Psychosocial interventions for fatigue during cancer treatment with palliative intent

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TABLE OF CONTENTS

[Intervention Review]

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ABSTRACT

Background

Fatigue is a prevalent and burdensome symptom for patients with incurable cancer receiving cancer treatment with palliative intent and is associated with reduced quality of life. Psychosocial interventions seem promising for management of fatigue among cancer patients.

Objectives

To assess the effects of psychosocial interventions for fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent.

Search methods

We searched the following databases: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, and seven clinical trial registries; we also searched the reference lists of articles. The date of our most recent search was 29 November 2016.

Selection criteria

We included randomised controlled trials that compared psychosocial interventions in adults aged 18 years or over undergoing cancer treatment with palliative intent for incurable cancer versus usual care or other controls. Psychosocial interventions were defined as various kinds of interventions provided to influence or change cognitions, emotions, behaviours, social interactions, or a combination of these. Psychosocial interventions of interest to this review had to involve at least two interactions between the patient and the care provider in which the care provider gave the patient personal feedback concerning changes sought by these interventions. We included trials that reported fatigue as an outcome of interest.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Two review authors independently considered trials for inclusion in the review, assessed risk of bias, and extracted data, including information on adverse events. We assessed the quality of evidence using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) and created a 'Summary of findings' table.

Main results

We identified 14 studies (16 reports) that met inclusion criteria for this review and involved 3077 randomised participants in total. Most of these studies included a mixed sample of participants; we obtained data for the subset of interest for this review (diagnosis of incurable cancer and receiving cancer treatment) from the study investigators of 12 studies, for which we included 535 participants in the subset meta-analysis for fatigue post intervention. Researchers investigated a broad range of psychosocial interventions with different intervention aims and durations. We identified sources of potential bias, including lack of description of methods of blinding and allocation concealment and inclusion of small study populations.

Findings from our meta-analysis do not support the effectiveness of psychosocial interventions for reducing fatigue post intervention (standardised mean difference (SMD) -0.25, 95% confidence interval (CI) -0.50 to 0.00; not significant; 535 participants, 12 studies; very low-quality evidence). First follow-up findings on fatigue suggested benefit for participants assigned to the psychosocial intervention compared with control (SMD -0.66, 95% CI -1.00 to -0.32; 147 participants, four studies; very low-quality evidence), which was not sustained at second follow-up (SMD -0.41, 95% CI -1.12 to 0.30; not significant; very low-quality evidence).

Results for our secondary outcomes revealed very low-quality evidence for the efficacy of psychosocial interventions in improving physical functioning post intervention (SMD 0.32, 95% CI 0.01 to 0.63; 307 participants, seven studies). These findings were not sustained at first follow-up (SMD 0.37, 95% CI -0.20 to 0.94; not significant; 122 participants, two studies; very low-quality evidence). Findings do not support the effectiveness of psychosocial interventions for improving social functioning (mean difference (MD) 4.16, 95% CI -11.20 to 19.53; not significant; 141 participants, four studies), role functioning (MD 3.49, 95% CI -12.78 to 19.76; not significant; 143 participants, four studies), emotional functioning (SMD -0.11, 95% CI -0.56 to 0.35; not significant; 115 participants, three studies), or cognitive functioning (MD -2.23, 95% CI -12.52 to 8.06; not significant; 86 participants, two studies) post intervention. Only three studies evaluated adverse events. These studies found no difference between the number of adverse events among participants in the intervention versus control group.

Using GRADE, we considered the overall quality of evidence for our primary and secondary outcomes to be very low. Therefore, we have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect. Limitations in study quality and imprecision due to sparse data resulted in downgrading of the quality of data. Additionally, most studies were at high risk of bias owing to their small sample size for the subset of patients with incurable cancer (fewer than 50 participants per arm), leading to uncertainty about effect estimates.

Authors' conclusions

We found little evidence around the benefits of psychosocial interventions provided to reduce fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent. Additional studies with larger samples are required to assess whether psychosocial interventions are beneficial for addressing fatigue in patients with incurable cancer.

PLAIN LANGUAGE SUMMARY

Psychological therapies to reduce tiredness in patients with incurable cancer

Background

Patients with incurable cancer often experience tiredness (fatigue) during cancer treatment. Psychological therapies may help to reduce this symptom. Tiredness in cancer patients receiving cancer treatment may be treated with psychological therapies aimed at influencing or changing thoughts, emotions, behaviours, social interactions, or a combination of these (e.g. cognitive-behavioural therapies, supportive-expressive group therapies). This review looked at how effective psychological therapies are in reducing tiredness in patients with incurable cancer receiving cancer treatment.

Study characteristics

In November 2016, we searched for clinical trials looking at psychological therapies in patients with incurable cancer receiving cancer treatment. We found 14 small studies of very low quality reporting data on tiredness outcomes, 12 of which provided data for analyses. A limited number (three studies) reported results about side effects; these studies investigated a psychological therapy combined with medication.

Key findings

Review authors found no support for the effectiveness of psychological therapies in reducing tiredness when assessed directly following the intervention. Very low-quality evidence suggests that psychological therapies may improve physical functioning directly after the intervention and may improve tiredness at first follow-up. Evidence shows no support for the effectiveness of psychosocial therapies in improving other domains of functioning. Limited evaluation of potential harm suggests no differences in side effects between patients receiving psychological therapy and those given usual care. Limited good quality evidence allows no conclusions on the use of psychological therapies in people with incurable cancer. Larger, high-quality trials are needed to find out whether psychological therapies help reduce tiredness for people with incurable cancer during cancer treatment.

Quality of the evidence

We rated the quality of study evidence using four levels: very low, low, moderate, and high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. Included studies had design problems and included a very small number of participants. Therefore, the quality of the evidence in this review is very low, and results of this review should be interpreted with caution.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Psychosocial interventions compared with control intervention for fatigue during cancer treatment with palliative intent

Patient or population: patients with incurable cancer receiving cancer treatment with palliative intent
Settings: university-affiliated hospitals, cancer centres, public hospitals
Intervention: psychosocial intervention
Comparison: usual care or control condition (not a psychosocial intervention)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Fatigue	Not known	Not known	Fatigue in the psychosocial interventions group was lower than in the control group (**SMD -0.25**, 95% CI -0.50 to 0.00)	535 (12)	⊕◯◯◯ **very low**[a,b]	
Physical functioning	Not known	Not known	Physical functioning in the psychosocial interventions group was higher (**SMD 0.32**, 95% CI 0.01 to 0.63)	307 (7)	⊕◯◯◯ **very low**[a,b]	An SMD of 0.32 represents a small effect size, with the upper end of the CI suggesting this may be clinically significant for some people
Social functioning	Not known	Not known	Social functioning in the psychosocial interventions group was higher (**MD 4.16**, 95% CI -11.20 to 19.53)	141 (4)	⊕◯◯◯ **very low**[a,b]	
Role functioning	Not known	Not known	Role functioning in the psychosocial interventions group was higher (**MD 3.49**, 95% CI -12.78	143 (4)	⊕◯◯◯ **very low**[a,b]	

			to 19.76)			
Emotional functioning	Not known	Not known	Emotional functioning in the psychosocial interventions group was lower (**SMD -0.11**, 95% CI -0.56 to 0.35)	115 (3)	⊕○○○ **very low**[a,b]	
Cognitive functioning	Not known	Not known	Cognitive functioning in the psychosocial interventions group was lower (**MD -2.23**, 95% CI -12.52 to 8.06)	86 (2)	⊕○○○ **very low**[a,b]	
Adverse events	See comment	See comment	Not estimable			No data available for meta-analysis.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; MD: mean difference; SMD: standardised mean difference

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded once: unclear risk of selection bias.
[b]Downgraded twice: imprecision due to very sparse data.

BACKGROUND

This review is based in part on suggested wording from the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS CRG).

Description of the condition

According to the World Health Organization, palliative care is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (WHO 2002). For a long time, cancer treatment with palliative intent for patients with incurable cancer was considered to represent the terminal phase, reflecting the last months or year before an expected death. However, owing to advances in the medical treatment of cancer, more patients with incurable cancer receiving cancer treatment with palliative intent can expect to be chronically ill for an extended period of years (Italiano 2008; Miller 2008). This leads to ambiguous medical prognoses: Patients with incurable cancer may be sick enough to die but could also live for many years (Lynn 2003). Nowadays, it is common to distinguish three stages of cancer treatment with palliative intent (Wanrooij 2010). The first phase - disease palliation - has the aim of reducing disease activity to improve survival time and quality of life. The second phase - symptom palliation - primarily aims to prevent and treat symptoms to improve quality of life. The last phase - terminal palliation - focuses on quality of life and quality of dying. The current review will focus on patients with incurable cancer receiving cancer treatment aimed at disease palliation (phase 1) or receiving cancer treatment aimed at disease palliation combined with symptom palliation (phase 1 and 2). This implies that patients need to receive some form of cancer treatment.

Fatigue is one of the symptoms most commonly reported by patients receiving cancer treatment with palliative intent (Barnes 2002); prevalence rates up to 99% have been reported (Butt 2008; Hauser 2008; Radbruch 2008; Stone 2008; Teunissen 2007). Fatigue is frequently cited among the most distressing symptoms (Butt 2008; Hofman 2007; Paiva 2013) and is associated with reduced quality of life, poor performance status, and difficulty in performing daily activities (Butt 2008; Hauser 2008; Tanaka 2002). Many factors are likely to contribute to fatigue in patients with incurable cancer receiving cancer treatment with palliative intent. Fatigue could result from the underlying disease itself, as well as from cancer treatments received by patients. Psychosocial factors (e.g. sleeping problems, mood disturbances such as depression and anxiety) can also contribute to fatigue (Peters 2014).

Fatigue can be defined and measured in various ways, and no consensus has been reached about the definition of fatigue in cancer patients (Minton 2009; Minton 2013). Cancer-related fatigue (CRF) is the term that is used most widely to describe this symptom. The National Comprehensive Cancer Network (NCCN) defines CRF as "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Mock 2000). A simpler distinction between a subjective lack of energy (symptom) and a confirmable decrease in strength over time (physical or muscular weakness) has been made (Stone 1999). The most simplified way to identify fatigue is to ask patients whether they feel fatigued or tired. We will use the NCCN definition of fatigue for this review. However, we will also include studies with tiredness, weakness, lack of energy, or exhaustion as an outcome of interest. According to NCCN guidelines, fatigue should be measured by self-report instruments with established cut-off scores (Mock 2000); however, we will also include studies that measure fatigue via other self-report instruments.

Efforts to manage fatigue during cancer treatment with palliative intent for patients with incurable cancer should focus first on identifying and treating somatic causes. Often, no specific somatic cause of fatigue can be identified other than the underlying disease itself or the cancer treatments patients receive. In these situations, management of fatigue usually involves multiple strategies, which can be divided into pharmacological and non-pharmacological interventions. Pharmacological interventions include stimulant drugs, corticosteroids, erythropoietic agents, and antidepressants. A Cochrane review focusing on pharmacological interventions for fatigue concluded that no recommendation could be given for a specific drug treatment for fatigue in palliative care patients (Mücke 2015). Non-pharmacological interventions include both psychosocial interventions and physical activity. Psychosocial interventions are the focus of this review and will be explained further in the next section. The role of physical activity/exercise in the management of fatigue during and after cancer treatment is supported by evidence from a Cochrane review (Cramp 2012). However, it remains unclear whether exercise is effective for patients receiving cancer treatment with palliative intent. Only a few included randomised controlled trials focused on this particular patient group.

Description of the intervention

Psychosocial interventions seem promising for management of fatigue among patients with incurable cancer. For this review, psychosocial interventions are defined as various kinds of interventions provided to influence or change cognitions, emotions, behaviours, social interactions, or a combination of these, to achieve better mental health and/or fewer problems, for example, less fatigue. Such interventions may include cognitive-behavioural therapy, coping skills training, motivational therapy, mindfulness-based stress reduction, and psychoeducational or educational therapies, which may be combined with mind-body elements such as

yoga, relaxation breathing, or progressive muscle relaxation. Psychosocial interventions of interest for this review involve systematic treatment with at least two interactions between patient and care provider in which the care provider gives the patient personal feedback concerning changes sought by these interventions. We will exclude exercise interventions that are primarily aimed at increasing physical fitness or level of physical activity.

How the intervention might work

Although various interventions aimed at CRF can be labelled as psychosocial, most draw techniques from cognitive therapies, behavioural therapies, and educational theories. Psychosocial interventions usually include a rationale or framework for therapy and collaborative goal setting (Peyrot 2007). Education about disease and an explanation of the role of behaviours, beliefs, and emotions in disease and symptoms are common elements of therapy (Authier 1975). In addition, establishing a therapeutic alliance between therapist and patient is a key component of a psychosocial intervention (Frank 1990; Martin 2000; Orlinsky 2004), which consists of an emotional bond, agreement on goals, and active collaboration (Bordin 1979; Gaston 1990).

Generally, psychosocial interventions are based on the assumption that thoughts, feelings, and actions are interconnected and can influence fatigue and its consequences. During the intervention, patients learn to change thoughts, actions, or feelings in relation to symptoms. Psychosocial interventions differ in terms of assumptions made about the mechanisms responsible for the change in fatigue brought on by the intervention. Assumed mechanisms of change are different for each intervention, depending on the theoretical models underpinning them. Psychosocial interventions can use one or a combination of techniques or treatment methods to influence symptoms and their consequences (Peyrot 2007). One mechanism for reducing fatigue consists of cognitive restructuring as used in cognitive therapies (Beck 1970; Beck 1976) to change dysfunctional beliefs (e.g. catastrophising, feeling helpless with respect to fatigue) and to encourage patients to develop more helpful beliefs (Beck 2011). This approach is thought to reduce symptoms or change negative emotional states that worsen symptoms like fatigue. Another possible mechanism for reducing fatigue is behaviour modification (Bandura 1969), which can be provided to change behavioural responses to fatigue (e.g. resting when fatigued). Influencing these behavioural patterns by, for example, gradually increasing physical activity can reduce symptoms and enhance self-efficacy (Bandura 1997). These are only examples of assumed mechanisms; other potentially effective techniques and treatment methods with specific therapeutic mechanisms responsible for CRF reduction are available, such as yoga and (psycho)educational therapies (see also the American Society of Clinical Oncology (ASCO) clinical practice guidelines; Bower 2014). Although research has provided empirical support for the efficacy of psychosocial interventions for fatigue (irrespective of the presence of a medical condition), knowledge about the therapeutic mechanisms of these interventions is lacking. Limited work has been done in the field of cognitive-behavioural therapy (CBT) for patients with medically unexplained fatigue (i.e. chronic fatigue syndrome (CFS)). Mediation analysis of CBT for CFS has revealed that changes in both beliefs and behaviours can mediate the effects of CBT (Chalder 2015; Wiborg 2011; Wiborg 2012). Mediation analysis of CBT for patients with multiple sclerosis shows that the decrease in fatigue may be explained by a change in beliefs about fatigue (Knoop 2012). The scarcity of knowledge about therapeutic mechanisms is even more evident for interventions that reduce fatigue in patients with cancer. Although CBT was found to be effective for reducing post-cancer fatigue (Gielissen 2006) and is now recommended in ASCO clinical practice guidelines for cancer-related fatigue (Bower 2014), the mechanisms of change remain unknown, and effects on fatigue have not been shown to be mediated by an increase in objective physical activity or fitness (Gielissen 2012; Prinsen 2013). To permit unequivocal conclusions about the therapeutic mechanisms of psychosocial interventions that may produce a reduction in fatigue, further research is needed.

Why it is important to do this review

Advances in medical treatment for patients with incurable cancer have led to prolonged survival. Maintaining quality of life is an important goal of cancer treatment with palliative intent. Fatigue is not only a prevalent symptom, it is also a factor that affects patient quality of life. A previous Cochrane review (Goedendorp 2009) investigated the effectiveness of psychosocial interventions among adult cancer patients receiving cancer treatment. However, few of the randomised controlled trials (RCTs) identified for this review included only patients with incurable cancer receiving cancer treatment with palliative intent, and the review did not analyse separately the effectiveness of psychosocial interventions for fatigue in these patients. The current review will replace Goedendorp 2009 and will differ by focusing exclusively on fatigue in patients with incurable cancer. Our current review will aid oncologists providing cancer treatment with palliative intent to inform patients about evidence-based psychosocial interventions for fatigue.

OBJECTIVES

To assess the effects of psychosocial interventions for fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs). We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis.

Types of participants

We included studies of adult patients (18 years of age and older) with a diagnosis of incurable (advanced or metastatic) cancer in which participants received some form of disease-focused treatment, such as chemotherapy, hormonal therapy, targeted therapy, immunotherapy, surgery, and/or radiation therapy. For studies with a mixed sample of participants with curable or incurable cancer and/or receiving cancer treatment or not receiving cancer treatment, we included only participants with incurable cancer and receiving cancer treatment. We contacted study authors to request data or results when the study did not report separate information on cancer diagnosis and/or treatment. If separate data could not be provided for the subset of participants of interest to this review, or if study authors did not respond to requests for information after two reminders, we included the study only if investigators reported that at least 80% of participants had incurable cancer and were receiving cancer treatment. We excluded studies in which patients received terminal care (i.e. hospice or end-of-life care).

Types of interventions

We included studies that compared a broad range of psychosocial interventions versus usual care or control conditions (no psychosocial intervention). These interventions included psychotherapy, psychoeducation, and support group programmes, as well as elements such as cognitive restructuring, changing in coping strategies, self-help or self-care, relaxation, energy conservation, and stress management. Psychosocial interventions could be given individually or in groups, and by care providers from different professions, such as psychologists or nurses. We included only psychosocial interventions involving systematic treatment with at least two contacts between patient and care provider in which personal feedback was given concerning changes the patient was trying to achieve. For example, during the first session, a care provider might advise a patient to change coping behaviours to reduce fatigue, whilst in subsequent sessions, discussion may focus on patient progress and feedback on patient behaviours. We excluded studies in which interventions were aimed exclusively at exercise.

Types of outcome measures

Studies used a variety of outcome measures. Included studies reported fatigue, tiredness, weakness, lack of energy, lack of vitality, or exhaustion as an outcome of interest. Fatigue could be assessed by specific validated fatigue questionnaires with multiple items or by other self-report methods. Examples of the latter include one or more items on fatigue inserted as part of a quality of life instrument, a numerical rating scale (NRS), a visual analogue scale (VAS), or assessment items included as part of a symptom list and scored as 'present' or 'absent'. Secondary outcomes included physical, social, role, emotional, and cognitive functioning assessed by a suitable instrument such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the Short-Form Health Survey.
We measured adverse events of psychosocial interventions as absent or present. We have provided a narrative description of these effects. In addition, we analysed measures of function when used as an outcome measure in studies.

Primary outcomes

- Fatigue post intervention (alternative terms: tiredness, weakness, lack of energy, lack of vitality, exhaustion)

Secondary outcomes

- Fatigue (first and second follow-up)
- Physical functioning (post intervention and at first and second follow-up)
- Social functioning (post intervention)
- Role functioning (post intervention)
- Emotional functioning (post intervention)
- Cognitive functioning (post intervention)
- Adverse events of psychosocial interventions (post intervention)

Search methods for identification of studies

Electronic searches

We searched the following databases without language or date restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Register of Studies Online (CRSO); searched 29 November 2016) in the Cochrane Library.
- MEDLINE (via Ovid) 1946 to November week 3, 2015.
- Embase (via Ovid) 1974 to 2016 November 29.
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1982 to November 2016.
- PsycINFO (via Ovid) 1806 to November week 3, 2016.

