The Effect of Cannabis-Based Medicine in the Treatment of Cachexia: A Systematic Review and Meta-Analysis

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Abstract

Background: Cachexia is a prevalent condition associated with underlying chronic disease. Wasting of skeletal muscle and adipose tissue loss in cachectic patients is associated with higher rates of disability, reduced quality of life (QoL), and worse prognosis. There is a large unmet need to develop strategies to treat cachexia as there are currently no standardized guidelines in the management of cachexia. Activation of endogenous cannabinoid receptors, through exogenous cannabinoids, has demonstrated potential in increasing appetite, reducing catabolism, and has shown anti-inflammatory properties. Since no single pharmacological agent is currently recommended for use in cachexia, the potential of cannabinoids as an appetite stimulant warrants further research and assessment of current evidence.

Objective: This review aims to evaluate the evidence for the efficacy of cannabis-based medicinal products, against placebo and other active treatments, in anorexia–cachexia syndrome in improving appetite, weight, and QoL.

Methods: A literature search of the Medline, EMBASE, CENTRAL, and the Web of Science Core Collection, for articles published up to February 2020, was conducted. All randomized controlled trials comparing the use of cannabis-based medicine versus placebo/active treatments for patients with cachexia were screened. The quality of evidence in included studies was assessed using the GRADE framework and any risk of bias was judged using the Cochrane risk of bias tool.

Results: A total of five studies, encompassing 934 participants, were found to be eligible. The pooled group effect size for change in appetite was −1.79 (95% confidence interval: −3.77 to 0.19) favoring the control group ($p = 0.08$). Additionally, no significant difference for weight change or change in QoL for cannabinoids versus placebo/other treatment was observed. The quality of evidence for all five studies was assessed to be low.

Conclusion: There is a lack of high-quality evidence to recommend the use of cannabinoids in the treatment of cachexia. Given the limited available pharmacological options for cachexia and the potential for cannabinoids to increase appetite and alter the immune system, further research is needed before clinical recommendations on the pharmacological management of cachexia can be made.

Keywords: cachexia; cannabinoids; cannabis; weight loss; appetite

Background

Cachexia is defined as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass."[1] It affects ∼9 million patients globally, with incidence rising in line with increasing multimorbidity of chronic disease.[2] Cachexia is particularly associated with cancer and AIDS affecting 30% and 35% of patients, respectively.[3] It has a prevalence of up to 80% in advanced cancer patients and an approximate mortality rate of

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30% and 80% in chronic heart failure and cancer patients, respectively.[4,5] Cachectic patients show higher rates of disability, prolonged hospital admission,[6] decreased psychological wellbeing,[7] reduced quality of life (QoL),[8] and an overall poorer prognosis.[9,10] There is a wide variety of cachexia–death associations, including increased risk of thrombosis,[11] immune deficiency,[12,13] reduced cardiac output,[14] and increased risk of adverse cardiovascular events.[11,12,15–17] There exist no standardized guidelines for the management of cachexia and there is currently no agreed gold-standard pharmacological agent for the treatment of cachexia.

Multiple pathways have been identified in the pathophysiology of cachexia. An upregulation of pathways that catabolize muscle and fat and a downregulation of pathways that stimulate muscle growth lead to an overall catabolic state, clinically manifesting as weight loss, weakness, and wasting.[3] Cytokines, such as tumor necrosis factor-α (TNF-α) and Interferon-γ, are upregulated in cachexia and directly inhibit synthesis of heavy chains of myosin.[18] Myoblast determination protein 1, a transcription factor essential for repair and differentiation of skeletal muscles, is also inhibited by TNF-α through activation of nuclear factor kappa-light-chain-enhancer of activated B cells leading to dysfunction of skeletal muscle production.[19,20] Cytokines activate proteolysis through a ubiquitin-mediated system—targeting specific proteins within skeletal muscle, breaking them down for use in hepatic synthesis of acute phase proteins.[3,21] Resistance of appropriate hypothalamic responses to orexigenic and anorexigenic signaling has been observed.[22] In cachexia proinflammatory cytokines mimic the negative feedback leptin exerts on orexigenic pathways.[23–25] This excess, unopposed negative feedback combined with resistance to orexigenic pathways leads to the loss of appetite and induction of an overall catabolic state resulting in the sustained, uncontrolled weight loss.[23]

The cannabinoid receptor type 1 (CB$_1$R) is thought to play a significant role in modulating appetite and satiety through presynaptic activity at both orexigenic and anorexigenic neurons. This serves to increase caloric intake and reduce catabolism.[26,27] Activation of this system has been observed to increase abdominal adiposity.[26,27] Hence, there is increasing interest in targeting the endocannabinoid system for the treatment of conditions, such as anorexia–cachexia syndrome. This has previously been suggested to potentially result in a better prognosis, owing to increased appetite and weight gain.[9,10] As such, there is on-going research into the potential benefits to treat anorexia–cachexia syndrome. The (−)-trans-Δ^9-tetrahydrocannabinol (THC), a partial agonist of CB$_1$R, and its isomers are currently the most widely researched cannabis-based medicine for cachexia treatment. THC has been shown to stimulate appetite, reduce nausea, and improve the functional status in cachexia patients.[28–31]

The aim of this systematic review and meta-analysis was to compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and QoL. The review assessed the quality of evidence for whether cannabis-based medicine is effective in the treatment of anorexia–cachexia syndrome and hopefully provides a rationale for any recommendation for use in clinical practice.

