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[Intervention Review]

Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia

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ABSTRACT

Background

Cancer cachexia is a distressing weight loss syndrome commonly seen in advanced cancer patients. It is associated with reduced quality of life and shorter survival time. Eicosapentaenoic acid (EPA) is a long chain polyunsaturated fatty acid found naturally in some fish which has been used to decrease weight loss, promote weight gain and increase survival times in patients affected with cancer cachexia.

Objectives

To evaluate the effectiveness and safety of EPA in relieving symptoms associated with the cachexia syndrome in patients with advanced cancer.

Search methods

Studies were sought through an extensive search of a range of electronic databases. Hand searching was conducted on selected journals and reference lists as well as contact made with investigators, manufacturers and experts. The most recent electronic search was conducted in February 2005.

Selection criteria

Studies were included in the review if they assessed oral EPA compared with placebo or control in randomised controlled trials of patients with advanced cancer and either a clinical diagnosis of cachexia or self-reported weight loss of 5% or more.

Data collection and analysis

Both methodological quality evaluation of potential trials and data extraction were conducted by two independent review authors.

Main results

Five trials (involving 587 participants) met the inclusion criteria. Three trials compared EPA at different doses with placebo with two outcomes, nutritional status and adverse events comparable across two of the three included trials. In addition, two trials compared different doses of EPA with an active matched control. It was possible to compare the outcomes of weight, quality of life and adverse events across these two trials. There were insufficient data to define the optimal dose of EPA.

Authors' conclusions

There were insufficient data to establish whether oral EPA was better than placebo. Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of an appetite stimulant (Megestrol Acetate) provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer.

PLAIN LANGUAGE SUMMARY

Using an omega-3 fatty acid made from fish oils to treat cancer related weight loss

There was insufficient evidence to support the use of oral fish oil (on its own or in the presence of other treatments) for the management of the weight loss syndrome often seen in patients with advanced cancer. Many people with advanced cancer develop a distressing weight loss syndrome. To date, treatment of associated symptoms has proved difficult. More recently, novel approaches have included the use of oral fish oils that can contain the omega-3 fatty acid eicosapentaenoic acid (or EPA) to stabilise weight loss and promote weight gain. This review of trials found that in weight losing persons with advanced pancreatic cancer, an EPA nutritional supplement was no better than a non EPA nutritional supplement. However, there was insufficient evidence to draw conclusions about its use in patients who have cancer of other tumour types.

BACKGROUND

Cancer cachexia is a debilitating weight loss syndrome characterised by disease-induced starvation and wasting (Giacosa 1994). Whilst there is no universally accepted definition of cachexia, the clinical signs that form the hallmark of cancer associated cachexia are anorexia and extreme weight loss. Although a 10% weight loss (from pre-illness weight) is often considered to be severe, the rate of the weight loss can also be of primary importance in the definition of cachexia. Categories of severe weight loss have been defined as more than 2% in one week, 5% in one month and 10% in six months (Blackburn 1977). Other clinical features include abnormalities in carbohydrate, fat, protein and energy metabolism which lead to weakness, lethargy, malaise and the loss of skeletal muscle and adipose tissue (Jaskowiak 1998). Patients have a "starved" or "cachetic" appearance and are often described as "looking ill" (Lindsey 1986). Cachexia is seen in approximately half of all terminally ill cancer patients and is particularly associated with solid cancer tumours of the stomach, lung and pancreas. The literature suggests that cachexia rates for these particular cancers can be more than 80% in pancreatic and gastric cancer (DeWys 1980). Cachectic patients have shorter survival time when compared to other terminally ill cancer patients without extreme weight loss (Tisdale 1997). Such severe weight loss has also been associated with reduced quality of life, impaired respiratory muscle function, fatigue and poor self-image have all been cited (Tisdale 1996). Profound muscle weakness may lead to loss of physical function and deterioration of performance status. Associated fatigue and weakness may impair a patient's ability to perform even simple activities of daily life such as dressing, preparing and eating meals. In addition physical fatigue coupled with dramatic weight loss can give rise to a change in body image which, in turn, can lead to the patient perceiving that they are progressively looking more ill and may contribute to depression and decreased social interactions (Lindgvist 2004).

The exact cause of cachexia is unknown, but it is likely to be multi-fold and can be grouped into three interrelated categories to include:

- biochemical and metabolic disturbances caused by systemic tumour related effects of some cancer tumour types;
- mechanical obstruction of the cancer tumour itself; or
- a consequence of cancer treatment induced toxicity.

Specific proteolysis and lipolysis tumour products have been identified (Belizario 1991; Smith 1993; Todorov 1996) but comparative studies of these factors which have been isolated have yet to be reported.

Past attempts to improve the patient's nutritional status using conventional oral nutritional supplements or parenteral nutrition have proved unsuccessful (Nixon 1981; Ovesen 1993). Although reduced appetite is often associated with cachexia, increasing calorific intake has not been shown to alter its progression. Corticosteroids, including prednisolone have been used successfully to temporarily increase the patient's appetite, but this has not improved nutritional status (Willox 1984). More recently, novel approaches have included the use of fish oils which may have an anti-cachectic effect after a period of three weeks or more to produce significant weight gain, performance status and increased appetite in patients with cancer cachexia (Barber 1999a). Fish oils contain the long chain polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In animal studies, using mice, EPA was found to stabilise weight loss in tumour induced cachexia. A similar anticachectic effect was not reproduced by the use of DHA alone (Hudson 1994). The biological rationale for using EPA is that it has been shown to inhibit tumour induced lipolysis and muscle protein degradation, probably by the suppression of the cytokine IL-6 and by decreasing the presence of a tumour specific product, a proteolysis-inducing factor (or PIF) (Beck 1991). EPA is found naturally in some seafood, including salmon, sardines and tuna. In its manufactured form, EPA is available in fish oil preparations over-the-counter, without prescription, in both a soft gelatin capsule or liquid form. Outside of clinical trials, commercially available over-the-counter products may vary in EPA concentration and quality since, to date, it is not compulsary for manufacturers to accurately record the EPA content on product labels. Generally, its use has raised few concerns regarding side effects and has been shown to be non-toxic, well tolerated and free of significant side effects in all but high dosage trials. In patients with pancreatic cancer the dosage tolerated was limited by a sensation of fullness, cramping abdominal pain, fatty stools and nausea (Barber 2001a).

Evidence from non-randomised trials, trials without a control group and randomised controlled trials suggest that there is some therapeutic use of EPA taken for at least a four week period to reverse cancer cachexia by decreasing weight loss or improving weight gain, or both, to increase survival time in patients with cancer cachexia (Barber 1999a; Gogos 1998; Wigmore 2000). Many of these trials have been small, using variable dosage rates and inadequate study design which may have over emphasised evidence of effect. Since the best evidence of effectiveness of health interventions comes from results of well-conducted randomised controlled trials, a systematic review of quality assessed randomised controlled trials, with a meta-analysis, may help to synthesise such data.

OBJECTIVES

The objective of this review was to determine the effectiveness and safety of the omega-3 fatty acid eicosapentaenoic acid (EPA) to alleviate cachexia and related symptoms in patients with incurable or advanced cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that were double blind, single blind or unblinded were included providing they met the methodological quality assessment process. Both inpatient and outpatient study settings were included. It was anticipated that we would include only trials with a minimum of three weeks after randomisation into the study in order that any meaningful weight change would be recorded. However, it was decided that instead, as there were few studies that met the methodological quality assessment threshold, all well conducted studies, including those of short duration, would be included.

Types of participants

Trials of patients with a confirmed diagnosis of incurable or advanced cancer and either a reported weight loss of 5% and above or a clinical diagnosis of cachexia (independent of gender, age or race) were included.

Types of interventions

This review focuses on the following treatment comparisons:

- oral fish oil supplementation (containing EPA) regardless of type (i.e., capsules or liquid supplementation) or dosage (in terms of level of EPA) versus placebo;
- oral fish oil supplementation (containing EPA) regardless of type and at any dose versus active matched control (without EPA).

Types of outcome measures

Primary outcomes

The primary outcome measures assessed were:

- weight gain,
- body composition,
- median survival.

Secondary outcomes

The secondary outcome measures assessed were:

- functional or performance status,
- improvement in quality of life,
- energy expenditure,
- reduction in fatigue,
- nutritional status,
- compliance rates,
- side effects,
- adverse events.

Search methods for identification of studies

Electronic searches

A search strategy (using both free text and MeSH terms and without methodological terms as filters) was designed for identifying studies from the following databases:

- The Cochrane Central Registers of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews, Issue 4, 2003;
- MEDLINE (1966 to 28/08/2004);
- EMBASE (1986 to 28/07/2004);
- CINAHL (1986 to 23/07/2004);
- SIGLE (1980 to 22/02/2005);
- Dissertations Abstracts On Line (1980 to 10/11/2004);
- National Research Trials Register (20/10/2003).

