ORIGINAL ARTICLE

# Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome – a systematic review and meta-analysis

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**KEY WORDS**

anorexia-cachexia syndrome, cachexia, cancer, megestrol acetate, neoplasm

**ABSTRACT**

**INTRODUCTION** Anorexia-cachexia syndrome (ACS) often occurs in patients with advanced cancer.
**OBJECTIVES** To review the effect of megestrol acetate (MA) in patients with ACS.
**PATIENTS AND METHODS** To identify eligible studies, systematic review by Lopez et al. (2004) was used, electronic databases (MEDLINE, EMBASE and CENTRAL) were searched and reference lists of included studies were reviewed. The studies were included in the review if they were randomized, enrolled patients with non-hormone-sensitive cancer and ACS and assessed the effects of MA compared with placebo, other drugs or different doses of MA.
**RESULTS** The study population is characterized by high mortality and progressive weight loss irrespective of the treatment. Compared to placebo, the effect of MA on survival is similar, but MA increases appetite (*number needed to treat* [NNT]: 3) and leads to weight gain (NNT: 8) in more patients. The data on other aspects of the quality of life are limited. The comparison of MA and glucocorticosteroids showed no statistical difference in their effect on appetite and weight.
**CONCLUSIONS** Compared to placebo, MA reduces the symptoms of ACS, with no effect on survival. The beneficial effect of MA on the overall quality of life has not been confirmed. In identified studies the effect of MA and glucocorticosteroids on anorexia and cachexia is similar. The estimation of the treatment utility in ACS depends on the weight attributed to discomfort caused by symptoms, adverse effects of the drugs and the treatment cost. Because of the low quality of the included studies a new randomized controlled trial is needed for valid assessment of the effects of MA.

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**INTRODUCTION** Megestrol acetate (MA) is a synthetic hormone (progestogen) used for the therapy of hormone-dependent cancer, mainly endometrial cancer and less commonly breast cancer. This drug is also used for symptom relief in anorexia-cachexia syndrome (ACS) patients.[1] This syndrome that occurs among other things in the advanced stage of cancer or in association with HIV infection, is characterized by weight and appetite loss, decline in muscle and adipose tissue mass, worsening of the performance status and decrease in the quality of life level (well-being).[2]

It is not easy to define cancer malnutrition. Biochemical, anthropometric and immunologic parameters are used for the diagnosis. The most important biochemical test to diagnose malnutrition is serum albumin levels, and to monitor nutritional status changes levels of proteins with shorter half-lives (prealbumin and transferrin). Among anthropometric tests, the unintended weight loss of >10% of the predicted value during the preceding 3 months is a very good index. Other parameters are: arm circumference (normal range: men >23 cm, women >22 cm) indicating the muscle tissue mass and skin fold thickness over the triceps muscle (normal range: men >10 mm, women >13 mm), an indicator of fat reserves, and the determination of total intracellular potassium using the K42

