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Review

Cannabinoids in the treatment of cancer anorexia and cachexia: Where have we been, where are we going?

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ABSTRACT

Cachexia–anorexia cancer syndrome remains an unmet clinical need with a dearth of treatment and no standard of care. Acting through the endocannabinoid system, cannabinoids are one potential cancer cachexia treatment. Herein, the potential mechanisms for cannabinoids for cancer cachexia are discussed as are previous and ongoing clinical trials.

Introduction

Cachexia–anorexia cancer syndrome (CACS) is defined as chronic disease–related malnutrition on a background of systemic inflammation[1] and affects over half of patients with advanced cancer,[2] resulting in increased mortality and decreased quality of life. It has been estimated that cancer cachexia is responsible for 22% of cancer patient deaths.[3] The pathophysiology of CACS is becoming increasingly understood as caused by the host-tumor response and subsequent inflammatory cascade that occurs thereafter but may also be directly influenced by systemic anti-cancer therapy causing myopenia. In addition, patients with cancer cachexia are more likely to suffer from toxicity during the chemotherapy.[4] CACS, loss of appetite, is a component of the multifactorial syndrome that is cancer cachexia. In some of the studies presented, CACS was examined as a subset of cachexia. While some tumors themselves have the ability to promote inflammation and cachexia, several pro-inflammatory cytokines (e.g., interleukin 1 [IL-1], IL-6, and tumor necrosis factor [TNF]-α) are able to induce hypermetabolism, which directly affects skeletal muscle.[5] TNF-α is involved in many pathways that produce symptoms similar to those seen in cachexia such as weight loss and decreased appetite.[6] This complex pathophysiology combined with the changing landscape that occurs at the tumour–host interface means that optimally treating cachexia is challenging. Although multiple treatments have been assessed, there is currently only one licensed therapy globally, which was trialled in Japan, and there is no standard of care. A need remains to develop therapies for cancer cachexia, and cannabinoids have been proposed as one such therapy.

Cannabinoids for CACS

Cannabis sativa L, commonly referred to as cannabis, has received a lot of attention for several years with regards to its medicinal effects in cancer. The focus has largely been on the compounds tetrahydrocannabinol (THC) and cannabidiol (CBD).[7] This has allowed the endocannabinoid pathway to be identified as a therapeutic target in cancer. Large amounts of heterogeneity have been seen in previous trials of cannabinoids and are further complicated by issues such as psychotropic side effects[8] and legalization of use. Pharmaceutical synthetic cannabinoids, namely nabilone and dronabinol, contain THC but not CBD, as opposed to naturally occurring cannabis, which contains both these compounds. Medical staff may encounter patients who have acquired their own cannabis or synthetic cannabinoids to take. Commonly,

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patients may take CBD-containing products in the form of oils, food, or naturally smoked. THC is the compound known to cause psychoactive effects, and Issa found that patients reported a similar sensation of a "high" when taking their study drug (dronabinol) when compared to marijuana inhalation, though the rate of onset was changed, and a dose-dependent relationship was determined.[9] Studies have focused on its ability to assist in cancer-related pain, vomiting, and even produce tumor-suppressive effects.[10] Recently, studies have begun to look at the possibility of the use of cannabis to target CACS.

Mechanism of action

An understanding of the mechanism of cannabinoids in the human body is necessary to consider how it may be used in medical treatment.

Mechanisms of the endocannabinoid system. The principal receptors involved in these pathways are cannabinoid receptor types 1 and 2 (CB1 and CB2), both of which are G-coupled protein receptors. To interact with these receptors, the body produces endocannabinoids, which have a similar structure to molecules in the cannabis plant, namely THC. The interaction between these forms the basis of the endocannabinoid system (ECS). Research has shown that THC does not activate the G-protein coupled with CB2, unlike its action with CB1.[11] CB1 and CB2 receptors are able to show functional selectivity depending on the interacting ligand, producing a wide range of effects on the host. This can be demonstrated with THC, which has a low efficacy for CB1; however, synthetic cannabinoids tend to be highly efficacious.[12]

