Efficacy and safety of pharmacological cachexia interventions: systematic review and network meta-analysis

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ABSTRACT

Aims Randomised controlled trials (RCTs) demonstrated benefits of pharmacological interventions for cachexia in improving weight and appetite. However, comparative efficacy and safety are not available. We conducted a systematic review and network meta-analysis (NMA) to evaluate the relative efficacy and safety of pharmacological interventions for cachexia.

Methods PubMed, Embase, Cochrane, and ClinicalTrials.gov were searched for RCTs until October 2019. Key outcomes were total body weight (TBW) improvement, appetite (APP) score and serious adverse events. Two reviewers independently extracted data and assessed risk of bias. NMA was performed to estimate weight gain and APP score increase at 8 weeks, presented as mean difference (MD) or standardised MD with 95% CI.

Results 80 RCTs (10579 patients) with 12 treatments were included. Majority is patients with cancer (7220). Compared with placebo, corticosteroids, high-dose megestrol acetate combination (Megace_H_Com) (≥400mg/day), medroxyprogesterone, high-dose megestrol acetate (Megace_H) (≥400mg/day), ghrelin mimetic and androgen analogues (Androgen) were significantly associated with MD of TBW of 6.45 (95% CI 2.45 to 10.45), 4.29 (95% CI 2.23 to 6.35), 3.18 (95% CI 0.94 to 5.41), 2.66 (95% CI 1.47 to 3.85), 1.73 (95% CI 0.27 to 3.20) and 1.50 (95% CI 0.56 to 2.44) kg. For appetite improvement, Megace_H_Com, Megace_H and Androgen significantly improved standardised APP score, compared with placebo. There is no significant difference in serious adverse events from all interventions compared with placebo.

Conclusions Our findings suggest that several pharmacological interventions have potential to offer benefits in treatment of cachexia especially Megace_H and short-term use corticosteroids. Nonetheless, high-quality comparative studies to compare safety and efficacy are warranted for better management of cachexia.

Key messages

What is already known about this subject
Cachexia is a complex wasting syndrome affecting patients with chronic disease (cancer and HIV) that is associated with decreased survival, health-related quality of life and increased treatment toxicities. A number of pharmacological interventions have been investigated in recent randomised controlled trials (RCTs) and have demonstrated benefits for cachexia in improving weight and appetite. However, their comparative efficacy and safety for management of cachexia have not been thoroughly investigated.

What this study adds
Single and comprehensive framework for comparison of efficacy and safety outcomes among various pharmacological treatments for cachexia.

The present review combines direct and indirect evidence from 80 RCTs (10579 patients) to estimate weight gain, change in appetite score and adverse events using different pharmacological agents for management of cachexia, excluding nutritional interventions and dietary supplement.

High-dose megestrol acetate and short-term use of corticosteroids offer benefit in the treatment of cachexia.

This study suggests that anamorelin has high potential in cachexia treatment and recommends further investigation into this pharmacological agent.
INTRODUCTION

Cachexia is a complex wasting syndrome associated with many chronic diseases, such as cancer, HIV and chronic obstructive pulmonary disease (COPD). It is characterised by involuntary loss of skeletal muscle mass (with or without loss of fat mass), asthenia and systemic inflammation resulting from an imbalance of metabolic demands and energy uptake. The prevalence of cachexia is high, affecting 5%–15% of patients with COPD and 60%–80% of patients with advanced cancer. Cachexia plays an important role in the morbidity and mortality of these patients, resulting in decreased survival, health-related quality of life and increased treatment side effects.