As recommended by the Cochrane Handbook, searching was carried out without using filters in order to maximise retrieval of as many studies as possible. Study reports were retrieved regardless of whether these were full publications, abstracts or letters to the editor. The search strategy was adapted as necessary to search different databases using the relevant Boolean and truncation terms for each database, as required. Please see Appendix 1 for the MEDLINE search strategy.

Studies were not excluded on the basis of language or publication status (published, unpublished, in press and in progress). Full text translations of all relevant non-English articles were obtained.

Searching electronic databases identified:

- 363 articles in MEDLINE (from 1966 to 2004);
- 134 articles in EMBASE (from 1966 to 2004);
- 30 articles in CINAHL (from 1986 to 2004);
- two articles from Dissertations on Line (1980 to 2004);
- 22 articles The Cochrane Central Register of Controlled Trials (Issue 4, 2004);
- 26 articles from SIGLE (1980 to 2005);
- 97 articles from Web of Science (search date November 2004);
- nine articles from Google (search date December 2003).

Searching other resources

Hand searching

The following journals were identified as being important to be hand searched for this review and searched as follows:

- Nutrition (1976 to 1981, 1997 to 1998, 2000 to 2003) Gut (1999 to 2003). We were unable to handsearch Nutrition & Cancer (1998 to 2003) as originally identified as we were unable to trace locally available copies;
- the bibliography of all relevant randomised trials, non-controlled trials and review articles obtained from the above search were hand searched to identify other potentially relevant trials missed by electronic searching;
- appropriate conference proceedings were also searched;
- scanning of own files.

Hand searching of secondary references revealed 50 potential articles. Contact with experts revealed 16 potential trials, and manufacturer's information revealed six potential trials. Hand searching of conference proceedings revealed a further four potential trials. Hand searching of specified, relevant journals revealed no new potential trials.

Personal contact

- We made personal contact with relevant trialists, palliative care organisations, experts and other groups working with this field who may have access to relevant research material and unpublished data
- The authors of all identified relevant studies were contacted. We requested unpublished data for three trials and obtained unpublished data for two of the three trials.
- Pharmaceutical manufacturers of oral forms of nutritional supplements containing eicosapentaenoic acid were contacted to find out if further published or unpublished data were available.

Data collection and analysis

Study selection

From the title, abstract or descriptors, one review author (AD) reviewed the literature searches to identify potentially relevant trials for the review. Searches of bibliographies and texts were conducted to identify additional studies. Trials to be included were determined independently by two review authors (AD and BH) and assessed for inclusion in the review. Duplicate trials using the same participants but different outcomes were included only once.

Study quality

Two review authors (AD and BH and where necessary TD) independently carried out quality assessment as follows:
a) the methodological quality of the studies were evaluated using the Oxford Quality Scale, a validated scale published by Jadad et al (Jadad 1996). Justification for exclusion was documented. The scale includes an evaluation of the randomisation procedure, blinding and patient attrition. The scale uses a zero to five point rating scale ranging from one (low quality) to five (high quality) - the maximum score attainable. The three-item scale is applied as follows:

- is the study randomised? (if 'yes' add one point) An additional one point is given if randomisation was described and appropriate/or one point is deducted if the method of randomisation is inappropriate.
- is the study described as double blind? (if 'yes' add one point). An additional one point is given if described and appropriate/ one point is deduced if the method of blinding is inappropriate.
- are withdrawals and dropouts described? Description to include the number and reasons for drop-outs / withdrawals for each of the treatment groups. One point to be added if adequately described.

b) the Cochrane Concealment Assessment criteria where the following scale can be applied:

- A = adequate concealment,
- B = uncertain,
- C = clearly inadequate.

Data extraction

Using a specially designed data extraction form, two review authors (AD and BH) extracted data on patients, methods, interventions, outcomes and results. Differences in data extraction were resolved by initial referral back to the original article, followed by discussion and consensus between the two review authors (AD and BH). Where necessary, missing information or clarification was sought from the authors of the primary study.

Correspondence with authors

Three of the included studies either did not report all of the desired outcomes of interest or presented them in a format unsuitable for inclusion in the meta-analysis. An e-mail or letter requesting missing information was sent.

Data analysis

Where appropriate outcome data was entered using Cochrane Review Manager software (version 4.2) for statistical analysis to obtain an estimate of treatment effect. Tests for heterogeneity were also performed on the data. Dichotomous data was expressed as the odds ratio (OR) and results presented with 95% confidence intervals using a fixed-effect analysis. Continuous outcomes were compared using weighted mean differences in a fixed effects analysis. There were an insufficient number of trials to conduct any meaningful sensitivity analysis.

The type of analysis for each trial was recorded as follows:

A) ***entry to trial***

- baseline weight,
- estimated weight loss on entry to trial (kilograms).

B) ***outcome data***

- weight,
- body composition,
- survival,
- quality of life,
- energy expenditure,
- reduction in fatigue,
- functional/performance status,
- nutritional status,
- appetite status,
- compliance rates,
- tolerance.

RESULTS

Description of studies

Although, 759 articles were located, we found many of the citations were replicated across the three databases or referred to review articles. We located 59 potential trials for inclusion in the review. However, many of these studies did not fully meet the inclusion criteria or quality assessment threshold. Reasons for rejecting individual studies are detailed in the 'Characteristics of Excluded Studies' table. In addition we located one unpublished trial (Fearon 2005) led by the chief investigator, Professor KC Fearon from the Department of Clinical and Surgical Sciences at the Royal Infirmary of Edinburgh, UK. This trial is currently undergoing peer review prior to publication. It is hoped that at the review date of this systematic review we will be able to include the data from this trial (see 'Characteristics of ongoing studies' table) (Fearon 2005).

A total of five trials fully met the inclusion criteria for this review and provided data for analysis (Bruera 2003; Fearon 2003; Gogos 1998; Jatoi 2004; Zuijdgeest 2000).

Risk of bias in included studies

Using the Oxford Quality Scale (Jadad 1996) and Cochrane Concealment Assessment Scale, three of the five included studies (Bruera 2003; Fearon 2003 and Jatoi 2004i) were rated the highest score of '5A', one study scored '3B' (Zuijdgeest 2000) and one scored '2C' (Gogos 1998). The design and details of the quality scores of the five included trials (including Cochrane Concealment assessment) are detailed in the 'Characteristics of included studies' table.

Effects of interventions

The five trials meeting the inclusion criteria involved a total of 587 patients. Three trials compared EPA at different doses with placebo (Bruera 2003; Gogos 1998 and Zuijdgeest 2000). Two trials (Fearon 2003; Jatoi 2004) compared different doses of EPA versus matched active control (but without EPA).

Patient characteristics

Bruera 2003 randomised 91 patients (46 to fish oil and 45 to placebo) with the following characteristics: advanced cancer (defined by locally recurrent or metastatic disease) more than 5% pre-illness weight loss (time period of weight loss not specified), presence of anorexia but the ability to maintain oral food intake over the two-week study period) as well as normal cognitive status. Cancer types included: genitourinary, breast, gastrointestinal, lung, hematologic, head and neck and sarcoma tumours. At baseline, there was no significant difference between arms.

Gogos 1998 randomised 64 patients with generalised solid tumour of the following cancer types: breast, gastrointestinal, lung, liver and pancreas. Each arm was then sub-divided into the following two subgroups, those considered to be in a good nutritional state or well nourished (WN) and malnourished (MN). Patients in the well-nourished (WN) subgroups in both arms included patients who had a less than 10% weight loss over the previous six months, serum albumin of more than 30 g/L, serum transferrin of more than 2.0 g/L and a Karnofsky Performance status of more than 60. Patients in the malnourished (MN) subgroups of both arms included patients that had a weight loss of more than 10% during the previous six months, serum albumin of less than 30 g/L, serum transferrin of less than 2.0 g/L and Karnofsky Performance status of less than 60. In addition a group of 15 healthy individuals served as controls.

Zuijdgeest 2000 randomised 17 patients with different cancer tumour types including: gastrointestinal tract, pancreatic, rectal, renal, breast, oesophageal, lung, mesothelioma, cervical, carcinoid and adenocarcinoma of unknown primary site. All but one patient in the fish oil arm had metastatic disease or locoregional relapse, or both. Weight loss ranged from 5.3% to 18.1% in the preceding six months. Baseline characteristics appear to be similar although despite randomisation, energy intake at baseline was significantly higher in the EPA arm compared to the placebo arm. Sixteen healthy subjects acted as controls.

