Integrative Cancer Therapies
Volume 18: 1–8
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735419881498
journals.sagepub.com/home/ict
SAGE

The Effects of Dosage-Controlled Cannabis Capsules on Cancer-Related Cachexia and Anorexia Syndrome in Advanced Cancer Patients: Pilot Study

Gil Bar-Sela, MD[1,2], Daniela Zalman, MD[3], Valerya Semenysty, MD[3], and Eyal Ballan, PhD[4]

Abstract

Background: Cancer-related cachexia and anorexia syndrome (CACS) is a common phenomenon in cancer patients. Cannabis has been suggested to stimulate appetite but research on this issue has yielded mixed results. The current study aimed to evaluate the effect of dosage-controlled cannabis capsules on CACS in advanced cancer patients. **Methods:** The cannabis capsules used in this study contained two fractions of oil-based compounds. The planned treatment was 2 × 10 mg per 24 hours for six months of tetrahydrocannabinol (THC) 9.5 mg and cannabidiol (CBD) 0.5 mg. If patients suffered from side effects, dosage was reduced to 5 mg × 2 per day (THC 4.75 mg, CBD 0.25 mg). Participants were weighed on every physician visit. The primary objective of the study was a weight gain of ≥10% from baseline. **Results:** Of 24 patients who signed the consent form, 17 started the cannabis capsules treatment, but only 11 received the capsules for more than two weeks. Three of six patients who completed the study period met the primary end-point. The remaining three patients had stable weights. In quality of life quaternaries, patients reported less appetite loss after the cannabis treatment (p=0.05). Tumor necrosis factor-α (TNF-α) levels decreased after the cannabis treatment but without statistical significance. According to patients' self-reports, improvement in appetite and mood as well as a reduction in pain and fatigue was demonstrated. **Conclusions:** Despite various limitations, this preliminary study demonstrated a weight increase of ≥10% in 3/17 (17.6%) patients with doses of 5mgx1 or 5mgx2 capsules daily, without significant side effects. The results justify a larger study with dosage-controlled cannabis capsules in CACS.

Keywords

cancer, cachexia, anorexia, cannabis capsules, appetite loss

Submitted June 10, 2019; revised August 27, 2019; accepted September 18, 2019

Introduction

Cachexia is defined as a "multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment."[1] Cachexia may be masked by excess weight, obesity, edema,[2] or tumor mass.[3] Anorexia is a subjective term describing reduction or loss of appetite. Although it is commonly known that patients coping with cancer and cancer treatments experience loss of appetite, the exact prevalence of anorexia is unknown. In one study on advanced cancer patients, more than half the patients experienced anorexia.[4] A North Central Cancer Treatment Group study of 1115 patients with colorectal and lung cancer found that cancer patients with anorexia had lower survival rates and experienced more toxicity from chemotherapy than similarly matched patients who maintained their appetite.[5] Cachexia primarily caused by anorexia or reduced intake has been defined as cancer-related cachexia and anorexia syndrome (CACS). CACS, unlike cachexia,

[1]Emek Medical Center, Afula, Israel
[2]Technion-Israel Institute of Technology, Haifa, Israel
[3]Rambam Health Care Campus, Haifa, Israel
[4]Bethesda Metro Center, Bethesda, MD, USA

Corresponding Author:
Gil Bar-Sela, Cancer Center, Emek Medical Center, 21 Yitzhak Rabin Blvd, Afula 1834111, Israel.
Emails: gil_ba@clalit.org.il

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

includes weight loss caused by muscle wasting, as well as lipolysis and decreased intake.

Cannabis has long been suggested to stimulate appetite, decrease nausea and vomiting, and improve quality of life (QoL) in cancer patients.[6-8] However, the few studies on these effects yielded mixed and inconclusive findings.[9-11] In addition, some studies included various methodological limitations that limit the ability to draw any firm clinical conclusions (eg, small sample,[12] unknown cannabis products, different ways of intake).