Methods

Selection criteria for studies

The PICOS (patient, intervention, control, outcome, study type) acronym was used to define the research question by specific criteria. The population in this case were patients with cachexia, from any underlying illness, as defined by official diagnostic criteria, having had a sustained weight loss >5% (or body mass index <20 kg/m^2) in less than 12 months with three of the five of the following characteristics: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry.[1] The intervention was the use of cannabis-based medicines or their synthetic analogs, which could be compared with either a placebo or other interventions used in the active treatment of cachexia. The chosen outcomes were objective measurements, such as weight gain and additionally subjective measurements such as patient-reported QoL and their change in appetite. Only randomized controlled trials (RCTs) were included, where sample size was >10 with follow-up ≥4 weeks. The following criteria were to be excluded: volunteers below 18 years of age; healthy volunteers; patients with anorexia nervosa; patients with a normal nutritional status in the presence of chronic illness; and animal studies and non-RCTs.

Search strategies for identification of studies

Extensive keywords and MeSH terms were used to search Medline and EMBASE databases using the OVID platform. Equally, similar keywords were used to search the Cochrane Central Register of Controlled Trials (CENTRAL) and the Web of Science Core Collection—to include gray literature in the search.

See Supplementary Appendix SA1 for a full description of search strategy developed in consultation with an experienced medical librarian. In addition, citations and bibliographic references of included studies and relevant reviews were manually searched to identify any further studies or search keywords.

Selection of studies

The search was performed by two authors independently (S.H. and S.E.); studies selected for full-text review were assessed independently and any disagreement would be resolved by a third author (M.H.S.)—however, this was not necessary in this instance.

Data extraction

The following data were extracted for analysis from the included studies for both the cannabis-based medicines and placebo/comparator arms:

- Sample size
- Patient demographics (age, sex, ethnicity (where possible), and weight loss history)
- Appetite change, through a Visual Analog Scale (VAS) score, at baseline and endpoint
- Weight change (kg)
- Change in QoL assessment (baseline to endpoint)
- Nausea, mood, and vomiting VAS score change (baseline to endpoint)
- Adverse outcomes (type and frequency)

Across studies, follow-up times and study length varied.

Quality of evidence and bias risk assessment

The GRADE framework was used to assess the quality of evidence within each study, where evidence from each study is given a certainty grading from very low to high. Where evidence has a very low certainty, the true effect is likely very different from the estimated effect seen in the study outcome. These levels of certainty are calculated based on a subjective approach. The risk of bias, level of imprecision in 95% confidence intervals (CIs), inconsistency, indirectness, and publication bias are all aspects that need to be analyzed before a GRADE level can be given.[32]

The Cochrane risk of bias tool for randomized trials was utilized to assess the risk of bias for each study.[33] The items assessed within the risk of bias tool include:

- Bias arising from randomization (selection bias)
- Bias from deviations from intended interventions (performance bias)
- Bias due to missing outcome data (attrition bias)
- Bias due to measurement of the outcome (detection bias)
- Bias in selection of the reported result (reporting bias)

Meta-analysis

Measures of treatment effect. For continuous outcomes, a pooled mean difference (MD) and 95% CI was calculated. However, in studies using different scales measuring appetite, pain, and nausea, the standardized MD and 95% CI were calculated. For studies that reported baseline and endpoint data, we calculated the standard deviation (SD) of the mean change from the baseline according to reported CI. A decision was made not to pool studies together if considerable clinical heterogeneity exists. All data were calculated using the Review Manager (Cochrane, v5.3).[34]

Unit of analysis issues. Unit of analysis issues were dealt with depending on the specific study design. The relevance of each intervention group to this systematic review was determined by types of population and types of intervention. The control arm was divided equally by the number of included intervention groups in studies that contain two or more groups as described by Deeks et al.[35] If the study already presented separate subgroup analyses, then the control group was considered as a whole.

Dealing with missing data. Where necessary, the authors of selected studies were contacted to obtain any missing data. When this was not be possible, SDs were calculated using the data available.[36]

Assessment of heterogeneity. Clinical heterogeneity (differences in participant type or characteristics, timing of outcome measurements, and intervention characteristics) was assessed by reviewing the treatments used across studies and the characteristics of included participants to assess for any substantial differences. Statistical heterogeneity was assessed using the χ^2 test and I^2 statistic. A p-value of 0.05 was considered statistically significant for the χ^2 test. The I^2 statistic was used to quantify the proportion of variation between studies that is due to heterogeneity rather than to chance. This interpretation was in keeping with the Cochrane Handbook of systematic reviews.[37] An I^2 value of 0–40% indicates heterogeneity may be not be important; 30–60% indicates moderate heterogeneity;

50–90% indicates substantial heterogeneity, and 75–100% indicates considerable heterogeneity. Forest plots were created and visibly inspected to identify any outliers.