Fearon 2003 randomised 200 unresectable pancreatic cancer patients who had lost more than 5% of pre-illness weight over the previous six months. The trial was included with patients having a Karnofsky performance score of 60 or more and a life expectancy of greater than two months. The average pre-illness weight loss was 17%. At baseline there was no significant difference between the treatment arms in terms of sex, performance status and quality of life characteristics. In the EPA arm there was a greater proportion of stage IV disease patients (52%) than in the placebo arm (41%).

Jatoi 2004 randomised 421 patients with incurable cancer; lung, gastrointestinal and others. All patients had associated weight loss defined as a self-reported two-month weight loss of at least 2.3 kgs or physician estimated calorific intake of less than 20 calories/kg of body weight/day, or both. At baseline, there was no significant difference found between the three treatment arms of patient groups in terms of Eastern Cooperative oncology group performance status, Karnofsky score physician estimate of survival, patient reported appetite or medical centre of enrolment. In addition, there were no significant difference on the basis of stratification factors:
a) cancer type (gastrointestinal versus thoracic versus other,
b) severity of weight loss: less than 4.6 kg versus more than 4.6 kg in the preceding two-months,
c) planned concurrent chemotherapy versus none, and
d) age: less than 50 years versus more than 50 years.
The stratification process used was a minimization algorithm that balanced the marginal distributions.

In summary the five trials that met the inclusion criteria involved a total of 587 patients. The mean age of patients included in the treatment arms across all trials was 66.4 years compared to a mean age of 65.6 in the control arms. The ratio of males to females in the treatment arms was 172M/117F compared to 174M/124F in the control arms. In terms of study size the Zuijdgeest 2000 trial was the smallest (n = 17) with Jatoi 2004 trial recruiting the largest number of patients (n = 421).

The majority of trials included patients with a variety of tumours. Only the Fearon 2003 trial was limited to patients with pancreatic cancer.

Use of steroids

Only one study (Zuijdgeest 2000) excluded patients taking any dosage of corticosteroids. Three studies stated that patients were included if taking corticosteroids, but in the Jatoi 2004 study only short term dexamethasone (dose unstated) with chemotherapy was permitted and in Fearon 2003 study patients taking long term low dose steroids for chronic benign conditions (such as asthma) and not for physiological replacement were included. In the Bruera 2003 study patients continued with corticosteroids for the two-weeks trial (n = 8) but no details of dosage were provided. In the Gogos 1998 study there is no mention of steroids being included or excluded and despite repeated efforts to contact the authors we were unsuccessful in gaining information for clarification.

Adjunct chemotherapy and/radiotherapy

Three studies stated that they excluded patients who were undergoing current chemotherapy (Fearon 2003; Gogos 1998; Zuijdgeest 2000). The Bruera 2003 study allowed chemotherapy (n = 5) and antineoplastic hormone therapy (n = 4) and the Jatoi 2004 study allowed concurrent chemotherapy and radiotherapy.

Interventions

Comparison one - EPA versus placebo

Three trials (Bruera 2003; Gogos 1998 and Zuijdgeest 2000) compared EPA at different doses with placebo as follows:
In the Bruera 2003 trial, 60 patients with mixed cancer tumour types were randomised to receive 18 gelatin capsules of 1000 mgs of fish oil (each containing: 180 mg EPA, 120 DHA (docosahexaenoic acid) with the addition of 1 mg of Vitamin E); or 1000 mgs of a placebo capsule (olive oil). After random assignment of 19 patients (nine fish oil and ten placebo) high level of complaints of vomiting in approximately ten patients (in both arms) suggested that these patients were unable to tolerate 18 capsules/day. The trial protocol was amended to six capsules/day with encouragement to take up to 18 capsules/day. The trial lasted two weeks with assessments (subjective and objective measurements) performed at baseline and on day 14.

- In the Gogos 1998 trial, 64 patients with mixed cancer tumour types were randomised to receive either 18 g of fish oil capsules (each containing: 170 mg EPA and 115 mg DHA) or placebo (sugar tablets). The supplements were taken as six capsules three times daily. Patients in the fish oil arm also received 200 mgs of Vitamin E daily. The rationale for the addition of Vitamin E was "to compensate for the oxidative effect of omega-3 PUFA" (Gogos 1998). The trial lasted for 40 days. Assessment took place at the end of the 40 days study period.
- In the Zuijdgeest 2000 trial, 17 patients with mixed cancer tumour types and 16 healthy subjects were randomised to receive either 6 g of EPA ethyl ester capsules or placebo capsules (containing 6 g of oleic acid ethyl ester capsules). The supplements were provided in 0.5 capsules and taken as four capsules three times daily. The trial lasted for one week with assessment (subjective and objective measurements) performed at baseline, day two and seven.

Comparison two - EPA versus matched active treatment control

Two trials (Fearon 2003 and Jatoi 2004) compared different doses of EPA versus matched active control.

1. In the Fearon 2003 trial, 200 patients with pancreatic cancer were randomised to receive either two cans of an oral nutritional supplement which provided 2.2 g EPA (each can providing 1.1 g EPA, plus antioxidants Vitamin A, E, C and selenium, 310 kcal, 16 g protein and 6 g fat) or two cans of an identical supplement, but without the addition of EPA and enhanced antioxidants. The trial lasted for eight weeks with assessment (both subjective and objective measurements) performed at baseline, four and eight weeks.
2. In the Jatoi 2004 trial, 421 patients with mixed cancer tumour types were randomised to one of three arms as follows:

- Arm one - received a twice daily EPA supplement (providing 1.09 g per can) plus placebo liquid suspension (instead of Megestrol Acetate liquid suspension);
- Arm two - received Megestrol acetate (MA) liquid suspension (600 mg/day) plus twice daily a matched nutritional supplement (without EPA);or,
- Arm three - received a combination of MA plus the same twice daily EPA supplement as Arm one.

The median number of days on the study was slightly more than three months for the arms as a whole. All patients were assessed weekly for four weeks and then monthly with patients continuing treatment as long as both the patient and treating oncologist considered it beneficial, or acceptable, to the patient.

Compliance

Two trials reported details on compliance. In the Bruera 2003 trial, patients in the EPA arm took a mean (SD) of 9.8 +/- 4 capsules per day compared to those in the placebo arm who took a mean (SD) of 9.2 +/- 3 capsules (P = not significant). In the EPA arm this resulted in patients consuming an average of 1.8 g EPA/day.

In the Fearon 2003 trial, patients in both arms consumed an average of 1.4 cans (equivalent to 40 kcal, 21 g protein/day). In the EPA arm this resulted in patients consuming an average of 1.5 g EPA/day.

No details were given for compliance for three trials (Gogos 1998; Jatoi 2004; Zuijdgeest 2000).

Withdrawals and dropouts

All five trials reported the total number of dropouts and withdrawals but the Gogos 1998 trial failed to give specific details for each arm of the trial. Gogos 1998 reported four withdrawals due to poor compliance, but details of which arm patients belonged to were not recorded.

For four trials (Bruera 2003; Fearon 2003; Jatoi 2004 and Zuijdgeest 2000) total numbers of patient withdrawal and dropout was 64 in the EPA arms and 62 in the control arms. None of the trials reported that withdrawals were due to lack of efficacy of treatment (see 'Additional Tables', Table one, for individual trial details of withdrawals and dropouts).

Tolerance

The patient's ability to tolerate the supplements was measured in relation to side effects and adverse events. These included gastrointestinal symptoms (e.g. mild abdominal discomfort, transient diarrhoea, nausea and vomiting) particularly in the higher dosage trials. In addition, there was a higher incidence of impotence in the Jatoi 2004 study in those patients receiving MA, although such patient-reported symptoms were not assessed at baseline. Only one of the trials (Fearon 2003) found there were significantly fewer adverse events in the EPA arm compared with the active control arm. The other four trials showed a tendency towards fewer adverse events in the EPA arm, but the differences were not significant. Combining data on adverse events from Comparison one (EPA versus placebo) and Comparison two (EPA versus active treatment control group) in a meta-analysis of all the trials supported Fearon 2003's findings that there were significantly fewer adverse events. A plausible explanation of this finding is that these adverse events were due to the patient's deteriorating condition and not the action of EPA, placebo or active control.

Results

As this review focuses on specific outcomes measured using validated tools, the results reflect these criteria. Whilst some trials also reported results (such as immune status) these have not been incorporated in the present work.

Comparison one - EPA versus placebo

Three trials looked at EPA versus Placebo (Bruera 2003; Gogos 1998 and Zuijdgeest 2000). Apart from adverse events, only one outcome, nutritional status as measured by total kilo joules intake had data that could be pooled across two trials (Bruera 2003; Zuijdgeest 2000).

