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REVIEW

Mechanisms and pharmacotherapy of cancer cachexia-associated anorexia

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Abstract

Cachexia is a multifactorial metabolic syndrome characterized by weight and skeletal muscle loss caused by underlying illnesses such as cancer, heart failure, and renal failure. Inflammation, insulin resistance, increased muscle protein degradation, decreased food intake, and anorexia are the primary pathophysiological drivers of cachexia. Cachexia causes physical deterioration and functional impairment, loss of quality of life, lower response to active treatment, and ultimately morbidity and mortality, while the difficulties in tackling cachexia in its advanced phases and the heterogeneity of the syndrome among patients require an individualized and multidisciplinary approach from an early stage. Specifically, strategies combining nutritional and exercise interventions as well as pharmacotherapy that directly affect the pathogenesis of cachexia, such as anti-inflammatory, metabolism-improving, and appetite-stimulating agents, have been proposed, but none of which have demonstrated sufficient evidence to date. Nevertheless, several agents have recently emerged, including anamorelin, a ghrelin receptor agonist, growth differentiation factor 15 neutralization therapy, and melanocortin receptor antagonist, as candidates for ameliorating anorexia associated with cancer cachexia. Therefore, in this review, we outline cancer cachexia-associated anorexia and its pharmacotherapy, including corticosteroids, progesterone analogs, cannabinoids, anti-psychotics, and thalidomide which have been previously explored for their efficacy, in addition to the aforementioned novel agents, along with their mechanisms.

KEYWORDS
anorexia, cachexia, cancer, mechanism, pharmacotherapy

Abbreviations: 2-AG, 2-arachidonylglycerol; 5-FU, 5-fluorouracil; 5-HT, 5-hydroxytryptamine; 5-HT3R, 5-hydroxytryptamine receptors.; AgRP, agouti-related peptide; AMPK, adenosine monophosphate-activated protein kinase; AMY, amygdala; ARC, arcuate nucleus; ASCO, American Society for Clinical Oncology; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CART, cocaine- and amphetamine-regulated transcript; CB1, cannabinoid receptor 1; CC, cancer cachexia; CNS, central nervous system; CRH, corticotropin-releasing hormone; DMN, dorsomedial nucleus; ESMO, European Society of Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism; Fn14, fibroblast growth factor-inducible 14; GDF-15, growth differentiation factor 15; GFRAL, GDNF family receptor α-like; GH, growth hormone; GLP-1, glucagon-like peptide 1; IGF, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein-3; IL-1, interleukin-1; IL-6, interleukin-6; JAK/STAT, Janus kinase/signal transducers and activators of transcription; LBM, lean body mass; LHA, lateral hypothalamic area; LMF, lipid mobilizing factor; MA, megestrol acetate; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; MIC-1, macrophage inhibitory factor; NPY, neuropeptide Y; NSCLC, non-small cell lung cancer; NST, nucleus of the solitary tract; PBN, parabrachial nucleus; PIF, proteolysis-inducing factor; PTHrP, parathyroid hormone-related proteins; PVN, paraventricular nucleus; QoL, quality of life; RCT, randomized placebo-controlled trial; TGF-β, transforming growth factor-β; TNF, tumour necrosis factor; TRH, thyrotropin-releasing hormone; UCP1, uncoupling protein 1; VMN, ventromedial hypothalamus nucleus; VTA, ventral tegmental area; α-MSH, α-melanocyte-stimulating hormone.

1 | INTRODUCTION

Cancer cachexia (CC) is a multifactorial syndrome characterized by a progressive decline in body weight, malnutrition, diminished skeletal muscle mass, frequent loss of fat mass, and impaired functional capacity.[1] CC has been associated with increased treatment-related toxicity, hospitalization, and reduced survival in patients with cancer.[2] In addition, CC is highly prevalent and is described to affect up to 80% of patients with advanced cancer, predominantly those with solid tumors.[3]

Recently, several societies have come together to propose recommendations to manage CC, including the European Society of Oncology (ESMO),[4] the American Society for Clinical Oncology (ASCO),[5] and the European Society for Clinical Nutrition and Metabolism (ESPEN).[6] These guidelines highlight the impact of CC on patients' quality of life (QoL), prognosis, strategies for management in clinical practice, and the healthcare burden of cachexia. Thus, our knowledge of the pathophysiology of CC has been greatly enhanced in recent years. Unfortunately, the treatment of CC has not evolved enough to yield a pharmacological agent able to deal with cachexia effectively. Due to its multifaceted features, there may never be a silver bullet for CC because, in more than four decades since the first drug was investigated, we are still finding new pathways and are trying new compounds to tackle CC.[7]

Although the main cause of weight loss, a key hallmark of CC, is the wasting of skeletal muscle and adipose tissue, reduced food intake due to anorexia is also directly and profoundly involved in the process of CC. The critical role of anorexia in the development and progression of cachexia should not be underestimated. Furthermore, anorexia precedes tissue wasting, emphasizing the need for early intervention.[8] Cancer cachexia-associated anorexia has been implicated in the suppression of orexigenic neurons and activation of anorexigenic neurons in the hypothalamus by tumor-induced cytokines, dysregulation of serotonin pathways, and alterations in the endocannabinoid system, which can be exacerbated by the side effects of cancer therapies, reduced activity, and tumor-induced compression or obstruction of the gastrointestinal tract.[9–12] More recently, evidence has emerged indicating that the stress-responsive cytokine Growth differentiation factor 15 (GDF-15) and the incretin hormone Glucagon-like peptide 1 (GLP-1) exert effects on the hindbrain, thereby regulating appetite.[13–17] Therefore, perturbations of those cytokines, hormones, and neuropeptides are the focus of many drug interventions in cancer cachexia-associated anorexia.

This narrative review focuses on the pathogenesis of cancer cachexia-associated anorexia and the pharmacotherapies discussed in recent ESMO, ASCO, and ESPEN guidelines[4–6] in the context of the pathogenesis of anorexia, as well as addressing some novel and promising anorexia therapies.

2 | CANCER CACHEXIA

There are three stages of CC progression: (1) pre-cachexia represented by early metabolic changes (e.g., anorexia and glucose intolerance) and involuntary body weight loss ≤5%, (2) cachexia encompassed by unintentional loss of body weight more than 5% in the past 6 months or either body mass index (BMI) lower than 20 kg/m^2 or presence of sarcopenia with weight loss more than 2%, and (3) refractory cachexia defined by uncontrolled stage of catabolism with no response to anti-cancer treatment and life expectancy of less than 3 months.[1] It is important to mention that the rate of progression is intrinsically related to the type of cancer, levels of systemic inflammation, initial body weight at diagnosis, food intake, associated pharmacological treatment, and genetic alterations.[18,19] Thus, body weight loss is a characteristic feature of CC, together with being important for its staging, which is caused by increased catabolism of skeletal muscle and adipose tissue and anorexia. It should also be mentioned that while anorexia can cause CC on its own, metabolic changes in skeletal muscle and adipose tissue can also cause CC even in the absence of anorexia.

Skeletal muscle mass is maintained by a refined balance between muscle protein synthesis and muscle protein breakdown, which depends on neuromuscular and metabolic regulation that, when disrupted, favors catabolism and leads to muscle wasting. In addition, antineoplastic agents may cause significant changes in protein turnover, proliferation, and differentiation of muscle as well as mitochondrial function. Changes in skeletal muscle mass due to anti-cancer therapy have been shown to reach up to 10% in patients undergoing chemotherapy lasting for about 3 months.[20,21] Considering a healthy age-related muscle loss of 1% per year after the fifth decade of life, these losses may represent a tremendous decline in skeletal muscle mass that can be representative of one decade of life.[22] Meanwhile, altered adipose metabolism in CC is characterized by increased lipolysis, decreased lipogenesis, and browning of white adipose tissue. Tumor-derived compounds such as interleukin-6 (IL-6) and parathyroid hormone-related proteins (PTHrP) induce the expression of mitochondrial uncoupling protein 1 (UCP1) in brown adipose tissue, leading to inefficient energy expenditure, and further hypercatabolism.[23,24] The pathogenesis of skeletal muscle and adipose tissue wasting in CC is closely associated with the activation of chronic cancer-induced systemic inflammatory responses in the host (cytokines such as interleukin-1 [IL-1], IL-6, and tumor necrosis factor [TNF]).[25,26] Furthermore, cancer-induced factors such as proteolysis-inducing factor (PIF), lipid mobilizing factor (LMF), and PTHrP exacerbate tissue catabolism.[27] Meanwhile, tumor-induced cytokines not only have wasting effects on skeletal muscle and adipose tissue but are also deeply involved in the development of anorexia in CC by inhibiting the appetite-promoting and stimulating the appetite-suppressing pathways in the appetite center of the hypothalamus.[9]

3 | ANOREXIA IN THE CONTEXT OF CANCER CACHEXIA

Cancer cachexia-associated anorexia is a significant unmet clinical problem with up to 60% of cases with advanced cancer, causing a

serious impact on QoL, therapeutic response, and even survival of cancer patients.[28–30] As mentioned earlier, multiple mechanisms are involved in the development of anorexia, including cytokines, alterations in neuropeptides or neurotransmitters such as leptin, ghrelin, and serotonin, and the endocannabinoid system.[31] A deep understanding of these underlying mechanisms is, therefore, essential for the development of effective treatments for cancer cachexia-associated anorexia.

3.1 | Appetite regulation in the central nervous system

3.1.1 | Hypothalamus

The hypothalamus is the key regulator of appetite in the central nervous system (CNS).[32] In the arcuate nucleus (ARC) of the hypothalamus, there are two neuronal populations with opposing effects on food intake: Neuropeptide Y (NPY)/agouti-related peptide (AgRP) as orexigenic neurons, while pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) as anorexigenic neurons regulate appetite, respectively. Both neuropathways innervate the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA), while the ARC also connects with other hypothalamic nuclei, including the ventromedial hypothalamus nucleus (VMN) and the dorsomedial nucleus (DMN).[33,34] POMC is involved in the production of the α-melanocyte-stimulating hormone (α-MSH), which binds to postsynaptic melanocortin 4 receptor (MC4R) in the PVN and releases anorexigenic hormones such as thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), and oxytocin, causing reduced feeding.[35,36] Brain-derived neurotrophic factor (BDNF), which is highly expressed in the VNM, has also been shown to regulate feeding via MC4R signaling.[37] On the contrast, the orexigenic effects of NPY/AgRP neurons are mediated by GABA-mediated inhibition of POMC neurons and by stimulating postsynaptic Y1 and Y5 receptors in the PVN.[38–40] Furthermore, AgRP exerts its orexigenic effects by acting as an antagonist of melanocortin 3 receptor (MC3R) and MC4R in the PVN.[41] As such, NPY/AgRP and POMC/CART neurons are intricately and interactively involved in appetite regulation.