Several formulations of cannabis with different pharmacokinetic and pharmacodynamics are available in the market. Pulmonary assimilation of inhaled THC (tetrahydrocannabinol) causes a maximum plasma concentration within minutes; psychotropic effects start within seconds to a few minutes, reach a maximum after 15 to 30 minutes, and taper off within 2 to 3 hours. Following oral ingestion, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60 to 120 minutes. In several studies, maximal plasma concentrations were observed as late as 4 hours, and even 6 hours in some cases.[13] Several subjects showed more than 1 plasma peak. In case of oral administration, psychotropic effects set in with a delay of 30 to 90 minutes, reach their maximum after 2 to 3 hours, and last for about 4 to 12 hours, depending on dose and specific effect.[13] Another common route of administration is sublingual. Pure cannabinoids are extracted from the raw plant, dissolved in different oils, and administered with a dropper. The therapeutic window of sublingual oil administration is 2 to 4 hours with a rapid onset due to quick absorption through the oral cavity.

The most common oral administration of cannabinoids is through eating edibles, mainly cookies, chocolate bars, and lozenges. Since absorption is attenuated when cannabinoids are ingested orally,[14] edibles usually contain high dosages of cannabinoids (50-300 mg). The high dosage may cause undesirable side effects, mainly dizziness, anxiety, and dissociation. These side effects may cause patients to withdraw from the therapeutic process. The oral administration route has the longest therapeutic window (4-8 hours)[14] and lacks the undesirable effects of smoking. The unmet need for an oral formulation with higher bioavailability and a lower peak of psychoactive effect led us to use a new oral capsule standardized with a longer therapeutic window and lower C_{max}.[13,14] In Israel, cannabis pills are given under the regulations of the Ministry of Health to advanced cancer patients with various symptoms to improve their QoL.[15,16]

Given the potential effect of cannabis use on CACS and the mixed findings regarding this subject, the current study aimed to evaluate the influence of cannabis pills on CACS in advanced cancer patients. Secondary objectives were to evaluate the safety and toxicity of the cannabis treatment and to observe changes in appetite and in TNF-α (tumor necrosis factor-α) levels.

To test the hypothesis that cannabis pills can improve body weight by more than 10%, the number needed to treat was calculated according to true response probability of less than 5%. This calculation with the same primary end point that achieved 3% true response on dronabinol and 11% on megestrol was based on the results of a phase III study.[9]

Based on a significance level of .05 (α) and a power of 0.90, the sample size for the pilot study should be 21 patients. If only 1 patient achieves the primary end-point, the study will be terminated.[17]

Methods

Participants and Procedure

The study enrolled patients with advanced cancer under treatment in the Division of Oncology at Rambam Health Care Campus in Haifa, Israel. Inclusion criteria comprised age older than 18 years, histological evidence of an incurable malignancy, estimated life expectancy ≥3 months, performance status ≤3 (ECOG [Eastern Cooperative Oncology Group]) classification, weight loss of at least 5% during the preceding 2 months (as documented in the patient's medical file), and the patient's belief that loss of appetite or weight loss is an ongoing problem for him. The use of chemotherapy or radiotherapy was allowed.

Exclusion criteria comprised patients with ongoing use of tube feedings or parenteral nutrition, edema or ascites, central nervous system metastases or brain tumors (patients with stable disease in the brain 28 days after treatment could be included in the study), treatment with adrenal corticosteroids (except for short-term dexamethasone during chemotherapy), androgens, progestational agents or other appetite stimulants during the previous 2 weeks, insulin-requiring diabetes, pregnancy or lactation or unwillingness to use oral contraceptives, other life-threatening medical conditions, anticipated alcohol or barbiturate use during the study period, mechanical obstruction of the alimentary tract, malabsorption, or intractable vomiting, and use of cannabis or synthetic cannabinoids in the preceding 4 weeks.

All patients provided written informed consent. The study protocol was approved by the Ministry of Health Unit for Medical Cannabis and by the hospital's institutional ethics committee (0275-14-RMB). The study (NCT02359123) was conducted in accordance with good clinical practice and the Helsinki Declaration.

