 year after medical cannabis therapy was initiated. Questionnaires on disease activity, patient function, and signs of addiction were completed by patients and by a significant family member to assess its effects.

Results: The average dose used was 31 ± 15 g/month. The average Harvey-Bradshaw index improved from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$) during a median follow-up of 44 months (interquartile range, 24-56 months). There was a slight, but statistically significant, average weight gain of 2 kg within 1 year of cannabis use. The need for other medications was significantly reduced. Employment among patients increased from 65 to 74% ($P < 0.05$). We conclude that the majority of inflammatory bowel disease patients using cannabis are satisfied with a dose of 30 g/month. We did not observe negative effects of cannabis use on the patients' social or occupational status.

Conclusions: Cannabis use by inflammatory bowel disease patients can induce clinical improvement and is associated with reduced use of medication and slight weight gain. Most patients respond well to a dose of 30 g/month, or 21 mg Δ9-tetra- hydrocannabinol (THC) and 170 mg Cannabidiol (CBD) per day.

Eur J Gastroenterol Hepatol. 2019 Nov;31(11):1376-1381.

Inflammatory bowel diseases (mainly Crohn's and colitis) are chronic, debilitating, non-infectious, inflammatory diseases of the digestive tract. Conventional treatment consists of anti-inflammatory and immunomodulating drugs. However, the rate of response to currently available treatments is limited to 40–60%, and many patients remain symptomatic despite maximal medical treatment. This study, conducted in collaboration with the Gastroenterology Unit at Meir Medical Center, is a large-scale, long-term study that included data on patients licensed to treat medical cannabis with inflammatory bowel disease to determine the effect of cannabis on disease symptoms on long-term treatment as well as side effects. Most patients reported significant improvement in their symptoms and the use of other medications after 1 year of cannabis consumption was significantly reduced.

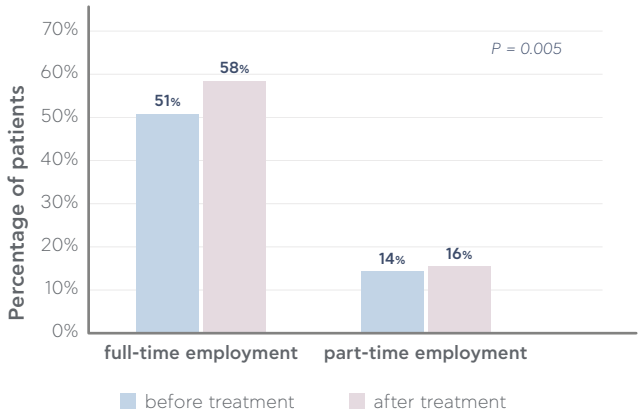
Study Population: 127 Crohn's and colitis patients who received a license for use of medical cannabis (86 males, mean age 39.6).

Study Product: Half of the patients in the study received the company's products regularly.

RESULTS

- During the study period, 127 patients received a license to use medical cannabis and entered the study.
- General improvement - the average Harvey-Bradshaw index, which measures the severity of the disease, improved from 14.0 to 7.0 ($P < 0.001$).
- Weight gain - During follow-up of 3.6 years (median 44 months), there was a slight but statistically significant weight gain of 2 kg.
- Decrease in drug consumption - the need for other medications was significantly reduced.

• Improve in employment rates - employment among patients increased from 65% to 74%.



• From the study it can be concluded that most Crohn's and colitis patients using cannabis are satisfied with a dose of 30 gram per month.

• No negative effects of cannabis use were observed on the patients' social or occupational status.

• The side effects described by the patients were mild. The most common were dry mouth (63%), memory decline (34%), eye irritation (14%), dizziness, (13%) confusion (9%), and restlessness (8%).

DISCUSSION

Cannabis use is prevalent among patients with IBD [13–15]. However, most of the published literature on this issue provides data on the prevalence and epidemiological aspects of cannabis use in these patients, but very limited information regarding the dose, mode of consumption, side-effects, and disease activity [18,19]. No information regarding development of drug dependency and patients' functioning has been collected. Cannabis use among IBD patients is increasing but evidence that will direct physicians how to manage this phenomenon is lacking; hence, the importance of characterizing these effects.

The current observational, real-life study takes advantage of the large clinical service at Meir Medical Center, where more than half of the IBD patients on medical cannabis in Israel are followed. We summarize our experience with patients with IBD using medical cannabis, focusing on their clinical experiences and information related to dose, mode of consumption, and side-effects. For the current study, we retrieved the dose of crude cannabis along with the exact content of THC and CBD consumed by 51 patients. Interestingly, most patients preferred to use higher doses of CBD, although this compound has no psychoactive effect. We found that the effective dose of cannabis was 30 g/month of crude cannabis, or 21 mg/day of THC and 170 mg/day of CBD. The cannabis used by our patients was plant-derived, and it was purchased from official dispensaries subject to strict quality control standards and analysis of contents. In our placebo-controlled studies of cannabis use in Crohn's disease [20,21], patients responded to 22 mg/day of THC, similar to the dose observed in this real-life cohort. In a study by Irving et al. [22] ulcerative colitis patients received 250 mg of CBD twice daily. The lower dose taken by our patients (who were free to titrate the dose according to their response) might explain why Irving et al. observed a very high number of major, compliance-related protocol deviations. As most of our patients reported that 30 g/month was effective, we suggest this should be regarded as the effective dose for IBD until more data are collected.

The most common mode of cannabis consumption (56% of the patients) was smoking. This form of consumption is obviously coupled with all the known harm of smoking and, therefore, cannot be recommended as a medical treatment [23]. If cannabis is proven in the future to have medical benefit, safer modes of consumption such as inhalation or oral ingestion should be developed.

We found that most of the patients were satisfied with medical cannabis treatment and experienced prolonged improvement in disease-related symptoms, specifically abdominal pain and number of bowel movements per day. Improvement was also supported by the significant decrease in the clinically based Harvey-Bradshaw disease activity index. In addition, we found that these clinical effects were sustained during the relatively prolonged duration (median of 44 months) of our study. Furthermore, our findings of increased full-time employment and family satisfaction with the treatment demonstrate that the clinical improvement achieved with medical cannabis treatment was also associated with improvements in the patients' daily functioning.

In our cohort, the prevalence of immunomodulation treatment was 63%, as opposed to 13% in the general IBD population [24]. Treatment with TNF inhibitors was 51%, also higher than the reported prevalence of 23.4% for patients with CD [25]. This indicates that our study population included patients with more severe disease. This could be because in Israel, only patients who do not respond to conventional therapy are eligible for medical cannabis. These findings may further support potential benefits for medical cannabis in IBD because the patient-reported improvement in our study was found in a cohort of patients with more severe, treatment-refractory disease. The reduction in the use of IBD-specific medication may seem encouraging, but 18 (14%) of our patients stopped treatment without consulting their physicians, 6 of them stopped thiopurines, and 3 stopped biologics. This observation raises a concern that the euphoria induced by cannabis may mask disease symptoms and temped patients to avoid necessary treatment.

When evaluating cannabis use in IBD, a major question is whether the observed improvement reflects reduction of inflammation, or whether it is the result of the tranquilizing effect of cannabis. Interestingly, despite the patient-reported symptomatic improvement with the use of medical cannabis, we were not able to demonstrate parallel improvement in inflammatory markers. Although platelets, which often act as acute phase reactants, were reduced, there were no significant changes in more specific inflammatory markers such as white blood cells and Creactive protein (CRP).

However, the reduction in platelet count cannot be attributed to a direct effect of cannabis use [26], so it could reflect reduction in inflammation. On the other hand, we did observe a decrease in the use of IBDspecific medications, particularly steroids. Nevertheless, because this was an observational study, we cannot conclude whether this reduction was due to decreased disease activity or symptom severity. In this study, we also addressed the concern of developing drug dependency or abuse in patients receiving medical cannabis. As our patients were using cannabis legally, only some of the DSM-V parameters for addiction applied [17]. Most of our patients used a stable dose of cannabis and their employment status improved. Since patients self reporting of drug abuse may be inaccurate [27], we questioned family members regarding patients function and observed that the functional improvement was also reported by the patients' relatives, so we can conclude that most patients did not present signs of addiction. However, 32% of the patients did increase the cannabis dose and 8 patients actually doubled it. Six of the 127 patients (5%) fulfilled 2 of the DSM criteria [17]. These patients did not present any functional impairment, but it seems that a subpopulation of cannabis users needs to be monitored more carefully and that effective doses of cannabis should be strictly defined.

Unemployment among IBD patients is a common and severe problem, contributing to patient distress. Leong et al.[28] reported an unemployment rate of 39% among patients with Crohn's disease and 44% with ulcerative colitis, whereas another study reported 34% [29]. These rates are comparable to the 27% unemployment rate in our cohort before cannabis use. However, the 18% unemployment rate after initiating cannabis use was significantly improved, indicating a beneficial effect on patient function. Side-effects of prolonged cannabis use are not negligible. In a meta-analysis of 79 trials including 6462 participants (but none for the indication of IBD), Whiting et al. noted a hazard ratio of 3.03 (95% confidence interval, 2.42–3.80) for any side-effect. The most common side-effect was dizziness, but more serious side-effects, such as confusion (13/1160 patients) and hallucinations (10/898 patients) were also noted [30]. Doses varied widely from 5 to 60 mg per day. The rate of mild side-effects in our study was similar; however, we did not observe any of the more severe side-effects. This could be attributed either to our smaller cohort or to a lower dose of cannabis used by our patients.

This observational study is limited by the lack of a placebo arm. Therefore, we cannot draw definite conclusions regarding the anti-inflammatory efficacy of cannabis. However, in view of the limited number of well-designed, prospective, placebo-controlled studies in this area, our study provides important information about the effective dose range, clinical benefit, and safety of cannabis treatment for IBD.

Another limit of the study is that 22% of the patients were using cannabis orally, whereas 68% were either smoking or inhaling it. These different modes of consumption result in different pharmacokinetics of the drug, but we do not have data comparing the response in these two groups. Despite the lack of randomized controlled studies, cannabis is used by many IBD patients, and our real-life data provide us with important information which can guide the management of these patients until more information is available.

In summary, this study presents a real-life cohort of long-term cannabis users with IBD. In this cohort, cannabis resulted in improvement in symptoms and general functioning. Long-term side-effects were mild, and optimal doses were defined. Larger, randomized, placebo-controlled studies are needed.

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Conflicts of interest

L.S. is an employee of Tikun Olam company for medical cannabis. otherwise there are no conflicts of interest.

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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.

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keywords

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

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 Δ⁹-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 Δ⁹-tetrahydrocannabinol, known as THC, which binds with high affinity (Ki = 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 (Ki > 10 μM) [6] to the CB1/CB2 receptors. The other cannabinoids are present in minute amounts.

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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 antiinflammatory and anti-pain dose-response could be achieved when applied either intraperitoneally or orally in an inflammatory mouse model.

MATERIAL AND METHODS

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. 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, Darmstadt, 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)).

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), Δ⁹-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.

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

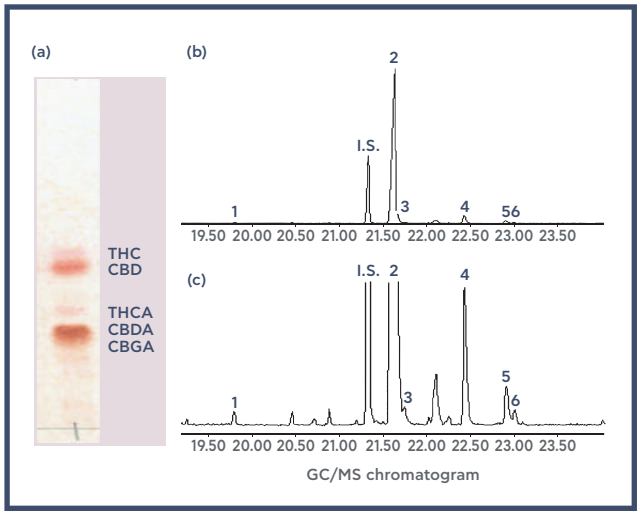

Figure 1. (a) TLC analysis of clone 202 extract. 1 µl of the extract was run on TLC as described in the Method section. CBD = Cannabidiol. CBDA = Cannabidiolic acid; (b) (c) GC/MS chromatograms of an extract from Cannabis clone 202. (b) The full chromatogram. (c) Magnification of weaker signals. Number keys: 1: Cannabidivarol (CBDV); 2: Cannabidiol (CBD); 3: Cannabichromene (CBC); 4: Δ⁹-Tetrahydrocannabinol (Δ⁹-THC); 5: Cannabigerol (CBG); 6: Cannabinol (CBN); I.S.-Internal Standard (Tetracosane).

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.

Table 1

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

Phytocannabinoid	Content
Cannabidiol (CBD)	17.9%
Δ⁹-Tetrahydrocannabinol (Δ⁹-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.

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.).

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.

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.

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.

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.

RESULTS

1. Effect of CBDand 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].

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 TNF α 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)).

Figure 2

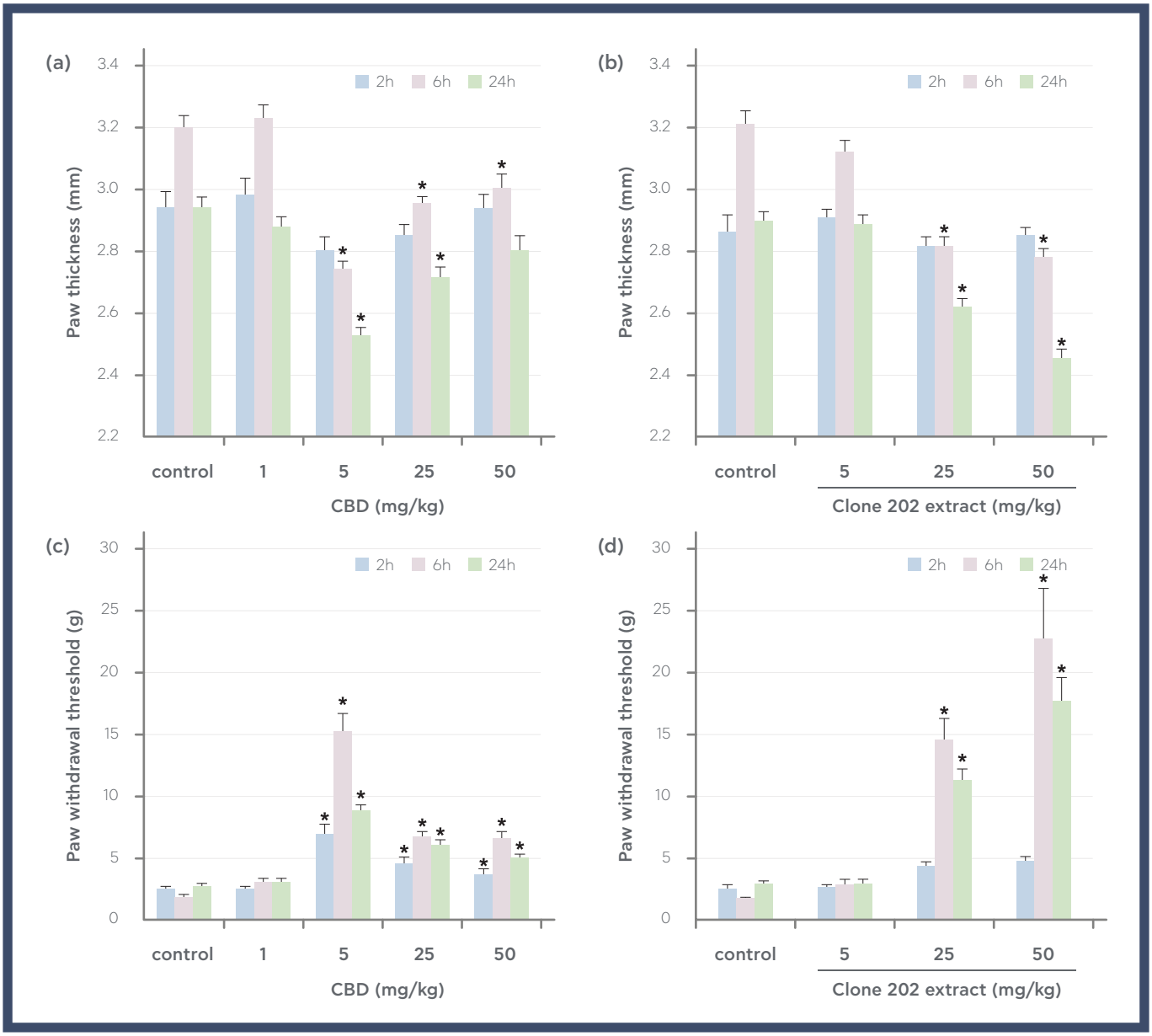

Figure 2. Anti-inflammatory and anti-nociceptive effects of intraperitoneally injected CBD and CBDenriched clone 202 extract. (a) (b) Prevention of zymosan-induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. Immediately thereafter, CBD (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) Antipain 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.

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)), 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()).

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 3

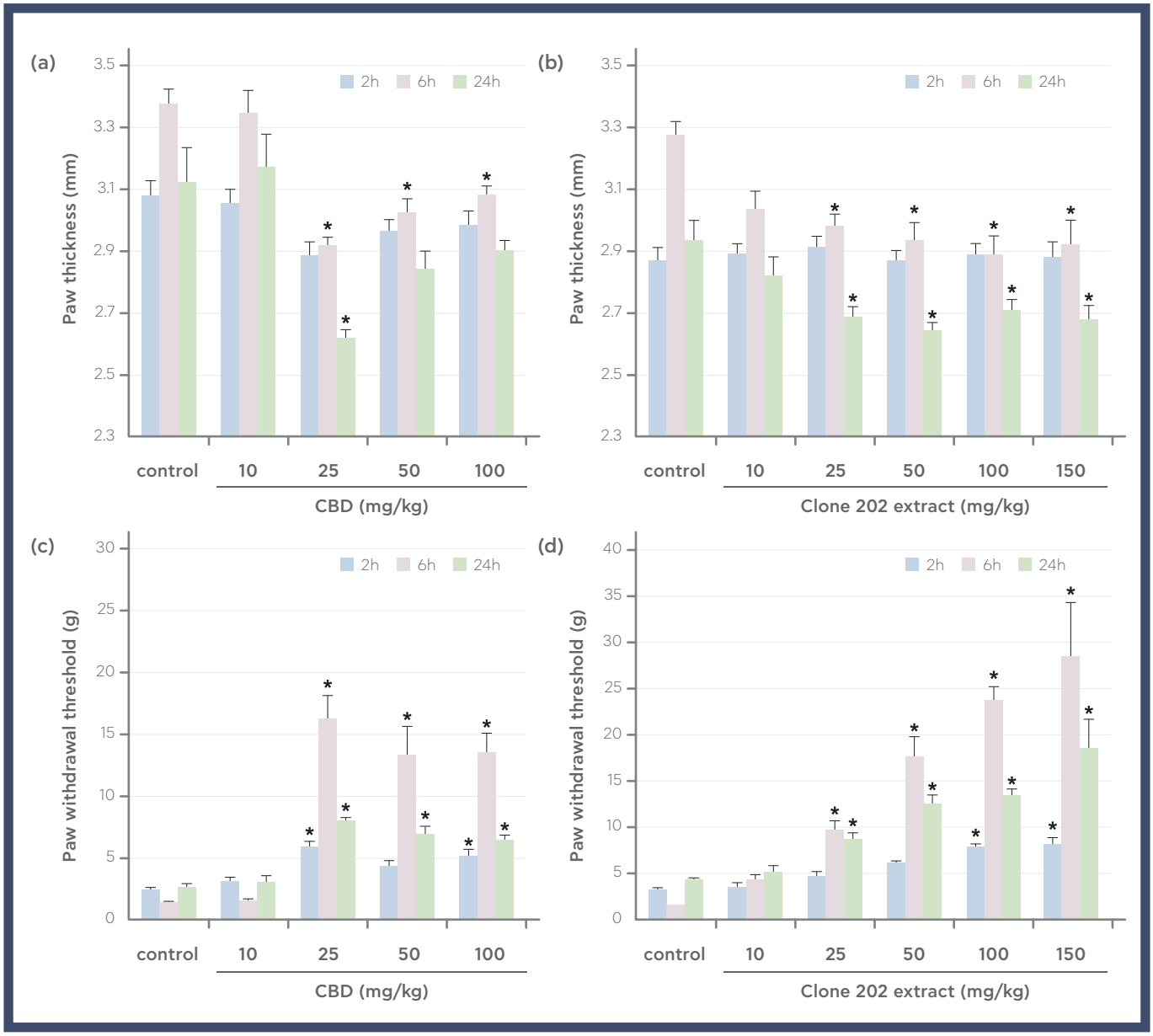

Figure 3. Anti-inflammatory and anti-nociceptive effects of CBD and CBD-enriched clone 202 extract administrated per os. (a) (b) Prevention of zymosan-induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. Immediately thereafter, CBD (a) or 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 dosedependent effect.

Figure 4

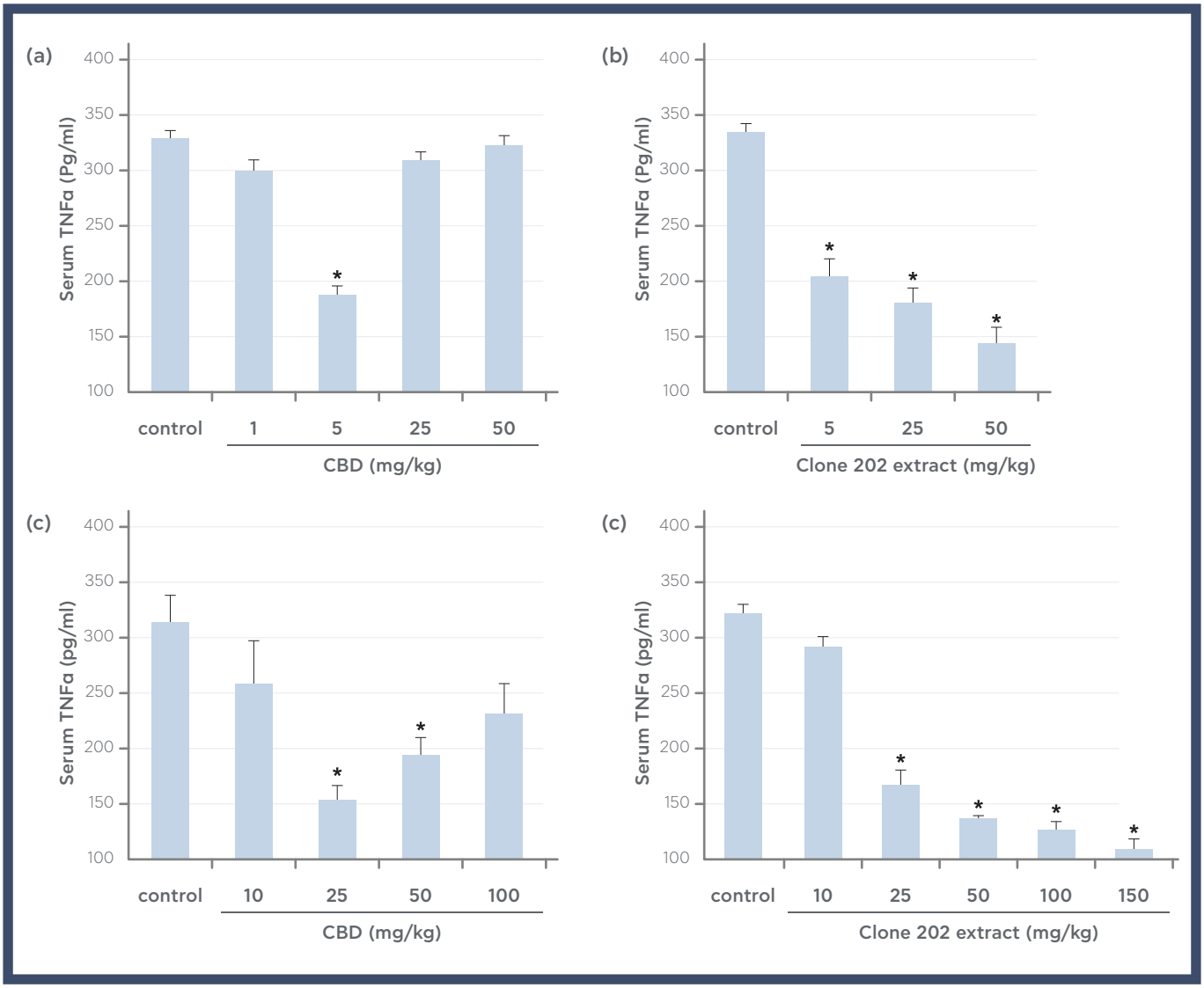

Figure 4. Prevention of zymosan-induced TNFα production by purified CBD and clone 202 extract. (a) (b) Twenty four hours after injecting zymosan and an intraperitoneal dose of CBD (a) or clone 202 extract (b), or a per os dose of CBD (c) or clone 202 extract (d), the TNFα concentration in the serum was 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. 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 antiinflammatory 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.

DISCUSSION

In this manuscript we have observed different dose-response patterns when using purified CBD or plant extract 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 nonpsychotropic 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 zymosaninduced TNFα production in mice, with an improved therapeutic effect upon increased dosages. Thus, the limitation 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.