3.1.2 | Hindbrain

The role of the hindbrain in appetite control has also been emphasized. GDF-15, also known as macrophage inhibitory factor (MIC-1), is a member of the transforming growth factor-β (TGF-β) superfamily.[42,43] This stress-induced cytokine is strongly associated with CC and anorexia. GDF-15 is expressed at high levels in the tissues of various carcinomas, accompanied by marked increases in serum levels.[44–46] The plasma concentration of GDF-15 in healthy individuals ranges from 100 to 1200 pg/mL,[47] whereas in patients with advanced cancer, the circulating levels of GDF-15 can reach from 10 000 to 100 000 pg/mL.[48] Several commonly used chemotherapeutic agents also elevate plasma levels of GDF-15.[49] A direct and positive correlation has been shown between serum GDF-15 levels and cancer anorexia and cachexia in clinical studies on gastrointestinal, lung, pancreatic, and prostate cancer.[50–52] Moreover, its elevated circulating levels are robustly associated with adverse clinical outcomes in aging, cardiovascular disease, cancer, and cachexia.[53–59]

Although the precise neural pathways through which GDF-15 regulates feeding behavior remain unclear, there is sufficient evidence to suggest that the neurons which respond to GDF-15 and induce anorexia are localized in the area postrema (AP) and nucleus of the solitary tract (NST) in the medulla oblongata. This was demonstrated by the distribution of GDNF family receptor α-like (GFRAL), a GDF-15 receptor, within a subset of cholecystokinin-positive neurons in the AP and NST of the mouse.[13–16] Mice in which the AP and NST areas were removed reversed the anorexigenic effects of MIC/GDF-15.[60] GFRAL gene knockout mice showed resistance to chemotherapy-induced anorexia and weight loss.[15] Similarly, in mice in which the GFRAL gene was targeted by monoclonal antibodies, the cancer-associated cachexia and anorexia effects of GDF-15 were reversed.[61] Meanwhile, in normal mice given systemic MIC-1 and transgenic mice overexpressing MIC-1, an increase in POMC mRNA levels and a decrease in NPY mRNA levels were observed in the ARC in a leptin-independent signaling pathway.[50] These findings suggest that GDF-15 mainly regulates appetite through the GDF-15/GFRAL pathway in the hindbrain, with a contributory role for the pathway via ARC neurons in the hypothalamus. In addition, GDF-15 induces anorexia via nausea and vomiting reactions. In an experimental model with musk shrews, exogenous administration of GDF-15 caused nausea and emesis within a few minutes and subsequently induced prolonged anorexia and weight loss.[62] This emetic response caused by GDF-15 may be related to the activation of the parabrachial nucleus (PBN)-amygdala (AMY) pathway and the expression of 5-hydroxytryptamine receptors (5-HT3R) in the brain stem, however, the exact mechanism has yet to be elucidated.[63]

Glucagon-like peptide 1 (GLP-1) is an incretin hormone derived from the ileum and the NTS of the medulla oblongata, which stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent manner.[64] GLP-1 receptors are distributed throughout the body, including the stomach, intestinal tract, kidneys, cardiovascular system, peripheral and central nervous system.[65] GLP-1 analogs that mimic the action of this incretin hormone have been shown to produce significant weight loss through mechanisms such as prolonging gastric emptying,[66] promoting satiety,[67] and increasing energy expenditure by brown remodeling of white adipose tissue and lipolysis.[68] Consequently, GLP-1 analogs are currently approved not only as a treatment of diabetes but also as an anti-obesity agent. In addition, many clinical trials have already demonstrated the favorable clinical outcomes of GLP-1 analogs in patients with liver and cardiovascular

diseases, which can be attributable to their weight loss and metabolic improvement effects.[64,69]

In the CNS, GLP-1 receptors are also widely distributed in the PVN and ARC, as well as the ventral tegmental area (VTA) of the midbrain,[17] with many of their functions having been addressed through research in rodents. Rinaman and Rothe[70] showed in animal experiments that GLP-1 receptor antagonists suppressed the anorexic effect of oxytocin originating in the PVN. Secher et al.[71] demonstrated that the GLP-1 analog liraglutide-induced weight loss is mediated by direct stimulation of POMC/CART in the ARC and indirect inhibition of neurotransmission in NPY/AgRP-expressing neurons via GABA-dependent signaling. In another experimental model, the endogenous GLP-1 released from NTS neurons reduced highly palatable food intake by suppressing mesolimbic dopamine signaling.[72] In addition, the activation of GLP-1R signaling in the CNS promoted weight loss independently of food intake by inducing thermogenesis in brown adipose tissue through increased sympathetic drive in mice.[73]

From the opposite perspective, it appears that the blockade of GLP-1 receptors would be an efficacious intervention for patients with cancer anorexia. Nevertheless, in a clinical trial examining the effects of GLP-1 receptor blockers in healthy subjects, peripheral administration of GLP-1 receptor blockade failed to suppress postprandial satiety or to promote food intake in humans.[74] Conversely, the intracerebroventricular administration of GLP-1 receptor blockers was effective in treating cancer cachexia-related anorexia and chemotherapy-induced anorexia in animal models.[75,76] This discrepancy may be attributable to differences in the administration pathway of GLP-1 receptor blockers, insufficient peripheral doses of GLP-1 receptor blockers, or differences in the response between cancer patients and healthy individuals, which require further verification.

3.2 | Inflammatory cytokines

Pro-inflammatory cytokines such as IL-1, IL-6, TNF, and interferon-γ (IFN-γ), which play a central role in systemic inflammation, are released by the host immune system and the tumor itself,[77–79] contributing to the onset and progression of the pathogenesis of cachexia by acting as paracrine and endocrine. IL-1 is one of the pro-inflammatory cytokines that cause potent appetite loss through a diverse range of mechanisms. POMC/CART anorexigenic neurons express type 1 IL-1 receptors,[80] and IL-1α injection into the ventromedial hypothalamus of normal rats activates POMC/CART neurons and stimulates the release of α-MSH.[81] IL-1 also activates the POMC/CART pathway through increased CNS serotonin secretion in rats.[82] Furthermore, administration of IL-1 to cancer patients and murine models of starvation has been shown to cause increased expression of leptin, an appetite-suppressing adipokine, in adipocytes.[83,84] In a phase III clinical trial of 333 patients with advanced colorectal cancer, MABp1, a human monoclonal antibody targeting IL-1α, significantly improved the primary composite outcome, which consisted of a stable or increased lean body mass and stability or improvement in two of three symptoms (pain, fatigue, or anorexia).[85]

IL-6 is a pro-inflammatory cytokine with pleiotropic effects on immune response, metabolism, and tumourigenesis. Its role as a mediator of muscle atrophy in cancer patients is well-established.[86] In a murine model of CC, IL-6 receptor antibody treatment prevented the progression of CC by suppressing muscle proteolysis, although it failed to restore muscle protein synthesis.[87] While it has been suggested that IL-6 may regulate the secretion of anorexigenic hormones such as CRH and oxytocin in the hypothalamus through neural gp130 receptor-mediated signaling in mice.[88] In a phase II clinical trial in advanced non-small cell lung cancer (NSCLC) patients with cachexia, treatment with humanized anti-IL-6 antibody also showed improvement in anorexia, although it failed to rescue the loss of lean mass.[89]

TNF, produced by monocytes, macrophages, and tumor cells, is one of the most prominent pro-inflammatory cytokines in CC, mediating proteolysis and adipose tissue wasting. Like IL-1, administration of TNF-α has been shown to increase plasma leptin levels in starved mice.[83] Intraperitoneal injection of a TNF-α receptor antagonist also improved anorexia in cancer-bearing rats with cachexia.[90] As such, the efficacy of thalidomide and infliximab, both of which are TNF inhibitors, in cancer cachexia-associated anorexia has been examined, with some studies showing improved appetite and QoL in CC.[91–93]

In contrast, there are conflicting results and tolerance issues.[94,95] Two small randomized placebo-controlled trials (RCT) found no benefit of thalidomide for cancer cachexia-associated anorexia.[94,96] In a clinical trial of 61 elderly and/or poorly performing NSCLC patients, infliximab was associated with a deterioration in QoL and did not prevent cancer-associated weight loss and anorexia compared with placebo.[95] A double-blind placebo-controlled trial of 63 patients with refractory malignancies showed that etanercept, a TNF blocker, did not palliate the cancer anorexia/weight loss syndrome.[97] Although much evidence supports the mediation and involvement of inflammatory cytokines in the development of cancer anorexia, the effects of anti-cytokine therapy are inconsistent, which implies that there is no one-to-one causal relationship between cancer cachexia-associated anorexia and each cytokine. Further investigation is required to determine the potential therapeutic effects of anti-cytokine drugs on cancer anorexia.[98]

3.3 | Ghrelin and leptin

Ghrelin is an amino acid peptide secreted mainly from the fundus of the stomach, acting as an orexigenic hormone that increases appetite and food intake by stimulating NPY/AgRP neurons and inhibiting POMC/CART neurons in the hypothalamic ARC.[99–101] Intriguingly, patients with cachexia in various cancers have elevated serum ghrelin levels,[102–104] with these counter-intuitive findings being considered to be a compensatory mechanism to buffer anorexia as well as to reflect “ghrelin resistance” in patients with CC.[105] In addition

to stimulating appetite, ghrelin also inhibits proteolysis by suppressing the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF, induces the anti-inflammatory cytokine,[106–108] promotes muscle protein synthesis via activating anabolic hormone pathways like growth hormone (GH)/insulin-like growth factor 1 axis,[109] regulates skeletal muscle apoptosis,[110] all of which contribute towards alleviating pathological conditions in CC. In this context, the ghrelin receptor agonist "anamorelin" is undergoing clinical trials as a promising pharmacological therapy for CC.[111,112]

Leptin is an anorexigenic hormone expressed and secreted by white adipose tissue that regulates adipose tissue mass.[113] It stimulates POMC gene expression, suppresses the expression of NPY/AgRP neurons in the hypothalamus, and activates anorexigenic hormones such as CRH, increasing energy expenditure and decreasing appetite.[114] So far, several experiments and clinical studies have demonstrated that inflammatory cytokines such as IL-1, IL-6, and TNF increase leptin expression in adipose tissue.[83,84,115] However, the exact role of leptin in cancer anorexia remains elusive. Leptin levels are reduced in patients with cachexia while not associated with increased compensatory food intake, as might be expected.[116,117] This phenomenon is thought to be involved in a disruption of feedback mechanisms in the hypothalamus and the release of inflammatory cytokines such as IL-1 that induce and mimic the hypothalamic effect of leptin under cachexia.[118]

3.4 | Endocannabinoid system

Endocannabinoids are bioactive lipid mediators, and historically, their receptor, cannabinoid receptor 1 (CB1), was first discovered in the CNS,[119] followed by *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonylglycerol (2-AG) were identified as physiologically active substances at CB1, i.e., endogenous cannabinoids.[120,121] Central cannabinoids are produced in postsynaptic neurons on demand and act retrogradely on CB1 at presynaptic axon terminals,[122] causing various physiological changes such as feeding and emotion.[123,124] Cannabinoids also increase NPY expression and inhibit the secretion of pro-inflammatory cytokines such as IL-1, IL-6, and TNF in rodent models.[125,126] Furthermore, cannabinoids reduce chemotherapy-induced nausea and vomiting responses.[127] These backgrounds raise hopes for a positive effect of cannabinoids on cancer cachexia-associated anorexia, but so far, only small trials have demonstrated their effectiveness.[128,129]

3.5 | Serotonin

Serotonin (5-hydroxytryptamine: 5-HT) is a classical monoamine neurotransmitter and may contribute to the development of cancer-associated anorexia. Increased serotonin levels and serotonin receptor (5-HT receptor) expression have been shown in various types of human cancer,[130–132] with accumulating findings further suggesting serotonin involvement in hypothalamic orexigenic and anorexigenic neurons.