**TABLE 1** Description of studies included in the systematic review

| Study (author, year) | Population | Intervention | Dose (mg/dl) | Number of participants in groups | Study duration (weeks) |
|---|---|---|---|---|---|
| Beller 1997 [8] | Advanced hormone-insensitive cancer, weight loss | MA | 480 | 81 | 12 |
| | | MA | 160 | 80 | |
| | | Placebo | 0 | 79 | |
| Bruera 1990 [6], cross-over trial | Advanced hormone-insensitive cancer, weight loss | MA | 480 | 31 + 9 | 1 |
| | | Placebo | 0 | 31 + 9 | |
| Bruera 1998 [27], cross-over trial | Advanced hormone-insensitive cancer, (local recurrence or metastases), anorexia | MA | 480 | 84 | 1.5 |
| | | Placebo | 0 | 84 | |
| Chen 1997 [9] | Head or neck cancer, full course of radiotherapy, no ACS (prevention only) | MA | 160 | 48 | 8 |
| | | Cisapride | 15 | 41 | |
| | | Placebo | 0 | 40 | |
| De Conno 1998 [33] | Advanced hormone-insensitive cancer, diminished appetite or anorexia | MA | 320 | 17 + 4 | 2 |
| | | Placebo | 0 | 16 + 5 | |
| Erkurt 2000 [32] | Confirmed cancer, weight loss, progressive anorexia | MA | 480 | 50 | 12 |
| | | Placebo | 0 | 50 | |
| Farmer 2005 [18] (abstract) | Lung, head or neck cancer, treated with radiotherapy | MA | 800 | 20 | 17–19 |
| | | Placebo | 0 | 18 | |
| Feliu 1992 [30] | Advanced hormone-insensitive cancer, only palliative care, weight loss >10% or anorexia | MA | 240 | 76 | ≥8 |
| | | Placebo | 0 | 74 | |
| Fietkau 1997 [10] | Histologically verified head or neck cancer, radiotherapy, weight loss >5% in 6 weeks or >10% in 6 months | MA | 160 | 31 | 12 |
| | | Placebo | 0 | 30 | |
| Gambardella 1998 [34] (abstract) | Hormone-insensitive cancer, elderly patients, weight loss >7 kg in last 3 months | MA | 320 | No data | 12 |
| | | Placebo | 0 | | |
| Gebbia 1996 [21] | Advanced hormone-insensitive cancer, irresponsive to chemotherapy. | MA | 320 | 60 | 4 |
| | | MA | 160 | 62 | |
| Giacosa 1997 [28] | Advanced cancer, weight loss >10% or daily calorie intake of <20 kcal/kg/d | MA + dietary counseling; | 320 | 10 | 4 |
| | | only dietary counseling | 0 | 8 | |
| Heckmayr 1992 [23] | Advanced lung cancer | MA | 480 | 33 | 12 |
| | | MA | 160 | 33 | |
| Jatoi 2002 [15] | Advanced hormone-insensitive, incurable cancer, weight loss >2,3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician's opinion, ECOG performance status 0–2 | MA + placebo | 800 + 0 | 159 | >4 |
| | | Dronabinol + placebo | 5 + 0 | 152 + 2 | |
| | | Dronabinol + MA | 5 + 800 | 158 | |
| Jatoi 2004 [14] | Advanced hormone-insensitive, incurable cancer, weight loss >2,3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician's opinion, ECOG performance status 0–2 | MA + placebo | 600 | 140 | 12 |
| | | Eicosapentaenoic acid + placebo | 2180 | 141 | |
| | | MA + eicosapentaenoic acid | 600 + 2180 | 140 | |
| Lai 1994 [11] | Pelvis radiotherapy, anorexia during radiotherapy, no prior treatment for anorexia | MA | 160 | 20 | 3 |
| | | Prednisolone | 30 | 19 | |
| | | Placebo | 0 | 19 | |
| Loprinzi 1990 [16] | Advanced, incurable cancer (other than breast or endometrial cancer), weight loss >2,3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician's opinion | MA | 800 | 67 + 1 | 10 |
| | | Placebo | 0 | 66 + 1 | |

| Study (author, year) | Population | Intervention | Dose (mg/dl) | Number of participants in groups | Study duration (weeks) |
|---|---|---|---|---|---|
| Loprinzi 1994 [26] | Advanced hormone-insensitive, incurable cancer, weight loss >2,3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg | MA | 160 | 88 | 10 |
| | | MA | 480 | 86 | |
| | | MA | 800 | 85 | |
| | | MA | 1280 | 83 | |
| Loprinzi 1999 [29] | Advanced hormone-insensitive, incurable cancer, weight loss >2,3 kg (5 lbs) in 2 months or daily calorie intake of <20 kcal/kg, weight loss perceived by the patient as a problem, weight gain potentially beneficial for the patient in the physician's opinion, ECOG performance status 0–2 | MA | 800 | 158 + 7 | 4 |
| | | Dexamethasone | 3 | 159 + 7 | |
| | | Fluoxymesterone | 20 | 158 + 7 | |
| Mc Millan 1994 [31] | Histologically verified cancer of the gastrointestinal tract, only palliative therapy, weight loss of >5% | MA | 480 | 12 | 12 |
| | | Placebo | 0 | 14 | |
| McQuellon 2002 [17] | Nasopharyngeal, oral, pharyngeal or lung cancer, radiotherapy, without weight loss, ECOG performance status 0–2 | MA | 800 | 28 | 12 |
| | | Placebo | 0 | 28 | |
| Pardo 2003 [24] (abstract) | Nonmetastatic lung cancer, radiotherapy, anorexia | MA | 600 | 66 | 4 |
| | | MA | 320 | 64 | |
| Rowland 1996 [7] | small-cell extensive stage lung cancer, ECOG performance status 0–2, weight loss of >5% in 6 weeks or >10% in 6 months | MA | 800 | 122 | 104 |
| | | Placebo | 0 | 121 | |
| Sancho Cuesta 1993 (abstract) [20] | Advanced cancer, palliative treatment, anorexia, weight loss | MA | 160 | 50 | 12 |
| | | MA | 320 | 50 | |
| Schmoll 1992 [25] | Advanced stage cancer, palliative treatment, weight loss of >5% | MA | 480 | 34 | 8 |
| | | MA | 960 | 29 | |
| | | Placebo | 0 | 28 | |
| Tchekmedyian 1992 [19] | Advanced hormone-insensitive cancer, weight loss of >5%, anorexia | MA | 1600 | 49 | 24 |
| | | Placebo | 0 | 40 | |
| Ulutin 2002 [22] | Advanced non-*small cell* lung cancer, loss of >10% weight in 6 months | MA | 160 | 59 | 12 |
| | | MA | 320 | 60 | |
| Vadell 1998 [12] | Incurable cancer, weight loss of >5% | MA | 480 | 49 | 12 |
| | | MA | 160 | 50 | |
| | | Placebo | 0 | 51 | |
| Westman 1999 [35] | Hormone-insensitive cancer, palliative therapy | MA | 320 | 128 | 12 |
| | | Placebo | 0 | 127 | |
| Zecca 1995 [13] (abstract) | Advanced hormone-insensitive cancer, anorexia | MA | 320 | 16 | 2 |
| | | Placebo | 0 | 17 | |

isotope, which enables body cell mass assessment. Considering immunological parameters the lymphocyte count (decreased in malnutrition) is most commonly used in practice.[3] In the diagnostic process these above mentioned criteria for ACS are often neglected, which is one of the factors responsible for MA abuse in Poland.