Assessment of reporting biases. Reporting bias was assessed by comparing prespecified outcomes in pretrial registry entries/study protocols to outcomes reported in final articles, where available. If registry entries or protocols were unavailable, reporting bias was assessed by comparing outcomes specified in the methodology compared with those reported in the results section. Publication bias could not be calculated using a funnel plot due to fewer than 10 studies being included.[38]

Results

Search results

A summary of the study selection process is provided in Figure 1. A total of 859 abstracts were identified through searches of databases, whereas 112 records were identified through hand-searching relevant bibliographies and from gray literature. Once duplicates ($n = 218$) were removed, 753 records were screened by the title and/or abstract, with 733 being excluded. Twenty full-text articles were assessed for eligibility and five articles were included in this review. Figure 1 lists the reasons for exclusion at the full-text level.

Characteristics of included studies

The characteristics of each study are presented in Table 1. Relevant information on participant demographics, interventional groups, control groups, any follow-ups, and outcomes were extracted as detailed in the methodology.

Intervention

Each of the five studies were RCTs that used some form of cannabis-based medicine (dronabinol $n = 3$; cannabis extract and THC $n = 1$; nabilone $n = 1$) in cachectic patients against a control group (placebo, $n = 3$) or alternative pharmacological agent (megestrol acetate $n = 2$). The median length of treatment was 6 weeks (range 4–12 weeks). Three of the studies implemented a twice-daily regimen of 2.5 mg of dronabinol as the intervention arm compared with either placebo or megestrol acetate once daily.[39–41] Two of these studies also investigated a combination of megestrol acetate and dronabinol together.[40,41] Jatoi et al.[40] investigated 2.5 mg dronabinol + placebo versus oral megestrol acetate 800 mg/day + dronabinol 2.5 mg versus oral meges-

trol acetate 800 mg/day + placebo. Timpone et al.[41] had four treatment arms looking at 2.5 mg dronabinol versus a combination of 2.5 mg dronabinol with either 250 mg or 750 mg of once daily megestrol acetate versus just 750 mg megestrol acetate. Turcott et al.[42] compared an initial 2-week 0.5 mg dose of nabilone against placebo followed by 6 weeks of 1.0 mg nabilone, whereas Strasser et al.[43] looked at the effects of oral cannabis extract, 2.5 mg THC, and 1 mg cannabidiol (CBD), versus both placebo and 2.5 mg THC alone.
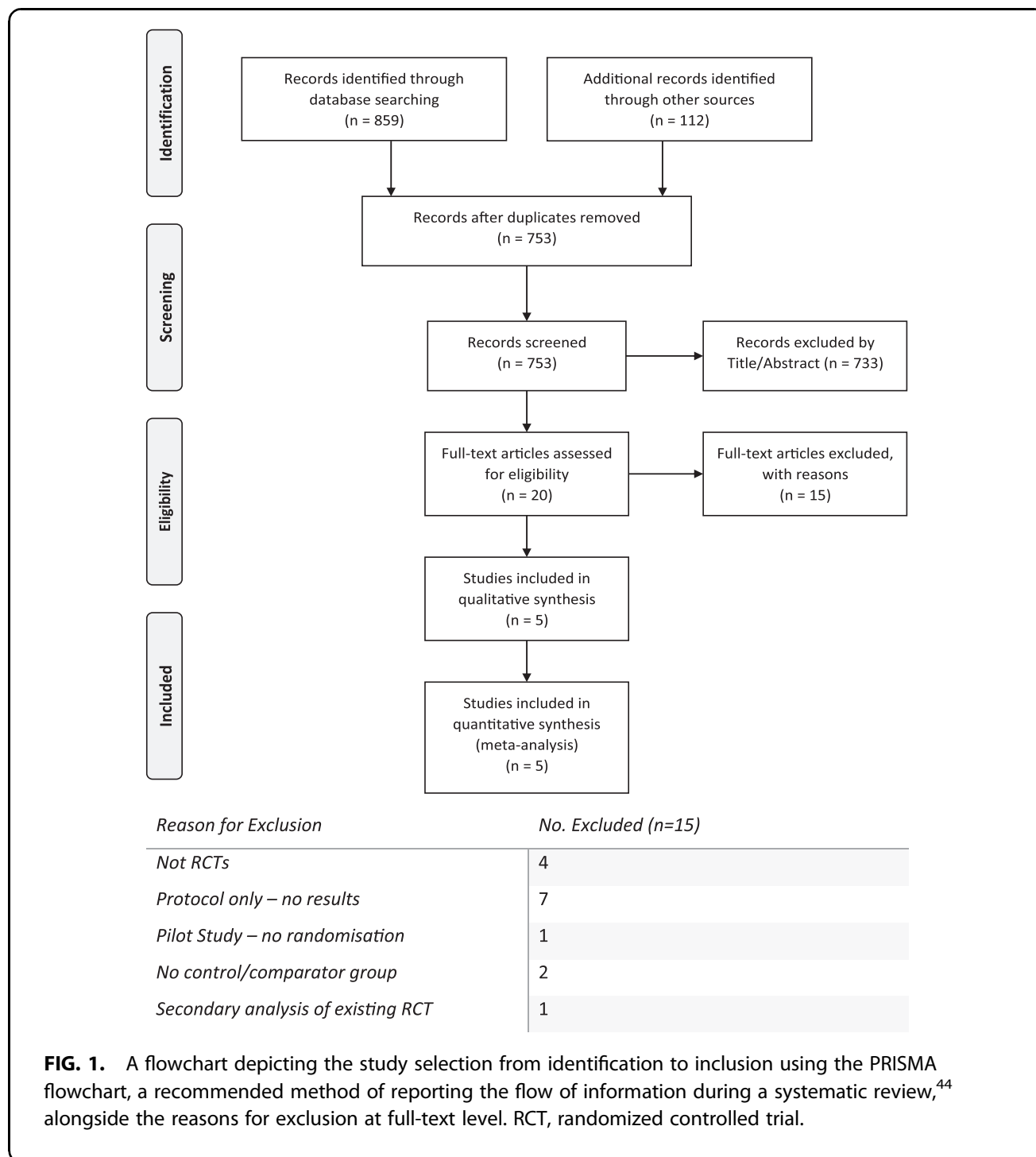
Participants