Study Design and Treatment

The cannabis capsules used in this study contained 2 fractions of oil-based compounds, provided by Cannabics Pharmaceuticals Inc, Bethesda, MD. A liquid and

transparent fraction, which contains pure cannabinoid extract dissolved in organic coconut oil, is responsible for the quick onset of the therapeutic effects within 20 to 60 minutes. A consolidated cannabinoid, lipid-based drug delivery systems fraction is responsible for a gradual and long-lasting therapeutic effect (6-8 hours), due to a proposed constant and steady release of active cannabinoids. The formulation contains a pure extract of cannabinoids, monoglyceride, and diglyceride (E471), combined with carrageenan, which is known for its controlled release properties[18] and organic coconut oil. The 2 highly abundant cannabinoids in cultivated cannabis plants are THC and CBD (cannabidiol). The study capsules contained either 10 mg of active cannabinoids of which THC is 9.5 mg and CBD is 0.5 mg or 5 mg of active cannabinoids (THC 4.75 mg and CBD 0.25 mg).

The planned treatment was 2 × 10 mg capsules per 24 hours. First intake is preferable in the morning. The second dosage could be administered after 8 hours according to patient's need or before sleep for patients who suffer from sleep deprivation. In this study, patients were treated initially for 2 weeks with 1 × 10 mg capsules per day for gradual adaptation and the dose could be increased to 2 × 10 mg capsules per 24 hours after. However, if patients suffered from side effects that reduced significant daily life activities, mainly related to dizziness, and/or anxiety, their dosage was reduced to 5 mg per day. The decision of dose reduction was taken in relation to patients' report of side effects and adherence to the protocol.

Assessment Tools

Physical examination, including weighing the patient and toxicity assessment according to CTCAE (Common Terminology Criteria for Adverse Events) recommendations,[19] was done every 2 weeks during the first month, every month in the following 2 months, and every 6 weeks in the following 3 months. The primary objective of the study was a weight gain of ≥10% from baseline weight.

Blood count, biochemistry blood test including electrolytes, renal and liver function tests, albumin level, and total cholesterol level, and TNF-α level were drawn on day 1 and after 3 months.

QoL was assessed at day 1 using the European Organization of Research and Treatment of Cancer core questions on the Quality of Life Questionnaire, version 2 (EORTC QLQ-C30.[20]

Urine THC levels were checked on day 1 to exclude the use of cannabis or synthetic cannabinoids.

Evaluation of side effects was done during every physician visit.

All outcome measures were calculated based on published normative data.

Results

Patients' Characteristics

Twenty-four patients signed the consent form and entered the study. Median age of the entire group of patients was 66 years, and 62.5% were male. Those patients had 12 different malignancies; the most prevalent types were pancreas and colon carcinoma (4 patients each) and lung and prostate carcinoma (3 patients each). Chemotherapy was administered to 21 (87.5%) patients, 3 together with radiation. Only 2 patients received immunotherapy and 1 received radiation alone. Median weight was 65.5 kg, and median ECOG performance status was 1.

Of 24 patients who signed the consent form, 17 started the cannabis capsules treatment (Figure 1). Seven patients withdrew from the study before beginning cannabis intake. Among these patients, 2 decided to receive cannabis in a different way, 3 withdrew from the study without any specific explanation, 1 began to suffer from dysphagia and did not meet the exclusion criteria, and 1 patient had rapid deterioration due to disease progression. Six patients withdrew from the study during the first 2 weeks of treatment. Four patients dropped out due to side effects of the cannabis treatment, 3 on the higher dose of cannabis capsules of 10 mg; 2 patients withdrew from the study due to rapid disease progression and severe chemotherapy side effects. Eleven patients participated in this study for more than 2 weeks of treatment; their demographics and characteristics are described in Table 1. Five patients dropped out between 2 weeks and 4.5 months. Three patients withdrew from the study due to disease progression and 2 patients due to side effects of cannabis intake. Six patients completed the study and received cannabis capsules for a period of 6 months (Table 1).

Six patients were included in the analysis of TNF-α levels before and after the cannabis treatment (these patients received cannabis capsules for a period of 6 months). Among these 6 patients, 4 demonstrated a decrease in TNF-α level with correspondence to weight gain or stability during this period (Table 1).