Effective treatment for cachexia requires early identification and multimodal intervention, including optimal disease therapy, symptom management, targeted exercise and nutritional support. Treatment for cachexia has largely focused on non-pharmacological strategies. Nutritional support may prevent and treat cachexia; however, it cannot be fully reversed by conventional nutritional intervention. The 2016 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in patients with advanced cancer recommend early nutrition screening and assessment to detect patients with malnutrition and suggest stepwise nutritional intervention from dietary counselling, oral nutrition supplement to enteral and parenteral nutrition. Only few pharmacological agents, such as progestin and corticosteroid, have been suggested in selected patients due to limited evidence and may produce potential serious adverse effect. In 2020, The American Society of Clinical Oncology (ASCO) released a guideline on management of cancer cachexia which recommended dietary counselling by a registered dietitian and a short-term trial of a corticosteroid or progesterone. However, there are currently no Food and Drug Administration (FDA)-approved medications for the indication of cancer cachexia. A number of pharmacological interventions have been investigated in recent randomised controlled trials (RCTs) and have demonstrated benefits for cachexia in improving weight and appetite. However, their comparative efficacy and safety for management of cachexia has not been thoroughly investigated.

A traditional pairwise meta-analysis would allow us to determine which pharmacological treatment is more efficacious than placebo but would not allow for comparison among multiple treatment options. The use of a network meta-analysis (NMA) will allow us to directly and indirectly compare multiple interventions. Therefore, we conducted a systematic review and an NMA to evaluate the relative efficacy and safety of pharmacological interventions on change in total body weight (TBW), improvement in appetite (APP) score and serious adverse events among patients with cachexia.

METHODS

This study was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA. The study protocol was registered and approved in PROSPERO international prospective register of systematic reviews database (CRD42020158219).

Data sources and search strategy

We searched PubMed, Embase, the Cochrane Library and ClinicalTrials.gov from inception to 27 October 2019. Combination of terms of medical subject headings (MeSH) and keywords were used in the search strategy. MeSH and keywords contain “cachexia”, “cachectic,” “anorexia cachexia syndrome”, “HIV Wasting Syndrome” or “Wasting Syndrome” (online supplemental appendices 1 and 2). References derived from a full-text review were screened to identify potential studies not indexed in the aforementioned databases. No language restriction was applied. Further details on data sources and search strategy are described in online supplemental appendices 1 and 2.

Study selection

We included RCTs that compared anorexia or cachexia treatment, whether given alone or in combination. We excluded trials investigating cachexia or anorexia treatment without medication.

Data extraction and quality assessment

Two authors (SS and MS) independently screened the titles and abstracts of retrieved citations to identify potentially relevant studies. Disagreement based on titles and abstracts were judged by full article evaluation. Relevant data were abstracted using a standardised extraction form, including study characteristics, patient characteristics, interventions, outcomes and other relevant findings. All extracted data were cross-checked by two authors (SS and MS) and any discrepancies were resolved by consensus.

Interventions

Fourteen pharmacological interventions, including high-dose megestrol acetate (Megace_H) (at least 400 mg/day), low-dose megestrol acetate (Megace_L) (less than 400 mg/day) (Megace_L), high-dose megestrol acetate (at least 400 mg/day) combination with another cachexia or anorexia treatment agent (Megace_H_Com), low-dose megestrol acetate (less than 400 mg/day) combination with another cachexia or anorexia treatment agent (Megace_L_Com), corticosteroid analogues (Steroid), androgen analogues (Androgen), drug-targeting proinflammatory cytokines (Proinflam), adenosine 5’-triphosphate (ATP), recombinant human growth hormone (Growth_hormone), ghrelin (Ghrelin), ghrelin mimetic (Ghrelin_mimetic), medroxyprogesterone (Medroxyprogesterone), dronabinol (Dronabinol) or melatonin.
(Melatonin) following established treatment for the three pathophysiological causes of cachexia. Dietary supplements were not included in our study. Details of interventions are described in online supplemental appendix 3.

