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Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial

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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.

Key words: anorexia/drug therapy, appetite/drug effects, neoplasms/complications, taste/olfaction disorders/diagnosis, tetrahydrocannabinol/therapeutic use

introduction

Anorexia and weight loss contribute to functional loss, decreased survival, and poor quality of life (QOL) of advanced cancer patients [1]. The potential of delta-9-tetrahydrocannabinol (THC) to palliate these symptoms was suggested [2–8] and early work seemed to hold promise [2–5, 7]. Of seven studies [2–8], two investigated THC as an anti-emetic with the assessment of appetite as a side effect [2, 3], two were uncontrolled [4, 5], and one of two placebo-controlled studies used weight gain as an outcome following just 1 week of treatment [7]. In a randomized comparison with megestrol acetate [6], THC stimulated appetite in 50% of patients but was inferior to megestrol acetate. The results of a randomized trial by Strasser et al. [8] are difficult to interpret, owing to a large number of early deaths in all arms of the study.

THC increases appetite via endocannabinoid receptors (CB1r); appetite stimulation is documented in animals [9, 10] and in healthy human [11, 12] and acquired immunodeficiency syndrome (AIDS) populations [13, 14]. Other potential benefits of THC therapy have been overlooked. Chemosensory alterations are common and distressing among advanced cancer patients, and these contribute to decreased food intake and enjoyment and diminished QOL [15, 16]. Patients frequently report loss of food ideation and desire to eat [17, 18]. THC may increase food intake by stimulating the orosensory reward pathway, increasing motivation to eat energy dense foods and enhancing food enjoyment [10, 19].

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CB1r are located in reward-related areas of the brain [20] and in the olfactory epithelium and bulb [20, 21] and are involved in peripheral odor processing [21] and potentially taste function [22]. We hypothesized that THC may favorably alter chemosensory perception. We therefore undertook a randomized placebo-controlled trial to determine THC's therapeutic potential to improve food-intake behavior for cancer patients with self-reported chemosensory alterations. Our approach included a panel of patient-reported outcomes related to food-intake behavior including perceived chemosensory alterations, macronutrient preference, caloric intake, appetite, and QOL. Safety and tolerability were also assessed.

patients and methods

This two-centre (Cross Cancer Institute, Edmonton, Alberta and Jewish General Hospital, Montreal, Quebec), phase II, randomized, double-blind, placebo-controlled 22-day pilot study (NCT00316563) was approved by Health Canada and the Research Ethics Boards of the Alberta Cancer Board, University of Alberta, and McGill University.

eligibility criteria

Adult patients with advanced cancer (defined as locally recurrent, locally advanced, or metastatic) of any site except brain who had a score ≥2 (out of 16) on a scored Taste and Smell Survey [23] were included (Table 1, see below). The survey identifies and quantifies chemosensory alterations; a score of ≥2 is associated with decreased caloric and protein intake and poorer QOL compared with no chemosensory alterations (T. Brisbois Clarkson, I. De Kock, S. Watanabe, V. Baracos, W. Wismer, unpublished data). Included patients had decreased food intake for ≥2 weeks (reported by subject or physician) and a physician-assessed life expectancy of >2 months. All patients spoke English and provided informed consent. Use of chemotherapy and radiation therapy was permitted during the trial, provided that no therapy-related adverse events (AEs) ensued. Eligibility of patients was determined by review of patient charts and verified by study physicians. Once approved, patients were enrolled by a research assistant.

exclusion criteria

Exclusion criteria included receiving enteral or parenteral nutrition; allergies or sensitivity to THC and/or sesame seed oil; history of substance abuse (determined by review of patients' medical records, alcohol abuse was often also assessed by CAGE questionnaire [24]) or psychotic episodes (e.g. diagnosis of schizophrenia or psychosis); mechanical obstruction of alimentary tract, mouth, or nose; radiation therapy to the head/neck; primary brain tumor; nausea score >5 on 11-point scale (0 = no nausea, 10 = worst possible nausea); medical conditions affecting chemosensory function (i.e. infection of the mouth or nasal cavity, active sinusitis, hay fever), history of tachyarrhythmias, angina pectoris, or uncontrolled hypertension; liver impairment determined by Child-Pugh score ≥10; use of marijuana within 30 days before start of trial.