Cannabis Dosage

The initial planned dose of 10 mg capsules was given to the first 4/17 patients who started the cannabis treatment. These 4 patients received 1 capsule of 10 mg daily for a minimum of 2 weeks and a maximum of 4.5 months. Among these 4 patients, 3 withdrew from the study because of cannabis side effects, while taking only one 10 mg capsule. The other patient took 2 capsules of 10 mg without side effects, but withdrew due to general deterioration related to disease progression.

The rest of the 13 patients were given a reduced dosage of 5 mg capsules. Of these 13 patients, 10 received

Table 1. Demographics and Medical Characteristics of Patients Treated With Cannabis Pills for More Than 2 Weeks.

Patient Number	Cancer Type	Cancer Treatment	Response to Treatment During the Study	PS	Age	Baseline Weight	Weight at End of Study	Baseline TNF-α (pg/mL)	TNF-α at End of Study (pg/mL)
1	Lung	Immunotherapy	TP	1	71	74.2	73.3		
2	Pancreas	Chemotherapy	PR	2	69	74	73.5	68.4	26.5
3	Prostate	Chemotherapy	SD	1	80	72	72		
4	Sarcoma	Chemotherapy + radiation	PR	1	66	56	62.5		
5	Stomach	Chemotherapy	PR	1	77	53	53		
6	Melanoma	Chemotherapy	TP	1	77	65	65	5.2	140.2
7	Gastric	Chemotherapy + biological	SD	1	70	58	62.5	5.3	0
8	Pancreas	Chemotherapy	PR	1	69	74	74	13.8	52
9	Head and neck	Chemotherapy + immunotherapy	PR	1	68	66	73	75.6	27.5
10	Stomach	Chemotherapy + biological	PR	2	57	54.4	54.2		
11	Lung	Immunotherapy	PR	1	67	55.5	67.5	82	3.4

Abbreviations: PS, performance status; TP, tumor progression; PR, partial response; SD, stable disease; TNF-α, tumor necrosis factor-α.