A total of 934 adult patients took part across all five studies. Two studies focused on HIV-positive wasting syndrome with a clinical diagnosis of cachexia through a >10% or >2.3 kg of weight loss in the preceding 2 months.[39–41] In three other studies, patients diagnosed with advanced cancer with an estimated life expectancy of at least 3 months and self-reported weight loss of >5% or >2.3 kg in the preceding months, not explained by other disease or recent surgery, were eligible.[40,42,43] These cancer patients all had to have a European Cooperative Oncology Group Performance Status (ECOG) of 0–2, which determined they were capable of self-care for example, independent in daily activities. All five studies mandated either no previous use or a greater-than-1-month washout period of any appetite stimulants, including corticosteroids and cannabis products for at least the past month. All patients were required to be able to tolerate oral intake with no parenteral nutrition. For four studies, the majority of patients were male with just the nabilone study on nonsmall-cell lung cancer patients[42] having a female majority. The mean age across all five studies was 53 years (SD = 12).

Risk of bias assessment

Figure 2 demonstrates the risk of bias across all five studies as assessed by the author using the Cochrane risk of bias tool.[33] Supplementary Appendix SA2 provides a table summarizing the risk of bias in each domain for each of the included studies as well as the quality of evidence assessment through the GRADE framework.[32]

Domain 1: Randomization process. All studies stated randomization occurred but provided no exact methodology to how (e.g., random number generator). Two studies[42,43] were assessed to have some concerns of bias owing to significant differences in baseline characteristics between intervention and control arms

FIG. 1. A flowchart depicting the study selection from identification to inclusion using the PRISMA flowchart, a recommended method of reporting the flow of information during a systematic review,[44] alongside the reasons for exclusion at full-text level. RCT, randomized controlled trial.

(weight loss, performance status, and age). Allocation was also concealed in four of five studies before assessment.

Domain 2: Deviations from intended interventions. Four of the five studies were stated to be double-blind, where unblinding was only permitted for safety

reasons. One study[41] explicitly states that participants were instructed on when and how to take their assigned intervention showing it was unblinded and was therefore assessed to have some concerns of bias. Beal et al.[39] excluded patients postrandomization, despite eligibility, due to protocol violations, taking less than 75%

Table 1. Table Displaying the Characteristics of Each Study

Study	Population	Intervention (n=number of participants)				Outcome		Duration
		Arm 1	Arm 2	Arm 3	Comparison	Primary	Secondary	
Beal et al. (1995)[39]	AIDS patients with anorexia-associated weight loss	2.5 mg dronabinol b.d. (n=72)	—	—	Placebo (n=67)	Change in appetite (VAS) Change in weight (kg)	Mood, nausea, and vomiting (VAS)	6 weeks
Jatoi et al. (2002)[40]	Cancer-associated Cachexia	2.5 mg dronabinol +placebo b.d. (n=152)	Oral megestrol acetate 800 mg/day suspension o.d. +2.5 mg dronabinol b.d. (n=158)	—	oral megestrol acetate 800 mg/day o.d.+placebo (n=159)	Change in appetite (VAS)	Patient and Physician reported weight change, kg QoL assessment (FAACT)	4 weeks
Strasser et al. (2006)[43]	Cancer-associated Cachexia	Cannabis Extract (2.5 mg THC +1 mg CBD) b.d. (n=95)	2.5 mg THC b.d. (n=100)	—	Placebo (n=48)	Change in appetite (VAS)	QoL Assessment (Global Health Status Score and EPRTC QLQ-C30)	6 weeks
Timpone et al. (1997)[41]	HIV wasting syndrome	2.5 mg Dronabinol b.d. (n=12)	750 mg megestrol acetate o.d. +2.5 mg dronabinol b.d. (n=13)	250 mg megestrol acetate o.d. +2.5 mg dronabinol b.d. (n=13)	750 mg megestrol acetate o.d. (n=12)	Pharmacokinetics (through plasma sampling)	Weight Change (kg and BMI) Appetite, mood, and nausea (VAS)	12 weeks
Turcott et al. (2018)[42]	Nonsmall-cell lung cancer patients with anorexia	0.5 mg Nabilone o.d. for 2 wks then 1.0 mg Nabilone o.d. (n=14)	—	—	Placebo (n=19)	Energy intake (g and kcal) QoL (EORTC-QLQ-C30 and LC13) AC/S score Change in appetite (VAS)	BMI Weight change Proinflammatory markers (through plasma sampling)	8 weeks