CONCLUSION

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

Figure 5

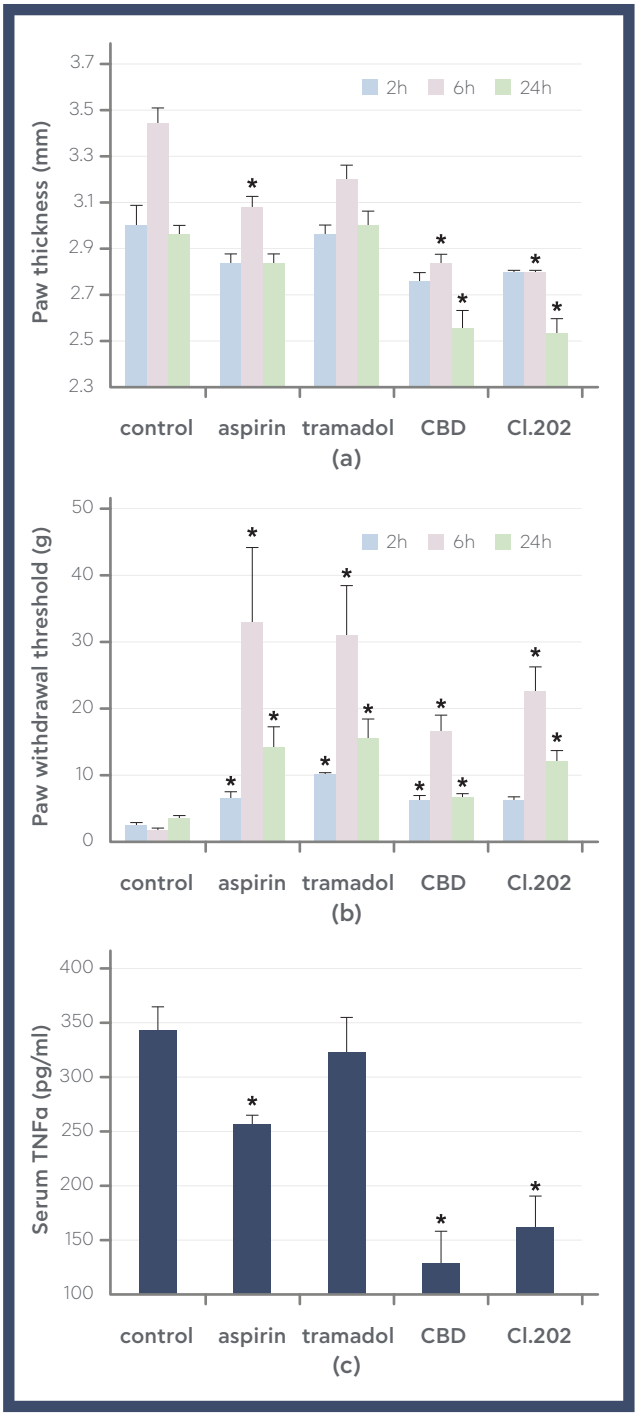

Figure 5. Comparison of anti-inflammatory and anti-nociceptive effects of CBD and Cannabis clone 202 extract with the commercial drugs aspirin and tramadol. (a) Prevention of zymosan- induced swelling of hind paw. 1.5% zymosan in 40 µl was injected into the sub-planter surface of the right hind paw. 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.

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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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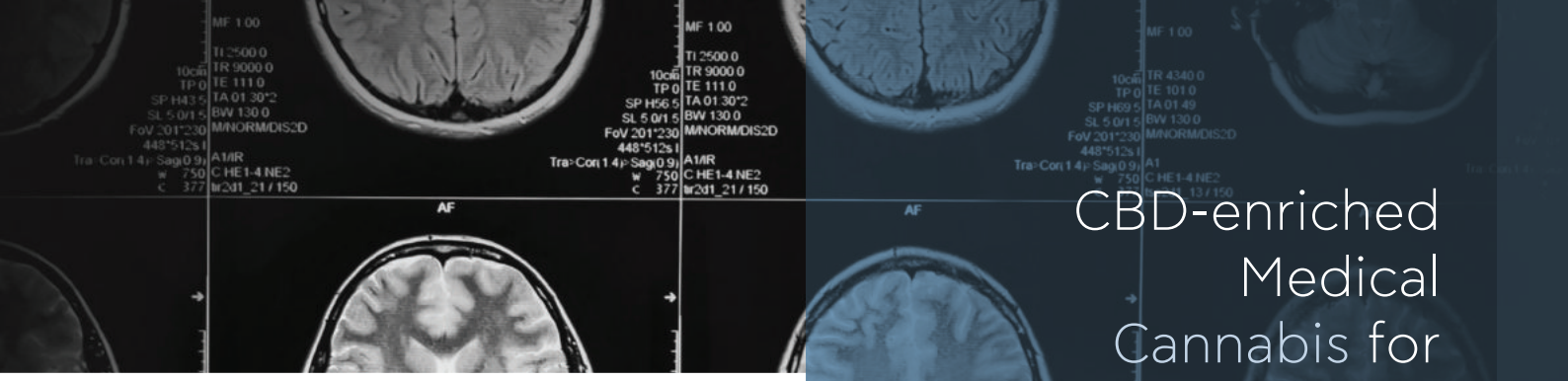

CBD-enriched Medical Cannabis for Intractable Pediatric Epilepsy

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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.

Seizure 2016;35:41-4.

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 anti-epileptic properties, particularly those agents that affect nove receptors.

The two main cannabis ingredients with central nervous system (CNS) activityarepsychoactiveD9-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 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.

MATERIALS AND METHODS

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)

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.

RESULTS

• 5 (6.7%) children discontinued treatment during 10 months of follow-up.

• Overall improvement - CBD treatment had a positive and significant effect on the frequency and intensity of seizures.

• Decrease in seizures - 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.

• Improvement in various aspects - there improvement in behavior and alertness, language, communication, motor skills and sleep.

• Side effects included somnolence, fatigue, gastrointestinal disturbances and irritability leading to withdrawal of cannabis use in 5 patients.

DISCUSSION

CBD-enriched cannabis in the pediatric epilepsy population, thosereports 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 (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 withor 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.

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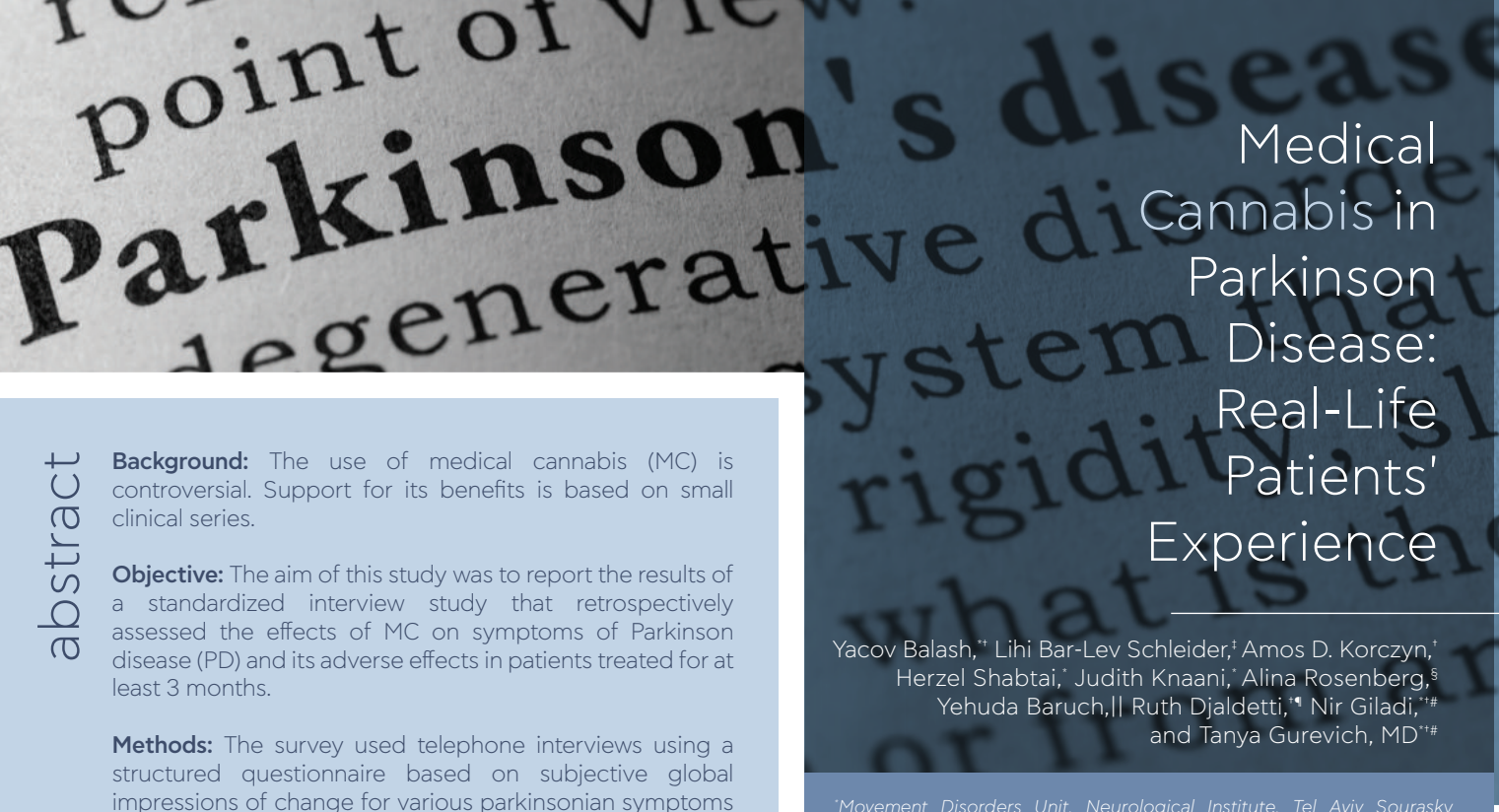

Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience

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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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abstract

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 ± 17.0months, and themean daily dosewas 0.9 ± 0.5 g. The delivery ofMCwas mainly by smoking cigarettes (38 cases, 80.9%). Effect size (r2) 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.

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keywords

- Parkinson disease
- Medical cannabis
- Adverse effects
- Motor symptoms
- Nonmotor symptoms
- Therapeutics

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 patientswith PD and physicians to try "alternative natural treatments," including the attractive option ofmedical 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 therewere no effects of oral cannabis extract on dyskinesias in a randomized, 4-week, double-blinded, crossover study on 17 ypatients 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 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 patientswith PD answered all the questions independently without any help. The data on the responses of patientswith 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 patientswith 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 resyponses.

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).

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%).

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

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 itemin 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%) 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%).

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

EFFECTS OF MC ON PD SYMPTOMS

General Satisfaction and Overall Effectiveness

Most yof 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).y

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 aremental 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.

Table 3

The Effects of at Least 3 Months of MCTreatment onMotor 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	18	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.

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 post treatment abstinence phenomena.[15,16] Another concern with the use of the herbal form of MC relates to various concentrations of themain 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.

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

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 activitywas 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, 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 nowintensively bred and widely cultivated Cannabis sativa.

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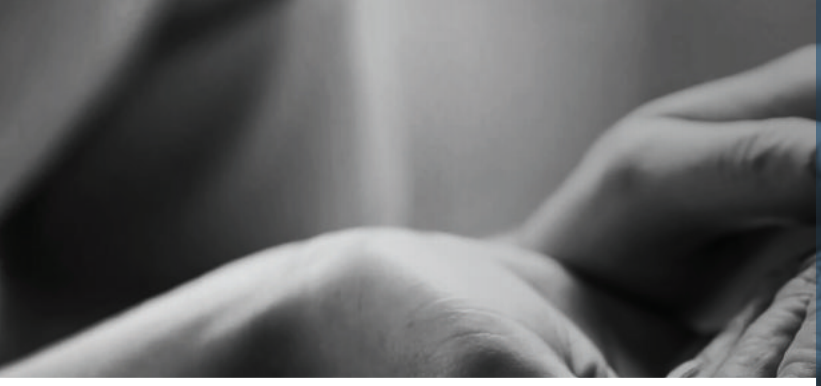

Epidemiological characteristics, safety and efficacy of medical Cannabis in the elderly

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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 evidencebased data, including data from double-blind randomized-controlled trials, in this special population is imperative.

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keywords

- Medical cannabis
- Medical marijuana
- Elderly
- Aged
- Opioids

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 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.

MATERIALS AND METHODS

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.

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.

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.y

PD Status Before MC Treatment

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 x2-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.

RESULTS

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).

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%).

Figure 1

Flow chart for the selection of the study population.

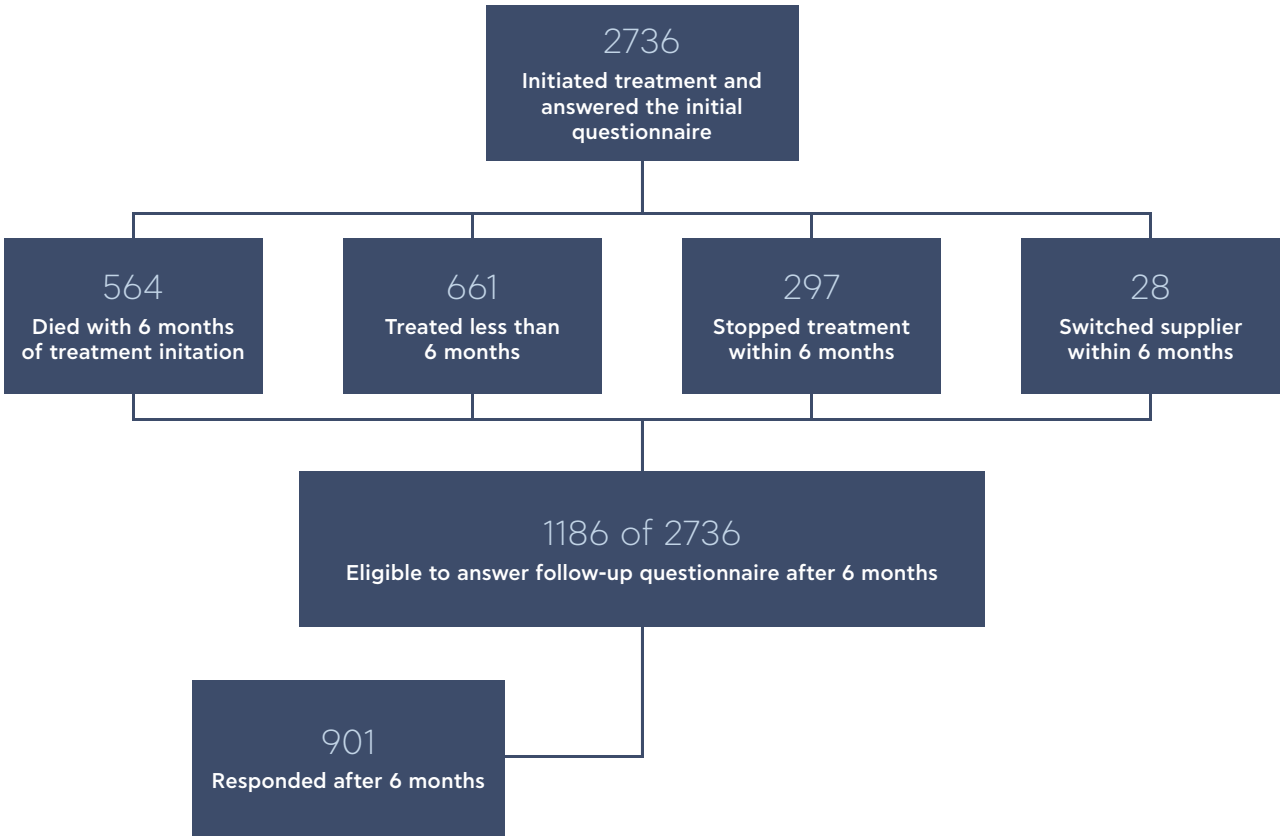


Table 1

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.

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 ($p < .001$).

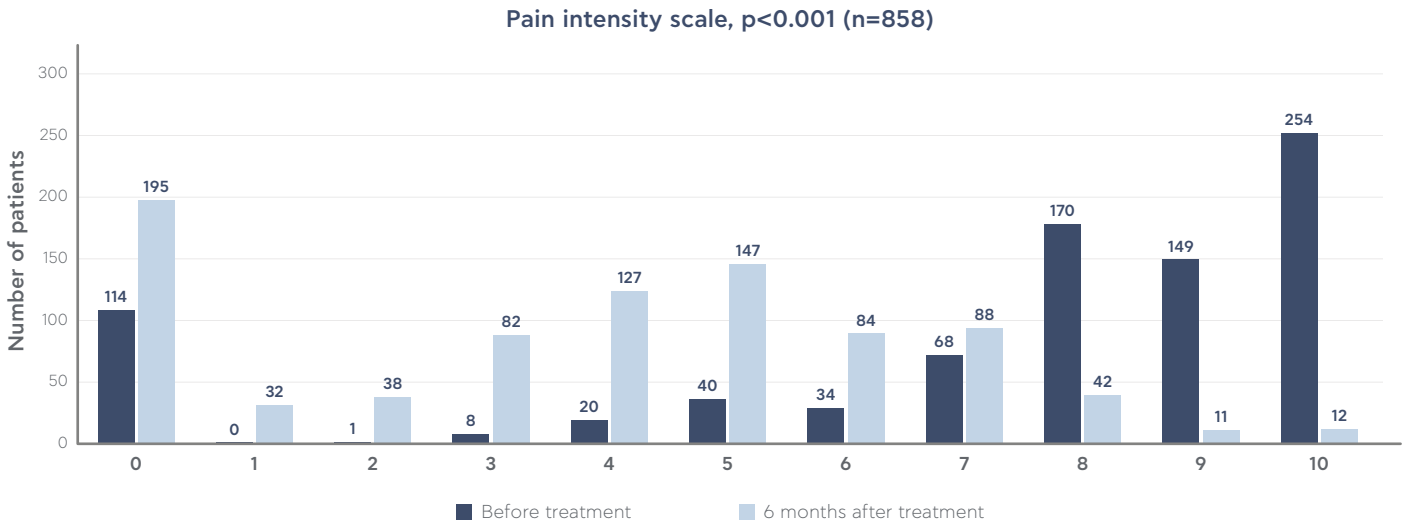
The general assessment of quality of life was improved with the treatment. At baseline, 540 (79.3% of respondents) defined their quality of life as either bad or very bad, while after the treatment, 505 (58.6%) defined their quality of life as either good or very good ($p < .001$, Fig. 3).

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.

Figure 2

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



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], $p < .001$).

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.

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.

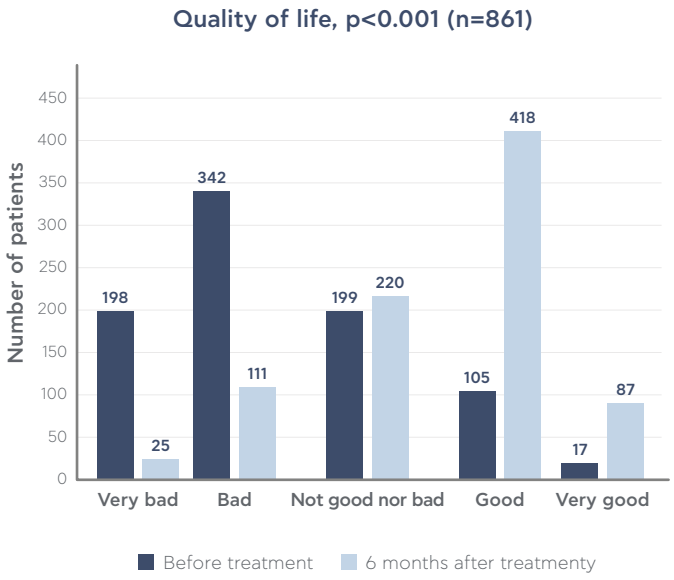
Cohort characteristics

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 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 selftreated 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.

Figure 3

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



Cohort characteristics

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]. 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].

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].

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%)

Cannabis safety

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.

Figure 4

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

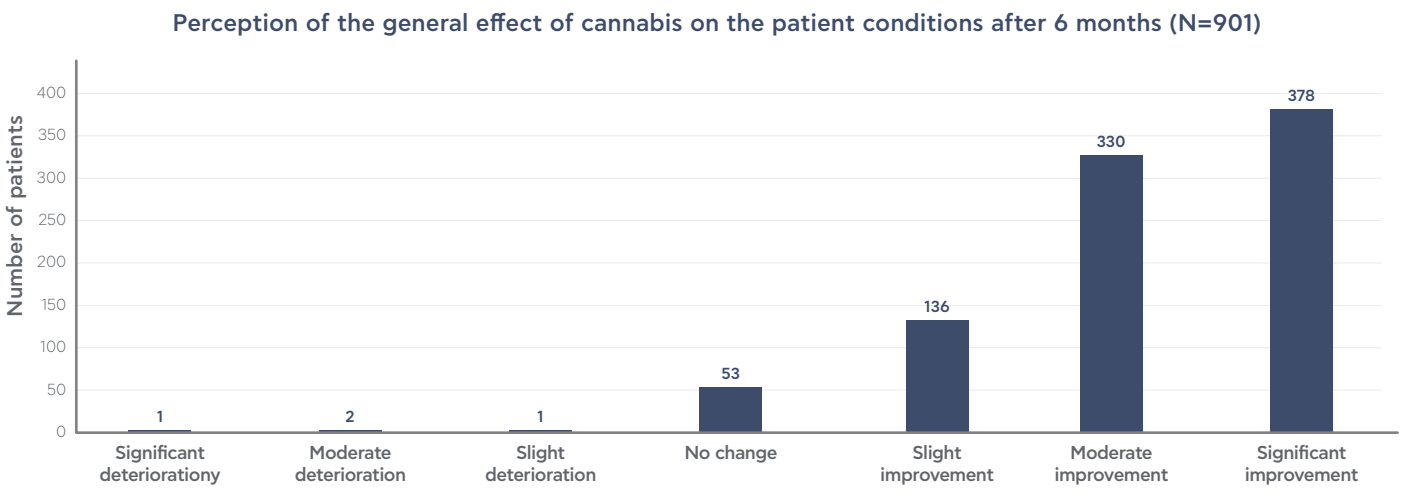


Table 4

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 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.

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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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.So/4s)t opped 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.

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keywords

- Cancer
- Medical cannabis
- Pain

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.

METHODS

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.

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.

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).

RESULTS

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).

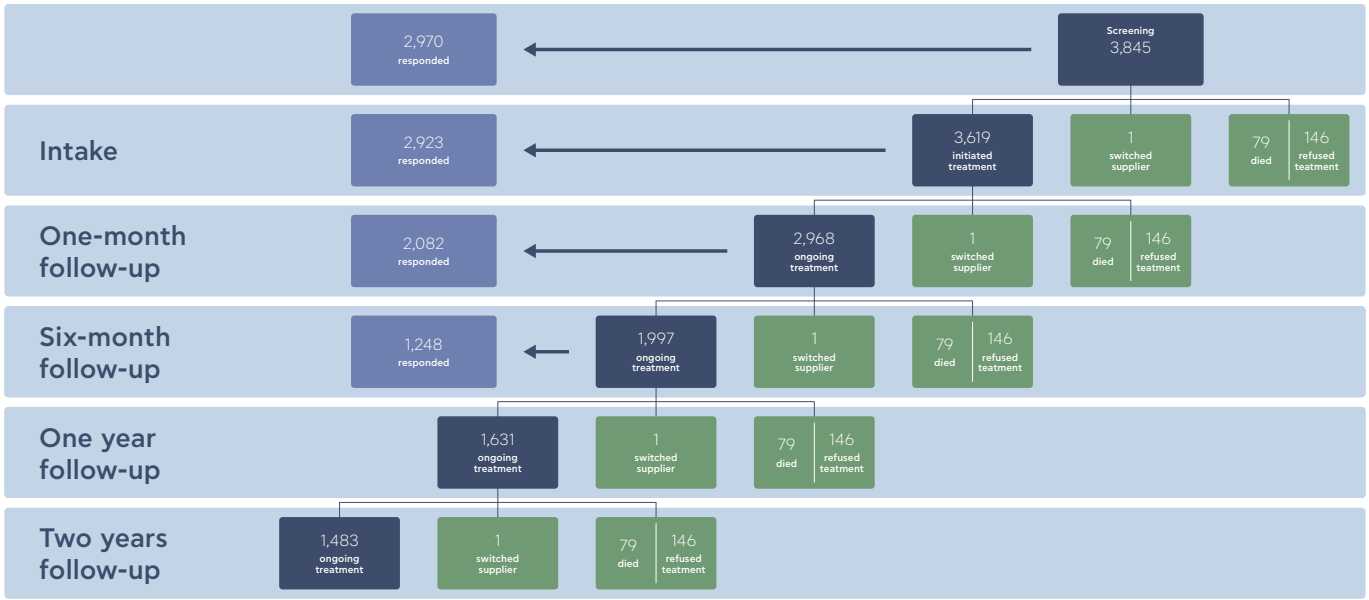
Table 1

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 MALIGNACY	
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)

Figure 1

The study population in the five follow-up periods.



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 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.

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%).

Follow-up, six months

At six months, of the 2968 patients that were assessed in the onemonth 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.

