Interventions for cancer-related fatigue

A scoping review

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Abstract

Cancer-related fatigue (CRF) is common and can be distressing for some survivors. There is increasing interest in measuring levels of cancer-related fatigue, highlighting its impact on quality of life. This review describes the nature and scope of evidence relating to interventions for cancer-related fatigue. Scoping review methodology was used to identify studies, extract data, collate and summarise results. Data were collated according to cancer tumour streams, stage of illness and the types of trial interventions. 447 trials and 37 systematic reviews met the inclusion criteria. Nine papers reported longitudinal results. Populations studied were predominantly of mixed cancer diagnoses and breast cancer. The most frequent interventions were exercise, pharmacological, psycho-education and mind-body interventions. Fatigue was identified as a primary outcome measure in 58% of studies, with 58 different fatigue measures reported. Emerging evidence exists for the effectiveness of fatigue interventions for some cancer types. More research on interventions with participants with the same cancer type and illness phase is needed. Measurement of severity and impact of CRF using fewer, robust outcome measures will permit comparisons across studies.

Keywords: Cancer, Supportive care, Symptom management , Cancer related fatigue, Scoping review, Fatigue measurement

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Introduction

According to the US National Comprehensive Cancer Network, cancer-related fatigue (CRF) is: '*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*' (NCCN, 2015). It can be distinguished from everyday fatigue by not being relieved by rest or sleep (Jean-Pierre et al., 2007). Around 10% of women with breast cancer have fatigue before chemotherapy (Andrykowski et al., 2010) and 54% of all cancer patients experience fatigue (Van Belle et al., 2005). Up to 35% of cancer survivors have CRF one to five years after finishing treatment (Bower et al., 2000, Oerlemans et al., 2013). Cancer-related fatigue can fluctuate (Payne, 2002) or be unrelenting (Holley, 2000). It has been identified as a common symptom for many people before, during and after cancer treatment (Jones et al., 2012, Weis, 2011, Hartvig et al., 2006). The distressing nature of CRF results from not only the sensation of CRF, but from its effect on physical, cognitive and occupational function (Rosedale and Fu, 2010). It has many features in common with depression, complicating diagnosis and measurement (Traeger et al., 2011).

The current guidelines for management of CRF, developed in North America, recommend that all people with cancer should be screened routinely for presence of fatigue and provided with information. People with moderate to severe fatigue are recommended to have an in-depth fatigue evaluation, and a wide range of interventions is listed (Howell et al., 2015, NCCN, 2015, Bower et al., 2014). CRF guidelines appear to be inconsistently implemented.

Many CRF intervention studies and several clinical guidelines for management of CRF have been published in the past decade. Subsequent systematic reviews of interventions contributing to current CRF guidelines have described specific interventions such as exercise (Cramp and Byron-Daniel, 2012, Baumann et al., 2012), yoga (Buffart et al., 2012), and drug treatments (Minton et al., 2008), non-pharmacological (Kangas et al.,

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2008, Jacobsen et al., 2007, Fors et al., 2011) or psychosocial interventions (Goedendorp et al., 2009, Fors et al., 2011).

There is a need to examine CRF interventions with regard to the medical and demographic details for specific groups (Minton and Stone, 2011, Barsevick et al., 2013). Current fatigue guidelines provide recommendations for different phases of treatment but not for cancer diagnosis (NCCN, 2015).

This current review examines the evidence for CRF interventions, and aims to describe the nature, number and scope of published research studies measuring CRF, related to different cancer populations, interventions and disease stages. The research questions for this enquiry were: ‘what interventions for CRF have been trialled?’; ‘with which populations?’; and ‘how has CRF been measured in trials?’

Method:

Scoping review methods are appropriate for answering broad research questions and to gain an appreciation of the nature of existing evidence (Armstrong et al., 2011). While a systematic review evaluates the quality of included studies and may provide a quantitative synthesis, scoping reviews do not focus on these elements. A scoping review may be used to identify gaps in knowledge, define the scope for systematic reviews or direct the development of focussed research questions (Armstrong et al., 2011).

The scoping review framework of Arksey and O'Malley (2005) was used to guide the process. Stages of the scoping review framework included: (1) identifying the research question(s); (2) identifying relevant studies; (3) selecting studies; (4) extracting the data, and (5) collating, summarising and reporting results (Arksey and O'Malley, 2005).

