



UNIVERSITY OF LEEDS

Determining Research Priorities for Cancer Survivorship: consultation and evidence review

TECHNICAL APPENDIX: No. 3

Systematic scope and collation of research
evidence regarding interventions

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AIM

Our aim was to conduct a rapid scoping review, taking no longer than six months, of recently published research evidence regarding the effectiveness of interventions addressing the problems faced by cancer survivors. The focus of this review was, therefore, on retrieving systematic reviews and randomised controlled trials (RCTs) of interventions.

METHODS

Subject area

We focused on studies of interventions for the following common problems:

Symptoms of:	Depression
	Anxiety and fear of recurrence
	Emotional distress
	Fatigue
	Pain
Impairment in:	Physical functioning
	Social functioning, including relationships
	Work and employment
	Cognitive functioning

We concentrated on stages of the cancer journey covered by:

- (a) the period immediately following treatment (acute phase)
- (b) the short and long term consequences of cancer including recurrence (sub acute phase)
- (c) living with active and advanced disease or disease free (long term phase)

Inclusion and exclusion criteria

Inclusion criteria:

- Listed in one of the following electronic databases Cochrane library, Amed, Embase, HMIC, Medline, Psychinfo
- English language

- Systematic reviews published since 1990
- Randomised controlled trials (RCTs) published since a relevant, high quality systematic review, in a journal with an impact factor of more than five
- Any intervention that had relief of one of the above common problems as its primary aim (including drug and non drug, professional delivered and self-help interventions)

Exclusion criteria:

- Childhood and adolescent cancer
- Review articles other than those of RCTs

Procedures

The listed databases were searched using the search terms described in Appendix 1.

We reviewed the titles, and where appropriate, abstracts of all systematic reviews found by the search. The full manuscript was reviewed for those considered potentially relevant. From the full manuscripts, two reviewers selected relevant systematic reviews for synthesis using the inclusion and exclusion criteria described above. 20% of potentially relevant articles were also examined by a third reviewer.

Data were extracted and summarised using data extraction sheets and were subsequently entered into a customised Microsoft Office 2003 ACCESS database. Data extraction for relevant systematic reviews included the following information: First author; year of publication; number of RCTs included; total number of participants and mean RCT sample size; cancer site(s); stage(s) of cancer journey; problem(s) addressed by interventions; type(s) of intervention. We also noted the authors' conclusions regarding the effectiveness of interventions in their review, coding these as (a) positive (regarded evaluated intervention as more effective than comparator); (b) negative (regarded evaluated intervention as less effective than comparator); (c) inconclusive (insufficient or conflicting evidence regarding effectiveness of evaluated intervention).

To assess the quality of the reviews different approaches were taken across the health and well being review and the solutions review. Most reviews in the solutions scoping review were high quality Cochrane type reviews and quality screening was not undertaken. Our judgement of study quality of the RCTs included in the reviews was taken from commentary available in the systematic reviews and is thus only a broad assessment of this feature of the research and relies on what we could infer from comments made by the review authors. For us to define the quality of each study included in the reviews would have required a detailed analysis of each individual study and was beyond the scope of a scoping review. Consequently in the tables that follow, we only provide a very broad and general indication of whether the quality of the research evidence encompassed low, medium, or high quality research

In terms of quantity of research contained in the reviews we found we could not always do this precisely and therefore do not offer a precise number in relation to the reviews. For example, sometimes review authors did not state explicitly the number of studies they reviewed on a topic area but may have referenced studies throughout the text in relation to that topic area and these were counted. Because there was scope for error in counting these we chose to use approximations (this was particularly the case for the health and well being review, exact figures were usually given in solutions-type reviews). Therefore we have provided bands as an indication of quantity of research in to indicate low, moderate or high amounts of research (whereby amount of research defined as approximate number of trials included in the systematic reviews : Low = ≤ 5 RCTs, Moderate = 6 – 10 RCTs, High = > 10 RCTs). Furthermore, we were not convinced that simply giving the number of studies without reviewing them all for size and quality would be that useful.

Randomised controlled trials published since a relevant, high quality systematic review, were selected using the inclusion and exclusion criteria described above. Data were extracted and summarised using similar data extraction sheets and were used to update the conclusions derived from the systematic reviews. A simple method of focussing on high quality publications was used in that we only included

those studies published in journals with an impact factor of more than 5 for the trials of solutions.

RESULTS

We identified 1,110 systematic reviews using the search strategy. Of these, 49 were included (see Tables 1 and 2). The details of how the final sample was derived and the reasons for exclusion are shown in Figure 1.

We identified 21 relevant RCTs that had been published since a relevant, high quality systematic review (see Table 3).

Table 4 provides an overview of the findings.

Methodological issues

In reviewing the published literature, we were struck by a number of recurrent methodological problems that were frequently highlighted by those conducting systematic reviews. These included:

1. Problems with the samples studied:

The origin of samples is sometimes poorly described and they may not be representative. Much research has been done on women with breast cancer and other cancers have been neglected. There has been little research into the needs of minority groups and certain cancers, such as lung cancer and the less common cancers. Mostly samples have been simply too small to yield robust results.

