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REVIEW ARTICLE

Geriatrics, Gerontology and Aging

Megestrol acetate for appetite stimulation and weight gain in older adults with unintentional weight loss: a systematic review and meta-analysis

Larissa de Freitas do Lago-Abreu[a], Raphael Lopes Olegário[b], Luciana Lilian Louzada Martini[a], Einstein Francisco Camargos[a,b]

[a]Centro Médico Geriátrico, Hospital Universitário, Universidade de Brasília – Brasília (DF), Brazil.
[b]Programa de Pós-Graduação em Ciências Médicas, Faculdade de Medicina, Universidade de Brasília – Brasília (DF), Brazil.

Correspondence data
Einstein Francisco Camargos. Universidade de Brasília, Campus Darcy Ribeiro, Asa Norte, CEP: 70910-900 – Brasília (DF), Brazil.
E-mail: einstein@unb.br

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Abstract

Unintentional weight loss in older adults is linked to multiple factors, being most often associated with comorbidities such as cancer, dementia syndromes, chronic obstructive pulmonary disease, and chronic kidney disease. Difficulty in managing this condition can quickly lead to malnutrition and, consequently, a state of cachexia. There is a dearth of studies in the literature regarding pharmacotherapeutic interventions for this population, with megestrol acetate (MA) being the most commonly studied medication. In this systematic review, we evaluated the use of MA to improve appetite and treat unintentional weight loss and/or the anorexia-cachexia syndrome in older adults. Randomized studies published up to December 2023 in three languages (Portuguese, Spanish, or English) were retrieved from five databases. We included 25 studies, most of which addressed the use of MA for treatment of patients diagnosed with cancer and the anorexia-cachexia syndrome. We used the PEDro scale to assess methodological quality of the included studies and calculated measures of heterogeneity, such as the tau-squared (τ^2), I-squared (I^2), and *Q* test, to assess consistency across studies. Although the studies selected for the systematic review suggest that patients with the anorexia-cachexia syndrome secondary to cancer may benefit from MA therapy, a meta-analysis of 8 selected studies (total n = 592) did not confirm this effect (p = 0.104). The indication of MA for treatment of patients with weight loss required further studies with better methodological designs to evaluate the efficacy and safety profile of this medication in older adults.
PROSPERO registry number CDR42024497640.

Keywords: appetite stimulants; aged; megestrol acetate; cachexia; anorexia; systematic review; meta-analysis.

Resumo

A perda de peso não intencional em pessoas idosas está ligada a múltiplos fatores, sendo comumente associada a comorbidades como câncer, síndromes demenciais, doença pulmonar obstrutiva crônica e doença renal crônica. A dificuldade no manejo deste quadro pode levar rapidamente à desnutrição e, consequentemente, a um estado de caquexia. Há na literatura uma escassez de estudos de intervenção farmacológica nessa população, sendo o acetato de megestrol (AM) a medicação mais comumente estudada. Nessa revisão sistemática, avaliamos o uso do AM para melhora do apetite e no tratamento da perda de peso não intencional e/ou síndrome anorexia-caquexia em idosos. Foram avaliados estudos randomizados, disponíveis em cinco bases de dados, até dezembro de 2023 e em três idiomas (português, espanhol e inglês). Foram incluídos 25 estudos que abordaram em sua maioria o uso do AM para o tratamento de pacientes com diagnóstico de câncer e síndrome anorexia-caquexia. A qualidade metodológica dos estudos incluídos foi avaliada utilizando a escala PEDro; e medidas de heterogeneidade, como tau-quadrado (τ^2), I-quadrado (I^2) e o teste de heterogeneidade *Q*, foram fornecidas para avaliar a consistência entre os estudos. Apesar de os estudos selecionados na revisão sistemática apontarem que pacientes com síndrome anorexia-caquexia secundária ao câncer podem se beneficiar do uso do AM, o resultado da metanálise de 8 estudos selecionados (total de 592 pacientes) não confirmou esse efeito (p = 0,104). A indicação desta medicação para tratamento de pacientes com perda de peso carece de estudos com melhor delineamento metodológico para avaliar a eficácia e o perfil de segurança do AM em idosos.
Registro PROSPERO número CDR42024497640.