We used medical subject headings (MeSH) or equivalent and text word terms. When appropriate, we exploded MeSH terms and applied the Cochrane filter for identification of RCTs, as published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We have provided search strategies in Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), the Australian New Zealand Trials Registry (http://www.anzctr.org.au/), the International Standard Randomized Controlled Trials Number (ISRCTN) register (http://www.isrctn.com/), the University hospital Medical Information Network (UMIN) Clinical Trials Registry (http://www.umin.ac.jp/ctr/), and the Netherlands Trial Register (http://www.trialregister.nl/trialreg/index.asp), using the keywords 'cancer' and 'fatigue' to identify additional completed or ongoing studies. In addition, we checked relevant reviews and reference lists of retrieved articles for additional studies, and we performed citation searches on key articles. When necessary, we contacted study authors for additional information.

Data collection and analysis

Selection of studies

Two review authors (HP, MP) independently determined eligibility by reading the abstract of each study identified by the search. These review authors independently eliminated studies that clearly did not satisfy inclusion criteria and obtained full copies of remaining studies. The same two review authors read these studies independently to select relevant studies; in the event of disagreement, a third review author adjudicated (HK). We did not anonymise the studies before assessment. We included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart, which shows the status of identified studies (Moher 2009), as recommended in Part 2, Section 11.2.1, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data extraction and management

Two review authors (HP, MP) independently extracted data using a standard form and checked for agreement before entering data into Review Manager (RevMan 2014). We included information about the following.

Participant characteristics

- Demographic characteristics such as age and gender
- Disease characteristics such as cancer diagnosis and cancer treatment
- Inclusion/exclusion criteria for participation in study

Psychosocial intervention characteristics (for each study arm)

- Nature, type of delivery, and content of the intervention and control condition
- Time point of delivery of intervention in relation to cancer treatment (during or after)
- Duration of the intervention and total number of sessions
- Description and number of intervention providers
- Duration and nature of training and supervision given to intervention providers
- Participant adherence and contamination
- Intervention provider treatment integrity and existence of treatment protocol

Methods and outcomes

- Random sequence generation
- Allocation concealment
- Incomplete outcome data (quantity, nature, and handling of missing data)
- Size of the study and power calculation
- Blinding of outcome assessors
- Quality of the control condition
- Equality of treatment expectations
- Therapist and/or researcher allegiance
- Key outcomes and measurement instruments used to assess fatigue
- Adverse events of the psychosocial intervention
- Timing, frequency, and duration of follow-up for each outcome

We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We collected characteristics of included studies in sufficient detail to populate the Characteristics of included studies table. We included in the Characteristics of ongoing studies table a study authored and co-authored by five of the review authors.

Assessment of risk of bias in included studies

Two review authors (HP, MP) independently assessed 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. We resolved disagreements by discussion. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan (RevMan 2014).

We assessed the following for each study.

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

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

- Blinding of outcome assessment (checking for detection bias): This is usually assessed by looking at the methods used to blind study participants and personnel from knowledge of which intervention a participant received. However, in RCTs investigating effects of psychosocial interventions, it is impossible to blind care providers to the intervention they are giving to participants. It is also nearly impossible to blind participants to the intervention to which they were assigned. We judged risk of bias in blinding of outcome assessment on whether measures were administered and collected by an assessor who was blind to treatment allocation. We assessed methods as having low risk of bias (study states that outcome assessment 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 description of how this was achieved); or high risk of bias (studies states that outcome assessors were not blinded).

- Incomplete outcome data (checking for possible attrition bias due to the quantity, nature, and handling of incomplete outcome data). We assessed methods used to deal with incomplete data as having low risk of bias (< 10% of participants did not complete the study or ≥ 10% with sensitivity analysis or mixed model analysis); unclear risk of bias (used 'last or baseline observation carried forward' analysis, as progression in terms of fatigue is not unexpected in advanced cancer patients with missing outcome data); or high risk of bias (used 'completer' analysis or post-intervention t-test)

- Selective reporting (checking for possible reporting bias). We assessed studies as being at low risk of bias (all data fully reported in the study); unclear risk of bias (data not fully reported in the study, but study authors responded to data requests); or high risk of bias (data not fully reported in the study, and study authors did not respond to data requests).

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

- Yates 2005 designed a quality rating scale to measure the quality of RCTs for psychological interventions. On the basis of recommendations provided by Yates and colleagues, we included two additional items that can be used to assess the quality of the control condition and efforts made to ensure that as many features as possible have been controlled for (adequate, partial, inadequate); and equality of treatment expectations (adequate, inadequate). Furthermore, when reported, we took into account the allegiance of the therapist and/or researcher to a particular psychosocial intervention (see Characteristics of included studies table) (Berman 1985; Dragioti 2015; Wampold 2001).

Measures of treatment effect

We evaluated fatigue outcomes at both post-intervention and follow-up assessments using RevMan (RevMan 2014). We calculated mean differences (MDs) and 95% confidence intervals (CIs) for continuous data. If not reported, we planned to calculate standard deviations using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We standardised mean differences of assessment tools measuring fatigue in different ways to combine results across tools and used mean differences otherwise. We planned to calculate risk ratios (RRs) and 95% CIs when dichotomous data were reported (i.e. for studies measuring fatigue as present or absent). We planned to report the proportions of participants experiencing any adverse events of psychosocial interventions, and to combine studies using RRs (and 95% CIs).

Unit of analysis issues

One study included more than two intervention arms (Johansson 2008). We decided that we would combine into one intervention group the three arms that provided relevant interventions for the aim of this review. We planned to report intra-cluster correlations and to make adjustments when necessary for any identified randomised cluster trials.

Dealing with missing data

We analysed data for all participants in the group to which they were randomised, regardless of whether they received the allocated treatment. We did not exclude trials on the basis of missing data. In the Discussion section, we address the potential impact of missing data on review findings.

Assessment of heterogeneity

We assessed clinical diversity by documenting participant characteristics represented in each study, with focus on factors such as age, gender, study eligibility criteria, cancer diagnosis, and cancer treatment. Furthermore, we documented heterogeneity in psychosocial interventions, such as duration, delivery, profession of care providers, and nature of the control condition. In addition, we assessed diversity among ways of measuring fatigue and timing fatigue assessment.

Assessment of reporting biases

We used a funnel plot to assess the possibility that publication bias affected this review as a whole.

Data synthesis

Two review authors (HP, MP) independently assessed heterogeneity through visual inspection of the forest plot and on the basis of quantitative results of both the X^2 and the I^2 statistic. We performed meta-analysis for clinically homogeneous studies according to the inverse-variance method for continuous outcomes. We planned to use a fixed-effect model, but given that participant populations were highly variable in cancer diagnosis and treatment (as were the interventions provided), we employed random-effects models. We expressed results as standardised mean differences (SMDs) or mean differences (MDs) for continuous outcomes. For dichotomous outcomes, we would have expressed results as risk ratios (RR) using the Mantel-Haenszel method. We used Review Manager software for analysis (RevMan 2014) and have presented a narrative synthesis of studies for which required data were unavailable for meta-analysis.

Quality of the evidence

Two review authors (HP, MP) independently rated the quality of each outcome. We applied the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system to rank the quality of evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro 2015) and guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The GRADE approach is based on five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) for assessment of the quality of evidence for each outcome. The GRADE system uses the following criteria to assign a grade to the quality of evidence.

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of effect.
- Very low: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the grade rating by one (- 1) or two (- 2) if we identified:

- serious (-1) or very serious (-2) limitations to study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1); or
- high probability of reporting bias (-1).

'Summary of findings' table

We included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of interventions examined, and the sum of available data on outcomes of fatigue, physical functioning, social functioning, role functioning, emotional functioning, cognitive functioning, and adverse events of psychosocial interventions.

Subgroup analysis and investigation of heterogeneity

When sufficient data were available, we planned to undertake subgroup analysis for the primary outcome based on aspects of the intervention that may influence its effectiveness: duration (short vs intermediate-long), intervention delivery (group vs individual, psychologist vs other profession), intervention type (monodisciplinary vs multi-disciplinary), and aim of the intervention (aimed at decreasing fatigue vs other). We did not perform subgroup analysis for the intervention deliverer (psychologist vs other professional), as insufficient data were available. In addition, we planned to perform subgroup analysis for the type of assessment tool (continuous vs dichotomous) and for studies in which some level of fatigue was an eligibility criterion for patient participation versus those in which it was not. Owing to insufficient available data, we were unable to perform these subgroup analyses. Given the few identified studies at low overall risk of bias (i.e. estimated low risk of bias in all domains of the 'Risk of bias' assessment), we did not use subgroup analysis based on overall risk of bias. We performed post hoc subgroup analyses on the basis of additional sessions provided between post intervention and first and second follow-up assessments of fatigue (no additional sessions vs booster sessions).

Sensitivity analysis

We performed post hoc sensitivity analyses based on the number of participants per treatment arm at post-intervention and follow-up assessments, while excluding studies with fewer than 10 participants per treatment arm.

RESULTS

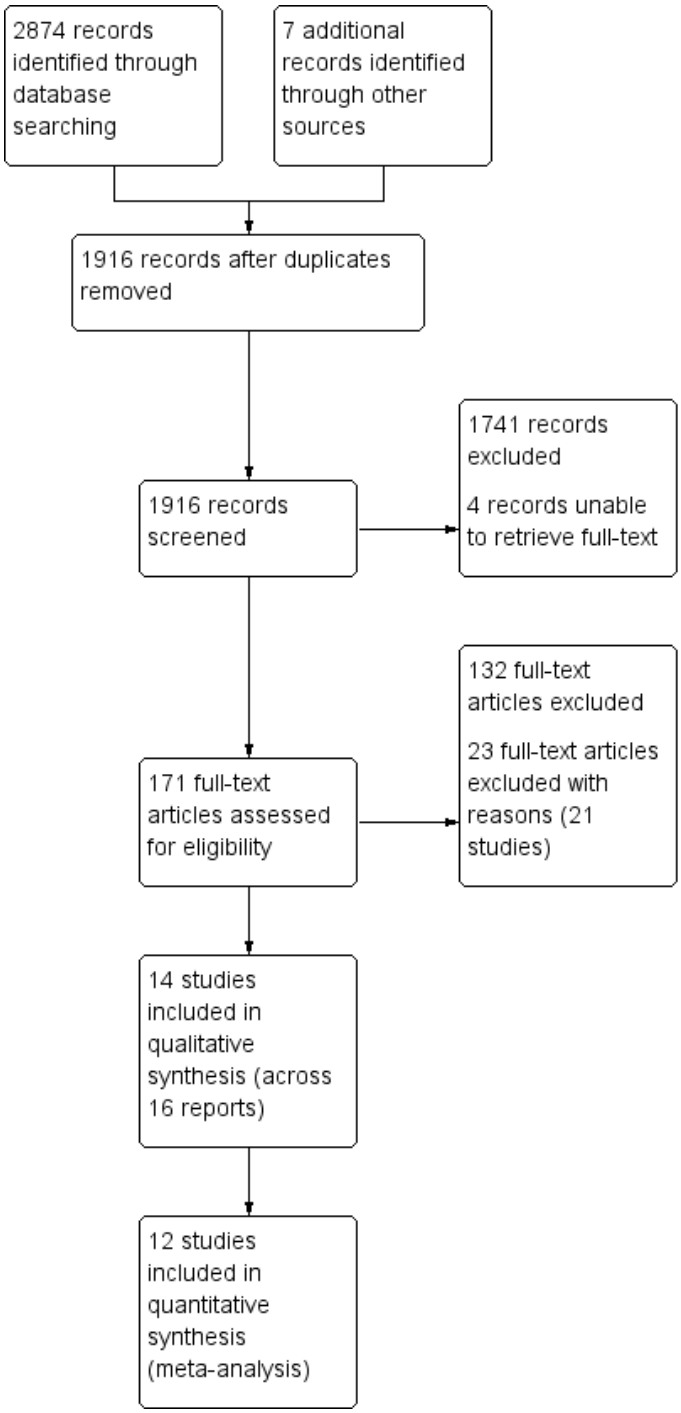
Description of studies

We have summarised key characteristics of the included studies below and in the Characteristics of included studies tables. We have listed excluded studies with potential relevance to this review along with reasons for their exclusion in the Characteristics of excluded studies table.

Results of the search

Our search identified 1909 unique citations after removal of duplicates through database searching. We identified an additional seven citations through conference abstracts or other references. After initial screening of the 1916 titles and abstracts for relevance to the review, we retained 171 citations. We were unable to retrieve full texts for four citations and excluded 132 additional citations when review of the full text and in some cases correspondence with original study investigators revealed that they did not meet review eligibility criteria. We excluded 21 studies (23 reports) with reasons. Therefore, we included in the review 14 studies (16 reports) that met the inclusion criteria. For further details of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Design

All 14 included studies were RCTs. In 13 studies, the unit of randomisation was the individual participant (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Classen 2001; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). In one study, the unit of randomisation was a group of 20 participants, 10 of whom were randomised to each condition (Edelman 1999).

Setting

Six studies were conducted in the United States of America (Barsevick 2004; Barsevick 2010; Bruera 2013; Classen 2001; Spiegel 1981; Steel 2016), three in the UK (Armes 2007; Sharpe 2014; Walker 2014), two in Canada (Bordeleau 2003; Savard 2006), one in Australia (Edelman 1999), one in Hong Kong (Chan 2011), and one in Sweden (Johansson 2008). Primary settings were university-affiliated hospitals in five studies (Bordeleau 2003; Classen 2001; Spiegel 1981; Johansson 2008; Savard 2006), cancer centres in seven studies (Armes 2007; Bruera 2013; Barsevick 2004; Barsevick 2010; Sharpe 2014; Steel 2016; Walker 2014), and a public hospital in two studies (Chan 2011; Edelman 1999).

Cancer diagnosis

In this review, we were interested in the effects of psychosocial interventions on participants with a diagnosis of incurable cancer. In six studies, all participants received a diagnosis of incurable cancer (Bruera 2013; Bordeleau 2003; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981). Five of these studies included participants with metastatic breast cancer (Bordeleau 2003; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981); the other study included patients with any diagnosis of advanced cancer (Bruera 2013). The eight remaining studies included a mixed sample of participants with a diagnosis of incurable and potentially curable cancer (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). The original study investigators of those eight studies were able to provide data for their subset of participants with incurable cancer; thus we included them in the review.

Cancer treatment

In this review, we focused on effects of psychosocial interventions for participants receiving cancer treatment. In five studies, all participants were receiving cancer treatment during the intervention (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001). In seven studies, although not all participants were receiving cancer treatment (Bordeleau 2003; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014), the original study investigators were able to extract data for their subset of participants receiving cancer treatment; thus we included these studies in the review. In the remaining two studies, it is unclear or unknown whether all participants were receiving cancer treatment (Bruera 2013; Edelman 1999). We sought clarification from the original study investigators. Bruera 2013 confirmed that all participants were receiving cancer treatment. Edelman 1999 did not collect data on who was receiving treatment at the time of study participation, but we believe it is likely that participants were receiving at least some form of cancer treatment during the intervention, given the study population of participants with metastatic breast cancer. Therefore, we included both studies in the review.

Participants

Total sample sizes for the included studies ranged from 45 (Savard 2006) to 500 randomised participants (Sharpe 2014). However, as noted before, not all participants were given a diagnosis of incurable cancer and/or were receiving cancer treatment. As a result, sample sizes for the subset of participants of interest to this review were much smaller, ranging from 15 (Walker 2014) to 110 evaluable participants (Chan 2011) at post-intervention assessment. Information on age and gender distribution was available for the total samples of included studies but not for the subset of interest to our review. Participants' mean age for the total sample ranged from 50 years (Edelman 1999) to 64 years (Walker 2014). Chan 2011 reported no information on age distribution but provided these data upon request. Nine studies included both men and women (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014), and the proportion of males in the total sample ranged from 10% (Sharpe 2014) to 83% (Chan 2011). Four studies targeted only women (Bordeleau 2003; Classen 2001; Savard 2006; Spiegel 1981). Edelman 1999 provided no information on the gender distribution of participants. We believe it is likely that only women were included, given the study population of participants with metastatic breast cancer. Finally, it is important to note that Sharpe 2014 and Walker 2014 recruited only patients with a diagnosis of major depression comorbid with cancer.

Content of the intervention

We have provided a detailed description of the interventions delivered in the Characteristics of included studies table. Interven-

tions from 10 studies fell into one of three categories: cognitive-behavioural therapies (n = 5; Armes 2007; Savard 2006; Edelman 1999; Johansson 2008; Steel 2016), supportive-expressive group therapies (n = 3; Bordeleau 2003; Classen 2001; Spiegel 1981), and energy conservation approaches combined with activity management or sleep modification techniques (n = 2; Barsevick 2004; Barsevick 2010). Four interventions did not fall within these categories. In Bruera 2013, the intervention included psychosocial support and education combined with methylphenidate or placebo. The intervention in Sharpe 2014 and Walker 2014 included antidepressant medication provided in combination with problem-solving therapy and behavioural activation. Chan 2011 examined the effects of a psychoeducational intervention consisting of education and relaxation. It was unclear whether the intervention protocol used in this study included some kind of personal feedback. We sought clarification from the original study investigators, who confirmed that participants received personal feedback.

Nature of the intervention

The purpose of the interventions varied. Six studies investigated interventions specifically aimed at addressing fatigue (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Steel 2016). In addition to fatigue, Steel 2016 aimed to reduce depression and pain with the intervention provided. The intervention of Chan 2011 aimed to reduce anxiety and breathlessness in addition to fatigue. Two of the six studies required some level of fatigue as an eligibility criterion for patient participation (Armes 2007; Bruera 2013). In the remaining eight studies, the intervention was aimed at mood disturbances and/or psychological benefit (Classen 2001; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014), quality of life (Bordeleau 2003), or survival benefit (Edelman 1999).

Duration of the intervention

The total intervention duration varied between studies and ranged from short (two to three weeks) in four studies (Bruera 2013; Barsevick 2004; Barsevick 2010; Chan 2011) to long (12 months) in three studies (Bordeleau 2003; Classen 2001; Spiegel 1981). In the remaining seven studies, the intervention was given over a period of two to eight months (classified as having an intermediate duration) (Armes 2007; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). Steel 2016 did not clearly state the total intervention duration, but it is likely that the intervention was given over a period of six months, after which the post-intervention assessment took place. In four studies, interventions consisted of an initial more intense intervention delivery during the first two (Edelman 1999; Savard 2006) or four months (Sharpe 2014; Walker 2014), followed by additional sessions (if needed) for a period ranging from nine weeks (Savard 2006) to eight months (Sharpe 2014).

Providers

In four studies, nurses delivered the intervention (Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011), and a combination of therapists (i.e. two or more psychologists, psychiatrists, counsellors, and/or social workers) delivered the intervention in five studies (Bordeleau 2003; Classen 2001; Edelman 1999; Spiegel 1981; Savard 2006). In one study, psychologists, physiotherapists, and nurses delivered the interventions (Johansson 2008). In two studies, non-clinicians (i.e. a research fellow (Armes 2007) or master's level/PhD therapists (Steel 2016)) did so. Finally, a team consisting of a nurse, a psychiatrist, and the participant's primary care physician delivered the interventions in Sharpe 2014 and Walker 2014.