The serotonin 1B (5-HT 1B) receptor is expressed on the orexigenic NPY/AgRP-containing neurons to downregulate their activity,[133–135] while the serotonin 2C (5-HT 2C) receptor is expressed on the anorexigenic POMC neurons to upregulate their activity,[136] each contributing to appetite reduction. Inflammation also enhances serotonin availability in the hypothalamus. Intraperitoneal administration of TNF and IL-6 to mice caused an increase in serotonin metabolism in the hypothalamus and reduced food intake.[137] IL-1β significantly increased hypothalamic serotonin secretion,[138] and intracerebroventricular infusion of an IL-1 receptor antagonist in rats with colitis drastically reduced serotonin release from the PVN and significantly restored food intake. These findings, together with the importance of serotonin and serotonin receptors in the pathogenesis of cancer anorexia, suggest their potential as therapeutic targets for cancer anorexia.

4 | PHARMACOTHERAPY OF CANCER-CACHEXIA ASSOCIATED WITH ANOREXIA

Strategies to treat or ameliorate cancer anorexia have been investigated for the past few decades, yet there are currently no FDA-approved drugs for this syndrome. To date, only corticosteroids and progestins have shown sufficient evidence of benefit for weight loss and anorexia in CC[29]—whereas cannabinoids, thalidomide, and antipsychotics such as olanzapine and mirtazapine have failed to show consistent efficacy due to side effects and the high heterogeneity of studies. Nevertheless, recently developed drugs with novel mechanisms of action against CC and anorexia, such as anamorelin and GDF-15 inhibitors, may represent a breakthrough in this syndrome. The following section elaborates on the medications for the treatment of anorexia in CC, with reference to the mechanism and the recommendations of each guideline (Table 1).

4.1 | Corticosteroids

A relatively long history of research into corticosteroids as a treatment for cancer anorexia was first published in 1974.[139] Following that, several RCTs and systematic reviews revealed that corticosteroids improved appetite and QoL in patients with advanced cancer.[29,140,141] Corticosteroids increase appetite by inhibiting the release of pro-inflammatory cytokines such as IL-1 and TNF and by enhancing NPY/AgRP gene expression via adenosine monophosphate-activated protein kinase (AMPK) signaling in the hypothalamus.[142–144] Based on these findings, the ESMO, ASCO, and ESPEN guidelines provide a moderate to high level of evidence for corticosteroids for anorexia in cancer patients; however, due to their short duration of effect and side effects such as increased insulin resistance, muscle atrophy, immunosuppression, and osteoporosis over time, their recommended use is limited to 1–3 weeks.[4–6]

TABLE 1 Drugs for the treatment of cancer cachexia-associated anorexia: their mechanisms and recommendations in each guideline.

Drug	Mechanism of appetite increase	Recommendations in each guideline			References
		ESMO	ASCO	ESPEN	
Corticosteroids	• Inhibit the release of pro-inflammatory cytokines (IL-1 and TNF). • Enhance NPY/AgRP gene expression via AMPK signaling in the hypothalamus.	Generally recommended	Moderate in favor	Weak	[29,139–141]
Megestrol acetate	• Inhibits pro-inflammatory cytokines (IL-1, IL-6, and TNF). • Directly increases hypothalamic NPY neuron expression.	Generally recommended	Moderate in favor	Weak	[148–151]
Cannabinoids	• Act on CB1 receptors in the CNS to stimulate appetite. • Increase NPY expression. • Inhibit the secretion of pro-inflammatory cytokines (IL-1, IL-6, and TNF).	Optional	Weak against	None	[128,129,153–156]
Anamorelin	• Acts on ghrelin receptors to stimulate NPY/AgRP neurons and inhibit POMC/CART neurons. • Suppresses the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF).	—	No recommendation	—	[111,112,158–160]
Olanzapine	• Antagonizes serotonin and dopamine receptors to exert antiemetic effects and stimulate appetite.	Generally recommended	No recommendation	—	[162–164,167,168]
Mirtazapine	• Antagonizes 5-HT 3 and 5-HT 2C receptors to exert anti-nausea and appetite-stimulating effects.	—	—	—	[171,172]
Thalidomide	• Inhibits the production of pro-inflammatory cytokines (TNF and IL-1β).	—	No recommendation	—	[91,92,94,176]
Anti-IL-6 therapy (Clazakizumab, Tocilizumab) and JAK inhibitors (Ruxolitinib)	• Antagonize the IL-6 receptor or inhibit its associated JAK/STAT signaling, reducing muscle and adipose tissue wasting and increasing appetite.	—	—	—	[184–187]
GDF-15 inhibitors (Ponsegromab)	• Inhibit GFRAL localized within a subset of cholecystokinin-positive neurons in the brainstem and stimulates appetite. • Decrease NPY mRNA expression and increase POMC mRNA in a leptin-different signaling pathway.	—	—	—	[13–16,50,60–62,188,189]
Melanocortin receptor antagonist	• Antagonizes MC4R in the PVN with α-MSH and inhibits the release of anorexigenic hormones such as CRH.	—	—	—	[190–192]

Abbreviations: 5-HT, 5-hydroxytryptamine; AgRP, agouti-related peptide; AMPK, adenosine monophosphate-activated protein kinase; ASCO, the American Society for Clinical Oncology; CART, cocaine- and amphetamine-regulated transcript; CB1, cannabinoid receptor 1; CNS, central nervous system; CRH, corticotropin-releasing hormone; ESMO, the European Society of Oncology; ESPEN, the European Society for Clinical Nutrition and Metabolism; GFRAL, GDNF family receptor α-like; IL-1, interleukin-1; IL-6, interleukin-6; INF-γ, interferon-γ; JAK/STAT, Janus kinase/signal transducers and activators of transcription; MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; TNF, tumor necrosis factor; TRH, thyrotropin-releasing hormone; α-MSH, α-melanocyte-stimulating hormone.

4.2 | Progesterone analogs (megestrol acetate)

Megestrol acetate (MA) is a pregestational agent initially administered to humans in 1968. Commercially introduced in the United States in 1971 as MA tablets, this drug has been integrated into oral contraceptive pills and employed in the treatment of melanoma, ovarian, breast, kidney, and prostate cancers, benign prostatic hypertrophy, endometrial hyperplasia, and endometrial carcinoma.[145]

As a synthetic progesterone derivative, megestrol affects lipid and carbohydrate metabolism, increasing fat deposition, basal insulin level, and the response to carbohydrate ingestion.

Megestrol is among the most studied treatments for anorexia-cachexia syndrome, with evidence that it mediates orexigenic effects by inhibiting pro-inflammatory cytokines such as IL-1, IL-6, and TNF and directly increasing hypothalamic NPY neuron expression,[146,147] yet meta-analyses of clinical trials have demonstrated controversial effects on body weight, appetite, and the safety of treating CC populations. In 2001, a systematic review included 15 RCTs that evaluated the effect of MA, progestins, and medroxyprogesterone acetate on more than 2000 terminally ill cancer patients. The authors showed the most impressive result on increasing appetite, but there was no significant effect on body weight.[148] To evaluate the effect of MA in patients with anorexia-cachexia syndrome in patients with cancer, AIDS, and other pathologies, Pascual López et al.[149] performed a systematic review and meta-analysis including 3887 patients and 26 RCTs. MA treatment was favorable in appetite improvement and weight gain compared with placebo, although inconclusive compared to other drugs. The authors also found that QoL, as assessed by the Karnofsky Performance Index, was significantly improved in MA-treated patients compared to placebo. Following these results, current guidelines provide low to moderate recommendations for using MA to increase appetite and body weight with moderate to high levels of evidence.[4–6] However, their optimal dosage and duration of treatment remain unclear, together with the potential for serious side effects such as thromboembolism, which limits their use in clinical practice. The results of two recent meta-analyses further emphasized that the effects of MA on appetite and weight improvement and its thromboembolic risk in patients with cancer anorexia/cachexia are still controversial.[150,151]

4.3 | Cannabinoids

Cannabinoids have been supported for their use in the treatment of cachexia in patients with HIV and multiple sclerosis,[127,152] but the evidence for cancer anorexia remains limited. Several small pilot RCTs in advanced cancer patients with anorexia have shown that tetrahydrocannabinol and cannabidiol, constituents of cannabis, improved appetite and increased body weight.[128,129] However, in other RCTs, cannabinoids did not provide efficacy against CC and anorexia,[153,154] nor their superiority in comparison with megestrol acetate.[155] From such inconsistent clinical data, current guidelines have no recommendation for the use of cannabinoids to control anorexia in patients with cancer anorexia.[4–6] In 2022, after each guideline was published, Simon et al.[156] reported a systematic review and meta-analysis including RCTs and non-randomized studies on cannabinoids in CC, which also failed to show any benefits for weight gain, appetite stimulation, or better QoL. The meta-analysis provided only very low-quality evidence on the benefit of cannabinoids for cancer-associated anorexia due to the high heterogeneity and small number of patients, and furthermore, all RCTs included in the meta-analysis used cannabinoids alone. Taken together, higher quality research, larger RCTs, or combination treatment strategies with other anorexia therapeutic agents are required to verify the potential of cannabinoids for the management of cancer cachexia-associated anorexia.

4.4 | Anamorelin

Anamorelin, a ghrelin receptor agonist, is an orally active ghrelin mimetic that has been most rigorously evaluated as a therapeutic agent for cancer anorexia. In a dose-escalation phase I study of RC-1291, a ghrelin mimetic and GH secretagogue, RC-1291 produced significant dose-related increases in appetite and body weight without serious laboratory or clinical adverse events.[157] A crossover pilot study of placebo in 16 patients with different cancer types also showed that anamorelin treatment significantly increased appetite, body weight, GH, insulin-like growth factor (IGF), and insulin-like growth factor binding protein-3 (IGFBP-3); most adverse events were also minor, indicating the safety of anamorelin.[158] Subsequently, in a phase II multicentre RCT involving 180 NSCLC patients with cachexia, anamorelin 50 mg, 100 mg, or placebo was orally administered daily for 12 weeks. While overall survival rates were not significantly different among the three groups, lean body mass (LBM), appetite, and daily activity improved significantly in the group receiving 100 mg, with increased serum IGF-1, IGFBP-3, and pre-albumin levels.[111]

Three randomized, double-blind, phase III trials evaluated the safety and efficacy of anamorelin in patients with advanced NSCLC with cachexia: 484 patients were enrolled in ROMANA 1 and 495 in ROMANA 2, where after 12 weeks of intervention (anamorelin 100 mg/day or placebo), anamorelin significantly increased body weight and LBM and improved the anorexia-cachexia symptoms compared to the placebo in both trials.[159] ROMANA 3, which combined the first two trials with an additional 12-week intervention, demonstrated that anamorelin continued to be well tolerated and improved body weight and anorexia-cachexia symptoms over the entire treatment period.[112] Following these favorable results, anamorelin was first approved in Japan in December 2020 for cancer anorexia-cachexia syndrome in four types of cancer, including NSCLC,[160] but it is not yet approved in Europe. As such, there is currently no recommendation for use in cancer anorexia, although mentioned in the respective guidelines.[4–6] A phase II study of anamorelin in patients with advanced pancreatic cancer is currently underway (NCT04844970), with changes in body weight and appetite as endpoints, which may reveal further potential for anamorelin as a treatment for CC and anorexia.