Palavras-chave: estimulantes do apetite; idoso; acetato de megestrol; caquexia; anorexia; revisão sistemática; metanálise.

INTRODUCTION

Unintentional weight loss in older adults – usually from age 65 years onward – is associated with multiple factors, with loss of appetite being most common.[1] Advanced age and acute and chronic comorbidities, which reduce food intake and increase catabolism, can quickly lead to malnutrition and, consequently, a state of cachexia.[2]

Cachexia is a metabolic syndrome resulting from loss of muscle mass with or without fat loss. Its diagnosis requires a loss of at least 5% of body weight in 6 to 12 months (or a body mass index [BMI] < 20 kg/m^2), as well as at least 3 of the following factors: reduced strength, fatigue, anorexia, low BMI, anemia, or low albumin.[2] Cachexia is associated with worse clinical outcomes, such as increased infection rates, prolonged hospitalization, and protracted convalescence after acute illness, as well as increased mortality and propensity for sarcopenia and/or frailty.[2]

The management of unintentional weight loss in older adults can be very challenging in clinical practice. Most evidence on the effectiveness of appetite stimulants is limited to specific populations and the outpatient setting.[3] In addition, older adults often have a number of comorbidities and chronic medical conditions, which can further complicate treatment.

Among the most studied appetite stimulants to improve weight gain is megestrol acetate (MA). In 1990, a large double-blind clinical trial demonstrated the benefit of MA in improving appetite in patients with incurable cancer (except breast and endometrial cancer).[4] For long-term use in patients with anorexia and cachexia related to heart disease, AIDS, or cancer, MA is the most commonly studied agent.[5]

MA is a synthetic progestin used to increase appetite and weight in various clinical settings.[6] It was first synthesized in England in 1963 and initially promoted as an oral contraceptive. In 1967, MA was tested for the treatment of breast and, subsequently, endometrial cancer. Since September 1993, it has been approved by the U.S. *Food and Drug Administration* (FDA) for the treatment of anorexia and cachexia in patients with AIDS.[7]

The mechanism whereby MA works as an appetite stimulant is still unknown, but it has been hypothesized to act on the metabolism and synthesis of pro-inflammatory cytokines[8] and in the destruction of cytokines such as tissue necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6.[5] Its structural similarity to glucocorticoids also explains the weight gain it causes, and the potential risk of adrenal insufficiency during and after discontinuation of prolonged therapy.[9]

There is a dearth of studies on pharmacological interventions older adults with unintentional weight loss and/or the anorexia-cachexia syndrome. Considering that MA is one of the most widely studied drugs in this context, the objective of the present study was to conduct a systematic review and meta-analysis of MA in older adults with unintentional weight loss and/or the anorexia-cachexia syndrome.

METHODS

This systematic review was conducted in strict adherence to the principles outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The detailed study protocol was preregistered on the International prospective register of systematic reviews (PROSPERO; accession number CDR42024497640), to ensure transparency and methodological rigor.

Search strategy

On December 26, 2023, we conducted a literature search, with no date restrictions, in Portuguese, English and Spanish. The search terms, based on the Medical Subject Headings (MeSH) controlled vocabulary, were: Megestrol [*Title/Abstract*] *AND Appetite* [*Title/Abstract*]. The search covered major databases, including *MEDLINE* (*via PubMed*), EMBASE, SCOPUS, *Web of Science*, and Latin American and Caribbean Literature in Health Sciences (LILACS). We also searched the gray literature and unpublished studies via the CAPES Digital Database of Theses and Dissertations, as well as conducted a *snowball* search strategy by examining all references and citations of the articles selected for this review.

Eligibility criteria

Article screening followed the PICOS strategy: population (older adults with weight loss); intervention (megestrol acetate for weight gain); comparison (other orexigenic drugs or placebo); outcome (improvement of appetite or weight gain); and study design (randomized controlled or quasi-experimental studies). The inclusion criteria were randomized controlled trials or quasi-experimental trials that compared MA versus placebo or versus other orexigenic drugs (such as mirtazapine, dexamethasone, or dronabinol). The target population comprised older adults (mean age ≥ 60 years) diagnosed with the anorexia-cachexia syndrome or unintentional weight loss. Cohort studies, case reports, abstracts, editorials, experimental research using animal models, and publications outside the field of medicine, aimed at the pediatric population, or reporting incongruent outcomes were excluded. Although the PROSPERO-registered protocol initially aimed to study unintentional weight loss, anorexia-cachexia

was reported in most studies as the diagnosis, and this term was then added to the study selection process.