2. Measures

A wide variety of measures have been used, with little consistency between studies, making the combination of the data across studies problematic. A standard set of measures would be highly desirable.

3. Design

A common criticism is that studies are not of generally high quality and are subject to multiple sources of bias which may make the result unreliable. Another major problem of design is the lack of long-term follow up.

4. Interventions

There are many problems with the interventions evaluated. They are often not well characterised and may not be in a form in which they can be implemented in practice.

5. General Issues

A key problem is the lack of precision in the research questions that have been asked (for example, the effect of a rather vaguely specified intervention on a wide range of rather vaguely specified outcomes). Such studies, not surprisingly, produce only vague answers.

Fatigue and physical functioning

Impairment in physical function has been commonly researched in relation to fatigue or other physical symptoms. Thirteen systematic reviews included interventions that aimed to improve either fatigue or physical functioning or both. Reviews tended to include patients at a number of stages of survivorship and a moderate number of clinical trials, mostly of relatively small size.

Pharmacological interventions that have been evaluated for fatigue include Epoetin and stimulant medications. Non-pharmacological interventions include, principally, exercise but also patient education and cognitive behavioural therapy.

Although Epoetin showed some initial promise, particularly for fatigue in patients with anaemia, there are now safety concerns associated with this medication and it cannot be recommended. There is accumulating evidence in small trials for the efficacy of stimulant medication but not sufficient to recommend their routine use.

The strongest evidence for non-pharmacological interventions is for exercise. A recent Cochrane review (Cramp and Daniel, 2009) identified 28 studies that included more than 2,000 participants, mainly breast cancer patients. This review concluded that there was reasonable evidence for the efficacy of exercise in cancer-related fatigue and fatigue following chemotherapy. However, this review also concluded that further work is needed to determine the most effective type of exercise and also to work out how best to maximise patient adherence.

Another recent Cochrane review (Goedendorp et al, 2009) identified 27 studies including more than 3,000 participants. A range of psychological interventions were included in the review. The authors concluded there was limited evidence that psychological interventions *during cancer treatment* are effective in reducing fatigue. It must be noted, however, that the studies in this review were restricted to those administered during active cancer treatment and not longer term survivors.

A third Cochrane review (Markes et al, 2009) considered exercise specifically for women receiving adjuvant therapy for breast cancer. Nine trials involving 450 women were identified. It was concluded there was evidence for the efficacy of exercise in improving physical fitness and activities of daily life but the evidence for improvement in fatigue was ambiguous. There was a lack of studies of long-term efficacy.

The randomised trials identified that were published since the most recent systematic review did not substantially alter these conclusions.

Of interest was a trial of giving breast cancer survivors step pedometers and information (Vallance et al, 2007) which indicated that this intervention improved physical exercise in the short term. Long term adherence to exercise programs is an important issue for implementation. A cognitive behavioural program which included increasing activity improved the physical functioning of breast cancer patients in a small trial (Armes et al, 2007).

In summary, the evidence to date indicates some support for the use of drug therapies, particularly stimulants and moderate evidence in support of exercise. There was also some evidence for psychological treatments, particularly those that include increases in activity. Overall, the intervention that shows most promise is exercise although there continues to be considerable uncertainty about the nature of the exercise that should be prescribed, how to maximise uptake by patients and how to ensure long-term adherence. As a means of improving physical function and reducing fatigue, increases in activity and exercise would qualify as an intervention that could then benefit from further high quality research that would address these questions as a step towards practical implementation. It seems likely that adding an informational and/or psychological component to simple exercise regimens is likely to be beneficial in achieving long term adherence.

Pain

14 systematic reviews evaluated interventions that aimed to reduce pain, including patients at various stages of survivorship.

There is very strong evidence that commonly used treatments for pain, namely, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates such as morphine and its synthetic variants are more effective than placebo in treating pain in general. The systematic reviews indicate that the amount of research into the management of pain, specifically in people with cancer, is less than one might expect. The systematic reviews considered confirmed the effectiveness of these agents, given by a variety of routes.

A Cochrane review (Wiffen and McQuay, 2009) examined the efficacy of oral morphine for cancer pain and concluded that while the randomised trial literature was small, given the importance of the problem, morphine was probably an effective treatment. Another Cochrane review (Zeppetella and Ribeiro, 2009) examined the effectiveness of opioids in treating so-called breakthrough pain in cancer patients and found it to be effective, but commented that the literature was small.

An important issue for pharmacological treatments is how to make sure they are optimally applied. A review by Irajpour et al (2006) found evidence that inter-professional education led to improved documentation of pain.

As well as pharmacological treatments, a variety of non-drug treatments including cognitive behaviour therapy and hypnosis have been evaluated in the systematic reviews. The evidence for the efficacy of these non-pharmacological strategies is only weak to moderate. Interestingly, the use of a widely prescribed treatment for pain (transcutaneous electrical nerve stimulation) indicated that it is of uncertain value for patients with cancer related pain.

For the specific problem of neuropathic pain, a Cochrane review (Challapalli et al, 2009) concluded that local anaesthetics were superior to placebo.

Of the trials published since the reviews one is of special interest. Syrjala et al (2008) found that a novel way of trying to improve the use of pharmacological pain relief by training patients in pain management using print and video material was of short-term benefit. Further work to address the barriers to the more effective use of existing treatments would be of value as described above.