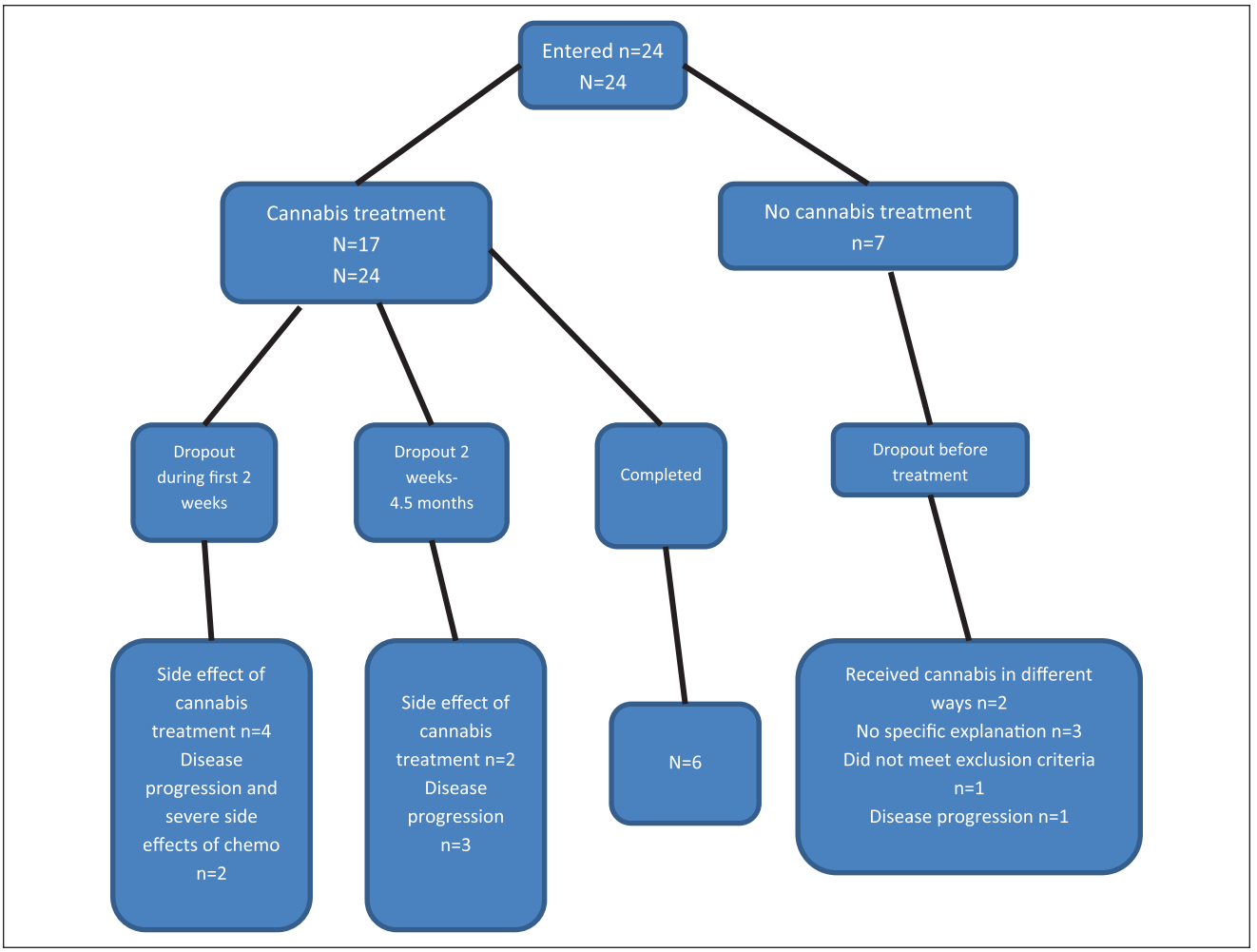


Figure 1. Study procedure.

Table 2. Patient's Body Weight Variations (Number of Patients).

Dropout Timeline	Loss of Weight	Stable Weight	Weight Increase <10%	Weight Increase >10%
0.5-4.5 months	4	1	0	0
6 months (study completion)	0	2	1	3

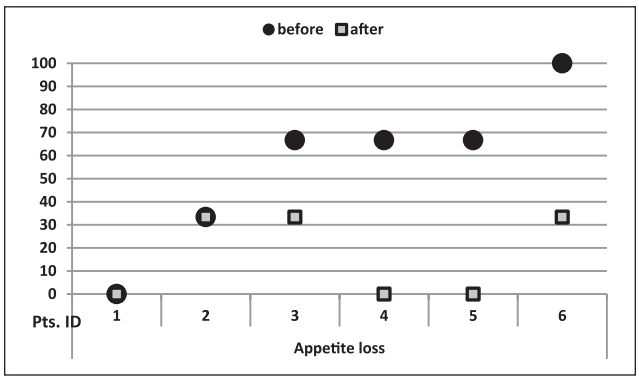


Figure 2. EORTC QLQ-C30 appetitive loss subscale among the 6 patients who completed the cannabis treatment (EORTC QLQ-C30, European Organization of Research and Treatment of Cancer Quality of Life Questionnaires).

one 5 mg capsule daily for periods ranging from 2 weeks to 6 months. Only 3 patients received 5 mg twice a day. Among these 3, one received 1 capsule of 5 mg daily for 5 days and then dosage was increased to 2 capsules daily for 9 days. This patient dropped out after 2 weeks due to severe chemotherapy-related side effects. The second patient received 1 capsule of 5 mg for 2 months and 2 capsules daily until study completion, and the third patient received one 5 mg capsule daily for 1 month and 2 capsules daily until study completion. Tachycardia was not reported as an adverse event during this study.

Body Weight Evolution

The patients' body weight variations are summarized in Table 2. Among the 7 patients who dropped out of the study during the first 2 weeks of treatment, no data were available regarding weight variations. Four of the 5 patients who dropped out between 2 weeks and 4.5 months lost weight during the study period, due to disease progression and changes in oncological treatment, with deterioration related to chemotherapy side effects.