o.d.—once daily; b.d.—twice daily; EORTC-QLQ—European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (C30 and LC13—specific for cancer and lung cancer, respectively). AC/S, anorexia–cachexia subscale of FAACT; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CBD, cannabidiol; FAACT, Functional Assessment of Anorexia–Cachexia Therapy instrument; QoL, quality of life; THC, tetrahydrocannabinol; VAS, Visual Analog Scale.
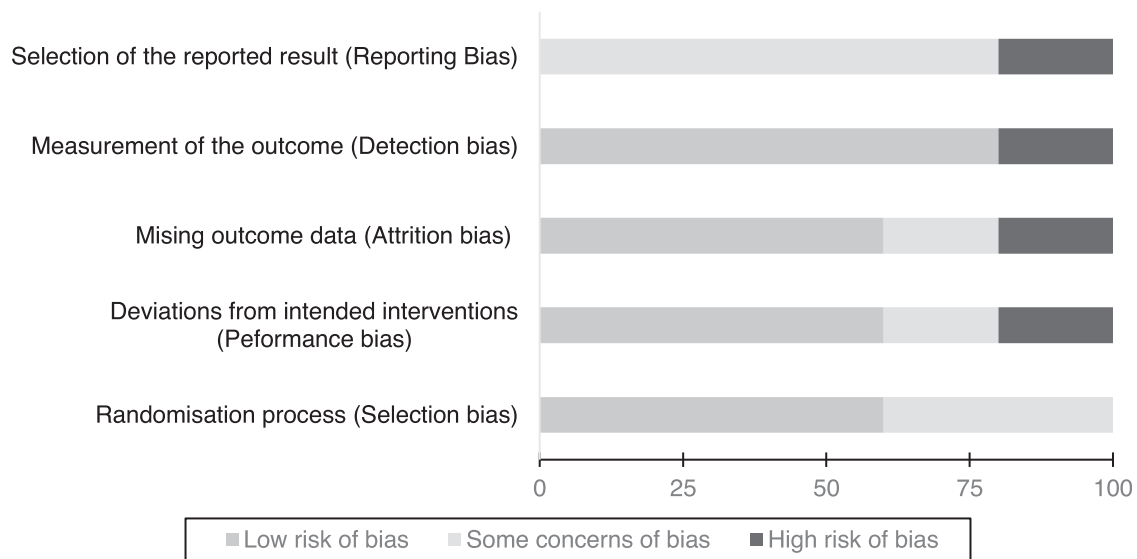
FIG. 2. Overall risk of bias graph: authors' judgments about each risk of bias item presented as percentages across all included studies, using the Cochrane risk of bias tool (RoB 2)[33]

of planned medication, and were observed less than 4 weeks. This naive "per-protocol" approach, only evaluating those strictly adhering to the assigned intervention, was deemed to be at high risk of bias, according to Cochrane.[33]

Domain 3: Missing outcome data. All five studies had missing outcome data mainly due to loss to follow-up or death, some studies handled this incomplete data appropriately using "intention-to-treat" (ITT) analyses. Strasser et al. explicitly states that missing values were substituted using the nearest neighbor approach to allow for an ITT analysis.[43] Beal et al. eliminated 41 of 139 patients from analysis based on protocol violations or taking less than the planned dosages of medication—since no sensitivity analysis was conducted to indicate that this missing outcome data had no effect on the estimations of the intervention's effects, this was deemed as high risk of bias.[39]

Domain 4: Measurement of the outcome. Blinding of the outcome measurements was described in four of the five studies. Timpone et al. did not describe any blinding, so it is assumed that both self-reported outcomes for QoL and physician measurements could have been influenced by knowledge of the intervention.[41] This study was therefore assessed to have high risk of bias for this domain.

Domain 5: Selection of the reported result. For all five studies, no prespecified trial protocols could be identified. Although attempts to contact the study authors were made, to identify any prespecified analysis plans, this was unsuccessful for all included articles. Raw data for outcome measurements was also missing in all five studies. Although the reported outcome measurements were in-keeping with the methodology described in each study—this was written retrospectively once the study had finished and as such all five studies were judged as having at least some concerns for reporting bias. However, four studies reported comprehensive outcome measurements at multiple time points for all intervention arms. Jatoi et al. only reported outcome measurements as "some point during the study" rather than specific time points and as such was judged as high risk of reporting bias.[40]

Change in appetite
Figure 3 is a forest plot showing the effect sizes of two included studies looking at the change in appetite for the cannabis-based medicine (experimental) and placebo (control) arms.[42,43] An effect size above 0 favors the experimental arm, whereas below 0 favors the control arm. Strasser et al. provided a unit of analysis issue as it contained two intervention arms (Cannabis Extract + THC vs. THC alone)—as such the control arm was divided equally into two groups for data