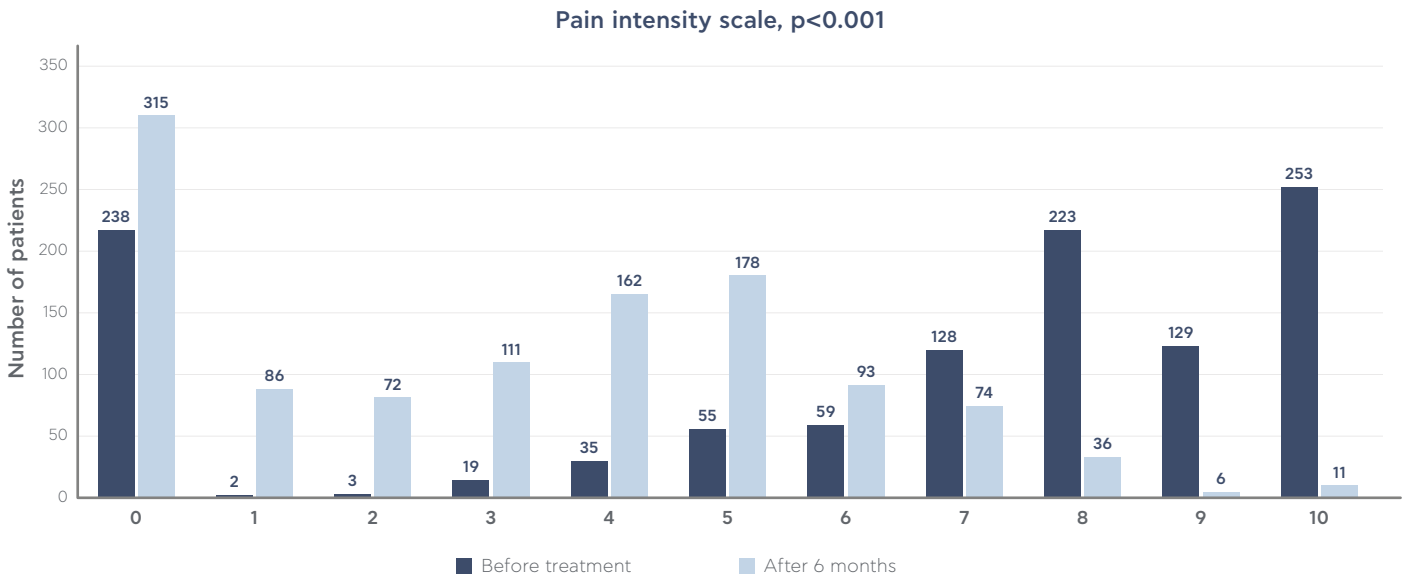
Pain intensity and quality of life were assessed at six months in 1144 and 1165 patients respectively. Prior to treatment initiation 52.9% of patients reported their pain to be in the interval of 8 to 10, while only 4.6% reported this intensity after six months of treatment ($p < 0.001$, Fig. 2). Similarly,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

Figure 2

Assessment of pain intensity. Pain intensity was assessed on 0–10 scale, before and after six months of cannabis therapy.



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 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.

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).

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. 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.

Table 3

	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

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.

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].

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

Opioids still constitute a central role in the management of moderateto-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 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].

Drugs consumption

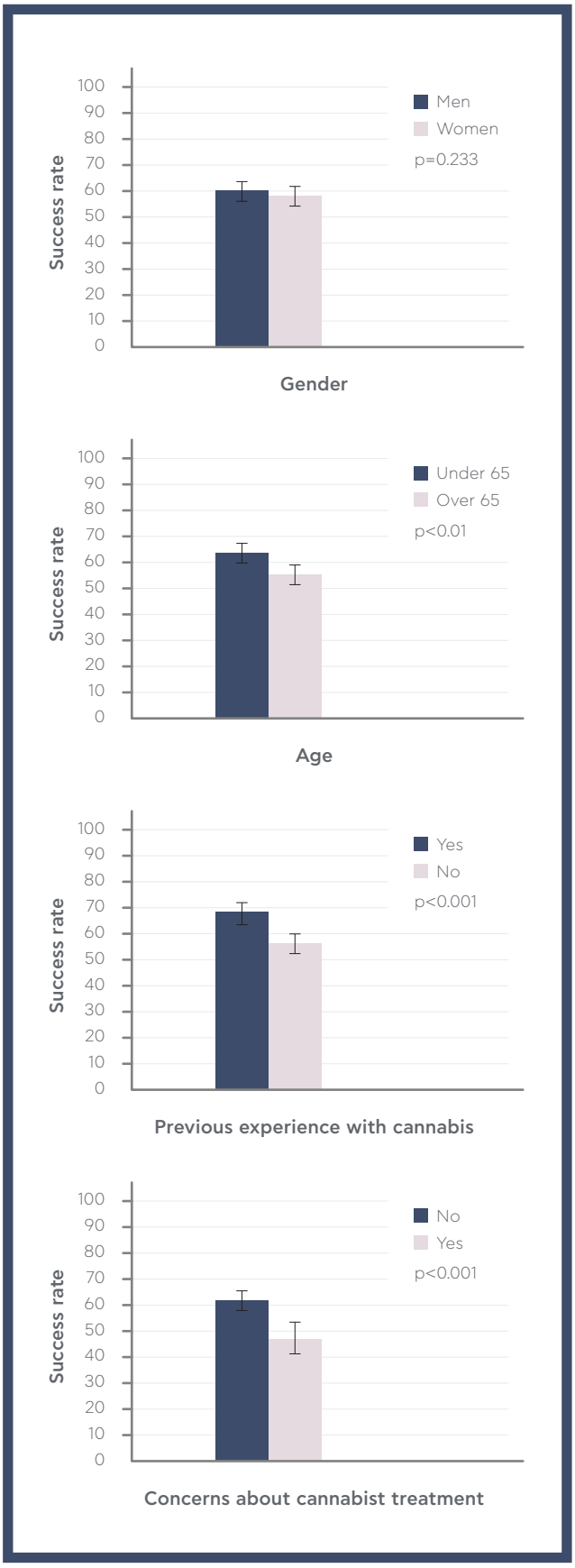
Patients using cannabis report a decrease in the consumption of pain medication in general [21] and a reduction of opioids intake in particular [22,23]. In the current sample, 1013 patients took together 3982 regularly used drugs and over a third of the patients reported a decreased in the drugs consumed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

Table 4

	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)

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.

Figure 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 effectsy

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.

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.

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

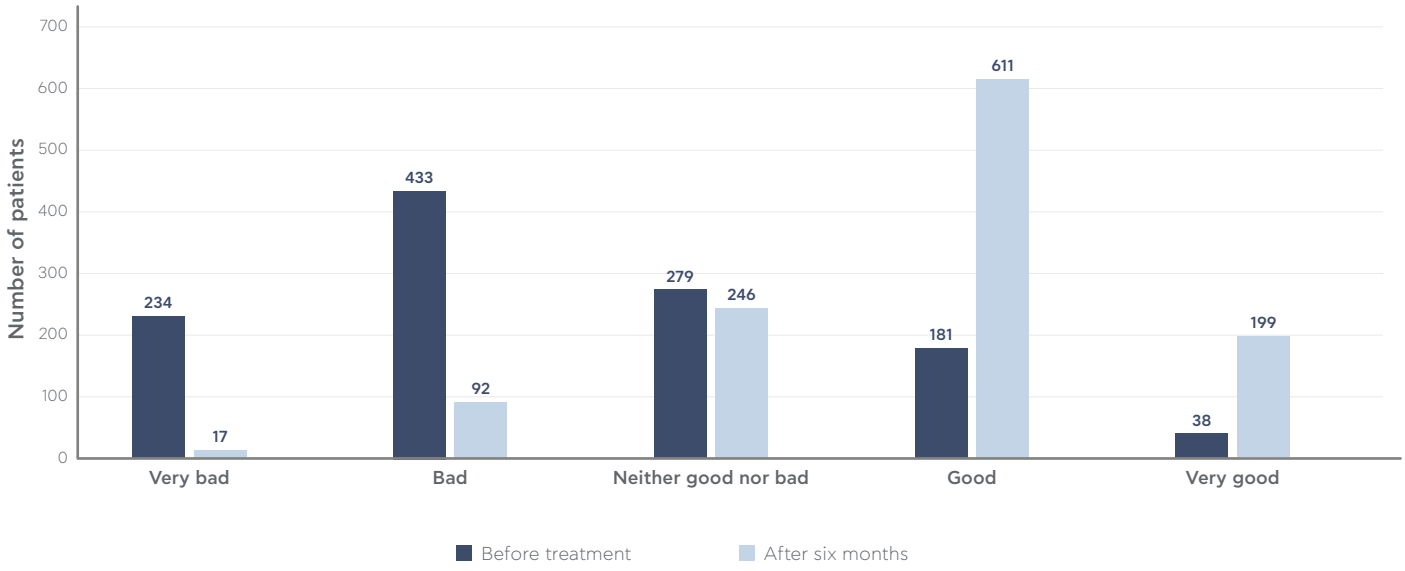
	Total responses, No. (%)	Median disease duration (IQR)
Hypertension	429 (14.4)	10 (5–15)
Diabetes	326 (11.0)	8 (4–15)
Ischemic heart disease	215 (7.2)	8 (3–15)
Nonspecific pain	146 (4.9)	3 (1–7)
Osteoporosis	57 (1.9)	5 (3–13.5)
Spinal disk herniation	52 (1.8)	10 (4.5–14)
Hypertriglyceridemia	52 (1.8)	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 month follow-up		
		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 ASSESMENT

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



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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% d-9-tetrahydrocannabinol (THC) 20:1 group, the other with 0.83% THC 6:1 group. Patients aged 1 to 17 years (n ¼ 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.

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keywords

- Dystonia
- Spasticity
- Movement disorders
- Cerebral palsy
- Cannabis
- CBD
- THC

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. Cannabinoidbased 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 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 andmay 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 g-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, nonendocannabinoid-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) questionnaire27 (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

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)	213 (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	N	NA	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.

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.

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 spasticity.[15] The dosages necessary to achieve a

Table 3 Outcome Measures Scores.[a]

	Visit 1	Visit 2	Visit 3	Visit 4	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.

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

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, noncannabis-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 womc.

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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, Δ9-THClow 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.

Abbreviations:

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

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keywords

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

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; 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 Δ9-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 Δ9-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.

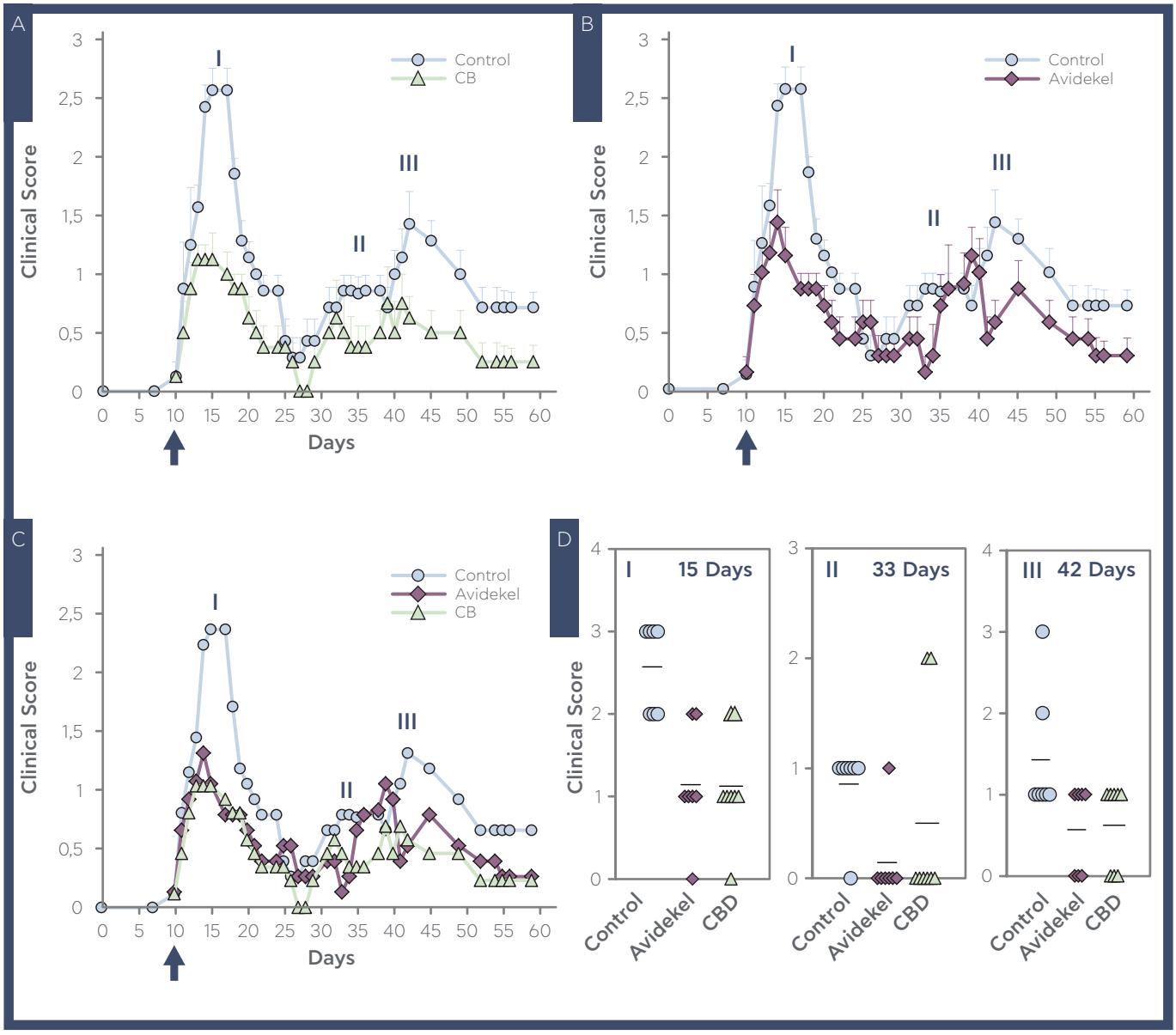
Neurological assessment

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.y

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.

Figure 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

RESULTS

Purified CBD and Avidekel extracts alleviate EAE symptoms

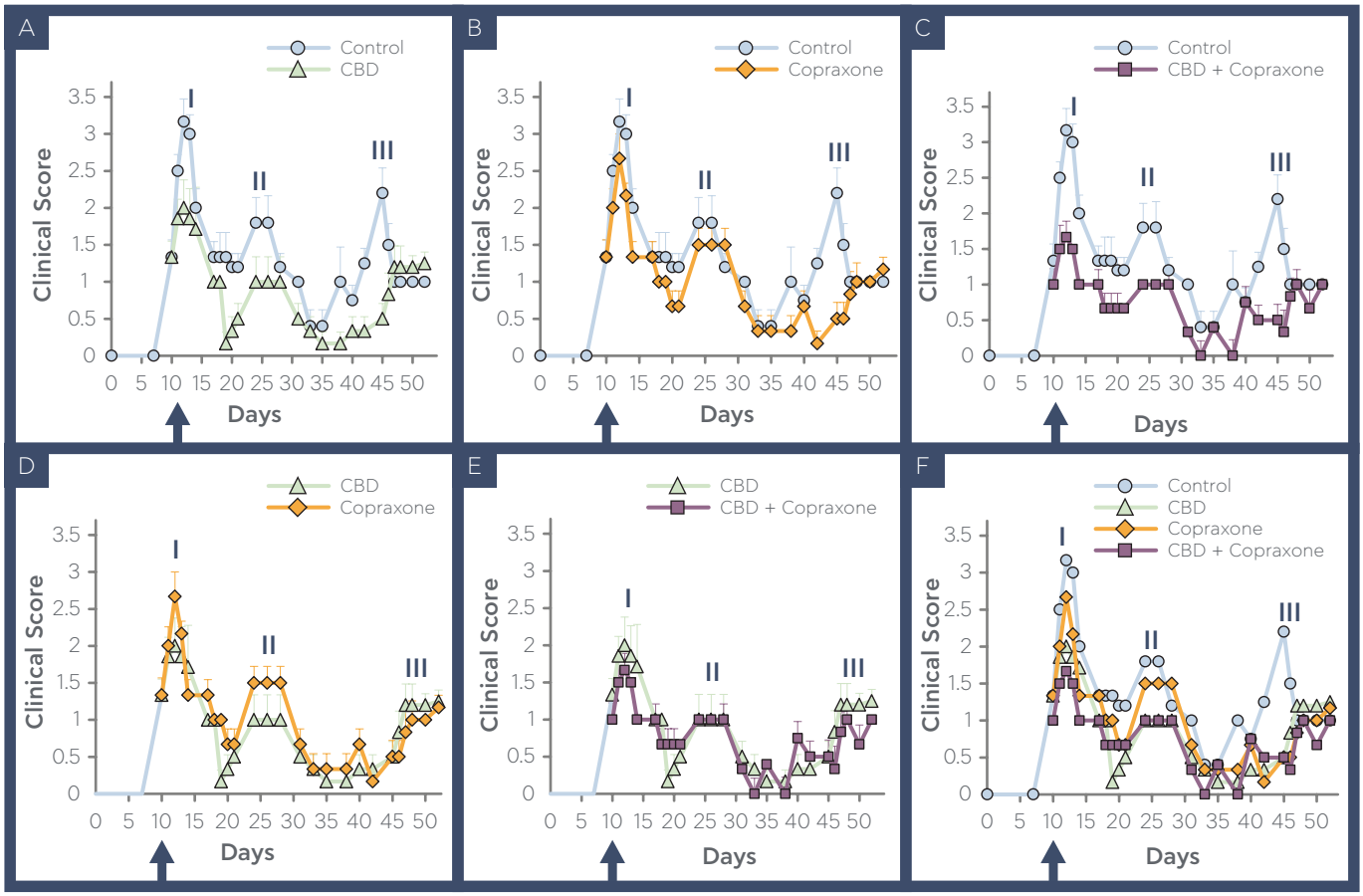
Experimental autoimmune encephalomyelitis (EAE) was induced in SJL/J mice by subcutaneous injection of $PLP_{139-151}$ emulsified in CFA followed by two intraperitoneal injections of pertussis toxin at days 0 and 2. The PLP-induced EAE model caused three distinct disease phases (I,II, III) (Fig. 1), 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 ± 1.8% ($p < 0.001$) and Avidekel extracts by 54.3 ± 5.2% ($p < 0.001$) at the average. During days 31–35 of phase II, CBD suppressed the symptoms by 39.1 ± 8.1% ($p < 0.005$) and Avidekel extracts by 48.9 ± 11.9% ($p < 0.01$) at the average. During days 41–49 of phase III, CBD suppressed the symptoms by 50.4 ± 5.8% ($p < 0.001$) and Avidekel extracts by 49.7 ± 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

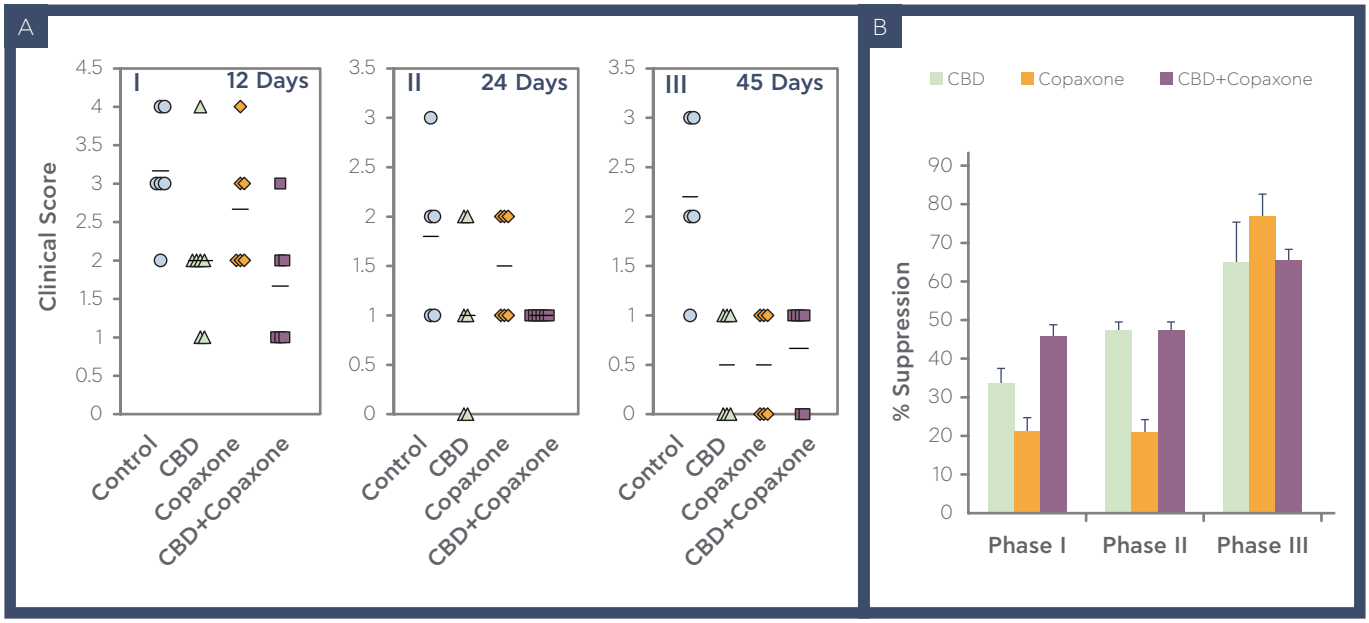
We next compared the efficacy of CBD and Avidekel extracts with that of Copaxone to suppress EAE symptoms. We observed that CBD at 5 mg/kg and Avidekel at 50 mg/kg were more efficient than the standard Copaxone dosage of 50 mg/kg during relapse phases I and II ($p < 0.05$), but showed similar suppression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

Figure 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

Figure 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

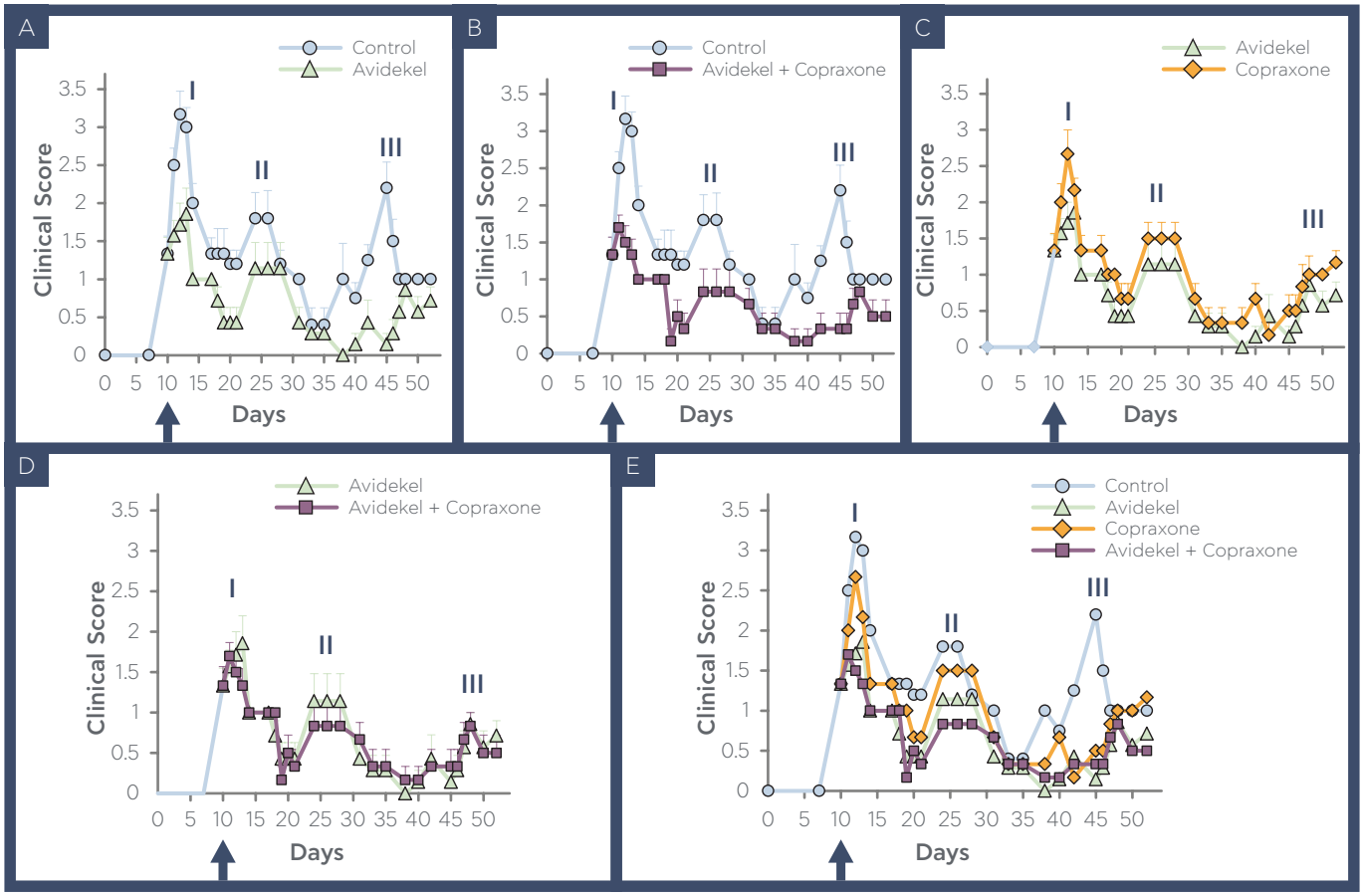
During days 42–46 of phase III, all three drugs showed strong suppression. During this phase, CBD suppressed the symptoms by 65.0 ± 10.3% ($p < 0.0001$), Avidekel extracts by 80.0 ± 8.0% ($p < 0.0001$), and Copaxone by 76.8 ± 5.7% ($p < 0.0001$) at the average (Figs. 2, 3, 4, 5). Concurrent administration 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 yMS 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 Δ9-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 Δ9-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 Δ9-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 Δ9-THC (1%) (Gallily et al. 2015). In contrast to 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 antinociceptive 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



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

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) (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.