Comparison two - EPA versus matched active treatment control

Two trials looked at EPA versus matched active treatment control. For each of these included studies the control used a matched active treatment as follows:

1. in the Fearon 2003 study an EPA nutritional supplement was compared with a matched nutritional supplement (without EPA) in the control arm;
2. in the Jatoi 2004 study, three comparison arms were incorporated in the study design:

- Arm one - patients received an EPA supplement twice daily, containing 1.09 g; EPA plus placebo liquid suspension (instead of the appetite stimulant, Megestrol Acetate liquid suspension);

- Arm two - patients received the appetite stimulant Megestrol Acetate (or MA) in a liquid suspension which provided 600 mgs/day plus twice daily a matched nutritional supplement as that in Arm one (without EPA);
- Arm three - patients received a combination of the same appetite stimulant, MA plus the same twice daily EPA supplement as Arm one.

For the purpose of this systematic review, however, we have selected two of the three comparisons (Arm two and Arm three) so that the only difference between these two arms of the study was the addition of EPA. In this way, we were able to compare some of the relevant outcome measures, namely: weight, Quality of Life and adverse events.

Although planned meta-analysis of data for both comparisons were not conducted for the majority of reported outcomes due to the lack of common measures, a narrative summary provides an indication of the likely benefits and harms of the remaining outcomes of interest.

Primary outcomes

1. Weight gain

Comparison one - EPA versus placebo

Only one of the three included studies, Bruera 2003 (Assessment based on 60 patients) reported weight gain. In this trial, although there was a slight increase in weight gain for patients in the EPA arm the results were not significant.

Comparison two - EPA versus matched active treatment control

- In Fearon 2003 study patients in both arms receiving either nutritional supplements (with or without EPA) had a statistically significant increase in overall weight gain. In addition, Fearon *et al.* conducted post-hoc analysis using Pearson's parametric test of correlation to examine possible dose-response relationships in either arm of the study over the eight week period. Fearon 2003 found there was a significant positive correlation in the EPA arm between daily supplement intake and increase in body weight (expressed as Pearson's correlation coefficient r = 0.50, P < 0.001). Maximum weight was achieved in the EPA arm with an intake which provided 1.5 to 2.2 g of EPA. There was no such correlation in the control arm. However, although interesting, it should be noted that this was exploratory analysis using post-hoc data analysis which is fraught with hazard.
- In the Jatoi 2004 study, the primary end point was a 10% weight gain above baseline. When weight gain was evaluated with increments of more than 10% weight increase, patient-reported weight gained showed 5%, 13% and 7% in the EPA treated, MA treated and combined treatment arms respectively, but the results were not statistically significant (P = 0.08). We requested clarification from the authors and obtained actual weight gain figures (rather than percentage).
- Combining data from these two included studies (Fearon 2003 and Jatoi 2004) showed there was no significant benefit of EPA for weight gain (P = 0.63). Indeed, the combination of EPA with MA (versus MA alone) resulted in the combined therapy being worse.

2. Body composition

Body composition refers to assessment of subcutaneous fat and muscle tissue and can be more useful to assess the patient's nutritional status than gross body weight which may be complicated by fluid retention if patients develop oedema or ascites. The use of techniques such as bioelectrical impedance analysis or anthropometry can provide a more accurate description of the nature of tissue loss. Bioelectrical impedance analysis is a non-invasive method of determining body composition based on the measurement of reactance and resistance to electrical flow (Kyle 2004). The most commonly used anthropometric measures are triceps skin fold thickness (or TSF) and mid-upper arm circumference (or MAC) which are combined to provide an indirect determinate of mid-arm muscle area (or MAMA). Other more specialised techniques such as dual-energy X-ray absorption and computer tomography can be used although both techniques involve high capital investment and may not be suitable for use in the clinical setting (Brodie 1998).

Comparison one - EPA versus placebo

Of the three included studies, only one study (Bruera 2003) reported body composition. Using anthropometry, lean body mass was estimated using anthropometric measurements carried out on days one and 14, but were not statistically significant difference for patients in the EPA treatment arm compared with those in the placebo arm.

Comparison two - EPA versus matched active treatment control

Of the two included studies, only the Fearon 2003 study measured lean body mass which was measured using bioelectrical impedance analysis. When compared to rate of loss at baseline there was a significant attenuation of lean body mass in both of the study arms (EPA and Control) at four and eight weeks (P < 0.001 for all within group comparisons). However, there was no significant difference between groups (P = 0.88). Again, although not the primary outcome of the study, Fearon 2003 conducted post-hoc analysis to examine for a potential dose-response relationship in either arm (EPA or Control). This post-hoc analysis showed a significant positive increase in the EPA arm between daily supplement intake and increase in lean body mass (r = 0.33, P = 0.036). The correlation between intake and lean body mass gain was significantly greater in the EPA arm than in the control arm (P = 0.0043).

3. Survival

Comparison one - EPA versus placebo

Of the three included studies, only the Gogos 1998 provided survival data. Actual numbers for survival days were not provided and we were unable to confirm these figures. Survival days have been estimated from the published diagram. This data suggests that all patients in the EPA arm (n = 30) had a statistically significant (P = < 0.025) increase in survival compared with the placebo arm. In the EPA arm, well-nourished (WN) patients survived 870 days and malnourished (MN) patients survived 600 days compared to all patients (n = 30) in the placebo arm (WN = 480 days, MN = 242 days). In addition, best survival was noted for the group of WN patients in the EPA arm compared to the MN patients in the placebo arm (870 days compared to MN = 242 days).

Comparison two - EPA versus matched active treatment control

Although both included studies (Fearon 2003; Jatoi 2004) reported some data on survival there were insufficient data available to combine in a meta-analysis.

- In the Fearon 2003 study there was no significant difference in median duration of survival between the two arms: EPA arm (Median 142 days) compared to Control arm (Median 128 days).
- In the Jatoi 2004 study there was no significant difference (P = 0.82) in median duration of survival across the three arms: EPA arm (Median 147 days), Megestrol arm (Median 128 days) and Combined EPA/Megestrol arm (Median 151 days).

Secondary Outcomes

4. Quality of life

Comparison one - EPA versus placebo

- Only one of the three included studies (Bruera 2003) reported the patient's overall sensation of well being which was measured using a Visual Analogue Scale (VAS) (zero to 100 mm where 0 mm = best and 100 mm worst). This study reported that there was no significant improvement in the treatment arm compared to that of the placebo arm.

Comparison two - EPA versus matched active treatment control

- There were two studies (Fearon 2003 and Jatoi 2004) that reported quality of life measures using different validated questionnaires: in the Fearon 2003 study, quality of life was measured using two quality of life self-administered questionnaires, the EQ-5D which is a generic quality of life measure that provides a single index score, and the EORTC Q30 questionnaire which is a multi-dimensional cancer specific questionnaire.
- Only the overall scores on physical performance and global health status components were reported.
- In the Jatoi 2004 study, a single item Uniscale quality of questionnaire which measured the global quality of life was reported in the published data.
- In the Fearon 2003 study post-hoc analysis to examine potential dose-response relationships in either the treatment or control, revealed that intake of the treatment supplement correlated positively with quality of life as measured by the EQ-5D questionnaire, but that there was no similar statistically significant correlation observed in the control arm.
- A meta-analysis was performed on the quality of life outcomes for these two studies (Fearon 2003; Jatoi 2004) which provided no evidence to suggest that quality of life in the treatment arm was significantly improved compared with that of the control arm (P = 0.45).

5. Energy expenditure

None of the included studies for either comparisons measured energy expenditure.

6. Reduction in fatigue

Comparison one - EPA versus placebo

- Of the three included studies, only one study (Bruera 2003) measured fatigue or tiredness using a VAS (zero to 100 mm where 0 mm = best, 100 mm = worst). Where negative numbers indicated an improvement in VAS rating, there was a trend for improvement for patients, in both arms of the study, but there was no significant improvement in reduction of tiredness in either arm.

Comparison two - EPA versus active treatment control

- None of the studies measured reduction in fatigue.

7. Functional or performance status

Functional or performance status refers to the patient's ability to function independently and includes the patient's ability to work and to be active. There are a number of validated, quick and simple to use performance tools (such as the Karnofsky Performance Scale and the World Health Organisation Scale) which have been used with cancer patients.

