Systematic review of the treatment of cancer-associated anorexia and weight loss

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CRD summary
The review authors concluded that there was evidence supporting the use of progestins and corticosteroids and strong evidence against hydrazine sulphate; further research is required. The evidence presented appears to support the authors' conclusions, but poor reporting of review methods and the lack of an adequate quality assessment make it difficult to confirm the robustness of the conclusions.

Authors' objectives
To evaluate the efficacy and safety of appetite stimulants for the treatment of cancer-associated anorexia.

Searching
MEDLINE (from 1966), CINAHL (from 1982) and the Cochrane Controlled Trials Register were searched to the third quarter of 2004 for peer-reviewed studies published in the English language. No attempts were made to search non peer-reviewed sources (grey literature). The search terms were not reported.

Study selection
Study designs of evaluations included in the review
Single-blinded, double-blinded and unblinded randomised controlled trials (RCTs) and phase III trials were eligible for inclusion in the review. The duration of the included studies ranged from 180 minutes to 2.5 years.

Specific interventions included in the review
Although inclusion criteria for the participants were not specified, it was clear that studies of drug treatments were eligible for inclusion. The included studies evaluated a variety of different drugs: progestins (megestrol acetate (MA) and medroxyprogesterone acetate (MPA)), corticosteroids (oral methylprednisolone (MP), intravenous methylprednisolone sodium succinate (MPSS), prednisolone and dexamethasone), prokinetics (metoclopramide), hydrazine sulphate, cyproheptadine, pentoxifylline, melatonin, erythropoietin, eicosapentanoic acid, androgenic steroids, ghrelin, interferon, non-steroidal anti-inflammatory drugs (indomethacin) and cannabinoid (dronabinol). In the included studies, MA was used in doses ranging from 160 to 1,600 mg/day for between 2 weeks and 2 years, while MPA was used in doses ranging from 300 to 1,200 mg per day for between 6 and 12 weeks. Control treatments included placebo, different regimens of the experimental drug and other drugs.

Participants included in the review
Studies of adults (aged 18 years or older) who had been diagnosed clinically with a non-haematological cancer and anorexia, or symptoms associated with anorexia, were eligible for inclusion in the review.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The review appeared to focus on appetite, weight and quality of life. The included studies measured appetite using a variety of tools.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state how the validity assessment was performed. Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding, and drop-outs and withdrawals. The maximum possible score was 5 points. Studies scoring 3 or more points were considered to be of a high quality.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, results for appetite and weight outcomes were extracted in terms of the level of statistical significance.

Methods of synthesis
How were the studies combined?
The studies were grouped by class of drug treatment and combined in a narrative, with accompanying tables presented. The review focused on the results from placebo-controlled RCTs.

How were differences between studies investigated?
Differences between the studies were apparent from the text and tables.

Results of the review
Fifty-five RCTs (n=6,741) were included in the review.

The Jadad scores for quality ranged from 1 to 5.

Progestins (29 RCTs, n=4,139). MA (23 studies): patients treated with MA showed improvements compared with those taking placebo (of 10 placebo-controlled RCTs, nine reported significant improvements in appetite and seven reported significant improvements in weight). The review authors described side-effects associated with MA as 'acceptable' but no data were reported. There was very little effect of MA on quality of life (10 RCTs).

MPA (6 studies): patients treated with oral MPA showed improvements compared with those taking placebo (of 6 placebo-controlled RCTs, four reported significant improvements in appetite and five reported significant improvements in weight). The review authors described side-effects associated with MPA as 'acceptable' but no data were reported. Two of the 3 RCTs assessing quality of life reported improvements in quality of life associated with MPA; the other study reported no measurable benefit.

Corticosteroids (6 RCTs, n=647).

Intravenous MPSS: 2 RCTs evaluated intravenous 125 mg/day MPSS for 8 weeks and reported improvements in appetite, pain, quality of life, vomiting and well-being, as well as a temporary improvement in appetite, compared with placebo. One of the RCTs assessed weight and found no treatment difference.

MP: one crossover RCT evaluated oral 32 mg/day MP for 14 days and reported improvements in appetite and performance status compared with placebo.

Prednisolone: one RCT evaluated 10 mg/day prednisolone for 6 weeks and reported significant improvements in appetite and well-being compared with placebo.

Dexamethasone: 2 placebo-controlled RCTs evaluated 3 to 8 mg/day dexamethasone. One reported significant improvements in weight of unclear onset and duration compared with placebo (table stated the improvement was at 4 weeks but not 2 weeks, whilst the text stated the improvement was at 2 weeks but not at 4 weeks); the other reported no significant treatment difference in appetite.

Hydrazine sulphate (5 RCTs, n=796). Four of the 5 RCTs reported no significant difference in appetite or weight gain between oral hydrazine (60 to 180 mg/day) and placebo; the fifth RCT reported improved appetite and increased or maintained weight with hydrazine.

Studies of other drugs reported mixed results or positive results only in individual studies, or were not placebo-controlled.
Authors' conclusions

There was evidence supporting the use of progestins and corticosteroids and strong evidence against hydrazine sulphate. However, the optimal dose, time to start and treatment duration for many appetite stimulants for cancer-associated anorexia is still unknown. Further research is required.

CRD commentary

The review question was clear in terms of the study design and participants; inclusion criteria for the interventions were broad, whilst those for the outcomes were not specified and this raises the possibility of potential bias in the reporting of selected outcomes. Restricting the search to peer-reviewed publications in English might have resulted in the omission of other relevant studies and increases the potential for publication and language bias. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Study quality was assessed using an established checklist, although only the composite score was presented; this makes it difficult for the reader to judge the study quality independently. In addition, information about the validity of the methods used to measure appetite was lacking.

In view of the diversity of the studies, a narrative synthesis that focused on evidence from placebo-controlled studies was appropriate. However, results data were not presented for measures other than appetite or weight, and the evidence was not considered in relation to study quality. The evidence presented appears to support the authors' conclusions, but the lack of reporting of review methods and the lack of an adequate quality assessment make it difficult to confirm the robustness of the conclusions.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice. Research: The authors stated that further placebo-controlled RCTs are required to evaluate the effects of different combinations of agents on resting energy expenditure, pro-inflammatory cytokine expression, acute phase reactants and appetite. Studies should use standardised measures for both subjective outcomes (e.g. appetite, associated symptoms and quality of life) and objective outcomes (e.g. food consumed and weight gain and loss).

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.