Delivery of the intervention

Researchers delivered psychosocial interventions using different approaches. Six studies delivered interventions individually, either face-to-face (Armes 2007; Chan 2011; Savard 2006) or by telephone (Barsevick 2004; Barsevick 2010; Bruera 2013). Four studies used blended methods for intervention delivery, consisting of individual face-to-face and telephone contacts (Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). In addition to these delivery channels, Johansson 2008 used face-to-face group-based interventions, and Steel 2016 used a Web-based platform. Four studies delivered interventions in groups (Bordeleau 2003; Classen 2001; Edelman 1999; Spiegel 1981).

Training and supervision

Ten studies (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014) reported that providers of the intervention were trained. The remaining four studies did not report whether providers were trained before delivering the intervention (Classen 2001; Edelman 1999; Johansson 2008; Savard 2006). Eleven studies reported supervision of intervention delivery (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). Three studies did not report whether intervention delivery was supervised (Chan 2011; Classen 2001; Edelman 1999).

Control condition

Nine studies compared the effects of a psychosocial intervention versus usual care. In eight of these studies, usual care consisted of no intervention (Armes 2007; Chan 2011; Edelman 1999; Johansson 2008; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014); the other study assigned participants to a wait list condition (Savard 2006). Three studies compared intervention effects versus an attentional control (Barsevick 2004; Barsevick 2010; Bruera 2013).

Classen 2001 provided participants in control conditions with a self-directed educational intervention but also provided the educational materials to participants randomised to the intervention condition. Bordeleau 2003 provided all participants with educational materials about breast cancer and its treatment, relaxation, and nutrition.

Outcome measures

Fatigue

All 14 included studies reported fatigue as a primary, secondary, or tertiary outcome. Ten studies used one instrument to measure fatigue (Bordeleau 2003; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). The remaining four studies used two or more instruments (Armes 2007; Barsevick 2004; Barsevick 2010; Bruera 2013). Five of the 14 studies used the fatigue subscale of the Profiles of Mood States (POMS) (Barsevick 2004; Barsevick 2010; Classen 2001; Edelman 1999; Spiegel 1981). Another five studies used the fatigue scale of the EORTC QLQ-C30 (Armes 2007; Bordeleau 2003; Johansson 2008; Sharpe 2014; Walker 2014). The four remaining studies used other instruments to evaluate fatigue: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Bruera 2013); Revised Piper Fatigue Scale, subscale intensity (Chan 2011); Multidisciplinary Fatigue Inventory (Savard 2006); and Functional Assessment of Cancer Treatment (FACT) Fatigue (Steel 2016). The four studies evaluating fatigue with more than one instrument used the following additional instruments: visual analogue scale (VAS) of global fatigue (Armes 2007); Schwartz Cancer Fatigue Scale (Barsevick 2004); General Fatigue Scale (Barsevick 2004; Barsevick 2010); and the fatigue subscale of the Edmonton Symptom Assessment Scale (ESAS) (Bruera 2013). Except for the single-item VAS of global fatigue used in the study of Armes 2007, all instruments comprise multiple items designed to measure fatigue.

Physical, social, role, emotional, and cognitive functioning

Many studies used several measures of function. Eight studies assessed physical functioning (Armes 2007; Barsevick 2010; Bordeleau 2003; Chan 2011; Johansson 2008; Savard 2006; Sharpe 2014; Walker 2014). Six of those eight studies used the physical functioning scale of the EORTC QLQ-C30, and the other two studies used the physical component of the Short-Form Health Survey (SF-12 and SF-36). Four studies assessed social and role functioning (Bordeleau 2003; Johansson 2008; Sharpe 2014; Walker 2014) using the scales of the EORTC QLQ-C30. Three studies assessed emotional functioning using the scale of the EORTC QLQ-C30 (Bordeleau 2003; Johansson 2008) or the mental component of the SF-12 (Barsevick 2010). Two studies assessed cognitive functioning using the scale of the EORTC QLQ-C30 (Bordeleau 2003; Johansson 2008). Two studies used other measures to evaluate functioning. Barsevick 2004 used total score for the Functional Performance Inventory - a 65-item scale consisting of six subscales, including body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. In addition to physical and mental component summary scores of the SF-12, Barsevick 2010 applied interference items from the adapted Brief Pain Inventory to symptoms rather than to pain only (SXINT) and assessed Eastern Cooperative Oncology Group Performance Status.

Adverse events

Only three studies assessed adverse events of the intervention and reported the number of adverse events for the total sample (Bruera 2013; Sharpe 2014; Walker 2014). Bruera 2013 recorded the number of grade $\geq$ 3 adverse events. Sharpe 2014 and Walker 2014 defined adverse events as death from any cause, admission to a psychiatric ward, or attempted suicide. In addition, Chan 2011 reported that the sole reason for drop-out of participants was death.

Post-intervention outcome assessments

As a result of variance in intervention duration, the time between baseline and post-intervention outcome evaluation ranged from two weeks in Bruera 2013, to eight weeks in Savard 2006, to 26 weeks in Steel 2016, to 12 months in Bordeleau 2003, Classen 2001, and Spiegel 1981. Two studies reported on the post-intervention assessment but did not clearly describe the number of weeks or months between pre-intervention and post-intervention assessment (Barsevick 2004; Edelman 1999). Armes 2007 provided an intervention consisting of three sessions coinciding with administration of chemotherapy but did not mention the total length of chemotherapy in number of days or weeks. Researchers assessed outcomes at the end of chemotherapy (T1), four weeks after the end of chemotherapy (T2), and nine months after recruitment to the study (T3). Although the original study investigators identified T2 as the main outcome for the study, we used T1, as this was the first post-intervention assessment. Barsevick 2010 performed post-intervention assessment at days 43 to 46 or days 57 to 60, depending on the type of cancer treatment participants received. Sharpe 2014 provided the intervention over a four-month period, then continued the intervention for a further eight months. The primary endpoint for this study was the 24-week assessment. Walker 2014 examined the same type of intervention as Sharpe 2014 in a group of participants with a poor prognosis for cancer. Given this poor prognosis, the intervention was continued for a further four months instead of eight months. Walker 2014 averaged fatigue data over participants' time in the study (up to a maximum of 32 weeks) into a single fatigue score, but averaged fatigue scores were not available for meta-analysis. Therefore, we used fatigue data collected at 24-week assessment,

in line with Sharpe 2014. Johansson 2008 randomised participants to one of four study arms and performed assessments at 3, 6, 12, and 24 months after randomisation. Researchers combined participants from the three intervention arms in this study into a single intervention group for the aim of this review. However, the three interventions had different durations and start points after randomisation. We selected the six-month assessment as the post-intervention assessment for our meta-analysis.

Follow-up outcome assessments

Eight studies included one (Barsevick 2004) or two follow-up assessments (Armes 2007; Chan 2011; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Walker 2014). However, four of these studies (Edelman 1999; Savard 2006; Sharpe 2014; Walker 2014) provided more than one additional session (if needed) during the follow-up period. Therefore, we excluded these studies from primary meta-analyses for follow-up effects and included them in subgroup analyses. The four remaining studies (Armes 2007; Barsevick 2004; Chan 2011; Johansson 2008) had different follow-up durations. First follow-up durations ranged from three weeks (Chan 2011) to six months (Johansson 2008) after post-intervention assessment. Second follow-up administration varied between studies and ranged from nine weeks (Chan 2011) to 18 months (Johansson 2008) after post-intervention assessment.

Excluded studies

Of the 155 full texts excluded from our review, only 21 studies (23 reports) had potential relevance to our study aim. We have listed details regarding these 21 excluded studies in the Characteristics of excluded studies table.

Ongoing studies

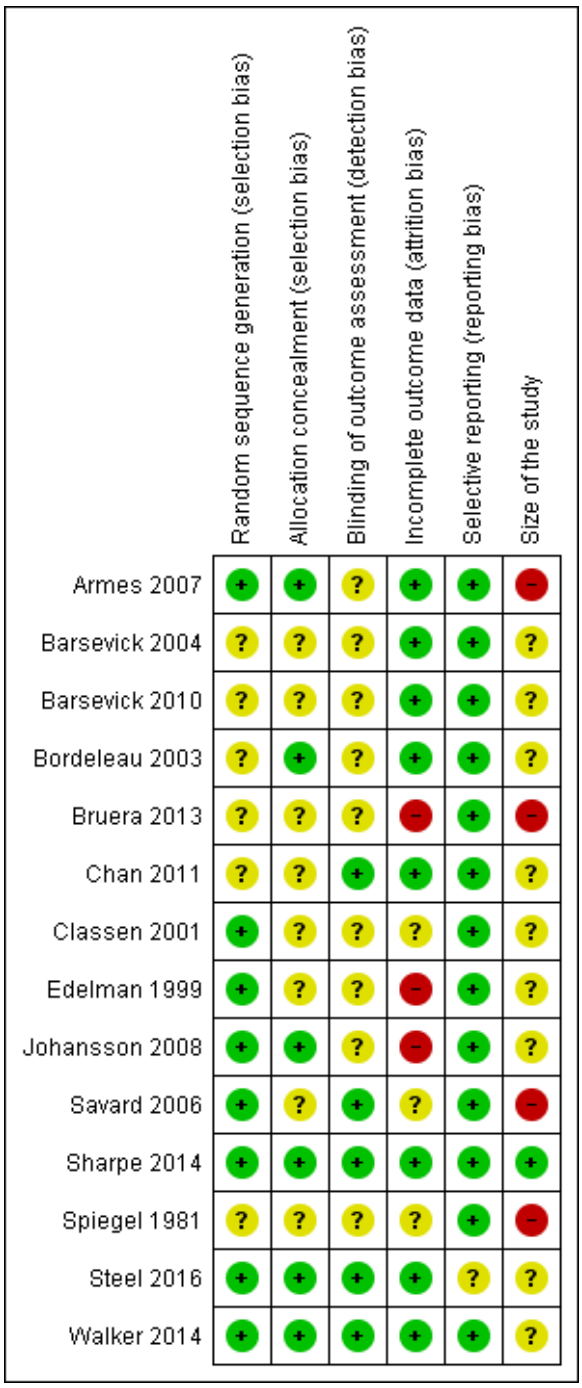
We identified two studies that have not been completed (Poort; Serfaty) and listed characteristics of these studies in the Characteristics of ongoing studies table.

Risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' tool (Figure 2; Figure 3) (Higgins 2011).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Eight studies adequately described the method used to generate the random sequence, and so we judged them to be at low risk of bias for this domain (Armes 2007; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). Five studies did not specify the method of randomisation used (Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Spiegel 1981), and we judged them to be at unclear risk of bias. In addition, Chan 2011 used a 'lucky draw method' but provided no description; therefore, we judged this study as having unclear risk of bias. We identified no studies at high risk of bias for this domain.

Allocation concealment

Six studies fully described how allocation of the sequence was concealed, and we judged them to be at low risk of bias for this domain (Armes 2007; Bordeleau 2003; Johansson 2008; Sharpe 2014; Steel 2016; Walker 2014). Eight studies did not adequately describe how allocation of the sequence was concealed, and we judged them to be at unclear risk of bias (Barsevick 2004; Barsevick 2010; Bruera 2013; Chan 2011; Classen 2001; Edelman 1999; Savard 2006; Spiegel 1981). We found no studies at high risk of bias for this domain.

Blinding

Five studies explicitly stated that outcome assessors were masked to allocation, and we judged them to be at low risk of bias for this domain (Chan 2011; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). Nine other studies did not mention blinding of outcome assessors or researchers, and we judged them to be at unclear risk of bias (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Classen 2001; Edelman 1999; Johansson 2008; Spiegel 1981). We identified no studies at high risk of bias for this domain.

Incomplete outcome data

Eight studies had less than 10% or 10% or more missing data in the original study sample but used adequate statistical analysis; therefore, we judged these studies to be at low risk of bias for this domain (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Chan 2011; Sharpe 2014; Steel 2016; Walker 2014). Three studies had more than 10% missing data and included only patients with at least one observation post randomisation in the mixed model or slopes analysis, and we judged them to be at unclear risk of bias (Classen 2001; Savard 2006; Spiegel 1981). The remaining three studies had 10% or more missing data, and we judged them to be at high risk of bias on the basis of their adopted method of analysis (Bruera 2013; Edelman 1999; Johansson 2008). Of note, we based all judgements on original study samples because information on attrition for the subset of interest for this review was not available.

Selective reporting

Thirteen studies adequately reported fatigue outcomes for the original study sample, and we judged them to be at low risk of bias for this domain (Armes 2007; Barsevick 2004; Barsevick 2010; Bordeleau 2003; Bruera 2013; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014). In Steel 2016, study authors performed two separate analyses but presented data from one analysis only (i.e. for the subgroup of participants reporting clinically significant symptoms at baseline). However, the original study investigators provided data for the total group on request; thus, we judged this study to be at unclear instead of high risk of bias. We identified no studies at high risk of bias for this domain. Visual inspection of the funnel plot did not suggest publication bias.

Other potential sources of bias

Size of study

We provided information on total sample size because we used this information in a few analyses. On the basis of total sample sizes, we found that four studies had fewer than 50 participants per treatment arm, and we judged them to be at high risk of bias for this domain (Armes 2007; Bruera 2013; Savard 2006; Spiegel 1981). Nine studies included between 50 and 199 participants per treatment arm, and we judged them to be at unclear risk of bias (Barsevick 2004; Barsevick 2010; Bordeleau 2003; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Steel 2016; Walker 2014). We identified one study with more than 200 participants per treatment arm, and we judged this study to be at low risk of bias (Sharpe 2014). However, sample sizes for the subset of participants with incurable cancer included in the meta-analysis were much smaller. In fact, eight studies included in the subset meta-analysis would be judged to be at high risk of bias for this domain on the basis of fewer than 50 participants per treatment arm at baseline (Armes 2007; Barsevick 2004; Barsevick 2010; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Walker 2014). The four remaining studies reported between 50 and 199 participants per treatment arm and we judged them to be at unclear risk of bias (Bordeleau 2003; Chan 2011; Classen 2001; Steel 2016).

Quality of the control condition

We judged the quality of the control condition to be adequate in three studies (Barsevick 2004; Barsevick 2010; Bruera 2013). In Barsevick 2004 and Barsevick 2010, control conditions were provided to control for the amount of time and attention received by intervention groups. In Bruera 2013, participants in the control condition also received (non-therapeutic) phone calls. We judged four studies to have partially controlled features of the control group (Bordeleau 2003; Chan 2011; Classen 2001; Steel 2016). We judged that efforts made to ensure that as many features as possible had been controlled for in the control group were inadequate in seven studies (Armes 2007; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014).

Equality of treatment expectations

We judged three studies to show adequate equality of treatment expectations between intervention and control groups (Bruera 2013; Barsevick 2004; Barsevick 2010). These three studies compared effects of the intervention versus an attentional control. We judged the remaining 11 studies to have inadequate treatment expectations (Armes 2007; Bordeleau 2003; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014).

Allegiance of the therapist

No studies reported allegiance of the therapist and/or researcher. Two studies (Bordeleau 2003; Classen 2001) were conducted to replicate the findings of previous research on effects of supportive-expressive group therapy (SEGT). Thus, we assumed that investigators had at least some allegiance to SEGT.

Effects of interventions

See: **Summary of findings for the main comparison**

See Summary of findings for the main comparison.

Review authors were interested in the effects of psychosocial interventions versus usual care or control conditions (not psychosocial interventions) in participants with incurable cancer receiving cancer treatment with palliative intent. As mentioned earlier, several studies had a mixed sample of participants with incurable and potentially curable cancer and/or receiving and not receiving cancer treatment during the psychosocial intervention. The analyses described in the following sections are subset meta-analyses, including only those participants of interest for our review.

Twelve of the 14 included studies were able to provide fatigue data for meta-analysis on the subset of interest for this review involving 535 participants in total at post-intervention assessment (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). With respect to measures of physical, social, role, emotional, and cognitive functioning, we received data from two to seven studies, depending on the specific domain of functioning. Although Bordeleau 2003 could not provide fatigue data, these investigators were able to provide data for all five domains of functioning. Data on adverse events were not available for the subset of interest for our review, but we have provided later in this section a narrative description of adverse events in the total sample.

As we were pooling data from heterogeneous populations and interventions, we used random-effects instead of fixed-effect models. Overall, we judged the quality of evidence for psychosocial interventions to be very low. We downgraded the quality of evidence by two levels for risk of bias and imprecision.

Fatigue

Subset meta-analysis did not suggest a post-intervention outcome benefit for the psychosocial intervention group compared with the control group on the fatigue outcome measured with different instruments (standardised mean difference (SMD) -0.25, 95% confidence interval (CI) -0.50 to 0.00; P = 0.05; participants = 535, studies = 12; I^2 = 43%; Analysis 1.1; Figure 4). We found very low-quality evidence to suggest benefit of psychosocial interventions for the secondary outcome of fatigue at first follow-up (SMD -0.66, 95% CI -1.00 to -0.32; P = 0.0001; participants = 147, studies = 4; I^2 = 0%; Analysis 1.2; Figure 5). Psychosocial interventions did not influence secondary fatigue outcomes at second follow-up (SMD -0.41, 95% CI -1.12 to 0.30; P = 0.26; participants = 91, studies = 2; I^2 = 29%; Analysis 1.3; Figure 6).

Figure 4. Forest plot of comparison: 1 Fatigue, outcome: 1.1 Post intervention.

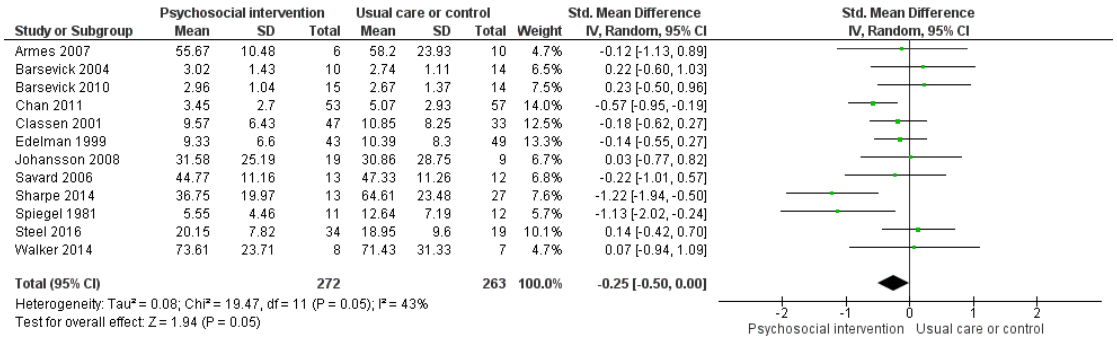


Figure 5. Forest plot of comparison: 1 Fatigue, outcome: 1.2 First follow-up.

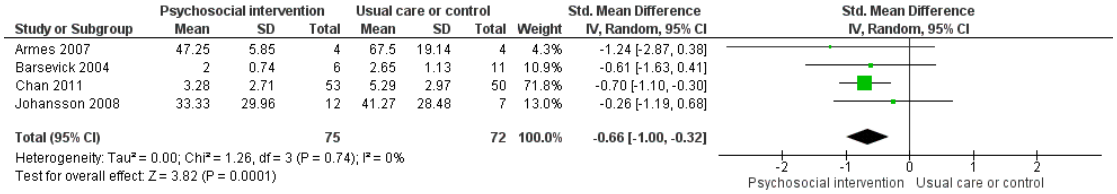
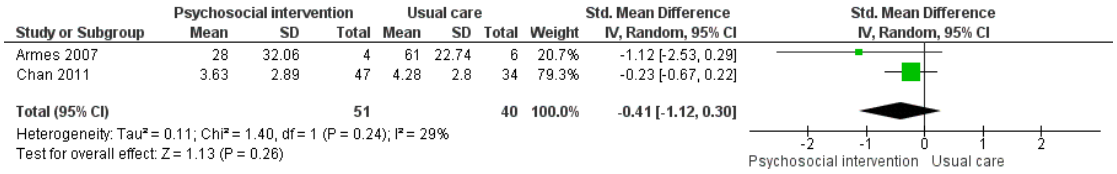


Figure 6. Forest plot of comparison: 1 Fatigue, outcome: 1.3 Second follow-up.



