Anorexia Evaluation Table 2023: Progestins

Systematic Review

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Lim, Y.L., Teoh, S.E., Yaow, C.Y.L., Lin, D.J., Masuda, Y., Han, M.X., . . . Ng, Q. X. (2022). A systematic review and meta-analysis of the clinical use of megestrol acetate for cancer-related anorexia/cachexia. *Journal of Clinical Medicine, 11*(13), 3756. https://doi.org/10.3390/jcm11133756	**Design:** Systematic review and meta-analysis **Methods:** Search of PubMed®, Embase®, OVID®, ClinicalTrials.gov, and Google Scholar databases for studies evaluating benefits of megestrol for cancer-related anorexia or cachexia, with outcome measures of weight or quality of life (QOL) was conducted. Paired data extraction and risk of bias (ROB) assessment were performed. **Sample:** 23 studies including 3,790 patients with sample sizes ranging from 6 to 475 adult and pediatric patients with various cancer types.	**Independent Variable(s)**: Megestrol **Dependent Variable(s)**: Weight, QOL **Intervention**: Megestrol at various doses and in varied combination with other treatments (dexamethasone, dronabinol, L-carnitine)	Outcome was measured by overall change in body weight. The study looked at overall weight change, and also change between groups with high-dose (greater than 320 mg) and low-dose (less than or equal to 320 mg) megestrol. QOL was measured differently between studies, and tools used for measurement were not consistently reported.	8 studies provided data for meta-analysis (n = 576). Overall mean change in weight was 0.75 kg (95% CI [−1.64, 3.15]. Mean change in weight in the high-dose group was −0.05 kg (95% CI [−2.71, 2.60]. Mean change of weight in the low-dose group 2.24 kg (95% CI [−7.19, 11.67]. In all groups, the change was not statistically significant.	High heterogeneity (different cancers, stages, and dosages) Dated literature (13 of 23 studies were more than 15 years old) Unclear determinations on adverse events Study durations were limited.	Quality reporting with valid methodology and reliable results. Additional study on more specific subpopulations may be useful. Findings do not support use of megestrol for cancer-related anorexia or cachexia.

Ruiz-García, V., López-Briz, E., Carbonell-Sanchis, R., Bort-Martí, S., & Gonzálvez-Perales, J.L. (2018). Megestrol acetate for cachexia-anorexia syndrome. A systematic review. *Journal of Cachexia, Sarcopenia and Muscle, 9*(3), 444–452. https://doi.org/10.1002/jcsm.12292	**Design:** Systematic review **Method:** Database search of Cochrane, Medline®, Embase®, International Clinical Trials Registry Platform, and clinicaltrials.gov was conducted. ROB and quality assessment were performed. **Sample:** 38 studies with 4,304 participants with a diagnosis of cachexia-anorexia syndrome with AIDS, cancer, or other underlying pathologies	**Independent Variable(s)**: Megestrol acetate **Dependent Variable(s)**: Weight, QOL, adverse events (AEs), death **Intervention:** Megestrol compared to placebo, no treatment, other treatments, and at varying doses in multiple studies.	Weight gain between baseline and completion of treatment Various tools used to measure QOL in individual trials AEs Deaths	**For megestrol versus placebo group:** Weight gain mean difference of 2.25kg (95% CI [1.19, 3.30]. **For megestrol at any dose vs. placebo outcomes:** Weight gain (9 studies, 575 participants): Mean difference of 2.25 kg (95% CI [1.19, 3.30], p = 0.0001). Overall AEs (8 studies, 638 participants): Higher in megestrol group at any dose (relative risk [RR] = 1.46, 95% CI [1.05, 2.04]. QOL (2 studies, 70 participants): No significant differences (p = 0.12). Deaths (2 trials, 90 participants): No significant differences in deaths, (RR = 1.01, 95% CI [0.42, 2.45]. **Megestrol at any dose versus no treatment outcomes:** Weight gain (2 trials, 101 participants with cancer): Mean difference of 1.45 kg (95% CI [0.15, 2.75]). QOL (2 studies, 99 participants): No significant differences. AEs (2 studies, 101 participants with cancer): No significant differences (RR = 0.9, 95% CI [0.39, 2.08]). Deaths (2 trials, 90 participants): No significant differences (RR = 1.01, 95% CI [0.42, 2.45]). **Megestrol at any dose vs. other treatments:** Weight gain (4 studies, 541 participants): Mean difference of 2.5 kg (95% CI [0.37, 4.64]). QOL (1 trial 469 participants): No significant differences between groups. AEs (7 studies, 1175 participants): No increase in participants with megestrol (RR = 1.05, 95% CI [0.95, 1.16]. **Megestrol at different doses**: No differences in weight gain, AEs, or QoL; no data available on deaths.	Limited applicable number of studies included. High heterogeneity Not likely to be easily applied to population of interest because of other populations studied Risk of bias downgraded the quality of evidence because of randomization sequence, unclear allocation concealment, and imprecision.	Megestrol showed an increase in weight compared to placebo group, but this was not clinically relevant and no changes in QOL were noted between groups. There was an increase in AEs in megestrol groups when compared to placebo groups, which should be considered when recommending this treatment. There were no differences in deaths reported. The results show efficacy of megestrol acetate for weight gain, but not QOL. The judged quality of evidence for many variables across groups was reported as low or very low.