Data collection and analysis

For a more efficient selection and organization of study titles and abstracts, we used the *Rayyan* (https://www.rayyan.ai/) open-source software suite. Two reviewers played an active role in the inclusion and exclusion phase by rigorously applying the eligibility criteria. The selected articles were read in full to allow an in-depth analysis of their relevance to the following research question: "are the studies published to date of sufficient quality to recommend the use of megestrol acetate in older adults with unintentional weight loss?" When the reviewers diverged regarding the inclusion of a study, a third reviewer performed the analysis.

In addition to the systematic review, a meta-analysis was carried out with eight studies that contained sufficient data for comparison. The meta-analysis was done in the *R* open-source software environment via the *RStudio* interface (version 2023.12.1), using the "*meta*" package and its specific functions for this purpose. The data were organized into vectors containing the effect estimates (MD), standard errors (or variances), and sample sizes of each study. The results of the analysis were stored in the *rvmeta* variable, with information on the number of studies included, the total number of observations, and effect estimates for the random-effects model. These results include the MDs for each model, with their corresponding 95% confidence intervals, z-values, and p-values. We used measures of heterogeneity, such as the tau-squared (τ^2), I-squared (I^2), and *Q* test, to assess consistency across studies.

To visualize the resulting data, forest plots and funnel plots were generated using the "*forest*" and "*funnel*" functions in R, respectively. These plots provide a visual representation of effect estimates and aid in the detection of publication bias. This analysis was conducted using appropriate methods to synthesize the available data and provide a quantitative estimate of the effect of MA as a weight gain promoter in older adults. The results were interpreted cautiously due to the limited number of studies available and the possibility of publication bias.

To explore the heterogeneity of the included studies, we visually inspected the funnel plots and carried out a detailed analysis of quantitative measures of heterogeneity. Visual inspection helped to verify the symmetry of the data, which is essential to assess whether the variability observed in the results could be attributed to factors unrelated to the effect of megestrol acetate. Measures of heterogeneity, such as the tau-squared (τ^2), tau (τ), I-squared (I^2), and *Q* test, were calculated to provide a more complete view of the variability among studies and strengthen our interpretation of the meta-analysis.

In the interest of transparency and to ensure the verifiability and reproducibility of our results, all relevant data have been made available as supplementary material on the Open Science Framework platform. The full record is available online at https://osf.io/k3mf8/?view_only=1561c41c840847a6ba22e72235502cad and has been assigned the Digital Object Identifier (DOI) 10.17605/OSF.IO/K3MF8.

In addition, we used the Physiotherapy Evidence Database (PEDro) scale to assess the methodological quality of the included studies.[10] The PEDro scale is a validated and widely recognized tool for quality assessment of randomized controlled clinical trials. It consists of 11 items that address aspects such as randomization, allocation concealment, blinding, statistical analysis, and participant follow-up. Each item is assigned a score from 0 to 10; higher total scores for a study denote greater methodological quality. The quality analysis of the studies was performed independently.

RESULTS

A total of 917 references were initially identified, with 297 duplicate articles and 136 articles excluded because they did not cover the topic of interest. After this step, the titles of the remaining 484 studies were independently analyzed by two reviewers. Of these, 377 were excluded as not meeting the inclusion criteria, leaving 107 studies, from which 29 randomized clinical trials were selected. A cohort study was identified in the grey literature and subsequently added. The study selection process is described in detail in the PRISMA flow diagram (Figure 1).[11]