Non meta-analysed data

Investigators of two included studies responded to our data request but were unable to provide separate fatigue outcome data for meta-analysis. Bruera 2013 had a homogeneous sample of participants with incurable cancer receiving cancer treatment and found no statistically significant differences in median improvement of FACIT Fatigue scores (P = 0.27) or ESAS Fatigue scores (P = 0.14) between intervention and control groups. Bordeleau 2003 had a homogeneous sample of participants with incurable cancer, but not all participants were receiving cancer treatment. This study found significant across-time deterioration in EORTC QLQ-C30 Fatigue scores (P = 0.003) using a mixed model for repeated measures. However, this deterioration did not differ between study arms; therefore, this study could not demonstrate a significant intervention effect.

Physical functioning

We found very low-quality evidence to suggest a post-intervention outcome benefit of psychosocial interventions for physical func-

tioning measured with different instruments (SMD 0.32, 95% CI 0.01 to 0.63; P = 0.04; participants = 307, studies = 7; I^2 = 35%; Analysis 2.1). Psychosocial interventions were not associated with statistically significant improvement in physical functioning at first follow-up (SMD 0.37, 95% CI -0.20 to 0.94; P = 0.21; participants = 122, studies = 2; I^2 = 36%; Analysis 2.2).

Non meta-analysed data

Armes 2007 provided raw values instead of transformed scores for physical functioning, and we could not use these for meta-analysis. This study had a mixed-stage sample of participants receiving cancer treatment for incurable and potentially curable cancer. Study investigators used a random-slope/random-intercept mixed model and reported significant improvement in physical functioning for the original study population (coefficient 10, 95% CI 2.5 to 17.5; P = .009). However, we cannot conclude whether this improvement also applies to the small subset of participants with incurable cancer.

Social functioning

We saw no effect of psychosocial interventions on post-intervention social functioning measured on the scale of the EORTC QLQ-C30 (mean difference (MD) 4.16, 95% CI -11.20 to 19.53; P = 0.60; participants = 141, studies = 4; I^2 = 55%; Analysis 3.1).

Role functioning

Psychosocial interventions did not influence post-intervention role functioning as measured with the EORTC QLQ-C30 scale (MD 3.49, 95% CI -12.78 to 19.76; P = 0.67; participants = 143, studies = 4; I^2 = 52%; Analysis 4.1).

Emotional functioning

Psychosocial interventions did not influence post-intervention emotional functioning as measured with different instruments (SMD -0.11, 95% CI -0.56 to 0.35; P = 0.65; participants = 115, studies = 3; I^2 = 23%; Analysis 5.1).

Cognitive functioning

Results showed no overall effect of psychosocial interventions on post-intervention cognitive functioning measured with the EORTC QLQ-C30 scale (MD -2.23, 95% CI -12.52 to 8.06, P = 0.67; participants = 86, studies = 2; I^2 = 23%; Analysis 6.1).

Adverse events

Data on adverse events were available only for the total samples of three studies (Bruera 2013; Sharpe 2014; Walker 2014). Bruera 2013 had a homogeneous sample of participants with incurable cancer receiving cancer treatment and reported that the number of grade $\geq$ 3 adverse events was similar between methylphenidate and placebo arms, which were combined with a nursing or control intervention. Sharpe 2014 had a mixed-stage sample of participants with incurable and potentially curable cancer either receiving or not receiving cancer treatment. This study reported 34 cancer-related deaths (7%) during the trial (19 in the intervention group and 15 in the usual care group), one admission to a psychiatric ward (intervention group), and one attempted suicide (intervention group) for the total sample. Study investigators determined that none of these events was related to trial treatments or procedures. Walker 2014 had a mixed-stage sample of participants with incurable and potentially curable cancer either receiving or not receiving cancer treatment. This study reported 43 cancer-related deaths (30%) during the trial for the total sample (21 in the intervention group and 22 in the usual care group). No other serious adverse events occurred.

Subgroup analyses

Intervention duration: short versus intermediate-long

Three studies (participants = 163) were classified as having short intervention durations (two to three weeks; Barsevick 2004; Barsevick 2010; Chan 2011). The remaining nine studies (participants = 372) had intermediate (two to eight months) or long (12 months) intervention durations (Armes 2007; Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Steel 2016; Walker 2014). Meta-analysis to examine post-intervention results for these subgroups did not demonstrate a subgroup difference (Chi^2 = 0.21; P = 0.65; participants = 535, studies = 12; I^2 = 0%; Analysis 7.1).

Intervention delivery: individual versus group

Three studies (participants = 195) delivered interventions in groups (Classen 2001; Edelman 1999; Spiegel 1981). Eight studies (participants = 312) had interventions delivered individually (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Savard 2006; Sharpe 2014; Steel 2016; Walker 2014). One study (Johansson 2008) delivered interventions individually or in groups; we did not include this study in the subgroup analysis. We found no evidence supporting a subgroup difference (Chi^2 = 0.14; P = 0.70; participants = 507, studies = 11; I^2 = 0%; Analysis 7.2).

Intervention type: monodisciplinary versus multidisciplinary

Nine studies (participants = 452) had interventions delivered by professionals from a single discipline (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Classen 2001; Edelman 1999;

Savard 2006; Spiegel 1981; Steel 2016). Three studies (participants = 83) had interventions delivered by professionals from two or more disciplines (Johansson 2008; Sharpe 2014; Walker 2014). We found no evidence supporting a subgroup difference (Chi^2 = 0.20; P = 0.66; participants = 535, studies = 12; I^2 = 0%; Analysis 7.3).

Intervention aim: fatigue specific versus other aim

Five studies (participants = 232) providing fatigue outcome data for meta-analysis investigated the effects of a psychosocial intervention aimed at fatigue (Armes 2007; Barsevick 2004; Barsevick 2010; Chan 2011; Steel 2016). The remaining seven studies (participants = 303) had different intervention aims (Classen 2001; Edelman 1999; Johansson 2008; Savard 2006; Sharpe 2014; Spiegel 1981; Walker 2014). We found no evidence supporting a subgroup difference (Chi^2 = 1.08; P = 0.30; participants = 535, studies = 12; I^2 = 7.5%; Analysis 7.4).

Additional sessions: no additional sessions versus booster sessions

Four studies (participants = 147) provided no additional sessions between post-intervention and first follow-up assessments and thus were included in the primary meta-analysis for fatigue at first follow-up (Armes 2007; Barsevick 2004; Chan 2011; Johansson 2008; Analysis 1.2). Four additional studies provided booster sessions between post-intervention and first follow-up assessments (Edelman 1999; Savard 2006; Sharpe 2014; Walker 2014). Three of these studies provided data for first follow-up (Edelman 1999; Sharpe 2014; Walker 2014). We found no evidence supporting a subgroup difference (Chi^2 = 0.61; P = 0.44; participants = 270, studies = 7; I^2 = 0%; Analysis 7.5). Two studies (participants = 91) provided no additional sessions between post-intervention and second follow-up assessments and were included in the primary meta-analysis for fatigue at second follow-up (Armes 2007; Chan 2011; Analysis 1.3). Three studies provided data for second follow-up but included booster sessions (Edelman 1999; Sharpe 2014; Walker 2014). We found no evidence supporting a subgroup difference (Chi^2 = 0.18; P = 0.67; participants = 202, studies = 5; I^2 = 0%; Analysis 7.6).

Sensitivity analysis

Three of the 12 studies with fatigue outcomes featured in the post-intervention meta-analysis included fewer than 10 participants per treatment arm post intervention (Armes 2007; Johansson 2008; Walker 2014). We performed a sensitivity analysis with data from these three studies removed. This analysis did not suggest a post-intervention outcome benefit for the psychosocial intervention group compared with the control group (SMD -0.30, 95% CI -0.59 to 0.00; P = 0.05; participants = 476, studies = 9; I^2 = 56%; Analysis 8.1). At first and second follow-up, only one included study assigned at least 10 participants per treatment arm (Chan 2011). Sensitivity analyses demonstrated that study findings (participants = 153) were consistent with results of the primary meta-analysis at first follow-up (SMD -0.70, 95% CI -1.10 to -0.30; P = 0.0005; Analysis 8.2) and at second follow-up (SMD -0.23, 95% CI -0.67 to 0.22; P = 0.32; Analysis 8.3).

DISCUSSION

Summary of main results

This review identified 14 studies for inclusion, with a wide range of patient samples and psychosocial interventions. Twelve of the 14 studies provided data on fatigue for our subset meta-analysis involving 535 participants post intervention. We found a lack of clear evidence to support or not support the use of psychosocial interventions for reducing fatigue in patients with incurable cancer during cancer treatment. Seven of the 14 studies provided data on physical functioning involving 307 participants post intervention. Psychosocial interventions may improve physical functioning post intervention, may reduce fatigue at first follow-up, or may achieve both. However, most subsets of data were too small to be reliable, and only a limited number of studies with a limited number of participants contributed to follow-up findings. Four of the 14 studies provided data on social and role functioning, three studies on emotional functioning, and two studies on cognitive functioning. We found no evidence to support or not support the use of psychosocial interventions for improving these domains of functioning post intervention. In addition, there was a broad range of interventions and follow-up durations across studies with considerable attrition between assessments. Data on adverse events were sparse. Only three studies that included pharmacological interventions in addition to psychosocial interventions (Bruera 2013; Sharpe 2014; Walker 2014) reported on adverse events and found no difference in the number of adverse events between intervention and control groups.

Overall completeness and applicability of evidence

We searched widely for evidence using five databases with no restriction on language and used search terms to identify as wide a range of psychosocial interventions as possible. We found some important gaps in the evidence.

The main limitation of this review involves the relative lack of data in this field. Six studies consisted of a homogenous sample of patients with incurable cancer. The remaining eight studies comprised a mixed sample of potentially curable and incurable patients. As a result, interventions from these eight studies were not

specifically tailored to patients with incurable cancer. Yet, tailoring of psychosocial interventions could be important in achieving intervention effects, especially given the major difference in prognosis between patients with incurable cancer and patients with potentially curable cancer. Although investigators from these mixed-sample studies were able to provide data for the subset of incurable cancer patients, the sample sizes of these subsets were quite small. This is likely to result in lack of power to detect treatment effects that may arise from the psychosocial interventions. In addition, our meta-analysis including means instead of individual patient data for subsets of the total randomised study population is limited in that we were unable to adjust for potential confounding factors. For these reasons, results of meta-analyses must be interpreted with caution.

We identified a limited number of studies (six) investigating interventions specifically aimed at addressing fatigue. However, only two of these six studies reported that the presence of some level of fatigue was an entry criterion for trial participation. This may lead to floor effects, restricting the potential range of fatigue scores and resulting in less room for improvement. Furthermore, a specific feature of data available from identified studies was the heterogeneity of intervention and follow-up durations. In addition, only four of the 12 studies contributed to findings on follow-up effects. Three additional studies provided data for follow-up assessments, but interventions in these studies continued between post-intervention and follow-up assessments. Therefore, we excluded these three studies from the primary follow-up analysis and included them in subgroup analyses that did not find a significant effect. Among the four studies included in the primary analysis for follow-up effects, we noted considerable attrition between post-intervention and first follow-up assessments (attrition rate 18.5%). Although specific information on reasons for attrition for the subset of interest for this review was not available, the attrition is unlikely to be random. In fact, attrition may be associated with deterioration of health or death of the participant. This has implications for interpretation of follow-up findings; thus these results should be interpreted with caution.

Overall, studies predominantly comprised female participants. This limits our ability to generalise research findings to male patients. Also, among the six studies that consisted of a homogeneous sample of patients with incurable cancer, only one study investigated intervention effects for a population other than metastatic breast cancer (Bruera 2013). Finally, in two studies (Sharpe 2014; Walker 2014), the investigated population had received a diagnosis of major depressive disorder comorbid with cancer. Fatigue outcomes in these participants may have been associated with this depression, making it difficult to distinguish fatigue as a symptom of depression from cancer-related fatigue.

Quality of the evidence

We evaluated the overall quality of evidence using GRADE (see Summary of findings for the main comparison). We downgraded the GRADE quality of evidence for all outcomes to very low because of unclear risk of selection bias and imprecision due to sparse data. We have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

Potential biases in the review process

We conducted this review in keeping with the principles of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed electronic database searches and manual follow-ups to look for additional references to maximise recall. None of the authors of this review was involved in any of the excluded or included studies. Two review authors independently assessed all studies for inclusion, so we are confident that we have attempted to reduce bias in the review process. However, as with all systematic reviews and meta-analyses, subjective judgement is involved at various stages in the review process - from identification of studies to data extraction and analysis. As a result, although search strategies, data extraction, and analyses were thorough, relevant studies and data may be missing.

Agreements and disagreements with other studies or reviews

In the Cochrane review Goedendorp 2009 (co-authored by review authors GB, MFG, and SV), which did not include a meta-analysis, review authors found limited evidence showing the effectiveness of psychosocial interventions during cancer treatment in reducing fatigue. They made no distinction in effectiveness between psychosocial interventions provided for patients receiving cancer treatment with curative or palliative intent. In our meta-analysis, we did not find clear evidence supporting the effectiveness of a range of psychosocial interventions for fatigue outcomes among the subset of incurable cancer patients. In addition, Goedendorp 2009 concluded that psychosocial interventions designed specifically to alleviate fatigue during cancer treatment are promising. Our meta-analysis found no indication that interventions specifically aimed at reducing fatigue had greater potential than interventions with a different aim for patients with incurable cancer receiving cancer treatment with palliative intent. This review highlights the current lack of evidence for psychosocial interventions aimed at reducing fatigue in patients with incurable cancer receiving treatment with palliative intent. The optimal approach to psychosocial intervention for fatigued patients with incurable cancer and the true extent of potential benefits and harms remain uncertain.

AUTHORS' CONCLUSIONS

Implications for practice

This review found insufficient evidence showing the effectiveness of psychosocial interventions used to treat fatigue in patients with incurable cancer receiving treatment with palliative intent. Therefore, specific implications for patients with incurable cancer, for clinicians, for policy makers, or for funders of the interventions cannot be given.

Implications for research

Evidence

Further evidence is needed from high-quality trials with large samples that fully report methodological characteristics and potential harms. We identified two ongoing studies that aim to enrol 240 participants (Serfaty) and 219 participants (Poort) with a diagnosis of incurable cancer. With large samples, both studies have the potential to provide substantial assistance to those seeking answers to the research question that is the topic of this review.

Population

Additional studies with a homogeneous study sample of patients with incurable cancer are needed. Targeting patients most in need (i.e. those reporting clinically significant levels of fatigue) to eliminate potential floor effects has been recommended before (Bower 2014) and would be a helpful approach in future studies. Also, future studies should expand the focus beyond patients with metastatic breast cancer, as it is unknown whether findings from this patient group can be generalised to patients with other cancer diagnoses. Therefore, enriching the evidence with studies that focus on patients diagnosed with other types of incurable cancer would be helpful. Moreover, future studies should include a substantial proportion of male participants and should determine whether gender moderates treatment outcomes, as most of the participants in studies conducted thus far have been females. Finally, given the difficulty of recruiting large enough samples in palliative care trials, multi-centre studies are recommended, as studies with larger patient samples may detect small but clinically relevant differences. Alternatively, application of novel research designs (e.g. replicated n-of-1 trials) might be worthwhile given the difficulties involved in conducting randomised controlled trials (RCTs) of patients receiving cancer treatment with palliative intent.

Intervention

Psychosocial interventions are part of a broader portfolio of available interventions for cancer-related fatigue, which includes interventions focused on physical activity and pharmacological approaches. For future research aimed at psychosocial interventions, we recommend that protocols for a trial, including a detailed description of the intervention and its components, should be published or otherwise made publicly available. Also, tailoring the content of interventions to patients with incurable cancer would be helpful, given the substantial difference in prognosis between patients with potentially curable and incurable cancer. This difference has implications for the psychosocial factors thought to maintain fatigue and addressed by the interventions. Moreover, we would recommend short interventions delivered over a period of several weeks or months, with follow-up assessments following shortly (within three to eight months) after intervention delivery. This is recommended not only to prevent participant attrition (which complicates interpretation of findings) as much as possible, but also to minimise the burden of participation.

Comparison

Given the current state of the evidence, we recommend that researchers conducting future trials should compare psychosocial interventions versus usual care or attentional controls.

Outcome

No consensus has been reached on which instruments should be used to measure fatigue and it would be helpful to reduce the variance among outcome instruments used to measure reduction in fatigue. Future studies should clearly assess benefits and potential adverse events (e.g. increased psychological distress) of the intervention.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Armes 2007

Methods	Design: RCT. Duration of study participation: 36 weeks.
Participants	UK, Guys and St. Thomas' Hospital NHS Trust and Bromley Hospitals NHS Trust 60 patients (aged 59.1 years, 60% female) receiving chemotherapy and reporting significant fatigue
Interventions	Intervention group: brief, cancer-related fatigue-specific, behaviourally oriented intervention consisting of cognitive, behavioural, and general components Control group: standard care; cancer-related fatigue was not assessed routinely and advice regarding its management was delivered in an ad hoc manner
Outcomes	VAS Fatigue, EORTC QLQ-C30 Fatigue, and EORTC QLQ-C30 Physical functioning. Adverse events were not described
Notes	Funding: Cancer Research UK Nursing Research Training Fellowship (CP1052/0101 and C1428/A180)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Originally, minimisation as the method of treatment allocation. After the first 10 patients, simple random, permuted, block randomisation implemented
Allocation concealment (selection bias)	Low risk	Statistician (unconnected to the study) generated the randomisation, provided a central telephone service for participant allocation, and kept a copy of the randomisation codes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Questionnaires posted or given to patients in the chemotherapy clinic by first study author. Insufficient information to permit judgement of low or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 10% missing data, but data analysed using *t* tests and random-slope/random-intercept mixed models using a generalised linear latent and mixed model
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.

Armes 2007 (*Continued*)

Size of the study	High risk	Fewer than 50 participants randomised per treatment arm at baseline

Barsevick 2004

Methods	Design: RCT. Duration of study participation: depended on type of cancer treatment
Participants	USA, University of Utah Health Science Center and Fox Chase Cancer Center 396 individuals (aged 56.3 years, 85% female) beginning chemotherapy, radiotherapy, or concurrent therapy for breast, lung, colorectal, advanced prostate, gynaecological, or testicular cancer or lymphoma
Interventions	Energy Conservation and Activity Management (ECAM): information provided to aid formation of an accurate representation of the symptom of fatigue, guide the formulation and implementation of a plan for energy conservation, and appraise the effectiveness of symptom-management efforts Control group: information on nutrition and a healthy diet. No therapeutic nutritional information or information on symptom management
Outcomes	POMS Fatigue, Schwartz Cancer Fatigue Scale, General Fatigue Scale, and Functional Performance Inventory. Adverse events were not described
Notes	Funding: National Institute of Nursing Research (R01NR04573)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on the method of randomisation was provided.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 10% missing data for at least one data point on at least one fatigue measure, but use of SAS mixed procedure restricted maximum likelihood method
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.