4.5 | Antipsychotic agents

Olanzapine is an atypical antipsychotic that blocks neurotransmission by antagonizing multiple receptors, including serotonin and

dopamine receptors,[161] whose antiemetic effects on chemotherapy-induced nausea and vomiting are well-known.[162–164] Besides that, several clinical studies have demonstrated that olanzapine improves cancer-related symptoms such as cancer pain, weight loss, and anorexia.[165–167] More recently, in an RCT including 124 patients with advanced cancer performed by Sandhya et al.,[168] low-dose olanzapine was well tolerated and led to significant weight gain (≥5% weight gain: 60% vs. 9%, $p < .001$) and improved appetite (43% vs. 13%, $p < .001$) compared to placebo, respectively. The antidepressant mirtazapine has also been investigated for its potential efficacy against CC and anorexia because of its anti-nausea and appetite-stimulating effects via antagonism of 5-HT 3 and 5-HT 2C receptors.[169,170] In a small open-label phase II trial in 17 patients with cancer-related cachexia/anorexia, mirtazapine was associated with weight gain of ≥1 kg ($n = 4$, 24%) and improved appetite ($n = 3$, 17%) at week 4.[171] However, in a subsequent double-blind RCT of 120 solid tumor patients with anorexia, mirtazapine did not improve appetite, body weight, or handgrip strength, although it significantly reduced the increase in depressive symptoms.[172] Such pharmacological mechanisms and clinical results of olanzapine and mirtazapine suggest that these anti-psychotics may be an option for chronic nausea and anorexia in patients with CC, with the ESMO guidelines generally recommending the use of olanzapine based on moderate levels of evidence.[4] Two clinical trials of olanzapine and mirtazapine in patients with CC are currently in progress, with both trials focusing on appetite and weight change as their outcomes (NCT05243251, NCT05380479).

4.6 | Thalidomide

Thalidomide is an immunomodulatory and anti-inflammatory agent that inhibits the production of pro-inflammatory cytokines such as TNF and IL-1β, important players in CC and anorexia.[173,174] Therefore, some researchers have proposed thalidomide as a treatment option for cachexia, but so far, there is limited clinical data available. In 2005, Gordon et al. conducted a double-blind RCT of thalidomide in 50 patients with advanced pancreatic cancer for 24 weeks. Thalidomide significantly reduced loss of body weight and arm muscle mass after 4 and 8 weeks but did not improve muscle strength, QoL, or survival.[175] In a subsequent phase II trial, thalidomide was shown to improve cancer-related anorexia and QoL,[91] while two small RCTs found no benefit of thalidomide on serum cytokines, metabolism, body composition, performance, cachexia/anorexia-related symptoms, and survival, further exposing poor tolerability due to its side effects.[94,96] Several studies have also investigated thalidomide in combination with other drugs in cancer patients. In a clinical study of 120 patients with cancer cachexia/anorexia, combination regimes of thalidomide and MA significantly improved body weight, handgrip strength, and fatigue, reduced IL-6 and TNF levels, and tended to increase appetite compared to MA alone.[92] In contrast to other studies, toxicity was negligible in both groups. In a phase III trial to establish the most effective and safest treatment of CC, a total of 332 cancer patients with cachexia were assigned to the following five treatment arms: arm 1, medroxyprogesterone or MA; arm 2, eicosapentaenoic acid; arm 3, L-carnitine; arm 4, thalidomide; arm 5, a combination of the above. Results showed the superiority of combination therapy on many endpoints (LBM, resting energy expenditure, fatigue, appetite, QoL, handgrip strength, performance status, and pro-inflammatory cytokines), with negligible toxicity and similar levels between groups.[176] These findings suggest that thalidomide might be potential of benefit for CC and anorexia, especially in combination therapy; however, due to the small number and high heterogeneity of studies and safety and tolerability concerns, there is currently insufficient evidence for the recommendation of thalidomide in the management of cancer anorexia, requiring further validation in well-conducted, large-scale clinical trials.

4.7 | Anti-IL-6 therapy and JAK inhibitor

Elevated IL-6 levels are a strong predictor of cachexia in various cancers,[177,178] and one of the underlying mechanisms is the activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway via the IL-6 receptor and gp130.[177] Persistent elevation of IL-6 levels in cancer causes activation of the JAK/STAT pathway to regulate the ubiquitin-proteasome system,[179] induce autophagy in myotubes,[180] and stimulate myostatin,[181] resulting in increased protein catabolism. Consequently, IL-6 and its associated JAK/STAT signaling could be promising therapeutic targets for CC. Clazakizumab, a humanized monoclonal antibody, is the only specific anti-IL-6 agent evaluated in clinical trials in CC. A phase II trial in 124 patients with refractory NSCLC with cachexia demonstrated its high tolerability, inhibition of lean mass reduction, and improvement in fatigue and anemia.[182,183] In experimental and clinical studies, Tocilizumab, another IL-6 receptor antibody, increased appetite, food intake, and body weight, showing the potential to improve cancer anorexia.[184,185] Whereas the JAK/STAT pathway inhibition has been demonstrated to prevent muscle and adipose tissue wasting and anorexia in several experimental models of CC,[186,187] a phase I trial is currently underway to assess the effect of ruxolitinib, a JAK1/2 inhibitor, on wasting, anorexia, and survival in stage IV NSCLC patients with cachexia (NCT04906746).

4.8 | GDF-15 inhibitors

As discussed above, GDF-15 is an appetite-suppressing cytokine that is strongly associated with cancer anorexia. Therefore, neutralization of GDF-15 is an innovative therapeutic strategy with the potential to improve CC and anorexia. Several experimental models have already shown that anti-GDF-15 therapy improved emesis, food intake, weight loss, and physical function.[15,188,189] A phase II clinical trial is currently underway to evaluate the effects of the

GDF-15 inhibitor 'Ponsegromab' on anorexia/appetite and physical activity in patients with NSCLC, pancreatic cancer, and colorectal cancer with cachexia and elevated GDF-15 levels (NCT05546476).

4.9 | Melanocortin receptor antagonist

It is well-recognized that the central melanocortin system, consisting of POMC neurons, their product α-MSH, and its receptor MC4R, is closely involved in the regulation of feeding. In experimental models, intracerebroventricular injections of MC4R agonists have shown anorexic effects via induction of CRH gene transcription in the PVN,[190] and administration of MC4R antagonists caused significant increases in food intake.[191,192] Therefore, MC4R is postulated to be a therapeutic target for diseases with negative energy balance, such as cachexia and anorexia, with a phase I clinical trial currently in progress to assess the safety, tolerability, and pharmacokinetics of the oral administration of the MC4R antagonist (NCT04628793).

4.10 | Targeting the TWEAK-Fn14 cytokine-receptor axis

The TNF family cytokine TWEAK and its cognate receptor Fn14 (fibroblast growth factor-inducible 14) regulate various physiological processes, including proliferation, migration, differentiation, apoptosis, and inflammation. In particular, the TWEAK-Fn14 axis plays a significant role in tissue repair following an acute injury.[193] Meanwhile, the expression of TWEAK and Fn14 is increased in solid tumors,[194–196] and their signaling contributes to carcinogenesis and the development of CC. Monoclonal antibodies targeting Fn14 signaling have been demonstrated to suppress tumor growth in vivo and in vitro studies with human subjects.[197–199] In a murine tumor model, Johnston et al.[200] found that a monoclonal antibody targeting Fn14 inhibited tumor growth by blocking Fn14 signaling in the tumor, rather than in the host, thereby preventing and reversing cancer-induced cachexia. Sezaki et al.[201] reported that the injection of 5-fluorouracil (5-FU) in colon carcinoma-bearing mice induced high Fn14 expression in epithelial cells and that the blockade of the TWEAK/Fn14 pathway by Fn14 knockout or the administration of anti-TWEAK antibody prevented 5-FU-induced diarrhea. Although interventions targeting the TWEAK/Fn14 signaling for anorexia have not yet been investigated, these results extend the role of the TWEAK-Fn14 axis in tissue repair to the development of cancer and CC and suggest that it may be a promising therapeutic target for cancer cachexia-related anorexia.[202]

5 | CONCLUSIONS

This narrative review mainly outlines cancer anorexia with a focus on its mechanisms and pharmacotherapy. However, anorexia is only one of the "subjective" phenotypes of CC, making its accurate and consistent assessment challenging, while interventions for other hallmarks of CC, 'objective' weight loss and skeletal muscle loss, are also crucial. Several other drugs besides those mentioned in this review are currently under scrutiny in clinical and pre-clinical studies for their potential to prevent tissue wasting, including selective androgen receptor modulators,[203] myostatin inhibitors,[204] and β-adrenergic blockade.[23] Also, as some studies have shown, a combination therapy may provide better clinical efficacy than a single-drug intervention for cancer anorexia.[92,167,176] The complex and multifactorial condition of CC requires not only pharmacotherapy but also nutritional, exercise, and psychosocial interventions. Appropriate assessment of appetite on a standardized scale, combination therapy, and multidisciplinary and comprehensive intervention in physical (e.g., metabolic shift, muscle wasting, and undernutrition), psychological (e.g., depression and anxiety), and social (e.g., reduced social activity and economic burden) aspects, may lead to better outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization: R.S., G.W.P.F., and S.H.; writing—original draft and revised draft preparation: R.S., G.W.P.F., and W.N.; writing—review and editing: G.W.P.F., W.N., and S.H.; supervision: S.H. All authors have read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

The information discussed within this article has been conducted inaccordance with ethical guidelines.