Comparison one - EPA versus placebo

- Although two studies reported performance status (Bruera 2003; Gogos 1998) there were insufficient data available to be combined in a meta-analysis;
- In the Bruera 2003, performance status was measured using both the Karnofsky Performance Scale and the Edmonton Functional Assessment Test, but there was no significant difference in the functioning status for patients in the treatment arm compared with placebo;
- In the Gogos 1998 study performance status was measured using the Karnofsky performance scale. This study reported a statistically significant increase (P = 0.01) in performance status 51+/-3 to 72 +/-4 (expressed as Mean with SD) in the group of malnourished cancer patients' treatment arm, compared to the control arm. However, there were no published or unpublished details available on the Karnofsky performance status for either the well nourished cancer patients of the treatment group or both malnourished and well nourished cancer patients in the control arm.

Comparison two - EPA versus matched active treatment control

- Only one of the two included studies (Fearon 2003) assessed functional or performance status using the Karnofsky Performance Scale and reported that there was no significant differences between the arms, but there were no published data given.

8. Nutritional status

A variety of subjective and objective methods may be used to assess nutritional status. As well as gross weight and lean body mass which have already been included in the systematic review as separate outcomes, other measurements of nutritional status may include administration of nutritional assessment questionnaires as well as assessment of dietary intake and changes in laboratory values related to nutritional status. Only data on dietary intake was available from three of the included studies as follows.

Comparison one - EPA versus placebo

Two studies (Bruera 2003; Zuijdgeest 2000) measured total energy intake as calorific intake per day (Bruera 2003) and kilo joules/day (Zuijdgeest 2000).

- In the Bruera 2003 study patients recorded dietary intake by estimating food quantities with reference to standard

portions or household measures. Data were collected for three consecutive days at the beginning and end of the 14 day treatment period. Food items were coded and the nutrient content estimated using a computer programme (Food Processor II nutrient analysis program).

- In the Zuijdgeest 2000 study patients recorded their own dietary intake before and during supplementation (baseline, day two and seven).
- For the purpose of the meta-analysis, calorific intake has been converted to kilo joules/day. Combination of the results from these two studies provided no evidence to suggest that total energy intake was significantly improved compared to that of the control arm (P = 0.55).

Comparison two - EPA versus matched active treatment control

Of the two included studies, one study (Fearon 2003) assessed nutritional status by measuring total calorific and protein intake per day. At baseline, patients in both arms of the study were consuming insufficient intakes of energy and protein to maintain body weight. Although spontaneous intake was partially reduced, when patients in both the EPA Control arm consumed an average 1.4 cans of oral supplement (equivalent to 420 kcal and 21 g protein/day) oral supplementation in both arms provided a net gain in total energy and protein intake.

9. Appetite status

Comparison one - EPA versus placebo

Only the (Bruera 2003) study measured appetite status which was measured using a VAS (zero to 100 mm where 0 mm = best and 100 mm = worse) and negative numbers denote improvement in VAS. Although there was a trend for appetite improvement in both arms (Treatment Arm: -9.8+/-20, Placebo Arm: -9.0+/-27) there was no significant improvement in appetite in either arm.

Comparison two - EPA versus matched active treatment control

Only the Jatoi 2004 study measured appetite status using the NCCTG questionnaire which provided useful data to describe the percentage of patients that reported varying levels of improvement above baseline intake. There was no significant difference between the two arms.

DISCUSSION

The aim of this review was to assess the effectiveness of EPA for the management of the distressing weight loss syndrome, cachexia, often seen in patients with advanced cancer. Despite a thorough search for evidence, too few well-conducted studies with common outcomes of interest were available to conduct a meta-analysis which has made it difficult to draw conclusions. At present, therefore, limited evidence does not support the use of fish oils containing EPA either on its own or in the presence of other treatments.

Comparison one - EPA versus placebo

Three small studies (Bruera 2003; Gogos 1998; Zuijdgeest 2000) met the methodological inclusion criteria and reported results on a total 150 patients with mixed cancer tumours and weight loss. Apart from adverse events, it was frustrating that there was only one common outcome measure, nutritional status, that could be compared across two of these three studies. There were, therefore, insufficient data to determine whether oral EPA was better than placebo for the patient identified outcomes of interest to this systematic review.

- Although the small study by Bruera 2003 which observed mixed tumour cancer patients over 14 days, and reported a non-significant weight gain (using a mean dose of 1.8 g EPA) compared to the placebo arm, it is possible that: 1) the study was underpowered and a larger study may be required; and, 2) it's doubtful whether EPA given over a longer study period could prove more effective than the placebo since 14 days may not be enough time to assess such outcomes. The supplement dose tolerated may be too low to produce meaningful improvement.
- Of particular interest was the results of the small study by Gogos 1998 which reported a significant increase in survival in the EPA arm. However, poor reporting as well as incomplete and unconfirmed survival data from this published study leaves questions unanswered. The potential survival advantage of EPA still needs to be explored in a larger, clearly reported study.

Comparison two - EPA versus matched active treatment control

Two large high quality multi-centered studies were identified (Fearon 2003; Jatoi 2004). In the Fearon 2003 study they compared a protein energy supplementation (with or without EPA). Whilst for the Jatoi 2004 study we took the data from two of the three arms (the appetite stimulant, Megestrol acetate combined with an EPA protein supplementation versus Megestrol acetate appetite stimulant and protein supplementation without EPA). In this way the only difference between the two arms was the addition of EPA.

- Both studies provided no evidence that EPA improves symptoms associated with the cachexia syndrome in patients with advanced cancer. On an intention to treat basis, it appears that EPA was the same or worse than the matched active control for all of the outcomes of interest.
- However, In the Fearon 2003 it is interesting to note the authors suggest that poor compliance may have resulted in patients not receiving sufficient EPA. When the authors did a dose response calculation on the amount of EPA supplement consumed versus non-EPA matched supplement, they found that there was a significant weight gain in the EPA compared to the matched control arm. It is possible that providing EPA in the form of a nutritional supplement (compared to say Bruera 2003 study that used EPA capsules) is difficult for patients to consume in sufficient quantities. However, the interpretation of this is not straightforward as any post-hoc analysis is fraught with hazards. Regression analysis where one or more indicators or independent variables are used to predict a particular outcome would have given a more meaningful result. In addition, no difficulty with compliance was noted in the Jatoi 2004 study.
- Although we used data from two trials, only the Fearon 2003 study made a direct comparison between the effect of the protein supplementation with and without EPA for patients with unresectable pancreatic cancer. In the Jatoi 2004 study, the combination of EPA and the appetite stimulant, megestrol acetate (MA) showed inferior results compared to using single-agent MA.

AUTHORS' CONCLUSIONS

Implications for practice

The conduct of this systematic review did not enable us to confirm or refute previous literature on the use of EPA and it was not possible to recommend its use in clinical practice. Whilst the results from this systematic review suggests that there is little evidence of harm from using EPA it may not be reasonable to suggest its use in people who are very ill or if palatability is low and problems of compliance occur. There appears to be no significant improvement in management of symptoms by the addition of EPA to that gained from patients taking a high calorie, high protein nutritional supplement with or without the addition of the appetite stimulant, Megestrol Acetate (MA). Indeed it may be that combining EPA with MA may have a slight inhibitory action on MA.

Implications for research

The conduct of this systematic review has revealed a paucity of well-conducted randomised controlled trials to adequately answer the review questions posed. Furthermore many of the trials were poorly reported which made it difficult and time-consuming to assess their suitability. However, we found improved reporting in those trials which appear to have been designed and reported in accordance with the Consolidated Standards of Reporting Trials statement (CONSORT Statement) which includes a 22-item checklist and a flow diagram and its use should be encouraged (Altman 2001). There is a need to conduct good quality large scale randomised controlled trials using EPA compared to placebo with different cancer types. In particular, the potential survival advantage of the addition of EPA needs to be explored. We also found that many of the included trials permitted concurrent use of other supportive therapies such as corticosteroids (four of the five trials) palliative chemotherapy (one trial) and radiotherapy (two trials) which may have masked the true benefit of the addition of EPA alone. Future trials could exclude other supportive therapies or incorporate appropriate stratification. In addition, it may be necessary for future studies to consider using a more palatable formulation of EPA. Finally, we found a paucity of studies that recruit patients at an early stage in their disease progression. Recruiting patients in to the study with minimal weight loss and at an earlier stage may provide a better opportunity to encourage compliance and provide enough time to assess meaningful improvements. The challenges will be identifying and recruiting suitable cancer patients into such a study.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bruera 2003

Methods	Randomised double-blind controlled parallel trial
Participants	N = 91 (E = 46 C = 45) Mixed Tumour Cancer
Interventions	E = Up to 18 capsules (1000 mg fish oil containing 180 mg EPA, 120 mg DSA) + 1 mg Vit E C = up to 18 capsules (1000 mg olive oil placebo)
Outcomes	Appetite, nausea, tiredness, well-being, performance, anthropmetric measurements, weight gain, calorific intake, tolerance
Notes	Jadad score 5 = 1+1+1+1+1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Fearon 2003