Identifying relevant studies: A systematic literature search was conducted to identify intervention studies that reported effect on CRF. The electronic search strategy included key words “cancer, fatigue, assessment” and their derivatives using MEDLINE, CINAHL, PsycINFO, EMBASE, AMED and Cochrane Library databases from the earliest available

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time to May 2013 and updated to August 2014. A MEDLINE search filter for outcome measures was used and adapted for the other databases (Brettelle et al., 1998). Seven journals¹ that frequently report on relevant clinical trials were also hand-searched from January 2013 to end October 2014. Bibliographies of systematic reviews of interventions were also searched.

Study selection: After removing duplicates, the titles were screened and studies with no obvious relevance to the research questions were removed by the lead author (EP), using a conservative approach as described by Higgins and Green (2011 section 7.2.3 and 7.2.4). The inclusion criteria (see Table 1) were then independently applied to the remaining titles and abstracts by two researchers to ensure that relevant studies were included. Importantly effect on, or assessment of, fatigue had to be reported in the abstract to ensure that fatigue was a major focus of the study. The inclusion criteria screening results were compared and any differences were resolved by discussion and by consulting the full text until consensus was reached.

[Insert Table 1: Study inclusion and exclusion criteria about here [portrait]]

Data extraction: After reading the full article of each study included in the scoping review, the following data from the full text of each study were entered into a Microsoft Excel spreadsheet by the lead author:

- Population: Geographical location, number of participants, tumour stream and stage of treatment.
- Intervention: Brief description of the intervention procedures and intervention dose.
- Study design and Oxford Centre for Evidence Based Medicine (CEBM) classification (OCEBM Levels of Evidence Working Group, 2011) for the purpose of describing the accepted level of evidence categories of the research.

¹ Journal of Cancer Survivorship, Journal of Clinical Oncology, Journal of Pain and Symptom Management, Oncology Nursing Forum, Psycho-Oncology, Rehabilitation Oncology, Supportive Care in Cancer

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- Outcome measures: Name of fatigue assessment instrument and use as primary or secondary outcome measurement tool; statistical significance of fatigue change; fatigue inclusion criteria; other outcome measures (objective/subjective) used.

Intervention categories previously described in the literature were refined to incorporate the intervention's hypothesised mechanisms or aims once extraction was completed. Sub-classifications were formed within some categories.

Collating and summarising the intervention study data: Data were collated according to different variables using Excel software sorting and calculation features. Study and participant numbers were aggregated to answer the following main questions:

1. How have intervention studies for CRF been reported across tumour streams and illness phases?
2. What studies in each intervention category exist in each tumour group and each illness phase?
3. What are the study designs in different intervention categories and sub-categories?
4. Which fatigue outcome measures and measurement tools were used, how frequently and were they the primary outcome of interest?

Results

The six databases yielded 15,250 records, 482 of which met selection criteria. The study selection process is outlined in Figure 1.

Four hundred and forty-seven intervention studies and 37 systematic reviews of interventions met the inclusion criteria. Nine identical populations from the same study were represented twice in follow up studies (Berger et al., 2009a, Berger et al., 2009b, Berger et al., 2002, Berger et al., 2003, Courneya et al., 2007a, Courneya et al., 2007b, Gielissen et al., 2006, Gielissen et al., 2007, Goedendorp et al., 2012, Goedendorp et al., 2010, Pinto et al., 2005, Pinto et al., 2008, Vallance et al., 2008, Vallance et al., 2007, Hoffman et al., 2014a, Hoffman et al., 2014b, Björneklett et al., 2012, Björneklett et al., 2013) while two papers reported different outcomes from the same trial. (Korstjens et al.,

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2008, van Weert et al., 2010). For the study reported here, follow up studies and dual reports from the same trial were grouped with the initial trial and counted only once when aggregating data to avoid inappropriate duplication, and acknowledged separately in parentheses. This resulted in a total of 437 primary intervention studies plus 10 linked studies that reported results.

[Insert Figure 1: CONSORT diagram of selection of studies (portrait) about here]

Populations studied in the primary research

More than half of the included studies (223 or 51%) were conducted in North America; 113 occurred in Europe predominantly in the United Kingdom, Netherlands and Germany. There were 50 trials across Asia and five intercontinental collaborations.

The tumour groups and illness stage distributions for the trial participants are shown in Table 2. Almost half (201 or 46%) of the included trials had mixed cancer populations. A further 136 trials included only women with breast cancer, accounting for 31% of included studies. One hundred and four trials (24% of sample) studied homogeneous tumour groups other than breast cancer, with none in sarcoma.