CB1 receptors are found primarily in the central nervous system on the plasma membranes of nerve endings. They are found in the highest levels in the cerebellum, hippocampus, and olfactory bulb. Its expression in the peripheral nervous system varies by tissue and primarily is found at synaptic nerve terminals.[13] CB1 receptors are able to inhibit the release of neurotransmitters by inhibiting voltage-gated calcium channels and adenylyl cyclase and by activating potassium channels and mitogen-activated protein kinase.[14] The level of expression of CB1 varies greatly depending on the cell type, e.g., high levels in GABAergic interneurons and low levels in cholinergic neurons.[15] CB1s found in astrocytes will release glutamate, once activated, and suppression of glutamate transmission will lead to increased appetite.[16] Dronabinol is a synthetic cannabinoid formed with the primary active compound THC, which has been used in a number of clinical trials including those by Timpone and Beal. It interacts primarily with CB1 receptors to produce effects on the hypothalamus-improving appetite.

CB2 receptors are peripheral receptors located near immune cells, and Galiegue described it particularly in the spleen, thymus, and tonsils.[17] Due to their location, they have been associated with effects on immunomodulation. While it is detected in the brain, it is in much lower levels than CB1. CB2 stimulates extracellular system-regulated kinase, which decreases intracellular levels of cAMP when activated, as well as influences gene expression by activating mitogen-activated protein kinase.[18] CB2 receptors are involved in the anti-inflammatory response that decreases TNF, IL-1, and IL-6.

Pro-inflammatory cytokines in CACS. It is now well established that an increased inflammatory environment, such as what is seen in cancer, promotes loss of lean mass (muscle). This is why CACS is seen in many inflammatory disorders such as sepsis and irritable bowel disease. Cancer patients will often have higher levels of inflammatory markers than other patient groups. Three primary inflammatory cytokines are implicated in these responses—TNF-α, IL-1, and IL-6. TNF-α is involved in pathways that produce symptoms similar to those seen in cancer CACS and increases metabolism and gluconeogenesis.[19] Shang described how THC is able to reduce its TNF-α paracellular permeability[20] and by this skeletal muscle catabolism both by activating the UPS(5) (ubiquitin proteasome system) and by activating the breakdown of protein.

Mantovi hypothesized that during cancer growth, there may be an increased production of IL-1.[21] IL-1 has many similar actions to the enteromedial hypothalamic serotonergic system, and therefore they are closely associated with one another. IL-1 increases levels of the serotonin precursor, tryptophan, which results in an increased level of serotonin.[22] This causes an increase in satiety and a decreased appetite. In addition, Tilders noted that IL-1 stimulates neurons in the hypothalamus to release corticotrophin-releasing hormone, affecting the hypothalamic pituitary adrenal (HPA) axis.[23] This will cause increased secretion of adrenocorticotrophic hormone and cortisol initiating an increased catabolic rate. The increased activity of IL-1 in cancer will also increase serotonin via HPA to increase satiety.[24] It is also able to modulate immune responses and induce local tissue–specific effects. Its receptors can be detected in areas of the hypothalamus that regulate food intake, and infusion of IL-1 in rodents has changed food intake and meal size.[14]

Similar to IL-1, IL-6 is a pro-inflammatory cytokine. IL-6 has been reported at increased levels in a number of cancers including ovarian[25] and gastroesophageal cancers.[26] IL-6 causes suppression of protein synthesis and modulates homeostasis.[27] Its action is closely related to that of IL-1, and reduction is associated with increased body mass so closely that it was found it to be the only cytokine raised in patients with CACS.[28] IL-6 is involved in pathways key to cancer pathogenesis including wound healing and tissue regeneration.[29] Rupert also suggested that tumors that contain a cell deletion of IL-6 have less activation of their muscular atrophy pathways.[30] IL-6 also has both pro-tumour and antitumor actions depending on which pathways are activated. IL-6 increases cell proliferation, evasion of apoptosis, and angiogenesis. In contrast, IL-6 can also increase T cell and CD8 proliferation, AMP-activated protein kinase stimulation and inhibit TNF-α.[31]

The ability of these inflammatory cytokines to interact with the ECS is what makes synthetic cannabinoids a possible therapeutic agent. IL-1 injection has been found to increase the sensitivity of cannabinoid receptor type 1 (CB1) receptors.[32] Cannabinoid receptor type 2 (CB2) is upregulated in the presence of IL-6 and TNF-α. This is due to IL-1 and IL-6 increasing CB1 and CB2 mRNA levels in the blood,[33] which can be further potentiated by the introduction of a synthetic cannabinoid.