Among the 6 patients who completed the study and took the capsules for a period of 6 months, 2 patients remained at a stable weight, 1 had a weight increase of 7.7%, and 3 patients met the primary end-point, showing a weight increase of more than 10% (10.6%, 11.6%, and 21.6%).

Quality of Life Analysis

Six patients were included in the statistical analysis of the EORTC QLQ-C30. Among these 6, five completed the study and received cannabis capsules for a period of 6 months and 1 patient took the cannabis treatment for a period of 4.5 months. The results showed no significant difference in the overall QoL score before and after the cannabis treatment. However, in the appetite loss subscale of the questionnaire, it was found that patients reported significantly fewer complaints about appetite loss after receiving the cannabis treatment ($P = .05$). Figure 2 demonstrates the scores of this subscale among the 6 patients who completed the cannabis treatment.

Patients' Self-Reports Regarding Cannabis Treatment

Table 3 summarizes the positive secondary effects from the cannabis capsules. Almost all patients who crossed the first 2 weeks of cannabis treatment reported an increase in appetite. Pain reduction and sleep improvement were reported by half the patients who completed the study. In addition, mood improvement and fatigue reduction were reported by 2 patients.

However, high numbers of patients reported side effects due to cannabis intake. Among the 4 patients who received 10 mg capsules, 3 (75%) reported side effects such as tiredness, dizziness, disorientation, anxiety, hallucinations, and altered general functioning. Among the 13 patients who received 5 mg capsules, 3 (23%) dropped out of the study because of similar side effects. All psychoactive side effects occurred 1 to 2 hours after the cannabis capsule intake, lasted for 2 to 3 hours, and caused incapacity to be physically active during these hours. All reported side effects were CTCAE grade 1 to 2 only, but interfered with daily life for those hours.

Discussion

The present study aimed at evaluating the effect of dosage-controlled cannabis capsules on CACS and, more specifically, on weight variations in advanced cancer patients. The current preliminary findings showed a weight increase of ≥10% for 3 patients (50% of those patients who completed the study). The remaining patients had stable weights. Also, all patients who were involved in the study for 4.5 months reported an increase in appetite, as did 83%

Table 3. Patients' Self-Reports Regarding Secondary Symptoms From Cannabis Capsules (Number of Patients).

	Appetite Increase	Pain Reduction	Sleep Improvement
Until 2 weeks	0	0	0
Between 2 weeks and 4.5 months	5 (100%)	0	0
6 months (study completion)	5 (83.3%)	3 (50%)	3 (50%)

of the patients who completed the study. For 50% of the patients who completed the study, there were reports of pain reduction and sleep improvement. Additional results showed a significant decrease of appetite loss complaints among 83% of the patients who completed the study.

TNF-α, a pro-inflammatory cytokine, has an important role in the pathological mechanisms of cachexia in cancer. No statistical significance was seen in TNF-α level changes during this study; however, 4 patients of 6 completed the study and received cannabis capsules for a period of 6 months and demonstrated a decrease in TNF-α levels. This decrease was in correspondence to weigh gain or stability for those patients.

None of the other studies currently in the literature were conducted with controlled cannabis dosages, and routes of administration varied greatly, and therefore their results remain ambiguous. Dronabinol, or synthesized delta-9-tetrahydrocannabinol, is a naturally occurring compound activated in the central nervous system by cannabinoid receptors, and closely mimics the action of *Cannabis sativa*. The use of oral dronabinol in the management of anorexia and weight loss in HIV/AIDS patients revealed a positive effect on weight gain and led to several studies that were done with cancer patients. Those studies did not meet their primary endpoint. However, dronabinol had been associated with improved taste, smell, and food enjoyment.[21]

A number of studies investigating the efficacy of synthetic cannabinoids or purified extracts of THC/CBD in the treatment of cancer-associated symptoms have been published.[22-27] A randomized study with 469 advanced cancer patients suffering from cancer-related cachexia compared dronabinol with megestrol acetate or both treatments together on appetite improvement and weight gain. Results showed greater appetite improvement among the megestrol acetate-treated patients compared with the dronabinol-treated patients, 75% versus 49% ($P = .0001$). One important limitation of that clinical trial is the lack of a placebo-controlled arm to evaluate the efficacy of THC for cachexia.[10]

Another randomized study compared the effects on appetite of a combination of THC and CBD to THC alone or placebo among patients suffering from cancer-related anorexia-cachexia for 6 weeks. No significant differences between the groups were seen regarding improvement in appetite or weight gain. It should be noted that CBD dosages in the study were low, even in comparison to other studies,[11] which might explain the lack of differences found between the groups.