Patients on treatments with the specific intention of increasing appetite or anabolism were excluded (e.g. dexamethasone 4-10 mg b.i.d., megestrol acetate, cannabinoids, oxandrolone). Low-dose corticosteroids for indications other than appetite were allowed provided that doses remained constant for the duration of the trial. Patients were screened for oral candidiasis; if present, patients were eligible to participate once the infection was successfully treated.

random treatment assignment, blinding, and intervention

After baseline assessments, patients were randomly assigned by a third party pharmacist in a double-blinded manner to receive either THC (Marinol®;

Table 1. (A) Scored elements[a] – Taste and Smell Survey questions with baseline responses ($n = 21$) and (B) additional open-ended questions on Taste and Smell Survey

(A)	
Chemosensory complaint	Pre-treatment (since onset of cancer)
	Yes, *n* (%)
1. I have noticed a change in my sense of taste	20 (95)
2. I have noticed a change in my sense of smell	10 (48)
3. A food tastes different than it used to	16 (76)
4. A food smells different than it used to	9 (43)
5. I have a persistent bad taste in my mouth	9 (43)
6. Specific drugs interfere with my sense of taste	4 (19)
7. Specific drugs interfere with my sense of smell	0 (0)
8. I am experiencing an abnormal sensitivity to salt	11 (52)
Salt tastes	
Stronger	4 (19)
Weaker	7 (33)
9. I am experiencing an abnormal sensitivity to sweet	15 (71)
Sweet tastes	
Stronger	9 (43)
Weaker	6 (29)
10. I am experiencing an abnormal sensitivity to sour	7 (33)
Sour tastes	
Stronger	5 (24)
Weaker	2 (10)
11. I am experiencing an abnormal sensitivity to bitter	7 (33)
Bitter tastes	
Stronger	5 (24)
Weaker	2 (10)
12. I have abnormal sensitivity to odors	11 (52)
odors are	
Stronger	5 (24)
Weaker	6 (29)
13. I would rate my abnormal sense of smell as	
Insignificant	5 (24)
Mild	5 (24)
Moderate	7 (33)
Severe to incapacitating[b]	4 (19)
14. I would rate my abnormal sense of taste as	
Insignificant	6 (29)
Mild	7 (33)
Moderate	6 (29)
Severe to incapacitating	1 (5)
No response	1 (5)
(B)	
Questions 1–4: Verbal description of the specific nature of the alteration	
Questions 8–12: Verbal description of whether change was pleasant or unpleasant	
Questions 13 and 14: Verbal description of how abnormal taste/smell affected QOL	
Questions 8–12: 'cannot perceive' responses were collapsed with 'weaker' responses.	

[a]One point awarded for each question answered with a complaint (no points awarded for 'insignificant' response).
[b]Two points awarded for 'severe to incapacitating' taste/smell complaint response

dronabinol 2.5 mg capsules, Solvay Pharma Inc.) or placebo according to a third-party computer-generated randomization scheme. Patients started on THC 2.5 mg or placebo once daily for the first 3 days (before bedtime for first 2 days and before supper on third day). The dose was increased to THC 2.5 mg or placebo twice daily (1 capsule before lunch and supper) on the fourth day (Figure 1). Patients had the option to increase their drug dose to a maximum of 20 mg/day [25].

outcome measures

Patients completed assessments at baseline (day 0) and after 18 days of treatment with 1 day latitude in posttreatment assessments (Figure 1). All assessments used patient-reported outcomes to capture and describe changes experienced and valued by the patients [26–28].

The Taste and Smell Survey [23] was used to identify and quantify chemosensory alterations 'since study treatment'. This tool has a maximum chemosensory complaint score of 16 (Table 1) [16]. Alterations in taste and smell emerging during study treatment could be pleasant or unpleasant. For example, a loss of sensation resulting in food being perceived as tasteless would be unpleasant, whereas the loss of a heightened and distressing sensitivity to tastes or odors could be perceived as a benefit. We therefore added the qualifying statements 'yes, it's better', 'yes, it's worse', and 'no, it's the same' to questions 1–4; 'chemosensory improvement' was calculated by tallying the 'yes, it's better' responses to these questions. Responses to questions 8–12 were further qualified as to whether change was 'pleasant or unpleasant'; responses of 'pleasantly stronger' comprised the 'chemosensory enhancement' outcome (maximum score of 5). The survey also includes open-ended questions for subjects to elaborate on the specific nature of chemosensory change(s) and their impact on QOL.

The 100 mm Satiety Labeled Intensity Magnitude (SLIM) scale [29] was completed 10–15 min before each meal for 1 day pretreatment and following 18 days of treatment for an assessment of appetite. This scale is anchored with greatest imaginable fullness = 0 and greatest imaginable hunger = 100 (neither hungry nor full = 50). The Macronutrient Preference Checklist (MPC) [30] was completed with the SLIM to assess concurrent macronutrient preferences. The MPC is scored on the number of food items selected (0–8) in each of four macronutrient categories (high protein, high fat, high carbohydrate, low energy). SLIM and MPC premeal scores were averaged for an overall day score. A 3-day dietary record [31] was used to estimate total calories and macronutrient intake (Food Processor II Nutrient Analysis Program™; Esha Research, Salem, OR).