The MA is commonly used in Poland, which is also reflected through its high rank on the list of reimbursed expenses. For ACS in the course of cancer treatment, the form of a suspension and for hormone-dependent cancer the tablets are being reimbursed.

## PATIENTS AND METHODS

The aim of this systematic review with a meta-analysis was the assessment of clinical effects of MA use in advanced stage cancer patients with ACS.

**The study source** For the identification of appropriate studies by systematic review the Lopez et al. was used[4] and the MEDLINE (2002–2007), EMBASE (2002–2007) and CENTRAL (Cochrane Library; Issue 3, 2007) bibliographic databases were searched. Reference lists of the studies included in the analysis have also been reviewed.

The following key words were employed for the search strategy: neoplasm, cancer, cachexia, anorexia, megestrol acetate. There were no language restrictions on publications. Conference abstracts were also analyzed.

**Study selection for analysis** The following criteria for study inclusion in the analysis were applied:

**1** randomization

**2** diagnosis of advanced stage cancer (with the exclusion of hormone-dependent cancer) and ACS

**3** intervention: MA in comparison with placebo or other drugs used in practice or in clinical studies in ACS (glucocorticosteroids, cisaprid, dronabinol, eicosapentaenoic acid, fluoxymesterone) or MA in various doses

**4** outcomes: survival rate, weight change, performance status (Karnofsky scale, ECOG scale), selected quality of life parameters (appetite, nausea, pain, fatigue, depression, well-being, mood).

**Methods of review – study quality assessment** Identified studies have been initially assessed and selected on the basis of their eligibility for the reviewed topic. Then the validity of selected studies was assessed considering randomization, the intention to treat analysis and the completeness of follow-up.[5]

The following persons were responsible for defining the clinical question, outcome selection, and assessment of clinical aspects of results: Roman Jaeschke, Maciej Krzakowski and Wiktoria Leśniak.

Available evidence review, methodology assessment, data identification, and their entering into the Review Manager was done independently by 2 persons (Wiktoria Leśniak and Małgorzata Bała or Roman Jaeschke).

**Statistical analysis** The results of primary studies were pooled by meta-analysis using the DerSimonian and Laird method, employing the Review Manager 4.2.10 program. The statistical significance of overall effects was calculated with the use of the Z test, and the homogeneity of results between studies was assessed with the $\chi^2$ and $I^2$ tests.

The results were summarized using the method developed by the GRADE group, which works on the grading of recommendations in clinical practice guidelines.

## RESULTS

**Description of included studies** Thirty studies have been included in the review, 5 of which were conference abstracts. The studies' description (population description, drugs compared and their doses, the number of participants, study duration) are shown in TABLE 1 (available in the electronic version of the article). All studies included advanced stage cancer patients with the exclusion of hormone-dependent cancer; most of the studies included patients suffering from various cancers, in several studies lung cancer was the inclusion criterion, in several others head and neck cancer.

The shortest duration of follow-up was 1 week[6], the longest 2 years[7]; in the remaining studies the median or mean follow-up period ranged from 2 to 24 weeks.

In the studies in which MA was compared with other drugs or a placebo, the doses of MA ranged from 160 mg/d [8-12] through 320 mg/d [13] up to over 480 mg/d (600 mg/d [14]); 800 mg/d [7,15-18]; 1600 mg/d [19]). In the other studies the daily dose ranged 240–480 mg.

In several studies various MA daily doses were compared (160 mg *vs* 320 mg [20-22], 160 mg *vs* 480 mg [8,12,23], 320 mg *vs* 600 mg [24], 480 mg *vs* 960 mg [25], 160 mg *vs* 480 mg *vs* 800 mg *vs* 1280 mg [26]).

Two studies with a short duration of drug administration (up to 10 days) were performed as cross-over trials[6,27], the remaining trials were parallel trials.

The majority of studies were performed with the use of placebo, or with blinding of the alternative intervention in the control group; with the exception of the Giacos et al. study [28] (lack of placebo, lack of blinding) and the Loprinzi et al.[29] (MA *vs* dexamethasone *vs* fluoxymesterone).