[Insert Table 2 here – Populations of included studies by tumour stream and illness phase]

[Footnote to Table 2

* Follow up studies – not included in trial or participant count

[1] duplicate study reporting different outcomes (Korstjens et al., 2008)

‡ Stage not specified]

When aggregated according to stage of illness, 187 of 437 studies (43%) were conducted during or before cancer treatment and one-third occurred after treatment. Timing of interventions post treatment varied from immediately after treatment to more than 10 years following treatment.

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The average sample size for the included studies was 132, ranging from three to 2432 participants. There were fewer than 50 participants in 194 (44.3%) studies. Only 22 trials had more than 400 participants; and in 10 trials (nine of which were pharmacological studies) there were more than 1,000 participants.

The presence of fatigue was a baseline inclusion criterion in 82 trials (19%). Related symptoms of anaemia or insomnia were specified in 18 trials and a further 5 trials required participants to have one or more specified symptoms including fatigue. Participation in 76% of studies included in this review did not require the presence of baseline fatigue or related symptoms.

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To categorise the diversity of interventions in trials measuring CRF, intervention types were defined. Previous authors have utilised categories of psycho-education, cognitive-behaviour therapy (CBT), social and emotional support (Fors et al., 2011), exercise, education and counselling, sleep therapy, complementary therapies (Wanchai et al., 2011), nutritional therapy (Mustian et al., 2007), mind-body interventions (Kwekkeboom et al., 2010), complementary and alternative (Finnegan-John et al., 2013) and pharmacological interventions (Minton et al., 2010). The current review used nine broad categories modified from earlier definitions, as outlined in Table 3. Except where indicated, primary research results are presented.

[Insert Table 3: Intervention categories here [portrait]]

Interventions varied not only in content or intent, but also duration and intensity. Study interventions ranged from a single 15-minute hypnosis session before surgery (Montgomery et al., 2007) to 15 sessions of psychotherapy over 6 months (Frick et al., 2006) and 90 minute group therapy per week for up to a year (Bordeleau et al., 2003). Two studies included in-depth assessment of fatigue as recommended in NCCN clinical guidelines (de Raaf et al., 2013, Escalante et al., 2010, NCCN, 2015).

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The distribution of studies according to intervention type and tumour stream is shown in Table 4. Over half (58%) the studies were randomised controlled trial (RCT) designs. See supplementary material available online for details of all studies.

[Insert Table 4: Study numbers by intervention and tumour stream here [landscape]]

Most frequently studied were exercise interventions with 103 primary exercise studies reporting CRF as an outcome. These comprised 33 home-based, 52 supervised and 18 trials including both supervised and home exercise. Fatigue was documented as a primary outcome measure in 72 studies (69%) and 57 (54%) were RCT designs. Improvements in fatigue were reported as statistically significant in 36 exercise RCTs in comparison to control groups (63%) and not significant in 21 RCTs ($p < 0.05$). Each of the 17 included systematic reviews of exercise interventions reported benefits for some populations. Meta-analytic findings were inconsistent across different populations and outcome scales, however small to large Cohen's effect sizes (Thalheimer and Cook, 2002) in favour of exercise were calculated in nine of the meta-analyses. Main findings from the systematic reviews are presented in the supplementary data file.

The 102 primary pharmacological trials reporting effect on fatigue included 65 randomised controlled trials (RCTs). Ingested, injected or inhaled substances encompassed 34 studies of various forms of erythropoietin, 23 trials of psycho-stimulants and 19 studies of complementary and alternative medicines (CAM). Fatigue was a primary outcome in 63 (62%) of drug studies. Of the primary pharmacological RCTs, 31 (48%) reported statistically significant changes in CRF compared to control groups and no significant change was reported in 33 RCTs ($p < 0.05$). Six systematic reviews of pharmaceutical treatments and two of CAM met review inclusion criteria. Meta-analyses have been performed for trials on erythropoietin, psycho-stimulants and a variety of medications (Minton et al., 2008). Ross et al. (2006) and Bohlius et al. (2014) (Ross et al., 2006, Bohlius et al., 2014) reported small effect sizes on fatigue severity for erythropoiesis-stimulating agents used to treat chemotherapy-induced anaemia, below the threshold of clinically important difference (CID) (Bohlius et al., 2014). Safety concerns have been identified and these drugs are no longer recommended for fatigue management (Minton et

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al., 2010). A review by Minton et al. (2011) concluded that psycho-stimulants had been insufficiently tested to recommend for treatment of fatigue beyond short term use during active treatment and in advanced disease. A later meta-analysis of three studies of psycho-stimulants found the mean difference using the FACT-F measure just reached the threshold for CID (Gong et al., 2014).