Barsevick 2004 (*Continued*)

Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Barsevick 2010

Methods	Design: RCT. Duration of study participation: 43-46 days and 57-60 days, depending on length of the chemotherapy cycle
Participants	USA, Fox Chase Cancer Center. 292 patients (aged 53.9 years, 82% female) beginning a new chemotherapy regimen for breast, lung, colorectal, prostate, gynaecological, bladder, or testicular cancer, or lymphoma
Interventions	Energy and Sleep Enhancement (EASE): information about the symptom's identity, cause, and pattern needed to form a mental image of the symptom and to identify and implement self-care strategies to manage the symptom. Evaluation of the effectiveness of strategies and adjustment of coping methods or symptom representation Control intervention: information about nutrition and a healthy diet. Therapeutic nutritional information or information on symptom management not included
Outcomes	POMS Fatigue, General Fatigue Scale, and SF-12 Physical and Mental component summary score. Adverse events not described
Notes	Funding: National Institute of Nursing Research (R01NR04573) Follow-up study of Barsevick 2004.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on the method of randomisation provided.
Allocation concealment (selection bias)	Unclear risk	Random assignments generated by statistician and placed in sealed envelopes, numbered and selected sequentially for each stratification group. Unclear whether envelopes were opaque
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% missing data and data were analysed using SAS mixed procedure (i.e. restricted maximum likelihood method)

Barsevick 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Bordeleau 2003

Methods	Study design: RCT. Duration of study participation: 12 months.
Participants	Canada, Samual Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, and 6 other (regional) cancer centres 237 women with metastatic breast cancer.
Interventions	Supportive-Expressive Group Therapy (SEGT): weekly 90-minute therapist-led support group adhering to principles of supportive-expressive therapy. Intended to foster support among group members while encouraging expression of emotions about cancer and its effects on lives. Relaxation exercise at the end of each seminar Control group: no participation in a support group. Every 6 months, all women received educational materials about breast cancer and its treatment, relaxation, and nutrition. All study participants could receive any medical or psychosocial treatment deemed necessary
Outcomes	EORTC QLQ-C30 Fatigue, POMS Fatigue, EORTC QLQ-C30 Physical, Social, Role, Emotional, and Cognitive functioning. Adverse events not described
Notes	Funding: Medical Research Council of Canada and Canadian Breast Cancer Research Initiative Summary data for functional scales of the EORTC-QLQ-C30 were provided, but fatigue data from the EORTC-QLQ-C30 or the POMS could not be provided (reason: "It would take too much time to retrieve the data") Allegiance effect: This trial was designed to replicate the findings of a previous study on the effects of SEGT, thus therapists and/or researchers probably had some allegiance to SEGT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on the method of randomisation provided.
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally, stratified for study centre and for the presence of visceral metastases
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Questionnaires given to participants by the research assistant during baseline assessment, and mailed out 4, 8, and 12 months

Bordeleau 2003 (*Continued*)

		after randomisation. No information on blinding of the research assistant provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 10% missing data, but data analysed using SAS mixed model for repeated measures
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Bruera 2013

Methods	Study design: RCT. Duration of study participation: 2 weeks.
Participants	USA, MD Anderson Cancer Center and Lundon B. Johnson General Hospital 190 patients with advanced cancer and reporting fatigue.
Interventions	Nursing Telephone Intervention (NTI): 3 components: (1) symptom assessment, (2) review of types and dosages of medications and adverse events, (3) psychosocial support and patient education. Research nurse asked open-ended questions regarding general well-being of participant and family, listened empathetically, answered participant's questions, and provided supportive statements Control group: non-therapeutic phone calls by a non-professional who assessed symptoms and asked about medications. No psychosocial support or education provided. If participants raised concerns, they were directed to discuss them with their physician
Outcomes	FACIT fatigue and ESAS Fatigue. Adverse events were documented
Notes	Funding: National Institute of Health-National Institute of Nursing and ACS Research Scholar Grant for Independent Investigators Not eligible for meta-analysis. Summary data were requested but not could not be provided (reason: "No staff support to deal with the request")

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported only that participants were randomly assigned to receive 1 of 4 treatments but not how randomisation was performed
Allocation concealment (selection bias)	Unclear risk	Not stated.

Bruera 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported that all members of the research team were blinded to treatment assignment (methylphenidate or placebo), but reported no information on blinding of outcome assessors for the nursing or control telephone intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% missing data, not described what was done with missing data, probably used complete-case analysis (only data from evaluable patients). Median differences between intervention and control groups analysed using Wilcoxon two-sample tests
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	High risk	Fewer than 50 participants randomised per treatment arm at baseline

Chan 2011

Methods	Study design: RCT. Duration of study participation: 3 months.
Participants	Tuen Mun Hospital, Hong Kong. 140 patients with advanced lung cancer.
Interventions	Psychoeducational intervention (PEI): PEI alters patients' perceptions and sensations of symptoms through stress reduction; clarification of misconceptions; and adoption of adaptive behaviours. A 40-minute educational package plus coaching of PMR delivered to patients within 1 week before the beginning of the course of radiotherapy, and reinforced 3 weeks after radiotherapy is commenced Usual care: mandatory individual briefing on the radiotherapy procedure and brief discussion of side effects by therapy radiographer
Outcomes	Revised Piper Fatigue Scale Intensity subscale and SF-36 Physical functioning. Adverse events not described
Notes	Funding: Hong Kong Health Service Research Fund. Personal feedback intended in the intervention protocol, as confirmed by the original study investigator

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Chan 2011 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No explanation on the method of randomisation (lucky draw method) provided
Allocation concealment (selection bias)	Unclear risk	Not reported how randomisation was performed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were collected by a research assistant blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% missing data post intervention. However, missing data imputed by a carry-forward method although missing data were not random but were related to outcomes that can lead to attrition bias
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Classen 2001

Methods	Study design: RCT. Duration of study participation: 12 months.
Participants	USA, Stanford University Medical Center. 125 women with metastatic breast cancer.
Interventions	Supportive-Expressive Group Therapy (SEGT): Participants were encouraged to confront their problems, strengthen their relationships, and find enhanced meaning in their lives in a supportive environment. Neither coping strategies nor psychoeducation taught in a didactic manner. Self-hypnosis exercise at end of each session Control group: self-directed educational intervention. Educational materials also offered to women in the treatment condition
Outcomes	POMS Fatigue. Adverse events not described.
Notes	Funding: National Institute of Mental Health, National Cancer Institute, John D. and Catherine T MacArthur Foundation, and the Fetzer Institute Allegiance effect: This trial was designed to replicate the findings of a previous study on the effects of SEGT, thus therapists and/or researchers probably had some allegiance to SEGT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Classen 2001 (*Continued*)

Random sequence generation (selection bias)	Low risk	Adaptive randomisation biased coin-design method.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	For the first 2 years of the study, baseline and post-baseline assessments completed on a computer. No information on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 10% missing data. Slopes analysis used, but only participants who provided at least one follow-up point included in the analysis
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Edelman 1999

Methods	Design: RCT. Duration of study participation: 12 months.
Participants	Australia, Royal North Shore Hospital. 124 women with metastatic breast cancer aged between 30 and 65 years
Interventions	Cognitive-Behavioural Therapy (CBT): cognitive and behavioural techniques, expression of feelings, and building of group support. Manual, handouts, and homework provided. Emphasis on gaining greater sense of control through problem solving and goal setting. Participants were instructed on effective communication strategies and were encouraged to communicate assertively with friends, family members, and medical staff Control group: No-therapy control group condition. Patients were informed about other community support groups that they could attend
Outcomes	POMS Fatigue. Adverse events not described.
Notes	Funding: not specified.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Edelman 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	For every 20 participants, a block randomisation procedure took place, with 10 randomised to each treatment condition
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% missing data and data analysed using independent samples *t*-tests.
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Johansson 2008

Methods	Design: RCT. Duration of study participation: 24 months.
Participants	Sweden, Uppsala University Hospital. 481 consecutive patients with newly diagnosed prostate, gastrointestinal, or breast cancer. Women with a mammography finding requiring surgery could also be included
Interventions	Intervention group: Individual support included individual psychological support, intensified primary health care, and nutritional support for some participants, and implied extra contact with at least two or three different professionals, irrespective of participants' need for support. All participants were contacted by a project psychologist. Current problems identified jointly by participants and by the psychologist were the focus of the intervention. Techniques used were derived from cognitive-behavioural therapy, including relaxation techniques, identification and challenging of negative automatic thoughts, and activity scheduling and daily planning. Group rehabilitation conducted by a psychologist, physiotherapist, and oncology nurse. Sessions included cognitive-behavioural techniques, light physical training, and relaxation. In 2 sessions, a physician presented information about cancer and cancer treatment, and a dietician provided dietary advice. All sessions offered opportunities to disclose and discuss concerns with group leaders and members Control group: Standard care did not include regular follow-ups by a dietician or medical social worker. Participants could be referred to such services
Outcomes	EORTC QLQ-C30 Fatigue and EORTC QLQ-C30 Physical, Social, Role, Emotional, and Cognitive functioning. Adverse events not described

Johansson 2008 (*Continued*)

Notes	Funding: Swedish Cancer Society. Three different intervention groups: individual support, group rehabilitation, and combined individual support and group rehabilitation. We combined these three groups into one to have sufficient sample size for the subset of patients with incurable cancer receiving systemic treatment with palliative intent (combined intervention groups n = 26 vs standard care group n = 17)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomised by an independent oncological centre (computer-generated allocation schedule). Randomisation stratified for diagnosis and stage
Allocation concealment (selection bias)	Low risk	Participants randomised by an independent oncological centre (computer-generated allocation schedule)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Research nurse gave participants the baseline questionnaire with a prepaid envelope. At subsequent assessments, participants were contacted by one of the investigators by phone. Investigator gave instructions and mailed the questionnaires, written instructions, and a prepaid envelope to participants. No information on whether investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% missing data and data analysed using one-way ANOVA with repeated measures
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Savard 2006

Methods	Design: RCT. Duration of study participation: 36 weeks.
Participants	Canada, three cancer clinics: Hôpital St-Sacrement, L'Hôtel-Dieu de Québec, and L'Hôtel-Dieu de Lévis 45 patients with metastatic breast cancer reporting depressive symptoms

Savard 2006 (*Continued*)

Interventions	Cognitive therapy: presentation of cognitive theory of emotions. Participants were encouraged to increase their level of daily activities and were trained to identify their negative thoughts, to use cognitive restructuring, and to redefine their life goals. Future high-risk situations were identified, as were strategies to cope with them Control group: Participants waited for a period corresponding to the duration of the intervention (8 weeks) and were reassessed on study variables before receiving cognitive therapy
Outcomes	Multidisciplinary Fatigue Inventory and EORTC QLQ-C30 Physical functioning. Adverse events not described
Notes	Funding: Canadian Breast Cancer Research Initiative (010436) and Canadian Institutes of Health Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Prepared by principal investigator before study initiation using a computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Group allocation was contained in individually sealed envelopes. Unclear whether envelopes were sequentially sealed and opaque
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the post-treatment evaluation, participants met the independent evaluator to complete self-report scales. Evaluator was blind to study objectives and procedures and to participants' group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 10% missing data. Linear mixed models used to analyse data, but only participants with at least one observation post randomisation included in the analysis
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	High risk	Fewer than 50 participants randomised per treatment arm at baseline

Sharpe 2014

Methods	Design: RCT. Duration of study participation: 48 weeks.
Participants	Scotland, UK, three cancer centres. 500 adults with a diagnosis of cancer, good cancer prognosis (predicted survival of at least 12 months), and major depression of at least four weeks' duration
Interventions	Depression care: intensive, manualised, collaborative care-based multi-component treatment programme specifically designed to be integrated with the patient's cancer treatment. Nurses establish a therapeutic relationship with participants, provide information about depression and its treatment, deliver brief evidence-based psychological interventions (problem-solving therapy and behavioural activation), and monitor participants' progress. Psychiatrists supervise treatment, advise primary care physicians about prescribing antidepressants, and provide direct consultations to patients who are not improving Usual care: participant's primary care physician and oncologist were informed about the major depression diagnosis and were asked to treat their patients as they normally would. Participants were encouraged to consult their primary care physician to obtain treatment
Outcomes	EORTC QLQ-C30 Fatigue and EORTC QLQ-C30 Physical, Social, and Role functioning. Adverse events defined as death from any cause, admission to a psychiatric ward, or attempted suicide
Notes	Funding: University of Edinburgh, NHS Lothian, Cancer Research UK (grant numbers C5547/A7375), Chief Scientist Office of the Scottish Government, and Scottish Mental Health Research Network funded by NHS Research Scotland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Database software algorithm allocated participants in a 1:1 ratio using a combination of stratification (by trial centre) and minimisation (by age, primary cancer, and sex)
Allocation concealment (selection bias)	Low risk	Secure Web-based randomisation database implemented by a trials unit
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial statistician and staff who collected outcome data masked to allocated interventions; however, participants could not be masked because of the nature of depression care for people with cancer
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% missing data. Analysis of covariance used for data analysis. In addition, sensitivity analysis using multiple imputation was performed

Sharpe 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Low risk	More than 200 participants randomised per treatment arm at baseline

Spiegel 1981

Methods	Design: RCT. Duration of study participation: 12 months.
Participants	USA, Stanford University School of Medicine. 86 women with metastatic breast cancer.
Interventions	Psychosocial Support Group (PSG): designed to be supportive, with a high degree of cohesion and relatively little confrontation and here-and-now interpersonal exploration. Interaction in the group often included a considerable amount of self-disclosure and sharing of mutual fears and concerns Control group: not described.
Outcomes	POMS Fatigue. Adverse events not described.
Notes	Funding: National Cancer Institute (N01-CN-55313 [DHEW]) and Veterans Administration

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information on method of randomisation provided.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding of outcome assessors provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More than 10% missing data. Slopes analysis used to analyse data, but only participants who completed at least two assessments included in the analysis
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	High risk	Fewer than 50 participants randomised per treatment arm at baseline

Steel 2016

Methods	Design: RCT. Duration of study participation: six months.
Participants	USA, University of Pittsburgh Medical Center's Liver Cancer Center 261 patients (aged 61 years, 73% male) with hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, neuroendocrine carcinoma, pancreatic carcinoma, or other primary cancers that had metastasised to the liver (e.g. ovarian, breast, colorectal cancer)
Interventions	Web-based stepped collaborative care intervention: access to a psychoeducational website and to a collaborative care co-ordinator with training and experience in cognitive-behavioural therapy and psycho-oncology Control group: usual care provided by the medical team. For ethical reasons, participants who scored high on a depression or pain measure were contacted by a care co-ordinator, who provided education about symptoms and referral options
Outcomes	FACT Fatigue. Adverse events not described.
Notes	Funding: National Cancer Institute (K07CA118576, R21CA127046, and P30CA047904)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomly assigned via a block randomisation design according to sex and vascular invasion
Allocation concealment (selection bias)	Low risk	Allocation concealment achieved through use of a random numbers table that assigned consecutive participants across the group. A research assistant who was not part of the study placed trial assignments in opaque envelopes consecutively per group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All data collected by trained interviewers using a structured computerised interview. Interviewers were blinded to study arm assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 10% missing data. Two separate general linear mixed-models analyses performed: first with all participants, then with participants with clinically significant symptoms at baseline

Steel 2016 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Effects of the intervention reported only for the subgroup of participants with clinically relevant symptoms at baseline (n = 132)l results for the entire sample not presented but provided upon request
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

Walker 2014

Methods	Design: RCT. Duration of study participation: 32 weeks.
Participants	Scotland, UK, three cancer centers. 142 adults with primary lung cancer, predicted survival of at least three months, and major depression for four weeks or longer
Interventions	Depression care: multi-component, systematic, team-delivered treatment programme based on the collaborative care model and integrated with lung cancer care. Nurses establish a therapeutic relationship with participants, provide information about depression and its treatment, deliver brief evidence-based psychological interventions (problem-solving therapy and behavioural activation), and monitor participants' progress. Psychiatrists supervise treatment, advise primary care physicians about prescribing to ensure rapid initiation and proactive adjustment of antidepressants, and provide direct consultations to patients who are not progressing Usual care: participant's primary care physician and oncologist were informed of the diagnosis of major depression and were asked to treat participant as they normally would. Participant was encouraged to see primary care physician to obtain treatment
Outcomes	EORTC QLQ-C30 Fatigue and EORTC QLQ-C30 Physical, Social, and Role functioning. Adverse events defined as death from any cause, admission to a psychiatric ward, or attempted suicide
Notes	Funding: University of Edinburgh, NHS Lothian, Cancer Research UK (grant numbers C5547/A7375 and C25786/ A10093), Chief Scientist Office of the Scottish Government, and Scottish Mental Health Research Network funded by NHS Research Scotland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Database software algorithm allocated participants in a 1:1 ratio using a combination of stratification (by trial centre) and minimisation (by age, sex, and lung cancer type)

Walker 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	Secure Web-based randomisation database implemented by a trials unit
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial statistician and staff who collected outcome data masked to allocated interventions; however, participants could not be masked because of the nature of depression care for people with cancer
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 10% missing data. A summary measure approach used in the analysis of covariance, which copes with missing data and sensitivity analyses using multiple imputations
Selective reporting (reporting bias)	Low risk	All data fully reported in the study.
Size of the study	Unclear risk	Between 50 and 199 participants randomised per treatment arm at baseline

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

Study	Reason for exclusion
Adamsen 2009	Mixed-sample study. No incurable cancer participants were receiving active cancer treatment
Anderson 2015	Unable to determine whether intervention fulfilled our formulated criteria; no response received from study investigators
Berglund 2007	Mixed-sample study. Study investigators were unable to retrieve the data
Bigatao 2016	Unable to determine whether intervention fulfilled our formulated criteria, and whether study sample also included participants with incurable cancer
Brown 2006	Does not meet our formulated criteria for psychosocial intervention. Study investigators confirmed that personal feedback was not intended
Cunningham 1989	Unknown whether study sample also includes patients with incurable cancer. Unable to retrieve professional contact address of study investigators
De Moor 2001	Did not meet our formulated criteria for psychosocial intervention
De Raaf 2013	Did not meet our formulated criteria for psychosocial intervention. Study investigators confirmed that personal feedback was not intended

(*Continued*)

Decker 1992	Mixed-sample study. Unable to retrieve professional contact address of study investigators
Fernandez 2011	No randomised controlled trial (RCT); study investigators confirmed that all baseline measures were taken after randomisation
Focan 2015	Unable to determine whether intervention fulfilled our eligibility criteria; no detailed intervention content information was received from study investigators
Forester 1985	Unknown whether study sample also included patients with incurable cancer. Unable to retrieve professional contact address of study investigators
Gaston-Johansson 2000	Mixed-sample study; no response received from study investigators
Given 2002	Mixed-sample study; study investigators not willing to provide data. Entire study sample included < 80% of patients with incurable cancer, thus excluded from the review
Godino 2006	Unknown whether study sample also included patients with incurable cancer; no response received from study investigators
Oh 2010	Unknown whether study sample also included patients with incurable cancer; no response received from study investigators
Ream 2006	Mixed-sample study, request for separate summary data sent to study investigators but no response received
Ream 2015	Unknown whether study sample also included patients with incurable cancer; no response received from study investigators
Serfaty 2012	Unknown whether study sample also included patients with incurable cancer. Study investigators confirmed not knowing whether incurable cancer patients were part of the sample
Strong 2008	Mixed-sample study; study investigators unable to provide data
Yorke 2015	Did not meet formulated criteria for receiving cancer treatment. Study investigators confirmed that none of the participants were receiving cancer treatment with palliative intent during the intervention