The methodological quality of studies included in the analysis:

**1** the majority of the studies were placebo controlled and blinded

**2** the randomization process has not been described in most cases

**3** patients who died within the follow-up period were excluded from the analysis in several studies; in the majority of studies the analysis did not include a large number of patients (30–40%), mainly because of their withdrawal

**4** in the present analysis, the proportion of patients in whom a certain outcome occurred was calculated, as far as possible, in relation to the number of patients randomized (intention-to-treat analysis); in some original studies the per-protocol analysis was used in which only patients who completed the study were included

**5** in several studies the authors did not show the numerical data regarding some predefined outcomes, or presented data were incomplete, which made it impossible to use them in the present meta-analysis; publication bias may be suspected, which lowers the validity of this meta-analysis

**6** despite the methodological limitations, studies included in the analysis represent the best available evidence on the effects of MA use in ACS associated with advanced cancer.

**Meta-analysis** The estimated effect size for various outcomes is shown in TABLE 2.

**1** In comparison with placebo, MA administration:

**A** resulted in any weight gain in (a meta-analysis of studies with different weight gain definitions) a statistically significant higher percentage of patients (TABLE 2)[7,10-12,16,19,25,30,31] (FIGURE 1)

**B** resulted in a weight gain of ≥5%[12,16,31] and weight gain of ≥10%[7,16,30-31] in a non significantly higher percentage of patients (TABLE 2); heterogeneity for the above mentioned results has not been demonstrated

**C** resulted in appetite improvement in a greater percentage of patients (TABLE 2)[11,16,25,30,32]; lack of homogeneity of results for this comparison has been demonstrated (FIGURE 2)

**D** in studies in which a 100-milimeter visual scale was used for appetite assessment[6,27,28] the mean difference between groups was 14 mm (95% CI 7–21); a difference of this range for a certain patient is regarded as a clinically significant one, when measuring symptoms and the quality of life. In the meta-analysis of all available studies with an assessment of appetite change from baseline values[6,9,27,28], standardized mean difference (SMD) expressed in standard deviation (SD) units was 0.44 (95% CI 0.20–0.68), which corresponds to medium effect size in the whole group of patients. It may also correspond to e.g. a large effect size of treatment in every other patient

**E** was associated with a trend toward a lower risk of patients' performance status worsening (according to the Karnofsky or ECOG scales) [12,30,32]

**F** did not influence the 1-year survival rate (TABLE 2).

**2** Among studies comparing MA with other interventions or placebo, the overall quality of life was measured with the use of different scales in 14 studies.[7,8,10,12,14,15,17-19,27,29,33-35] Except for 2 studies[27,33] the authors did not give any numerical data necessary to perform the meta-analysis. However, in 13 of 14 studies, there was no significant difference between patients receiving MA and those taking placebo, dronabinol, eicosapentaenoic acid or glucocorticosteroids.

In 2 cross-over studies[6,27] the specific aspects of the quality of life were also measured. With the use of a 100-millimetrevisual scale (a difference of about 7 millimetre may be considered as clinically important), comparing MA with placebo, the following have been demonstrated:

**A** a decrease of nausea of c. 6 millimetre (95% CI 1–11)

**B** lack of a statistically significant difference in pain perception (an increase of 9 millimetre [95% CI: from a decrease of 4 up to an increase of 22])

**C** lack of a statistically significant difference in intensity of depression symptoms (a decrease of 5 millimetre [95% CI: from a decrease of 15 up to an increase of 6])

**D** an improvement in the overall well-being (an improvement of 8 millimetre [95% CI 1–15]).

**3** On the basis of results of single studies it has been demonstrated that MA use in comparison with:

**A** cisapride[9] was associated with a more beneficial effect on weight gain and with no difference in the effect on appetite

**B** dronabinol[14] and in comparison with eicosapentaenoic acid[15] had a more beneficial effect on a weight gain and appetite improvement

**C** fluoxymesterone[29] was associated with a beneficial trend toward MA regarding the rate of patients with appetite improvement and weight gain.

**4** Comparing MA with z glucocorticosteroids (prednisolone 30 mg/d[11], dexamethasone 3 mg/d[29]) the following have been demonstrated (TABLE 2):

**A** a comparable rate of patients with an appetite improvement

**B** a comparable rate of patients with weight gain.

**5** In several studies with longer follow up, thromboembolic syndromes occurred more often in patients using MA (5% *vs* 1%[29], 9 *vs* 2%[7]).

**6** In studies with available data, the probability of the one-year survival was less than 25%. In several studies[7,8,29,30,35] survival was assessed and no differences were demonstrated between those using MA and placebo or glucocorticosteroids[29]. The numerical data regarding MA influence on the one-year survival in comparison with placebo, was reported in 2 studies (TABLE 2)[7,35].