Acknowledgment

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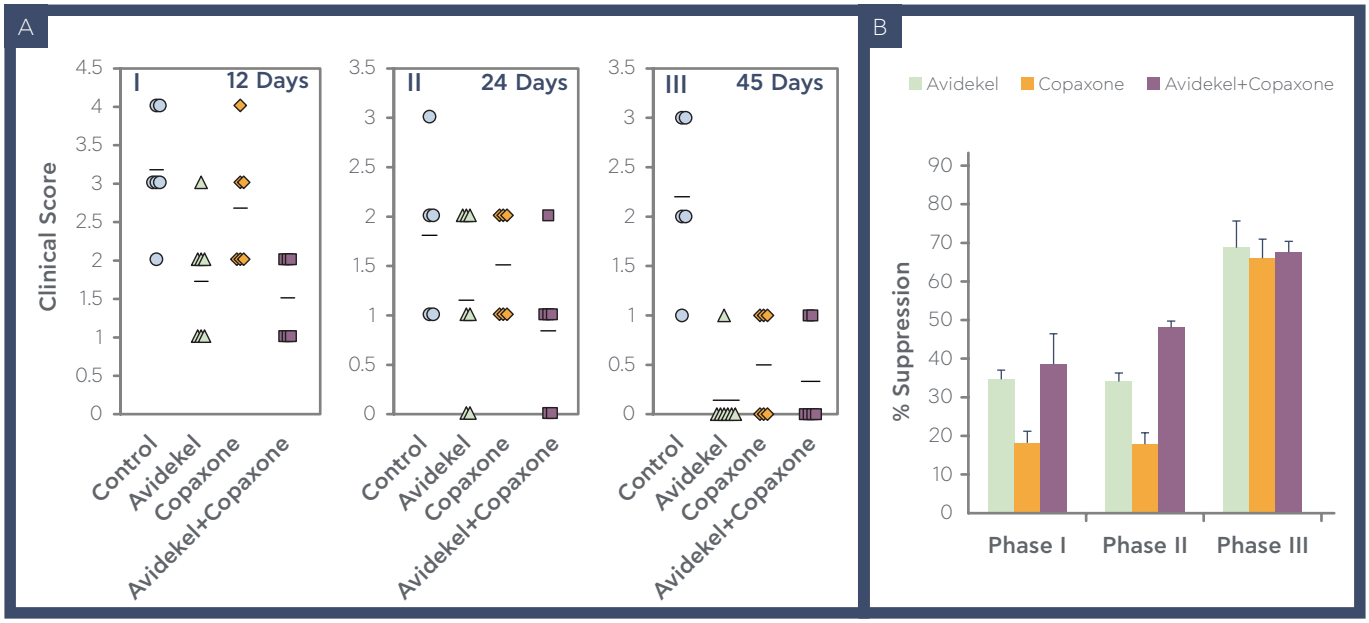
Figure 5



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

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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.

Parkinsonism Relat Disord. 2019 Apr;61:211-213.

keywords

- Medical cannabis
- Gilles de la Tourette syndrome

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 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.

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).

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.

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.

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.

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.

LIMITATION

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.

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

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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.

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

MATERIALS AND 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 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.

Table 4

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%)

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

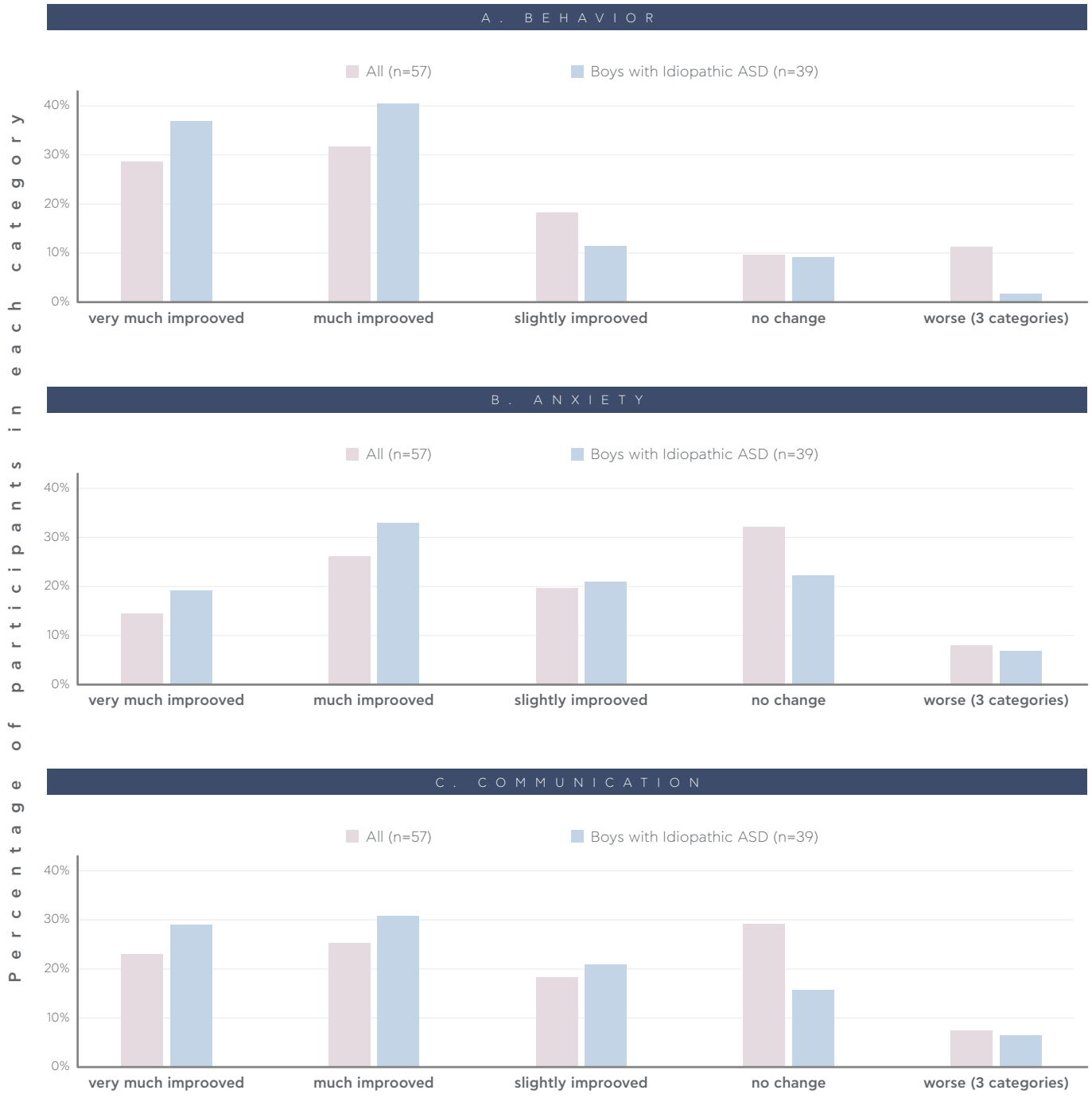
To our knowledge, this is the first report on the impact of CBD-rich medical cannabis in children with ASD. Specifically, following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients. Moreover, 16 children (33%) received less medications or lower 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).

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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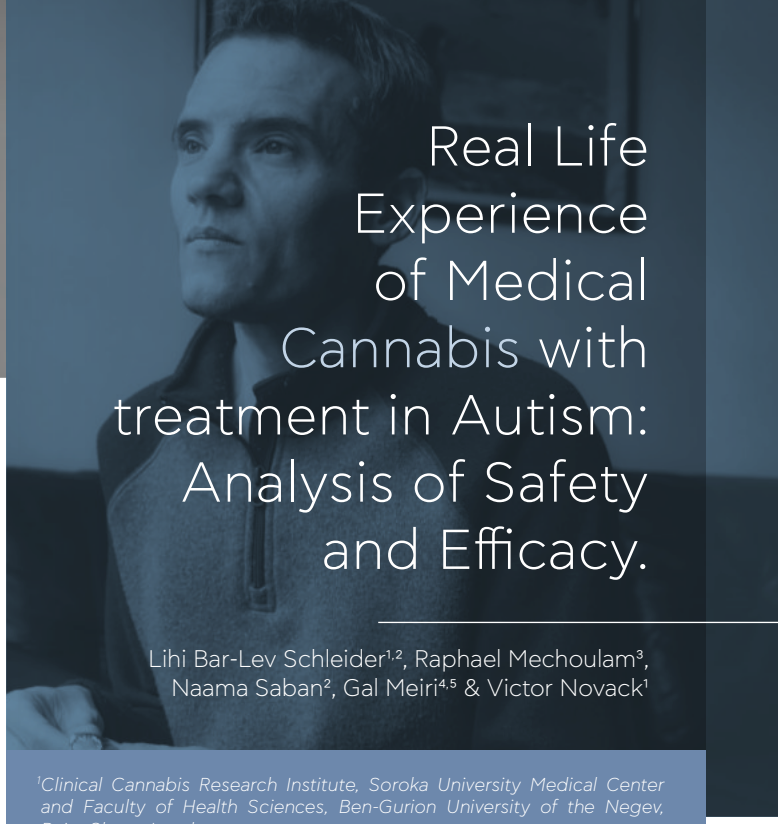

Real Life Experience of Medical Cannabis with treatment in Autism: Analysis of Safety and Efficacy.

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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.

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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 activity8. 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.

Table 1

Demographic and clinical characteristics of patients at intake.

	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)

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 (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%).

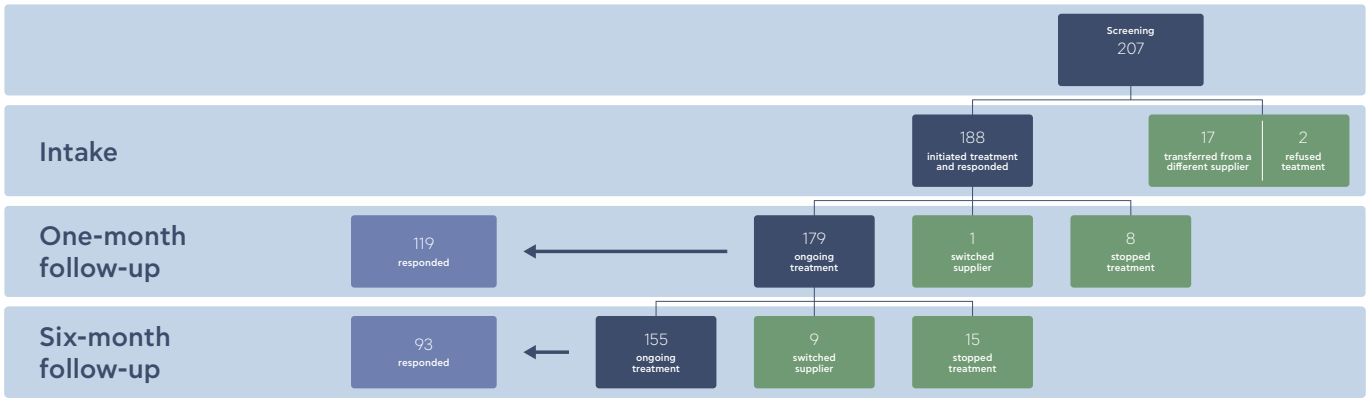
Table 2

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.

	Intake prevalence Total (188)	Change at six months		
		Symptom disappeared	Improvement	No change or deterioration
Opioids, n (%)	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)	-

Figure 1

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



Follow-up, six months

After six ymonths, 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.

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.

Medication family	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 4

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

Medication family	Intake	Change at six month follow-up				
	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

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.

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 importantfor 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

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Author Contributions

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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Declaration of Conflicting Interests

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

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

Supplementary information accompanies this paper at https://doi.org/10.1038/s41598-018-37570-y.

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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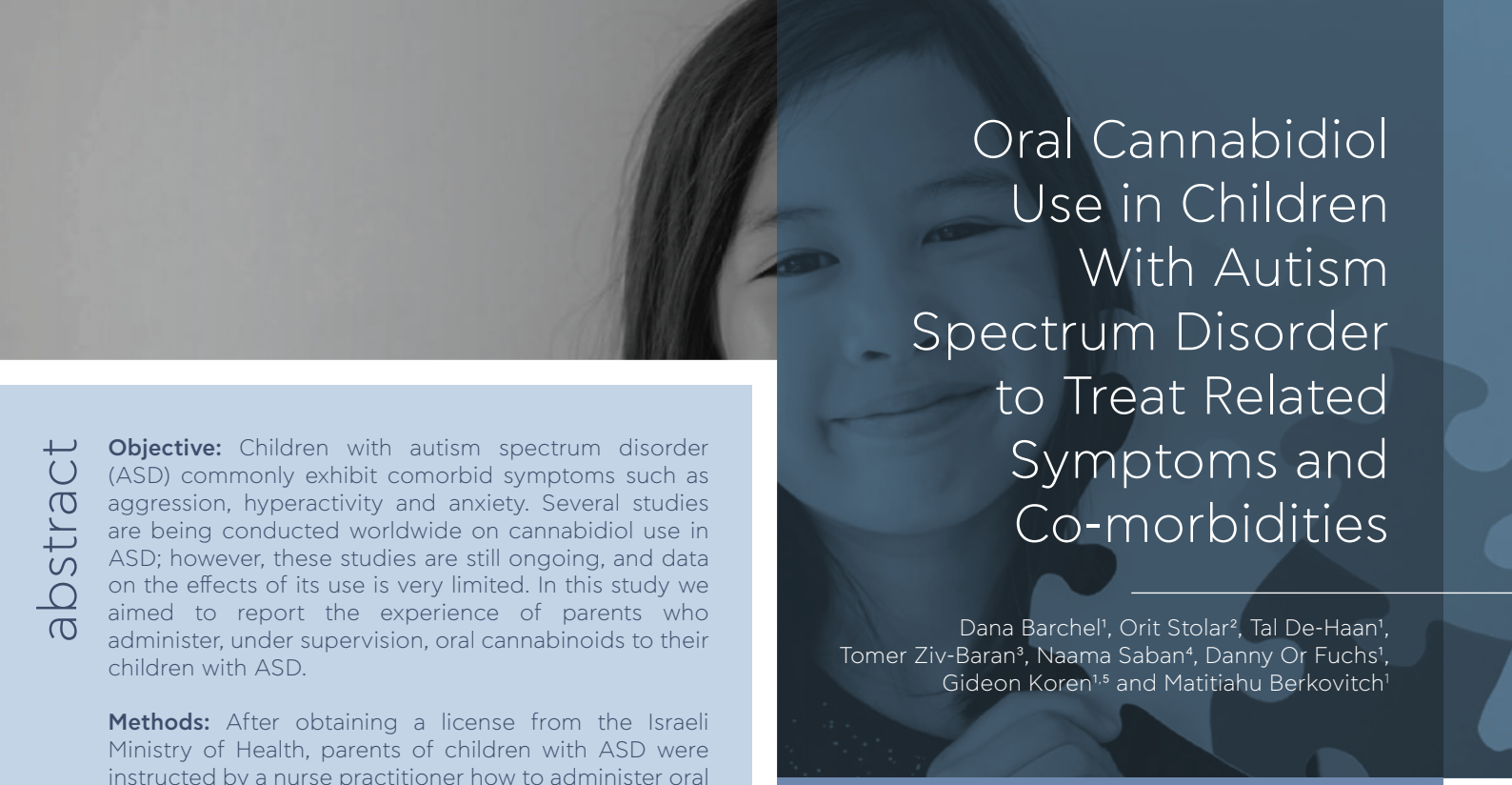

Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities

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abstract

Objective: Children with autism spectrum disorder (ASD) commonly exhibit comorbid symptoms such as aggression, hyperactivity and anxiety. Several studies are being conducted worldwide on cannabidiol use in ASD; however, these studies are still ongoing, and data on the effects of its use is very limited. In this study we aimed to report the experience of parents who administer, under supervision, oral cannabinoids to their children with ASD.

Methods: After obtaining a license from the Israeli Ministry of Health, parents of children with ASD were instructed by a nurse practitioner how to administer oral drops of cannabidiol oil. Information on comorbid symptoms and safety was prospectively recorded biweekly during follow-up interviews. An independent group of specialists analyzed these data for changes in ASD symptoms and drug safety.

Results: 53 children at a median age of 11 (4–22) year received cannabidiol for a median duration of 66 days (30–588). Self-injury and rage attacks (n = 34) improved in 67.6% and worsened in 8.8%. Hyperactivity symptoms (n = 38) improved in 68.4%, did not change in 28.9% and worsened in 2.6%. Sleep problems (n = 21) improved in 71.4% and worsened in 4.7%. Anxiety (n = 17) improved in 47.1% and worsened in 23.5%. Adverse effects, mostly somnolence and change in appetite were mild.

Conclusion: Parents' reports suggest that cannabidiol may improve ASD comorbidity symptoms; however, the long-term effects should be evaluated in large scale studies.

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keywords

- Cannabidiol
- Autism spectrum disorder
- ASD comorbid symptoms
- ASD treatment
- Pediatrics
- Clinical research trial
- THC – tetrahydrocannabinol

INTRODUCTION

Children with autism spectrum disorder (ASD) commonly exhibit co-morbid symptoms of hyperactivity, self-injury, aggressiveness, restlessness, anxiety and sleep disorders (Mannion and Leader, 2013; South et al., 2017). Conventional medical treatment includes various psychotropic medications such as atypical anti psychotics, selective serotonin reuptake inhibitors (SSRI's), stimulants and anxiolytics (Canitano and Scandurra, 2008;Stachnik and Gabay, 2010; Wink et al., 2010; Hurwitz et al., 2012). Several studies are being conducted worldwide on the use of cannabidiol in children with ASD to treat comorbid symptoms. However, there is limited published data on the use of cannabinoids in this population (Kurz and Blaas, 2010; Kuester et al., 2017). A recent review has suggested cannabidiol as a candidate for treatment of ASD (Poleget al., 2019). Cannabis contains numerous chemically active compounds, including 19-tetrahydrocannabinol (19-THC), cannabidiol (CBD) and terpenoids (Russo, 2011). 19-THC activates the endocannabinoid system in the central nervous system, affecting appetite, anxiety, cognitive function and memory (Palmieri et al., 2017). In contrast, CBD is anxiolytic, anti-inflammatory, antiemetic and antipsychotic (Detyniecki and Hirsch, 2015). Studies in mice models of ASD have demonstrated the involvement of the endocannabinoid system in the pathogenesis of ASD symptoms (Foldy et al., 2013; Wei et al., 2015).

In this study we aimed to record the experience of parents who administered under supervision cannabidiol to their children with ASD.

MATERIALS AND METHODS

Included were children from all over Israel diagnosed with ASD based on DSM IV (American Psychiatric Association, 2000) or DSM V (American Psychiatric Association, 2013) criteria, between three and 25 years of age, who were followed up for at least 30 days after commencement of cannabidiol treatment.

An independent group of specialists including a pediatric neurologist specialized in ASD, clinical pharmacologists and pharmacists objectively analyzed the data recorded during the follow up to assess symptom response and adverse effects. Four ASD comorbidity symptoms were evaluated: (a) hyperactivity symptoms (b) sleep problems, (c) self-injury and (d) anxiety.

For each comorbid symptom, the evaluations marked improvement, no change, or worsening of symptoms, as compared to the baseline, according to the parent's reports. An overall change was defined based on the summation of all parent's reports. Children were recruited from a registry of patients with authorization to obtain cannabidiol (Tikun Olam Inc., Israel).

Parents received a license for pediatric use of CBD from the Israeli Ministry of Health. The cannabinoid oil solution was prepared by "Tikun Olam" company, which is an approved supplier, at a concentration of 30% and 1:20 ratio of cannabidiol (CBD) and 19-tetrahydrocannabinol (THC). Quality assurance of the cannabidiol concentrations are routinely performed by HPLC on an Ultima 3000 Thermo Dionex instrument. Recommended daily dose of CBD was 16 mg/kg (maximal daily dose 600 mg), and for THC- daily dose of 0.8 mg/kg (maximal daily dose of 40 mg).

For all participating children this was their first experience with cannabidiol and no other cannabinoids were used before this study. During the first meeting, parents were instructed by an experienced nurse practitioner how to administer the preparation. Thereafter, a biweekly follow-up telephone interview was conducted with the parents. During the telephone interview, parents were asked on the status of the various ASD comorbid symptoms (graded as improvement, no change, worsening), emerging adverse effects and medications that had been used.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (Food Drug Administration, 2004). The change in each comorbid symptom in the study cohort was compared to published data using conventional treatment. For this purpose we used the following values: Hyperactivity symptoms- Improvement was considered as 80% (Handen et al., 2000), for self-injury an improvement was considered as 82% (Richards et al., 2016), for sleep problems an improvement was considered as 60% (Devnani and Hegde, 2015), and improvement in anxiety symptoms was considered as 64% (Moore et al., 2004).

The Study Was Not Financially Supported by Tikun Olam Company The study was approved by the local research ethics committee. The need for written parental consent for this study was waived by the Assaf Harofeh Medical Center research ethics committee.

STATISTICAL ANALYSIS

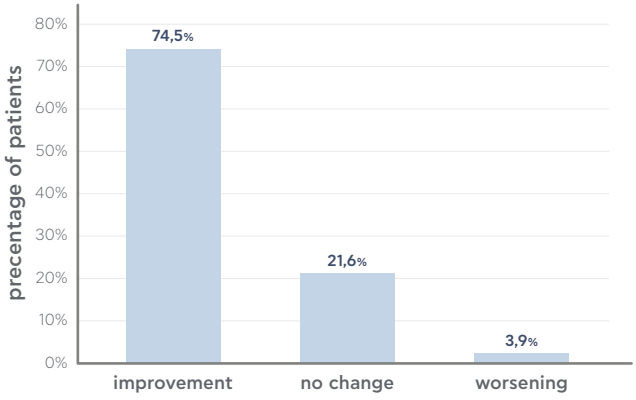
Categorical variables such as gender, related ASD comorbid symptoms, were described using frequency and percentage. Continuous variables such as age and daily CBD dose were evaluated for normal distribution using histograms and Q–Q plots. Normally distributed continuous variables were described as mean and standard deviation and skewed variables were expressed as median and interquartile range or range. Length of follow-up was described using a reverse censoring method.

A comparison of improvement in symptoms between CBD treatment and conventional treatment was analyzed using binomial test. All statistical analyses were performed using SPSS (IBM Corp 2016. IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.).

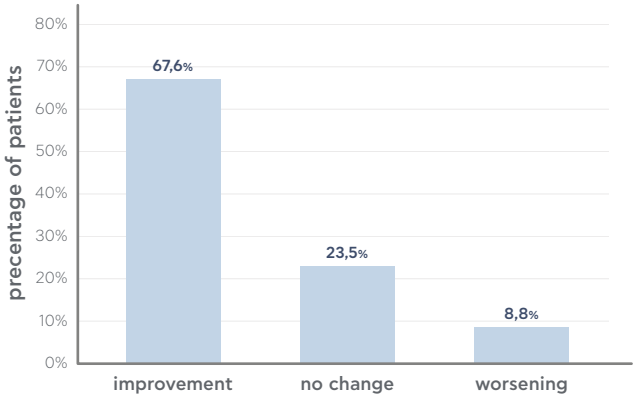
RESULTS

• 2 patients (3.7%) discontinued treatment during the study (lasting 66 days on average) and another 2 patients continued cannabis treatment with another provider.

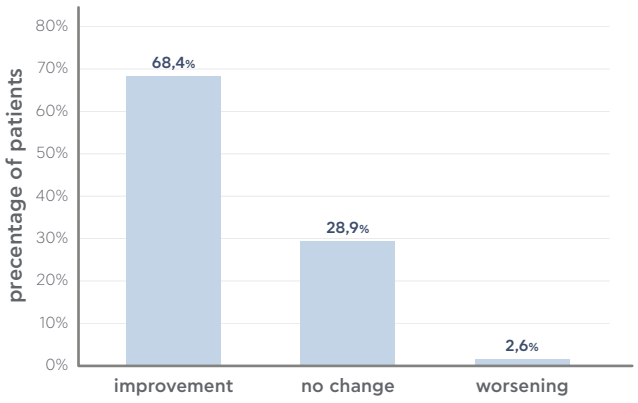
• Overall improvement - An improvement in ASD symptoms was reported in 74.5% of patients.



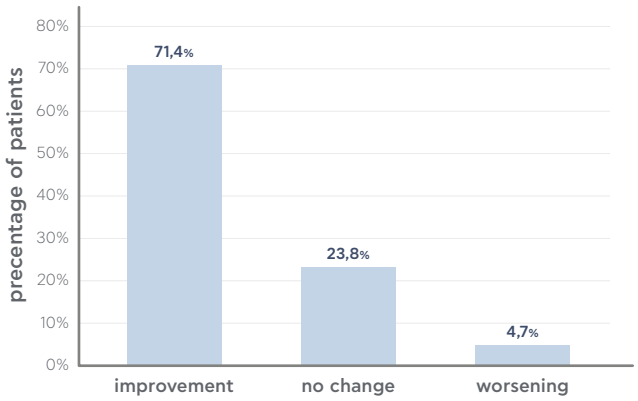
• Decreased self-injury and rage attacks - Self-injury and rage attacks improved in 67.6% of patients.