Hypothetical mechanisms for endocannabinoids in CACS. There is a well-established link between peripheral CB1 receptor activation and the gastrointestinal response leading to increased appetite and weight gain. CB1 activation increases sweet sensitivity and causes activation of the vagus nerve. This causes direct modification of the gut–brain signalling and modulates gastric vagal afferent mechanosensitivity.[34] Activation of CB1 receptors is able to increase palatability of high fat-percentage food and leads to increased ghrelin release,[35] causing delayed gastric emptying. This is linked to decreased release of acetylcholine and gastric secretions.[35] Subsequent effects on the intestines include the inhibition of cholecystokinin release and increased tissue permeability.[36] The liver will then increase fatty acid synthesis, lipogenesis, gluconeogenesis, and primary liver regeneration.[37] CB1 will then stimulate insulin secretion from the pancreas. Further downstream, CB1 has marked effects on both fat tissue and muscle. In fat tissue, there is increased fat-cell differentiation and storage, as well as decreased mitochondrial respiration.[38] In muscle, there is decreased insulin-mediated glucose uptake and regulation of oxidative activity.[20] All of these actions can contribute to improvement in CACS symptoms.

Work to date using Cannabinoids for CACS

Table 1 illustrates the key trials investigating synthetic cannabinoids for CACS. The key trials were identified by searching Medline and Embase using key words to identify (number) trials. Exclusion criteria included that the study must have been published in English and must have assessed changes in body weight, calorie intake, or appetite. After removal of duplicates, six papers were included for analysis.

Of the six papers included, two (Beal, Brisbois) assessed both appetite and weight changes/calories consumed, three (Timpone, Jatio, Turcott) assessed only weight changes/calories consumed, and one paper

Table 1
Key characteristics of main studies investigation Cannabinoids in the treatment of cachexia–anorexia cancer syndrome.

Study	Population	Intervention	Comparison	Outcome	Duration
Beal et al. (1995)	AIDS patients with CACS	2.5 mg dronabinol ($n = 72$)	Placebo ($n = 67$)	Change in appetite (VAS) Change in weight (kg)	6 weeks
Timpone et al. (1997)	HIV associated anorexia	A: 2.5 mg dronabinol ($n = 12$) B: 750 mg megestrol acetate + 2.5 mg dronabinol ($n = 13$) C: 250 mg megestrol acetate + 2.5 mg dronabinol ($n = 13$)	750 mg megestrol acetate ($n = 12$)	Pharmacokinetics	12 weeks
Jatoi et al. (2002)	CACS	A: 2.5 mg dronabinol + placebo ($n = 152$) B: 800 mg megestrol acetate + 2.5 mg dronabinol ($n = 158$)	800 mg megestrol acetate + placebo ($n = 159$)	Change in appetite (VAS)	4 weeks
Strasser et al. (2006)	CACS	A: 2.5 mg THC + 1 mg CBD ($n = 95$) B: 2.5 mg THC ($n = 100$)	Placebo ($n = 48$)	Change in appetite (VAS)	6 weeks
Brisbois et al. (2011)	CACS	2.5 mg dronabinol ($n = 24$)	Placebo ($n = 22$)	Food chemosensory perception (taste) Premeal appetite Calories consumed	3 weeks
Turcott et al. (2018)	Patients with non-small cell lung cancer	0.5 mg nabilone ($n = 14$)	Placebo ($n = 19$)	Energy intake QoL Change in appetite (VAS)	8 weeks