In summary there is considerable evidence for the efficacy of standard analgesics in cancer survivors with pain. However the issue of recognition of who has pain and the best way of delivering pharmacological pain treatments remains and further research is required. There needs to be more evaluation of the advantages and disadvantages of long-term analgesic use, especially of opiates in cancer survivors. Non drug treatments alone appear to be of limited efficacy. Research into implementing systems for identifying which cancer survivors have pain and efficiently delivering treatments will be of value. Combinations of drug and non drug interventions merit further study. The issue of the systematic identification and management of pain in longer-term cancer survivors is an important area for further research.

Sexual function

Four systematic reviews evaluated interventions that aimed to improve sexual function; in the sub-acute phase of survivorship, the long term phase and in a mixture of phases. Only a small number of systematic reviews were identified that addressed this problem area. The amount of research is low compared to the importance of this problem for patients.

A Cochrane review by Denton and Maher (2009) examined various interventions for sexual dysfunction in women who had received pelvic radiotherapy. The treatments considered were various, including dilators, reconstruction and oestrogens. They found some evidence for use of topical oestrogen and vaginal dilators, although the evidence as a whole was considered to be of poor quality. Another Cochrane review by Flynn et al (2009) found some supportive evidence for the use of vaginal oestrogen cream in female cancer patients but the quality of the evidence was poor.

A Cochrane review by Myles et al (2009) examined the range of treatments for sexual dysfunction following cancer treatment and concluded that Viagra was an effective treatment for men with prostate cancer, though the evidence for the efficacy of other treatments and for other sexual problems was unclear.

In summary, the quality of the evidence for interventions to address the important matter of sexual problems in people who have had cancer and treatment for cancer is very poor. Most of the evidence seems to be on biological interventions. Viagra, undoubtedly, has an important role, particularly for male impotence but it would appear that more concerted and long-term research is required to address the sexual problems of women. There also appears to be a dearth of research into non-drug treatments. We did not identify any randomised trials relevant to sexual function of cancer survivors published since the systematic reviews.

Cognitive functioning

We were unable to find any systematic reviews of RCTs of interventions that aimed to improve cognitive functioning.

Employment, finance and return to work

We were unable to find any systematic reviews of RCTs of interventions that aimed to assist with employment, finance and return to work.

Depression, Anxiety and General Distress

28 systematic reviews included interventions that aimed to improve depression, anxiety or general distress. The majority included interventions delivered in a number of survivorship phases.

There is a reasonably large literature on interventions for emotional distress of mild to moderate severity but less for the more specifically defined anxiety and depressive disorders.

First we consider mild to moderate general emotional distress. There are many reviews of the effect of various aspects of cancer care on the severity of patients' emotional distress. These include the nature of follow up care, information giving and communication. The results of most of these are inconclusive, although many of them (such as improved communication) do appear to improve satisfaction with care. There have been many trials of psychological interventions for emotional distress but we found no recent high quality systematic reviews. Whilst there are many weakly positive trials of a variety of psychological treatments the best evidence is probably for CBT (Tatrow and Montgomery, 2006). However the quality of the literature is not high and most of the interventions would not be feasible to deliver in practice to the large numbers of patients with this problem

Second we turn to anxiety disorder. There is surprisingly little literature on the treatment of anxiety, and even less on fear of cancer recurrence. Sheard and Maguire (1999) reviewed the effect of psychological interventions on anxiety and depression in cancer patients. They found 25 trials of treatment for anxiety of a

variety of types of therapy and concluded there was moderate evidence of efficacy. However they noted that most of the studies had recruited patients on the basis of a diagnosis of cancer, rather than a diagnosis of anxiety. There appears to be a dearth of both primary trials and systematic reviews of interventions specifically tailored for cancer patients who have a diagnosis of anxiety disorder. This will be an important area for further research.

Third we consider depressive disorder. There is a more coherent literature on the management of depression in cancer patients. Sheard and McGuire (1999) concluded that psychological interventions were less effective for depression than for anxiety. A systematic review by Williams and Dale (2006) concluded that there had been a surprisingly small number of trials of drug treatments for depression in cancer patients, although there was some evidence that antidepressants were as effective for them as they are for patients in general. They also noted there was very limited evidence on the efficacy of psychotherapeutic interventions for depression, although the evidence did suggest that cognitive behaviour therapy might be effective. The main conclusion was that there is a need for more rigorous investigation of the efficacy of both drug and non-drug interventions. Another systematic review (Rogan et al, 2007) also concluded that there was limited evidence for the effectiveness of drug and non-drug interventions but that based on evidence from other populations, a combined drug and non-drug approach to the treatment of depression may be most effective.

Several trials published subsequent to the systematic reviews are worthy of comment. A trial by Wilkinson et al (2007) of aromatherapy massage for anxiety and depression found some short term benefit but no evidence of sustained effect. An interesting trial by Kornblith et al (2006) examined the effect of pro-active telephone monitoring in older people with advanced cancer and found that monthly telephone calls had a moderately beneficial effect on anxiety, depression and stress. This trial highlights the potential use of outreach by telephone to cancer patients and is a model that could be further developed.