Outcomes of interest
The primary outcome was TBW difference from baseline and ≥8 weeks. Secondary efficacy outcomes were TBW and lean body weight (LBW) differences from baseline and <8 weeks, LBW difference from baseline and ≥8 weeks, and APP score difference from baseline and <8 weeks and ≥8 weeks. Secondary safety outcomes included overall adverse events and serious adverse events (grade at least 3) classified by common terminology criteria for adverse event.11

Assessment of risk of bias in included studies
The quality of included studies was assessed using Cochrane Risk of Bias Tool.12 13 Each study was judged to be high, low or unclear risk of bias based on their random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases.12 13 Quality assessment was undertaken by one reviewer and was checked by a second reviewer. Disagreements were resolved by consensus or consultation with a third party.

Quality of evidence
Evaluation of evidence quality from systematic review and NMA was performed using Confidence in Network Meta-Analysis (CINeMA), a web application (https://cinema.ispm.unibe.ch/, accessed May 2020).14 There were three levels of quality of evidence, including high, low or unclear.14 Grading of evidence for each outcome was performed based on six domains, including within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence.14

Data synthesis and statistical analysis
The intervention effects were estimated mean difference (MD) for TBW and LBW, standardised MD for APP score and risk ratios (RR) for overall adverse events and serious adverse events from individual studies. A meta-analysis using a random-effects model was applied to pool intervention effects.15 The Cochran Q test and the I² statistics were used to assess heterogeneity.16 Heterogeneity was present if Cochran Q test was significant (p<0.10) or I²≥50%.

NMA was used for direct and indirect comparisons between pharmacological interventions of each intervention effect outcome using placebo as the common comparator.17 18 The assumption of inconsistency between direct and indirect estimates was evaluated using the global inconsistency test by fitting design-by-treatment interaction in the inconsistency model.19 The rankograms, surface under the cumulative ranking curves20 and mean ranks were calculated to rank all interventions in the NMA model. A comparison-adjusted funnel plot was used to evaluate publication bias.21

Prespecified subgroup analyses were performed in all primary and secondary outcomes for groups of people with different diseases (eg, cancer, HIV and other diseases) (online supplemental appendix 13). Additionally, we conducted a prespecified sensitivity analyses of all primary and secondary outcomes by excluding studies with high risk of bias, small sample size (<25th percentiles) and restricting studies with dual X-ray absorptiometry (DXA) evaluation method (only for LBW outcomes).22 All analyses were performed in STATA V.14.0, using the self-programmed STATA routines for NMA described elsewhere. A two-sided p value of <0.05 was considered statistically significant.

Net clinical benefit (NCB) analysis
NCB analysis was performed to determine the value of using corticosteroids for improving TBW when balanced with infectious related mortality. The mortality risk of corticosteroids was determined using a meta-analysis study of 4198 patients by Stuck et al that included data from 71 studies using corticosteroid treatment.23 The use of corticosteroids increased mortality rate by 0.65% (95% CI 0.25% to 1.04%) compared with the control group.23 The mortality benefit of corticosteroids was determined using a population-based cohort study of 237305 patients from the National Health Insurance System health check-up data from 2005 to 2015 by Kim et al.24 The HR of mortality in patients who had a 5%–10% weight gain was 0.986 (95% CI 0.943 to 1.031).24 Monte Carlo stimulation was applied to estimate overall mortality effects of weight gain and showed that the mortality among those with weight improvement of 5%–10% was reduced by 0.13% (95% CI −0.02% to 0.29%) compared with weight stable patients.24 A detailed description of NCB analysis is provided in online supplemental appendix 11.

RESULTS
Study selection
We identified 6818 studies by searching strategies (online supplemental appendix eTable 2). A total of 6735 articles were excluded because of observational study design (2002 articles), followed by duplicated articles (1825 articles), non-relevant studies (1390 articles), in vitro or in vivo studies (951 articles), and paediatric studies (540 articles), respectively. Eighty-three articles were assessed for eligibility. Of the 83 articles, 79 (80 clinical studies) with 10579 participants, in which 1 article was a combined two clinical studies result, were included in our quantitative analysis since 4 articles27–30 compared treatment regimens regarded as the same in our NMA. The details of literature search were reported in online supplemental.
appendix 2. The PRISMA flowchart is presented in online supplemental appendix 2. Reference is presented in online supplemental appendix, p143).