Mind-body interventions were examined in 63 primary trials with 43 of RCT design. These are practices focusing on the mind, body and behaviour with the aim of improving health (National Center for Complementary and Alternative Medicine). Three sub-categories were identified. In 22 studies were movement-based therapies included yoga, Pilates, Qi Gong or T'ai Chi. Mind-based practices of relaxation, meditation, hypnosis, virtual reality or music therapy were studied in 15 trials. Twenty-six studies tested touch-based modalities of massage, acupuncture, Reiki, biofield therapy or warm footbaths. Fatigue was a documented primary outcome in 36 (57%) trials. Statistical significance ($p < 0.05$) for a change in fatigue in RCTs was reported in 12 of 14 touch-based, five of 11 mind-based and eight of 18 movement-based therapies. Twenty-four (39%) of the primary studies reported no statistically significant change in fatigue. A systematic review of seven RCTs using acupuncture for CRF found inconclusive results from low quality studies (Posadzki et al., 2013). Meta-analysis of 13 RCTs of yoga interventions reported a moderate reduction in CRF (Buffart et al., 2012), and a large effect was reported in analysis of two Qi Gong trials (Zeng et al., 2014).

Psycho-educational interventions (PEIs) are a form of health education aiming to relieve stress and improve mood (Chan et al., 2011). Labelling of interventions as 'educational', 'psycho-educational', 'psychosocial' or 'cognitive-behavioural' (CBT) was inconsistent throughout the 65 primary studies reviewed. For this reason CBT, which aims to change unhelpful thinking and modify behaviour (Beck, 2011), and sleep therapy were included in the PEI category in this review. Interventions categorised as PEIs were diverse in content and intensity and 41 studies were RCTs. Five papers reported longitudinal results. Several elements such as health education, stress management and coping strategies were commonly included in the trial interventions. Twenty-three studies of PEIs involved education on health, quality of life or symptom management. Behavioural change

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interventions were present in 15 studies of motivational interviewing for exercise-dietary programs, ten studies with the goal of improving sleep patterns, and four studies using CBT focused on fatigue. Seven trials focused on general coping and stress management. Fatigue was nominated as a primary outcome measure in 30 PEI studies. Twenty-five primary psycho-educational RCTs (61%) reported statistically significant changes in fatigue, energy or vigour ($p < 0.05$). Only one of the five studies involving follow-up had statistically significant findings for fatigue. A meta-analysis of psychosocial interventions during cancer treatment reported limited evidence for effectiveness in reducing CRF but promising results for psycho-educational interventions that specifically focused on fatigue (Goedendorp et al., 2009). A systematic review of CBT for insomnia suggested that improvements in fatigue may be achieved for cancer patients with sleep problems (Garland et al., 2014).

Multi-modality interventions, defined (for the purposes of this review) as the application of interventions found in two or more categories, were used in 57 primary studies including 30 RCTs and six follow up studies. Exercise was a component in 34 multi-modal studies, while 40 included psycho-education. Twenty-eight had mind-body components and 10 studies included three or more subcategories. The distribution of components is outlined in Table 5. Fatigue was a primary outcome in 27 of the multi-modality trials. Statistically significant improvements in fatigue between groups were reported in 20 RCTs ($p < 0.05$).

[Insert Table 5: Frequency of components in 57 multi-modality trials about here:]

The 22 non-pharmacological symptom management studies included six trials involving multidisciplinary symptom management clinics. Bright light therapy, electrical nerve stimulation, biofeedback and lymphatic decongestive therapy were also grouped in this category. Only one trial required the presence of CRF. Eight of the 13 RCTs reported statistically significant improvement in CRF against comparator groups ($p < 0.05$).

Primary rehabilitation studies included multidisciplinary rehabilitation, cognition, lymphoedema or occupational therapy programs. One of the four rehabilitation trials with RCT design reported a statistically significant improvement in fatigue ($p < 0.05$). Although

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none of the rehabilitation studies had fatigue as a participant eligibility criterion, two studies had CRF as a primary outcome measure.