An additional study explored the effects of oral dronabinol with dosages varying from 2.5 to 20 mg per day on appetite, taste perception and food consumption in 50 cancer patients with decreased appetite, and chemosensory alterations, compared with placebo.[12] Results showed a significant improvement in appetite and protein consumption in the dronabinol group, thus supporting the claim that the failure of the previous trials to show any effects may be due to a suboptimal dosage. It appears clear that the main limitations of the existing literature on cannabis and CACS are the lack of controlled dosage of cannabis extracts used by patients, their administration and daily consumption, as well as the lack of objective measures of weight variations.

Over the years, as the therapeutic effects of cannabis have been explored, new routes of administration, including oral-mucosal, vaporization, or sublingual, have been examined.[28] While clinical studies show contradictory data regarding a correlation between smoking cannabis and respiratory diseases,[29] most physicians agree that smoking medical cannabis, while having its benefits, is not a healthy or standardized therapy. Depending on the route of administration, the absorption properties of cannabinoids and THC and the bioavailability vary greatly.

The formulation of the study capsule is a lipid-based drug delivery system, which highly improves the relatively low oral bioavailability (related to absorption, degradation, and metabolism). To the best of our knowledge, no prospective clinical trials exploring the effects of natural cannabis in the form of capsules with specific controlled dosage, according to the Good Clinical Practice criteria, on CACS in advanced cancer patients have been published. The initial dosage of cannabis that was given to the patients was 10 mg. In a prestudy use of capsules with 25 mg THC that were available in the Israeli market for cancer patients, minor side effects were reported by the patient to the company. The decision to lower the dosage to 10 mg THC came from the need to be in line with the regulation in the US market where the capsule is being sold as a medical cannabis product. The side effects of 10 mg of THC were mainly due to the patients being treatment-naïve with very high sensitivity/low tolerance to the psychoactive effect.

However, during the study, some patients reported several psychoactive side effects and it was decided to reduce the capsules' dosage to 5 mg. Almost no side effects were

reported with the 5 mg dosage. It seems that this dosage is appropriate for the treatment of CACS in advanced cancer patients under active treatment.

This study has several limitations. One is the number of patients who dropped out before study completion. This may be explained by the level of disease progression in a number of patients. Most patients suffered from various types of advanced cancer and received heavy oncological treatments at the time of the study. These conditions may have caused difficulties for these patients to take the cannabis capsules and to stay in the study until its completion. Another limitation is the lack of data collected throughout the study. This limitation may be explained mainly by the patients' physical condition that may have influenced their compliance regarding completing the questionnaires and returning them on time.

To the best of our knowledge, this is the first study investigating the effect of dosage-controlled cannabis capsules on CACS and, more specifically, on weight variations in advanced cancer patients.

Conclusions

Despite various limitations, the current preliminary study demonstrated a weight increase of ≥10% in 3/17 (17.6%) of the patients with doses of 5 mg × 1 or 5 mg × 2 capsules daily, without significant side effects. The results justify a larger study with dosage-controlled cannabis capsules in CACS.

Authors' Note

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

The authors thank Cannabics Pharmaceuticals for their contributions.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Gil Bar-Sela, Daniela Zalman, Valerya Semenysty, and Hedva Sheinman-Yofe declare no conflicts of interest. Eyal Ballan works for Cannabics Pharmaceuticals Inc.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research received funding from Cannabics Pharmaceuticals Inc, Bethesda, MD, USA.

Ethical Approval and Informed Consent

All patients provided written informed consent. The study protocol was approved by the Ministry of Health Unit for Medical Cannabis and by the hospital's institutional ethics committee (0275-14-RMB). The study (NCT02359123) was conducted in accordance with good clinical practice and the Declaration of Helsinki.