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REFERENCES

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495. doi:10.1016/s1470-2045(10)70218-7
2. Shukuya T, Takahashi K, Shintani Y, et al. Epidemiology, risk factors and impact of cachexia on patient outcome: results from the Japanese Lung Cancer Registry Study. *J Cachexia Sarcopenia Muscle*. 2023;14(3):1274-1285. doi:10.1002/jcsm.13216
3. von Haehling S, Anker MS, Anker SD. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. *J Cachexia Sarcopenia Muscle*. 2016;7(5):507-509. doi:10.1002/jcsm.12167
4. Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO clinical practice guidelines. *ESMO Open*. 2021;6(3):100092. doi:10.1016/j.esmoop.2021.100092
5. Roeland EJ, Bohlke K, Baracos VE, et al. Management of cancer cachexia: ASCO guideline. *J Clin Oncol*. 2020;38(21):2438-2453. doi:10.1200/jco.20.00611
6. Muscaritoli M, Arends J, Bachmann P, et al. ESPEN practical guideline: clinical nutrition in cancer. *Clin Nutr*. 2021;40(5):2898-2913. doi:10.1016/j.clnu.2021.02.005
7. da Fonseca GWP, Sato R, de Nazaré Nunes Alves MJ, von Haehling S. Current advancements in pharmacotherapy for cancer cachexia. *Expert Opin Pharmacother*. 2023;24(5):629-639. doi:10.1080/14656566.2023.2194489
8. Yeom E, Shin H, Yoo W, et al. Tumour-derived Dilp8/INSL3 induces cancer anorexia by regulating feeding neuropeptides via Lgr3/8 in the brain. *Nat Cell Biol*. 2021;23(2):172-183. doi:10.1038/s41556-020-00628-z
9. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. *Curr Opin Clin Nutr Metab Care*. 2004;7(4):427-434. doi:10.1097/01.mco.0000134363.53782.cb
10. van Norren K, Dwarkasing JT, Witkamp RF. The role of hypothalamic inflammation, the hypothalamic-pituitary-adrenal axis and serotonin in the cancer anorexia-cachexia syndrome. *Curr Opin Clin Nutr Metab Care*. 2017;20(5):396-401. doi:10.1097/mco.0000000000000401
11. Ota K, Ota T, Nitta SI, Ueda T, Yamashita T, Ozawa T. The association of circulating endocannabinoids with cancer cachexia: a cross-sectional study. *Clin Nutr ESPEN*. 2023;55:20-29. doi:10.1016/j.clnesp.2023.02.020
12. Oberholzer R, Hopkinson JB, Baumann K, et al. Psychosocial effects of cancer cachexia: a systematic literature search and qualitative analysis. *J Pain Symptom Manage*. 2013;46(1):77-95. doi:10.1016/j.jpainsymman.2012.06.020
13. Emmerson PJ, Wang F, Du Y, et al. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. *Nat Med*. 2017;23(10):1215-1219. doi:10.1038/nm.4393
14. Mullican SE, Lin-Schmidt X, Chin CN, et al. GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. *Nat Med*. 2017;23(10):1150-1157. doi:10.1038/nm.4392
15. Hsu JY, Crawley S, Chen M, et al. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. *Nature*. 2017;550(7675):255-259. doi:10.1038/nature24042
16. Yang L, Chang CC, Sun Z, et al. GFRAL is the receptor for GDF15 and is required for the anti-obesity effects of the ligand. *Nat Med*. 2017;23(10):1158-1166. doi:10.1038/nm.4394
17. Geloneze B, de Lima-Júnior JC, Velloso LA. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the brain-adipocyte axis. *Drugs*. 2017;77(5):493-503. doi:10.1007/s40265-017-0706-4
18. Tan S, Xu J, Wang J, et al. Development and validation of a cancer cachexia risk score for digestive tract cancer patients before abdominal surgery. *J Cachexia Sarcopenia Muscle*. 2023;14(2):891-902. doi:10.1002/jcsm.13207
19. Krauss T, Heisz S, Honecker J, et al. Specific miRNAs are associated with human cancer cachexia in an organ-specific manner. *J Cachexia Sarcopenia Muscle*. 2023;14(3):1381-1394. doi:10.1002/jcsm.13224
20. Jang MK, Park C, Hong S, Li H, Rhee E, Doorenbos AZ. Skeletal muscle mass change during chemotherapy: a systematic review and meta-analysis. *Anticancer Res*. 2020;40(5):2409-2418. doi:10.21873/anticanres.14210
21. Wang P, Wang S, Li X, et al. Skeletal muscle wasting during neoadjuvant therapy as a prognosticator in patients with esophageal and esophagogastric junction cancer: a systematic review and meta-analysis. *Int J Surg*. 2022;97:106206. doi:10.1016/j.ijsu.2021.106206
22. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. *Clin Nutr*. 2007;26(4):389-399. doi:10.1016/j.clnu.2007.03.008
23. Petruzzelli M, Schweiger M, Schreiber R, et al. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab*. 2014;20(3):433-447. doi:10.1016/j.cmet.2014.06.011
24. Kir S, White JP, Kleiner S, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. *Nature*. 2014;513(7516):100-104. doi:10.1038/nature13528
25. Puigserver P, Rhee J, Lin J, et al. Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. *Mol Cell*. 2001;8(5):971-982. doi:10.1016/s1097-2765(01)00390-2
26. Bonetto A, Aydogdu T, Kunzevitzky N, et al. STAT3 activation in skeletal muscle links muscle wasting and the acute phase response in cancer cachexia. *PLoS One*. 2011;6(7):e22538. doi:10.1371/journal.pone.0022538
27. Tisdale MJ. Are tumoral factors responsible for host tissue wasting in cancer cachexia? *Future Oncol*. 2010;6(4):503-513. doi:10.2217/fon.10.20
28. Van Lancker A, Velghe A, Van Hecke A, et al. Prevalence of symptoms in older cancer patients receiving palliative care: a systematic review and meta-analysis. *J Pain Symptom Manage*. 2014;47(1):90-104. doi:10.1016/j.jpainsymman.2013.02.016
29. Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol*. 2005;23(33):8500-8511. doi:10.1200/jco.2005.01.8010
30. Tarricone R, Ricca G, Nyanzi-Wakholi B, Medina-Lara A. Impact of cancer anorexia-cachexia syndrome on health-related quality of life and resource utilisation: a systematic review. *Crit Rev Oncol Hematol*. 2016;99:49-62. doi:10.1016/j.critrevonc.2015.12.008
31. Ezeoke CC, Morley JE. Pathophysiology of anorexia in the cancer cachexia syndrome. *J Cachexia Sarcopenia Muscle*. 2015;6(4):287-302. doi:10.1002/jcsm.12059
32. Mayer J, Thomas DW. Regulation of food intake and obesity. *Science*. 1967;156(3773):328-337. doi:10.1126/science.156.3773.328
33. Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocr Rev*. 1999;20(1):68-100. doi:10.1210/edrv.20.1.0357
34. Inui A. Ghrelin: an orexigenic and somatotrophic signal from the stomach. *Nat Rev Neurosci*. 2001;2(8):551-560. doi:10.1038/35086018
35. Woods SC, Schwartz MW, Baskin DG, Seeley RJ. Food intake and the regulation of body weight. *Annu Rev Psychol*. 2000;51:255-277. doi:10.1146/annurev.psych.51.1.255
36. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000;404(6778):661-671. doi:10.1038/35007534
37. Xu B, Goulding EH, Zang K, et al. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat Neurosci*. 2003;6(7):736-742. doi:10.1038/nn1073

38. Roseberry AG, Liu H, Jackson AC, Cai X, Friedman JM. Neuropeptide Y-mediated inhibition of proopiomelanocortin neurons in the arcuate nucleus shows enhanced desensitization in ob/ob mice. *Neuron*. 2004;41(5):711-722. doi:10.1016/s0896-6273(04)00074-1
39. Schneeberger M, Gomis R, Claret M. Hypothalamic and brainstem neuronal circuits controlling homeostatic energy balance. *J Endocrinol*. 2014;220(2):T25-T46. doi:10.1530/joe-13-0398
40. Rau AR, Hentges ST. The relevance of AgRP neuron-derived GABA inputs to POMC neurons differs for spontaneous and evoked release. *J Neurosci*. 2017;37(31):7362-7372. doi:10.1523/jneurosci.0647-17.2017
41. Rossi M, Kim MS, Morgan DG, et al. A C-terminal fragment of agouti-related protein increases feeding and antagonizes the effect of alpha-melanocyte stimulating hormone in vivo. *Endocrinology*. 1998;139(10):4428-4431. doi:10.1210/endo.139.10.6332
42. Bootcov MR, Bauskin AR, Valenzuela SM, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. *Proc Natl Acad Sci USA*. 1997;94(21):11514-11519. doi:10.1073/pnas.94.21.11514
43. Böttner M, Laaff M, Schechinger B, Rappold G, Unsicker K, Suter-Crazzolara C. Characterization of the rat, mouse, and human genes of growth/differentiation factor-15/macrophage inhibiting cytokine-1 (GDF-15/MIC-1). *Gene*. 1999;237(1):105-111. doi:10.1016/s0378-1119(99)00309-1
44. Welsh JB, Sapinoso LM, Kern SG, et al. Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum. *Proc Natl Acad Sci USA*. 2003;100(6):3410-3415. doi:10.1073/pnas.0530278100
45. Uhlen M, Zhang C, Lee S, et al. A pathology atlas of the human cancer transcriptome. *Science*. 2017;357(6352):eaan2507. doi:10.1126/science.aan2507
46. Wischhusen J, Melero I, Fridman WH. Growth/differentiation factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. *Front Immunol*. 2020;11:951. doi:10.3389/fimmu.2020.00951
47. Kempf T, Horn-Wichmann R, Brabant G, et al. Circulating concentrations of growth-differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. *Clin Chem*. 2007;53(2):284-291. doi:10.1373/clinchem.2006.076828
48. Tsai VW, Macia L, Feinle-Bisset C, et al. Serum levels of human MIC-1/GDF15 vary in a diurnal pattern, do not display a profile suggestive of a satiety factor and are related to BMI. *PLoS One*. 2015;10(7):e0133362. doi:10.1371/journal.pone.0133362
49. Altena R, Fehrmann RS, Boer H, de Vries EG, Meijer C, Gietema JA. Growth differentiation factor 15 (GDF-15) plasma levels increase during bleomycin- and cisplatin-based treatment of testicular cancer patients and relate to endothelial damage. *PLoS One*. 2015;10(1):e0115372. doi:10.1371/journal.pone.0115372
50. Johnen H, Lin S, Kuffner T, et al. Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. *Nat Med*. 2007;13(11):1333-1340. doi:10.1038/nm1677
51. Molfino A, Amabile MI, Imbimbo G, et al. Association between growth differentiation factor-15 (GDF-15) serum levels, anorexia and low muscle mass among cancer patients. *Cancer*. 2020;13(1):99. doi:10.3390/cancers13010099
52. Suzuki H, Mitsunaga S, Ikeda M, et al. Clinical and tumor characteristics of patients with high serum levels of growth differentiation factor 15 in advanced pancreatic cancer. *Cancer*. 2021;13(19):4842. doi:10.3390/cancers13194842
53. Wallentin L, Zethelius B, Berglund L, et al. GDF-15 for prognostication of cardiovascular and cancer morbidity and mortality in men. *PLoS One*. 2013;8(12):e78797. doi:10.1371/journal.pone.0078797
54. Emmerson PJ, Duffin KL, Chintharlapalli S, Wu X. GDF15 and growth control. *Front Physiol*. 2018;9:1712. doi:10.3389/fphys.2018.01712
55. Alcazar J, Frandsen U, Prokhorova T, et al. Changes in systemic GDF15 across the adult lifespan and their impact on maximal muscle power: the Copenhagen Sarcopenia Study. *J Cachexia Sarcopenia Muscle*. 2021;12(6):1418-1427. doi:10.1002/jcsm.12823
56. Lu WH, Gonzalez-Bautista E, Guyonnet S, et al. Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults. *J Cachexia Sarcopenia Muscle*. 2023;14(2):930-939. doi:10.1002/jcsm.13163
57. Raffin J, Rolland Y, Parini A, et al. Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: a longitudinal mediation analysis. *J Cachexia Sarcopenia Muscle*. 2023;14(2):771-780. doi:10.1002/jcsm.13152
58. Wang J, Zhang T, Xu F, et al. GDF-15 at admission predicts cardiovascular death, heart failure, and bleeding outcomes in patients with CAD. *ESC Heart Fail*. 2023;10(5):3123-3132. doi:10.1002/ehf2.14484
59. Yin D, Yan X, Bai X, Tian A, Gao Y, Li J. Prognostic value of growth differentiation factors 15 in acute heart failure patients with preserved ejection fraction. *ESC Heart Fail*. 2023;10(2):1025-1034. doi:10.1002/ehf2.14271
60. Tsai VW, Manandhar R, Jørgensen SB, et al. The anorectic actions of the TGFβ cytokine MIC-1/GDF15 require an intact brainstem area postrema and nucleus of the solitary tract. *PLoS One*. 2014;9(6):e100370. doi:10.1371/journal.pone.0100370
61. Suriben R, Chen M, Higbee J, et al. Antibody-mediated inhibition of GDF15-GFRAL activity reverses cancer cachexia in mice. *Nat Med*. 2020;26(8):1264-1270. doi:10.1038/s41591-020-0945-x
62. Borner T, Shaulson ED, Ghidewon MY, et al. GDF15 induces anorexia through nausea and emesis. *Cell Metab*. 2020;31(2):351-362.e5. doi:10.1016/j.cmet.2019.12.004
63. Li J, Hu X, Xie Z, Li J, Huang C, Huang Y. Overview of growth differentiation factor 15 (GDF15) in metabolic diseases. *Biomed Pharmacother*. 2024;176:116809. doi:10.1016/j.biopha.2024.116809
64. Andersen A, Lund A, Knop FK, Vilsbøll T. Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol*. 2018;14(7):390-403. doi:10.1038/s41574-018-0016-2
65. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155(4):1280-1290. doi:10.1210/en.2013-1934
66. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond)*. 2014;38(6):784-793. doi:10.1038/ijo.2013.162
67. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest*. 1998;101(3):515-520. doi:10.1172/jci990
68. Xu F, Lin B, Zheng X, et al. GLP-1 receptor agonist promotes brown remodelling in mouse white adipose tissue through SIRT1. *Diabetologia*. 2016;59(5):1059-1069. doi:10.1007/s00125-016-3896-5
69. Sato R, von Haehling S. Targeting obesity for therapeutic intervention in heart failure patients. *Expert Rev Cardiovasc Ther*. 2024;22(6):217-230. doi:10.1080/14779072.2024.2363395
70. Rinaman L, Rothe EE. GLP-1 receptor signaling contributes to anorexigenic effect of centrally administered oxytocin in rats. *Am J Physiol Regul Integr Comp Physiol*. 2002;283(1):R99-R106. doi:10.1152/ajpregu.00008.2002
71. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124(10):4473-4488. doi:10.1172/jci75276