**Study characteristics**

Across 80 clinical trials, 14 interventions were used, including Megace_H (1428 participants), Megace_L (715 participants), Megace_H_Com (427 participants), Megace_L_Com (263 participants), Steroid (379 participants), Androgen (922 participants), Proinflam (766 participants), ATP (79 participants), Growth_hormone (566 participants), Ghrelin (187 participants), Ghrelin_mimetic (917 participants), Medroxyprogesterone (285 participants), Dronabinol (431 participants) and Melatonin (38 participants).

The majority of our studies were performed in patients with cancer, in 48 studies (7220 participants). Among those studies, 37 studies (6007 participants) had advanced cancer; 2 studies (81 participants) had localised disease; and 9 studies (1132 participants) had no information given.

A total of 23 studies (2643 participants) were done in patients with HIV, and 9 studies (716 participants) in other conditions. Seventy-six studies had a parallel study design and another 4 studies had a crossover design. Most studies (72 studies) were with two-arm comparison, while 8 trials were with multiple comparisons. Seventy-two studies were conducted in a single country; most of the studies were done in the USA (30 studies), followed by Europe (26 studies), Asia and Oceania (12 studies) and Canada (four studies). Eight studies were conducted in multiple countries. Of the 10579 participants, 71.4% were male. The mean age was 56.3 (SD 19.7) years. The mean baseline body weight was 62.9 (SD 13.5) kg. Additional details of included studies, patients and treatment protocol are summarised in table 1 and online supplemental appendix 4.

**Risk of bias**

Based on the Cochrane risk-of-bias tool for randomised trials, 12 5%, 66% and 29% of studies were considered as at low risk, unclear and high risk of bias, respectively (online supplemental appendix 5, eTable 5.1). Among seven domains evaluated, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias) were the three most common reasons for potential bias. For trials with high risk of bias (23 trials with 2547 patients which represented about 24% of total population), the trials were relatively small, with <1000 patients in each trial. Additional details for the assessment of risk of bias are provided in online supplemental appendix 5.

**Effects of pharmacological intervention on primary and secondary outcomes**

A network map of eligible comparisons for TBW difference compared between baseline and assessed at least 8 weeks after randomisation (primary endpoint) was presented in figure 1. Network maps for secondary efficacy and safety outcomes are presented in online supplemental appendix 6 and details of all comparators are presented in online supplemental appendix 3. Treatment effects estimated using direct meta-analysis are presented in appendix 8. Comparisons among all treatment options for all outcomes are presented in online supplemental appendix 9. Global inconsistency test was performed and found no evidence of inconsistency of treatment effects for the outcomes, with the exception of TBW difference of less than 8 weeks (p value for test of global inconsistency=0.0247) (online supplemental appendix 7, eTable 7).

**Primary outcomes**

A total of 49 studies (5488 participants) assessed the primary endpoint of TBW difference compared between baseline and at least 8 weeks after randomisation across 13 interventions. The NMA comparison between all interventions is presented in figure 2A. Compared with placebo, Steroid, Megace_H_Com, Medroxyprogesterone, Megace_H, Ghrelin_mimetic and Androgen significantly improved TBW after treatment with MDs of 6.45 kg (95% CI 2.45 to 10.45), 4.29 kg (95% CI 2.23 to 6.35), 3.18 kg (95% CI 0.94 to 5.41), 2.66 kg (95% CI 1.47 to 3.84), 1.73 kg (95% CI 0.27 to 3.20) and 1.50 kg (95% CI 0.56 to 2.44), respectively.