Methods	Randomised double-blind controlled parallel trial
Participants	N = 200 (E = 95, C = 105) Pancreatic cancer.
Interventions	E = two cans nutritional supplement containing 32 g protein and 2.2 g EPA C = two cans nutritional supplement containing 32 g protein. Duration: eight weeks
Outcomes	Body weight gain kg/month LBM gain kg/month Survival/days Quality of life, Karnofsky scores
Notes	Jadad score 5 = 1+1+1+1+1

Risk of bias

Bias	Authors' judgement	Support for judgement

Fearon 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Gogos 1998

Methods	Randomised controlled parallel trial
Participants	N = 60 E = 30 C1 = 30 Mixed tumours
Interventions	E = 18 g Fish oil (ea = 170 mg EPA, 115 DHA) + 200 mg Vit E C = placebo sugar tablets
Outcomes	Immune status Survival
Notes	Jadad score 2 = 1+0+0+1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	C - Inadequate

Jatoi 2004

Methods	Randomised double-blind controlled parallel trial
Participants	N = 421 E = 141 C1 = 140 C2 = 140
Interventions	E = 2 cans EPA supplement 1.09 g + placebo C1 = MA liq susp 600 mg/d + placebo C2 = Both
Outcomes	- Body weight gain - Quality of Life - Appetite - Survival - Tolerance
Notes	Jadad score 5 = 1+1+1+1+1

Risk of bias

Bias	Authors' judgement	Support for judgement

Jatoi 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Zuijdgeest 2000

Methods	Randomised double-blind controlled parallel trial
Participants	N = 17 (E = 9, C = 8) Upper GI N = 4, Pancreatic N = 2, Rectal N = 1, Carcinoid = 1, Mesothelioma N = 1, Cervix N = 1, Oesophageal N = 1, Breast N = 2, Renal N = 1, NSC Lung = 2, Adenocarcinoma N = 1
Interventions	E = 6 g EPA ethyl esters (96.8 % purity) C = 6 g oleic acid ethyl esters (79 % purity) Duration: seven days
Outcomes	Resting Energy Expediture Energy intake (kJ/d) Day 0, 2, 7)
Notes	Jadad score 3 = 1+0+0+1+1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Atkinson 1998	Participants not cancer patients
Barber 1998	Before and after trial Jadad score = 0+0+0
Barber 1999a	Part of Barber's 2001 study Non-randomised open labelled trial No control group Jadad score = 1 (0+0=1)
Barber 1999b	Non-randomised open labelled trial Jadad score = 1 (0+0+1)
Barber 2000	Non-randomised open labelled trial Jadad score = 1 (0+0+1)
Barber 2001a	Non-randomised open labelled dose escalation trial No control group Jadad score = 1 (0+0=1)
Barber 2001b	Non-randomised open labelled trial No Control group

Study	Reason for exclusion
	Jadad score = 1 (0+0+1)
Barber 2004	Non randomised open labelled Before and After Trial No control group Jadad score = 1 (0+0+1)
Bauer 2005	Non randomised open trial No control group Jadad score = 1 (0+0+1) Part of Fearon's 2001 study
Braga 1995	Post operative administration of EPA supplementation Eligible for curative elective surgery only Excludes palliative cancer patients
Braga 1996a	Postoperative administration of EPA supplementation Eligible for curative elective surgery only Excludes palliative cancer patients/evidence of metastasis
Braga 1996b	Preoperative administration of EPA supplementation Eligible for curative elective surgery only Excludes palliative cancer patients
Braga 1999	Perioperative administration of EPA supplementation Eligible for curative elective surgery only Excludes palliative cancer patients
Braga 2002	Preoperative administration of EPA supplementation Eligible for curative elective surgery only
Braga 2002a	Perioperative and preoperative administration of EPA supplementation Excludes patients with equivalent or more than 10% weight loss
Brosnahan 2003	Review of the Gianotti 2002 study
Burns 1999	Phase I dose response cohort study No control group Jadad score = 1 (0+0+1)
Burns 2004	Non-randomised open trial No control group Jadad score = 1 (0+0+1)
Daly 1992	Postoperative administration of EPA supplementation Published outcomes: immune data, postoperative complications, length of stay in hospital
Daly 1995	Pre and Postoperative administration of EPA supplementation Not clear if curative or palliative Published outcomes: wound healing complications, infections, postoperative inpatient death, length of stay in hospital
Davidson 2004	Retrospective study on survival data from weight stabilisation Part of Fearon 2003 study
Di Carlo 1999	Postoperative administration of EPA supplementation Published outcomes: route of administration, postoperative complications, infectious complications, length of stay in hospital

Study	Reason for exclusion
Falconer 1994	Non-randomised open trial No control group Jadad Score = 0 (0+0+0)
Fearon 2001	Duplication of included study (Fearon 2003) multi-centered trial
Gianotti 1997	Postoperative administration of EPA supplementation Eligible for curative elective surgery only Excludes palliative care Published outcomes: post-operative infections and length of hospital stay
Gianotti 1999	Perioperative administration of EPA supplementation Excludes weight loss of equal to or more than 10 % with respect to usual body weight last six months Only two palliative cancer patients included (control) Published outcomes: post-operative infections and length of hospital stay
Gianotti 2002	Preoperative administration of EPA supplementation Excludes weight equal to or more than 10 % with respect to usual body weight in past six months Published outcomes: post-operative infections and length of hospital stay
Gramaglia 1999	Retrospective Study; no controls Jadad Score = 0 (0+0+0)
Heller 2004	Post operative TPN (Total parenteral nutrition) of either Fish oil emulsion and soya oil versus soya oil alone
Heslin 1997	Early Postoperative enteral feeding with EPA supplementation Published outcomes: postoperative complications, length of hospital stay, postoperative mortality
Keman 1995	Early Postoperative enteral feeding with EPA supplementation Published outcomes Immunological data only
Mantovani 2004	A Phase II Non-randomised open trial (on-going) No control group Jadad score = 1 (0+0+1)
McCarter 1998	Preoperative administration of EPA supplementation 8/51 >10% weight loss Published outcomes: Immune function, infectious complications
Moses 2001	Poster presentation Sub-analysis of included study (Fearon 2003) looking at 19 patients Outcomes: total energy expenditure and resting energy expenditure
Moses 2002	Poster presentation Sub-analysis of included study (Fearon 2003) looking at 24 patients Outcomes: total energy expenditure and resting energy expenditure
Persson 2005	No control or placebo arm Fish oil capsules (4.9 g of EPA, 3.2 g of DSA) versus melatonin 18 mg/day 1+0+1 = 2
Pratt 2002	Part of Bruera 2003 study Published outcome measures: plasma and neutrophil fatty acid composition
Read 2004	Open pilot study using 2 g EPA within a high protein concentrated supplement No randomisation, no blinding

Study	Reason for exclusion
	Description of dropouts given Jadad score = 0+0+1 = 1
Rodrigo 1997	Randomised open trial No description of withdrawals/dropouts Only 7/30 cancer patients Jadad score = 0+0+0 = 0 Jadad Score =1(1+0++0)
Schilling 1995	Postoperative administration of EPA supplementation Published outcomes: immune function, infectious complications, postoperative hospital stay
Senkal 1995	Postoperative administration of EPA supplementation Published outcome: immune function
Senkal 1997	Early postoperative feeding with EPA supplementation Published outcomes: reduced infections, wound complications, decreased treatment costs
Senkal 1999	Perioperative Enteral administration of EPA supplementation Published outcomes: postoperative complications, length of hospital stay, decreased treatment costs
Swails 1997	Postoperative enteral feeding of EPA supplementation Published outcome: prostaglandin release from mononuclear cells
Synderman 1999	Pre and postoperative administration of EPA supplementation Eligible for curative surgery cancer patients only Published outcomes: reduction of postoperative infections, wound healing complications, length of stay in hospital
Tashiro 1998a	Open controlled trial no control group Published outcome: post-operative immunity function only Jadad score = 0 (0+0+0)
Tashirom 1998b	Open controlled trial postoperative Chemoradiation therapy No weight loss recorded No relevant clinical outcomes recorded (i.e., postoperative immunity function only) Jadad Score = 0 (0+0+0)
Vignali 1995	Preoperative administration of EPA supplementation Published outcomes: immune and nutritional parameters evaluated No relevant clinical outcomes
vonMeyenfeldt 2002	Poster presentation Sub-analysis of included study (Fearon 2003) Outcomes: quality of life and grip strength
Wachtler 1995	Preoperative administration of EPA supplementation Published outcomes; immune status, post-operative infection No relevant clinical outcomes
Wigmore 1996	Before and after study No control group Jadad score = 0 (0 = +0+0)
Wigmore 1997	Part of a Phase 1

