
Ghrelin for the management of cachexia associated with cancer

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**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>1</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>6</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>7</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>10</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>11</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>11</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>11</td>
</tr>
</tbody>
</table>
Ghrelin for the management of cachexia associated with cancer

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.


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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of ghrelin on improving food intake, body composition and survival in patients with cachexia associated with cancer.

BACKGROUND

This protocol is partly based on suggested wording from the Pain, Palliative and Supportive Care Review Group (PaPaS CRG).

Description of the condition

Cancer and its co-morbidities, like cancer cachexia, have afflicted humans for centuries and still continue to be a major public health problem. Patients suffering from cancer are amongst the most malnourished of all the patient groups (Ryan 2016). It has been estimated that cachexia affects 60% to 80% of all advanced cancer patients (Baracos 2011) and more than 30% of patients die due to cachexia (von Haehling 2012). Cancer cachexia is commonly associated with decreased life expectancy and poor quality of life (Utech 2012).

Cancer cachexia is defined as "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon 2011). Cachexia syndrome can develop progressively, through stages of pre-cachexia to cachexia to refractory cachexia (Fearon 2011). The incidence of cancer cachexia varies according to tumor type (Teunissen 2007; Tisdale 2009; Sun 2015). The prevalence of cachexia is highest in people with pancreatic cancer (88.9%), followed by gastric cancer (76.5% to 87%) and esophageal cancer (52.9%) (Sun 2015; Tisdale 2009). The frequency of weight loss is lowest in patients with breast can-
Description of the intervention

The approach to treatment for cancer cachexia is multimodal and includes nutritional support, pharmacological treatments, and non-pharmacological therapies like physical training (Madeddu 2015a). Caloric supplementation or appetite stimulants like megestrol acetate, medroxyprogesterone acetate (MPA), cyproheptadine, marijuana, and corticosteroids such as dexamethasone, prednisolone and methylprednisolone have been used for enhancing appetite in cancer patients (Fearon 2011; Tisdale 2009). However, these interventions have limited efficacy. No definitive pharmacological treatment is available to address the relevant components of the syndrome (Esposito 2015).

Ghrelin, a novel orexigenic gut hormone, is primarily secreted by the endocrine X/A-like cells of the stomach mucosa and also by intestinal mucosa, arcuate nucleus of the hypothalamus, pituitary gland, pancreatic islets, and other tissues (Khatib 2015b). Studies have shown that this 28-amino acid peptide hormone is an endogenous ligand for the growth hormone secretagogue receptor and can be a potential therapeutic agent for cachexia-associated cancer (Chen 2015; Garcia 2015; Pietra 2014; Tsubouchi 2014; Zhang 2015). It has shown promising results in randomised clinical trials (Garcia 2007; Garcia 2013; Garcia 2015; Khatib 2014b; Khatib 2014c; Madeddu 2015b). Ghrelin has the potential to increase body weight and body composition through increased appetite, increased growth hormone (GH) secretion and prevention of muscle catabolism, which suggests that ghrelin could be an effective treatment for cancer anorexia (DeBoer 2007; Fujitsuka 2011; Garcia 2005; Garcia 2013; Khatib 2014a; Khatib 2014d; Khatib 2014f; Khatib 2015b; Klok 2007; Neary 2004; Tsubouchi 2014; Wren 2001). Ghrelin is well tolerated with no reported side effects (Akamizu 2010; Khatib 2015a; Neary 2004).

Ghrelin agonists are being developed and tested for the treatment of anorexia/cachexia. Anamorelin, a first-in-class, potent orally-active and highly-specific ghrelin receptor agonist, increases food intake, body weight and lean body mass (Northrup 2013; Pietra 2014). It is well tolerated with no dose-limiting toxicities (Zhang 2015). Anamorelin treatment for 12 weeks had a favourable clinical response profile in patients with cancer anorexia-cachexia syndrome in one study (Garcia 2015). Administration of RC-1291, a ghrelin mimetic, in cachectic cancer patients increased lean body mass in another study (Garcia 2007); it represents a new class of drug for patients with cancer cachexia.