**7** The appetite improving and weight increasing effect of MA was noticeable after a few weeks of its administration.[6,9,27,32,33]

**8** A direct comparison of the effect of a daily dose of 160 mg MA and the dose of 320––480 mg[12,20-23,26] demonstrated a significantly beneficial effect of a higher dose on weight gain (relative risk [RR] 0.73, 95% CI 0.57–0.94) and lack of a significant effect on appetite (relative risk [RR] 0.93, 95% CI 0.79–1.08). The comparison of a 480 mg dose with 800–960 doses[25,26] showed similar results: a beneficial trend towards weight gain with a higher dose (RR 0.77, 95% CI 0.55–1.09) and lack of the effect on appetite (outcome assessed only in 1 study[25]).

**9** An assessment of the quality of data on the effects of MA administration in ACS and a summary of the results are shown in TABLE 2 according to the GRADE system.[36]

**10** The diversity of studies included in the meta-analysis, regarding study populations and interventions, does not allow the isolation of patients with the greatest chance of benefiting from MA treatment.

**DISCUSSION** The presented systematic review and the attempt at summarizing quantitatively the results did not bring unexpected conclusions. Similarly to the previously published meta-analyses[4,37,38], an appetite improvement shown in absolute values (number needed to treat [NNT] c. 3–4) and weight gain (NNT c. 8) can be noticed. In the previously published meta-analyses comparable results regarding weight gain (RB 2.16, 95% CI 1.45–3.21 and relative benefit [RB] 2.14, 95% CI 1.41–3.24)[4,38] and appetite improvement (RB 2.33; 95% CI 1.52–3.59 and RB 3.03; 95% CI 1.83–5.01) were obtained[4,38]. For appetite improvement, a difference in favor of MA, shown in the present publication and in the Berenstein and Ortiz review, results from the inclusion of an additional study.[32]

**TABLE 2** Data quality assessment and results summary according to GRADE system

| Data quality assessment | | | | | | Results summary | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patient number | | Effect | | | |
| Nº of studies | Type of studies | Quality of studies | Results consistency | Possibility of a clinical reference of the results | Other factors | Megestrol | | Relative (95% CI) | Absolute (95% CI) | Quality | Weight |
| Weight gain (any weight gain, follow up time mean c. 3 months). MA vs. placebo | | | | | | | | | | | |
| 9 | Randomized studies | No serious limitations | Without serious discrepancy | Doubts (–1)[1] | Dose-effect relation (+1) | 179/547 (32.7%) | 83/447 (18.6%) | RR 1.71 (1.24–2.36) | 140/1000 (90–190) | ⊕⊕⊕⊕ High | 6 |
| Weight gain of at least 5%. MA vs. placebo | | | | | | | | | | | |
| 3 | Randomized studies | No serious limitations | Without serious discrepancy | Doubts (–1)[1] | None | 38/187 (20.3%) | 16/136 (11.8%) | RR 1.65 (0.94–2.87) | 80/1000 (0–160) | ⊕⊕⊕○ Mediocre | 6 |
| Weight gain of at least 10%. MA vs. placebo | | | | | | | | | | | |
| 4 | Randomized studies | No serious limitations | Serious discrepancy (–1) | No doubts | None | 45/286 (15.7%) | 10/280 (3.6%) | RR 3.83 (0.73–20.18) | 100/1000 (20–180) | ⊕⊕⊕○ Mediocre | 6 |
| One-year survival MA vs. placebo | | | | | | | | | | | |
| 2 | Randomized studies | No serious limitations | Without serious discrepancy | No doubts | High probability of publication selectivity (–1) | 55/250 (22%) | 53/248 (21.4%) | RR 1.02 (0.73–1.42) | 10/1000 (–60–80) | ⊕⊕⊕○ Mediocre | 8 |
| Appetite improvement. MA vs. placebo | | | | | | | | | | | |
| 5 | Randomized studies | No serious limitations | Serious discrepancy (–1) | No doubts | Strong intervention-effect relation (+1) | 170/301 (56.5%) | 47/262 (17.9%) | RR 3.00[2] (1.86–4.84) | 380/1000 (160–610) | ⊕⊕⊕⊕ High | 8 |
| Physical status worsening (ECOG, Karnofsky). MA vs. placebo | | | | | | | | | | | |
| 3 | Randomized studies | No serious limitations | Serious discrepancy (–1)[3] | No doubts | High probability of publication selectivity (–1) | 103/225 (45.8%) | 107/175 (61.1%) | RR 0.65 (0.39–1.08) | 190/1000 (0–380) | ⊕⊕○○ Poor | 8 |
| Absolute weight gain in 1–4 weeks (Higher result indicates a more beneficial effect). MA vs. placebo | | | | | | | | | | | |
| 6 | Randomized studies | No serious limitations | Serious discrepancy (–1)[3] | Doubts (–1)[1] | Strong intervention-effect relation (+1) | | | – | WMD 1.98 kg[4] (0.49–3.48) | ⊕⊕⊕○ Mediocre | 6 |
| Absolute weight gain in 8–12 weeks (higher result indicates a more beneficial effect). MA vs. placebo | | | | | | | | | | | |
| 6 | Randomized studies | No serious limitations | Serious discrepancy (–1)[3] | Doubts (–1)[1] | Strong intervention-effect relation (+1) | | | – | WMD 2.91 kg[5] (–0.06–5.89) | ⊕⊕⊕○ Mediocre | 6 |
| Weight gain – 160 mg/d MA vs. placebo | | | | | | | | | | | |
| 3 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1)[1] | None | 34/101 (33.7%) | 22/100 (22%) | RR 1.51 (0.94–2.41) | 120/1000 (–20–260) | ⊕⊕⊕○ Mediocre | 6 |