The remaining intervention categories of activity management, nutrition and supportive-expressive therapies had fewer than ten studies in each, with a combined study count of 14 including six RCTs. Typically these studies had low participant numbers. One activity management and one nutrition study had fatigue as a participant eligibility criterion. Four activity management studies using principles of energy conservation had fatigue as the primary outcome and three used RCT design. Statistically significant changes in some fatigue dimensions were reported in two RCTs compared to control groups ($p < 0.05$). Neither of the two nutrition-only interventions for cancer patients with anorexia/cachexia, and during radiotherapy for breast and prostate cancer used RCT designs. Seven trials of supportive-expressive therapies (as defined in Table 3) included three RCTs and three had a primary outcome of fatigue. One RCT identified statistically significant improvement in fatigue for expressive writing compared to neutral writing groups ($p < 0.05$). A meta-analysis of seven creative arts therapies found no significant reduction in CRF (Puetz et al., 2013).

Nine trials compared interventions from different categories and eight utilised RCT designs. One RCT found relaxation training significantly more effective for fatigue than CBT ($p < 0.01$) (Cohen and Fried, 2007). Two structured physical training programs resulted in statistically significant reductions in fatigue when compared to multidisciplinary rehabilitation (Heim et al., 2007, Baumann et al., 2011) or standard individual physiotherapy ($p < 0.05$) (Baumann et al., 2011). A study comparing exercise with relaxation and massage reported significance in favour of exercise at 30 days yet not at 3 months follow-up (Houborg et al., 2006). However, fatigue improved significantly for breast cancer survivors with persistent fatigue following multimodal psycho-education and expressive therapy but not for those in the exercise comparator group ($p < 0.05$) (Kröz et al., 2013). Three studies reported no statistically significant difference in the effect of exercise on fatigue compared to Pilates (Eyigor et al., 2010), T'ai Chi (Galantino et al., 2003) or progressive relaxation (Dimeo et al., 2004). A three-arm RCT of exercise with or without CBT found no significant differences in fatigue between intervention groups, but both

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significantly improved compared to the wait listed controls ($p < 0.001$) (Korstjens et al., 2008, van Weert et al., 2010).

Further data regarding interventions, numbers of participants, level of evidence and stage of illness may be found in Appendix 1.

A meta-analysis of the full range of non-pharmacological interventions for CRF reported that exercise and psychosocial interventions generally showed clinically significant small to moderate overall effect sizes for CRF. They also improved vigour or vitality, defined as 'healthy or robust physical and mental energy, strength, and drive' (Kangas et al., 2008). Multimodal exercise and walking programs, restorative, supportive–expressive, and cognitive–behavioural psychosocial interventions showed potential for lowering CRF. Moderate to large effect sizes were reported for interventions with a specific CRF aim or hypothesis while those without an a priori CRF aim had small to moderate effect sizes (Kangas et al., 2008). 'Restorative' therapies that evaluated cognitive parameters not fatigue were excluded from this review.

Fatigue outcome measures

Fatigue was identified as a primary outcome measure (OM) in 254 trials (58%) and a secondary outcome in 162 trials (37%). The remaining studies did not clearly indicate what the primary and secondary outcomes were. The number of trials in each intervention category with fatigue as a primary outcome is summarised in Appendix 1.

Fifteen different scales were used to assess study eligibility. The most common measures were numeric rating scales (NRS - 28 studies), Brief Fatigue Inventory (Mendoza et al., 1999) (BFI - 10 studies) and visual analogue scales (VAS - 8 studies). Most of the studies with a fatigue eligibility criterion required fatigue to be present at moderate-to-severe (59 studies) or severe (6 studies) levels. Commonly used criteria for 'moderate' fatigue using NRS were ratings of four to six on a scale 0-10; on the VAS ≥ 40 and with BFI an average of four. The criteria for 'severe' were seven or more on NRS and ≥ 70 on VAS. Seven studies stipulated that fatigue must be persistent or experienced for a minimum time period

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of either one week or one month. One study utilised the proposed International Classification for Diseases (ICD) criteria for CRF syndrome (Lower et al., 2009, Cella et al., 2001) while another used a physician-rated linear analogue scale (Reinhardt et al., 2005).

Across all studies, change in fatigue was measured using 58 self-report instruments and two objective assessments (medical assessment and vital signs). Six ad hoc scales were developed for use in a particular study. The most frequently used patient reported outcome measures (PROMs) are outlined in Table 6, including use as primary OM, frequency of use with another fatigue PROM and trials in languages other than English.