Of the 30 studies selected for this review, all were published between 1990 and 2023, and carried out in a variety of countries: the United States (n = 11),[4,7-9,12-18] Australia (n = 2),[19,20] Spain (n = 2),[21,22] Italy (n = 6),[23-28] Brazil (n = 1),[29] China (n = 1),[30] Iran (n = 1),[31] Sweden (n = 1),[32] Scotland (n = 1),[33] Turkey (n = 1),[34] Taiwan (n = 1),[35] Germany (n = 1),[36] and Canada (n = 1).[37]

The studies were quite heterogeneous in terms of sample size, duration of intervention, methodology, and outcome assessment (Table 1). Regarding the populations of participants enrolled in the clinical trials selected for this review, the most studied population was patients undergoing cancer treatment[4,8,13-16,19,20,22-24,29,31-33,35-37] who developed the anorexia-cachexia syndrome, followed by two studies of patients diagnosed with obstructive pulmonary disease,[9,21] two studies

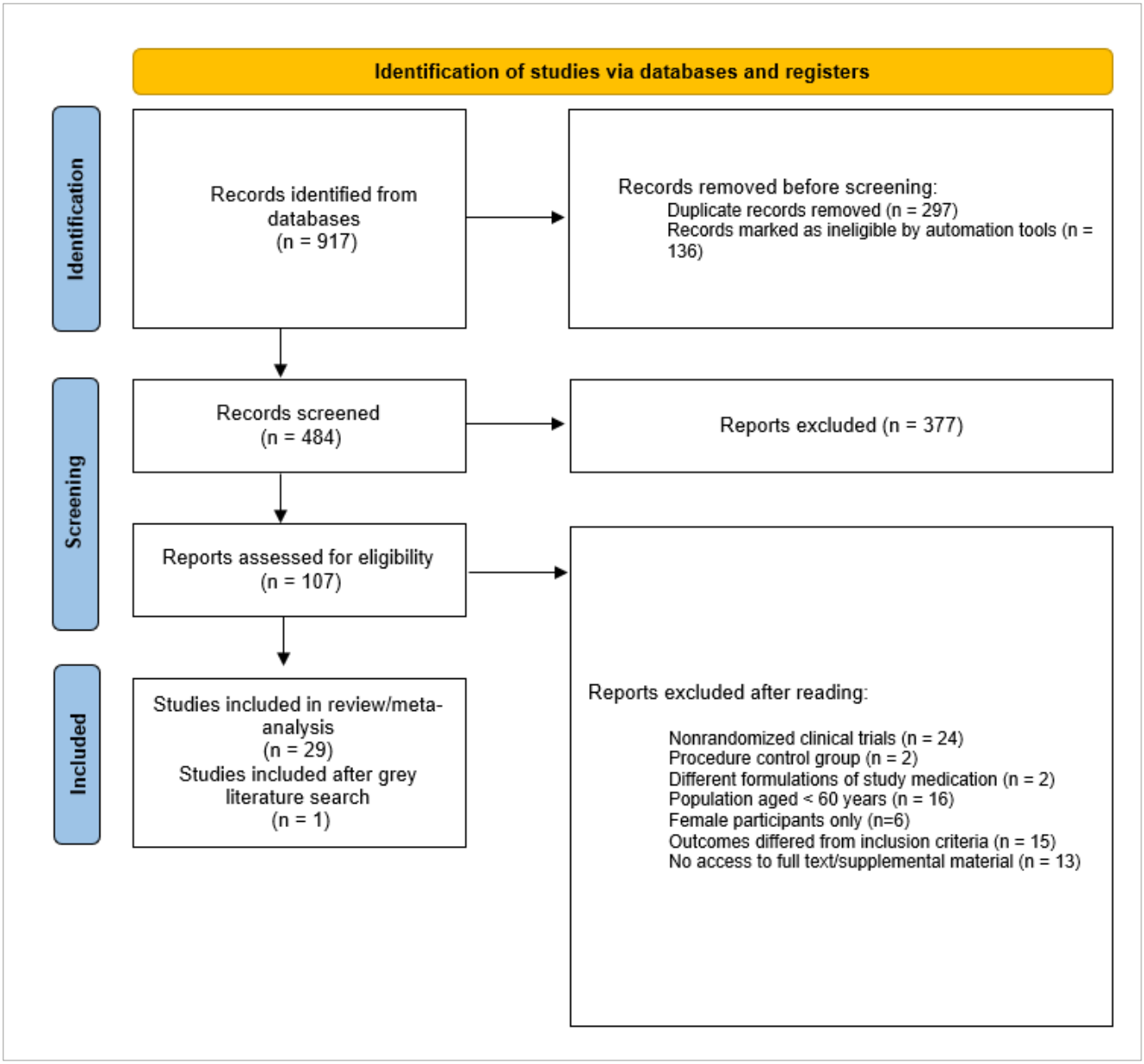

FIGURE 1. Flow diagram of study search and selection (adapted from PRISMA statement).[11]