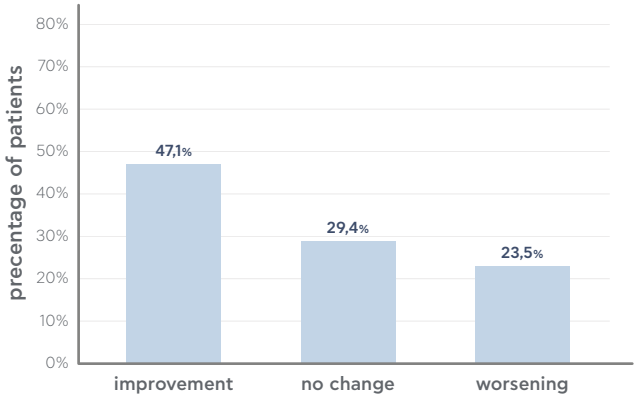
• Decreased hyperactivity - Hyperactivity symptoms improved in 68.4%.



• Improved sleep - Sleep problems improved in 71.4%.



• Decreased anxiety - Anxiety improved in 47.1%.



• Side effects included drowsiness, decreased appetite, and increased appetite.

DISCUSSION

In this study, based on recorded data reported by parents of children with ASD, in all four ASD comorbidity symptoms described, parents have reported an overall improvement.

This is one of the first publications on the use of cannabidiol to treat comorbid symptoms of patients with ASD. There are studies which are being conducted these days in several countries such as the United States and Israel, to examine the efficacy and safety of cannabidiol in this population; however, these studies are still ongoing.

The incidence of hyperactivity symptoms in the ASD population ranges between 41 and 78% (Sturm et al., 2004; Murray, 2010). In our study there was an overall improvement of 68.4% [95%CI (51.4–82.5%)] in hyperactivity symptoms as reported by the parents. Conventional treatments for hyperactivity include treatment with methylphenidate. In one study, methylphenidate improved symptoms in 80% (Handen et al., 2000). Comparing the overall improvement in hyperactivity symptoms in children treated with cannabidiol to that achieved with methylphenidate, non-inferiority of cannabidiol was observed (p = 0.125).

Self-injurious behavior is common in ASD, with incidence ranging between 35 and 60% (Richards et al., 2016). Our study presented an overall improvement of 67.6% [95%CI (49.5–82.6%)] and worsening of 4.9% [95%CI (1.9–23.7%)] in these symptoms. Currently, atypical antipsychotics are recommended for the treatment serious behavioral symptoms and self-injury (Marcus et al., 2009). Aripiprazole improves symptoms in 82% (any improvement) while 4% presented worsening in symptoms (Marcus et al., 2009). Comparing the overall improvement and worsening in self-injury symptoms in children treated with cannabidiol in our study to that described in the literature with aripiprazole, non-inferiority of cannabidiol was observed (p = 0.063, p = 0.307, respectively).

Sleep problems in children and adolescents with ASD range between 40 and 80% (Devnani and Hegde, 2015). Conventional treatment with melatonin improved sleep problems in 60% of the patients (Devnani and Hegde, 2015). In our present study cannabidiol was reported to be effective in 71.4% [95%CI (47.8–88.7%)] of the patients in improving sleep problems. Comparing the overall improvement in sleep problems in children treated with cannabidiol to that reported in children treated with melatonin, non-inferiority of cannabidiol was observed (p = 0.40).

Anxiety symptoms in children with ASD are common (Sukhodolsky et al., 2008) and are usually controlled with selective serotonin reuptake Inhibitors (SSRI's) treatment in 55–73% (Moore et al., 2004). In our study, reports on 17 patients with these symptoms were recorded and in 47.1% [95%CI (23.0–72.2%)] of the children an improvement of symptoms was reported. It has been suggested that by improving sleep and disruptive behavior, the motivation and the ability to communicate with the family and the caregivers is improved. Comparing the overall improvement in anxiety symptoms in children treated with cannabidiol to that reported in children treated with SSRI's, non-inferiority of cannabidiol was observed (p = 0.232).

Δ9-THC and CBD are substrates and inhibitors of cytochrome P450 enzymatic pathways relevant to the biotransformation of commonly prescribed psychotropic agents (Rong et al., 2018). Δ9-THC is rapidly metabolized by CYP2C9 and CYP3A4 isoenzymes and CBD is metabolized by CYP2C19 and CYP3A4 (Stout and Cimino, 2014). Data suggest minimal induction of CYPs 1A2, 2C9, 2C19, and 3A4 by Δ9-THC and CBD. However, drug–drug interaction should be considered; phenytoin plasma concentration might be increased, even up to toxic range (Rong et al., 2018). Animal studies have demonstrated that the exposure to Δ9-THC may reverse the neurobehavioral effects of risperidone, which may be less effective (Brzozowska et al., 2017). Other potential drug–drug interactions of cannabidiol include SSRI's, tricyclic antidepressant and CNS depressants which may result in toxic levels of these medications (Lindsey et al., 2012). In our study, signs and symptoms of toxicity of these medications were not reported.

Most frequent adverse effects, as reported by the parents, were somnolence and change in appetite (Table (Table3).3). These symptoms were perceived by the parents as related to the treatment with cannabidiol. All adverse effects were reported to be transient and resolved spontaneously. Several studies have demonstrated that the most common adverse effects associated with CBD use in children and adults are somnolence, change in appetite, diarrhea, and weight changes (Devinsky et al., 2016). Case-studies indicate that cannabinoids may induce acute psychosis which is self-limited over time (Shah et al., 2017); however, cannabis is not considered as the only cause for persistent psychotic disorder. More likely it is the interaction of several factors, such as age at onset of cannabis use, childhood abuse, genetic vulnerability.

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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 e ectiveness 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 e ects 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.

Journal of Autism and Developmental Disorders

keywords

- Medical cannabis
- Fibromyalgia
- Quality of life
- Chronic pain

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 forgeneralized 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 e ectiveness and relatively low rate of serious adverse e ects [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 e ect 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 e ectiveness of fibromyalgia patients receiving medical cannabis.

EXPERIMENTAL SECTION

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.

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 e ects; 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 a ects pain, appetite, orientation, and emotions, through CB1 and CB2 receptors. CBD has analgesic, anti-inflammatory, and anti-anxiety e ects 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 e ect, pharmacokinetics, and adverse events. In addition, more than 60 other cannabinoids have been identified, with a variety of clinical e ects (e.g., anti-inflammatory and analgesic e ects) 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 e ect (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 e ect (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 e ect 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, diseaseand medical cannabis-related symptoms, and alteration in the use and dosage of other medications.

Study Outcomes

For safety analysis, we assessed the frequency of medical cannabis-related side e ects, 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 e ects. Patients lost to follow-up were

considered as failures for the purposes of the e ectiveness 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 e ect 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.

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 coe cients, 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.

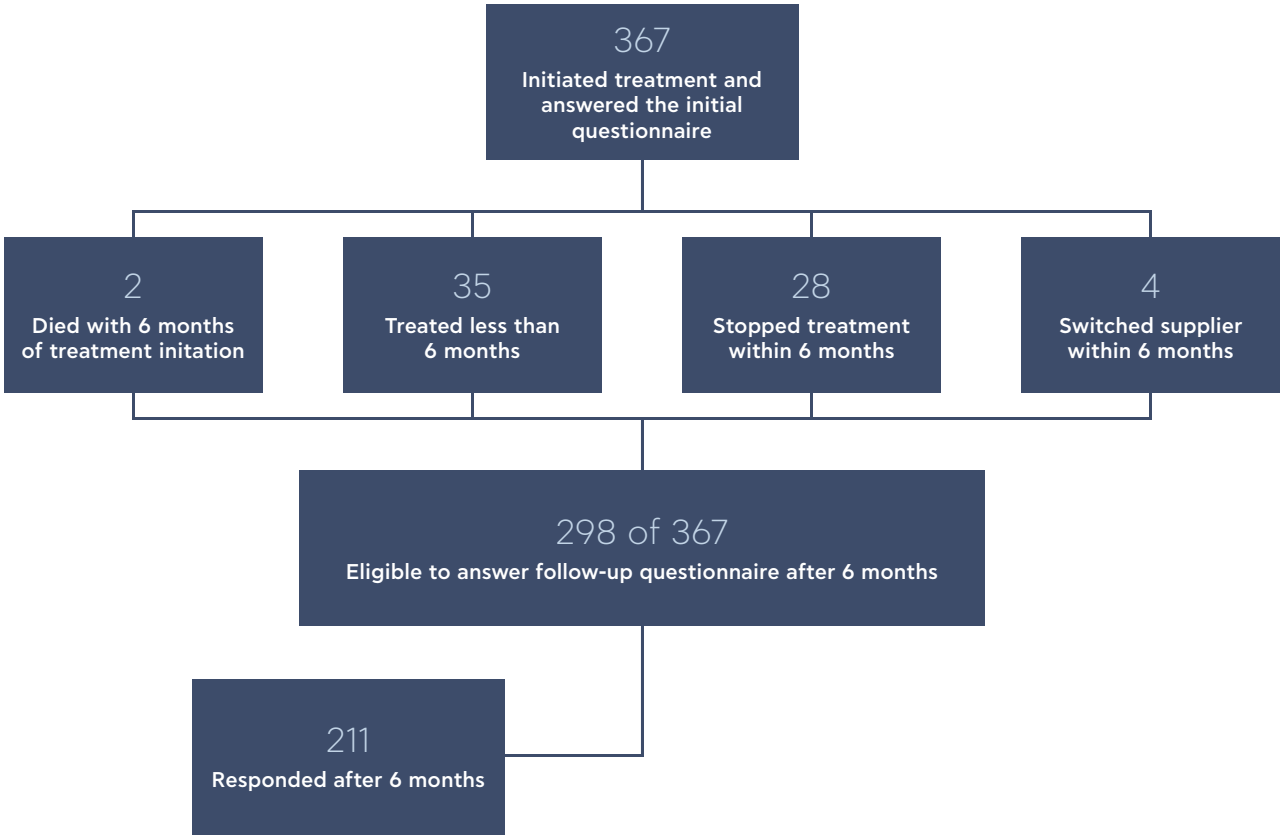
RESULTS

Cohort Characteristics

We identified 367 patients with fibromyalgia who had started the treatment with medical cannabis.

Figure 1

Flow chart of the study population.



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 di erences in baseline characteristics among those who responded to the six months follow-up questionnaire compared to those who did not.

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/m2. Patients had reported previous experience with recreational cannabis in the past in 45.2% of cases.

Table 1

Baseline characteristics of the patient population.

Variable	Number of Patients (N = 367)
Age (years)	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/m2), 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 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.

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 the same THC dosages as the secondary patients (median of 140.0 mg/day for both, $p = 0.95$) and similar CBD dosages (median of 40.0 vs. 28.0 mg/day respectively, $p = 0.52$).

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%).

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%, $p < 0.001$).

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

Figure 2

Perception of the general e ect of cannabis on the patient's condition after six months of treatment.

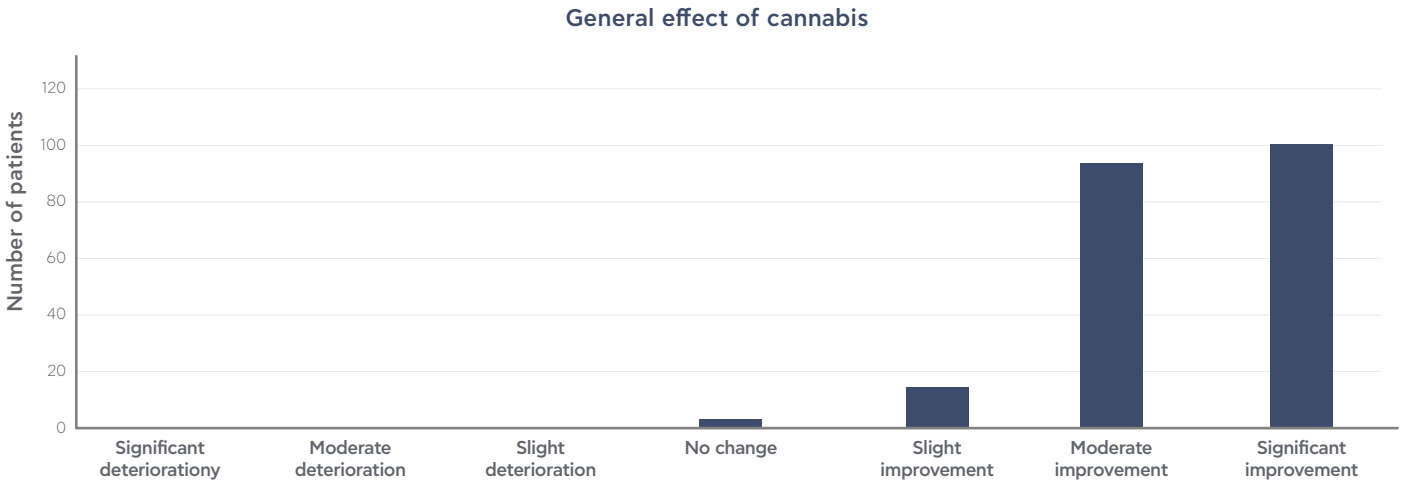


Table 2

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

cannabis (O.R 2.46 95% C.I 1.06–5.74) were associated with treatment success.

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 ($p < 0.001$).

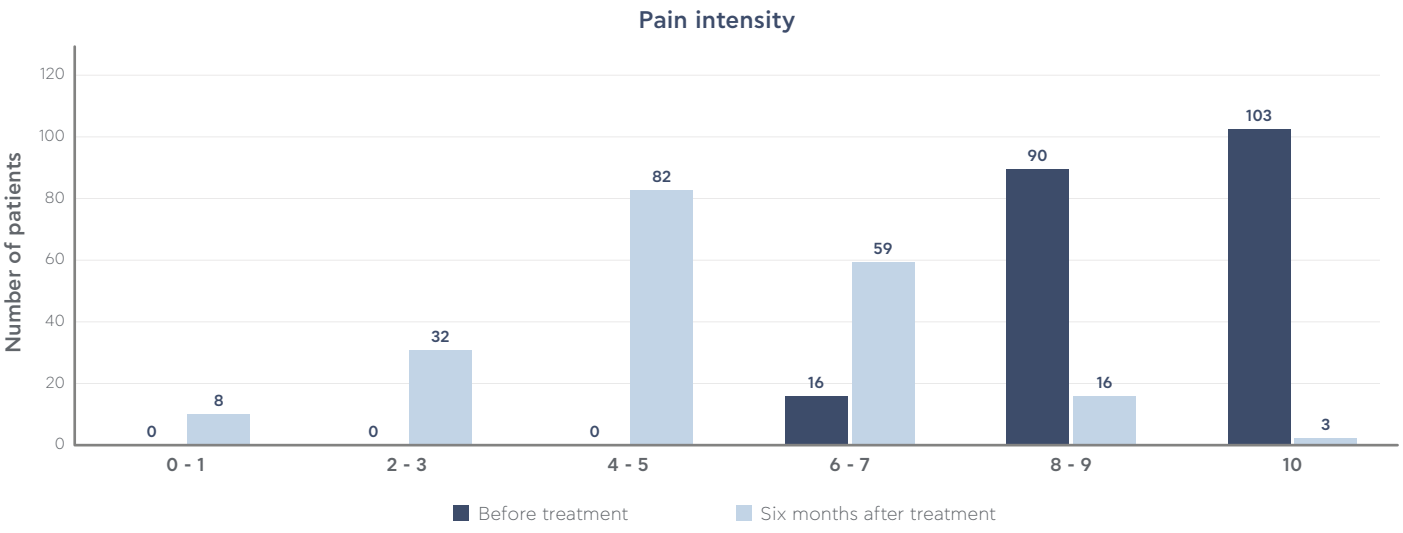
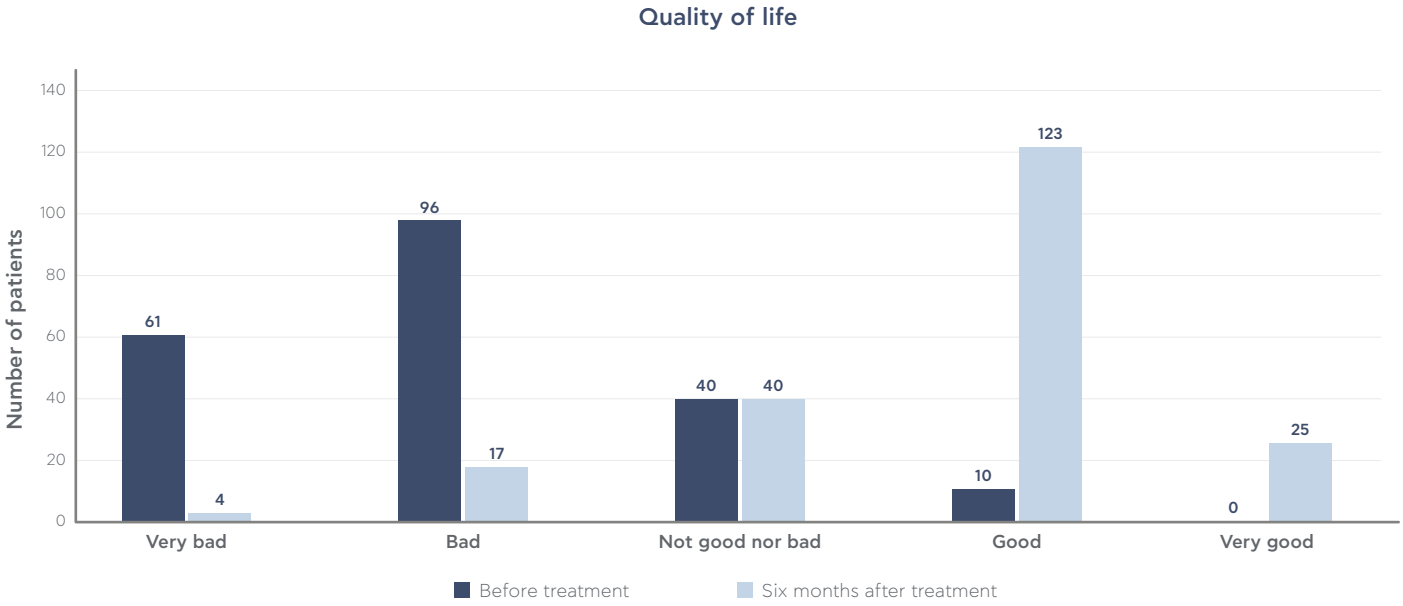


Figure 4

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



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 ($p < 0.001$).

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.

DISCUSSION

In the present study, we demonstrated that medical cannabis is an e ective 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 e ect 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 e ect 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 e ect 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 e ects 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 e ects 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 a ected 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 e ects 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 e ects 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 e ect 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 e ectiveness 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 di erences 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 di erent strains, which prevented us from conducting a comparison between THC and CBD strains and products in terms of e ectiveness 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.

CONCLUSIONS

Not with standing these limitations, the present observational study innovates by showing that medical cannabis may be an e ective 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 e ective and safe when titrated slowly and gradually. Considering the low rates of addiction and serious adverse e ects (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 e ect 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 http://www.mdpi.com/2077-0383/8/6/807/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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Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis

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abstract

Background: Cannabis is often used by patients with ulcerative colitis, but controlled studies are few. We aimed to assess the effect of cannabis in improving clinical and inflammatory outcomes in ulcerative colitis patients.

Methods: In a double-blind, randomized, placebo-controlled trial, patients received either cigarettes containing 0.5 g of dried cannabis flowers with 80 mg Tetrahydrocannabinol (THC) or placebo cigarettes for 8 weeks. Parameters of disease including Lichtiger disease activity index, C reactive protein (CRP), calprotectin, Mayo endoscopic score and quality of life (QOL) were assessed before, during and after treatment.

Results: The study included 32 patients. Mean age was 30 years, 14 (43%) females. Lichtiger index improved in the cannabis group from 10.9 (IQR 9-14) to5 (IQR 1-7), (p<0.000), and in the placebo group from 11 (IQR 9-13) to 8 (IQR 7-10) (p = 0.15, p between groups 0.001). QOL improved in the cannabis group from 77±4 to 98±20 (p = 0.000) but not in the placebo group (78±3 at week 0 and 78±17 at week 8;p = 0.459; p between groups 0.007). Mayo endoscopic score changed in the cannabis group from 2.13±1 to 1.25±2 (p = 0.015) and in the placebo group from 2.15±1to 1.69±1 (p = 0.367, p between groups 0.17).

Conclusion: Short term treatment with THC rich cannabis induced clinical remission and improved quality of life in patients with mild to moderately active ulcerative colitis. However, these beneficial clinical effects were not associated with significant anti-inflammatory improvement in the Mayo endoscopic score or laboratory markers for inflammation. (clinicaltrials.gov NCT01040910).

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by inflammation of the large intestine. The incidence of UC has increased over the past few years with a higher prevalence in the developed world [1, 2]. The disease poses a significant personal and socioeconomic burden due to its effects on patients' quality of life, daily functioning and use of healthcare system. The overall response to currently available treatments is limited to 40–60% [3, 4], and secondary loss of response occurs in about 50% of the patients [5]. Moreover, the current treatment carries many long-term risks including malignancies, infections, and decreased bone density. Therefore, it is not surprising that many patients with IBD seek alternative treatments for their illnesses. A common such alternative treatment is the use of cannabis. Indeed, epidemiological data indicate that as many as 15% of patients with IBD use cannabis [6, 7].

Cannabinoids have been shown to decrease motility and secretions in the gastrointestinal tract [8, 9]. They also have an important role in the regulation of inflammatory response in the colon [10]. In several models of murine colitis Cannabinoids were also shown to improve inflammation [11].

However, despite the growing number of IBD patients using medical cannabis, data about its clinical therapeutic efficacy is limited. Several studies reported the prevalence of cannabis use among IBD patients and suggested clinical benefit, but they were not randomized controlled studies and did not include information about the doses, extent of endoscopic disease and the effect of the treatment on disease activity and inflammatory markers [6, 7].

We have previously conducted several studies to look at the effect of medical cannabis in patients with IBD. In an observational prospective open label study on 30 patients with Crohn's disease we found a significant clinical improvement with an average decrease in Harvey Bradshaw index from 14 ± 6.7 to 7 ± 4.7 (P < 0.001). We also found that the improvement was sustained over an average period of 2 years (ranging from 3 months to 9 years) [12]. In a double-blind placebo-controlled study of 21 patients with Crohn's disease who were treated with cannabis over a period of 8 weeks, we found a significant improvement in Crohn's disease activity index (CDAI) in the cannabis active group compared to the placebo group (152±109 vs. 306 ±143, P <0.05) [13]. However, the results of studies investigating the effect of cannabis in IBD are not

always consistent. For example, in a study on 20 patients with Crohn's disease who were treated with cannabidiol vs. placebo over 8 weeks, we did not find significant improvement in CDAI compared to placebo, [14]. Similarly, a recent study by Irving PM et al. [15] failed to show significant difference in remission rate in UC patients who were treated with cannabidiol (n = 29) vs. placebo (n = 31)over a period of 10 weeks. Taken together, the current data on the beneficial effect of cannabis in patients with IBD is limited due to the small number of prospective placebo-controlled studies and the focus on clinical outcome without comprehensive assessment of the effect of this treatment on objective disease parameters including mucosal inflammation and inflammatory markers. Thus, the key question of whether the reported beneficial clinical effect of cannabis in patients with IBD relates to relief of symptoms or improvement in patients' ability to tolerate their symptoms, or to the anti-inflammatory effects of cannabis remained unanswered.

The aim of the current study was to investigate the clinical, laboratory and endoscopic effects of medical cannabis in patients with mild to moderate UC.

We hypothesized that the use of cannabis as an adjunct therapy in patients with mild to moderate UC will be associated with better clinical outcomes compared to placebo and that this beneficial effect of treatment will be associated with improvement in objective inflammatory disease parameters including laboratory and colonic mucosal markers for inflammation.

MATERIALS AND METHODS

Study design

We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-arm clinical study. The protocol included a two-week screening period to evaluate for baseline symptoms, an eight-week treatment period and a two-week follow-up period after the intervention was discontinued. Non-responders were offered to participate in an open arm eight-week treatment period.

Patients were evaluated by medical interview, physical examination, blood, and stool tests at baseline (end of screening; week 0), after two weeks of study intervention (week 2), end of intervention (week 8), and end of the follow-up period (week 10). Colonoscopy was performed at screening (week 0) and after 8 weeks of treatment. (Fig 1, consort checklist). Participant eligibility criteria. The study population included male and female patients age 20 to 80 years with mild to moderate UC diagnosed at least three months prior to enrollment. Mild to moderate disease severity was determined by Lichtiger Scoring Index of 4 and Mayo endoscopic subscore 1 [16]. Exclusion criteria included the use of cannabis, whether medical or recreational, pregnant or lactating, severe UC (Mayo score >10), proctitis (i.e. inflammatory segment of less than 15 cm), known psychiatric diagnosis or addiction traits based on self-reporting or noted in the patient's electronic medical record. Patients were allowed to continue their chronic UC medications as long as they were on a stable dose; specifically, at least 4weeks for 5 ASA and at least 3 months immunomodulators and biologic treatments. Steroids were permitted if the patients were on a stable dose for at least 8 weeks prior to enrollment. Patients were specifically asked to avoid any change in their stable medications and study medication during participation in the study.

Study compounds

Treatment was provided in the form of cigarettes. The cigarettes were machine made to ensure they were identical and comprised of dried flowers of genetically identical plants of Cannabis sativa var. Indica "Erez" (courtesy of Tikun-Olam Ltd., Tel Aviv, Israel). Every batch used in the study was analyzed and the content was 16% THC (80mg THC), 0.5% CBG, 0.1% CBD and traces (less than 0.1%) of CBC, CBDV and Δ8THC. Terpenes content was: Myrcene, βcaryophyllene, Selina-3,7(11)-diene, γ-Selinene, 10-epi-γ-eudesmol, β-eudesmol, guaiol, αpinene(analysis performed in the Lumirlab, Hebrew University Biotechnology Park Jerusalem, Israel. Tel: +972 (73) 733 0300).