[Insert Table 6: Most frequently used fatigue outcome measures (portrait) here]

Discussion

This review confirms the high proportion of studies having breast cancer populations as noted by Goedendorp and colleagues (2009). Relatively few trials that focused on people with cancers such as lung, colorectal, gynaecological and neurological met review inclusion criteria. The advanced cancer population is under-represented and almost half of trials with this population were of pharmacological agents. Studies with mixed cancer populations provided limited information about similarities or differences in fatigue for different cancers as subgroup analyses were rarely performed.

There was limited evidence to support or dispute the benefit of most interventions. Very few primary studies of some intervention types recommended in all the treatment guidelines, such as activity management, nutrition and rehabilitation, met this review's inclusion criteria. Some multi-modality and psycho-educational interventions included these elements, and analysis of different combinations may reveal synergies. However, challenges exist in interpreting results due to a lack of homogeneity amongst complex interventions with components that are not also separately evaluated in an RCT (van Weert et al., 2006). The NCCN (2015) guidelines recommend detailed assessment of possible causes of fatigue before implementing interventions for people with moderate to severe

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fatigue. It is surprising that only two studies referred to such an assessment in their methods. Prospective evaluation of the practice guidelines and more research into commonly prescribed interventions is needed to increase the level of evidence for the current guidelines.

The diversity of self-report measures used in studies highlighted in this review means that the same construct or domain may not have been measured (Whitehead, 2009). Some of the studies reported results using single item measures of fatigue, energy or drowsiness. These measures are practical in the clinical setting and useful for rapidly monitoring severity (Jean-Pierre et al., 2007). However, they are not recommended as primary measures in research studies due to issues of responsiveness, ability to capture different fatigue attributes other than severity (Barsevick et al., 2010a) and/or lack of validation (Dittner et al., 2004). Although there is currently no ‘gold standard’ for fatigue measurement (Barsevick et al., 2010a), lack of recommendations regarding measurement may be hindering research. More rigorous study eligibility criteria related to fatigue (Barsevick et al., 2013) and a recommended shortlist of robust instruments that measure both severity and impact of fatigue on physical function (Mortimer et al., 2010, Barsevick et al., 2010a) would enhance CRF research.

Conclusions

There is emerging evidence for the effectiveness of fatigue interventions for people with different cancer types. Use of consistent CRF inclusion criteria and a smaller selection of robust outcome measures that measure both severity and impact of CRF could enable a more accurate estimate of intervention effectiveness and allow comparisons across studies.

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Interventions for cancer-related fatigue – a scoping review

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TABLES: Appendix 1 Interventions for cancer-related fatigue – a scoping review

	N trials (Follow-up /2 ⁰ studies)	Fatigue primary outcome measure	Fatigue eligibility criterion	Study design			During treatment		Post treatment		Advanced & End of life		Mixed phases		Total Participants in primary trials
				Level 1 ¹	Level 2	Level 3+	Trials	Partici- pants	Trials	Partici- pants	Trials	Partici- pants	Trials	Partici- pants	
Activity management	4	4	1		3	1	3	850	1	12					862
Exercise	103 (3)	72	7	17	57	46	51	2750	38	3153	8	486	6	587	6976
Mind-body	63	36	15	6	43	20	27	2007	26	1550	5	205	5	229	3991
Nutrition	2	1	1			2	1	60			1	39			99
Psycho-education	60 (5)	30	14	2	38	22	21	2131	32	3069	2	430	5	355	5985
Rehabilitation	7	2			4	3	1	23	3	153	1	20	2	236	432
Supportive-expressive	8	3		1	3	5	4	374	2	49	1	237	1	49	709
Pharmacological	102	63	37	8	65	37	54	18949	8	1636	30	4874	10	1600	27059
Non-pharmacol symptom mx	22	8	1	3 ²	13	19	6	814	2	228	11	1557	3	560	3159
Multi-modality	57 [1]	27	3		30	27	17	1849	27	4218	4	478	9	992	7537
Different modality comparison	9 (1)	8	3		7	2	2	150	7	559					709
Totals	437	25	82	37	263	174	187	29957	145	14627	63	8326	41	4608	57,518

¹ Oxford Centre for Evidence-Based Medicine (2011). <http://www.cebm.net/index.aspx?o=5653>

² Include several non-pharmacological intervention categories

TABLES: Appendix 1 Interventions for cancer-related fatigue – a scoping review

	(9[1])						
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Five of the pharmacological, ten exercise and two of the mind-body systematic reviews performed a meta-analysis.