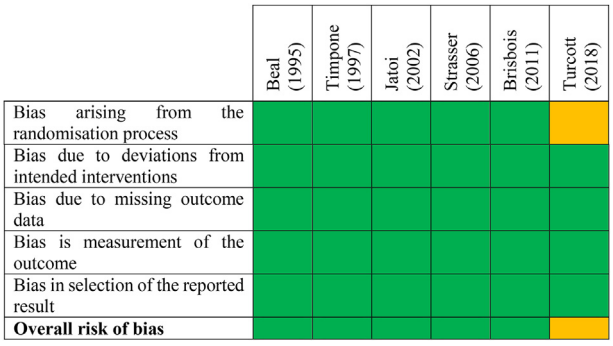
QoL, quality of life; VAS, Visual Analog Scale; CACS, cachexia–anorexia cancer syndrome; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; THC, tetrahydrocannabinol; CBD, cannabidiol.

(Strasser) assessed only changes to appetite. Brisbois' randomized controlled trial in 2011 demonstrated that THC improved food sensory experience, appetite, and calories consumed as protein when compared to placebo. Total calorific intake and quality of life improved in both groups.[39] The study included 46 patients with advanced cancer. No patients receiving THC showed a decrease in appetite, whereas the majority of patients receiving the placebo experienced a decrease in appetite. Johnson included 177 patients in an randomized controlled trial where the primary inclusion criteria was related cancer pain. He described that appetite improved in the placebo group and decreased in the THC and THC CBD extract group. Results were unclear as to whether there was any difference in nausea between the two groups depending on the statistical analysis used; however, the authors' accounts of results for appetite were due to the general improvement in health in the placebo group patients.[40] Strasser's 2006 randomized controlled trial found no difference in improvements seen in body weight or appetite between CE (cannabis extract), THC, or placebo groups,[41] and the study therefore terminated early. Ninety-five patients received CE (2.5 mg THC and 1 mg cannabidiol), 100 received THC, and 48 received placebo. Turcott 2017 assessed 65 patients to receive either nabilone or placebo. Patients who received nabilone reported an increased intake of calories and increased quality of life. Timpone assessed 52 patients taking either dronabinol or dronabinol and megestrol acetate. Their results were mixed, and it was found that dronabinol only increased weight when combined with high-dose megestrol acetate. Variation in trial results regarding changes in appetite may relate to our limited understanding of the dosage relationship with appetite change, and whether this is a linear relationship or forms a bell-shaped curve response similar to analgesia.

Adverse effects are of concern to legislators due to their close links with dependence and legality across different areas of the world. The majority of trials have found no adverse effects in the synthetic cannabinoids, namely Timpone, Brisois, and Turcott. In the remaining studies, Beal found that the adverse effects reported were dose-related and resolved independently when doses were reduced. Jatoi reported higher rates of neurotoxicity in the study group but decreased rates of haemotoxicity compared to those of the placebo group. Strasser found that only 4% of the adverse events reported in the study were linked to the study drug. Overall, this is a positive finding when considering the safety of synthetic cannabinoids.

Risk-of-bias assessment

A risk-of-bias assessment was carried out on the six primary trials mentioned earlier. Six areas of possible bias were assessed and ranked green for low risk of bias, yellow for some risk of bias, and red for high risk of bias. Johnson 2021 was a literature review, so it was not included in the below table.



Trials were of high quality and had overall low risk of bias, with the exception of Turcott, which had some concerns of bias due to the randomization process. Trial durations were short, ranging from three weeks to twelve weeks.

Future trial designs

As can be seen from the trials listed in Table 1, many trials have had small sample sizes due to their nature of being pilot studies and weak evidence due to allocation bias being present. Trials have also had short durations with little follow-up of participants. Comparisons between studies are also limited by the use of different patient-reported outcomes. Turcott discussed the importance in future trials of considering time since the start of CACS and the effect this will have on weight loss and response to treatment.[14] As discussed by Timpone, results have showed variations in weight changes to dronabinol depending on the dose of megestrol acetate it is combined with. This shows the need to assess multiple doses of drug combinations in future trials. It is known that side-effects are largely associated with THC, whereas CBD provides the antineuroinflammatory effects, which researchers are aiming for. It is important to consider then when undergoing drug design in the future should there be inclusion of both compounds.