Perhaps, most interesting is the application of the collaborative care model for managing depression to cancer patients. In collaborative care a case manager (often a nurse), who receives supervision from a specialist, coordinates the patient's care. It has been developed in America and shown to be effective and cost-effective for depressed patients in primary care. A study of low income, mainly Hispanic, patients with cancer in Los Angeles (Ell et al, 2008) evaluated this approach compared with usual care in nearly 500 patients. Although there were difficulties in achieving the follow up on this patient group, the trial showed fairly substantial benefits for the intervention group.

Perhaps of more relevance to the UK, is a trial by Strong et al (2008) which compared a cancer nurse delivered collaborative care intervention (including education, encouragement to take antidepressant medication and problem solving) with usual care in patients attending a cancer centre many of whom were survivors in follow up and found very substantial and persistent benefits with the intervention which also appeared to be cost-effective. Further trials examining the effectiveness and cost-effectiveness of this collaborative care approach (Depression Care for People with Cancer) are currently underway.

In summary, the problems of distress, anxiety and depression have consistently been found to be prevalent amongst, and important to, cancer patients. Although there appears to have been a lot of effort to address them, the quality of the work has in general been disappointing. Many of the trials of the management of distress have used poorly characterised interventions, in poorly characterised samples and often of patients who simply had cancer and no evidence of distress. All we can conclude from this literature is it appears that 'doing something psychological' often appears to help in the short-term. Better trials are needed There is a dearth of evidence of the efficacy of treatments for anxiety in general and anxiety about recurrence in particular. The best evidence we have is for the management of depression. More recent trials are larger and of higher quality and indicate that a system of care, combining drug and pharmacological intervention with overall co-ordination of patient management appears to offer considerable benefits. This collaborative care

model could offer a way of improving supportive care in general, not only for depression. This approach for managing depression is close to implementation and would benefit from research examining how it could be established in routine NHS practice and what barriers would need to be overcome.

Figure 1: Derivation of final sample of systematic reviews

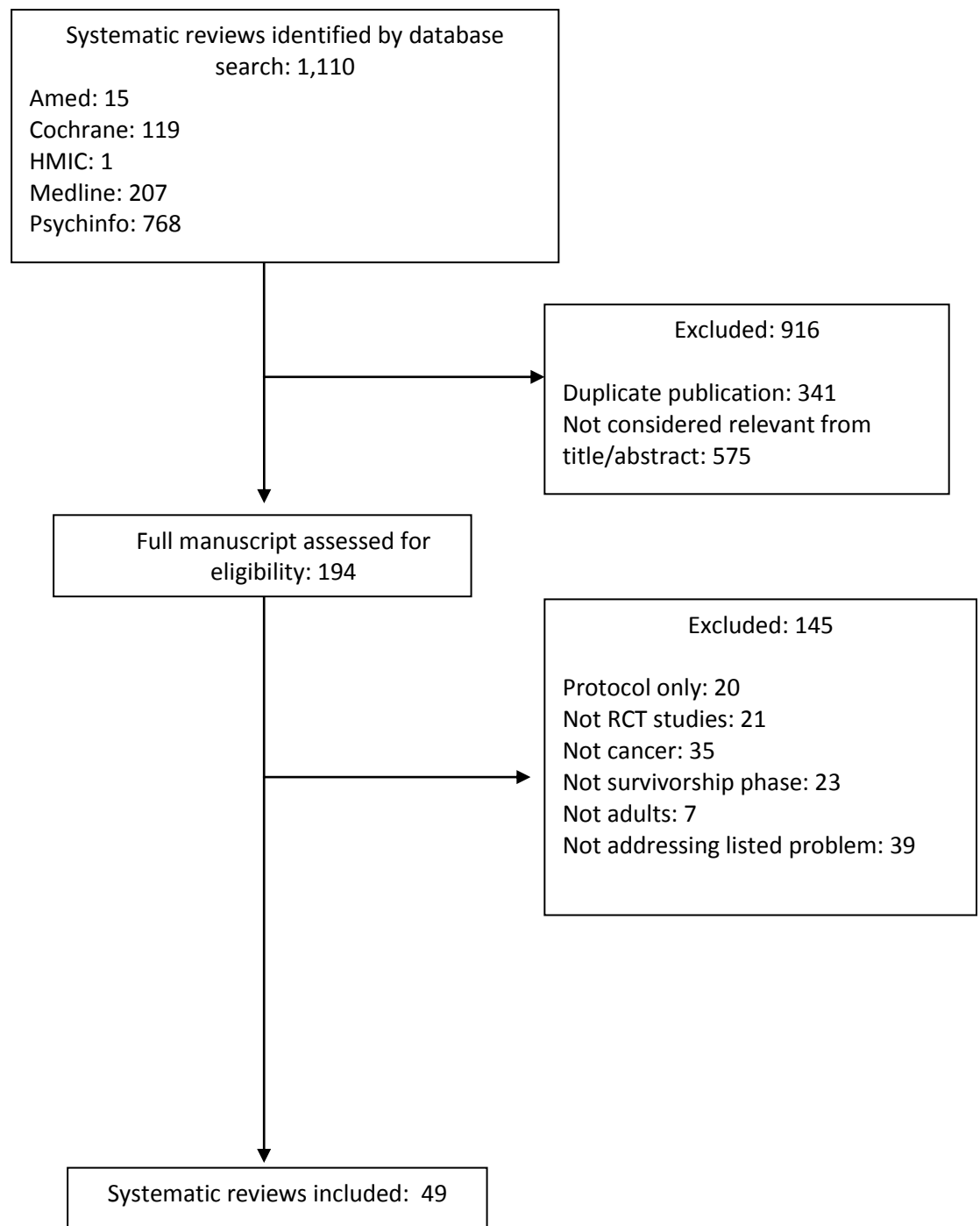


Table 1: Solutions to the Problems of Cancer Survivors: Summary of systematic reviews