General Evidence

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Kouchaki, B., Janbabai, G., Alipour, A., Ala, S., Borhani, S., & Salehifar, E. (2018). Randomized double-blind clinical trial of combined treatment with megestrol acetate plus celecoxib versus megestrol acetate alone in cachexia-anorexia syndrome induced by GI cancers. *Supportive Care in Cancer, 26*(7), 2479–2489. https://doi.org/10.1007/s00520-018-4047-y	**Design:** Phase 3 double-blind randomized trial **Method:** Use of megestrol plus celecoxib or megestrol plus placebo daily for 2 months in patients with gastrointestinal (GI) cancers. Measurements of outcomes of interest were taken at baseline, 1 month, and 2 months. **Sample:** 90 patients with GI cancers were initially enrolled. Participants were permitted but not required to be on antineoplastic or palliative therapy. **Setting**: Single center in northern Iran	**Independent Variable(s)**: Megestrol or megestrol with celecoxib **Dependent Variable(s)**: **Primary:** Body weight **Secondary:** QOL, grip strength, appetite score, performance status, serum albumin, and inflammatory markers (C-reactive protein, IL-6) **Intervention:** **Arm 1 (n = 45):** Megestrol 320 mg per day plus placebo in two doses **Arm 2 (n = 45):** Megestrol 320 mg per day plus Celecoxib 200 mg per day in two doses Treatment length was 2 months.	Glasgow Prognostic Score for cancer outcomes European Organisation for Research and Treatment of Cancer QOL Questionnaire–Core 30 (EORTC-QLQ-30) Jamar hydraulic hand dynamometer Ten-point visual analog scale (VAS) measuring appetite Eastern Cooperative Oncology Group (ECOG) performance status Serum blood samples Adverse events (AEs)	**Analyzed after 1 month**: n = 33 in control group and n = 27 in intervention group after attrition. Weight response was considered at 5% increase, and no significant differences in outcome measures were noted between groups. **Analyzed after 2 months:** n =17 in control group and n = 16 in intervention group after attrition. Significant improvements in body weight and other secondary outcomes were noted, but Mann Whitney U test for comparison between groups showed no differences between groups. **AEs**: 12 patients experienced AEs warranting discontinuation of treatment. Arm 1: grade 3 thromboembolic event (1), extreme fatigue (2), dyspepsia (4) Arm 2: dyspepsia (4), extreme fatigue (2)	Limited sample size after attrition to draw conclusions Findings not generalizable	Sound methodology and results reported with reliability. Small sample size and limited diagnoses studied limits applicability of findings to the generalized population of interest. Although this study does not support adding celecoxib to a megestrol acetate regimen for anorexia or cachexia, it does support that megestrol acetate is a pharmacologic treatment option for cancer-related anorexia or cachexia in patients who are not at an increased risk for thromboembolic events.