72. Wang XF, Liu JJ, Xia J, Liu J, Mirabella V, Pang ZP. Endogenous glucagon-like peptide-1 suppresses high-fat food intake by reducing synaptic drive onto mesolimbic dopamine neurons. *Cell Rep*. 2015;12(5):726-733. doi:10.1016/j.celrep.2015.06.062
73. Lockie SH, Heppner KM, Chaudhary N, et al. Direct control of brown adipose tissue thermogenesis by central nervous system glucagon-like peptide-1 receptor signaling. *Diabetes*. 2012;61(11):2753-2762. doi:10.2337/db11-1556
74. Melhorn SJ, Tyagi V, Smeraglio A, Roth CL, Schur EA. Initial evidence that GLP-1 receptor blockade fails to suppress postprandial satiety or promote food intake in humans. *Appetite*. 2014;82:85-90. doi:10.1016/j.appet.2014.07.009
75. Borner T, Liberini CG, Lutz TA, Riediger T. Brainstem GLP-1 signalling contributes to cancer anorexia-cachexia syndrome in the rat. *Neuropharmacology*. 2018;131:282-290. doi:10.1016/j.neuropharm.2017.12.024
76. De Jonghe BC, Holland RA, Olivos DR, Rupprecht LE, Kanoski SE, Hayes MR. Hindbrain GLP-1 receptor mediation of cisplatin-induced anorexia and nausea. *Physiol Behav*. 2016;153:109-114. doi:10.1016/j.physbeh.2015.10.031
77. Matthys P, Billiau A. Cytokines and cachexia. *Nutrition*. 1997;13(9):763-770. doi:10.1016/s0899-9007(97)00185-8
78. Moldawer LL, Copeland EM 3rd. Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. *Cancer*. 1997;79(9):1828-1839.
79. Tisdale MJ. Biology of cachexia. *J Natl Cancer Inst*. 1997;89(23):1763-1773. doi:10.1093/jnci/89.23.1763
80. Scarlett JM, Jobst EE, Enriori PJ, et al. Regulation of central melanocortin signaling by interleukin-1 beta. *Endocrinology*. 2007;148(9):4217-4225. doi:10.1210/en.2007-0017
81. Yang ZJ, Blaha V, Meguid MM, Laviano A, Oler A, Zadak Z. Interleukin-1alpha injection into ventromedial hypothalamic nucleus of normal rats depresses food intake and increases release of dopamine and serotonin. *Pharmacol Biochem Behav*. 1999;62(1):61-65. doi:10.1016/s0091-3057(98)00136-1
82. Heisler LK, Cowley MA, Tecott LH, et al. Activation of central melanocortin pathways by fenfluramine. *Science*. 2002;297(5581):609-611. doi:10.1126/science.1072327
83. Sarraf P, Frederich RC, Turner EM, et al. Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *J Exp Med*. 1997;185(1):171-175. doi:10.1084/jem.185.1.171
84. Janik JE, Curti BD, Considine RV, et al. Interleukin 1 alpha increases serum leptin concentrations in humans. *J Clin Endocrinol Metab*. 1997;82(9):3084-3086. doi:10.1210/jcem.82.9.4214
85. Hickish T, Andre T, Wyrwicz L, et al. MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2017;18(2):192-201. doi:10.1016/s1470-2045(17)30006-2
86. Narsale AA, Carson JA. Role of interleukin-6 in cachexia: therapeutic implications. *Curr Opin Support Palliat Care*. 2014;8(4):321-327. doi:10.1097/spc.0000000000000091
87. White JP, Baynes JW, Welle SL, et al. The regulation of skeletal muscle protein turnover during the progression of cancer cachexia in the Apc(Min/+) mouse. *PLoS One*. 2011;6(9):e24650. doi:10.1371/journal.pone.0024650
88. Benrick A, Schéle E, Pinnock SB, et al. Interleukin-6 gene knockout influences energy balance regulating peptides in the hypothalamic paraventricular and supraoptic nuclei. *J Neuroendocrinol*. 2009;21(7):620-628. doi:10.1111/j.1365-2826.2009.01879.x
89. Bayliss TJ, Smith JT, Schuster M, Dragnev KH, Rigas JR. A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. *Expert Opin Biol Ther*. 2011;11(12):1663-1668. doi:10.1517/14712598.2011.627850
90. Torelli GF, Meguid MM, Moldawer LL, et al. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *Am J Physiol*. 1999;277(3):R850-R855. doi:10.1152/ajpregu.1999.277.3.R850
91. Davis M, Lasheen W, Walsh D, Mahmoud F, Bicanovsky L, Lagman R. A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage*. 2012;43(1):78-86. doi:10.1016/j.jpainsymman.2011.03.007
92. Wen HS, Li X, Cao YZ, et al. Clinical studies on the treatment of cancer cachexia with megestrol acetate plus thalidomide. *Chemotherapy*. 2012;58(6):461-467. doi:10.1159/000346446
93. Miksza DR, de Souza CO, de Morais H, et al. Effect of infliximab on metabolic disorders induced by Walker-256 tumor in rats. *Pharmacol Rep*. 2013;65(4):960-969. doi:10.1016/s1734-1140(13)71077-6
94. Wilkes EA, Selby AL, Cole AT, Freeman JG, Rennie MJ, Khan ZH. Poor tolerability of thalidomide in end-stage oesophageal cancer. *Eur J Cancer Care*. 2011;20(5):593-600. doi:10.1111/j.1365-2354.2011.01255.x
95. Jatoi A, Ritter HL, Dueck A, et al. A placebo-controlled, double-blind trial of infliximab for cancer-associated weight loss in elderly and/or poor performance non-small cell lung cancer patients (N01C9). *Lung Cancer*. 2010;68(2):234-239. doi:10.1016/j.lungcan.2009.06.020
96. Yennurajalingam S, Willey JS, Palmer JL, et al. The role of thalidomide and placebo for the treatment of cancer-related anorexia-cachexia symptoms: results of a double-blind placebo-controlled randomized study. *J Palliat Med*. 2012;15(10):1059-1064. doi:10.1089/jpm.2012.0146
97. Jatoi A, Dakhil SR, Nguyen PL, et al. A placebo-controlled double blind trial of etanercept for the cancer anorexia/weight loss syndrome: results from N00C1 from the North Central Cancer Treatment Group. *Cancer*. 2007;110(6):1396-1403. doi:10.1002/cncr.22944
98. Prado BL, Qian Y. Anti-cytokines in the treatment of cancer cachexia. *Ann Palliat Med*. 2019;8(1):67-79. doi:10.21037/apm.2018.07.06
99. Silva Elipe MV, Bednarek MA, Gao YD. 1H NMR structural analysis of human ghrelin and its six truncated analogs. *Biopolymers*. 2001;59(7):489-501. doi:10.1002/1097-0282(200112)59:7<489::Aid-bip1054>3.0.Co;2-s
100. Guan JL, Wang QP, Kageyama H, et al. Synaptic interactions between ghrelin- and neuropeptide Y-containing neurons in the rat arcuate nucleus. *Peptides*. 2003;24(12):1921-1928. doi:10.1016/j.peptides.2003.10.017
101. Toshinai K, Date Y, Murakami N, et al. Ghrelin-induced food intake is mediated via the orexin pathway. *Endocrinology*. 2003;144(4):1506-1512. doi:10.1210/en.2002-220788
102. Wang HS, Oh DS, Ohning GV, Pisegna JR. Elevated serum ghrelin exerts an orexigenic effect that may maintain body mass index in patients with metastatic neuroendocrine tumors. *J Mol Neurosci*. 2007;33(3):225-231. doi:10.1007/s12031-007-0004-9
103. Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. *Int J Clin Oncol*. 2009;14(4):315-320. doi:10.1007/s10147-008-0856-1
104. Karapanagiotou EM, Polyzos A, Dilana KD, et al. Increased serum levels of ghrelin at diagnosis mediate body weight loss in non-small cell lung cancer (NSCLC) patients. *Lung Cancer*. 2009;66(3):393-398. doi:10.1016/j.lungcan.2009.02.006
105. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer*. 2014;14(11):754-762. doi:10.1038/nrc3829
106. Gonzalez-Rey E, Chorny A, Delgado M. Therapeutic action of ghrelin in a mouse model of colitis. *Gastroenterology*. 2006;130(6):1707-1720. doi:10.1053/j.gastro.2006.01.041
107. Dixit VD, Schaffer EM, Pyle RS, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by

human monocytes and T cells. *J Clin Invest*. 2004;114(1):57-66. doi:10.1172/jci21134