TABLE 1. Assessment of methodological quality using the PEDro criteria.

Study	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	Σ
De Conno et al.[23]	1	1	1	0	1	1	1	0	1	1	1	9
Yeh et al.[7]	1	1	1	0	1	0	0	0	1	1	1	7
Weisberg et al.[9]	1	1	1	0	1	1	1	1	1	1	1	10
Mantovani et al.[28]	1	1	1	0	1	1	1	0	1	1	1	9
Mantovani et al.[27]	1	1	1	0	1	1	1	1	1	1	1	10
Madeddu et al.[26]	1	1	1	0	1	1	1	1	1	1	1	10
Macciò et al.[25]	1	1	1	0	1	1	1	0	1	1	1	9
Kanat et al.[34]	1	1	1	0	1	1	1	1	1	1	1	10

1: Yes; 2: No.

of patients with dialytic chronic kidney disease,[18,30] and one study each on institutionalized older adults[7] and acutely ill older adults.[17]

Methodological analysis using the PEDro Scale (Table 1) revealed substantial variation in methodological quality among the 8 studies selected for meta-analysis, reflecting a diversity of approaches and levels of scientific rigor.

Data from the eight studies included in the meta-analysis[7,9,23,25-28,34] comprised 592 observations (304 in the experimental group and 288 in the control group) (Figure 2). A random effects model was used to assess the overall impact of the intervention on weight gain. The data were not sufficient to evaluate the impact of MA on appetite. The model estimated a mean difference (MD) of 1.44 (95% CI [-0.30; 3.18]), with a z-value of 1.62 and a p-value of 0.104. Although the effect of the intervention was positive, it did not reach statistical significance at the conventional alpha level.

We also performed a detailed exploration of heterogeneity across studies. The estimated tau-squared (τ^2) value was 2.48, indicating moderate heterogeneity. The I-square (I^2) statistic suggested that 50% of the observed variability was due to true heterogeneity between studies, while Higgins' H was 1.41. The Q test produced a p-value of 0.051, indicating some evidence of heterogeneity between studies.

DISCUSSION

To the best of our knowledge, this is the first systematic review with meta-analysis to investigate the use of MA for weight gain in older adults. Although the studies selected for the systematic review suggest that patients with the anorexia-cachexia syndrome secondary to cancer may benefit from MA therapy, the meta-analysis of eight selected studies did not confirm this benefit (p = 0.104). According to studies, weight gain tends to be modest and does not amount to complete recovery of weight lost.

Although MA is often used to promote weight gain in older adults, the lack of significant benefits demonstrated by this meta-analysis may be explained by several reasons. First, the efficacy of megestrol acetate may be limited by individual factors, such as comorbidities or specific nutritional condition, which can influence the response to treatment. Furthermore, heterogeneity among the studies included in the meta-analysis, such as differences in dosage administered and treatment durations, may have masked any positive results, precluding observation of a consistent beneficial effect. Another point to be considered is the possibility that the weight gain promoted by MA is not necessarily sustainable or beneficial in the long term, and that the adverse effects associated with the drug may outweigh its possible benefits.