Currow, D.C., Glare, P., Louw, S., Martin, P., Clark, K., Fazekas, B., & Agar, M.R. (2021). A randomised, double blind, placebo-controlled trial of megestrol acetate or dexamethasone in treating symptomatic anorexia in people with advanced cancer. *Scientific Reports, 11*(1), 2421. https://doi.org/10.1038/s41598-021-82120-8	**Design:** Multisite double-blinded, parallel-arm, fixed-dose, placebo-controlled phase 3 study **Method:** Megestrol acetate 480 mg/day compared with dexamethasone 4 mg/day and placebo for effect on appetite. Participants were randomized 1:1:1. **Sample:** 190 patients with advanced cancer and anorexia **Setting**: Multisite: recruitment from 12 centers at 23 institutions across Australia	**Independent Variable(s)**: Megestrol or dexamethasone **Dependent Variable(s)**: Appetite response, weight stability, QOL, performance status	Primary outcome of 25% or greater improvement in appetite on numeric rating scale over baseline measured at day 7 Weekly assessments of blood glucose levels Australia-modified Karnofsky Performance Status (AKPS) Eastern Cooperative Oncology Group (ECOG) performance status Weight Functional Assessment of Anorexia-Cachexia Therapy (FAACT) Memorial Symptom Assessment Scales (MSAS)	Primary endpoint: The overall association between treatment group and numeric rating scale appetite response was not statistically significant ($p = 0.067$). There were no differences in weight stability between groups ($p = 0.2417$). Treatment had a significant effect on MSAS appetite response rates at week 1 (68.2% in megestrol group, 38.3% in the dexamethasone group, and 48.9% in the placebo group, $p = 0.0162$); however, the pairwise comparisons for megestrol and placebo ($p = 0.0697$) and dexamethasone and placebo ($p = 0.3114$) were not significant. Other measures: No differences in QOL and AKPS.	The study design required participants to cease randomized treatment if an insufficient response was documented at 1 week. The primary endpoint was measured at 1 week; the placebo group experienced the greatest attrition between week 1 and 2.	Level I/II quality of evidence Appropriate randomization and power, valid methodology Findings do not establish a new standard of care but may inform clinicians when considering appetite stimulants in the context of anorexia. Although AEs were similar between all arms, hyperglycemia for those prescribed dexamethasone will need to be closely monitored. Anorexia in adult patients with advanced cancer may have physical and emotional effects on the patient and caregiver. This trial did not demonstrate improved appetite, weight, or QOL with the use of megestrol or dexamethasone versus placebo at week 1 of treatment. The common use of dexamethasone in oncology for a variety of indications other than appetite should be noted. Risk and benefit need to be considered, including risk of hyperglycemia, deep vein thrombosis, insomnia, and mood changes.

Clinical Practice Guidelines

Guideline Citation	Purpose	Sample/Setting	Significant Recommendations	Limitations	Quality and Nursing Implications
Roeland, E.J., Bohlke, K., Baracos, V.E., Bruera, E., Del Fabbro, E., Dixon, S., . . . Loprinzi, C.L. (2020). Management of cancer cachexia: ASCO Guideline. *Journal of Clinical Oncology, 38*(21), 2438–2453. https://doi.org/10.1200/JCO.20.00611	Provide an evidence-based clinical guideline for the management of cancer cachexia in adult patients with advanced cancer.	Sample: Adult patients with advanced cancer and one or more of the following: loss of body weight, lean body mass, and/or appetite	1. Guidelines are moderately in favor of nutritional support and counseling with a registered dietitian. 2. Considerations for pharmacologic interventions for cancer cachexia include: • Moderately in favor of recommending short trials of progesterone analogs or corticosteroids, weighing risk and benefit for patient. Megestrol improves appetite and body weight (adipose not skeletal mass) but has risk of thromboembolic events, adrenal suppression, and edema. • No recommendation was made for anamorelin, which was FDA-reviewed but not approved. It is not commercially available in the U.S. • Cannabinoids and derivatives did not show improvement in appetite, weight change, or QOL alone or in combination with megestrol. Guideline panel ranks strength as weak against use of this intervention. • Olanzapine data is lacking to make a recommendation on use in cachexia. • No recommendation on use of thalidomide because of low strength of evidence and low benefit with side effects of somnolence and constipation. • Exercise was not included in any eligible trials related to cachexia in patients with advanced cancer.	Small sample sizes High rates of patient dropout reported in several studies. The majority of the RCTs had risk of bias assessed as intermediate or high.	The methodology was valid and rigorous. A panel of experts reviewed the literature, developed the draft guideline, and allowed public comment prior to finalizing the guideline. A thorough process was followed for the finalization, publication, and implementation of the guideline. The recommendations ranked "moderately in favor" are feasible, relevant, and can be applied to the patient population of interest. Nurses work collaboratively with interprofessional colleagues to manage patient symptoms; awareness of the interventions, the harm versus benefit grading, and the strength of the recommendation will enable the nurse to actively participate in discussions regarding the management of cachexia. The guideline also provides key information regarding how to reduce patient and caregiver frustration related to changes in eating habits, nutritional intake, and physical manifestations associated with cachexia. Nurses will be able to use this information in addition to information related to out-of-pocket costs and health disparities when caring for patients with cancer-related cachexia.