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI [VAS change]	Year
	Mean [VAS change]	SD [VAS change]	Total	Mean [VAS change]	SD [VAS change]	Total			
Strasser 2006	24.7	5.4	95	23.8	5.8	24	3.4%	-0.40 [-11.14, 10.34]	2006
Strasser 2006	18.5	0.6	100	23.8	5.8	24	3.8%	-5.20 [-15.39, 4.99]	2006
Turcott 2018	-2.8	2.3	14	-1.1	3.7	19	92.8%	-1.70 [-3.75, 0.35]	2018
Total (95% CI)			209			67	100.0%	-1.79 [-3.77, 0.19]	

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
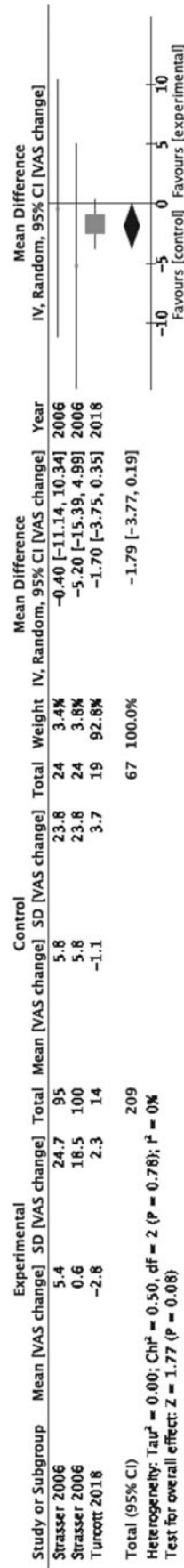Test for overall effect: Z = 1.77 (P = 0.08)

FIG. 3. Forest plot displaying effect sizes of studies comparing change in appetite, as scored using VAS, for cannabis-based medicines versus control in adults. VAS, Visual Analog Scale.

analysis.[43] The pooled group effect size for change in appetite was −1.79 (95% CI: −3.77 to 0.19) favoring control but this effect was found to be not significant ($p = 0.08$). Low heterogeneity existed between these studies ($I^2 = 0\%$).

Change in weight

Figure 4 illustrates a forest plot for the effect sizes of change in weight reported in two studies between cannabis-based medicine and the control groups.[41,42] The pooled between-group effect size for change in weight was −4.26 (95% CI: −12.28 to 3.76) although this result was not statistically significant ($p = 0.30$). Moreover, the I^2 value is 95% suggesting a high likelihood of study heterogeneity.

Quality of life

Figure 5 displays a forest plot for the effect sizes for change in QoL reported in three studies.[40,42,43] The pooled between-group effect size for change in QoL was −0.14 (95% CI: −0.32 to 0.03) favoring control, although this was not statistically significant ($p = 0.11$). The I^2 value of 0% suggests there was low heterogeneity between included studies. The standard MD was used here due to the QoL measurements using different scales/instruments.

Acceptability of treatment

All five included studies utilized some form of patient self-reporting through QoL questionnaires allowing additional monitoring of adverse events.

Beal et al. reported that 43% of the experimental arm reported treatment-related adverse events compared with 13% of the control group ($p < 0.001$).[39] Additionally, nervous system events (dizziness, euphoria, and drowsiness) were the most common adverse events seen in the experimental group (35%) compared with placebo (9%) with a p-value < 0.001.

In the two studies that compared cannabis-based medicine with megestrol acetate, neither found a statistically significant difference with respect to the frequency of adverse events.[40,41] Jatoi et al. found that 18% of male patients receiving megestrol acetate reported impotence contrasting with 4% on dronabinol ($p = 0.002$).[40]

Three studies comparing cannabis-based medicines against placebo found no statistically significant difference with respect to the frequency of adverse events.[39,42,43] Turcott et al. observed a significant reduction in both pain and insomnia for the nabilone arm compared with the placebo group.[42]

Discussion

This systematic review and meta-analysis aimed to assess the effect of cannabis-based medicine on patients with cachexia. The primary objective being to compare the available evidence on how appetite is affected while secondarily looking at change in body mass and QoL.

The literature search identified five RCTs evaluating the efficacy of cannabis-based medicine in the treatment of cachexia in both advanced cancer (three studies) and HIV patients (two studies). GRADE methodology and the risk of bias tool were utilized for the analysis and interpretation of study results.

Although two studies found an overall trend that appetite scores had improved with cannabis-based medicine use, no statistically significant change in appetite was observed across all five studies.[39,42] For two pooled studies, an MD of −1.79 ($p = 0.08$) favoring the control group of patients was calculated.[42,43] The quality of evidence was assessed to be low. These studies had small sample sizes and wide CIs that crossed 0.

No statistically significant change in weight was observed in the three studies measuring weight change.[39,41,42] However, the quality of evidence for this outcome was assessed as very low due to identified risk of bias in outcome measurement and a likelihood of high study heterogeneity. Patients in one study measuring weight change as an outcome were aware of their intervention, which could have influenced their self-reported weight change.[45–47] Moreover, study duration varied from 4 to 12 weeks, this relatively short duration combined with an increasing loss to follow-up, observed as trial duration continued, calls in to question the validity of these findings.[48] Clinical heterogeneity in the form of different routes of administration, dosage, and plasma levels may confound the outcomes leading to the overall study outcome. Future clinical studies may better benefit from pharmacological evaluation to identify an optimum treatment regimen particularly in view to identifying if a dose–response relationship exists.