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

Poort

Trial name or title	TIRED study.
Methods	Randomised controlled trial (RCT).
Participants	Netherlands, Radboud University Medical Center with sites set up across the Netherlands 219 patients with a diagnosis of incurable cancer and reporting severe fatigue

Poort (*Continued*)

Interventions	Cognitive-behavioural therapy (CBT): 12-week CBT intervention designed to treat severe fatigue during systemic cancer treatment with palliative intent for incurable cancer. CBT consists of 10 individual, clinic-delivered sessions and will be delivered by trained psychologists Control condition: usual care. Participants may be referred to psychological or exercise interventions by their general practitioner or oncologist
Outcomes	Checklist Individual Strength, EORTC QLQ-C30 Fatigue, Sickness Impact Profile, and EORTC-QLQ C30 Physical, Social, Role, Emotional, and Cognitive functioning
Starting date	January 2013, recruitment ongoing.
Contact information	Hanneke Poort, MSc, Department of Medical Psychology, Radboud University Medical Center, Nijmegen, The Netherlands
Notes	Funding: Dutch Cancer Society (KUN2011-5259). This study is performed by five of the review authors (HP, MP, GB, SV, HK)

Serfaty

Trial name or title	CanTalk study.
Methods	Randomised controlled trial (RCT).
Participants	UK, University College London with sites set up across England 240 patients with advanced, non-curative cancer and a clinical diagnosis of depression
Interventions	Cognitive-behavioural therapy (CBT) in addition to treatment as usual (TAU): up to 12 sessions of individual CBT delivered face-to-face or on the telephone over three months TAU: All participants receive TAU from oncology teams and from their general practitioners (GPs). Specific psychological support may be available for those who present with psychological needs at any time
Outcomes	Beck Depression Inventory-II single item for fatigue.
Starting date	July 2012, recruitment completed.
Contact information	Dr Marc Serfaty, Division of Psychiatry, University College London, London, UK
Notes	Funding: National Institute for Health Research (NIHR) Health Technology Assessment Programme

DATA AND ANALYSES

Comparison 1. Fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	12	535	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.50, 0.00]
2 First follow-up	4	147	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [1.00, -0.32]
3 Second follow-up	2	91	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.12, 0.30]

Comparison 2. Physical functioning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	7	307	Std. Mean Difference (IV, Random, 95% CI)	0.32 [0.01, 0.63]
2 First follow-up	2	122	Std. Mean Difference (IV, Random, 95% CI)	0.37 [-0.20, 0.94]

Comparison 3. Social functioning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	4	141	Mean Difference (IV, Random, 95% CI)	4.16 [-11.20, 19.53]

Comparison 4. Role functioning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	4	143	Mean Difference (IV, Random, 95% CI)	3.49 [-12.78, 19.76]

Comparison 5. Emotional functioning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	3	115	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.56, 0.35]

Comparison 6. Cognitive functioning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Post intervention	2	86	Mean Difference (IV, Random, 95% CI)	-2.23 [-12.52, 8.06]

Comparison 7. Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue post intervention	12	535	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.50, 0.00]
1.1 Short intervention duration	3	163	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.72, 0.48]
1.2 Intermediate-long intervention duration	9	372	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.57, 0.02]
2 Fatigue post intervention	11	507	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.53, -0.00]
2.1 Group intervention delivery	3	195	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.78, 0.11]
2.2 Individual intervention delivery	8	312	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.58, 0.14]
3 Fatigue post intervention	12	535	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.50, 0.00]
3.1 Monodisciplinary intervention type	9	452	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.44, 0.04]
3.2 Multi-disciplinary intervention type	3	83	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.30, 0.47]
4 Fatigue post intervention	12	535	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.50, 0.00]
4.1 Fatigue-specific intervention aim	5	232	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.48, 0.31]
4.2 Other intervention aim	7	303	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.72, -0.02]
5 Fatigue first follow-up	7	270	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-0.78, -0.28]
5.1 No additional sessions	4	147	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [1.00, -0.32]
5.2 Additional sessions	3	123	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.90, 0.04]
6 Fatigue second follow-up	5	202	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.58, 0.07]
6.1 No additional sessions	2	91	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.12, 0.30]
6.2 Additional sessions	3	111	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.74, 0.30]

Comparison 8. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue post intervention	9	476	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.59, 0.00]
2 Fatigue first follow-up	1	103	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.10, -0.30]
3 Fatigue second follow-up	1	81	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.67, 0.22]

Analysis 1.1. Comparison 1 Fatigue, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 1 Fatigue

Outcome: 1 Post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Armes 2007	6	55.67 (10.48)	10	58.2 (23.93)		4.7 %	-0.12 [-1.13, 0.89]
Barsevick 2004	10	3.02 (1.43)	14	2.74 (1.11)		6.5 %	0.22 [-0.60, 1.03]
Barsevick 2010	15	2.96 (1.04)	14	2.67 (1.37)		7.5 %	0.23 [-0.50, 0.96]
Chan 2011	53	3.45 (2.7)	57	5.07 (2.93)		14.0 %	-0.57 [-0.95, -0.19]
Classen 2001	47	9.57 (6.43)	33	10.85 (8.25)		12.5 %	-0.18 [-0.62, 0.27]
Edelman 1999	43	9.33 (6.6)	49	10.39 (8.3)		13.3 %	-0.14 [-0.55, 0.27]
Johansson 2008	19	31.58 (25.19)	9	30.86 (28.75)		6.7 %	0.03 [-0.77, 0.82]
Savard 2006	13	44.77 (11.16)	12	47.33 (11.26)		6.8 %	-0.22 [-1.01, 0.57]
Sharpe 2014	13	36.75 (19.97)	27	64.61 (23.48)		7.6 %	-1.22 [-1.94, -0.50]
Spiegel 1981	11	5.55 (4.46)	12	12.64 (7.19)		5.7 %	-1.13 [-2.02, -0.24]
Steel 2016	34	20.15 (7.82)	19	18.95 (9.6)		10.1 %	0.14 [-0.42, 0.70]
Walker 2014	8	73.61 (23.71)	7	71.43 (31.33)		4.7 %	0.07 [-0.94, 1.09]
Total (95% CI)	**272**		**263**			**100.0 %**	**-0.25 [-0.50, 0.00]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 19.47$, df = 11 (P = 0.05); $I^2 = 43\%$

Test for overall effect: Z = 1.94 (P = 0.052)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Fatigue, Outcome 2 First follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 1 Fatigue

Outcome: 2 First follow-up

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Armes 2007	4	47.25 (5.85)	4	67.5 (19.14)		4.3 %	-1.24 [-2.87, 0.38]
Barsevick 2004	6	2 (0.74)	11	2.65 (1.13)		10.9 %	-0.61 [-1.63, 0.41]
Chan 2011	53	3.28 (2.71)	50	5.29 (2.97)		71.8 %	-0.70 [-1.10, -0.30]
Johansson 2008	12	33.33 (29.96)	7	41.27 (28.48)		13.0 %	-0.26 [-1.19, 0.68]
Total (95% CI)	**75**		**72**			**100.0 %**	**-0.66 [-1.00, -0.32]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 3.82 (P = 0.00014)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Fatigue, Outcome 3 Second follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 1 Fatigue

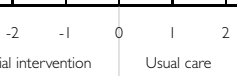
Outcome: 3 Second follow-up

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Armes 2007	4	28 (32.06)	6	61 (22.74)		20.7 %	-1.12 [-2.53, 0.29]
Chan 2011	47	3.63 (2.89)	34	4.28 (2.8)		79.3 %	-0.23 [-0.67, 0.22]
Total (95% CI)	**51**		**40**			**100.0 %**	**-0.41 [-1.12, 0.30]**

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 1.40$, df = 1 (P = 0.24); $I^2 = 29\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

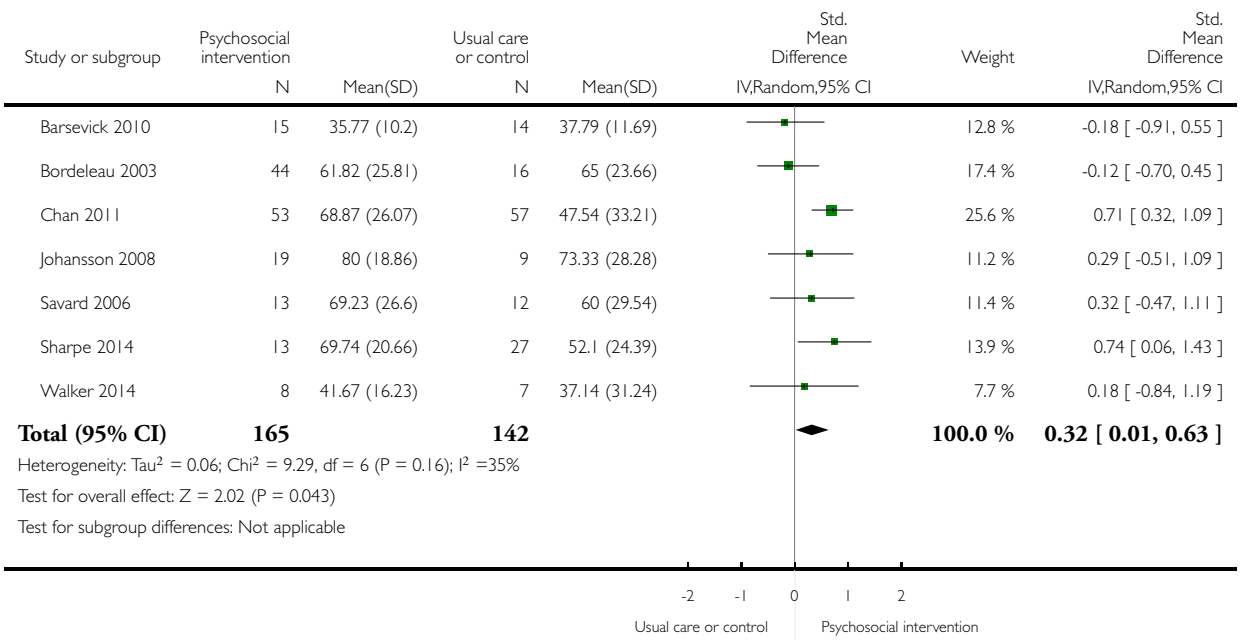


Analysis 2.1. Comparison 2 Physical functioning, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 2 Physical functioning

Outcome: 1 Post intervention

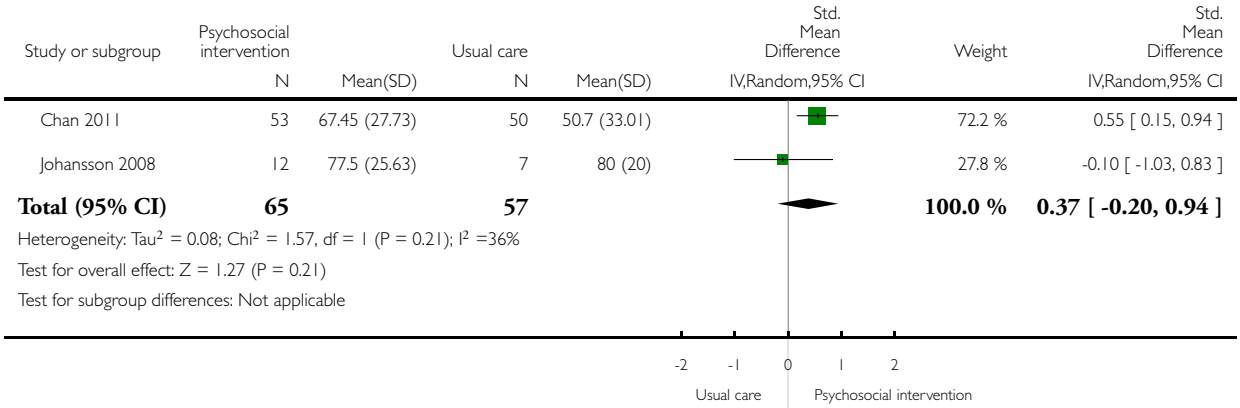


Analysis 2.2. Comparison 2 Physical functioning, Outcome 2 First follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 2 Physical functioning

Outcome: 2 First follow-up

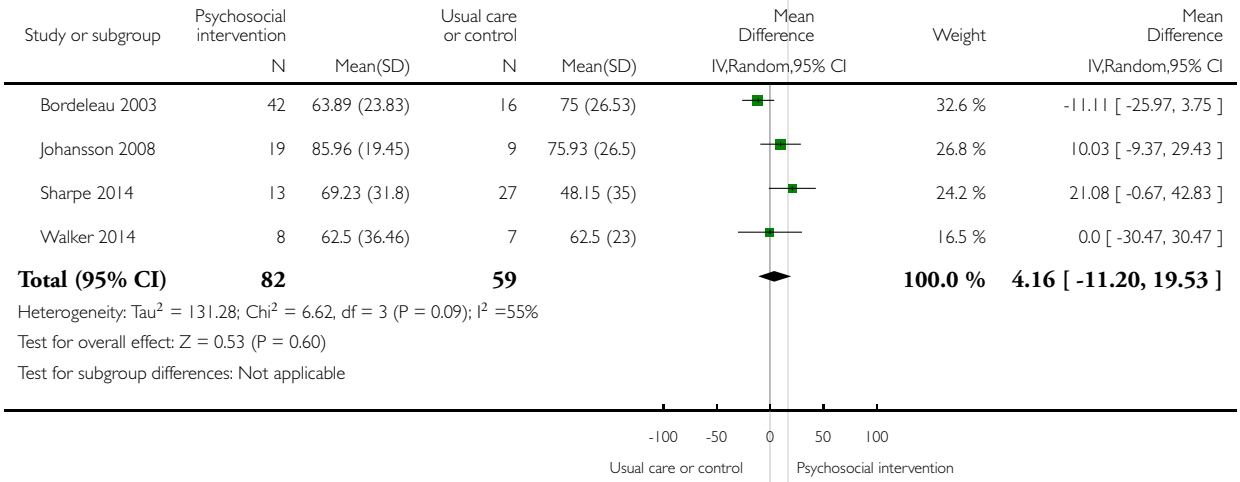


Analysis 3.1. Comparison 3 Social functioning, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 3 Social functioning

Outcome: 1 Post intervention

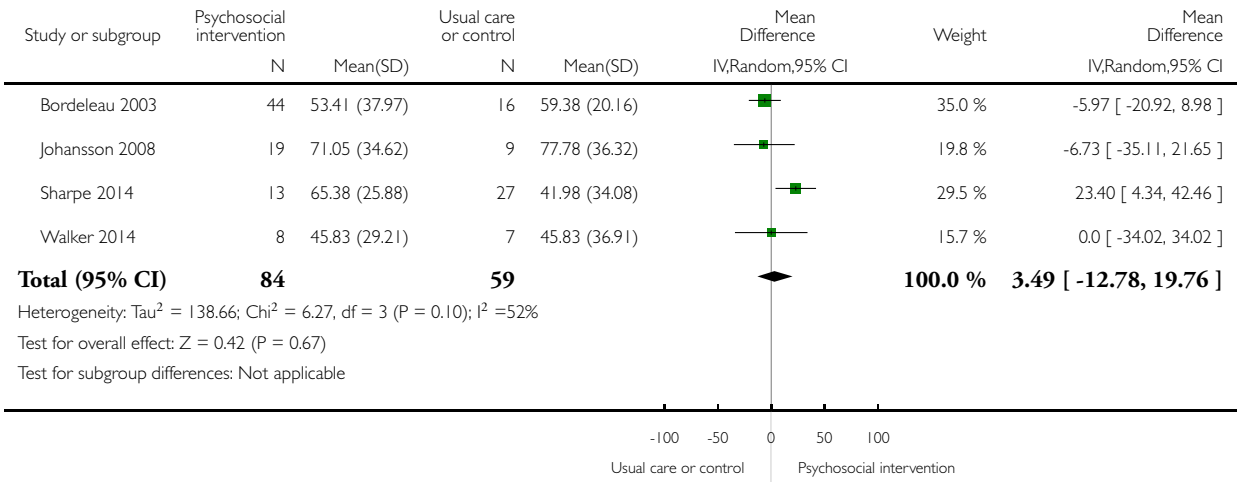


Analysis 4.1. Comparison 4 Role functioning, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 4 Role functioning

Outcome: 1 Post intervention



Analysis 5.1. Comparison 5 Emotional functioning, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 5 Emotional functioning

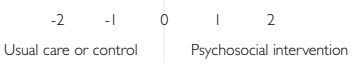
Outcome: 1 Post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Barsevick 2010	15	50.41 (8.11)	14	54.21 (5.64)		29.9 %	-0.53 [-1.27, 0.22]
Bordeleau 2003	42	68.45 (19.61)	16	70.83 (26.18)		43.5 %	-0.11 [-0.69, 0.47]
Johansson 2008	19	83.77 (17.45)	9	76.85 (18.99)		26.6 %	0.37 [-0.43, 1.17]
Total (95% CI)	**76**		**39**			**100.0 %**	**-0.11 [-0.56, 0.35]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.61$, df = 2 (P = 0.27); $I^2 = 23\%$

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: Not applicable



Analysis 6.1. Comparison 6 Cognitive functioning, Outcome 1 Post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 6 Cognitive functioning

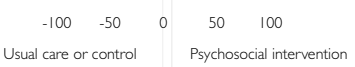
Outcome: 1 Post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bordeleau 2003	42	72.22 (20.71)	16	79.17 (20.64)		55.3 %	-6.95 [-18.85, 4.95]
Johansson 2008	19	85.09 (16.57)	9	81.48 (17.57)		44.7 %	3.61 [-10.07, 17.29]
Total (95% CI)	**61**		**25**			**100.0 %**	**-2.23 [-12.52, 8.06]**