| Data quality assessment | | | | | | Results summary | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patient number | | Effect | | | |
| Nº of studies | Type of studies | Quality of studies | Results consistency | Possibility of a clinical reference of the results | Other factors | Megestrol | | Relative (95% CI) | Absolute (95% CI) | Quality | Weight |
| Weight gain – 160 or 240 mg/d MA vs. placebo | | | | | | | | | | | |
| 4 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1)[1] | None | 55/177 (31.1%) | 27/174 (15.5%) | RR 1.99 (1.09–3.63) | 160/1000 (60–260) | ⊕⊕⊕○ Mediocre | 6 |
| Weight gain – all doses vs. placebo | | | | | | | | | | | |
| 9 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1)[1] | None | 179/547 (32.7%) | 83/447 (18.6%) | RR 1.71 (1.24–2.36) | 140/1000 (90–190) | ⊕⊕⊕○ Mediocre | 8 |
| Weight gain – MA 160 mg/d vs. 320 or 480 mg/d | | | | | | | | | | | |
| 6 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1) | None | 127/328 (38.7%) | 167/321 (52%) | RR 0.73 (0.57–0.94) | 140/1000 (–250–40) | ⊕⊕⊕○ Mediocre | 6[6] |
| Weight gain – MA 160 mg/d vs. 800 mg/d | | | | | | | | | | | |
| 1 | Randomized studies | No serious limitations | One study | Doubts (–1)[1] | Too little evidence (1) | 30/88 (34.1%) | 37/85 (43.5%) | RR 0.78 (0.54–1.14) | 90/1000 (–250–50) | ⊕⊕○○ Poor | 6 |
| Weight gain – MA 480 mg/d vs. 800–960 mg/d | | | | | | | | | | | |
| 2 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1)[1] | None | 37/120 (30.8%) | 46/114 (40.4%) | RR 0.77 (0.55–1.09) | 90/1000 (–210–30) | ⊕⊕⊕○ Mediocre | 6 |
| Appetite improvement – MA 160 mg/d vs. placebo | | | | | | | | | | | |
| 1 | Randomized studies | No serious limitations | One study | No doubts | Too little evidence (–1) | 11/20 (55%) | 4/19 (21.1%) | RR 2.61 (1.0–6.8) | 340/1000 (50–620) | ⊕⊕⊕○ Mediocre | 8 |
| Appetite improvement – MA 160 or 240 mg/d vs. placebo | | | | | | | | | | | |
| 2 | Randomized studies | No serious limitations | No serious discrepancy | No doubts | Strong intervention-effect relation ( + 1) | 49/96 (51%) | 14/93 (15.1%) | RR 3.34 (1.99–5.61 | 360/1000 (240–480) | ⊕⊕⊕⊕ High | 8 |
| Appetite improvement – all doses vs. placebo | | | | | | | | | | | |
| 5 | Randomized studies | No serious limitations | Serious discrepancy (–1)[3] | No doubts | Strong intervention-effect relation ( + 1) | 110/227 (48.5%) | 36/188 (19.1%) | RR 3.07 (1.72–5.46) | 380/1000 (160–610) | ⊕⊕⊕⊕ High | 8 |
| Appetite improvement – MA 160 mg/d vs. 360 or 480 mg/d | | | | | | | | | | | |
| 3 | Randomized studies | No serious limitations | No serious discrepancy | No doubts | None | 97/154 (63%) | 106/153 (69.3%) | RR 0.93 (0.79–1.08) | 60/1000 (–160–50) | ⊕⊕⊕⊕ High | 8 |

| Data quality assessment | | | | | | Results summary | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patient number | Effect | | Quality | |
| Nº of studies | Type of studies | Quality of studies | Results consistency | Possibility of a clinical reference of the results | Other factors | Megestrol | Relative (95% CI) | Absolute (95% CI) | | Weight |
| MA vs. glucocorticosteroids – weight gain | | | | | | | | | | |
| 2 | Randomized studies | No serious limitations | No serious discrepancy | Doubts (–1)[1] | None | 17/178 (9.6%) | 12/178 (6.7%) | RR 1.4 (0.7–2.79) | 20/1000 (–30– 70) | ⊕⊕⊕○ Mediocre | 6 |
| MA vs. glucocorticosteroids – appetite improvement | | | | | | | | | | |
| 2 | Randomized studies | No serious limitations | Serious discrepancy (–1)[7] | No doubts | None | 64/178 (36%) | 70/178 (39.3%) | RR 1.09 (0.53–2.25 | 50/1000 (–250–340) | ⊕⊕⊕○ Mediocre | 8 |
| Cost of drug administration at the dose of 160 mg/d for 100 days | | | | | | | | | | |
| 0 | | | | | | | – | WMD 310 PLN[8] | ⊕⊕⊕⊕ High | 7 |