QOL was assessed with the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire [32]. The 11-point Edmonton Symptom Assessment System [33] was used to assess nausea. A Side Effect Survey [34] documented the tolerability of the study drug. Interviews were conducted to determine patients' treatment-related changes in food preferences and chemosensory alterations.

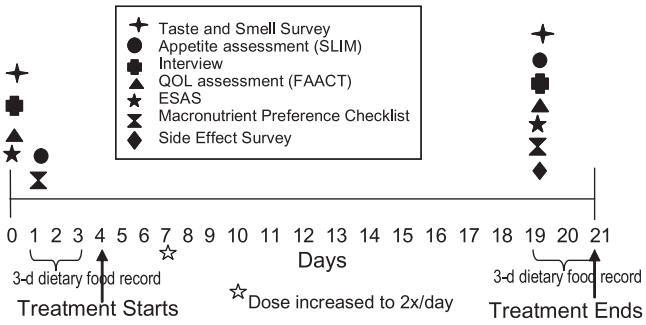

Figure 1. Experimental timeline for a double-blind, randomized, placebo-controlled THC trial in advanced cancer patients. SLIM, Satiety Labeled Intensity Magnitude scale; QOL, quality of life; FAACT, Functional Assessment of Anorexia/Cachexia Therapy questionnaire; ESAS; Edmonton Symptom Assessment Scale.

patient characteristics

Patients were recruited from either the palliative home care program or outpatient clinics at local cancer clinics in Edmonton, Alberta, and Montreal, Quebec, Canada, over 2.5 years (2006–2008). There were no differences for any outcomes between study sites ($P < 0.05$). Patient characteristics (Table 2) and dropout rates (Figure 2) were similar for THC and placebo groups. Of factors that could affect chemosensory perception, 33% of patients were receiving chemotherapy at the time of data collection (although all patients had previously received multiple rounds of various therapies). Similar proportions of participants in each treatment arm reported wearing dentures, experiencing previous mouth or gum infections, and previous taste or smell problems and were previous or current smokers. No patients were taking concurrent appetite stimulants. All participants were treated with various prior chemotherapies (Table 2); however, their effect on chemosensation is impossible to deconvolute in a sample of this size with diverse cancer diagnoses.

statistical analyses

Statistical analyses were performed on a per protocol analysis basis [35] using SAS (Statistical Analysis System for Windows, Cary, NC) [36]. Total and subdomain scores of the Taste and Smell Survey were treated as the primary outcomes, with secondary outcomes of appetite, macronutrient intake, nausea, and QOL. In this exploratory study, the nature of treatment effects and potential effect size(s) were unknown and for that reason, 10 participants per arm were assessed. Descriptive statistics were used to describe prevalence, nature, and severity of chemosensory alterations. Chi-square and Fisher's exact tests were used to evaluate patient characteristics, yes/no responses,

Table 2. Baseline patient characteristics

Characteristic	THC ($n = 11$)	Placebo ($n = 10$)
Male, *n* (%)	7 (64)	5 (50)
Age (years), mean ± SD	67.0 ± 10.9	65.5 ± 8.0
Survival (months), median ± SD	7.5 ± 5.5	6.0 ± 4.6
Chemotherapy[a], *n* (%)	3 (27)	4 (40)
Nausea, 11-point scale, mean ± SD	1.5 ± 2.0	0.9 ± 1.0
Cancer diagnosis, *n* (%)		
Lung	5 (45)	5 (50)
Breast	1 (10)	0 (0)
Genitourinary (including bladder, renal, vaginal, ovarian, peritoneal, cervical, testicular, prostate)	3 (27)	2 (20)
Gastrointestinal (including liver, pancreas, colorectal, stomach, esophageal)	2 (18)	2 (20)
Other (including unknown primary)	0 (0)	1 (10)

[a]Patients received chemotherapy in the 2 weeks before baseline assessments. Types of chemotherapy included gemcitabine, capecitabine, erlotinib, cisplatin, carboplatin, oxaliplatin, etoposide, vincristine, cyclophosphamide, vinorelbine and fluorouracil as sole agent or in combination therapy.
THC, delta-9-tetrahydrocannabinol; SD, standard deviation.