How the intervention might work

Although the mechanisms of action of ghrelin have not been fully elucidated, an increase in appetite and decrease in energy expenditure via hypothalamic effects (Fujitsuka 2014; Garcia 2013; Murphy 1998); promotion of anabolic activity (Chen 2015); decrease in inflammation (Dixit 2004; Tsubouchi 2014); an increase in growth hormone (Garcia 2009; Khatib 2014a; Khatib 2014d;
Ghrelin and synthetic ghrelin receptor agonists cause weight gain by increasing food intake and by food intake-independent mechanisms (Garcia 2013; Sugiyama 2012; Tschop 2000). Ghrelin promotes weight gain and lean body mass via anti-inflammatory action and effects involving orexigenic neuropeptides (DeBoer 2007; Khatib 2014c; Khatib 2015b). Animals treated with ghrelin exhibit a decreased expression of IL-1 receptor-1 transcript in the hypothalamus and brainstem and an increased expression of orexigenic peptides and neuropeptide Y (NPY) in the hypothalamus (DeBoer 2007; Tisdale 2009). Administration of ghrelin prevents muscle atrophy by down-regulating inflammation and activating protein kinase B (a protein kinase that plays a key role in apoptosis, cell proliferation, and cell migration), myogenin (a transcription factor involved in myogenesis and repair) and myoD (a protein that plays a major role in regulating muscle differentiation) (Chen 2015). Both acetylated and unacylated ghrelin blocks skeletal muscle atrophy in a growth hormone-independent manner (Porporato 2013). In vitro studies have demonstrated that ghrelin may regulate mesenchymal cell development by stimulating myogenesis (Zhang 2007). Cells expressing ghrelin have demonstrated a significant increase in the differentiation of premyoctyes into myocytes (Zhang 2007). Ghrelin inhibits the production and prevents the increase of pro-inflammatory cytokines released by the tumour cells (Chen 2015; Dixit 2004; Tsoubouchi 2014). Activation of the ghrelin receptor in the central nervous system releases GH which regulates insulin-like growth factor-1 (IGF-1) (Khatib 2014f; Khatib 2014a; Velloso 2008). GH/IGF-1 axis acts directly on bone, muscle and fat tissue and also indirectly by producing anti-cachectic cytokines and muscle-restricted insulin-like growth factor-1 (mIGF-1) (Fuoco 2015). Since GH secretagogue receptors (GHS-R) are expressed in vagal afferent neurons, the gastric vagus nerve is involved in the effect of ghrelin on food intake and GI motility (Date 2002). Gastric ghrelin signaling via vagal afferents suppresses the activity of the sympathetic nerves and increases the discharge of both the gastric and the vagus efferent nerves (Fujitsuka 2009). Ghrelin also promotes faster motor activity by activating the NPY neurons in the brain (Fujino 2003). Anamorelin increases GH, IGF-1 and body weight with good tolerability and selectivity (Garcia 2009). Oral administration of rikkunshito increases plasma acyl ghrelin levels in humans, mice, rats and dogs (Fujitsuka 2009; Fujitsuka 2011; Takeda 2008). It may be a viable treatment modality for cancer-associated cachexia.

O B J E C T I V E S

To assess the efficacy and safety of ghrelin on improving food intake, body composition and survival in patients with cachexia associated with cancer.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with unblinded or blinded assessment of outcomes. Full journal publication is required, with the exception of extended abstracts of otherwise unpublished clinical trials. We will exclude short abstracts (usually meeting reports), non-randomised studies, studies of experimental pain, case reports, and clinical observations.’

Types of participants

We will include cachexic adults of 18 years and over with a histological or clinical diagnosis of cancer; or meeting any of the international criteria for cancer cachexia (Bozzetti 2009; Fearon 2006; Fearon 2011). Both inpatients and outpatients with any stage of cancer irrespective of gender or race will be considered for inclusion. We will include patients in any healthcare setting (including hospice, hospital, oncology centre or community).

Types of interventions

We will include studies in which the intervention is the administration of ghrelin in any form, at any dose, at any frequency, by any route and for any duration, administered for improving food intake, body composition and survival, compared to placebo stimulatory therapies for patients with this condition. Several studies have demonstrated positive and encouraging effects of ghrelin or GH secretagogues (GHS) in patients with cancer cachexia (Esposito 2015; Garcia 2007; Garcia 2013; Molfino 2014; Neary 2004). However, the safety and efficacy of ghrelin for cancer-associated cachexia have not been systematically reviewed. There is a need to synthesise the evidence for patients, practitioners and policy makers to decide whether ghrelin can be incorporated in the management of cachexia associated with cancer and, if data permit, to explore the optimal drug programme for this group of patients. Therefore, systematic evaluation of the role of ghrelin in the treatment of cancer cachexia is warranted.