Heterogeneity: $Tau^2 = 12.96$; $Chi^2 = 1.30$, df = 1 (P = 0.25); $I^2 = 23\%$

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

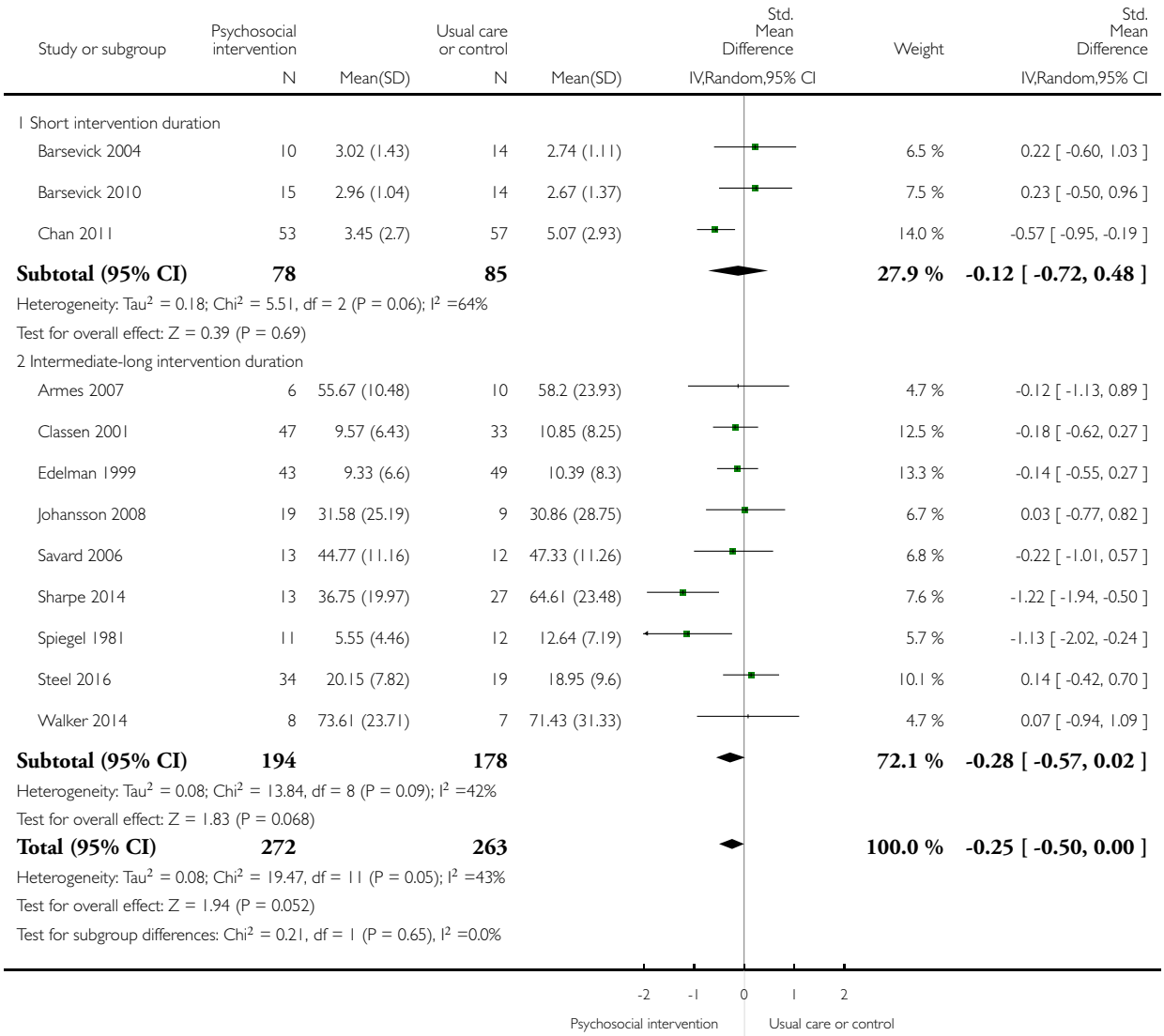


Analysis 7.1. Comparison 7 Subgroup analyses, Outcome 1 Fatigue post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 1 Fatigue post intervention



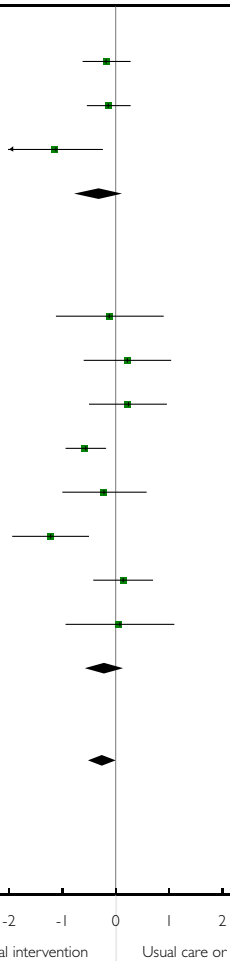
Analysis 7.2. Comparison 7 Subgroup analyses, Outcome 2 Fatigue post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 2 Fatigue post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Group intervention delivery							
Classen 2001	47	9.57 (6.43)	33	10.85 (8.25)		13.2 %	-0.18 [-0.62, 0.27]
Edelman 1999	43	9.33 (6.6)	49	10.39 (8.3)		14.0 %	-0.14 [-0.55, 0.27]
Spiegel 1981	11	5.55 (4.46)	12	12.64 (7.19)		6.2 %	-1.13 [-2.02, -0.24]
Subtotal (95% CI)	**101**		**94**			**33.4 %**	**-0.33 [-0.78, 0.11]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 4.12$, df = 2 (P = 0.13); $I^2 = 51\%$							
Test for overall effect: Z = 1.47 (P = 0.14)							
2 Individual intervention delivery							
Armes 2007	6	55.67 (10.48)	10	58.2 (23.93)		5.2 %	-0.12 [-1.13, 0.89]
Barsevick 2004	10	3.02 (1.43)	14	2.74 (1.11)		7.0 %	0.22 [-0.60, 1.03]
Barsevick 2010	15	2.96 (1.04)	14	2.67 (1.37)		8.1 %	0.23 [-0.50, 0.96]
Chan 2011	53	3.45 (2.7)	57	5.07 (2.93)		14.7 %	-0.57 [-0.95, -0.19]
Savard 2006	13	44.77 (11.16)	12	47.33 (11.26)		7.4 %	-0.22 [-1.01, 0.57]
Sharpe 2014	13	36.75 (19.97)	27	64.61 (23.48)		8.3 %	-1.22 [-1.94, -0.50]
Steel 2016	34	20.15 (7.82)	19	18.95 (9.6)		10.8 %	0.14 [-0.42, 0.70]
Walker 2014	8	73.61 (23.71)	7	71.43 (31.33)		5.2 %	0.07 [-0.94, 1.09]
Subtotal (95% CI)	**152**		**160**			**66.6 %**	**-0.22 [-0.58, 0.14]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 14.79$, df = 7 (P = 0.04); $I^2 = 53\%$							
Test for overall effect: Z = 1.20 (P = 0.23)							
Total (95% CI)	**253**		**254**			**100.0 %**	**-0.27 [-0.53, 0.00]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 18.94$, df = 10 (P = 0.04); $I^2 = 47\%$							
Test for overall effect: Z = 1.97 (P = 0.049)							
Test for subgroup differences: $Chi^2 = 0.14$, df = 1 (P = 0.70), $I^2 = 0.0\%$							



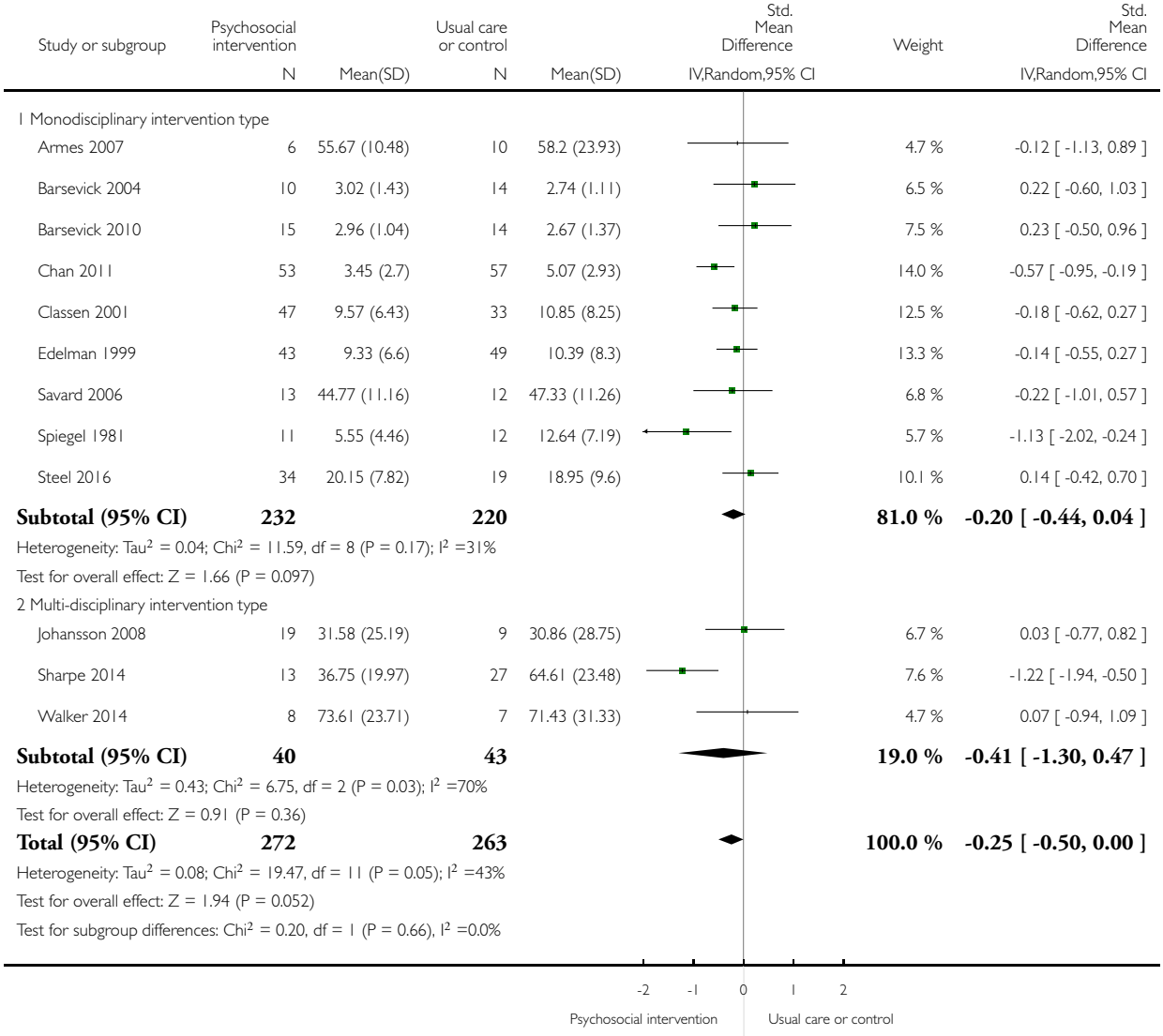
Analysis 7.3. Comparison 7 Subgroup analyses, Outcome 3 Fatigue post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 3 Fatigue post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 Monodisciplinary intervention type							
Armes 2007	6	55.67 (10.48)	10	58.2 (23.93)		4.7 %	-0.12 [-1.13, 0.89]
Barsevick 2004	10	3.02 (1.43)	14	2.74 (1.11)		6.5 %	0.22 [-0.60, 1.03]
Barsevick 2010	15	2.96 (1.04)	14	2.67 (1.37)		7.5 %	0.23 [-0.50, 0.96]
Chan 2011	53	3.45 (2.7)	57	5.07 (2.93)		14.0 %	-0.57 [-0.95, -0.19]
Classen 2001	47	9.57 (6.43)	33	10.85 (8.25)		12.5 %	-0.18 [-0.62, 0.27]
Edelman 1999	43	9.33 (6.6)	49	10.39 (8.3)		13.3 %	-0.14 [-0.55, 0.27]
Savard 2006	13	44.77 (11.16)	12	47.33 (11.26)		6.8 %	-0.22 [-1.01, 0.57]
Spiegel 1981	11	5.55 (4.46)	12	12.64 (7.19)		5.7 %	-1.13 [-2.02, -0.24]
Steel 2016	34	20.15 (7.82)	19	18.95 (9.6)		10.1 %	0.14 [-0.42, 0.70]
Subtotal (95% CI)	**232**		**220**			**81.0 %**	**-0.20 [-0.44, 0.04]**
Heterogeneity: Tau^2 = 0.04; Chi^2 = 11.59, df = 8 (P = 0.17); I^2 =31%							
Test for overall effect: Z = 1.66 (P = 0.097)							
2 Multi-disciplinary intervention type							
Johansson 2008	19	31.58 (25.19)	9	30.86 (28.75)		6.7 %	0.03 [-0.77, 0.82]
Sharpe 2014	13	36.75 (19.97)	27	64.61 (23.48)		7.6 %	-1.22 [-1.94, -0.50]
Walker 2014	8	73.61 (23.71)	7	71.43 (31.33)		4.7 %	0.07 [-0.94, 1.09]
Subtotal (95% CI)	**40**		**43**			**19.0 %**	**-0.41 [-1.30, 0.47]**
Heterogeneity: Tau^2 = 0.43; Chi^2 = 6.75, df = 2 (P = 0.03); I^2 =70%							
Test for overall effect: Z = 0.91 (P = 0.36)							
Total (95% CI)	**272**		**263**			**100.0 %**	**-0.25 [-0.50, 0.00]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 19.47, df = 11 (P = 0.05); I^2 =43%							
Test for overall effect: Z = 1.94 (P = 0.052)							
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.66), I^2 =0.0%							

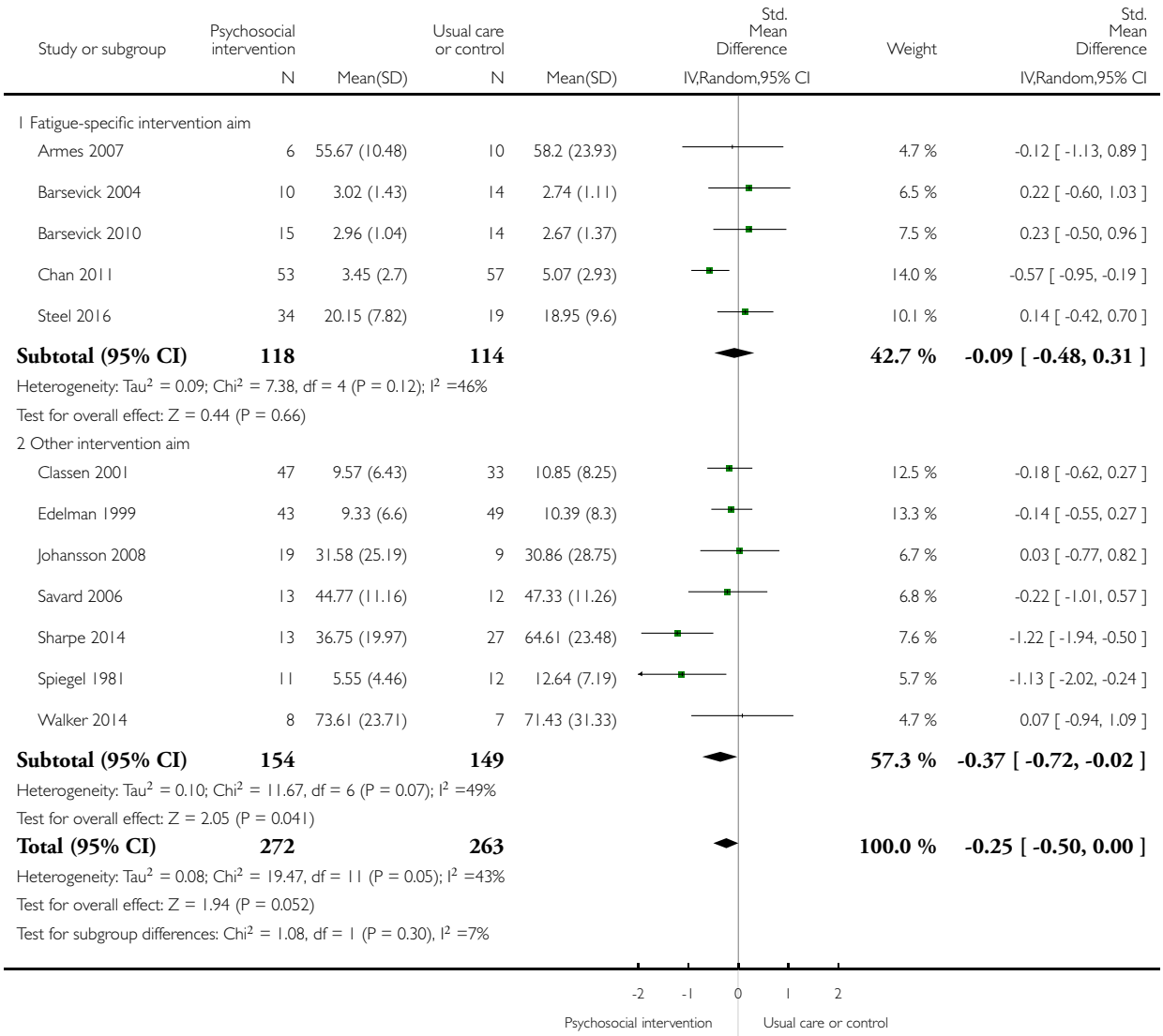


Analysis 7.4. Comparison 7 Subgroup analyses, Outcome 4 Fatigue post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 4 Fatigue post intervention



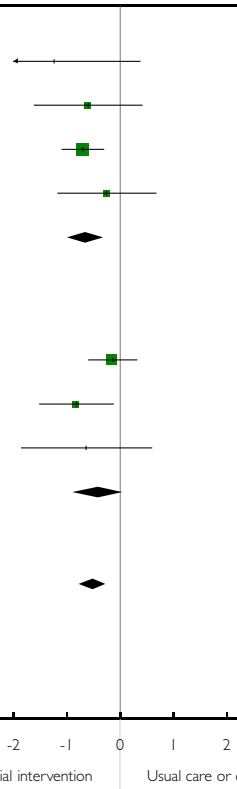
Analysis 7.5. Comparison 7 Subgroup analyses, Outcome 5 Fatigue first follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 5 Fatigue first follow-up

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 No additional sessions							
Armes 2007	4	47.25 (5.85)	4	67.5 (19.14)		2.3 %	-1.24 [-2.87, 0.38]
Barsevick 2004	6	2 (0.74)	11	2.65 (1.13)		5.9 %	-0.61 [-1.63, 0.41]
Chan 2011	53	3.28 (2.71)	50	5.29 (2.97)		38.9 %	-0.70 [-1.10, -0.30]
Johansson 2008	12	33.33 (29.96)	7	41.27 (28.48)		7.1 %	-0.26 [-1.19, 0.68]
Subtotal (95% CI)	**75**		**72**			**54.2 %**	**-0.66 [-1.00, -0.32]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.82 (P = 0.00014)							
2 Additional sessions							
Edelman 1999	36	9.44 (7.37)	37	10.62 (8.61)		29.3 %	-0.15 [-0.61, 0.31]
Sharpe 2014	12	44.44 (20.65)	27	63.79 (23.79)		12.4 %	-0.83 [-1.53, -0.12]
Walker 2014	6	68.52 (14.77)	5	80 (18.26)		4.1 %	-0.64 [-1.87, 0.59]
Subtotal (95% CI)	**54**		**69**			**45.8 %**	**-0.43 [-0.90, 0.04]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.71$, df = 2 (P = 0.26); $I^2 = 26\%$							
Test for overall effect: Z = 1.79 (P = 0.074)							
Total (95% CI)	**129**		**141**			**100.0 %**	**-0.53 [-0.78, -0.28]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.21$, df = 6 (P = 0.52); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.16 (P = 0.000032)							
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.44), $I^2 = 0.0\%$							