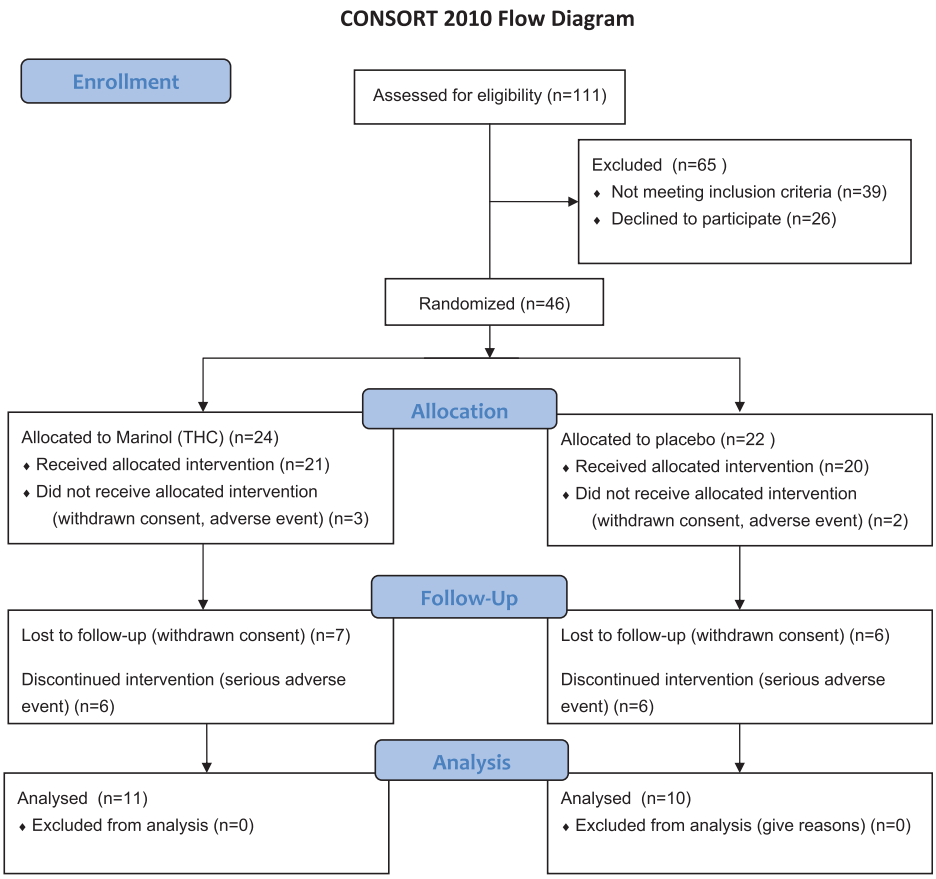

Figure 2. Patient flow. *N*, number; THC, delta-9-tetrahydrocannabinol.

treatment side effects, and AEs. Time series analysis of variance [37] with baseline assessments as covariates were significant [38] and were used to assess differences in chemosensory complaint scores, caloric intake, appetite, macronutrient preferences, QOL, and nausea between- and within-treatment groups as these data met assumptions of normality. Pairwise differences of least squares means (pdiff) were used for post hoc comparisons.

results

In the THC group, eight patients followed the dosing protocol (i.e. 2.5 mg b.i.d.) and three patients increased to 2.5 mg t.i.d. by taking an additional 2.5 mg before supper. In the placebo group, seven patients followed the dosing protocol and three patients increased their dose to 3 capsules/day.

taste and smell perception – results of the scored questions

Total chemosensory complaint scores decreased with THC treatment compared with baseline but were not different from placebo (Table 3). Chemosensory enhancement (frequency of response 'pleasantly stronger' on questions 8–12; Table 1) was increased from baseline with THC treatment compared with placebo ($P = 0.018$) (Table 3). Chemosensory improvement (frequency of response 'yes, it's better' on questions 1–4; Table 1) was twice as frequent with THC treatment (36%) compared with placebo (15%) ($P = 0.026$).

taste and smell perception – responses to open-ended questions and interview

Responses to open-ended questions and interview were concordant with the outcomes described above. The majority (73%) of THC-treated patients reported an increased overall appreciation of food compared with patients receiving placebo (30%) and more often stated that study medication 'made food taste better' (55%) compared with placebo (10%) ($P = 0.04$). Half of the patients who reported odors to be unpleasant at baseline no longer found odors offensive with THC treatment ($P = 0.083$). The majority of THC-treated patients (73%) indicated a renewed ability to discriminate tastes, flavors, and food odors. By contrast, 80% of patients in the placebo group reported their taste and smell function to be the 'same as before' (60%) or 'worse' (20%) compared with baseline.

appetite

For the THC group, SLIM appetite scores increased relative to baseline and placebo (Table 3). The majority of THC-treated patients (64%) had increased appetite, three patients (27%) showed no change and one patient's data were incomplete. No THC-treated patients showed a decrease in appetite. By contrast, the majority of patients receiving placebo had either decreased appetite (50%) or showed no change (20%).