W h y it is important to do this review

Despite the high prevalence of cancer cachexia, effective therapies are still limited and no definitive pharmacological treatment is available to address the relevant components of this syndrome (Esposito 2015). There is a strong need for more effective appetite-stimulatory therapies for patients with this condition. Several studies have demonstrated positive and encouraging effects of ghrelin or GH secretagogues (GHS) in patients with cancer cachexia (Esposito 2015; Garcia 2007; Garcia 2013; Molfino 2014; Neary 2004). However, the safety and efficacy of ghrelin for cancer-associated cachexia have not been systematically reviewed. There is a need to synthesise the evidence for patients, practitioners and policy makers to decide whether ghrelin can be incorporated in the management of cachexia associated with cancer and, if data permit, to explore the optimal drug programme for this group of patients. Therefore, systematic evaluation of the role of ghrelin in the treatment of cancer cachexia is warranted.

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or any active comparator (such as appetisers, nutritional supplements, etc.).
The following comparisons will be made in the review:
1. Ghrelin versus placebo;
2. Ghrelin versus no treatment;
3. Ghrelin versus alternative experimental treatment modality (like appetisers, nutritional supplements, etc);
4. Ghrelin in combination with other treatments versus ghrelin treatment alone;
5. Ghrelin treatment versus ghrelin analogues/ghrelin mimetics (anamorelin, ipamorelin, eganamorelin, hexarelin, MK-677, etc.) or ghrelin potentiators/enhancers (rikunshito).

Types of outcome measures

Primary outcomes
1. Change in food intake as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced an increase in food intake) or a continuous variable (actual change in food intake).
2. Change in body weight as difference between baseline and at the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced change in body weight) or a continuous variable (actual change in body weight).
3. Adverse events as the number of patients who suffered an event described as an adverse event by the authors of the studies.

Secondary outcomes
1. Change in survival measured as increase in survival in days. We will use hazard ratios for how many times more (or less) likely a participant is to suffer the event at a particular point in time if they receive ghrelin rather than the control intervention.
2. Change in body composition (lean body mass, fat mass) as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced change in body weight) or a continuous variable (actual change in body weight).
3. Plasma ghrelin levels as difference between baseline and the end of treatment. We will express this outcome as a dichotomous variable (number of patients who experienced increase in plasma ghrelin levels) or a continuous variable (actual change in plasma ghrelin levels).
4. Change in the Quality of Life (QoL) using Health-Related Quality of Life (HRQoL) (CDC 2016).

Search methods for identification of studies

Electronic searches
We will search the following databases without language restrictions.
- The Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library).
- MEDLINE (via Ovid).
- EMBASE (via Ovid).

Medical subject headings (MeSH) or equivalent and text-word terms will be used. Full text translations of all relevant non-English articles will be obtained. Searches will be tailored to individual databases. The search strategy for MEDLINE can be found in Appendix 1.

Searching other resources
We will search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), National Cancer Institute (http://www.cancer.gov/clinicaltrials), clinicaltrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials. We will also search ClinicalStudyResults.org (www.clinicalstudyresults.org) for clinical trials. In addition, reference lists of reviews and retrieved articles will be checked for additional studies, and citation searches will be performed on key articles. Authors will be contacted where necessary for additional information. We will perform handsearching of abstracts from relevant conferences, such as the International Cachexia Conference. Experts in the field will be contacted for unpublished and ongoing trials to identify any additional literature related to the review.

Data collection and analysis

Selection of studies
Two review authors (MNK, SG) will independently screen the articles retrieved from the searches using the Rayyan online screening tool (Elmagarmid 2014) and determine eligibility by reading the abstract of each study identified by the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors (ZQS, AG) will read these studies independently to select relevant studies, and in the event of disagreement, a third author will adjudicate (AS). We will not anonymise the studies in any way before assessment. We will include a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart in the full review which will show the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1.
of the *Cochrane Handbook* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a ‘usable’ way.

**Data extraction and management**

Two review authors (MNK, SG) will independently extract data using a standard form and check for agreement before entry into Review Manager (*RevMan* 2014). We will include information about all the primary outcomes. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of ‘Characteristics of included studies’ in the full review.