**Secondary outcomes**

For LBW difference compared with baseline, 24 studies (3540 participants) assessed LBW difference compared between baseline and at least 8 weeks (bioimpedance analysis (BIA), 10 studies; DXA, 14 studies) across eight interventions (figure 2B). Compared with placebo, Growth_hormone, Androgen and Ghrelin_mimetic significantly improved LBW after treatment with an MD of 2.54 kg (95% CI 1.90 to 3.19), 1.47 kg (95% CI 1.05 to 1.89) and 1.38 kg (95% CI 0.90 to 1.86), respectively. Ten studies (735 participants) assessed LBW difference compared between baseline and at least 8 weeks (BIA, five studies; DXA, five studies) across six interventions (figure 2C). Only Androgen significantly improved LBW after treatment with an MD of 2.57 kg (95% CI 1.00 to 4.13) when compared with placebo.

For APP score difference compared with baseline, 19 studies (2632 participants) assessed APP score difference compared between baseline and at least 8 weeks across eight interventions (figure 2D). The APP measurement method for each included study is summarised in online supplemental appendix 4. Compared with placebo, Megace_H_Com, Megace_H...
Review and Androgen significantly improved APP score after treatment with a standardised MD of 1.83 (95% CI 1.14 to 2.52), 1.04 (95% CI 0.63 to 1.46) and 0.44 (95% CI 0.01 to 0.88), respectively. Fourteen studies (1333 participants) assessed APP score difference compared between baseline and at less than 8 weeks across 10 interventions (figure 2E). Compared with placebo, Ghrelin significantly improved APP score after treatment with a standardised MD of 1.11 (95% CI 0.17 to 2.04). Compared with placebo, Ghrelin significantly improved APP score after treatment with a standardised MD of 1.11 (95% CI 0.17 to 2.04).

For secondary safety endpoints, 23 studies (2329 participants) assessed adverse events across 10 interventions (figure 2F). Compared with placebo, Growth_hormone, Dronabinol and Megace_H significantly increased adverse events after treatment with RR of 10.69 (95% CI 3.12 to 36.69), 1.66 (95% CI 1.03 to 2.67) and 1.35 (95% CI 1.01 to 1.82), respectively. Ten studies (1670 participants) assessed serious adverse events across eight interventions (figure 2G). No significant increase in serious adverse events was seen from all interventions compared with placebo.

### NCB analysis

NMA results showed that corticosteroids increase TBW difference at ≥8 weeks by 6 kg compared with placebo; thus, the TBW of patients on corticosteroids improved 10% from baseline. NCB was calculated using Monte Carlo stimulation by subtracting the mortality rate benefit of corticosteroids (0.13%)24 from the mortality rate risk of corticosteroids (0.65%).23 NCB analysis showed corticosteroid treatment increased mortality rate by 0.52% (95% CI 0.08% to 0.94%).23 24 Detailed description of NCB analysis is provided in online supplemental appendix 11.
Subgroup analyses

We performed subgroup NMA in primary and secondary outcomes according to different disease conditions (cancer, HIV and other diseases) (online supplemental appendix 13). For TBW difference compared with baseline at 8 weeks, global inconsistency was found in 23 patients with cancer subgroup studies (2851 participants). One study31 has been excluded from analysis because 80% of study participants have received analgesics, which is a proinflammatory agent and may affect TBW improvement. Twenty-two studies (2785 participants) assessed TBW difference at 8 weeks in patients with cancer. Corticosteroids (Steroid), Megace_H_Com, Medroxyprogesterone and Ghrelin mimetic significantly improved TBW after treatment compared with placebo, with an MD of 6.67 kg (95% CI 3.56 to 9.78), 3.03 kg (95% CI 1.18 to 4.88), 2.95 kg (95% CI 1.55 to 4.35) and 1.68 kg (95% CI 1.28 to 2.08), respectively. However, Megace_H showed a significant decrease in TBW after treatment compared with placebo with an MD of −3.12 kg (95% CI −5.45 to 0.79).