Table 3. Baseline and posttreatment assessments for advanced cancer patients receiving either THC or placebo treatment for 18 days

	THC (n = 11)				Placebo (n = 10)				Between-posttreatment groups	Within-THC group
	Baseline		Posttreatment		Baseline		Posttreatment			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	P	P
Taste and Smell Survey scores										
Total chemosensory complaints/16	7.3[a]	0.4	5.7[b]	0.4	7.3[a]	0.4	6.4[ab]	0.4	0.225	0.008
Chemosensory enhancement/5	1.3[a]	0.2	2.5[b]	0.2	1.3[a]	0.2	1.8[a]	0.2	0.018	<0.001
Appetite										
Average premeal SLIM appetite score	49.4[a]	3.3	60.7[b]	3.4	51.7[a]	3.4	50.9[a]	3.4	0.05	0.03
Protein intake										
Average protein (kcal)/average Kcal	0.16[ab]	0.01	0.18[a]	0.01	0.17[ab]	0.01	0.15[b]	0.01	0.008	0.217
Average protein (g)/day	65	9	82	9	62	9	62	9	0.121	0.179
Carbohydrate intake										
Average carbohydrate (kcal)/average Kcal	0.54	0.03	0.48	0.10	0.54	0.02	0.54	0.07	0.107	0.051
Average carbohydrate (g)/day	236	28	2223	26	184	29	200	27	0.546	0.325
Fat intake										
Average fat (kcal)/average Kcal	0.32	0.02	0.35	0.09	0.29	0.02	0.32	0.07	0.390	0.161
Average fat (g)/day	62	8	73	10	47	10	52	8	0.126	0.178
Caloric intake										
Average Kcal/day	1594	114	1726	114	1543	120	1647	120	0.637	0.425
Food preferences (MPC)										
Average premeal high protein preference	1.6	0.3	2.1	0.3	1.4	0.3	1.2	0.3	0.063	0.341
QOL (FAACT)										
Global QOL	76.2[a]	5.8	98.5[b]	6.1	76.6[a]	6.1	101.8[b]	6.1	0.704	0.026
Anorexia–cachexia-related nutritional well-being subscale	23.9[a]	1.9	29.6[b]	2	23.4[a]	2.1	28.5[ab]	2.1	0.7	0.05
Number of subjects responding change was 'pleasant' on Side Effect Survey[a]			n				n			
Quality of sleep			6				1		0.043	
Relaxation			5				1		0.046	

All data (unless otherwise specified) are means (±SE) analyzed using time series analysis of variance with baseline values as covariates were significant. Means in a row with different superscript letters are significantly different, $P \leq 0.05$.

[a]Data are frequencies analyzed using Fisher exact test.

THC, delta-9-tetrahydrocannabinol; SE, standard error; MPC, Macronutrient Preference Checklist; SLIM, Satiety Labeled Intensity Magnitude Scale; FAACT, Functional Assessment of Anorexia/Cachexia Therapy.

food preferences and caloric intake

Compared with placebo, THC-treated patients increased their protein intake as a proportion of total energy. There was a trend for THC-treated patients to express preference for high protein foods on the MPC (Table 3). During interview, patients in the THC group (55%) commonly reported savory foods (e.g. hamburgers, chicken, fish, baked beans, and mushrooms) to 'taste better' and to be 'more appealing' since the study treatment. No patients in the placebo group reported an increased liking of meats.

Total caloric intake (Table 3) or intake per kilogram body weight (P = 0.557) did not differ between-treatment groups. Relative to baseline, 73% of THC-treated patients increased their caloric intake (range 100–775 kcal/day) compared with 50% patients in the placebo group (100–965 kcal/day).

quality of life

FAACT global QOL scores improved similarly for both THC and placebo groups (Table 3). The FAACT subdomain of anorexia–cachexia-related nutritional well-being improved in the THC group but was not different from placebo.

side effects and AEs

Nausea scores were unaffected by THC treatment ($P = 0.532$). Quality of sleep and relaxation were more frequently reported to be 'pleasant' by THC-treated patients compared with placebo on the Side Effect Survey (Table 3). There were no other differences in survey responses between-treatment groups ($P > 0.05$; Table 4).

THC was well tolerated. No differences were reported during the trial or within the 30-day follow-up period between THC and placebo groups for the number of AEs or serious AE (SAE) ($P = 0.622$ and $P = 0.244$, respectively). Most AEs were unrelated to THC therapy, six were unclear, and four were possibly related (Table 5). Most SAE were also unrelated to THC therapy, four were unclear and one was possibly related to treatment (irregular heart beat).

discussion

main findings

Our pilot study demonstrates that THC, compared with placebo, improved and enhanced chemosensory perception, altered macronutrient preference, appeal of savory foods, appetite, relaxation, and quality of sleep for advanced cancer patients with chemosensory alterations.