The placebo cigarettes contained cannabis flowers from which THC had been extracted as previously described [13]. In short, dried flowers of Cannabis sativa var. Indica "Erez" (TikunOlam Ltd., Tel Aviv, Israel), known to contain 23% THC and <0.5% CBD and other cannabinoids weres oaked in 95% ethanol for two weeks. The procedure was repeated 3 times. Following this, the flowers were covered with a mixture of herbal spirits and 0.025% Saccharomyces cerevisiae var. "18" (Courtesy Rimontest Ltd., Haifa, Israel) for three more days and then allowed to dry in the ambient air with ventilation for 72 hours. The final product was tested for cannabinoids and shown to possess <0.4% THC with undetectable amounts of all other cannabinoids including CBD.

Blinding and randomization

Before the study began cannabis and placebo cigarettes were prepared by the cannabis dispensary personnel that had no access to the patients, in packages that were numbered randomly.

The code was kept outside the hospital in "Tikun-Olam" and was accessible only to people who had no access to the patients. Patients were randomly assigned using a block method in blocks of 5 [17] in a 1:1 ratio to receive either medical cannabis or placebo. Patients and investigators were blind to the treatment throughout the duration of the study and the data analysis.

Study intervention

Treatment was provided in the form of cigarettes. We chose this form because in "real life" it is reported by patients as the most effective form, with a rapid response and improvement of pain and general wellbeing. Therefore, despite the known hazards of smoking, we thought it should be the first form to be investigated [12]. Patients were required to start gradually, smoking half a cigarette (0.25gr) in the first day and increasing by 0.25 gr until a final dose of 0.5 gr twice daily was reached. To assess adherence, patients were required to bring the packages on each visit and the number of remaining cigarettes was counted.

Outcome assessment

The primary endpoint was statistically significant improvement of the Lichtiger score, Secondary end points were: statistically significant improvement of the bowel movements, abdominal pain and quality of life. Another secondary endpoint was statistically significant improvement of the Mayo endoscopic score.

Assessment of clinical effect

Patients were evaluated by medical interview, physical examination, blood and stool tests. Demographic data, smoking history, past medical history (including history of drug abuse and psychiatric co-morbidity), ulcerative colitis history, past and present medications, family history of IBD, results of recent blood tests, last endoscopic and imaging findings were collected from patients' records. For clinical assessment, we used the overall Lichtiger Score [18] as well as additional sub-analysis on Lichtiger Score specific variables of interest including the number of bowel movements per day, abdominal pain and rectal bleeding. The primary outcome was statistically significant reduction of the Lichtiger score after 8 weeks of intervention.

Quality of life (QOL) was assessed at baseline (week 0) and end of the intervention (week 8) using the Short Form (SF36)survey [19]. Patients were also asked to report their general satisfaction with the treatment on a 7 point Likert scale (1 = not at all satisfied to 7 = very satisfied) and overall improvement on specific symptoms including general health, appetite, libido and concentration on a 5 points Likert scale (1 = significant improvement to 5 = worsening).

Assessment of effect on inflammation

Inflammatory activity was assessed with laboratory blood tests, stool calprotectin, and endoscopic parameters. Blood tests included complete blood count, liver and kidney function and C-reactive protein (CRP). Colonoscopies were performed at baseline (week 0) and end of intervention (week 8) by physicians who were blinded to the patient's study treatment. Endoscopic disease activity was assessed using the Mayo score [20].
All side effects, including symptoms of drug addiction as defined by the DSM- IV [21] were captured at week 2 and week 8 and rated for severity on a 0 to 7 scale.

STATISTICAL ANALYSIS

Categorical variables were reported as number and percentage. Continuous variables were evaluated for normal distribution using histogram and QQ plot. Baseline characteristics at first visit evaluation and third visit were compared between groups using independent sample t-test or Mann-Whitney test for continuous and ordinal variables, while Chi-square test or Fisher exact test were used for categorical variables. In each group, differences between the first and third visits were tested using paired sample t-test or Wilcoxon test for continuous and ordinal variables, while McNemar test was used for categorical variables. Generalized estimating equations models were used to observe changes between the groups at two time points, the first week and the 8 weeks visits. This was evaluated using interaction between time and group.

Corrections for multiple comparisons were done using the False Discovery Rate method [22]. In order to identify a4 point difference in the Lichtiger score between the two groups after 8 weeks, we used a standard deviation of 2.5, [23] an alpha of 0.01and a power of 90%. The calculated sample size was 14 patients in each group. Taking into account the possibility of 10% dropout we aimed at 16 patients in each group.

All statistical tests were 2-sided, $p<0.05$ was considered statistically significant. SPSS software was used for statistical analysis (IBM SPSS statistics for windows, ver. 25, IBM Corp, Armonk, NY, USA).

ETHICAL CONSIDERATIONS

The study was approved by the Ministry of Health cannabis authority ethics committee and the Meir Medical Center ethics committee. All participants provided informed consent before any study-related procedure was carried out. All methods were carried out in accordance with relevant guidelines and regulations. The study protocol and results are registered on the clinicaltrials.gov website. NCT01040910, first posted 30 December 2009, and modified on October 2013.

RESULTS

A total of 126 patients were screened, among them,43 did not consent, 39 had inactive disease with a Lichtiger score 1, inclusion criteria were not met by 9 patients, and3 were already taking medical cannabis treatment. Thus, 32 patients were recruited and all completed the study. The mean age was 30, range 26–40, 14 (43%) women. Left-sided colitis was noted in 8 (25%) and extended or pancolitis in 24 (75%) patients. The mean length of the colonic involved segment was 46±20 cm. Twenty-four (75%) patients had never smoked tobacco, 6 (18%) smoked in the past and 2(6.3%) were still smoking during the study.

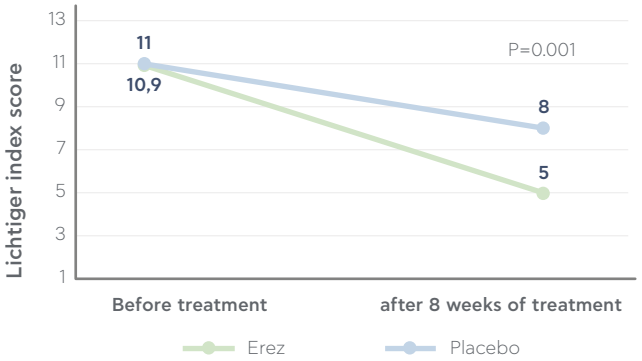
Demographic data are presented in Table 1. IBD related treatments prior to enrollment included 5 (15%) patients using steroids, 5 (15%)immunomodulators, and 6 (18%) biologics. Seven patients did not respond or had lost response to TNF inhibitors after at least a full induction dose (Table 2). No change in UC treatment was made during the study. Lichtiger disease activity index improved in the active arm group from 10.9 (IQR 9–14) to 5 (IQR 1–7, p<0.001), and in the placebo group from 11 (IQR 9–13) to 8 (IQR 7–10, p = 0.37). (p between groups 0.006). When looking at the delta of the Lictiger score, the average change was 6.4 ±3.1 in the cannabis group and 2 ±2.5 in the placebo group (p<0.05), only two patients, both from the placebo treated group, had an increase in the Lichtiger score, but the change was less then 3 points, and thus not defined as a disease flare. The number of bowel movements per day decreased from 2.6 (IQR 2–4) to 1 (IQR 0–1, p<0.001)and from 2.6 (IQR 2–4) to 2 (IQR 2–3, p = 0.168) in the active arm and placebo groups respectively (p between groups 0.006). The number of patients who reported severity of abdominal pain of >2 decreased from 10 (59%) at baseline to 1 (6%) after 8 weeks of treatment(p = 0.006) in the cannabis group and from9 (60%) to8 (55%),(p = 0.429) in the placebo group, (p between groups = 0.04). The number of patients who reported blood in stool decreased from 13 (76%) to 5 (30%) in the cannabis group (p = 0.015). and from 9 (60%) to 6 (40%) in the placebo group (p = 0.589)(p between groups = 0.64) (Table 3). QOL improved in the cannabis group from 77±4 to 98±20 (p = 0.001) but not in the placebo group (78±3 at week 0 and 78±17 at week 8;p = 0.631; p between groups 0.026) (Table 3).

Colonoscopy at baseline and at the end of treatment was performed in 29 out of 32 (90%) patients, Mayo endoscopic score improved in the cannabis-treated group from an average of 2.13±1 to 1.25±2 (p = 0.015) and in the placebo group from 2.15±1to 1.69±1 (p = 0.367). However, pre- to post-intervention differences between the groups (delta between pre-intervention and post intervention score) did not reach statistical significance (1.25±2and 1.69±1 in the study and placebo groups, respectively, p = 0.374). Baseline to end of 8 weeks treatment laboratory parameters of inflammation, including blood count, CRP, and fecal calprotectin did not change in both groups (Table 3). When asked about the effect of treatment on specific symptoms, patients in the cannabis group reported improvement in their general health, appetite, libido, concentration, and pain.

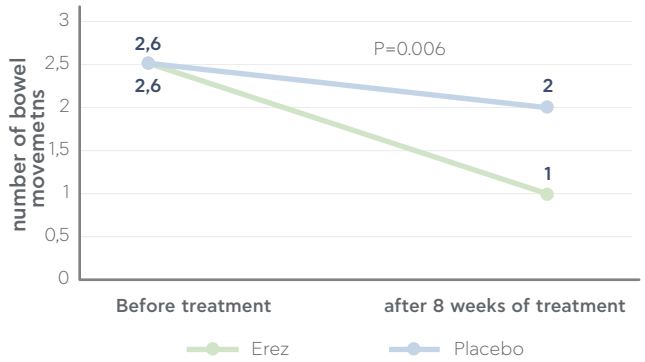
The placebo group did not report similar changes. General satisfaction with treatment was high among the cannabis treated group. Interestingly, the improvement was noted within one week (Table 4). The reported side effects were minor and did not lead to cessation of treatment in any patients (Table 5).

• No patient stopped treatment during the 8 weeks of follow-up. 17 patients (53%) continued treatment for another year after the study ended.

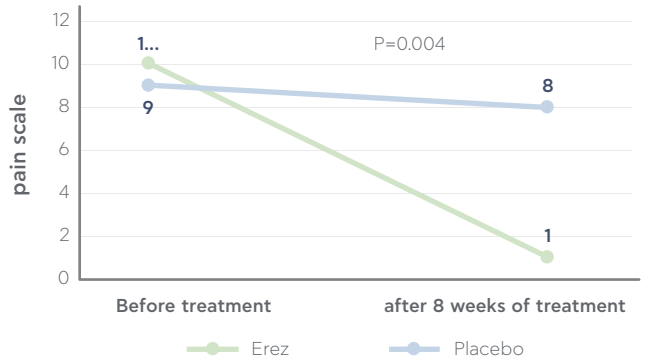
• Overall improvement - a clinical response (considered to be above 3 points in the Lichtiger index score) was observed in the cannabis group more significantly than in the placebo group; Cannabis group patients improved from 10.9 to 5.0. There was also a decrease in the score of the placebo group, due to the placebo effect, but was more moderate from 11.0 to 8.0.



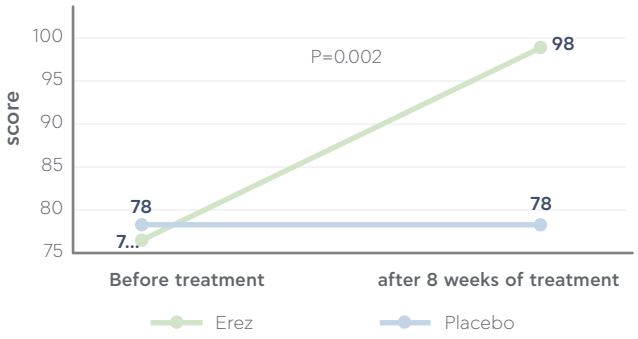
• Decrease in the number of bowel movements per day - In the cannabis group, the number of bowel movements per day decreased from 2.6 to 1.0. In the placebo group, the number of bowel movements decreased from 2.6 to 2.



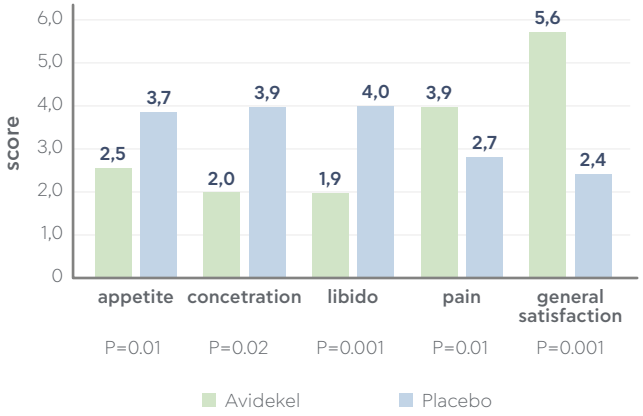
• Decrease in abdominal pain – of the patients who reported severity of abdominal pain of ≥2 (on a scale of 1 to 10, with 10 being the highest level of pain), in the cannabis group the level of pain decreased from 10 to 1. In the placebo group, the level of pain decreased from 9 to 8.



• Improvement in quality of life - The cannabis group observed a significant improvement in quality of life (from a score of 77 to a score of 98), compared to the placebo group whose quality of life remained at the same level (score of 78 all the way).



• Symptomatic improvement - The cannabis group patients reported a significant improvement compared to the placebo group also in appetite, concentration, libido, pain, general satisfaction with the treatment (on a grade from 1 to 7, 1 = improved, 4 = no change, 7 = deteriorated).



• Side effects - No significant differences were observed between the cannabis group and the placebo group.

DISCUSSION

Epidemiological studies indicate that between 15–45% of patients with IBD use cannabis [6, 7] and anecdotal clinical reports suggest improvement in patient's wellbeing and IBD-related symptoms [7, 12, 24]. In addition, preclinical animal and laboratory investigational models have demonstrated anti-inflammatory effects of cannabis, thus further supporting a potential benefit of using cannabis in patients with IBD [7, 10, 11].

The endocannabinoid system has an important role in the regulation of inflammatory response in the colon [10]. Cannabinoids were shown to ameliorate colitis in various murine models of colitis, with an anti-inflammatory effect mediated thorough activation of the cannabinoid receptors CB1 and CB2, inhibition of the endocannabinoid degrading enzymes Monoacylglycerol lipase(MAGL) and fatty acid amid hydrolase (FAAH), and activation of the G protein-coupled receptor 55 (GPR55) and Transient receptor potential vanilloid 1 (TRPV1) receptors [25, 26]. However, despite the increasing anecdotal reports suggesting a clinical benefit of cannabis in patients with IBD and the accumulating data on its intestinal, and specifically colonic antiinflammatory effects in animal models of IBD, only a few prospective, placebo-controlled studies have been conducted. Furthermore, most of the studies focused on clinical outcomes and did not include investigation of objective anti-inflammatory effects [6, 12, 24]. Therefore, the question whether the observed effect is limited to symptomatic improvement or due to a reduction in inflammation remains open.

In the current study, we investigated clinical as well as endoscopic and laboratory responses to cannabis treatment in patients with UC in a randomized placebo-controlled study. Unlike previous studies we were specifically interested to see if the clinical effects of cannabis treatment will be associated with a reduction of inflammation. From a clinical perspective, we found that treatment with cannabis led to a significant reduction in the Lichtiger Disease Activity Index and improvement in major IBD-related clinical symptoms including abdominal pain and number of bowel movements per day. We also observed a significant improvement in quality of life, general health, appetite, libido, concentration, and patient satisfaction with the treatment.

Regarding the effect on inflammation, we found a significant pre- to post-intervention improvement in the Mayo endoscopic score in both study groups, This effect was greater in the cannabis than in the placebo group, however it did not reach statistical significance in between groups' analysis. In addition, we could not find significant pre- to post-intervention changes in laboratory markers of inflammation including blood count, CRP and fecal calprotectin within the cannabis and the placebo groups, nor in between groups analysis.

In a study from our group using THC rich cannabis in patients with Crohn's disease, we found significant clinical improvement, reduction of CDAI and improved quality of life, but no change in CRP [12, 13]. Similarly, Irving et al, who gave Cannabidiol (CBD)to patients with UC showed clinical improvement in partial Mayo score without improvement in inflammatory markers including endoscopic Mayo score [15]. The lack of association between clinical beneficial observation and anti-inflammatory effects could result from differences in the effect of various chemical components of cannabis. The two major active components of cannabis are cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). While CBD works mainly peripherally without a central effect, THC works mainly centrally and is responsible for the dominant psychoactive effects of cannabis [25]. These two components seem to act synergistically onCB1 and CB2 at the level of the enteric nervous system [26]. In the current study, we used THC rich cannabis., Thus it is quite likely that the observed effect was rather central than peripheral and therefore resulted in a weaker anti-inflammatory effect. Another possibility is that the onset of the central clinical effect is faster while the antiinflammatory effect may take longer and therefore we could not detect an accompanying effect on peripheral inflammatory markers in this relatively short, 8 weeks study. Lastly, through its effect on CB1 and CB2 receptors in the gut, cannabis also

affects GI physiology including reducing intestinal motility, increasing fluid absorption and inducing analgesia [8, 24]. Therefore, it is possible that the symptomatic improvement observed in our study reflects the effect on intestinal physiology without a significant effect on inflammation.

Smoking tobacco is known to have a positive effect in UC. We chose smoking as a mode of cannabis consumption because this is the most common form used by patients in "real life". However, this may have lead to the high rate of response in the placebo group. Regardless of the mechanism by which cannabis exerts its clinical effect, the endpoint of patient wellbeing, quality of life and daily functioning is of no lesser value than improvement in inflammation.

Overall, cannabis was well tolerated in our study. Patients reported only minor side effects, mostly dizziness (n = 6, 35%) and confusion (n = 5,29%) and none of our patients dropped out of the study due to side effects. A study among 3,341 patients using cannabis reported the most common side effects of dry mouth (26%) and feeling foggy (23%). These side effects were associated with THC and much less with CBD [27, 28]. In the study by Irving et al [15], doses of up to 500mg/day of CBD produced a high rate of side effects which led to violation of protocol and/or dropouts by 41% of the participants. The low level of side effects and lack of drop out in our study could be explained by our treatment protocol which started cannabis treatment at a low dose and increased the dose gradually, hence enabling the patients time to develop tolerance to the treatment.

Our study has several strengths including the stable dose of cannabis used, the placebo-controlled design and the examination of inflammatory parameters, including endoscopic and laboratory markers for disease activity, in addition to clinical parameters. The weaknesses of the study are the small sample size, short duration of the study, lack of histological data and the inherent difficulty of blinding cannabis use. Future studies are needed with higher sample sizes, and combining other populations. Another weakness is the consumption of cannabis as cigarettes. Although in "real-life" most patients who report beneficial effects of cannabis consume it by smoking, this mode of delivery is not advisable and could not be acceptable for medical treatment. Other healthier modes of consumption should be investigated. Vaping could be an option since vaporizers do not produce toxic compounds formed by pyrolysis and the pharmacokinetics of vaporized and smoked cannabinoids is comparable. Oral consumption is another possibility, but oral THC formulations exhibit variable absorption and undergo extensive hepatic first-pass metabolism, producing lower peak plasma concentrations relative to inhalation. Further studies are needed to evaluate the various modes of cannabis consumption and select those that safest and most efficient [29–31].

Placebo controlled studies are particularly challenging when using psychoactive substances. We tried to overcome this difficulty by recruiting only patients who did not experience previous cannabis use. Indeed, at least 3 patients receiving placebo were convinced they were receiving cannabis, but we do not have this data on all the study participants. Our study was designed as a short (8 weeks) intervention study. However, we had the opportunity to follow a third of the patients for another year and found that endoscopic remission was retained (with a Mayo score of 0–1) in 10/11 patients. This long-term remission suggests a possible durable beneficial effect of cannabis. Larger, long-term studies are warranted to investigate this finding.

CONCLUSION

This study demonstrates that treatment with THC-rich cannabis in patients with mild to moderate UC is associated with clinical improvement. Our findings indicate that the reported cannabis-induced clinical effect is not directly linked to an anti-inflammatory effect of cannabis.

However, the results demonstrate a signal for associated reduction in mucosal inflammation in patients with UC. This preliminary observation requires additional investigation in larger and longer intervention clinical studies. Such studies will enable us to determine whether cannabis has mainly a symptom relieving role or a more specific anti-inflammatory therapeutic effect. Future research should focus on alternative ways of providing cannabis (other than smoking), and explore various cannabinoid compounds in order to reveal the most effective and safe mode of cannabis use by patients with IBD.

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Adherence, Safety, and Effectiveness of Medical Cannabis and Epidemiological Characteristics of the Patient Population: A Prospective Study

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abstract

Background: Despite the absence of rigorous prospective studies, there has been an increase in the use of cannabis-based medicinal products. During the study period, the use of medical cannabis in Israel was tightly regulated by national policy. Through a prospective study of approximately 10,000 patients, we aimed to characterize the medical cannabis patient population as well as to identify treatment adherence, safety, and effectiveness.

Methods and Findings: In this study of prescribed medical cannabis patients, adherence, safety, and effectiveness were assessed at 6 months. Treatment adherence was assessed by the proportion of patients purchasing the medication out of the total number of patients (excluding deceased cases and patients transferred to another cannabis clinic). Safety was assessed by the frequency of the side-effects, while effectiveness was defined as at least moderate improvement in the patient condition without treatment cessation or serious side-effects. The most frequent primary indications requiring therapy were cancer (49.1%), followed by non-specific pain (29.3%). The average age was 54.6 ± 20.9 years, 51.1% males; 30.2% of the patients reported prior experience with cannabis. During the study follow-up, 1,938 patients died (19.4%) and 1,735 stopped treatment (17.3%). Common side-effects, reported by 1,675 patients (34.2%), were: dizziness (8.2%), dry mouth (6.7%), increased appetite (4.7%), sleepiness (4.4%), and psychoactive effect (4.3%). Overall, 70.6% patients had treatment success at 6 months. Multivariable logistic regression analysis revealed that the following factors were associated with treatment success: cigarette smoking, prior experience with cannabis, active driving, working, and a young age. The main limitation of this study was the lack of data on safety and effectiveness of the treatment for patients who refused to undergo medical assessment even at baseline or died within the first 6 months.

Conclusions: We observed that supervised medical-cannabis treatment is associated with high adherence, improvement in quality of life, and a decrease in pain level with a low incidence of serious adverse events.

keywords

- Cannabis
- Cannabidiol (CBD)
- Tetrahydrocannabinol (THC)
- Prospective
- Cohort
- Pain
- Quality of life
- Adherence

INTRODUCTION

In recent years, there has been an increase in the use of cannabis-based products for a wide range of medical purposes, despite a lack of sufficient scientific evidence supporting cannabis therapies (1). Non-purified products of the cannabis plant are the most frequently consumed by cannabis users (2), and contain three families of components, terpenes, flavonoids, and cannabinoids (3). Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most common cannabinoids found in the cannabis plant (4). THC is the primary psychoactive ingredient (5) and has shown therapeutic benefit for pain, nausea, and sleep (1). CBD is non-intoxicating at medically relevant doses (4); and when combined with THC, may counterbalance the psychoactivity of THC (6), while increasing THC tolerance (7). Cannabidiol has antiinflammatory, neuroprotective, antipsychotic, anxiolytic, and antidepressant properties (8).

Although the UK has begun to develop a registry of medical cannabis patients (9), rigorous observational studies and prospective clinical trials have yet to be undertaken and most of the available data is derived from

surveys of cooperating users. These surveys are usually limited in scope, retrospective, and rarely collect data on variables beyond basic demographic elements, comorbidities, modes of consumption, and overall satisfaction (2, 6–8, 10–23).

Medical cannabis is now available in many countries, where it is primarily used for its analgesic effect (2, 10–12, 15, 16, 18, 24–26). In 2007, the Israeli Ministry of Health (IMOH) began issuing licenses for the use of cannabis for patients with specific indications, including: nausea and vomiting due to chemotherapy treatment, cancer associated pain, inflammatory bowel disease (IBD), neuropathic pain, fibromyalgia, cachexia in AIDS (acquired immunodeficiency syndrome) patients, multiple sclerosis (MS), Parkinson's disease (PD), Tourette syndrome, epilepsy, autism, and post-traumatic stress disorder (PTSD). A physician can recommend medical cannabis under one of the indications approved by the IMOH, only following the exhaustion of all traditional medications options. A license to receive medical cannabis may then be granted to a patient, and that license associated with a specialized clinic. Because of this aspect of the regulation, we could assess the effect of treatment of all patients enrolled in the clinic, where all are tested, with no collection bias. Asmore countries legalizemedical Abbreviations: CBD, cannabidiol; IBD, inflammatory bowel disease; IMOH, Israeli Ministry of Health; IQR, interquartile range; MS, multiple sclerosis; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; QOL, quality of life; THC, delta-9-tetrahydrocannabinol. cannabis use and some legalize recreational use, accrual of scientific data on treatment adherence, safety, and effectiveness is essential. The first step in this process should be based on the evaluation of rigorously accumulated observational data. Therefore, the aim of this study is to prospectively assess the characteristics of the patient population and evaluate adherence, safety, and effectiveness of medical cannabis in a tightly regulated environment.