1 The effect of weight gain on physical status improvement, survival or quality of life is not obvious
2 With the exclusion of one of the studies causing result diversity (Erkurt), RR was 2.45 (95% CI: 1.71–3.52)
3 Results discrepancy = diversity (heterogeneity)
4 With exclusion of study causing result incoherence – 0.95 kg (95% CI: 0.49–1.42)
5 With exclusion of study causing result incoherence – 1.44 kg (95% CI: 0.1–2.98)
6 Little evidence on the 160 mg dose.
7 Two studies, inverse results. Small study with a trend to the advantage of MA, large study with a trend to the advantage of GKS. Statistical analysis with a trend to MA, however more patients with improvement on GKS.
8 Lowest tested dose.

The inclusion of this study also caused lack of result homogeneity, though the results of individual studies indicated at least a trend of beneficial effect of MA. The absolute benefit increase in appetite improvement in the previous meta-analysis[4] was c. 27%, which corresponded to the NNT of c. 4. In the Lopez et al. publication[4], the relative benefit of Karnofsky performance status improvement with MA administration, in comparison with the probability of improvement with the placebo administration, was 1.64 (95% CI 1.06–2.55).

To obtain appetite improvement, a low dose (160 mg) seems to be as efficient as higher doses; in the case of weight gain there is probably dose-response relationship.

The conclusions regarding MA influence on other symptoms occurrence, quality of life indexes, overall well-being and the performance status are less obvious and less convincing (scarce evidence, probability of publication bias), however studies with available data seem to indicate superiority of the drug. The influence of MA on survival in comparison with placebo could be assessed only in 2 studies (**TABLE 2**).

One of the potential interpretations of the evidence is that MA administration is associated with appetite improvement, an increased probability of weight gain and with a greater probability of delaying the performance status deterioration (the assessment of the latter effect is less certain).

Available data shows no difference between MA and glucocorticosteroids.

In the present publication the effects of drug administration have been shown with the use of relative (RR, RB) and absolute (absolute benefit increase [ABI], NNT) values, which enables to assess the balance between beneficial and harmful aspects of the drug effect and its costs. As such assessments are by their nature subjective (i.e. it may be estimated that with MA the weight increases additionally in only 10––15% of patients or in as much as 10–15% of patients), clinical decisions may also reflect subjective circumstances, for example, the significance attributed by patients and their families to the emotional and symbolic aspects of food intake and absorption.

## Implications for clinical practice

**1** The influence of MA on the survival rate in the advanced cancer patients has not been demonstrated.

**2** In the majority of patients weight loss progresses independently of treatment, and the drug administration is associated with at least short-term weight gain in additional 10–15% of patients.

**3** Although a decrease in appetite or its loss persist in most individuals, the drug administration improves this aspect of the quality of life in c. 30% of patients.

**4** Compared with placebo, MA induces weight gain and appetite improvement. In a single study an overall improvement of well-being has been