We opted for self-reported chemosensory perception as the most relevant predictor of food preference and enjoyment in lieu of objective clinical measures (i.e. millimolar concentration thresholds for detection of individual tastants and odorants). Along with Bartoshuk, we speculate that taste and smell alterations are not merely quantifiable physiological changes but also involve the loss of food enjoyment [18]. Bernhardson et al. [39] and Steinbach et al. [40] have recently used self-reported chemosensory perception to comprehensively describe taste and smell changes experienced by cancer patients. Clinical measures of chemosensation cannot capture dimensions such as flavor, food enjoyment, or impact on patient's food-intake behavior. The millimolar concentration threshold for perception of salt dissolved in water is not a surrogate for the complex perceptions that contribute to the ingestion and enjoyment of food.

Our findings parallel earlier results of enhanced sensory perception and improved food enjoyment among healthy marijuana users [41, 42]. THC also reduces the unpleasantness of a bitter taste solution in animals [19]. Our THC-treated patients reported odors and the taste of meat to be less offensive, possibly contributing to increased calories ingested as protein. These results suggest that THC improved chemosensory perception through reward systems [42].

Our findings are important as there is no accepted treatment for chemosensory alterations experienced by cancer patients [15, 16]. THC treatment may hold multiple clinical benefits for cancer patients, beyond its indication as a treatment for nausea and its effects on appetite. THC may palliate an array of symptoms: chemosensory alterations, food enjoyment, pain, depression, anxiety, poor quality of sleep, and inflammation [43]. Food enjoyment is a component of QOL, and while food enjoyment is intangible in terms of tools for its quantification, we nonetheless suggest that THC may well contribute to the overall enjoyment of food in cancer patients. Improved sleep may be due to the presence of CB1r in the basal forebrain [20] or related to increased relaxation noted in various populations [7, 44]. Here, improved quality of sleep and relaxation may have increased appetite and improved chemosensory perception, encouraging a positive outlook on food [45].

prior and future clinical trials of THC

THC stimulates appetite in healthy volunteers [11, 12] and AIDS patients [13, 14], but its ability to do so in cancer patients has not been consistently reported. THC increased appetite for 34%–72% of cancer patients with doses ranging from 5 to 45 mg/day [3–8, 44]. Nelson et al. [4] showed promising THC appetite stimulation in cancer and 6 of 18 patients opted to remain on THC treatment for improved appetite and food intake [46]. However, this study was criticized for the lack of a control group. Jatoi et al. [6] reported THC to stimulate appetite in 50% of patients. Strasser et al. [8] noted no differences between THC or THC + cannabidiol and placebo for appetite or QOL. In our study, 64% of THC-treated patients showed improved SLIM appetite scores and this assessment was not susceptible to placebo effect. The verbally anchored SLIM scale shows greater sensitivity and specificity than unlabelled visual analog scales [29], which had been used in other studies [8].

Jatoi et al. [6] and Strasser et al. [8] selected 5 mg THC daily to minimize side effects; however, Nelson et al. [4] showed more promising results with 7.5 mg THC daily. AIDS patients tolerated doses as high as 40 mg THC daily well [13]. We

Table 4. Patient responses to Side Effect Survey poststudy treatment

	Pleasant (*n*)	Neutral (*n*)	Unpleasant (*n*)
THC	Quality of sleep has changed (6), relaxation (5), feeling sleepy (3), reduced anxiety (1)	Feeling 'high' (2), relaxation (2), unsteady feet (1)	Fast heart rate (1), unsteady feet (1), dizziness (1), abdominal pain (2), nausea (1), heaviness in limbs (1), noises seem louder (1)
Placebo	Quality of sleep has changed (1), relaxation (1)	Quality of sleep has changed (1), relaxation (1), feeling sleepy (2), dizziness (1), abdominal pain (1)	

THC, delta-9-tetrahydrocannabinol.