**Assessment of risk of bias in included studies**

This section is taken from the PaPaS template for protocols. Two authors (MNK, PS) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We will complete a ‘Risk of bias’ table for each included study using the ‘Risk of bias’ tool in *RevMan* (*RevMan* 2014).

We will assess the following for each study.

- Random sequence generation (checking for possible selection bias): We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) will be excluded.

- Allocation concealment (checking for possible selection bias): The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated).

- Blinding of participants and personnel (checking for performance bias): We will assess the methods used to blind study participants and personnel about the receipt of the intervention. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding); unclear risk of bias (study states that it was blinded but does not provide an adequate information of how it was done); high risk of bias (no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of participants and personnel was attempted, but it is likely that the blinding could have been broken).

- Blinding of outcome assessment (checking for possible detection bias): We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how blinding was achieved).

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): We will assess the methods used to deal with incomplete data as: low risk (<10% of participants did not complete the study and/or used ‘baseline observation carried forward’ analysis); unclear risk of bias (used ‘last observation carried forward’ analysis); high risk of bias (used ‘completer’ analysis).

- Size of study (checking for possible biases confounded by small size). We will assess studies as being at low risk of bias (≥200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (<50 participants per treatment arm).

- Selective outcome reporting (checking for reporting bias): We will assess studies as being at low risk of bias (the study protocol is available; or the study protocol is not available but the study reported all expected and pre-specified outcomes); high risk of bias (the study reported one or more outcomes of interest incompletely); unclear risk of bias (the study provides insufficient information to permit judgement of ‘low risk’ or ‘high risk’).

- Other bias: We will assess the study as: low risk of bias (the study appears to be free of other sources of bias); unclear risk of bias (there may be a risk of bias, but there is insufficient information to judge whether risk of bias exists; or insufficient evidence that a problem under consideration will introduce bias); or high risk of bias (there is at least one important risk of bias).

**Measures of treatment effect**

We will use a fixed-effect model or random-effects model to estimate the overall direction, size and consistency of an effect. For dichotomous variables, we will compute treatment effects as risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI). For continuous data we will use mean differences (MD) with 95% CI when the results are measured in the same way in different studies. We will use standardised mean differences (SMD) when the results obtained are conceptually the same but used different measurement scales. We will record means and standard deviations. The mean change in each group will be obtained by subtracting the final mean from the baseline mean. The change in standard deviation will be obtained from CI, standard errors,
Dealing with missing data
We will carry out an intention-to-treat analysis. When published data are missing, incomplete or inconsistent with RCT protocols, we will ask for further information from the authors/manufacturers. We will contact authors by email if studies did not report the outcome measures of interest, did not describe randomisation or intention-to-treat analysis or had missing data.

Assessment of heterogeneity
We plan to assess clinical heterogeneity by using the Chi² test (P value < 0.10 for statistical significance) and use the I² statistic to quantify heterogeneity. Heterogeneity will be regarded as considerable if I² is more than 75%; substantial if it is between 50% and 90%; moderate if it is between 30% and 60% and mild if less than 40% (Higgins 2011). If we identify statistical heterogeneity (I² greater than, or equal to 50%) we will report it and explore possible causes by prespecified subgroup analysis, and will apply a random-effects model.

Assessment of reporting biases
If there are 10 or more included studies, we plan to conduct a funnel plot test for asymmetry to assess for any evidence of reporting bias. Additionally, possible sources of asymmetry in a funnel plot will be explored.

Data synthesis
We will undertake a meta-analysis only if participants, interventions, comparisons and outcomes are judged to be sufficiently similar to ensure an answer that is clinically meaningful and relevant. For analysis, we plan to use RevMan 2014, the statistical package provided by the Cochrane Collaboration.

Assessment of reporting biases
If statistical heterogeneity (I² greater than, or equal to 50%) is detected, we will attempt to identify the sources of the heterogeneity and will perform subsequent meta-analysis using a random-effects model. If the meta-analysis is inappropriate for any other reason, we will not pool the results of the included studies, but will present a qualitative description of these studies with supporting tables. If there are sufficient and homogeneous data with consistent or comparable outcomes, we will perform a meta-analysis using a fixed-effect model.