Studies in progress

A current major clinical trial is taking place at the time of writing is the *Cancer Appetite Recovery Study* (CAReS) trial (EudraCT 2020-000-464-27), which is trialling a drug called ART 27.13 in patients with CACS. ART 27.13 is a dual CB1 and CB2 agonist[42] aimed at increasing lean body

mass in patients. The CAReS trial is a two-stage trial with a dose escalation Phase 1 portion followed by a randomized, double-blinded, placebo-controlled portion, which will yield high-value research upon completion. This trial aims to explore endpoints (e.g., patient-reported outcome measures of CACS). Table 1 shows the major trials that have taken place so far in this area and their characteristics.

Cannabinoids and the nursing role

A thorough knowledge of the physiology of the ECS and the interactions it has with synthetic cannabis has been recommended by the National Council of State Boards Nursing. This includes knowledge regarding the ethical and legal challenges synthetic cannabis presents. In the future, this role may be its own subspecialised area, which the American Nurses Association have been recommending since 2022.[43]

Nurses play a key role in assessing the patient's symptoms, medication compliance, and side-effects. Nurses may also be responsible for dispensing cannabinoids and play a role in monitoring it. Cannabinoids are viewed as a controlled drug and therefore additional precautions are involved when dispensing. It is likely that nurses will be involved in assessing the drugs' effectiveness due to the increased time spent with patients compared to the rest of the healthcare team. Depending on the center, effectiveness may be assessed by weight gained, calories consumed, or increased appetite, all which the nursing staff would be involved in monitoring, either through daily weights of the patients or by having them complete a food or appetite diary.

Nurses may be more likely to be confronted with the concerns from patients or families who have stigmatized cannabis use. This will require a level of knowledge about how the cannabinoid is being used and what side-effects they can warn patients and families about. It will be essential that nurses be educated on the important side-effects from cannabinoids to monitor for such as psychoactive effects, which may indicate the need for dose adjustment. Nurses have reported in the past concerns that there has been lack of education regarding cannabis use, which has led to challenges when communicating with patients.[44]

Conclusions

The aim of this review was to assess the use of cannabinoids in the treatment of CACS. There were concerns regarding the side-effects of cannabinoid compounds; however, results have shown that major side-effects have been avoided in the major trials. This review has demonstrated the advantageous effects that cannabinoids have on weight gain, appetite, and quality of life. The overall results are consistent with the previous meta-analysis performed. Limitations of this review are largely accountable to the limitations of the individual studies as mentioned previously. Aspects of this include small sample size, short durations, and follow-up periods as well as variation in the dose of cannabinoids used. The trials included were of overall low bias and high-quality design. With increased media coverage and public knowledge on the medicinal use of cannabis, it is likely that healthcare workers will face an increasing number of patients asking about its uses and how it may benefit their treatment. It is paramount for prescribers to understand the beneficial uses of cannabinoids in certain medical conditions and be able to provide accurate information on this.

In conclusion, synthetic cannabinoids are a promising future treatment for CACS. There have been few high-quality trials in the recent years, which has limited evaluation of its uses. Theories have demonstrated that cannabinoids could be ideal treatment targets in patients suffering with CACS. Future high-quality research is required in this area to quantify dosage and treatment applicability.

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CRediT author statement

Emily Seymour-Jackson: Formal analysis, investigation, resources, writing – original draft, visualisation, project administration. Barry Laird: Conceptualization, supervision, project administration, writing – review & editing. Judith Sayers: Writing – review & editing. Marie Fallon: Writing – review & editing. Tora S Solheim: Writing – review & editing. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

BS has received consultancy and is a scientific advisor to Artelo Biosciences, Faraday, Actimed.

RS is an artelo bioscienes and received consultancy from Helsinn, Actimed, Avidity, Faraday.

MF is a chief investigatory for an EME/NIHR study of which Ananda Deveelopments are providing CBD.

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Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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