Table 5. Patient-reported toxic effects

	THC, *n* (%)	Placebo, *n* (%)
Nausea/vomiting	5 (45)	2 (20)
Hives/rash	3 (27)	3 (30)
Bowel obstruction/ constipation	0	3 (30)
Shortness of breath/fluid on lungs	3 (27)	1 (10)
Stomach cramps	1 (9)	2 (20)
Tired/drowsy	1 (9)	2 (20)
Pain	2 (18)	1 (10)
Diarrhea	2 (18)	0
Headache	2 (18)	0
Dehydration	1 (9)	1 (10)
Pneumonia	1 (9)	1 (10)
Seizure	1 (9)	0
Unsteady feet	1 (9)	0
Low blood count	1 (9)	0
Irregular heart beat	1 (9)	0
Thrush	1 (9)	0
Confusion	0	1 (10)
Fever	0	1 (10)
Edema	1 (9)	0
Vaginal discharge	1 (9)	0
Troubles sleeping	1 (9)	0

THC, delta-9-tetrahydrocannabinol.

started patients at a low dose to build-up tolerance and minimize negative psychoactive effects [25] and allowed patients to titrate their dose upward and this was well tolerated. We noted dropouts and withdrawn consents due to changes in health status unrelated to study treatment. The dropout rate was not uncommon for an advanced cancer population [6]. Clinical trials in advanced cancer have the added complexity of comorbidities and expected death. The exclusion of data that are confounded by poor prognosis is critical for interpretable results, which may be a criticism of previous work [8].

One consideration for future trials will be the situation of therapy for taste and smell alterations within the disease trajectory, as these problems have been characterized both during first-line therapy in treatment naïve patients [47] as well as in advanced stage patients with progressive disease who have received multiple lines and cycles of treatment, as here. These may be related or distinct clinical entities.

Our sample size and study duration within a placebo-controlled design showed statistical significance for several outcomes responsive to THC: chemosensory perception, appetite, relaxation, and quality of sleep. However, our results require verification in larger trials. Our goal was to conduct a proof of principle study to provide direction for future trials. The data here would assist in the development of larger phase II trials by facilitating sample size calculations given our preliminary indications of effect sizes and variance (e.g. total chemosensory complaint scores as the primary outcome would require ~50–60 patients in each treatment group based on the variance determined here). Our results offer a reasonable starting point from which future studies may investigate the use of THC in cancer anorexia where chemosensory alterations are present.

For the design of future trials, it seems important to (i) include a placebo group as outcomes may appear more favorable when compared with drug alone; (ii) include patient-reported assessments to capture relevant aspects of food-intake behavior, such as chemosensory and food preference changes; and (iii) power studies around differentiable outcomes, such as chemosensory complaint scores. As absorption of oral THC varies greatly between individuals [25, 48], and given the controversy surrounding the appropriate dose in cancer, future trials may allow patients to titrate their dose or compare different dose levels. Inevitably, questions are raised about the ability to blind THC treatment based on its well-known psychoactive characteristics; however, the timed administration of low doses and the lack of differences in AEs between-treatment groups suggest that this problem was likely minimal. THC merits further investigation as a therapy for patients who suffer from chemosensory alterations and loss of food enjoyment.

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disclosure

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references

1. MacDonald N, Easson AM, Mazurak VC et al. Understanding and managing cancer cachexia. J Am Coll Surg 2003; 197: 143–161.
2. Ekert H, Waters KD, Jurk IH et al. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. Med J Aust 1979; 2: 657–659.
3. 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.
4. 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.
5. Plasse TF, Gorter RW, Krasnow SH et al. Recent clinical experience with dronabinol. Pharmacol Biochem Behav 1991; 40: 695–700.
6. 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.