Reference	Focus of review
Bardia (2006)	Effects of complementary and alternative therapies on cancer pain
Barsevick (2002)	Psycho-educational interventions for depression for patients with cancer
Bottomley (1997)	Group interventions with cancer patients
Campbell (2004)	Cancer peer support programs
Carr (2002)	Management of pain, depression and fatigue in cancer patients
Challapalli (2005)	Systemic local anaesthetics for neuropathic pain
Collins (2004)	Follow-up care of patients treated for breast cancer
Cooke (2000)	Aromatherapy
Cramp (2008)	Exercise for cancer-related fatigue
Denton (2003)	Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy
Edwards (2008)	Psychological interventions for women with metastatic breast cancer
Ezzo (2006)	Acupuncture for chemotherapy-induced nausea or vomiting
Flynn (2009)	Interventions for psychosexual dysfunction in women treated for gynaecological malignancy
Friedenreich (1996)	Exercise as rehabilitation for cancer patients
Goedendorp (2009)	Psychosocial interventions for fatigue during cancer treatment
Goudas (2001)	Management of cancer pain
Gysels (2007)	Interactive technologies and videotapes for patient education in cancer care
Horneber (2008)	Mistletoe therapy in oncology
Irajpour (2006)	Interprofessional education to improve pain management
Jeffery (2007)	Follow-up strategies for patients treated for non-metastatic colorectal cancer
Kassab (2009)	Homeopathic medicines for adverse effects of cancer treatments
Kirschbaum (2007)	Benefits of whole body exercise during and after treatment for breast cancer
Knols (2005)	Physical exercise during and after cancer treatment
Mansky (2006)	Benefits of Tai Chi for cancer survivors
Markes (2006)	Exercise for women receiving adjuvant therapy for breast cancer
McPherson (2001)	Effective methods of giving information in cancer
Miles (2007)	Interventions for sexual dysfunction following treatments for cancer

Reference	Focus of review
Minton (2008)	Drug therapy for cancer-related fatigue
Newell (2002)	Psychological therapies for cancer patients
Nicholson (2007)	Methadone for cancer pain
Osborn (2006)	Psychosocial interventions for depression, anxiety and quality of life in cancer survivors
Pitkethly (2008)	Recordings or summaries of consultations for people with cancer
Quigley (2002)	Hydromorphone for cancer pain
Rehse (2003)	Psychosocial interventions for cancer patients
Richards (2000)	Effects of massage
Robb (2008)	TENS for cancer pain
Rodin (2007)	Treatment of depression in cancer patients
Sellick (1998)	Nonpharmacologic strategies for cancer pain
Servaes (2002)	Interventions for fatigue during and after cancer treatment
Sheard (1999)	Psychological interventions for anxiety and depression in cancer patients
Smith (2005)	Mindfulness based stress reduction as supportive therapy in cancer care
Sola (2004)	Non-invasive interventions for improving well-being and quality of life in patients with lung cancer
Tatrow (2006)	Cognitive behavioural therapy for distress and pain in cancer patients
Walsh (1998)	Breaking bad news
Wessex Institute (1998)	Counselling services for women with breast cancer
Wiffen (2007)	Oral morphine for cancer pain
Williams (2006)	Effectiveness of depression treatments in people with cancer
Zabalegui (2005)	Nursing and cancer support groups
Zeppetella (2006)	Opioids for breakthrough (episodic) cancer pain

Table 2: Solutions to the Problems of Cancer Survivors: Summary of findings from reviews

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research ¹	Quality of research ²	Scope	Conclusions
Fatigue & physical functioning				
Carr (2002)	Low	Low	Patients with anaemia	Drugs for anaemia effective in reducing fatigue.
Cramp (2008)	High	Low-mod	Small trials	Some evidence for the effectiveness of exercise.
Ezzo (2006)	High	Mod	Patients who had had chemotherapy	Moderate effects of acupuncture on chemotherapy-induced nausea and vomiting.
Friedenreich (1996)	Low	Low	Breast cancer	Some evidence for exercise but numerous methodologic limitations.
Goedendorp (2009)	High	Mod	Mixed samples	Limited evidence that psychosocial interventions specifically for fatigue during cancer treatment are effective.
Kassab (2009)	Low	Low	Mixed samples	Evidence for homeopathy is inconclusive.
Kirschbaum (2007)	Low	Mod	Breast cancer	Some evidence for exercise improving levels of fatigue.
Knols (2005)	High	Mod	Mixed samples	Cancer patients may benefit from exercise during and after treatment.