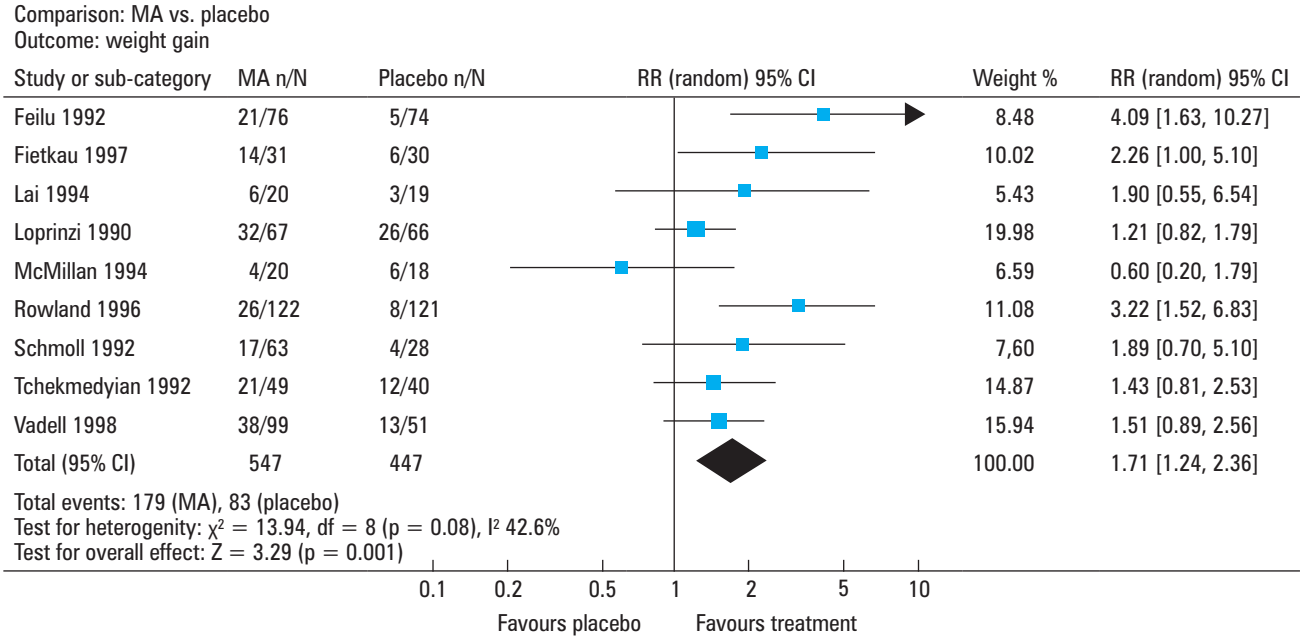


**FIGURE 1** The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on weight gain

demonstrated, the assessment of other quality of life aspects did not lead to practical implications. Beneficial effects on body weight increased with the dose. However, even the lowest daily dose (160 mg) showed a beneficial trend compared to placebo. A statistically significant influence of a dose increase on appetite improvement has not been demonstrated.

**5** A comparison of the effects of MA and glucocorticosteroid administration did not show difference in appetite improvement and weight gain.

**6** Lower extremity edema in short-term follow-up, and probably the thromboembolic complications risk increase in long-term follow-up are the adverse effects of MA demonstrated in previous publications [4].

**Implications for further studies** Further determination of the MA role in ACS syndrome treatment requires determining the relative value (utility) attributed by patients to individual health conditions associated with the drug administration, including appetite improvement and weight gain.

Because of a low value of available studies, for a more reliable assessment of MA efficacy in cancer-associated ACS it is necessary to perform a randomized controlled tral of high methodological quality.

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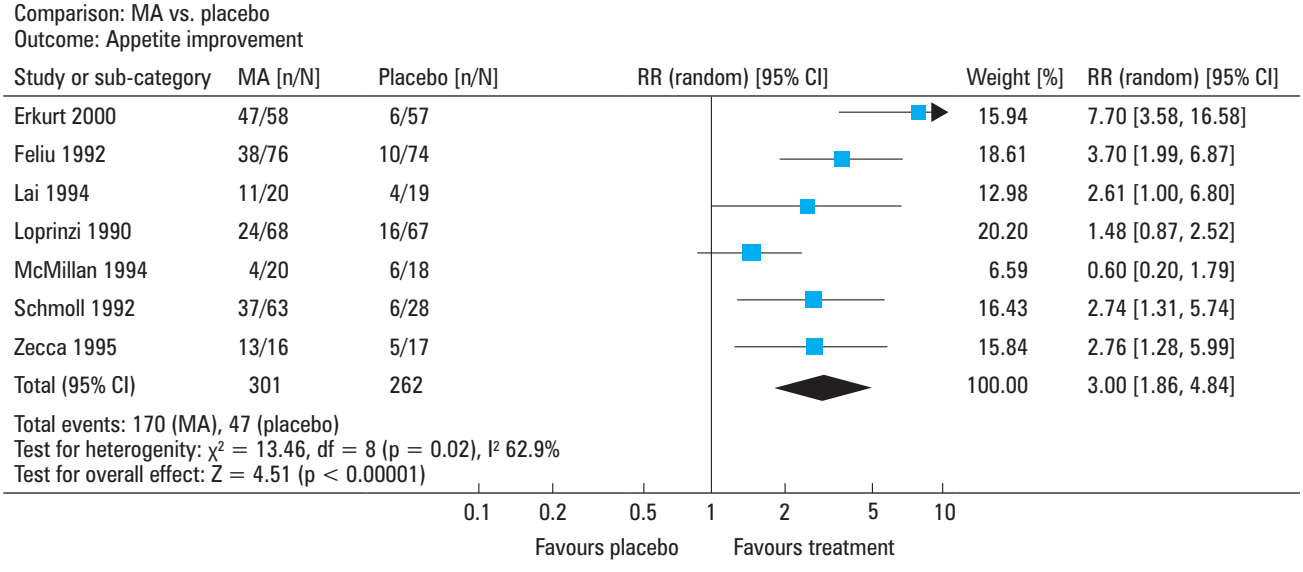
**FIGURE 2** The effects of megestrol acetate use in advanced stage cancer anorexia-cachexia syndrome on appetite improvement



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