QoL data were pooled for three studies but no statistically significant change was observed.[40,42,43] The quality of evidence here was again considered low. The risk of bias in reporting outcomes was also high in one included study.

All five studies suffered from missing outcome data due to loss to follow-up. In some cases, evaluable patients postrandomization were also excluded following protocol violations. Only one study explicitly explained how it handled missing outcome data through a nearest
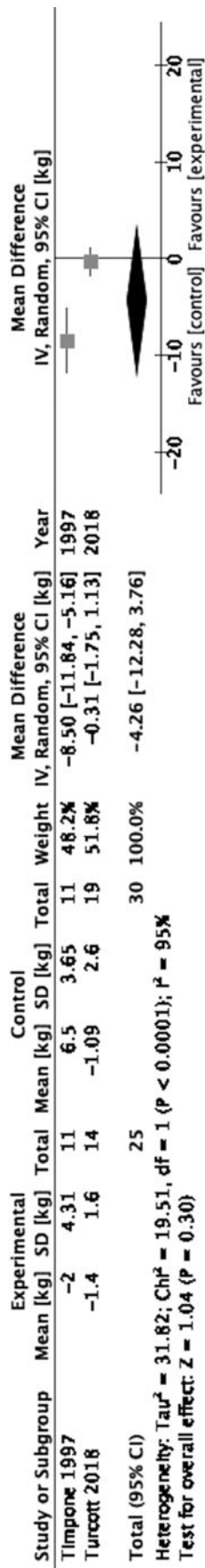
Study or Subgroup	Experimental Mean [kg]	SD [kg]	Total	Control Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]	Year
Timpone 1997	-2	4.31	11	6.5	3.65	11	48.2%	-8.50 [-11.84, -5.16]	1997
Turcott 2018	-1.4	1.6	14	-1.09	2.6	19	51.8%	-0.31 [-1.75, 1.13]	2018
Total (95% CI)			25			30	100.0%	-4.26 [-12.28, 3.76]	

Heterogeneity: Tau² = 31.82; Chi² = 19.51, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 1.04 (P = 0.30)

FIG. 4. Forest plot displaying effect sizes of studies comparing change in weight for cannabis-based medicines versus control in adults.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Jatoi 2002	12	8	152	15	19	159	62.5%	-0.20 [-0.43, 0.02]	2002
Strasser 2006	1.1	19.2	95	3	19.5	24	15.5%	-0.10 [-0.55, 0.35]	2006
Strasser 2006	5.1	21.2	100	3	19.5	24	15.6%	0.10 [-0.35, 0.55]	2006
Turcott 2018	52.7	31.4	14	60.8	25.7	19	6.4%	-0.28 [-0.97, 0.41]	2018
Total (95% CI)			361			226	100.0%	-0.14 [-0.32, 0.03]	

Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 3 (P = 0.66); I² = 0%
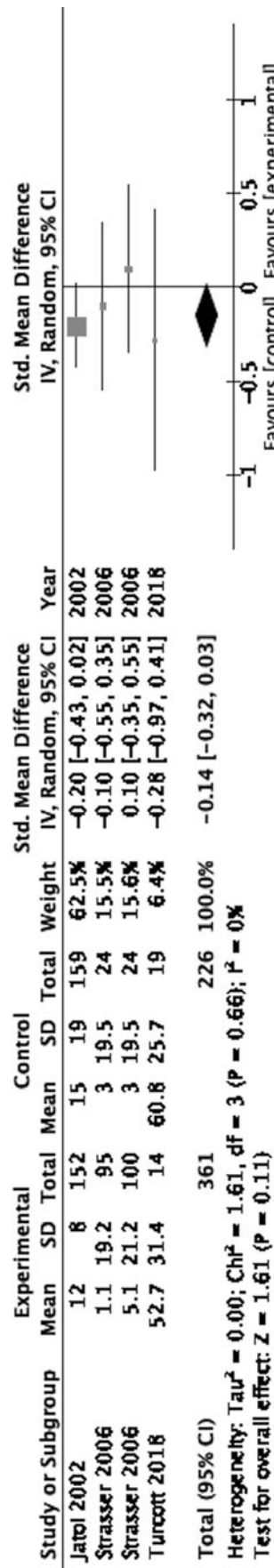Test for overall effect: Z = 1.61 (P = 0.11)

FIG. 5. Forest plot displaying effect sizes of studies comparing change in QoL for cannabis-based medicines versus control in adults. QoL, quality of life.

neighbor approach.[43] The inappropriate handling of missing outcome data in some of the studies calls in to question the interpretation of the results. If the characteristics of patients that dropped out differed across treatment arms or the reasons for their loss to follow-up were not thoroughly explored, the estimate of the effect of cannabis may be incorrect.[49] For example, drop-out patients could have been of certain ethnicities, disease status, or age ranges that suffered more severe adverse events or felt insufficient benefit from the treatment to warrant continuation.