Most likely, weight gains reported in single studies are significant when evaluated separately but become less significant when added to the meta-analysis. For example, a randomized, double-blind, placebo-controlled clinical trial of a 12-week intervention in 51 institutionalized patients (mean age 76 ± 1.4 years) demonstrated good efficacy of MA 800 mg in the treatment of malnutrition.[9] Patients in this study showed significant improvement in appetite (p = 0.004), but an initial weight gain of only 1.05 (± 1) kg. Moreover, it is worth noting that, in this study, 38% of patients did not gain weight at all while on MA.[7]

On the other hand, some studies reported more robust weight gains, such as three studies by Loprinzi et al., who evaluated weight gain while on MA therapy in cancer patients with the anorexia-cachexia syndrome. The first study, carried out in 1990, demonstrated weight gain (at least 6.8 kg) in 67 (16%) older adults (mean age 69 years) receiving MA 800 mg/day compared to placebo (p = 0.003).[4] In a later study, weight gain of at least 10% of baseline weight was

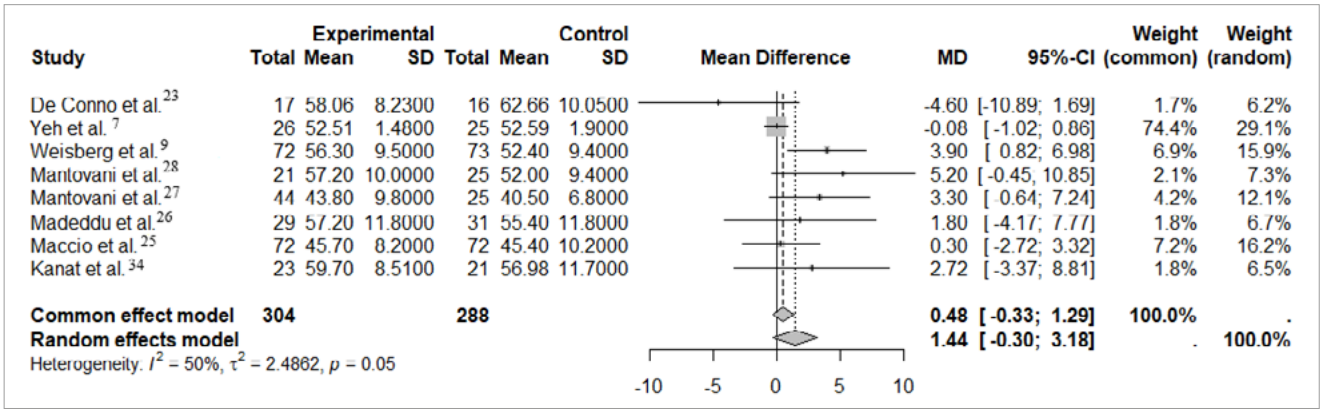

FIGURE 2. Forest plot of megestrol acetate *versus* control for outcome weight gain.

observed in 275 outpatients with cancer, with no significant difference between the doses of MA administered (160 mg, 480 mg, 800 mg, and 1280 mg) (p = 0.31).[13] These positive results were confirmed in a third study with 348 participants (mean age 67 years) who received MA 800 mg versus dexamethasone 0.75 mg or fluoxymesterone 10 mg, with a mean weight gain of 2.5 kg for patients in the MA arm.[14]

Some studies selected in this review compared MA with other appetite stimulants and/or weight gain promoters, such as corticosteroids and mirtazapine (an atypical tetracyclic antidepressant). The literature available for this review does not allow us to conclude in favor of any superiority of MA compared to corticosteroids in terms of weight gain or improvement in appetite. A study carried out with patients in palliative care for advanced malignancy (mean age 71.4 years) did not show superiority in weight gain with MA 480 mg/day versus dexamethasone 4 mg/day or placebo after an average 9 days of treatment (p = 0.241), nor in appetite as assessed by questionnaires (p = 0.067).[20] There was also no superiority of MA over dexamethasone for weight maintenance (p = 0.241). These findings are similar to those reported previously, in which MA 800 mg/day was slightly superior to dexamethasone 0.75 mg/day for appetite stimulation and weight gain (p = 0.08), but the difference was not statistically significant. However, MA was associated with a higher incidence of thromboembolic adverse events than dexamethasone (5% *versus* 1%), although again there was no statistically significant difference.