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Mansky (2006)	Low	Low	Mixed samples	Some evidence for the practice of Tai-Chi in improving physical function but the research is poor.
Markes (2006)	Low	Low-Mod	Breast cancer	No evidence for exercise
Minton (2008)	High	Mod	Mixed samples	Drugs for anaemia the only clear recommendation.
Newell (2002)	Low	Mod	Mixed samples	No psychological treatment could be recommended.
Servaes (2002)	Low	Low	Short-term follow-up	Some evidence for the benefit of exercise, counselling and group therapy during treatment.
Pain				
Bardia (2006)	Low	Low	Mixed cancer and acute stage	Promising evidence for hypnosis and relaxation but can't be recommended
Carr (2002)	High	Low-Mod	Mixed samples	Direct inter-class comparisons of efficacy do not differentiate between the relative efficacy of opioids and NSAIDs administered through various routes for mild, moderate or severe cancer pain.
Challapalli (2005)	High	Mod	Mixed samples	Local anaesthetics effective in reducing neuropathic pain

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Goudas (2001)	High	Low	Mixed samples	Evidence for various opiates and NSAIDs but quality of research poor.
Irajpour (2006)	Low	Low	Mixed samples	Interprofessional education leads to improved documentation of pain
Newell (2002)	Mod	Mod	Mixed samples	No psychological treatment could be recommended.
Nicholson (2007)	Mod	Mod	Mixed samples	Methadone similar effectiveness to morphine.
Quigley (2002)	High	Mod	Mixed samples	Hydromorphone is an effective analgesic
Richards (2000)	Low	Low	Mixed samples	Limited evidence (not just in cancer) that massage can reduce pain.
Robb (2008)	Low	Low	Mixed samples	Inconclusive evidence for the use of TENS
Sellick (1998)	Low	Low	Mixed cancer and acute stage	Inconclusive evidence for complementary therapies such as acupuncture and hypnosis.
Tatrow (2006)	High	Mod	Mixed samples	Some evidence for CBT for pain.
Wiffen (2007)	High	Low-Mod	Mixed samples	Oral morphine effective in relieving pain.
Zeppetella (2006)	Low	Mod-High	Mixed samples	Synthetic opioids effective in reducing episodic pain

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Sexual function				
Denton (2003)	Low	Low	Women following pelvic radiotherapy	Support for the use of topical oestrogen and vaginal dilators.
Flynn (2009)	Low	Low	Cervical cancers	Vaginal oestrogen cream have short term benefits.
Miles (2007)	High	Low	Prostate cancer	Evidence for the effectiveness of Viagra.
Newell (2002)	Mod	Mod	Mixed samples	No psychological treatment could be recommended.
Depression, anxiety, distress				
Barsevick (2002)	High	Low-Mod	Mixed samples	Weak evidence for counselling and moderate evidence for psychoeducation for depression.
Bottomley (1997)	High	Low	Mixed samples	Modest evidence for group interventions for general distress but research is of poor quality.
Campbell (2004)	Low	Low	Mixed samples	No evidence for the effectiveness of peer support for general distress.
Carr (2002)	High	Low	Mixed samples	Evidence for mild benefits from antidepressants for depression.

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Collins (2004)	Low	Low	Breast cancer	Little evidence for the effectiveness of different follow-up strategies (frequency and location).
Cooke (2000)	Mod	Low	Mixed samples	Some evidence that aromatherapy can be of minor benefit in reducing anxiety in the short term.
Cramp (2008)	Low	Low-Mod	Mixed samples	Inconclusive evidence for the benefits of exercise for depression and anxiety.
Edwards (2008)	High	Low	Breast cancer	No clear evidence to recommend any treatments for anxiety or general distress.
Gysels (2007)	Low	Low	Mainly breast cancer	Preliminary evidence for patient education for general distress but research inadequate.
Horneber (2008)	High	Low-Mod	Mixed samples	Inconclusive evidence for mistletoe therapy.
Jeffrey (2007)	Mod	Mod	Patients with non-metastatic colorectal cancer	Intensive follow-up may confer survival benefit but effects on depression, anxiety and general distress are unknown.

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Kirschbaum (2007)	Low	Mod	Breast cancer	Potential for exercise improving depression and anxiety.
Knols (2005)	Low	Mod	Mixed samples	Modest evidence for mindfulness based stress reduction for general distress.
Mansky (2006)	Low	Low	Mixed samples	Equivocal evidence for Tai-Chi for general distress.
Markes (2006)	Low	Low-Mod	Breast cancer	No evidence for effectiveness of exercise for depression, limited evidence for anxiety.
McPherson (2001)	Mod	Mod	Mixed samples	Recordings of information can improve patient knowledge.
Newell (2002)	High	Mod	Mixed samples	No treatment recommended for depression. One trial indicating that music therapy can be effective in reducing anxiety.
Osborn (2006)	High	Low	Mixed samples	Weak evidence for the use of CBT in reducing depression and anxiety.