Twenty studies (2122 participants) assessed TBW difference at least 8 weeks in patients with HIV. Megace_H, Megace_H_Com, Androgen and Growth hormone significantly improved TBW after treatment compared with placebo, with an MD of 3.81 kg (95% CI 2.31 to 5.32), 3.14 kg (95% CI 0.42 to 5.86), 1.88 kg (95% CI 1.07 to 2.68) and 1.67 kg (95% CI 0.34 to 2.99), respectively. However, Dronabinol showed a significant decrease in TBW after treatment compared with placebo with an MD of −4.78 kg (95% CI −8.68 to 0.88).

Six studies (515 participants) assessed TBW difference at least 8 weeks in patients with other diseases. No significant difference in TBW was seen from all interventions compared with placebo.

Sensitivity analyses and publication bias

We performed sensitivity analyses by excluding studies with high risk of bias and small sample size (<25th percentile) in all primary and secondary outcomes and restricting studies with DXA evaluation method for LBW outcomes. For TBW difference assessed at least 8 weeks after randomisation, sensitivity analysis for global inconsistency was performed in 37 trials (5203 participants), excluding trials with small sample size (<25th percentile). Thirty-seven trials (4680 participants) were used for sensitivity analysis, excluding trials with overall high risk of bias. Megace_H_Com, Megace_H, Ghrelin mimetic and Androgen significantly improved TBW after treatment compared with placebo, with an MD of 4.52 kg (95% CI 2.18 to 6.87), 2.20 kg (95% CI 0.86 to 3.54), 1.73 kg (95% CI 0.32 to 3.14) and 1.61 kg (95% CI 0.66 to 2.55), respectively. The effect estimates were generally robust among sensitivity analyses (online supplemental appendix 14). Comparison-adjusted funnel plots for all outcomes showed no evidence of asymmetry (online supplemental appendix 13). More details...
on sensitivity analyses are described in online supplemental appendix 14.

Quality of evidence
The confidence in the relative treatment effect estimated in NMA for the primary outcome will be evaluated using the CINeMA framework, a modification of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Some trials were excluded from CINeMA due to missing mean, SD or number of patients. To assess imprecision, heterogeneity and incoherence we considered 0.8 to be a clinically relevant OR (NB: log(0.8) = −0.2231436 or 0.2231436). When applying GRADE to NMA evidence, most comparison of interventions were rated as moderate quality for our primary outcome. Secondary outcomes were generally rated as moderate or low quality. The safety outcome ‘adverse events’ was rated as moderate or low quality. The safety
outcome ‘serious adverse events’ were generally rated as moderate quality.\textsuperscript{32} More details of quality of evidence is described in online supplemental appendix 12.

**DISCUSSION**

To the best of our knowledge, this is the first systematic review and NMA in the field of pharmacological interventions for cachexia. Many pharmacological agents have been studied in anorexia–cachexia management. However, current clinical studies remain insufficient to recommend pharmacological intervention in cachexia treatment. ASCO\textsuperscript{8} and ESPEN\textsuperscript{7} suggest the use of pharmacological intervention to improve clinical outcomes in cachectic patients. It is important to note that these agents cannot substitute for nutritional intervention. The present review, combining direct and indirect evidence from 80 RCTs (10,579 patients), with the majority of studies involving patients with cancer (48 studies, 7220 patients) to estimate weight gain and change in APP score using different pharmacological agents for management of cachexia, excluding all nutritional interventions and dietary supplement, is the largest analysis in this field. Based on the comprehensive dataset and the use of NMA, we were able to conclude that Megace_H, Megace_H_Com, corticosteroids and Ghrelin_mimetic (anamorelin) are the most efficacious agents for improving TBW at 8 weeks of treatment. Such findings were robust and remain significant in various sensitivity and subgroup analyses. According to CINeMA grading system, the levels of evidence supporting the efficacy of these agents were moderate compared with placebo.