TABLE 1 Interventions for cancer-related fatigue – a scoping review

Study Characteristics	Inclusion criteria	Exclusion criteria
Design	<ul style="list-style-type: none"> Systematic review of interventions for CRF Randomised and non-randomised controlled Pre-test/post-test 	<ul style="list-style-type: none"> Descriptive report Case report/study Correlation, prevalence, diagnostic, prognostic or comparison study Trial protocol
Publication	<ul style="list-style-type: none"> Peer-reviewed journal Published in English Abstract and full text available 	<ul style="list-style-type: none"> Doctoral dissertation Conference proceeding, abstract or poster
Participants	<ul style="list-style-type: none"> Adults aged ≥ 18 Any cancer diagnosis Any disease or treatment phase 	<ul style="list-style-type: none"> Non-cancer fatigue Chronic fatigue syndrome
Intervention	<ul style="list-style-type: none"> Clinical trial of any CRF intervention/s 	<ul style="list-style-type: none"> Cancer control/ treatment Other symptom treatment Study in which fatigue is only assessed once No intervention
Outcome measures	<ul style="list-style-type: none"> Fatigue, energy or vitality change reported in abstract Patient reported or objective 	<ul style="list-style-type: none"> Fatigue, energy or vitality not reported in abstract

TABLE 2 Interventions for cancer-related fatigue – a scoping review

Diagnosis -tumour stream	Before/During treatment		Post treatment (all)		Advanced / palliative		Not specified‡, or any/mixed phase		Total for tumour / stream		
	No. trials	Total participants	No. trials	Total participants	No. trials	Total participants	No. trials	Total participants	No. trials	Total participants	Mean per trial
Heterogeneous	76	17920	49	5537	50	4432	26	3198	201	31,087	155
- Follow up*	1*	210	1*	68					2*	278	139
- [Duplicate]			[1]	[209]							
Bone/Soft tissue									0		
Breast	58	7313	66	5555	3	380	8	907	135	14,155	105
F/up studies*	2*	222	4*	943					6*	11,165	194
GI colorectal	4	656	5	636	1	90			10	1,382	138
GI other	3	90					1	102	4	192	48
Gynaecology	3	98	1	33					4	131	33
Haematology	16	1746	10	492	1	1303			27	3,541	131
Head & Neck	3	416	3	395			1	59	7	870	124
Lung	9	558	3	82	3	724			15	1,364	91
	1*	5							1*	5	5
Thyroid	1	84	1	33					2	117	59
Neurology	1	68	2	62			2	175	5	305	61
Skin / Melanoma	2	73	3	1563					5	1636	327
Prostate	10	658	3	239	5	1397	3	167	21	2461	117
Renal	1	277							1	277	277
Total per phase	187	29957	145	14627	63	8326	41	4608	437	57,518	132
	4*	437	5*	1011					9*	1448	161

TABLE 2 Interventions for cancer-related fatigue – a scoping review

* Follow up studies – not included in trial or participant count [1] duplicate study reporting different outcomes (Korstjens et al., 2008)

‡ Stage not specified

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TABLE 3 Interventions for cancer-related fatigue – a scoping review

Category	Definition used in this scoping review	Included interventions	No of studies
Activity management	Pro-active management of personal energy resources (Barsevick et al., 2004)	Energy conservation strategies: pacing, prioritising and scheduling activities (not only education)	4
Exercise	Physical activity interventions in which structured and repetitive bodily movements are performed to improve or maintain one or more components of physical fitness (Howley, 2001), prescribed and monitored by an exercise professional	Includes aerobic and resistive exercise; home and centre-based, group and individual. Excludes motivational interviewing	103
Mind-body therapies	Practices that focus on the interactions between brain, mind, body, and behaviour with the goal to maintain or improve health (National Center for Complementary and Alternative Medicine)	Movement, mind- and touch-based therapies for well being - including yoga, Qi Gong, T'ai Chi, Pilates, hypnosis, meditation, relaxation, music, virtual reality, massage, acupuncture/pressure, biofield and energy therapies, Reiki and warm foot baths	63
Nutrition	Dietary intervention designed to modify protein, energy, fibre or mineral intake	Dietary education and/or ingested or parenteral supplements	2
Psycho-education	A form of health education aiming to alleviate stress and low mood by preparing people for the symptom experience; thereby promoting a	Talking-based therapies and education. Includes cognitive behavioural therapy, motivational interviewing for behaviour change/exercise, stress	60