Study	Reason for exclusion
	Non-randomised Trial No control group No relevant clinical outcomes In vitro and in vivo study looking at ability of EPA to down-regulate the acute-phase response Jadad score = 0 (0+0+0)
Wigmore 2000	Before and after trial Jadad score = 0 (0+0+0)

Studies rejected if they scored less than two on the Oxford Jadad scale

Characteristics of ongoing studies *[ordered by study ID]*

Fearon 2005

Trial name or title	A DBPCR Multi-centre Phase Dose Response study of EPA 95% Diester Capsules in patients with cancer cachexia
Methods	
Participants	243 lung & gastrointestinal patients to be recruited 81 patients in each of three groups
Interventions	One group = 4 g EPA. Two groups = 2 g EPA Three groups = placebo Eight weeks duration
Outcomes	Primary Ourcomes: Total body weight Secondary Outcomes Body composition Acute protein response Quality of Life Performance Status Plasma & Red cells phospholipids
Starting date	1998
Contact information	Professor KC Fearon Depart of Clinical & Surgical Sciences, Royal Infirmary of Edinburgh, The Lothian University Hospitals NHS Trust, Lauriston Place, EDINBURGH EH3 9YW
Notes	Trial sponsored by Scotia Pharmaceutical Industry which subsequently went into liquidation Professor Fearon has obtained data and is currently analysing this data

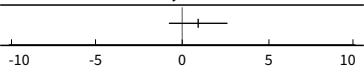
DATA AND ANALYSES

Comparison 1. Oral EPA at any dose versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Differences in weight	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Differences in lean body mass	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Resting Energy expenditure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Any Adverse Events	2	77	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.31, 1.95]
5 Appetite status	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Fatigue	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Performance status - karnofsky score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Performance scales = Edmonton Functonal Assessment Test	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Total Calorific intake	2	77	Std. Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.25, 0.65]
10 Nausea	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Wellbeing	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

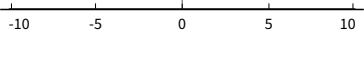
Analysis 1.1. Comparison 1 Oral EPA at any dose versus placebo, Outcome 1 Differences in weight.

Study or subgroup	EPA N	EPA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bruera 2003	30	0 (2.8)	30	-0.9 (3.8)		0.92[-0.77,2.61]



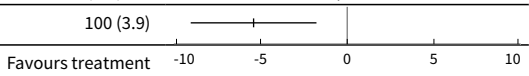
Analysis 1.2. Comparison 1 Oral EPA at any dose versus placebo, Outcome 2 Differences in lean body mass.

Study or subgroup	EPA N	EPA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bruera 2003	30	0.5 (6.2)	30	0.3 (3)		0.15[-2.31,2.61]



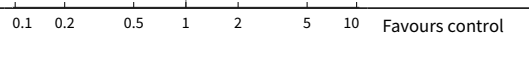
Analysis 1.3. Comparison 1 Oral EPA at any dose versus placebo, Outcome 3 Resting Energy expenditure.

Study or subgroup	Placebo		EPA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Zuijdgeest 2000	9	94.6 (3.7)	8	100 (3.9)		-5.4[-9.03,-1.77]



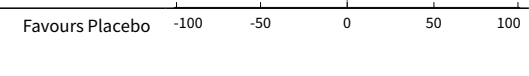
Analysis 1.4. Comparison 1 Oral EPA at any dose versus placebo, Outcome 4 Any Adverse Events.

Study or subgroup	EPA	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Bruera 2003	13/30	14/30		76.25%	0.87[0.32,2.42]
Zuijdgeest 2000	2/9	3/8		23.75%	0.48[0.06,3.99]
Total (95% CI)	**39**	**38**		**100%**	**0.78[0.31,1.95]**
Total events: 15 (EPA), 17 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.26, df=1(P=0.61); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					



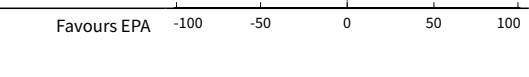
Analysis 1.5. Comparison 1 Oral EPA at any dose versus placebo, Outcome 5 Appetite status.

Study or subgroup	EPA		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bruera 2003	30	-9.8 (20)	30	-9 (27)		-0.8[-12.82,11.22]



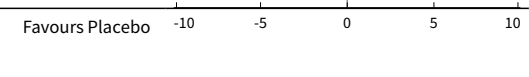
Analysis 1.6. Comparison 1 Oral EPA at any dose versus placebo, Outcome 6 Fatigue.

Study or subgroup	EPA		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bruera 2003	30	-5.5 (22)	30	4.2 (33)		-9.7[-23.89,4.49]

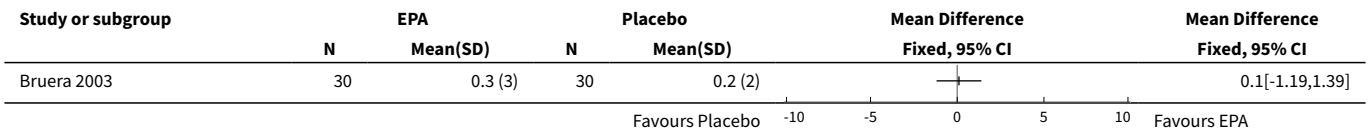


Analysis 1.7. Comparison 1 Oral EPA at any dose versus placebo, Outcome 7 Performance status - karnofsky score.

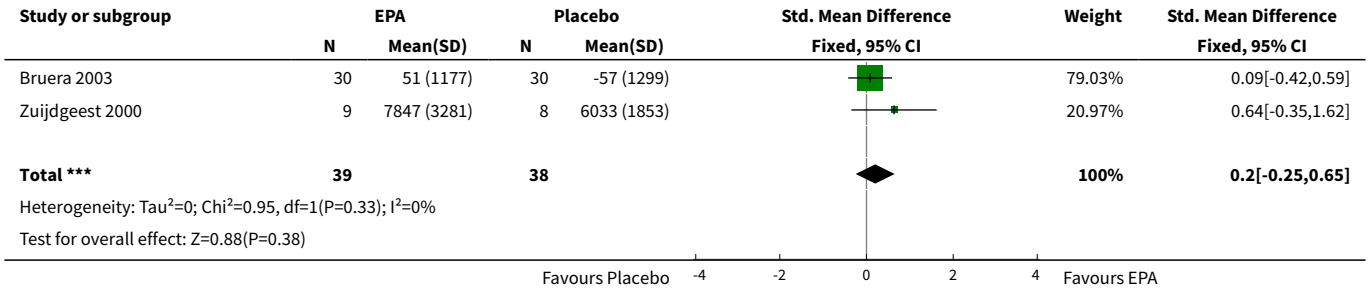
Study or subgroup	EPA		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bruera 2003	30	0 (8)	30	-1 (10)		1[-3.58,5.58]



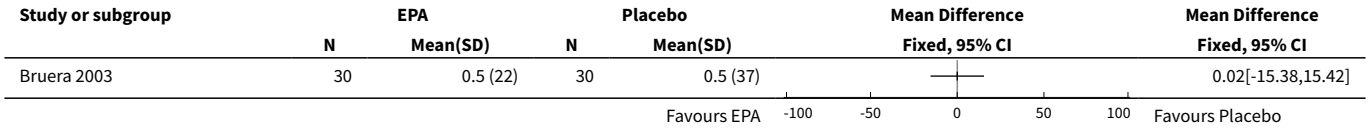
Analysis 1.8. Comparison 1 Oral EPA at any dose versus placebo, Outcome 8 Performance scales = Edmonton Functonal Assessment Test.



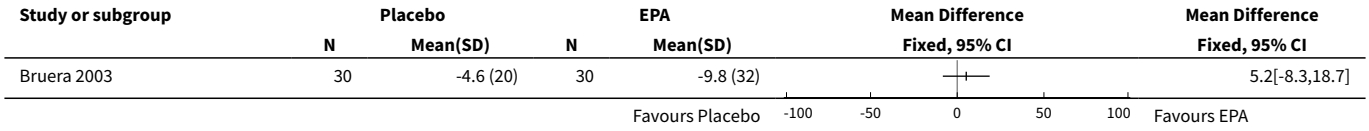
Analysis 1.9. Comparison 1 Oral EPA at any dose versus placebo, Outcome 9 Total Calorific intake.