Mirtazapine, a drug widely used in geriatric practice, was evaluated in two studies selected in this review; both suggested that MA was superior to mirtazapine as an appetite stimulant and weight-gain promoter. One study compared MA and mirtazapine for management of the anorexia-cachexia syndrome in patients with cancer (mean age 65.8 ± 8.4 years) and found benefits from MA (160 mg/day) in terms of appetite stimulation (p = 0.007) and weight gain (p = 0.040). As in other studies, only half of the participants maintained weight gain with either medication, with no statistically significant difference between groups after 8 weeks of follow-up (p = 0.166).[29]

Mortality should be considered an important outcome in studies of weight gain, but only two studies selected for this review evaluated the impact of MA on mortality and neither found promising results. Conversely, a cohort study of institutionalized frail older adults with weight loss (>5% in 3 months or >10% in 6 months) evaluated the effect of MA on weight and mortality, and the results were discouraging. There was no weight gain among those receiving MA, but survival was significantly shorter in this group: 23.9 months (95%CI 20.2 – 27.5) versus 31.2 months (95%CI 27.8 – 35.9) in the control group (p < 0.001).[12] The retrospective design and lack of randomization of this study may justify the negative findings of the MA arm, since more frail individuals (mostly with dementia) were probably selected for the treatment group. Another study that compared MA to mirtazapine for appetite stimulation in older adults with cancer did not identify statistical or clinical differences in mortality (12% versus 7%, respectively; p = 0.23).[15]

An important aspect regarding MA therapy concerns the recommended dose. The doses used in the studies included herein ranged from 160 mg to 1280 mg. Overall, the selected studies showed benefits with MA therapy for appetite stimulation and weight gain regardless of dose, with a trend toward a positive dose-dependent effect on appetite stimulation starting at 480 mg; conversely, for weight gain, effect appeared to plateau at 800 mg. The aforementioned studies provide interesting insights into the efficacy of MA at different doses. Although some studies did not find statistically significant differences between MA doses in relation to weight gain, there was consistent evidence of improvement in appetite in many of the studies reviewed and a trend toward progressive weight gain with doses starting at 480 mg. In addition to efficacy, potential adverse effects and the cost of treatment—which can be limiting factors in therapeutic decision-making—should also be analyzed.

Regarding the safety profile of MA, despite the heterogeneity of the studies, there was no significant increase in serious adverse events compared to the other drugs studied (mirtazapine, dexamethasone, prednisolone, prednisone, dronabinol, celecoxib, and ibuprofen).[14,15,20,29,31] Gavioli et al. found no significant differences in mortality between patients taking MA and those on mirtazapine.[15]

This review has limitations that warrant attention. Most of the selected studies had small sample sizes, which limits the statistical power of any tests. Although the average age of patients in the included studies was > 60 years, there were many younger patients, which precluded extrapolation of results to the oldest old. Another very relevant factor was the wide range of underlying diseases implicated in weight loss, which included cancer, chronic obstructive pulmonary disease (COPD), and chronic renal failure (CRF), which have different pathophysiologies that can interfere with the response to MA. Finally, the moderate heterogeneity observed between studies, which may impact the interpretation of results and the robustness of conclusions, must be considered.

CONCLUSION

Although the studies selected for this review demonstrated that MA could improve appetite and modestly increase weight compared to placebo or other substances, a meta-analysis of eight selected studies showed no statistically significant difference. The particular characteristics of each patient, as well as the underlying cause of the anorexia-cachexia syndrome, must be carefully considered when deciding whether to treat unintentional weight loss with MA in older adults. Future studies with more robust designs are essential to evaluate the actual effectiveness of this drug in the older population.

DECLARATIONS

Conflict of interest
The authors report no conflicts of interest.
Einstein Francisco Camargos currently serves as one of the journal's executive editors. The editor-in-chief led the masked peer review process and invited ad hoc reviewers to preserve its transparency and integrity.

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Author contributions
Larissa de Freitas do Lago-Abreu: conceptualization, writing – original draft. Raphael Lopes Olegário: writing – review & editing. Luciana Lilian Louzada Martini: writing – review & editing. Einstein Francisco Camargos: conceptualization, supervision, writing – review & editing.

Ethical approval and informed consent
This study was preregistered on the International prospective register of systematic reviews (PROSPERO) with accession number CDR42024497640.

Data availability statement
Data will be made available on request.

Reporting standards guidelines
This study was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

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