MATERIALS AND METHODS

Study Population and Treatment Program

This study was conducted based on clinical data collected as part of the treatment program in Israel's largest cannabis clinic. The study included all patients who received a medical cannabis treatment license through the clinic between March 2015 and February 2018. According to the clinic's standard protocols, each patient had the option to receive a 45-min intake session. This session was designed so that the attending nurse could assess the patient's complete medical history, advise on a suitable selection from cannabis chemovars of varying cannabinoid concentrations, and to explain the recommended method of administration and titration process. Six months after the initiation of treatment, willing patients participated in a telephone interview to assess changes in symptom intensity and side-effects. If needed, the nurse recommended treatment adjustments.

We have published data based on this database in four previous studies, on cancer patients (27), patients over the age of 65 (28), fibromyalgia patients (29), and children with autism(30). There is a certain overlap between the patients presented in these studies and the current study, especially in the cancer patient study, published in 2018, which included 1,248 patients, and the study on patients over the age of 65 which included 901 patients, where we assessed the effect of at least 6 months' active medical cannabis treatment. However, in this study, we expanded the focus to all indications for cannabis treatment, over a prolonged recruitment period. Moreover, in this study, we analyzed only patients who answered the intake questionnaire after receiving a new cannabis treatment license, so that the baseline represents a pre-medical cannabis treatment state.

Outcome Measures

Patient Characterization

The characteristics of the medical cannabis patient population were analyzed as one large group and divided based on the main indication for medical cannabis treatment of each patient. We included all patients who filled the intake questionnaire, i.e., 85.7% of patients who initiated treatment.

Adherence

Patient adherence to the treatment regimen was assessed based on actual refill orders, calculated as the proportion of patients purchasing the medication out of the total number of patients at both 1 month and at 6 months treatment duration, excluding deceased cases and patients transferred to another cannabis clinic. Treatment adherence was assessed in all patients, and not only in patients answering the questionnaire.

Safety

Side-effects were assessed at 6 months by first asking the patient "Have you experienced side-effects due to the use of cannabis?" If the answer was "yes," the patient was asked to specify the side-effects via a free text response coded as a predefined list of the common side-effects. Patients were asked details of incidence (rarely, sometimes, often, or always), duration (several minutes, half hour, several hours, all day), and severity (1–10) of any reported side-effects. We included all active and inactive patients that answered this 6-month follow-up questionnaire.

Abbreviations: CBD, cannabidiol; IBD, inflammatory bowel disease; IMOH, Israeli Ministry of Health; IQR, interquartile range; MS, multiple sclerosis; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; QOL, quality of life; THC, delta-9-tetrahydrocannabinol.

Effectiveness

For analysis of treatment effectiveness, we used the global assessment approach where patients were asked at 6 months: "How would you rate the general effect of cannabis on your condition?" The seven response options were: significant, moderate, or slight improvement, no change, slight,moderate, or significant deterioration. For the primary effectiveness endpoint analysis, we selected a conservative approach, and so treatment success was defined as (a) at least moderate or significant improvement in the patient's condition and (b) none of the following: treatment cessation or serious side-effects defined as 9–10 on severity scale and incidence of often or always. We included all patients who discontinued treatment during the first 6 months of treatment and all patients who remained in active treatment during this period and answered the 6-month follow-up questionnaire. All patients who discontinued treatment and patients who were lost to follow-up were classified as a treatment failure.

For effectiveness in specific parameters like pain, quality of life (QOL), and change in concomitantmedication consumption, we analyzed patients who answered the relevant question in both time points (before treatment and after 6 months of active treatment). We used a numeric rating scale to assess pain level on an 11-point scale (0 = no pain, 10 = worst pain imaginable) (31), and a Likert scale to assess QOL (very poor, poor, neither poor nor good, good, very good) (32). We analyzed the changes over time in the pain and QOL rating scales of each patient as a paired comparison.

Furthermore, patients were asked, both at intake and in the 6-months follow-up questionnaire, to report all the prescribed medications they regularly take, dose, and number of administrations per day. The medications were sorted in classes according to the international ATC (Anatomical Therapeutic Chemical) drugs classes distribution to assess changes over time.

A significant principle in cannabis treatment is to map all the symptoms the patient suffers from, and to match expectations with the patient on the symptoms that usually are improved with cannabis products (pain, sleep disturbances, nausea and vomiting, spasticity, depression, and others); these are the treatment goals. The first step is to focus on the symptom that is most bothersome—and to match a product for that symptom. The therapeutic dose is a dose that achieves a balance betweenmaximum reduction of target symptom and a minimum of sideeffects. To reach the therapeutic dose, the patient must undergo a process of titration. After an improvement in the main symptom, we may incorporate another product and another treatment goal. The recommendation for chemovars and products was based on the experience accumulated at the clinic regarding which product has the highest effectiveness rate for a specific symptom. The products are based on chemovars (sativa or indica dominant, high THC, high CBD, or balanced) and consumption method (flowers for inhalation or smoking, oil under the tongue, and capsules).

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 a t-test for the analysis of continuous variables with normal distribution, Mann–Whitney U-test whenever parametric assumptions could not be satisfied, and χ^2-test for categorical variables. For paired comparisons, we have used paired t-test, non-parametric Wilcoxon signed rank test, and χ^2-test for dependent variables. We used multivariable logistic regression analysis for the factors associated with the treatment success to control possible confounders. We have included the following baseline variables into the models based on clinical considerations: age, gender, weight, indication for cannabis treatment, presence of pain, number of chronic medications, hospitalization in the past 6 months, employment, car use, previous experience with cannabis, cigarette smoking, QOL, and concerns about cannabis treatment as reflected in the intake form. The final model was selected according to the model characteristic, evaluated by calculating the c-statistic, in addition to choosing the minimal −2 log likelihood of each model.y

Ethics Approval and Consent to Participate

This study was approved by the IRB at the Soroka University Medical Center, Beer-Sheva, Israel, study number: SCRC-0415-15. Although data was collected prospectively, the need for informed consent was waived due to the non-intervention nature of the study and the retrospective data analysis.

RESULTS

Patient Population

During 3 years of study period, 10,713 subjects received their first cannabis treatment license: 2.6% died before starting treatment, 4.2% opted not to receive the treatment, and 9,985 patients (93.2%) initiated treatment. Out of these, 8,560 (85.7%) responded to the intake questionnaire (see Figure 1 for a detailed flow diagram and for the cohort in each of the outcome analyses). The patients,mean age 54.6 years, 51.1%men, received a cannabis treatment license for the following indications: cancer (49.1%: chemotherapy related symptoms 23.5% and pain related treatment 25.5%), non-specific pain (29.4%), PTSD (6.4%), autism (3.6%), epilepsy (2.7%), PD (2.5%), IBD (2.2%), MS (0.9%), compassionate care (0.6%), Tourette

syndrome (0.6%), and others (1.9%) (full demographic characteristics are presented in Table 1). Each patient has one indication for the cannabis treatment license, but usually more than one medical condition. Supplementary Table 1 shows the full list of comorbidities with the disease duration: 52.1% had cancer, 18.7% suffered from pain, 14.0% suffered from hypertension, and 10.6% had diabetes. The median disease duration was 4 years (range 1–21).

Out of the patients responding to the intake questionnaire, 7,056 reported on regular consumption of prescription medications (82.4%). The main families of drugs used were: opioids (32.5%), anti-depressants (29.9%), anti-epileptics (26.2%), and drugs for peptic ulcer and gastroesophageal reflux disease (23.2%) (Supplementary Table 2).

At baseline, patients reported an average of 9.8 ± 7.4 symptoms. Table 2 shows the prevalence of symptoms at the time treatment was initiated: 79.1%reported sleep disturbances, 77.1% pain, and 55.6% reported weakness and fatigue.

At baseline, a total of 15.0% reported having concerns over the initiation of cannabis treatment. Themost common concerns were potential side-effects (3.5%), lack of knowledge regarding the effect (1.2%), lack of effect (0.8%), addiction (0.8%), loss of control (0.7%), worsening medical condition (0.5%), cannabis being an illicit drug (0.5%), and the "high" effect (0.4%). For comparison between patients with and without cannabis previous experience, please refer to Supplementary Table 3.

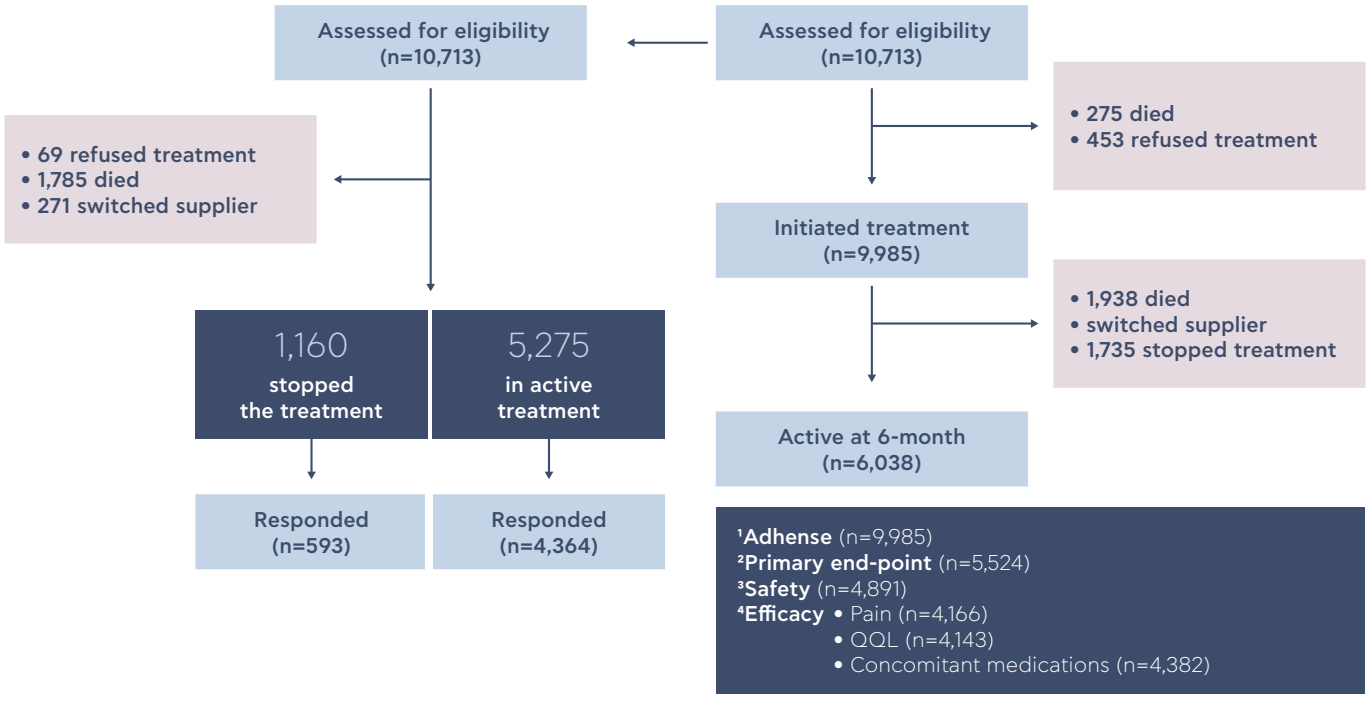
Adherence

Adherence was assessed for all patients who initiated treatment in the cannabis clinic. After1 month, of the 9,985 patients who started the treatment, 4.8% died, 5.2% stopped treatment, and 0.3% switched to a different cannabis supplier, while 89.7% continued active treatment. Of those who continued active treatment, 6,699 (74.8%) responded to the questionnaire. Of them, 2,562 patients (38.2%) experienced side-effects or reported that the cannabis did not improve their condition during the first month of the treatment and needed the advice and guidance of a nurse to adjust the dose or the treatment. At 6 months of 7,773 patients, 6,038 (77.7%) remained in active treatment (excluding 19.4% patients who died and 2.7% who switched to a different cannabis supplier).

Safety Analysis

Of the 4,891 patients who responded to the side-effect followup questionnaire, 1,675 patients (34.2%) reported experiencing at least one side-effect. The most common were dizziness (8.2%), dry mouth (6.7%), increased appetite (4.7%), sleepiness (4.4%), and psychoactive effects (4.3%) (Table 3). This analysis included all active patients and patients who discontinued the cannabis treatment.

Figure 1



The study population. Detailed description of the patients included into the adherence assessment, primary endpoint assessment, and the safety and effectiveness analysis population. [1]Adherence analysis was performed on all patients who initiated treatment. [2]Primary end-point analysis was performed on patients who responded the intake questionnaire and: responded to the 6-month follow-up questionnaire and all patients who stopped the treatment. [3]Safety analysis was performed on all patients who responded to the side-effect section of the 6-month follow-up questionnaire, both active patients and responders that stopped the treatment. [4]Efficacy analysis was performed on patients who answered the specific chapter at the intake session and at the 6-month follow-up questionnaire (active patients only).

Table 1

Patient's demographic characteristics.

	Total (8,560)	Cancer (4,205)	Non-specific pain (2,515)	PTSD (551)	Autism (311)	Epilepsy (232)	PD (215)	IBD (190)	MS (79)	Compassionate (55)	Tourette syndrome (48)	Others (159)
Mean age	54.6	61.1	57.0	41.4	12.2	16.6	71.9	38.0	47.4	35.4	31.4	44.0
(SD)	(20.9)	(16.2)	(18.7)	(13.7)	(6.1)	(13.4)	(9.6)	(14.4)	(11.3)	(27.8)	(13.2)	(26.7)
Gender	4,379	1,908	1,287	382	261	122	124	103	34	35	36	87
(male), no. %	(51.1)	(45.4)	(51.2)	(69.3)	(83.9)	(52.6)	(57.7)	(54.2)	(43.0)	(63.6)	(75.0)	(54.7)
Working	2,017	693	765	266	3	36	17	122	35	20	27	32
(Yes), no. %	(23.5)	(16.4)	(30.4)	(48.2)	(0.9)	(15.5)	(7.9)	(64.2)	(44.3)	(36.3)	(56.2)	(20.1)
Driving a car	4,165	2,008	1,403	389	0	5	55	161	53	13	29	49
(Yes), no. %	(48.6)	(47.7)	(55.7)	(70.5)	(0.0)	(2.1)	(25.5)	(84.7)	(67.0)	(23.6)	(60.4)	(30.8)
Median number of hospitalization	0	3	0	0	0	0	0	0	0	0	0	0
days in the past 6 months (IQR)	(0–7)	(0–14)	(0–0)	(0–0)	(0–0)	(0–1.7)	(0–0)	(0–2)	(0–0)	(0–3.5)	(0–0)	(0–2.5)
Median number of medications	3	3	4	2	1	3	7	2	3	2	1	3
(IQR)	(1–6)	(1–6)	(2–7)	(0–4)	(0–2)	(2–4)	(4–9)	(1–3)	(1.5–5)	(1–4)	(0–3)	(1–5.5)
Previous experience with cannabis	2,590	927	1,010	356	17	22	54	95	35	4	26	44
(Yes), no. %	(30.2)	(22.3)	(40.7)	(65.7)	(5.5)	(9.6)	(25.2)	(50.5)	(45.5)	(7.5)	(54.2)	(27.8)
Cigarette smoking	2,081	743	904	272	1	16	22	50	26	4	16	27
(Yes), no. %	(24.3)	(17.6)	(35.9)	(49.3)	(0.3)	(6.8)	(10.2)	(26.3)	(32.9)	(7.2)	(33.3)	(16.9)
Median pain scale 0–10	8	7	9	5	0	0	8	8	8	0	0	5
(IQR)	(4–10)	(3–9)	(8–10)	(0–8)	(0–0)	(0–0)	(5.7–9)	(7–9)	(6–10)	(0–0)	(0–8)	(0–9)

Characteristics are for all patients and per medical indication for the cannabis license of each patient. PTSD, post-traumatic stress disorder; PD, Parkinson's disease; IBD, inflammatory bowel disease; MS, multiple sclerosis.

Table 2

Symptoms prevalence at intake.

Symptom no. (%)	Total (8,560)	Cancer (4,205)	Non-specific pain (2,515)	PTSD (551)	Autism (311)	Epilepsy (232)	PD (215)	IBD (190)	MS (79)	Compassionate (55)	Tourette syndrome (48)	Others (159)
Sleep disturbances	6,772 (79.1)	3,279 (78.0)	2,152 (85.6)	518 (94.0)	180 (57.9)	110 (47.4)	163 (75.8)	147 (77.4)	57 (72.2)	42 (76.4)	27 (56.3)	107 (67.3)
Pain	6,567 (77.1)	3,173 (76.0)	2,445 (99.4)	308 (55.8)	3 (1.0)	39 (17.3)	179 (85.6	178 (95.2)	68 (88.3)	12 (22.6)	20 (43.5)	142 (62.6)
Weakness and fatigue	4,756 (55.6)	2,903 (69.0)	1,158 (46.0)	302 (54.8)	8 (2.6)	66 (28.4)	93 (43.3)	102 (53.7)	42 (53.2)	28 (50.9)	14 (29.2)	58 (36.5)
Digestion problems	4,071 (47.6)	2,458 (58.5)	962 (38.3)	199 (36.1)	17 (5.5)	54 (23.3)	100 (46.5)	179 (94.2)	21 (26.6)	21 (38.2)	7 (14.6)	61 (38.4)
Anxiety	3,492 (41.7)	1,737 (42.0	883 (36.4)	472 (87.1)	110 (35.9)	40 (17.5)	86 (40.0)	55 (28.9)	20 (26.0)	24 (43.6)	16 (37.2)	49 (31.4)
Restlessness	3,090 (36.9)	1,253 (30.3)	863 (35.5)	349 (64.4)	267 (87.3)	90 (39.5)	77 (35.8)	65 (34.2)	19 (24.7)	37 (67.3)	17 (39.5)	53 (34.0)
Depression	3,695 (44.1)	1,839 (44.5)	1,122 (46.2)	439 (81.0)	7 (2.3)	30 (13.2)	102 (47.4)	47 (24.7)	23 (29.9)	21 (38.2)	11 (25.6)	54 (34.6)
Lack of appetite	3,694 (44.1)	2,350 (56.8)	803 (33.1)	224 (41.3)	14 (4.6)	46 (20.2)	68 (31.6)	106 (55.8)	18 (23.4)	18 (32.7)	5 (11.6)	42 (26.9)
Nausea	3,023 (36.1)	2,162 (52.3)	530 (21.8)	154 (28.4)	3 (1.0)	16 (7.0)	25 (11.6)	96 (50.5)	7 (9.1)	11 (20.0)	2 (4.7)	17 (10.9)
Movement limitation	2,961 (35.4)	1,303 (31.5)	1,159 (47.7)	96 (17.7)	18 (5.9)	97 (42.5)	120 (55.8)	26 (13.7)	43 (55.8)	17 (30.9)	5 (11.6)	77 (49.4)
Paresthesia	2,721 (32.5)	1,337 (32.3)	1,085 (44.7)	129 (23.8)	1 (0.3)	8 (3.5)	45 (20.9)	28 (14.7)	49 (63.6)	8 (14.5)	7 (16.3)	24 (15.4)
Spasticity	2,460 (29.4)	992 (24.0)	924 (38.0)	138 (25.5)	3 (1.0)	51 (22.4)	163 (75.8)	41 (21.6)	60 (77.9)	14 (25.5)	8 (18.6)	66 (42.3)
Dizziness	2,005 (23.9)	1,201 (29.0	531 (21.9)	140 (25.8)	1 (0.3)	15 (6.6)	35 (16.3)	38 (20.0)	20 (26.0)	5 (9.1)	4 (9.3)	15 (9.6)
Agitation	1,981 (23.7)	814 (19.7	554 (22.8)	248 (45.8)	190 (62.1)	39 (17.1)	24 (11.2)	34 (17.9)	15 (19.5)	26 (47.3)	11 (25.6)	26 (16.7)
Burning sensation	1,659 (19.8)	760 (18.4	704 (29.0)	99 (18.3)	2 (0.7)	5 (2.2)	16 (7.4)	30 (15.8)	19 (24.7)	6 (10.9)	2 (4.7)	16 (10.3)
Dry mouth	1,635 (19.5)	1,072 (25.9	363 (14.9)	108 (19.9)	1 (0.3)	9 (3.9)	34 (16.2)	13 (6.9)	8 (10.4)	9 (16.4)	2 (4.7)	16 (10.3)
Headache	1,574 (18.8)	788 (19.1	517 (21.3)	151 (27.9	2 (0.7)	22 (9.6)	15 (7.0)	35 (18.4)	12 (15.6)	5 (9.1)	8 (18.6)	19 (12.2)
Respiratory problems	1,537 (18.4)	955 (23.1)	376 (15.5)	79 (14.6)	4 (1.3)	31 (13.6)	21 (9.8)	22 (11.6)	7 (9.1)	11 (20.0)	2 (4.7)	29 (18.6)
Cognitive impairment	1,266 (15.1)	574 (13.9	282 (11.6)	97 (17.9)	91 (29.7)	113 (49.6)	26 (12.1)	8 (4.2)	10 (13.0)	28 (50.9)	3 (7.0)	34 (21.8)
Tremor	1,203 (14.4)	535 (12.9)	323 (13.3)	95 (17.5)	1 (0.3)	35 (15.4)	154 (71.6)	8 (4.2)	13 (16.9)	11 (20.0)	1 (2.3)	27 (17.3)
Pruritus	1,198 (14.3	639 (15.5)	369 (15.2)	102 (18.8)	3 (1.0)	9 (3.9)	13 (6.0)	29 (15.3)	4 (5.2)	12 (21.8)	7 (16.3)	11 (7.1)
Rage attacks	1,191 (14.2)	371 (9.0)	262 (10.8)	220 (40.6)	224 (73.2)	37 (16.2)	9 (4.2)	12 (6.3)	8 (10.4)	24 (43.6)	4 (9.3)	20 (12.8)
Visual impairment	937 (10.9)	530 (12.8)	242 (10.0)	49 (9.0)	4 (1.3)	39 (17.1)	18 (8.4)	6 (3.2)	9 (11.7)	14 (25.5)	3 (7.0)	22 (14.1)

PTSD, post-traumatic stress disorder; PD, Parkinson's disease; IBD, inflammatory bowel disease; MS, multiple sclerosis.

Increased appetite was reported as a side effect by 232 patients (4.7% overall and 2.0% as a lone side effect); 36.6% of them received their cannabis license for pain indication, 34.4% for cancer, 11.7% for PTSD, 4.3% for Crohn's and colitis, and 3.9% for autism.

Table 3

Frequency of adverse events at the 6-months follow-up questionnaire.

Side-effects experienced due to the use of cannabis (4,891), no. (%)	Total responses, no. (%)
Have you experienced side-effects due to the use of cannabis? (Yes)	**1,675 (34.2)**
Physiological	
Dizziness	399 (8.2)
Dry mouth	329 (6.7)
Increased appetite	232 (4.7)
Sleepiness	217 (4.4)
Nausea	143 (2.9)
Weakness	141 (2.9)
Drop in sugar	105 (2.1)
Headaches	83 (1.7)
Cough	75 (1.5)
Vomiting	55 (1.1)
Burning sensation in throat	48 (1.0)
Red/irritated eyes	43 (0.9)
Increased heart rate	41 (0.8)
Stomachache	28 (0.6)
Drop in blood pressure	27 (0.6)
Decreased appetite	20 (0.4)
Blurred vision	19 (0.4)
Tremor	14 (0.3)
Sleep disturbance	12 (0.2)
Difficulty breathing	12 (0.2)
Itching	10 (0.2)
Slurred speech	10 (0.2)
Diarrhea	10 (0.2)
Constipation	6 (0.1)
Chills	2 (0.04)
Cognitive	
Psycho-active effects (feeling "high")	399 (8.2)
Confusion and disorientation	329 (6.7)
Restlessness	232 (4.7)
Hallucinations	217 (4.4)
Decreased concentration	143 (2.9)
Decreased memory	141 (2.9)
Fear	105 (2.1)
Anxiety	83 (1.7)
Gloominess	75 (1.5)
Nervousness	55 (1.1)
Apathy	48 (1.0)
Other	43 (0.9)

Of those responding to the side-effects chapter, 2.9% reported nausea. This rate varied between different chemovars in the interval of 1.2–3.8%, with THC rich indica chemovar "Dorit" being the highest.

Table 4

Logistic regression multivariable analysis of factors associated with treatment success after 6 months.

	Odds ratio	95% Confidence interval	P value
Current cigarette smoking vs. non-smokers	2.40	2.01–2.86	<0.001
Previous experience with cannabis vs. no previous experience	2.16	1.83–2.54	<0.001
Active drivers vs. non-drivers	1.36	1.17–1.56	<0.001
Employed vs. unemployed	1.30	1.08–1.55	<0.01
Mean age	0.98	0.98–0.99	<0.001

Treatment success was defined as at least a moderate or significant improvement in the patient's condition and none of the following: cessation of treatment or serious side-effects.

Primary Effectiveness Outcome

The primary effectiveness outcome was assessed for all respondents to the intake questionnaires except for patients refusing treatment (69), deceased patients (1,785), patients switching to other providers (271), and active patients who did not respond to the follow-up questionnaire (911). Thus, the primary effectiveness outcome was assessed for 5,524 of the 8,560 patients responding to the intake questionnaire (64.5%, Figure 1). Overall, 3,902 (70.6%) patients out of 5,524 experienced treatment success. Multivariable analysis revealed the following factors as associated with treatment success: cigarette smoking (O.R 2.4, 95% C.I 2.0–2.2), prior experience with cannabis (O.R 2.1, 95% C.I 1.8–2.5), driving (O.R 1.3, 95% C.I 1.1–1.5), employment (O.R 1.3, 95% C.I 1.0–1.5), and young age (O.R 0.9, 95% C.I 0.9–0.9), (Table 4).