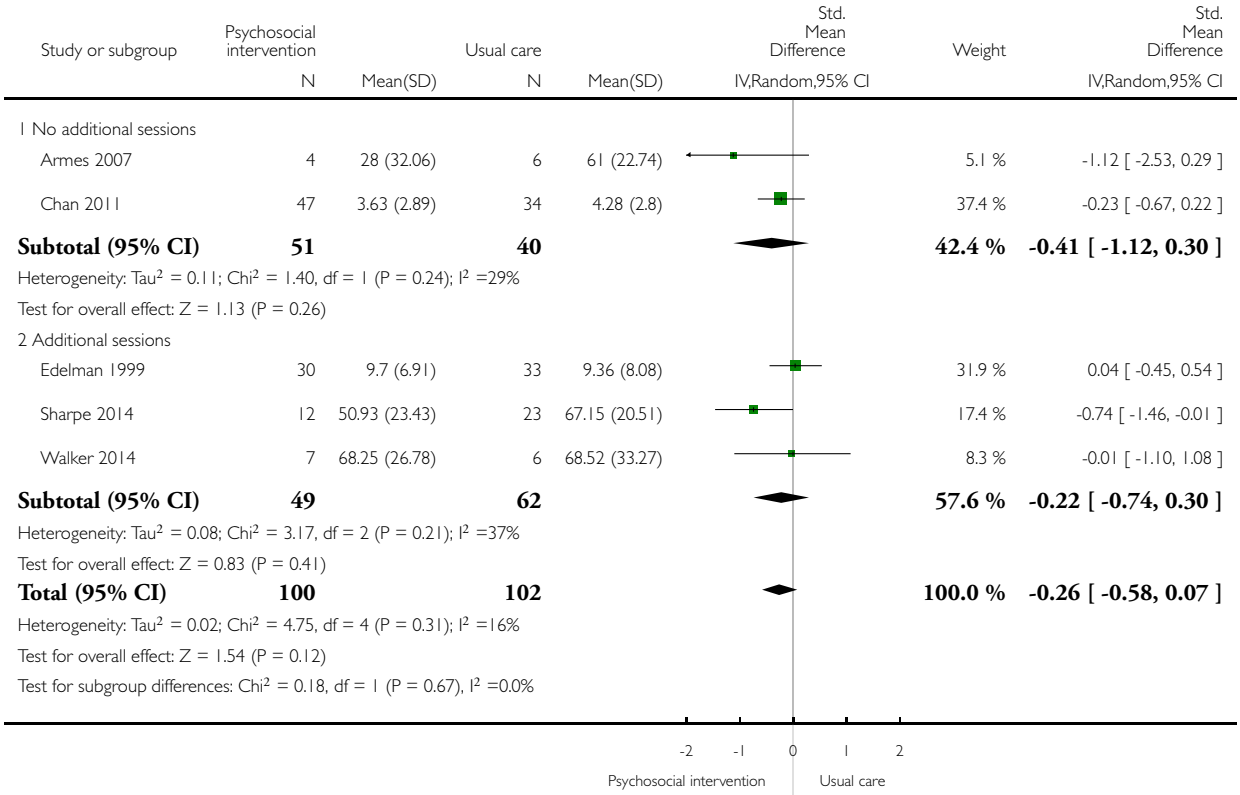


Analysis 7.6. Comparison 7 Subgroup analyses, Outcome 6 Fatigue second follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 7 Subgroup analyses

Outcome: 6 Fatigue second follow-up



Analysis 8.1. Comparison 8 Sensitivity analyses, Outcome 1 Fatigue post intervention.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 8 Sensitivity analyses

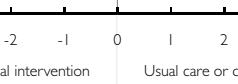
Outcome: 1 Fatigue post intervention

Study or subgroup	Psychosocial intervention N	Mean(SD)	Usual care or control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Barsevick 2004	10	3.02 (1.43)	14	2.74 (1.11)		8.2 %	0.22 [-0.60, 1.03]
Barsevick 2010	15	2.96 (1.04)	14	2.67 (1.37)		9.3 %	0.23 [-0.50, 0.96]
Chan 2011	53	3.45 (2.7)	57	5.07 (2.93)		15.7 %	-0.57 [-0.95, -0.19]
Classen 2001	47	9.57 (6.43)	33	10.85 (8.25)		14.3 %	-0.18 [-0.62, 0.27]
Edelman 1999	43	9.33 (6.6)	49	10.39 (8.3)		15.1 %	-0.14 [-0.55, 0.27]
Savard 2006	13	44.77 (11.16)	12	47.33 (11.26)		8.5 %	-0.22 [-1.01, 0.57]
Sharpe 2014	13	36.75 (19.97)	27	64.61 (23.48)		9.5 %	-1.22 [-1.94, -0.50]
Spiegel 1981	11	5.55 (4.46)	12	12.64 (7.19)		7.3 %	-1.13 [-2.02, -0.24]
Steel 2016	34	20.15 (7.82)	19	18.95 (9.6)		12.1 %	0.14 [-0.42, 0.70]
Total (95% CI)	**239**		**237**			**100.0 %**	**-0.30 [-0.59, 0.00]**

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 18.35$, df = 8 (P = 0.02); $I^2 = 56\%$

Test for overall effect: Z = 1.95 (P = 0.051)

Test for subgroup differences: Not applicable

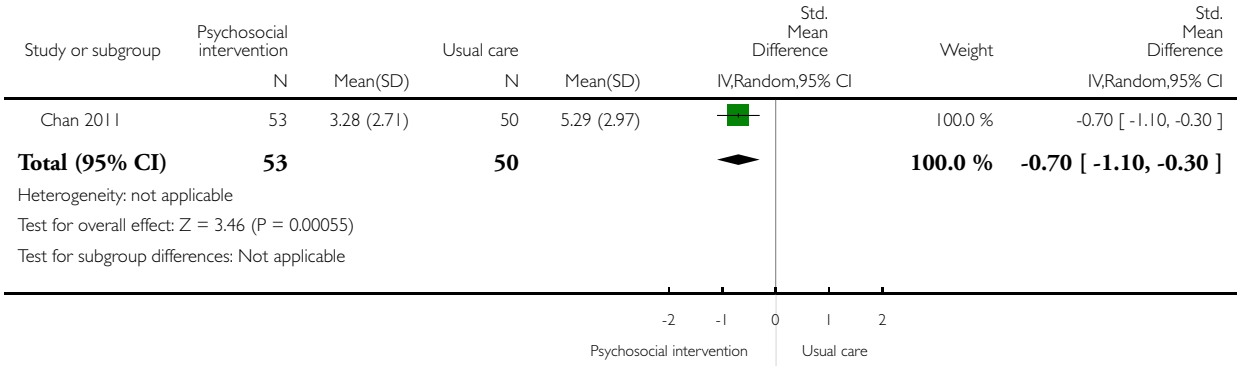


Analysis 8.2. Comparison 8 Sensitivity analyses, Outcome 2 Fatigue first follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 8 Sensitivity analyses

Outcome: 2 Fatigue first follow-up

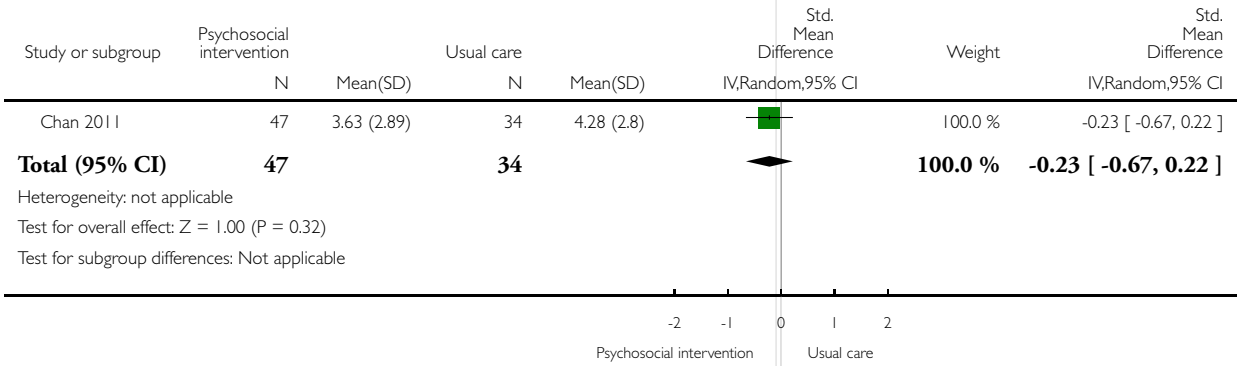


Analysis 8.3. Comparison 8 Sensitivity analyses, Outcome 3 Fatigue second follow-up.

Review: Psychosocial interventions for fatigue during cancer treatment with palliative intent

Comparison: 8 Sensitivity analyses

Outcome: 3 Fatigue second follow-up



APPENDICES

Appendix 1. GRADE system

The GRADE system uses the following criteria for assigning grades of evidence:
High: We are very confident that the true effect lies close to the estimate of effect.
Moderate: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect but may be substantially different.
Low: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of effect.
Very low: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.
The grade of evidence is decreased further if the following are present.

- 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).

The grade of evidence may be increased if:

- strong evidence of association: significant relative risk > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- very strong evidence of association: significant relative risk > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose-response gradient (+1); or
- all plausible confounders would have reduced the effect (+1).

Appendix 2. CENTRAL search strategy

#1 ((neoplas* or cancer*)):TI,AB,KY
#2 (carcinoma* or tumour* or adenocarcinoma*):TI,AB,KY
#3 (leukemi* or leukaemia* or lymphoma*):TI,AB,KY
#4 (tumor* or malignan* or melanoma* or sarcoma*):TI,AB,KY
#5 ("bone marrow transplant*" or "stem cell transplant*"):TI,AB,KY
#6 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
#7 MESH DESCRIPTOR Bone Marrow Transplantation
#8 MESH DESCRIPTOR Stem Cell Transplantation EXPLODE ALL TREES
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 MESH DESCRIPTOR Fatigue EXPLODE ALL TREES
#11 ((fatigue* or asthenia or asthenic or astheni*)):TI,AB,KY
#12 ((exhaustion or exhausted)):TI,AB,KY
#13 (((loss adj4 energy) or (loss adj4 vitality))):TI,AB,KY
#14 ((weary or weariness or weakness)):TI,AB,KY
#15 ((apathy or apathetic or lassitude or lethargic or lethargy)):TI,AB,KY
#16 ((sleepy or sleepiness or drowsy or drowsiness)):TI,AB,KY
#17 ((tired or tiredness)):TI,AB,KY
#18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 MESH DESCRIPTOR Psychotherapy EXPLODE ALL TREES
#20 ((psychosocial* or psycho-social*)):TI,AB,KY
#21 management" or psychotherapy* or "self
#22 educati* or psychoeducat* or relaxation
#23 counsel$ or (behaviour$ adj4 therap$) or "autogenic training"
#24 (behavior* adj4 therap*) or (relax* adj4 therap*) or (relax* adj4 treatment*) or (support* adj4 group*)
#25 management" or psychotherapy* or "self

#26 imagery or "energy conservation" or "stress management" or psychotherapy* or "self care" or "self help"
#27 "nursing support"
#28 biofeedback or educati* or psychoeducat* or relaxation therap*
#29 "nursing intervention" or "nursing support"
#30 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31 #9 AND #18 AND #30

Appendix 3. MEDLINE search strategy

1 exp Neoplasms/
2 Bone Marrow Transplantation/
3 exp Stem Cell Transplantation/
4 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignan$ or melanoma$ or sarcoma$ or "bone marrow transplant$" or "stem cell transplant$").mp.
5 or/1-4
6 exp Fatigue/
7 (fatigue$ or asthenia or asthenic or astheni$).mp.
8 (exhaustion or exhausted).mp.
9 ((loss adj4 energy) or (loss adj4 vitality)).mp.
10 (weary or weariness or weakness).mp.
11 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
12 (sleepy or sleepiness or drowsy or drowsiness).mp.
13 (tired or tiredness).mp.
14 or/6-13
15 exp Psychotherapy/
16 (psychosocial$ or psycho-social$).mp.
17 (counsel$ or (behaviour$ adj4 therap$) or "autogenic training" or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or "energy conservation" or "stress management" or psychotherapy$ or "self care" or "self help" or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or "nursing intervention" or "nursing support").mp.
18 or/15-17
19 5 and 14 and 18
20 randomized controlled trial.pt.
21 controlled clinical trial.pt.
22 randomized.ab.
23 placebo.ab.
24 drug therapy.fs.
25 randomly.ab.
26 trial.ab.
27 groups.ab.
28 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 exp animals/ not humans.sh.
30 28 not 29
31 19 and 30

Appendix 4. Embase search strategy

1 exp Neoplasms/
2 Bone Marrow Transplantation/
3 exp Stem Cell Transplantation/
4 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignan$ or melanoma$ or sarcoma$ or "bone marrow transplant$" or "stem cell transplant$").mp.
5 or/1-4
6 exp Fatigue/
7 (fatigue$ or asthenia or asthenic or astheni$).mp.
8 (exhaustion or exhausted).mp.
9 ((loss adj4 energy) or (loss adj4 vitality)).mp.
10 (weary or weariness or weakness).mp.
11 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
12 (sleepy or sleepiness or drowsy or drowsiness).mp.
13 (tired or tiredness).mp.
14 or/6-13
15 exp Psychotherapy/
16 (psychosocial$ or psycho-social$).mp.
17 (counsel$ or (behaviour$ adj4 therap$) or "autogenic training" or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or "energy conservation" or "stress management" or psychotherapy$ or "self care" or "self help" or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or "nursing intervention" or "nursing support").mp.
18 or/15-17
19 5 and 14 and 18
20 random$.tw.
21 factorial$.tw.
22 crossover$.tw.
23 cross over$.tw.
24 cross-over$.tw.
25 placebo$.tw.
26 (doubl$ adj blind$).tw.
27 (singl$ adj blind$).tw.
28 assign$.tw.
29 allocat$.tw.
30 volunteer$.tw. (201718)
31 Crossover Procedure/ (45499)
32 double-blind procedure.tw. (229)
33 Randomized Controlled Trial/ (391636)
34 Single Blind Procedure/ (21265)
35 or/20-34 (1643586)
36 (animal/ or nonhuman/) not human/ (4924135)
37 35 not 36 (1458151)
38 19 and 37 (956)

Appendix 5. CINAHL search strategy

S28 S18 AND S27
S27 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
S26 (allocat* random*)
S25 (MH "Quantitative Studies")
S24 (MH "Placebos")
S23 placebo*
S22 (random* allocat*)
S21 (MH "Random Assignment")
S20 (Randomi?ed control* trial*)
S19 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S18 S5 AND S13 AND S17
S17 S14 OR S15 OR S16
S16 (counsel$ or (behaviour$ adj4 therap$) or "autogenic training" or (behavior* N4 therap*) or (relax* N4 therap*) or (relax* N4 treatment*) or (support* N4 group*) or imagery or "energy conservation" or "stress management" or psychotherapy* or "self care" or "self help" or biofeedback or educati* or psychoeducat* or relaxation therap* or "nursing intervention" or "nursing support")
S15 psychosocial* or psycho-social*
S14 (MH "Psychotherapy+")
S13 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12 tired or tiredness
S11 sleepy or sleepiness or drowsy or drowsiness
S10 apathy or apathetic or lassitude or lethargic or lethargy
S9 weary or weariness or weakness
S8 (loss N4 energy) or (loss N4 vitality)
S7 exhaustion or exhausted
S6 (fatigue* or asthenia or asthenic or astheni*)
S5 S1 OR S2 OR S3 OR S4
S4 (neoplas* or cancer* or carcinoma* or tumour* or adenocarcinoma* or leukemi* or leukaemia* or lymphoma* or tumor* or malignan* or melanoma* or sarcoma* or "bone marrow transplant*" or "stem cell transplant*")
S3 (MH "Hematopoietic Stem Cell Transplantation")
S2 (MH "Bone Marrow Transplantation")
S1 (MH "Neoplasms")

Appendix 6. PsycINFO search strategy

1 exp Neoplasms/
2 (neoplas$ or cancer$ or carcinoma$ or tumour$ or adenocarcinoma$ or leukemi$ or leukaemia$ or lymphoma$ or tumor$ or malignan$ or melanoma$ or sarcoma$ or "bone marrow transplant$" or "stem cell transplant$").mp.
3 exp Fatigue/
4 (fatigue$ or asthenia or asthenic or astheni$).mp.
5 (exhaustion or exhausted).mp.
6 ((loss adj4 energy) or (loss adj4 vitality)).mp.
7 (weary or weariness or weakness).mp.
8 (apathy or apathetic or lassitude or lethargic or lethargy).mp.
9 (sleepy or sleepiness or drowsy or drowsiness).mp.
10 (tired or tiredness).mp.
11 or/3-10
12 exp Psychotherapy/
13 (psychosocial$ or psycho-social$).mp.

14 (counsel$ or (behaviour$ adj4 therap$) or “autogenic training” or (behavior$ adj4 therap$) or (relax$ adj4 therap$) or (relax$ adj4 treatment$) or (support$ adj4 group$) or imagery or “energy conservation” or “stress management” or psychotherapy$ or “self care” or “self help” or biofeedback or educati$ or psychoeducat$ or relaxation therap$ or “nursing intervention” or “nursing support”).mp.
15 or/12-14
16 1 or 2
17 11 and 15 and 16
18 clinical trials/
19 (randomis* or randomiz*).tw.
20 (random$ adj3 (allocat$ or assign$)).tw.
21 ((clinic$ or control$) adj trial$).tw.
22 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
23 (crossover$ or “cross over$”).tw.
24 random sampling/
25 Experiment Controls/
26 Placebo/
27 placebo$.tw.
28 exp program evaluation/
29 treatment effectiveness evaluation/
30 ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
31 or/18-30
32 17 and 31

CONTRIBUTIONS OF AUTHORS

Hanneke Poort, Marlies Peters, and Hans Knoop developed and wrote the review. Hanneke Poort and Marlies Peters selected studies, evaluated the quality of studies, and extracted data from included studies. Stans Verhagen, Gijs Bleijenberg, Marieke Gielissen, Martine Goedendorp, and Paul Jacobsen discussed the review and contributed to its development and writing, along with the other members of the review team.

DECLARATIONS OF INTEREST

HP: none known. HP is the coordinating investigator on a study included in the ’ongoing studies’ section (Poort).

MP: none known. MP is co-investigator on a study included in the ’ongoing studies’ section (Poort).

GB: none known. GB is co-investigator on a study included in the ’ongoing studies’ section (Poort).

MFMG: none known.

MMG: none known.

PJ has been involved in the development of cancer-related fatigue guidelines for the American Society of Clinical Oncology and the National Comprehensive Cancer Network. He has also consulted with Onyx Pharmaceuticals, Inc. (2012-2014) and On Q Health, Inc. (2014-Sep 2016) about quality of life and quality of care issues in people with cancer.

SV: none known. SV is principal investigator on a study included in the ’ongoing studies’ section (Poort). SV is a medical oncologist and manages patients with incurable cancer.

HK: none known. HK is principal investigator on a study included in the ’ongoing studies’ section (Poort). HK is a clinical psychologist and manages patients with incurable cancer.

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Internal sources

- No sources of support supplied

External sources

- Dutch Cancer Society, Netherlands.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The final review differs from the protocol in five ways. First, we originally intended to select only participants with a diagnosis of incurable cancer who were receiving some form of active cancer treatment. However, several original study investigators of mixed-sample studies did not respond to our request for subset data or were unable to select the subset of those participants. In those instances, we included studies when the sample involved more than 80% of participants with incurable cancer receiving some form of active cancer treatment. Second, we planned to use fixed-effect models in all meta-analyses for this review. However, patient populations were quite variable in cancer diagnosis and treatment (as were the interventions); thus we employed random-effects models. Third, we originally used the overall term 'measures of function' in our protocol to reflect physical, social, role, emotional, and cognitive functioning as secondary outcomes of this review. In the final review, we have defined this outcome more clearly and have changed our wording to all five individual domains instead of using an overall term. Fourth, we did not include different time points for outcomes in the protocol. Yet, some studies reported outcomes not only for post-intervention assessment but also for one or two follow-up assessments. We aimed to be as complete as possible in reporting our findings and thus also included fatigue and physical functioning data for first and second follow-up as secondary outcomes. Last, we added a subgroup analyses to the review to examine follow-up effects for studies that included additional (booster) sessions between post-intervention assessment and follow-up versus studies without additional sessions. We did not foresee in the protocol the use of additional (booster) sessions.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Cognition; Fatigue [etiology; physiopathology; psychology; *therapy]; Neoplasms [*complications; physiopathology; psychology; therapy]; Palliative Care [*methods]; Psychotherapy [*methods]; Quality of Life; Randomized Controlled Trials as Topic; Social Skills

MeSH check words

Adult; Female; Humans; Male; Middle Aged