Small sample sizes and low quality of evidence were consistent limitations at study level. A limited number of studies were identified as suitable for inclusion and the lack of raw data available for each included study restricted the quality of analysis possible. The small study number also meant that it was not possible to conduct subgroup analyses despite study differences (treatment type, study duration, and methodology). Publication bias could not be assessed using funnel plot asymmetry because fewer than 10 studies were included within the meta-analysis.[34,50]

The average age of the entire cohort for the included studies is ~53 years old with the majority being Caucasian males. The applicability of findings in these studies may be less generalizable to the population due to differences in pharmacokinetics among age, gender, and ethnicity.[51] Differences in fat distribution and muscle mass across different populations may affect the pharmacodynamics of cannabinoids.[52,53] Formal phase I/II studies to elicit pharmacokinetic data on cannabinoids in cachexia are still awaited.[54] This study aimed to mitigate this by only specifically including those with diagnosed cachexia who would therefore share a more similar body phenotype, in contrast to previous systematic reviews, which had included patients without meeting a definition for cachexia.[29] Patients being entered onto trials concerning nutritional status could also be more likely to be better informed and more knowledgeable about good nutritional regimes versus the general population. This could confound findings in studies that assess pharmacological interventions for appetite and weight change, biasing toward the null.

The findings in this review are in line with a previous systematic review on cannabinoid use in palliative medicine that observed no significant effect of cannabinoids on appetite or weight change.[28] A larger systematic review and meta-analyses on multiple pharmacological management options for cachexia found no robust evidence to recommend any single pharmacological agent, including cannabis, for the treatment of cachexia.[55] Both reviews similarly found that most studies suffer from at least some risk of bias and low quality of evidence.

Cannabinoids possess sufficient pharmacological potential for use in cachexia. CB_1R agonists increase appetite in orexigenic and anorexigenic neurones.[26,27] Moreover, THC and in particular CBD have demonstrated immunoregulatory function, particularly through TNF-α and interleukin-6, suggesting a mechanism through which to treat cachexia.[56,57] Most patients are accepting of cannabis-based medicines as therapeutics, despite negative connotations associated with its recreational use. Multiple studies conducted in different patient populations (cancer, acute perioperative pain, and chronic pain) confirm this notion.[58–61] Over 500 patients surveyed in the United States judged oral administration in capsules or pills as the most acceptable, which is the format of administration used in all five included studies.[62]

Besides the low quality of evidence in the included studies for cachexia and cannabinoid use, there exist a myriad of barriers and challenges to conducting wider research into cannabinoids in general. Aside from legal, regulatory, and funding barriers, cannabis can exist as a whole plant extract or active pharmaceuticals can be isolated and administered to patients.[63–65] Cannabis cultivation yields highly heterogeneous products based on growth techniques (light, temperature, humidity, and nutrient type), and therefore all studies utilizing plant-sourced cannabinoids need assurance that good manufacturing practice was used throughout.[66] The Cannabis plant contains over 100 cannabinoids, in addition, hundreds of terpenes, flavonoids, stilbenoids, amino acids, fatty acids, alkaloids, hydrocarbons, carbohydrates, and phenols.[67,68] Ben-Shabat et al. first highlighted how varying concentrations of each constituent compound in the plant may alter the end effect on a patient, known as the "entourage effect."[69] While there is much controversy over the strength of this posited theory, with evidence both supporting and refuting its existence, the heterogony of cannabis chemovars does provide challenges in performing RCTs on whole plant extract of unprocessed flower as the effects of each compound need to be considered for their effects on the clinical results.[69,70–73] Successful clinical trials require large sample sizes over long durations with tightly controlled methodology that can be replicated and consistent results be reproduced.[74]

Conclusion

This review found no high-quality evidence to recommend the use of cannabis-based medicine for the treatment of cachexia. It supports previous findings that there is no high-quality evidence to support the use of any pharmacological agents in isolation for cachexia. In view of this, it is recommended that, based on the pharmacological potential of cannabinoids for increasing appetite and modulating immune function combined with the unmet need to develop an effective treatment option for cachectic patients, further trials be conducted. Studies with larger sample sizes and longer trial durations, to produce a higher quality of evidence, are required. In particular, THC/CBD combination regimens may warrant specific further evaluation, as THC induces appetite stimulation through CB_1R agonist activity, while CBD is immunomodulatory. Moreover, further studies are needed to identify if whole plant extract does exhibit an "entourage effect" over single agent isolates and how this alters treatment efficacy for patients.

Ethical Considerations

The authors have reviewed the journal guidance on ethical standards and have nothing to declare.[75]

Acknowledgment

Author Disclosure Statement

Funding Information

Supplementary Material

Supplementary Appendix SA1
Supplementary Appendix SA2

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Abbreviations Used

AC/S	anorexia–cachexia subscale of FAACT
AIDS	acquired immunodeficiency syndrome
BMI	body mass index
CB_1R	cannabinoid receptor type 1
CBD	cannabidiol
CI	confidence interval
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire
FAACT	Functional Assessment of Anorexia–Cachexia Therapy instrument
ITT	intention-to-treat
MD	mean difference
PICOS	patient, intervention, control, outcome, study type
QoL	quality of life
SD	standard deviation
THC	tetrahydrocannabinol
TNF-α	tumor necrosis factor-α
VAS	Visual Analog Scale