Of 4,364 patients who answered to the 6-months followup questionnaire, the most common chemovar used was an 18% THC indica (Erez, 2,551 patients, 55.7%). This chemovar was most often consumed by smoking or vaporization (1,306 patients), at an average dried flowers weight of 0.3 g (54mg THC) per administration, and a frequency of 3.4 administrations per day. A total of 935 patients consumed Erez sublingual oil 300mg THC/10ml, consuming an average dose of 5.7mg THC per administration, and a frequency of 2.4 administrations per day (further description in Table 5).

The most improved symptoms were rage attacks (decrease of 91.5%), restlessness (89.5%), sleep disturbances (89.1%), and nausea (88.9%). For more information about the changes in the specific symptoms after 6 months, please refer to Supplementary Table 4. Of the patients reporting nausea at intake and responding to the follow-up questionnaire, 30.5% reported that they no longer suffer from nausea, 58.4% reported that the symptomimproved, 10.0% reported no change in nausea they experience, and 1.1% of patients reported deterioration in the nausea they experienced.

Table 5

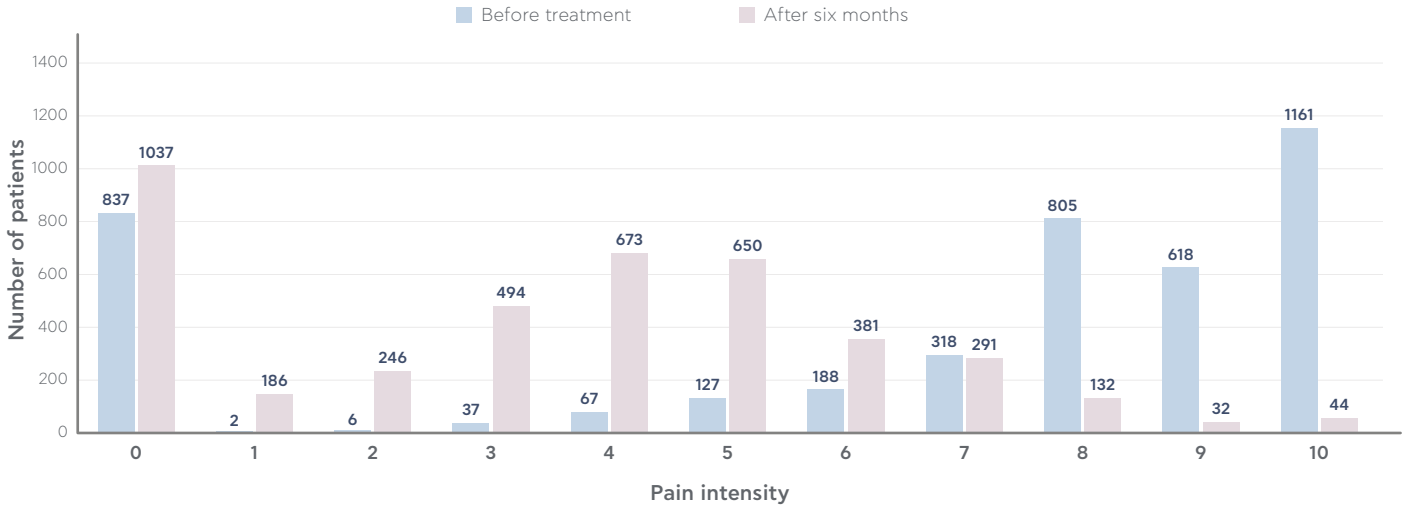
Cannabis consumption characteristics.

Chemovar	Description	Number of patients (%)	Most common consumption time	Most common methods of administration	Average number of administration per day	Average dose per administration	Average cannabinoid dose per administration
Erez	18% THC, 0% CBD Indica	2,551 (55.7%)	Evening (1,590 patients) and night (1,030 patients)	1,306 smoking or evaporation	3.4	0.3 g	54 mg THC
				935 sublingual oil (300mg THC/10ml)	2.4	3.8 Drops*	5.7 mg THC
Alaska	18% THC, 0% CBD Sativa	2,144 (46.8%)	Morning (1,382 patients) and afternoon (1,388 patients)	1,870 smoking or evaporation	4.3	0.3 g	54 mg THC
				221 sublingual oil (300mg THC/10ml)	3.3	3.5 Drops*	5.2 mg THC
Avidekel	15% CBD, 0.5% THC Indica	1,451 (31.7%)	Morning (908 patients) and afternoon (753 patients)	210 smoking or evaporation	4.2	0.26 g	39 mg CBD
				976 sublingual oil (300mg CBD/10ml)	2.5	4.5 Drops*	6.7 mg CBD

*One drop is equivalent to 0.04 ml.

Figure 2

Assessment of pain intensity. Pain intensity was assessed on a 0–10 scale, before and after 6 months of cannabis therapy ($p < 0.001$). The assessment was made on 4,166 patients who responded to this question at the two time points. Pain level was measured on an 11-point scale (0 = no pain, 10 = worst pain imaginable).



Pain intensity was assessed both at intake and at 6 months in 4,166 patients. Prior to treatment initiation, 62.0% of patients reported their pain at between 8 and 10, while only 5.0% reported this intensity at 6 months ($p < 0.001$, Figure 2); 7.3% of the patients demonstrated deterioration in their pain scale. In 17.8%, the level of pain did not change while in 74.7% it improved, of which 64.3% of patients showed an improvement of 30% or more in their reported pain intensity and 47.2% reported an improvement of 50% or more in their pain intensity. In 1,580 patients, only under the pain indication, 85.9% experienced an improvement of 30%ormore, and 59.3% an improvement of 50% or more in their VAS pain scale.

Quality of life (QOL) was assessed both at intake and at 6 months in 4,143 patients. While only 12.9% of patients reported good QOL prior to treatment initiation, 69.9% reported good QOL at 6 months ($p < 0.001$, Figure 3).

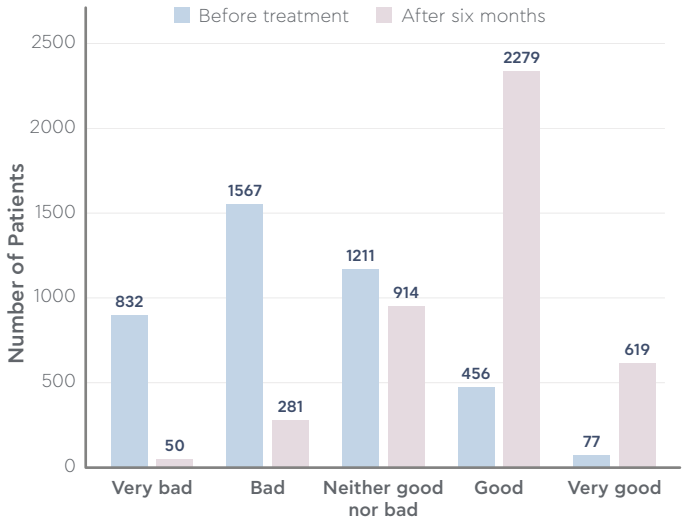
Concomitantmedications consumption was evaluated both at the intake and in the follow-up questionnaires in 3,544 patients. The most reduced medications classes were opioids (52.5%), other analgesics and antipyretics (39.2%), anti-psychotics (36.9%) anti-epileptics (35.7%), and hypnotics and sedatives (35.3%) (Table 6).

Figure 4A presents rates of the primary outcome of treatment effectiveness and safety at 6 months, stratified by the primary indication for use, ranging between 55.4% for epilepsy to 90.8% for PTSD. Figure 4B presents the proportion of patients experiencing any side-effect, and ranges between 28.9% for Tourette syndrome to 40.0% in patients with epilepsy.

In the analysis of the subgroup of 1,500 patients with only one chemovar used, we found significant differences in success rate. The two chemovars utilized by more than 50 patients that differ in the success rate were Alaska 91%chance of success vs. Avidekel with 66.4% ($p < 0.001$). However, these chemovars were utilized by patients with different medical conditions and therefore the direct comparison of the success rates is not fully informative.We have not found a difference of safety rates between the different chemovars ($p > 0.05$).

Figure 3

Quality of life assessment. Quality of life was assessed prior to and 6 months after initiation of cannabis treatment ($p < 0.001$). Assessment was done on 4,143 patients who responded twice to this question.



Missing Data Analysis

We compared baseline characteristics between patients responding to the 6-month questionnaire (4,364) and active patients with an intake questionnaire, without the 6-month follow-up (911). Patients without follow-up data had less experience with cannabis prior to the treatment initiation, had lower rates of tobacco use, consumed fewer medications, and recorded lower rates of driving (Supplementary Table 5). Even imputing a worst-case scenario in which all patients unavailable for follow-up were categorized as "treatment failure," most patients nonetheless achieved therapeutic success with a marked improvement in their condition (3,902 patients of 6,435, 60.6%). These patients were certainly not "lost to follow-up" because they were all active patients who came month after month to the medical dispensary to buy their monthly quota.

DISCUSSION

In this prospective study, we describe the characteristics and outcomes of approximately 10,000 patients treated with medical cannabis. Results showed high adherence, high safety with a low incidence of adverse events, and a high rate of effectiveness in the prescribed treatment, as well as a decrease in pain levels, improvement in QOL, and a reduction in the consumption of concomitant medications.

Demographic Characteristics

The characteristics of medical cannabis users (age, severity of diseases, number of comorbidities, number of symptoms, number of medications, employment status, etc.) depend upon and are determined by the limitations and laws set by governmental and regulatory authorities. During the study period, Israeli national regulation of medical cannabis provided strict guidelines for the patients and their physicians on the use of the medication. The demographic and medical characteristics of our cohort differ from most reported populations. The Israeli medical cannabis patients are on average (55 years old) two and a half-decade older than patients in comparable reports (2, 8, 10, 12–16, 18–21), with a more balanced gender distribution (51.3% men compared to 60–80% in most studies) (2, 11, 13–19, 21–24). In the current cohort, themain indication for cannabis treatment was cancer (48.9%), while in other studies the main indications were pain (2, 10–12, 15, 18, 24, 25, 33–35), anxiety (13, 14, 36), and depression (19); cancer was diagnosed in only 7.4–11.4% of the patients (2, 10–12, 14, 15, 19, 24, 25).

Almost 20% of the study population died within the first 6 months of follow-up primarily due to malignancies (90.1%).

Treatment Adherence

Adherence to cannabis treatment was 77.7%, similar to the treatment withdrawal of 23.8% that was found in a retrospective cohort study on medical cannabis patients with a mean age similar to the patients' ages in our study (33).

Treatment adherence in our cohort was favorably comparable to the expected adherence in patients taking chronicmedications: in a systematic review of 76 studies, patients taking medication on a schedule similar to the cannabis treatment regimen of at least four times daily, demonstrated average adherence rates of 50% (range 31–71%) (37). Furthermore, in a study of long-term treatment with opioids, treatment was discontinued in 51% of the patients (38).

Safety

The safety of cannabis treatment in this heterogeneous population of patients was found to be high, especially

Table 6 Prescription medication use at 6 months follow-up.

Drug class	Total responders	Same dose	Stopped consuming this medication	Dose decreased	Dosage increased	Other*	Patients who started taking a drug that was not taken during intake session
Opioids	1,216	553 (45.5)	472 (38.8)	167 (13.7)	24 (2.0)	3 (0.2)	63
Antidepressants	1,232	815 (66.2)	310 (25.2)	83 (6.7)	24 (1.9)	3 (0.2)	93
Antiepileptics	1,098	680 (61.9)	282 (25.7)	110 (10.0)	26 (2.4)	0 (0.0)	61
Drugs for peptic ulcer and gastroesophageal reflux disease (GERD)	713	568 (79.7)	119 (16.7)	21 (2.9)	5 (0.7)	2 (0.3)	61
Antithrombotic agents	697	606 (86.9)	79 (11.3)	11 (1.6)	1 (0.1)	2 (0.3)	38
Anxiolytics	657	496 (75.5)	109 (16.6)	46 (7.0)	6 (0.9)	0 (0.0)	17
Lipid modifying agents	679	565 (83.2)	102 (15.0)	9 (1.3)	3 (0.4)	2 (0.3)	22
Hypnotics and sedatives	600	386 (64.3)	166 (27.7)	46 (7.7)	2 (0.3)	3 (0.5)	27
Other analgesics and antipyretics	471	285 (60.5)	141 (29.9)	44 (9.3)	1 (0.2)	2 (0.4)	22
Ace-inhibitors	350	298 (85.1)	39 (11.1)	11 (3.1)	2 (0.6)	5 (1.4)	10
Blood glucose lowering agents, excluding insulin	324	270 (83.3)	38 (11.7)	15 (4.6)	1 (0.3)	0 (0.0)	21
Selective calcium channel blockers with mainly vascular effects	299	258 (86.3)	37 (12.4)	3 (1.0)	1 (0.3)	2 (0.7)	6
Corticosteroids for systemic use	242	159 (65.7)	65 (26.9)	17 (7.0)	1 (0.4)	1 (0.4)	21
Beta blocking agents	255	220 (86.3)	27 (10.6)	7 (2.7)	1 (0.4)	1 (0.4)	10
Antipsychotics	276	169 (61.2)	64 (23.2)	38 (13.8)	5 (1.8)	0 (0.0)	21
Thyroid preparations	248	222 (89.5)	16 (6.5)	8 (3.2)	2 (0.8)	1 (0.4)	12

Change in consumption of main medications families that were consumed regularly during intake session in active patients responded to the 6-months follow-up questionnaire, for all the patients and per indication. PTSD, post-traumatic stress disorder; IBD, inflammatory bowel disease; PD, Parkinson's disease; MS, multiple sclerosis.
*Other: the two most reported answers under this rubric were: I do not remember and as needed.

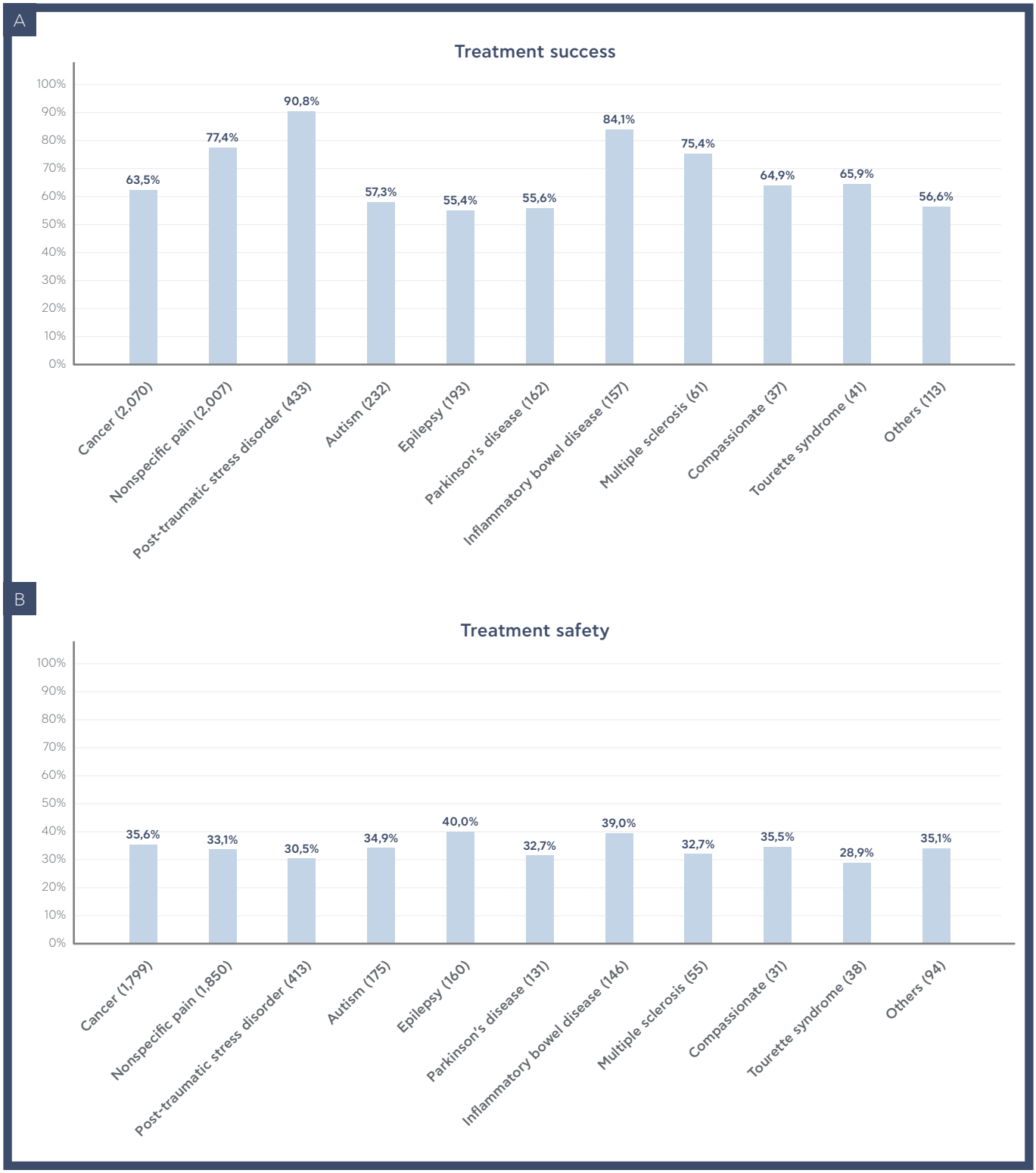
when compared with the safety of long-term opioid treatment. Side effects of medical cannabis were infrequent, minor, and rarely the cause of discontinuation. The most common side-effect, dizziness, was reported by 8.2% of the active responders, while the usual prevalence of side-effects in patients on opioid therapy is substantially higher: more than 40% of the patients report dizziness, more than 35% report constipation, more than 30% report nausea, and more than 25% report fatigue (38). In addition, long-term opioid treatment is associated with sedation, cognitive impairment, depression, addiction (39), and subtle neuropsychological changes (40–42). These high-safety results are similar to a large, controlled study that prospectively measured the safety of a high-THC medical cannabis product in 215 patients treated in chronic pain clinics. The patients were compared with 216 patients in the clinics who did not use medical cannabis and were followed-up for 1 year. The adverse events in this study were modest, and no significant difference in the occurrence of serious adverse effects was found (43). These results may be attributed to the safety-focused approach implemented; a guided choice of chemovar and route of administration, a slow titration method, an initial follow-up after 1 month, and a follow-up after 6 months, could be the strategy that ensured that harms from medical cannabis were mitigated (44).

Effectiveness

Although this study is observational and thus no causality can be established, the treatment seems effective in reducing pain, in increasing QOL, and in reducing concomitant medication consumption. In our cohort, the primary effectiveness outcome was achieved by more than 70% of the patients, while only 17.4% of the patients discontinued treatment. Although further head-to-head comparative study between opioids and cannabis for palliation is needed, our results demonstrate numerically comparable effectiveness in pain treatment (e.g., opioids treatment provides adequate relief for 70–90% of patients with cancer pain) (45). However, long-term opioid treatment in non-specific pain patients delivered good pain relief in only 51% of patients (37). Although Cochrane review of neuropathic pain treated with cannabis-based medicines against placebo, found a modest gain from 16 studies (n = 1,750) with 21 vs. 17% achieving a 50% reduction in pain; and 39 vs. 33% achieving a 30% reduction (46), a multiplecriteria decision analysis found that the benefit-safety profiles for cannabinoids were higher than for other commonly used medications for chronic neuropathic pain largely because they contribute more to QOL and have a more favorable side-effect profile (47). Furthermore, for patients with chronic pain, opioids may contribute to substantial functional impairment (48), so serious adverse effects of opioids may limit effectiveness in some patients, even if adequate analgesia is achieved (48). The lack of serious side-effects of broad-spectrum cannabis products together with the effectiveness albeit shown in the small studies makes cannabis products a possible alternative for the treatment chronic pain.

The fact that previous experience with cannabis was associated with a higher chance of treatment success, can suggest that the placebo effect contributed to the overall improvement, as an expectation of a positive influence may increase the magnitude of the placebo effect. Moreover, young patients (usually with fewer comorbidities) that drive, smoke cigarettes, and are employed seems more likely to experience and report improvement following treatment.

Figure 4



Safety and effectiveness rates by indications. (A) Treatment success in 4,345 patients who responded to the 6-month follow-up questionnaire (and to the general effect question) and in 1,160 patients who discontinued treatment, by the primary indication for the cannabis treatment. Treatment success was defined as at least a moderate or significant improvement in the patient's condition and none of the following: cessation of treatment or serious side-effects defined as 9–10 out of 10 on the severity scale. (B) Treatment safety—presence of any side-effect in 4,891 active and inactive patients who responded to the side-effect questions at the 6-months follow-up questionnaire, by the primary indication for the cannabis treatment.

It is also possible that patients who smoke cigarettes know how to perform the inhaling action and are more likely to benefit from the treatment.

The broad effect of medical cannabis treatment, which has a beneficial effect on a variety of symptoms, can potentially explain the reduction in drug consumption (especially of

painkillers). Cannabis may be a viable alternative to opioids for those experiencing pain (49, 50).

Out of 1,160 patients responded to the intake questionnaire and discontinued treatment, 593 filled the follow-up questionnaire at 6 months. The most common reasons for discontinuing treatment were side-effects (25.0%), no therapeutic effect (24.6%), no longer a need for cannabis treatment (23.2%), or failed renewals of mandatory cannabis treatment licenses (6.8%). Furthermore, 44.3% of the patients who discontinued the treatment have reported at least moderate improvement in their symptoms following cannabis treatment. Even though all patients who discontinued treatment were classed as "treatment failures", we have recorded high rates of treatment success.

Treatment with medical cannabis is complex for several reasons: (1) the multiplicity of potential treatment chemovars, (2) the multiplicity of consumption options, (3) and because each patient will receive a different therapeutic dose, patients need to "find" their therapeutic dose in a slow titration process that is dictated by the psychoactive effect and other treatment side-effects.

A significant percentage of patients expressed concerns about initiating cannabis treatment. In addition, in the short term follow-up (after about a month of active treatment), a large group of patients needed additional consultation with an experienced cannabis clinic nurse in order to adjust the dosage or the treatment product, emphasizing the great importance of professional guidance and instruction during the first 2months of treatment. Without guidance, patients may take too high a dose, experience a side-effect, and abandon the treatment. In addition, without setting expectations regarding the patience required in the first weeks of treatment (until the body adapts to the product, and until reaching the therapeutic dose, especially with CBD products), the patient may conclude that, if after several attempts his condition does not improve, the treatment is unhelpful and so may eventually quit.

Limitations

The present findings should be interpreted with caution for several reasons. This is an observational study 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 patients with a specific disease (self-selection bias). The QOL and symptoms changes were assessed by non-validated questionnaires (though, the assessment was based on frequently used qualitative scales). Unfortunately, we have no data on the blood pressure and blood sugar control in our study population. Therefore, we cannotspeculate on the effect of the decrease of use of the blood pressure, diabetic, steroid medications observed in our population. 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. Furthermore, 14.2% of the patients initiating the treatment refused to undergo medical assessment even at baseline; we therefore could not assess safety and effectiveness of the treatment in this specific group of patients. As we have measured the refill adherence rather than the consumption adherence, some inaccuracies can emerge from including the patients who have bought the medications but did not consume it. Lastly, while the response rate at 6 months in living patients was above 70%, because of our population's morbidity, many had died within first 6 months, making it impossible to assess the safety and effectiveness of cannabis treatment in that subset of patients.

CONCLUSIONS

This is a large study describing certain characteristics of medical cannabis users in a tightly regulated environment. The treatment appears to be safe and efficacious. Establishing national and international clinical research programs to assess the true therapeutic effect of cannabis on various diseases is needed. To further elucidate the safety and effectiveness of medical cannabis therapy using objective measures, the next step requires the performance of high-quality double-blind placebo-controlled clinical trials.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Statement

The studies involving human participants were reviewed and approved by the IRB at the Soroka University Medical Center, Beer-Sheva, Israel, study number: SCRC-0415-15. Written informed consent from the participants or their legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author Contributions

LB-L and VN conceived the study, wrote the protocol, drafted the manuscript, and verified the underlying data. All authors acquired, analyzed, or interpreted the data. LB-L was the principal investigator and oversaw study design. All authors approved the final article.

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Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.827849/full#supplementary-material

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MEDICAL CANNABIS RESEARCH SYNOPSIS

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Medical Cannabis Research Synopsis

Interest in medical applications of Cannabis sativa has increased dramatically during the past 20 years. A 1999 report from the National Academies of Sciences, Engineering, and Medicine supported the use of medical cannabis in medicine, leading to several regulatory medical colleges providing recommendations for its prescription to patients. Proponents of medical cannabis support its use for a highly varied range of medical conditions, most notably in the fields of pain management and multiple sclerosis but also in other conditions. Medical cannabis can be consumed by patients in a variety of ways including smoking, vaporizing, ingesting, or administering sublingually or rectally. The plant consists of more than 100 known cannabinoids, the main ones of relevance to medical applications being tetrahydrocannabinol (THC) and cannabidiol (CBD).

Tikun is a proud pioneer and global leader in medical cannabis research. Rooted in Israel's regulatory environment, Tikun's 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 30,000 patients. Through extensive research and development, Tikun's 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, autism, cancer, IBD, and more.

This book contains a selected outline of global medical cannabis research as of February 2022.