ORCID iDs

Gil Bar-Sela https://orcid.org/0000-0001-6579-1841
Eyal Ballan https://orcid.org/0000-0002-4113-3876

References

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12:489-495. doi:10.1016/S1470-2045(10)70218-7
2. Martin L, Watanabe S, Fainsinger R, et al. Prognostic factors in patients with advanced cancer: use of the patient-generated subjective global assessment in survival prediction. *J Clin Oncol*. 2010;28:4376-4383. doi:10.1200/JCO.2009.27.1916
3. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res*. 2009;15:6973-6979. doi:10.1158/1078-0432.CCR-09-1525
4. Sarhill N, Mahmoud F, Walsh D, et al. Evaluation of nutritional status in advanced metastatic cancer. *Support Care Cancer*. 2003;11:652-659.
5. Loprinzi CL, Laurie JA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. *J Clin Oncol*. 1994;12:601-607.
6. Ekert H, Waters KD, Jurk IH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Med J Aust*. 1979;2:657-659.
7. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med*. 1980;302:135-138.
8. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med*. 1979;91:819-824.
9. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10:89-97.
10. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol*. 2002;20:567-573.
11. Cannabis-In-Cachexia-Study-Group;Strasser F, Luftner D, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol*. 2006;24:3394-3400.
12. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011;22:2086-2093. doi:10.1093/annonc/mdq727

13. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42:327-360.
14. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4:1770-1804.
15. Waissengrin B, Urban D, Leshem Y, Garty M, Wolf I. Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. *J Pain Symptom Manage*. 2015;49:223-230. doi:10.1016/j.jpainsymman
16. Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. *Evid Based Complement Alternat Med*. 2013;2013:510392. doi:10.1155/2013/510392
17. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10:1-10.
18. Gupta VK, Hariharan M, Wheatley TA, Price JC. Controlled-release tablets from carrageenans: effect of formulation, storage and dissolution factors. *Eur J Pharm Biopharm*. 2001;51:241-248.
19. US Department of Health and Human Services. Common terminology criteria for adverse events v4.0 (CTCAE). https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf. Published May 28, 2009. Accessed September 24, 2019.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
21. Turgeman I, Bar-Sela G. Cannabis for cancer—illusion or the tip of an iceberg: a review of the evidence for the use of cannabis and synthetic cannabinoids in oncology. *Expert Opin Investig Drugs*. 2019;28:285-296. doi:10.1080/13543784.2019.1561859
22. Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. The intersection between cannabis and cancer in the United States. *Crit Rev Oncol Hematol*. 2012;83:1-10. doi:10.1016/j.critrevonc.2011.09.008
23. Rocha FCM, Stefano SC, De Cassia Haiek R, Oliveira LMR, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl)*. 2008;17:431-443. doi:10.1111/j.1365-2354.2008.00917.x
24. Zutt M, Hänssle H, Emmert S, Neumann C, Kretschmer L. Dronabinol for supportive therapy in patients with malignant melanoma and liver metastases [in German]. *Hautarzt*. 2006;57:423-427.
25. Regelson W, Butler JR, Schulz J. Delta-9-tetrahydrocannabinol (delta-9-THC) as an effective anti-depressant and appetite-stimulating agent in advanced cancer patients. In: Braude MS, Szara S, eds. *Proceedings of an International Conference on the Pharmacology of Cannabis*. New York, NY: Raven Press; 1976:763-776.
26. Nelson K, Walsh D, Deeter P, Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *J Palliat Care*. 1994;10:14-18.
27. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav*. 1991;40:695-700.
28. Reuter SE, Martin JH. Pharmacokinetics of cannabis in cancer cachexia-anorexia syndrome. *Clin Pharmacokinet*. 2016;55:807-812. doi:10.1007/s40262-015-0363-2
29. Howden ML, Naughton MT. Pulmonary effects of marijuana inhalation. *Expert Rev Respir Med*. 2011;5:87-92. doi:10.1586/ers.10.87