7. Regelson W, Butler JR, Schulz J et al. Delta-9-Tetrahydrocannabinol as an Effective Antidepressant and Appetite-Stimulating Agent in Advanced Cancer Patients. New York: Raven Press 1976.
8. Strasser F, Luftner D, Possinger K 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.
9. Williams CM, Rogers PJ, Kirkham TC. Hyperphagia in pre-fed rats following oral delta9-THC. Physiol Behav 1998; 65: 343–346.
10. Cota D, Marsicano G, Lutz B et al. Endogenous cannabinoid system as a modulator of food intake. Int J Obes Relat Metab Disord 2003; 27: 289–301.
11. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite 1988; 11: 1–14.
12. Abel EL. Effects of marihuana on the solution of anagrams, memory and appetite. Nature 1971; 231: 260–261.
13. Haney M, Gunderson EW, Rabkin J et al. Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. J Acquir Immune Defic Syndr 2007; 45: 545–554.
14. 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.
15. Wickham RS, Rehwaldt M, Kefer C et al. Taste changes experienced by patients receiving chemotherapy. Oncol Nurs Forum 1999; 26: 697–706.
16. Hutton JL, Baracos VE, Wismer WV. Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. J Pain Symptom Manage 2007; 33: 156–165.
17. Shragge JE, Wismer WV, Olson KL, Baracos VE. Shifting to conscious control: psychosocial and dietary management of anorexia by patients with advanced cancer. Palliat Med 2007; 21: 227–233.
18. Bartoshuk LM. Chemosensory alterations and cancer therapies. NCI Monogr 1990; 9: 179–184.
19. Jarrett MM, Scantlebury J, Parker LA. Effect of delta9-tetrahydrocannabinol on quinine palatability and AM251 on sucrose and quinine palatability using the taste reactivity test. Physiol Behav 2007; 90: 425–430.
20. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol 2005; 168: 299–325.
21. Czesnik D, Schild D, Kuduz J, Manzini I. Cannabinoid action in the olfactory epithelium. Proc Natl Acad Sci U S A 2007; 104: 2967–2972.
22. Oike H, Wakamori M, Mori Y et al. Arachidonic acid can function as a signaling modulator by activating the TRPM5 cation channel in taste receptor cells. Biochim Biophys Acta 2006; 1761: 1078–1084.
23. Heald AE, Pieper CF, Schiffman SS. Taste and smell complaints in HIV-infected patients. AIDS 1998; 12: 1667–1674.
24. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry 1974; 131: 1121–1123.
25. Unimed. Marinol (Dronabinol) Capsules. In Solvay Pharmaceuticals, Inc., Edition 2003.
26. Shun SC, Lai YH, Hsiao FH. Patient-related barriers to fatigue communication in cancer patients receiving active treatment. Oncologist 2009; 14: 936–943.
27. The Cochrane Collaboration, Patient Reported Outcomes Measurement Group. In http://www.cochrane-pro-mg.org/Objective.html (5 July 2009, date last accessed).
28. Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 2008; 26: 1355–1363.
29. Cardello AV, Schutz HG, Lesher LL, Merrill E. Development and testing of a labeled magnitude scale of perceived satiety. Appetite 2005; 44: 1–13.
30. Brisbois-Clarkson TD, Mclsaac TM, Goonewardene LA, Wismer WV. Modification and validation of a Macronutrient Preference Checklist for use in North America. Appetite 2009; 53: 461–464.
31. Larkin FA, Metzner HL, Guire KE. Comparison of three consecutive-day and three random-day records of dietary intake. J Am Diet Assoc 1991; 91: 1538–1542.
32. Ribaudo JM, Cella D, Hahn EA et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Qual Life Res 2000; 9: 1137–1146.
33. Bruera E, Kuehn N, Miller MJ et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991; 7: 6–9.
34. Ware MA, Doyle CR, Woods R et al. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 2003; 102: 211–216.
35. Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. Physical Therapy Reviews 2008; 14: 36–49.
36. SAS Institute. Statistical Analysis System for Windows, Version 8.2. In Edition 8.2. Cary, NC: Institute Inc 1999[39].
37. Steel R, Torrie J, Da D. Principles and Procedures of Statistics a Biometrical Approach. New York: McGraw-Hill, Inc 1997.
38. Freund RJ, Wilson WJ. Statistical Methods. San Diego, CA: Academic Press 2003.
39. Bernhardson BM, Tishelman C, Rutqvist LE. Self-reported taste and smell changes during cancer chemotherapy. Support Care Cancer 2008; 16: 275–283.
40. Steinbach S, Hummel T, Bohner C et al. Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 2009; 27: 1899–1905.
41. Nail R, Gunderson E, Kolb D. Motives for drug use among light and heavy users. J Nerv Ment Dis 1974; 159: 131–136.
42. Roth W, Tinklenberg J, Kopel B. Subjective benefits and drawbacks of marihuana and alcohol. In Cohen S, Stillman R (eds), The Therapeutic Potential of Marihuana, Edition. New York: Plenum Medical Book Co. 1976; 255–269.
43. Robson P. Human studies of cannabinoids and medicinal cannabis. Handb Exp Pharmacol 2005; 168: 719–756.
44. Noyes RJ, Brunk S, Avery D, Canter A. Psychological effects of oral delta-9-tetrahydrocannabinol in advanced cancer patients. Compr Psychiatry 1976; 17: 641–646.
45. Mela DJ. Food choice and intake: the human factor. Proc Nutr Soc 1999; 58: 513–521.
46. Walsh D, Kirkova J, Davis MP. The efficacy and tolerability of long-term use of dronabinol in cancer-related anorexia: a case series. J Pain Symptom Manage 2005; 30: 493–495.
47. Sanchez-Lara K, Sosa-Sanchez R, Green-Renner D et al. Influence of taste disorders on dietary behaviors in cancer patients under chemotherapy. Nutr J 2010; 9: 15.
48. Mattes RD, Shaw LM, Engelman K. Effects of cannabinoids (marijuana) on taste intensity and hedonic ratings and salivary flow of adults. Chem Senses 1994; 19: 125–140.