‘Summary of findings’ tables
We will include a ‘Summary of findings’ (SoF) table as set out in the PaPaS author guide (AUREF 2012) and recommended in the Cochrane Handbook, chapter 4.6.6 (Higgins 2011). We will present the SoF tables under the following comparisons for all of the primary outcomes:
1. Ghrelin versus placebo;
2. Ghrelin versus an alternative experimental treatment modality; and
3. Ghrelin in combination with other treatments versus ghrelin treatment alone.

Two review authors (ZQS, MNQ) will assess the overall quality of the evidence for each outcome using the GRADE system (GRADEpro GDT 2015) and present the findings in the ‘Summary of findings’ tables. In particular, we will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.
We will decrease the grade if there is:
• A serious (-1) or very serious (-2) limitation to study quality;
• Important inconsistency (-1);
• Some (-1) or major (-2) uncertainty about directness;
• Imprecise or sparse data (-1);
• High probability of reporting bias (-1).

We will justify all decisions to down-grade the quality of studies using footnotes.

Subgroup analysis and investigation of heterogeneity
Subgroup analyses are planned for form, dose, duration and route of administration of ghrelin, and for different types of cancer.

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Ghrelin for the management of cachexia associated with cancer (Protocol)
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We acknowledge the support of Dr Alka Rawekar, Dr Tripti Shrivastava and Mahafroz Khatib during the preparation of the protocol.

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Centre for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Health-Related Quality of Life (HRQOL) | CDC. http://www.cdc.gov/hrqol/ May 2016.

Chen 2016

Date 2002
Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Minton, consultant and senior lecturer in palliative medicine, Roger Goucke, anaesthesia/palliative Care, Maria J Silveira, palliative care specialist and researcher, and Marilia Seelaender, head of the Cancer Metabolism Group, University of São Paulo, for providing valuable input to the protocol.

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Elbourne 2002

Elmagarmid 2014

Esposito 2015

Fearon 2006

Fearon 2011

Fujino 2003

Dixit 2004

BELMOURNE 2002

**Fujitsuka 2009**
Fujitsuka N, Asakawa A, Hayashi M, Sameshima M, Ami

**Fujitsuka 2011**

**Fujitsuka 2014**

**Fuoco 2015**

**Garcia 2005**

**Garcia 2007**

**Garcia 2009**

**Garcia 2013**

**Garcia 2015**

**GRADepro GDT 2015 [Computer program]**

**Higgins 2011**

**Khatib 2014a**

**Khatib 2014b**

**Khatib 2014c**

**Khatib 2014d**

**Khatib 2014e**

**Khatib 2014f**

**Khatib 2015a**

**Khatib 2015b**

**Klok 2007**
Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight...

Kos 2009

Madeddu 2015a

Madeddu 2015b

Mendes 2015

Moher 2009

Mollino 2014

Murphy 1998

Neary 2004

Northrup 2013

Penn 2010

Penna 2016

Pietra 2013

Porporato 2013

Reid 2012

RevMan 2014 [Computer program]

Ryan 2016

Stephens 2008

Stewart 2006

Sugiyama 2012

Sun 2015
Sun L, Quan QX, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its...

Takeda 2008

Teunissen 2007

Tisdale 2009

Tschop 2000

Tsubouchi 2014

Utech 2012

Velloso 2008

von Haehling 2012

Watanabe 1996

Windsor 1988

Wren 2001

Zhang 2007

Zhang 2015

* Indicates the major publication for the study

APPENDICES

Appendix 1. Appendix. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
1 Ghrelin/
2 (ghrelin or ppghrelin or (motilin adj2 peptide) or ghrl or obestatin or ppmtlrp or “appetite regulating hormone” or Anamorelin or Ipamorelin or Eganamorelin or Hexarelin or MK-677 or Rikkunshito).tw.
3 Cachexia/
4 cachexia.tw.
5 cachexic.tw.
6 (weight or underweight or malnutrition or wasting).tw.
7 Weight Loss/
8 or/3–7

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CONTRIBUTIONS OF AUTHORS

MNK and ZQS designed and developed the protocol with input from AG, SG, PS, RK and AS. MNK and SG developed the search strategy with the help of the PaPaS Group Information Specialist, and ZQS wrote the Background section. MNK and SG will be responsible for data extraction in the full review. All authors will be responsible for completing the protocol, full review, and updating the review in future.

DECLARATIONS OF INTEREST

MNK: none known.
AS: none known.
RK: none known.
AG: none known.
SG: none known. SG is a specialist physician and manages patients with cancer cachexia.
PS: none known.
ZQS: none known.

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