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Pitkethly (2008)	High	Mod	Mixed samples	Recordings and summaries of consultations can improve patient knowledge.
Rehse (2003)	High	Low-Mod	Mixed samples	A modest improvement in quality of life from various psychological interventions but unclear which types.
Rodin (2007)	High	Low-Mod	Mixed samples	Modest evidence for drugs and various psychological interventions (e.g. CBT and education) for depression.
Sheard (1999)	High	Mod	Mixed samples	Some evidence for a variety of psychological interventions in reducing depression. Robust effects for a variety of psychological interventions in reducing anxiety.
Smith (2005)	Low	Mod	Mixed samples	Modest evidence for mindfulness base stress reduction for general distress.

PROBLEM ADDRESSED	SUMMARY OF REVIEW FINDINGS			
	Amount of research	Quality of research	Scope	Conclusions
Sola (2004)	Mod	Low-High	Lung cancer	Modest evidence for nursing interventions and follow-up, specifically for breathlessness. Inconclusive evidence for counselling.
Tatrow (2006)	High	Mod	Mixed samples	Some evidence for CBT for general distress.
Walsh (1998)	Mod	Low	Mixed samples	Little evidence that a range of methods of breaking bad news benefits patients.
Wessex Institute (1998)	Low	Mod	Breast cancer	Some evidence for short-term benefits from counselling for general distress.
Zabalegui (2005)	High	Mod	Mixed cancers at acute survivorship stage	Modest evidence for participating in support groups for depression, general distress and anxiety.

¹ Amount of research defined as approximate number of trials included in the systematic reviews : Low = ≤ 5 RCTs, Moderate = 6 – 10 RCTs, High = > 10 RCTs.

² Quality of research: This refers to the original systematic reviewers comments on the overall quality of RCTs included in their review.

Table 3: Summary of randomised controlled trials published since relevant high quality systematic reviews

Reference	Design	Sample	Interventions	Outcome of interest	Results
Armes (2007)	2 arm parallel group RCT	60 patients receiving chemotherapy	Behaviourally-oriented intervention for cancer-related fatigue v usual care	Fatigue, physical functioning	Improved physical functioning in intervention group compared to usual care.
Bakitas (2009)	2 arm parallel group RCT	322 people with advanced cancer	Psycho-educational intervention v usual care	Depression	Improved depressed mood in intervention group compared to usual care.
Bruera (2007)	2 arm parallel group RCT	142 cancer patients with fatigue	Donepezil v placebo	Fatigue	No significant difference between groups.
Courneya (2007)	3 arm parallel group RCT	242 breast cancer patients initiating adjuvant chemotherapy	Usual care v supervised resistance exercise v supervised aerobic exercise	Fatigue (secondary outcome)	No significant difference between groups.
Daley (2007)	3 arm parallel group RCT	108 women treated for breast cancer 12-36 months previously	Aerobic exercise v exercise-placebo (body conditioning) v usual care	Depression (secondary outcome)	Depression scores improved modestly in both exercise groups compared to usual care.
Elkins (2008)	2 arm parallel group RCT	60 breast cancer survivors with hot flashes	Hypnosis v no treatment	Anxiety, depression (secondary outcomes)	Patients who received hypnosis had lower anxiety and depression scores at the end of treatment.
Eli (2008)	2 arm parallel group RCT	472 low income, predominantly female Hispanic patients with major depression, dysthymia or both	Collaborative care with specially trained social worker supervised by psychiatrist v usual care	Depression	Collaborative care more effective than usual care in reducing depression.

Reference	Design	Sample	Interventions	Outcome of interest	Results
Espie (2008)	2 arm parallel group RCT	150 patients who had completed active cancer therapy and had chronic insomnia	Group CBT program for insomnia delivered by specially trained cancer nurses v usual care	Fatigue, anxiety, depression, physical functioning (secondary outcomes)	Group CBT program more effective than usual care in reducing fatigue, depression and anxiety and improving physical functioning.
Jones (2006)	2x2x2 factorial RCT of different forms of information	400 patients starting radiotherapy	General v personalised printed information, Interactive v automatic information selection, anxiety advice v no anxiety advice	Anxiety, depression	No differences in anxiety or depression by any intervention factors.
Kornblith (2006)	2 arm parallel group RCT	192 patients with advanced disease, currently receiving treatment	Educational materials v educational materials plus telephone monitoring	Distress	Educational materials plus telephone monitoring more effective than educational materials alone in reducing distress, anxiety and depression.
Krischer (2007)	2 arm parallel group RCT	310 patients about to begin radiotherapy treatment	Usual care v self-administered stress management training	Distress	No difference between groups.
McNeeley (2008)	2 arm parallel group RCT	52 head and neck cancer survivors	Progressive resistance exercise training v standardized therapeutic exercise protocol	Fatigue (secondary outcome)	No difference between groups.
Milne (2008)	2 arm crossover RCT	58 breast cancer survivors within 2 years of completing adjuvant therapy	Immediate exercise group v delayed exercise group	Fatigue (secondary outcome)	Exercise improved fatigue.