TABLE 3 Interventions for cancer-related fatigue – a scoping review

	sense of control and self-care practices (Chan et al., 2011)	management, problem solving, coping skills, sleep management, information and education	
Rehabilitation	Interventions designed to minimise specific impairments or participation restrictions resulting from cancer (Franklin et al., 2010), based on clinical assessments and facilitated by rehabilitation professionals	Goal-oriented group and individual rehabilitation conducted by one or more health professionals with a focus on body structures and functions, activity and participation outcomes	6
Supportive-expressive	Interventions including either supportive or expressive components, utilising group or other means to express and explore feelings in a supportive environment to improve coping (Kissane et al., 2004)	Focus is expression and psychological support. Included: writing, art, singing, support groups and pet therapy	8
Pharmacological	Any chemical agent that alters the biochemical physiological processes of tissues or organisms (World Health Organisation, 2014)	Non-dietary injected, inhaled or ingested substances for symptom management including drug, herbal, vitamin, mineral or homeopathic preparations, blood and oxygen	102
Non-drug symptom management	Management of physical symptoms using other non-drug interventions	Symptom monitoring and management by nurse, doctor and/or patient; multidisciplinary symptom clinic; light exposure and transcutaneous electrical nerve stimulation (TENS)	22
Multi-modality	Interventions that include more than one of	Includes elements from more than one of above	57

TABLE 3 Interventions for cancer-related fatigue – a scoping review

	above categories	categories	
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TABLE 4 Interventions for cancer-related fatigue – a scoping review

Study Intervention	Activity Management	Exercise	Mind-body therapies	Nutrition	Psycho-education / CBT / Education	Rehabilitation	Supportive-expressive therapies	Symptom Management – pharmacol + CAM	Symptom management non-pharmacological	Multi-modality	Cat A vs Cat B	Total tumour stream
Diagnosis – tumour stream												
Mixed	4	27	28	2	31	2	3	64 (7 CAM)	16	27	1	201
					2*						[1]	2* [1]
Breast		32	31		20	3	3	18	4	18	5	135
		2*			3*			(9 CAM)		1*		6*
GI Colorectal		1	1		2			2 (1 CAM)	1	1	2	10
GI other		3			1							4
Gynaecology			2		1			1				4
Haematology		16	3		1		1	4		1	1	27
Head & Neck		2						2	1	2		7
Lung		7						12				15
		1*						(1 CAM)				1*
Thyroid		2										2
Neurology						2		3				5
Skin/Melanoma					3			1		1		5
Urology prostate		12	2		1			2		4		21
Urology renal							1					1
TOTALS TYPE	4	103	63	2	60	7	8	102	22	57	9	437
Follow up study*		3*			5*			(18 CAM)			[1]	9* [1]

TABLE 4 Interventions for cancer-related fatigue – a scoping review

* follow up studies; [1] dual report with same participants; (CAM) number of complementary or alternative medicines trials included

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TABLE 5 Interventions for cancer-related fatigue – a scoping review

	Psycho-education	Mind-body	Psycho-ed and mind-body	Nutrition	Other
Exercise	14	7	8	2	1 All 1 pharma 2 rehab
Psycho-education		19			1 Pharma
Supportive-expressive		2			1 Exercise

TABLE 6 Interventions for cancer-related fatigue – a scoping review

Fatigue outcome measure	Used in N trials	Primary Outcome Measure	Used with other fatigue PRO	Language other than English
Single item methods: Visual analogue scale (VAS)-fatigue; Numeric Rating Scale (NRS)- fatigue; Ecological momentary assessment; Likert scale; Rhoten Fatigue Scale; Verbal rating scale	65	32	32	21
Functional Assessment of Chronic Illness Therapy (FACIT-F) or FACT-Anaemia fatigue subscale (Cella, 1997)	64	34	22	12
Brief Fatigue Inventory (BFI) (Mendoza et al., 1999)	61	49	16	10
Profile of Mood States (short form) (POMS-SF) fatigue-inertia subscale (McNair et al., 1992)	43	17	14	14
Piper Fatigue Scale / PFS-Revised (Piper et al., 1998)	43	31	9	12
European Organisation for Research and Treatment of Cancer Quality of Life	35	7	5	23

TABLE 6 Interventions for cancer-related fatigue – a scoping review

Questionnaire – Cancer (EORTC-QLQ-C30)				
fatigue subscale (Aaronson et al., 1993)				
Functional Assessment of Cancer Therapy –	32	18	10	11
Fatigue (FACT-F) (Yellen et al., 1997)				
Multidimensional Fatigue Inventory (MFI)	29	19	7	17
(Smets et al., 1995)

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