Our NMA revealed that megestrol acetate improved TBW and appetite at 8 weeks in high dose (at least 400 mg/day) without significant increases in both overall and serious adverse events with a moderate quality of evidence. Lower dose (less than 400 mg/day) did not show a benefit in both body weight and appetite gain with a moderate and low quality of evidence. This finding is different from the previous meta-analysis of Garcia et al.,\textsuperscript{35} which did not show a dose–response relationship of the benefit on body-weight improvement. In addition, both ASCO and ESPEN guidelines suggested the use of megestrol acetate without specifying the dose for cachexia treatment.\textsuperscript{7,8} This NMA demonstrates the clear benefit of Megace_H over other pharmacological interventions. Moreover, our findings provide evidence to strongly support clinicians to consider titrating the megestrol acetate dose to at least 400 mg/day in patients who can tolerate it without any major adverse events.

Based on comprehensive evaluation investigating the effects of corticosteroids, we were able to show that corticosteroids result in improvement in TBW at 8 weeks with moderate quality of evidence and limited evidence on long-term safety. Results of NMA strengthen the current recommendation in the ASCO and ESPEN guidelines on the short-term use of corticosteroid therapy for cancer cachexia.\textsuperscript{7,8} NCB analysis was used to simultaneously evaluate effects of corticosteroids on infectious related mortality along with increase in TBW. NCB analysis showed that the benefits on weight increase is not sufficient to outweigh the long-term risk of infection associated with its use. To our knowledge, we performed the first NCB analysis of corticosteroids analysing their overall value while objectively considering the balance of risk and benefit simultaneously. Hence, we suggest that clinicians consider the overall risk and benefit before treatment in a restricted short period of time.

Our study also evaluated the benefit of other new pharmacological agents for patients with cachexia. Compared with previous studies, our study compiled the highest number of anamorelin studies for analysis. This study found that anamorelin not only increased TBW but also LBWt at 8 weeks without an increase in adverse events with moderate and low quality of evidence. Anamorelin works by activating the ghrelin receptor and is mediated through transient increases in growth hormone and insulin-like-growth factor, resulting in anabolic and appetite stimulation. Ghrelin promotes myocyte differentiation and protects the muscle from atrophy without fluid retention. This pharmacological effect can explain the improvement in LBW from anamorelin treatment. Anamorelin is currently not included in the recommendations of ASCO/ESPEN as it has not yet been FDA-approved.\textsuperscript{7,8} The improvement in LBW (which is a better marker of nutrition improvement than TBW) finding from our study suggests that anamorelin has high potential in cachexia treatment. However, given the limited evidence, it would be prudent to have more investigation into this pharmacological agent.

Dronabinol (a cannabinoid analogue) failed to show a significant benefit in improvement in all body weight and appetite with moderate quality evidence. Moreover, treatment with dronabinol was found to decrease TBW in patients with HIV and to increase overall adverse events with moderate-quality evidence. Treatment-related adverse events of cannabinoids are the major barrier in achieving a beneficial outcome with cannabinoids for cachexia treatment. Based on current evidence, there remain insufficient data to recommend cannabinoids in cachexia treatment, which is consistent with recommendation made by ASCO/ESPEN guidelines.\textsuperscript{7,8}

Even though new single agents show potential for improving outcomes, a more effective approach might be combination therapy targeting the different mechanisms contributing to cancer–anorexia–cachexia syndrome. Our NMA study found that Megace_H in combination with another pharmacological agent significantly increased TBW and appetite at 8 weeks without a significant increase in overall and serious adverse events compared with placebo with
moderate-quality and low-quality evidence. Despite these promising findings, when compared with high dose megestrol acetate alone, the Megace_H_Com failed to increase TBW at 8 weeks. The role of combination therapy remains unclear and warrants more investigation to further improve overall evidence.