Reference	Design	Sample	Interventions	Outcome of interest	Results
Moadel (2007)	2 arm parallel group RCT	128 cancer patients	Yoga v waiting list control	Fatigue, psychological distress	No difference between groups.
Northouse (2007)	2 arm parallel group RCT	263 prostate cancer patients and their spouses	Standard care v standard care plus family intervention	Mental quality of life	No significant difference between groups.
Parker (2009)	3 arm parallel group RCT	159 men with prostate cancer undergoing radical prostatectomy	Pre-surgical stress management intervention v supportive attention group v standard care	Mood disturbance, physical functioning	Mood disturbance before surgery less in men who received stress management intervention or supportive attention. Physical functioning at 1 year better in men who received stress management intervention or supportive attention.
Passalacqua (2009)	2 arm cluster RCT	38 Italian cancer centers	Point of information and support system v control	Distress	No significant difference between groups.
Strong (2008)	2 arm parallel group RCT	200 patients with mixed cancers and major depression	Collaborative care with specially trained cancer nurse & psychiatrist supervision v enhanced usual care	Depression	Collaborative care more effective in reducing depression.
Syrjala (2008)	2 arm parallel group RCT	93 cancer patients with disease-related persistent pain	Pain training v nutrition training	Pain	Pain training more effective in reducing usual pain in the short-term.

Reference	Design	Sample	Interventions	Outcome of interest	Results
Vallance (2007)	4 arm parallel group RCT	377 breast cancer survivors	Standard public health recommendation for physical activity v breast cancer-specific physical activity print materials v step pedometer v breast cancer-specific physical activity print materials plus pedometer	Physical functioning	All breast cancer-specific groups were more effective than standard recommendations in increasing physical activity.
Wilkinson (2007)	2 arm parallel group RCT	288 cancer patients referred to complementary therapy services with clinical anxiety and/or depression	Aromatherapy massage v usual supportive care	Anxiety, depression	No significant difference between groups.

Table 4: Overview of review findings

PROBLEM	SOLUTIONS			
	Amount of research ¹	Quality of research ²	Scope	Conclusion and opportunity
Fatigue	Moderate	Moderate	Mainly mixed cancer samples and early stages of survivorship	Some evidence for the benefit of exercise during treatment, but inconclusive after treatment. Lack of long term follow-up. Evidence for drugs reducing fatigue for patients with anaemia. Weak evidence for CBT in treating fatigue.
Physical functioning/ Functional impairment	Low	Low	Mixed samples	Possible benefit of practising tai-chi but weak evidence base.
Pain	High	Moderate	Mainly mixed cancer samples and mixed stages of survivorship	Analgesics given by various routes effective in reducing pain. Limited evidence for the use of massage (short term benefits) and the evidence for complementary therapies, CBT and TENS are inconclusive.
Sexual functioning	Low	Low	Gynae and urological cancer samples at various survivorship stages	Limited evidence for the use of drug treatment and mechanical devices. The evidence for psychological treatment is inconclusive.
Cognitive functioning	-	-	-	No reviews or RCTs found.
Work/ employment	Low	Low	Breast cancer	No RCTs found in recent review.

PROBLEM	SOLUTIONS			
	Amount of research	Quality of research	Scope	Conclusion and opportunity
Finance	-	-	-	No reviews or RCTs found.
Depression	Moderate	Moderate	Mainly mixed samples but some focused on breast cancer	There is evidence for the effectiveness of antidepressants and CBT in reducing depression. There is modest evidence for group interventions, but the evidence for non-CBT treatments is weak or inconclusive.
Anxiety	Low	Low	Mainly mixed samples but some focused on breast cancer	There is modest evidence for treating anxiety with music therapy and CBT. The evidence for exercise was inconsistent. Participating in support groups can also reduce anxiety.
General distress	Moderate	Low	Mainly mixed samples but some focused on breast cancer	There is a moderate body of evidence for a range of psychological interventions (e.g. CBT and counselling) although strong recommendations cannot be made. The evidence supporting group interventions is inconsistent. Patient education looks to be a promising area of research.
Fear of recurrence	-	-	-	No reviews or RCTs found.
Social needs (function)	Moderate	Moderate	Marital relationships	Modest evidence for the effectiveness of support groups.
Social support	-	-	-	No reviews or RCTs found

¹ Amount of research defined as approximate number of trials included in the systematic reviews: Low = ≤ 5 RCTs, Moderate = 6 – 10 RCTs, High = > 10 RCTs.

² Quality of research: This refers to original systematic reviewers comments on the overall quality of RCTs included in their review.

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Appendix 1: Final Medline search strategy with RCT filter 10.7.09 3588 results (2.7.09 2058 results).

1. exp Neoplasms/ and exp Survivors/
2. ((cancer or oncology) adj (patient* or suffer* or surviv*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. 1 or 2
4. depression/
5. depress*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. exp anxiety disorders/
7. Adaptation, Psychological/
8. anxiety/ or guilt/ or panic/ or panic disorder/
9. fear/
10. anxi*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11. ((fear* or concern* or worry*) adj3 recurr*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. distress*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13. fatigue/
14. fatigue*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. pain*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. cogniti*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 3 and 17
19. randomized controlled trial.pt.
20. controlled clinical trial.pt.
21. randomized.ab.
22. placebo.ab.
23. drug therapy.fs.
24. randomly.ab.
25. trial.ab.
26. groups.ab.
27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. humans.sh.
29. 27 and 28
30. 29 and 18
31. limit 30 to english language
32. limit 31 to yr="1990 -Current"