Analysis 1.10. Comparison 1 Oral EPA at any dose versus placebo, Outcome 10 Nausea.



Analysis 1.11. Comparison 1 Oral EPA at any dose versus placebo, Outcome 11 Wellbeing.

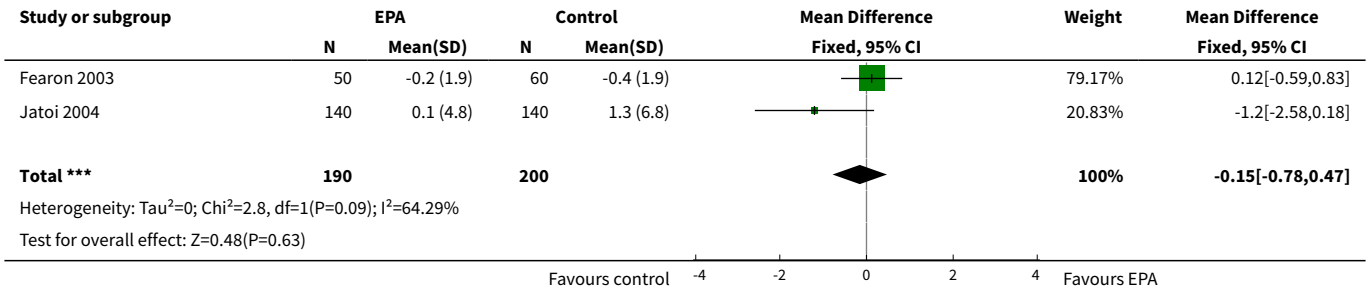


Comparison 2. Oral EPA versus control

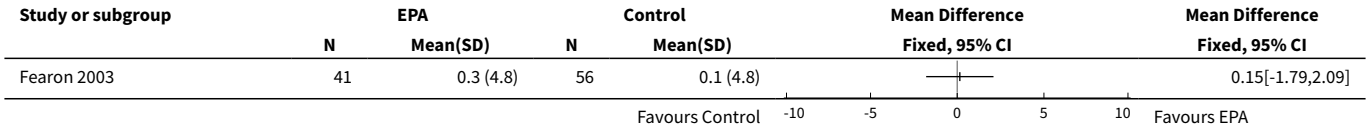
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight or weight change	2	390	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.78, 0.47]
2 lean body mass or change in LBM	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Any Adverse Events	2	456	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.25, 0.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Performance status	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Quality of Life	2	384	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-6.11, 2.70]
6 Total Calorific intake	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

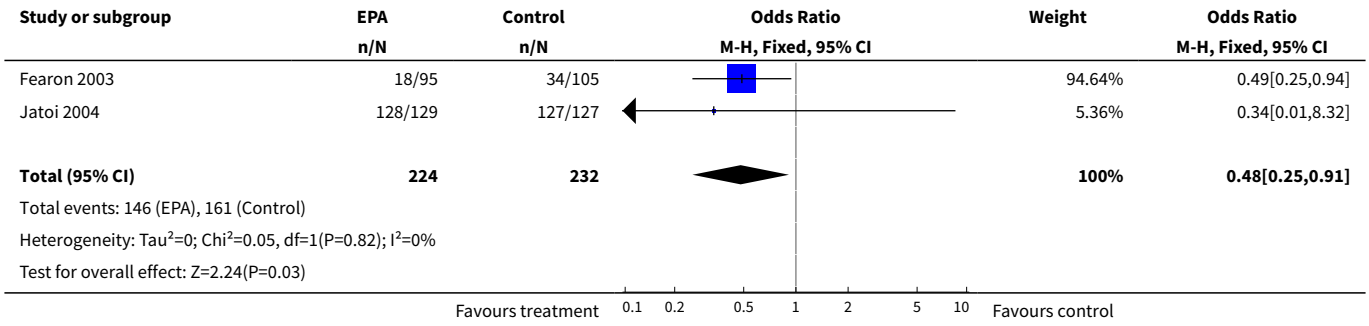
Analysis 2.1. Comparison 2 Oral EPA versus control, Outcome 1 Weight or weight change.



Analysis 2.2. Comparison 2 Oral EPA versus control, Outcome 2 lean body mass or change in LBM.

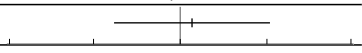


Analysis 2.3. Comparison 2 Oral EPA versus control, Outcome 3 Any Adverse Events.



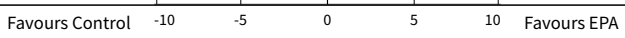
Analysis 2.4. Comparison 2 Oral EPA versus control, Outcome 4 Performance status.

Study or subgroup	EPA N	EPA Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Fearon 2003	50	-4 (10.9)	62	-4.7 (13.4)		0.68[-3.81,5.17]



Analysis 2.5. Comparison 2 Oral EPA versus control, Outcome 5 Quality of Life.

Study or subgroup	EPA N	EPA Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Fearon 2003	48	-3.3 (19)	56	-3.6 (23.7)		28.79%	0.27[-7.94,8.48]
Jatoi 2004	140	13.4 (19.7)	140	15.9 (24.6)		71.21%	-2.5[-7.72,2.72]
Total ***	**188**		**196**			**100%**	**-1.7[-6.11,2.7]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%							
Test for overall effect: Z=0.76(P=0.45)							



Analysis 2.6. Comparison 2 Oral EPA versus control, Outcome 6 Total Calorific intake.

Study or subgroup	EPA N	EPA Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
Fearon 2003	44	224 (451.1)	56	68 (478.9)		0.33[-0.07,0.73]

APPENDICES

Appendix 1. MEDLINE search strategy

Note: Controlled vocabulary (Mesh terms) are presented in uppercase, free text terms are presented in lowercase text

1. CACHEXIA
2. cachexia
3. cachectic OR cachexic
4. disease-induced adj starvation
5. wasting
6. (weight adj loss) OR (weight adj3 gain$)
7. (weight adj3 lost) OR (weight adj3 lose) OR (weight adj3 losing)
8. WEIGHT LOSS
9. ANOREXIA
10. anorex$
11. OR/1-10
12. exp FISH OILS
13. 58111417-EICOSAPENTAENOIC ACID
14. DOCOSAHEXAENOIC ACIDS
15. FATTY ACIDS OMEGA-3
16. FATTY ACIDS UNSATURATED
17. Fatty acid$
18. EFA.ti.ab

19. MaxEPA.ti.ab
20. (oil$ adj6 cod$)
21. (oil$ adj6 marin$)
22. (oil$ ad6 fish$)
23. omega3$
24. omega-3$
25. EPA OR DHA.ti.ab
26. (eicosapentaen$ OR icosapentaenoic) OR docosahexaeno$)
27. OR/12-26
28. Exp NEOPLASMS
29. neoplasm$ OR cancer$ OR carcino$ OR malignan$ OR tumor$ OR tumour*)
30. 28 OR 29
31. 11 AND 27 AND 30

The search strategy was organised into three distinct groups as follows:
Group 1 Terms for cachexia (lines 1 to 11)
Group 2 Terms for fish oils (lines 12 to 27)
Group 3 Terms for cancer (lines 28 to 30)

WHAT'S NEW

Date	Event	Description
6 December 2017	Amended	See Published notes.

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 1, 2007

Date	Event	Description
25 January 2017	Amended	See Published notes.
9 April 2015	Amended	This review has been identified as a priority for updating, but additional authors are required. See Published notes.
19 April 2012	Amended	Additional tables not linked within the text were deleted from this version of the review and the Risk of bias tables were updated.
24 September 2010	Amended	Contact details updated.
27 October 2008	Amended	Further RM5 changes
1 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

CB, TD, IJ, AD: conceived and designed review.
AD: coordinated review.
AD: developed search strategy, undertook searches/screened searches/organised retrieval of papers.
AD, BH: screened retrieved papers against inclusion criteria.
AD, BH, TD: appraised quality of papers.

AD, BH: abstracted data from papers.
AD: wrote to authors of papers for additional information.
AD, TD, BH, CB, IJ: wrote up review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health R & D Programme, National Researcher Development Award, UK.

NOTES

The updated review is planned for publication in 2016. The lead author requires additional systematic reviewers to join the author team in order to complete this important update. Please contact the lead author or the PaPaS team (anna.erskine@ndcn.ox.ac.uk) directly if you would like to apply to support the development of this update.

At January 2017, the author team has been established and the update is being prepared.

At December 2017, this is no longer being updated, the author team does not have the time or resources to complete this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Cachexia [etiology] [*therapy]; Eicosapentaenoic Acid [*therapeutic use]; Neoplasms [*complications]; Nutritional Status; Randomized Controlled Trials as Topic

MeSH check words

Humans