Malnutrition and loss of lean body mass are common in patients with cancer and are associated with many adverse outcomes. Early nutrition screening and assessment to detect patients with malnutrition at the time of diagnosis are recommended for all patients with cancer. Prompt nutrition care accompanied by exercise training is critical to improve not only the nutritional status but also clinical outcomes. Stepwise nutritional intervention, starting from dietary counselling, oral nutritional supplement to enteral and parenteral nutrition, is usually recommended in clinical practice. Nutritional counselling with or without oral nutrition supplement with the goals of providing high protein, high calories, nutrient-dense food is recommended to achieve macronutrient and micronutrient requirements. Enteral tube feeding can be initiated in patients with inadequate oral intake, and parenteral nutrition may be offered in selected patients with impaired gut function, such as reversible bowel obstruction. Nevertheless, routine enteral and parenteral nutrition should not be routinely offered to treat cancer cachexia particularly for patient with advance disease. Risk and benefit of nutritional intervention should be considered in patients with advance cancer.

Many pharmacological agents have been studied in anorexia–cachexia management. However, current clinical studies remain insufficient to recommend pharmacological intervention in cachexia treatment. ASCO and ESPEN suggest pharmacological intervention to improve clinical outcomes in cachectic patients. These agents cannot substitute for nutritional intervention. Providing appropriate nutritional intervention, including dietary advice and nutritional therapy based on the patient’s disease and nutritional status, must be applied for all cachectic patients.

The strengths of our study include a comprehensive analysis of the efficacy (TBW, LBW and AP score) and safety (overall adverse events and serious adverse events) of pharmacological agents for cachexia in a single network. Previous RCTs compared single pharmacological agents only, without making direct and indirect comparisons between treatments. The main results in our NMA are also presented by simultaneous clustered ranking of efficacy and safety outcomes, allowing us to explore the intervention that has the best balance of both benefits and risks.

Our review has several limitations. Our analyses were restricted by the modest amount of data in the included studies. The sample sizes of many interventional studies were small (melatonin and olanzapine). The implementation of intervention could be more intense in studies with smaller sample size. More clinical studies are warranted to strengthen the study outcome. Second, while our study can be considered as the most comprehensive evaluation for cachexia, readers should be prudent when interpreting the findings as heterogeneity may exist among study populations. Heterogeneity may be attributed to differences in patient population, disease state (cancer, HIV and other diseases), trial conducts and trial methodology across studies. Sensitivity analyses were performed to assess the robustness of our conclusion for all outcomes. Overall, findings were robust across the three patient populations (cancer, HIV and other). Third, despite our best attempt with statistical analysis, conclusion drawn from our analysis is still far from being definitive. This stems from the fact that approximately one third of included trials were at high risk of bias while quality of evidence among included data were considered moderate. We therefore caution readers to consider this limitation when interpreting our results. Fourth, this study looked only at pharmacological interventions for cachexia and did not consider the impact that nutritional supplements could have on the primary and secondary outcomes. Studies are warranted to study the impact of nutritional supplements on management of cachexia compared to pharmacological intervention. Fifth, our analysis on the benefit of combination pharmacological therapy can be perceived as hypothesis generated since data are still too limited to make a definitive conclusion. There were different pharmacological agents used for combination therapy with megestrol acetate; thus, the effect of megestrol acetate combination group may be varied, depending on the combined pharmacological agent used. However, we still believe that multimodal therapy is best supported by not only our study but also previous reports. Finally, comparative studies to compare safety and efficacy of pharmacological agents are warranted to better manage cachexia.

In summary, this NMA offers a single and comprehensive framework for comparison of efficacy and safety outcomes among various pharmacological treatments for cachexia in a broad range of patient populations. Such information may be useful to guide clinical decision or formulate clinical practice guideline for cachexia. Our findings suggest that several pharmacological interventions have potential to offer benefits in treatment of cachexia especially Megace_H and short-term use corticosteroids. It is also important to note that cachexia is not a primary condition; it is secondary to other disease states. Therefore, it is necessary to treat the primary cause of disease in order to properly manage cachexia. Effective management of cachexia is multimodal and involves a combination of pharmacological intervention, nutritional support, adequate protein intake and the possible use of dietary supplements. Further research into the risk–benefit, along with cost-effectiveness analysis, of these therapeutic options should be warranted.
REFERENCES