108. Theil MM, Miyake S, Mizuno M, et al. Suppression of experimental autoimmune encephalomyelitis by ghrelin. *J Immunol*. 2009;183(4):2859-2866. doi:10.4049/jimmunol.0803362
109. Akamizu T, Kangawa K. Ghrelin for cachexia. *J Cachexia Sarcopenia Muscle*. 2010;1(2):169-176. doi:10.1007/s13539-010-0011-5
110. Yu AP, Pei XM, Sin TK, et al. Acylated and unacylated ghrelin inhibit doxorubicin-induced apoptosis in skeletal muscle. *Acta Physiol (Oxf)*. 2014;211(1):201-213. doi:10.1111/apha.12263
111. Takayama K, Katakami N, Yokoyama T, et al. Anamorelin (ONO-7643) in Japanese patients with non-small cell lung cancer and cachexia: results of a randomized phase 2 trial. *Support Care Cancer*. 2016;24(8):3495-3505. doi:10.1007/s00520-016-3144-z
112. Currow D, Temel JS, Abernethy A, Milanowski J, Friend J, Fearon KC. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. *Ann Oncol*. 2017;28(8):1949-1956. doi:10.1093/annonc/mdx192
113. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372(6505):425-432. doi:10.1038/372425a0
114. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*. 2001;411(6836):480-484. doi:10.1038/35078085
115. Zumbach MS, Boehme MW, Wahl P, Stremmel W, Ziegler R, Nawroth PP. Tumor necrosis factor increases serum leptin levels in humans. *J Clin Endocrinol Metab*. 1997;82(12):4080-4082. doi:10.1210/jcem.82.12.4408
116. Mantovani G, Macciò A, Mura L, et al. Serum levels of leptin and proinflammatory cytokines in patients with advanced-stage cancer at different sites. *J Mol Med (Berl)*. 2000;78(10):554-561. doi:10.1007/s001090000137
117. Demiray G, Değirmencioğlu S, Uğurlu E, Yaren A. Effects of serum leptin and resistin levels on cancer cachexia in patients with advanced-stage non-small cell lung cancer. *Clin Med Insights Oncol*. 2017;11:1179554917690144. doi:10.1177/1179554917690144
118. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. *CA Cancer J Clin*. 2002;52(2):72-91. doi:10.3322/canjclin.52.2.72
119. Elphick MR, Egertová M. The neurobiology and evolution of cannabinoid signalling. *Philos Trans R Soc Lond B Biol Sci*. 2001;356(1407):381-408. doi:10.1098/rstb.2000.0787
120. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258(5090):1946-1949. doi:10.1126/science.1470919
121. Mechoulam R, Ben-Shabat S, Hanus L, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol*. 1995;50(1):83-90. doi:10.1016/0006-2952(95)00109-d
122. Ohno-Shosaku T, Maejima T, Kano M. Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. *Neuron*. 2001;29(3):729-738. doi:10.1016/s0896-6273(01)00247-1
123. Kirkham TC, Williams CM, Fezza F, Di Marzo V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Br J Pharmacol*. 2002;136(4):550-557. doi:10.1038/sj.bjp.0704767
124. Sumislawski JJ, Ramikie TS, Patel S. Reversible gating of endocannabinoid plasticity in the amygdala by chronic stress: a potential role for monoacylglycerol lipase inhibition in the prevention of stress-induced behavioral adaptation. *Neuropsychopharmacology*. 2011;36(13):2750-2761. doi:10.1038/npp.2011.166
125. Gamber KM, Macarthur H, Westfall TC. Cannabinoids augment the release of neuropeptide Y in the rat hypothalamus. *Neuropharmacology*. 2005;49(5):646-652. doi:10.1016/j.neuropharm.2005.04.017
126. Puffenbarger RA, Boothe AC, Cabral GA. Cannabinoids inhibit LPS-inducible cytokine mRNA expression in rat microglial cells. *Glia*. 2000;29(1):58-69.
127. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358
128. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011;22(9):2086-2093. doi:10.1093/annonc/mdq727
129. Bar-Sela G, Zalman D, Semenysty V, Ballan E. The effects of dosage-controlled cannabis capsules on cancer-related cachexia and anorexia syndrome in advanced cancer patients: pilot study. *Integr Cancer Ther*. 2019;18:1534735419881498. doi:10.1177/1534735419881498
130. Dizeyi N, Bjartell A, Nilsson E, et al. Expression of serotonin receptors and role of serotonin in human prostate cancer tissue and cell lines. *Prostate*. 2004;59(3):328-336. doi:10.1002/pros.10374
131. Sui H, Xu H, Ji Q, et al. 5-Hydroxytryptamine receptor (5-HT1DR) promotes colorectal cancer metastasis by regulating axin1/β-catenin/MMP-7 signaling pathway. *Oncotarget*. 2015;6(28):25975-25987. doi:10.18632/oncotarget.4543
132. Soll C, Riener MO, Oberkofler CE, et al. Expression of serotonin receptors in human hepatocellular cancer. *Clin Cancer Res*. 2012;18(21):5902-5910. doi:10.1158/1078-0432.Ccr-11-1813
133. Makarenko IG, Meguid MM, Gatto L, et al. Normalization of hypothalamic serotonin (5-HT 1B) receptor and NPY in cancer anorexia after tumor resection: an immunocytochemical study. *Neurosci Lett*. 2005;383(3):322-327. doi:10.1016/j.neulet.2005.04.031
134. Makarenko IG, Meguid MM, Gatto L, et al. Hypothalamic 5-HT1B-receptor changes in anorectic tumor bearing rats. *Neurosci Lett*. 2005;376(2):71-75. doi:10.1016/j.neulet.2004.11.026
135. Heisler LK, Jobst EE, Sutton GM, et al. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. *Neuron*. 2006;51(2):239-249. doi:10.1016/j.neuron.2006.06.004
136. Xu Y, Jones JE, Kohno D, et al. 5-HT2CRs expressed by pro-opiomelanocortin neurons regulate energy homeostasis. *Neuron*. 2008;60(4):582-589. doi:10.1016/j.neuron.2008.09.033
137. Dwarkasing JT, Witkamp RF, Boekschoten MV, Ter Laak MC, Heins MS, van Norren K. Increased hypothalamic serotonin turnover in inflammation-induced anorexia. *BMC Neurosci*. 2016;17(1):26. doi:10.1186/s12868-016-0260-0
138. Iuras A, Telles MM, Andrade IS, et al. L-arginine abolishes the hypothalamic serotonergic activation induced by central interleukin-1β administration to normal rats. *J Neuroinflammation*. 2013;10:147. doi:10.1186/1742-2094-10-147
139. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer*. 1974;33(6):1607-1609. doi:10.1002/1097-0142(197406)33:6<1607::aid-cncr2820330620>3.0.co;2-v
140. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol*. 2014;32(29):3221-3228. doi:10.1200/jco.2013.54.3926
141. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *J Clin Oncol*. 2013;31(25):3076-3082. doi:10.1200/jco.2012.44.4661

142. Kovalovsky D, Refojo D, Holsboer F, Arzt E. Molecular mechanisms and Th1/Th2 pathways in corticosteroid regulation of cytokine production. *J Neuroimmunol*. 2000;109(1):23-29. doi:10.1016/s0165-5728(00)00298-8
143. Shimizu H, Arima H, Watanabe M, et al. Glucocorticoids increase neuropeptide Y and agouti-related peptide gene expression via adenosine monophosphate-activated protein kinase signaling in the arcuate nucleus of rats. *Endocrinology*. 2008;149(9):4544-4553. doi:10.1210/en.2008-0229
144. Liu L, Song Z, Jiao H, Lin H. Glucocorticoids increase NPY gene expression via hypothalamic AMPK signaling in broiler chicks. *Endocrinology*. 2014;155(6):2190-2198. doi:10.1210/en.2013-1632
145. Schacter L, Rozencweig M, Canetta R, Kelley S, Nicaise C, Smaldone L. Megestrol acetate: clinical experience. *Cancer Treat Rev*. 1989;16(1):49-63. doi:10.1016/0305-7372(89)90004-2
146. Femia RA, Goyette RE. The science of megestrol acetate delivery: potential to improve outcomes in cachexia. *BioDrugs*. 2005;19(3):179-187. doi:10.2165/00063030-200519030-00004
147. Morley JE, Farr SA. Cachexia and neuropeptide Y. *Nutrition*. 2008;24(9):815-819. doi:10.1016/j.nut.2008.06.020
148. Maltoni M, Nanni O, Scarpi E, Rossi D, Serra P, Amadori D. High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: a systematic review of randomised clinical trials. *Ann Oncol*. 2001;12(3):289-300. doi:10.1023/a:1011156811739
149. Pascual López A, Roqué i Figuls M, Urrútia Cuchi G, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *J Pain Symptom Manage*. 2004;27(4):360-369. doi:10.1016/j.jpainsymman.2003.09.007
150. Ruiz-García V, López-Briz E, Carbonell-Sanchis R, Bort-Martí S, Gonzálvez-Perales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. *J Cachexia Sarcopenia Muscle*. 2018;9(3):444-452. doi:10.1002/jcsm.12292
151. Lim YL, Teoh SE, Yaow CYL, et al. A systematic review and meta-analysis of the clinical use of megestrol acetate for cancer-related anorexia/cachexia. *J Clin Med*. 2022;11(13):3756. doi:10.3390/jcm11133756
152. 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(2):89-97. doi:10.1016/0885-3924(94)00117-4
153. 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(21):3394-3400. doi:10.1200/jco.2005.05.1847
154. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. *Support Care Cancer*. 2018;26(9):3029-3038. doi:10.1007/s00520-018-4154-9
155. 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(2):567-573. doi:10.1200/jco.2002.20.2.567
156. Simon L, Baldwin C, Kalea AZ, Slee A. Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2022;13(1):23-41. doi:10.1002/jcsm.12861
157. Garcia JM, Polvino WJ. Effect on body weight and safety of RC-1291, a novel, orally available ghrelin mimetic and growth hormone secretagogue: results of a phase I, randomized, placebo-controlled, multiple-dose study in healthy volunteers. *Oncologist*. 2007;12(5):594-600. doi:10.1634/theoncologist.12-5-594
158. Garcia JM, Friend J, Allen S. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. *Support Care Cancer*. 2013;21(1):129-137. doi:10.1007/s00520-012-1500-1
159. Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol*. 2016;17(4):519-531. doi:10.1016/s1470-2045(15)00558-6
160. Wakabayashi H, Arai H, Inui A. The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. *J Cachexia Sarcopenia Muscle*. 2021;12(1):14-16. doi:10.1002/jcsm.12675
161. Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. *Psychopharmacology (Berl)*. 1996;124(1–2):87-94. doi:10.1007/bf02245608
162. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res*. 2009;28(1):131. doi:10.1186/1756-9966-28-131
163. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375(2):134-142. doi:10.1056/NEJMoa1515725
164. Navari RM, Pywell CM, Le-Rademacher JG, et al. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. *JAMA Oncol*. 2020;6(6):895-899. doi:10.1001/jamaoncol.2020.1052
165. Khojainova N, Santiago-Palma J, Kornick C, Breitbart W, Gonzales GR. Olanzapine in the management of cancer pain. *J Pain Symptom Manage*. 2002;23(4):346-350. doi:10.1016/s0885-3924(02)00378-0
166. Parsons B, Allison DB, Loebel A, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res*. 2009;110(1–3):103-110. doi:10.1016/j.schres.2008.09.025
167. Navari RM, Brenner MC. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. *Support Care Cancer*. 2010;18(8):951-956. doi:10.1007/s00520-009-0739-7
168. Sandhya L, Devi Sreenivasan N, Goenka L, et al. Randomized double-blind placebo-controlled study of olanzapine for chemotherapy-related anorexia in patients with locally advanced or metastatic gastric, hepatopancreaticobiliary, and lung cancer. *J Clin Oncol*. 2023;41(14):2617-2627. doi:10.1200/jco.22.01997
169. Halford JC, Cooper GD, Dovey TM. The pharmacology of human appetite expression. *Curr Drug Targets*. 2004;5(3):221-240. doi:10.2174/1389450043490541
170. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good antinausea effects. *Eur J Cancer Care*. 2007;16(4):351-354. doi:10.1111/j.1365-2354.2006.00760.x
171. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. *Am J Hosp Palliat Care*. 2010;27(2):106-110. doi:10.1177/1049909109345685
172. Hunter CN, Abdel-Aal HH, Elsherief WA, Farag DE, Riad NM, Alsirafy SA. Mirtazapine in cancer-associated anorexia and cachexia: a double-blind placebo-controlled randomized trial. *J Pain Symptom Manage*. 2021;62(6):1207-1215. doi:10.1016/j.jpainsymman.2021.05.017
173. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. *J Exp Med*. 1993;177(6):1675-1680. doi:10.1084/jem.177.6.1675

174. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet*. 2004;363(9423):1802-1811. doi:10.1016/s0140-6736(04)16308-3
175. Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM. Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial. *Gut*. 2005;54(4):540-545. doi:10.1136/gut.2004.047563
176. Mantovani G, Macciò A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist*. 2010;15(2):200-211. doi:10.1634/theoncologist.2009-0153
177. Eskiler GG, Bezdegumeli E, Ozman Z, et al. IL-6 mediated JAK/STAT3 signaling pathway in cancer patients with cachexia. *Bratisl Lek Listy*. 2019;66(11):819-826. doi:10.4149/bll_2019_136
178. Pototschnig I, Feiler U, Diwoky C, et al. Interleukin-6 initiates muscle- and adipose tissue wasting in a novel C57BL/6 model of cancer-associated cachexia. *J Cachexia Sarcopenia Muscle*. 2023;14(1):93-107. doi:10.1002/jcsm.13109
179. Baltgalvis KA, Berger FG, Peña MM, Davis JM, White JP, Carson JA. Muscle wasting and interleukin-6-induced atrogin-I expression in the cachectic Apc (Min/+) mouse. *Pflugers Arch*. 2009;457(5):989-1001. doi:10.1007/s00424-008-0574-6
180. Pettersen K, Andersen S, Degen S, et al. Cancer cachexia associates with a systemic autophagy-inducing activity mimicked by cancer cell-derived IL-6 trans-signaling. *Sci Rep*. 2017;7(1):2046. doi:10.1038/s41598-017-02088-2
181. Zhang L, Pan J, Dong Y, et al. Stat3 activation links a C/EBPδ to myostatin pathway to stimulate loss of muscle mass. *Cell Metab*. 2013;18(3):368-379. doi:10.1016/j.cmet.2013.07.012
182. Rigas JR, Schuster M, Orlov SV, et al. Efect of ALD518, a humanized anti-IL-6 antibody, on lean body mass loss and symptoms in patients with advanced non-small cell lung cancer (NSCLC): results of a phase II randomized, double-blind safety and efficacy trial. *J Clin Oncol*. 2010;28(E15 Suppl):7622. doi:10.1200/jco.2010.28.15_suppl.7622
183. Schuster M, Rigas JR, Orlov SV, et al. ALD518, a humanized anti-IL-6 antibody, treats anemia in patients with advanced non-small cell lung cancer (NSCLC): results of a phase II, randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2010;28(15 Suppl):7631. doi:10.1200/jco.2010.28.15_suppl.7631
184. Ando K, Takahashi F, Kato M, et al. Tocilizumab, a proposed therapy for the cachexia of interleukin6-expressing lung cancer. *PLoS One*. 2014;9(7):e102436. doi:10.1371/journal.pone.0102436
185. Hirata H, Tetsumoto S, Kijima T, et al. Favorable responses to tocilizumab in two patients with cancer-related cachexia. *J Pain Symptom Manage*. 2013;46(2):e9-e13. doi:10.1016/j.jpainsymman.2013.01.009
186. Bonetto A, Aydogdu T, Jin X, et al. JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. *Am J Physiol Endocrinol Metab*. 2012;303(3):E410-E421. doi:10.1152/ajpendo.00039.2012
187. Arora G, Gupta A, Guo T, et al. JAK inhibitors suppress cancer cachexia-associated anorexia and adipose wasting in mice. *JCSM Rapid Commun*. 2020;3(2):115-128. doi:10.1002/rco2.24
188. Breen DM, Kim H, Bennett D, et al. GDF-15 neutralization alleviates platinum-based chemotherapy-induced emesis, anorexia, and weight loss in mice and nonhuman primates. *Cell Metab*. 2020;32(6):938-950.e6. doi:10.1016/j.cmet.2020.10.023
189. Kim-Muller JY, Song L, LaCarubba Paulhus B, et al. GDF15 neutralization restores muscle function and physical performance in a mouse model of cancer cachexia. *Cell Rep*. 2023;42(1):111947. doi:10.1016/j.celrep.2022.111947
190. Lu XY, Barsh GS, Akil H, Watson SJ. Interaction between alpha-melanocyte-stimulating hormone and corticotropin-releasing hormone in the regulation of feeding and hypothalamo-pituitary-adrenal responses. *J Neurosci*. 2003;23(21):7863-7872. doi:10.1523/jneurosci.23-21-07863.2003
191. Vergoni AV, Bertolini A, Wikberg JE, Schiöth HB. Selective melanocortin MC4 receptor blockage reduces immobilization stress-induced anorexia in rats. *Eur J Pharmacol*. 1999;369(1):11-15. doi:10.1016/s0014-2999(99)00045-x
192. Fleming KA, Ericson MD, Freeman KT, et al. Structure-activity relationship studies of a macrocyclic AGRP-mimetic scaffold c[Pro-Arg-Phe-Phe-Asn-ala-Phe-DPro] yield potent and selective melanocortin-4 receptor antagonists and melanocortin-5 receptor inverse agonists that increase food intake in mice. *ACS Chem Nerosci*. 2018;9(5):1141-1151. doi:10.1021/acschemneuro.7b00495
193. Winkles JA. The TWEAK-Fn14 cytokine-receptor axis: discovery, biology and therapeutic targeting. *Nat Rev Drug Discov*. 2008;7(5):411-425. doi:10.1038/nrd2488
194. Kawakita T, Shiraki K, Yamanaka Y, et al. Functional expression of TWEAK in human hepatocellular carcinoma: possible implication in cell proliferation and tumor angiogenesis. *Biochem Biophys Res Commun*. 2004;318(3):726-733. doi:10.1016/j.bbrc.2004.04.084
195. Gu L, Dai L, Cao C, et al. Functional expression of TWEAK and the receptor Fn14 in human malignant ovarian tumors: possible implication for ovarian tumor intervention. *PLoS One*. 2013;8(3):e57436. doi:10.1371/journal.pone.0057436
196. Pettersen I, Baryawno N, Abel F, et al. Expression of TWEAK/Fn14 in neuroblastoma: implications in tumorigenesis. *Int J Oncol*. 2013;42(4):1239-1248. doi:10.3892/ijo.2013.1800
197. Chao DT, Su M, Tanlimco S, et al. Expression of TweakR in breast cancer and preclinical activity of enavatuzumab, a humanized anti-TweakR mAb. *J Cancer Res Clin Oncol*. 2013;139(2):315-325. doi:10.1007/s00432-012-1332-x
198. Lassen UN, Meulendijks D, Siu LL, et al. A phase I monotherapy study of RG7212, a first-in-class monoclonal antibody targeting TWEAK signaling in patients with advanced cancers. *Clin Cancer Res*. 2015;21(2):258-266. doi:10.1158/1078-0432.Ccr-14-1334
199. Ye S, Fox MI, Belmar NA, et al. Enavatuzumab, a humanized anti-TWEAK receptor monoclonal antibody, exerts antitumor activity through attracting and activating innate immune effector cells. *J Immunol Res*. 2017;2017:5737159. doi:10.1155/2017/5737159
200. Johnston AJ, Murphy KT, Jenkinson L, et al. Targeting of Fn14 prevents cancer-induced cachexia and prolongs survival. *Cell*. 2015;162(6):1365-1378. doi:10.1016/j.cell.2015.08.031
201. Sezaki T, Hirata Y, Hagiwara T, et al. Disruption of the TWEAK/Fn14 pathway prevents 5-fluorouracil-induced diarrhea in mice. *World J Gastroenterol*. 2017;23(13):2294-2307. doi:10.3748/wjg.v23.i13.2294
202. Cao Z, Scott AM, Hoogenraad NJ, Osellame LD. Mediators and clinical treatment for cancer cachexia: a systematic review. *JCSM Rapid Commun*. 2021;4(2):166-186. doi:10.1002/rco2.30
203. Fonseca G, Dworatzek E, Ebner N, Von Haehling S. Selective androgen receptor modulators (SARMs) as pharmacological treatment for muscle wasting in ongoing clinical trials. *Expert Opin Investig Drugs*. 2020;29(8):881-891. doi:10.1080/13543784.2020.1777275
204. Padhi D, Higano CS, Shore ND, Sieber P, Rasmussen E, Smith MR. Pharmacological inhibition of myostatin and changes in lean body mass and lower extremity muscle size in patients receiving androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab*. 2014;99(10):E1967-E1975. doi:10.1210/jc.2014-1271

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