Management of cancer symptoms: pain, depression, and fatigue
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Authors' objectives
The objective was to determine the prevalence, method of assessment and the effectiveness of treatment for cancer-related pain, depression and fatigue in patients with cancer. This abstract will focus only on the effectiveness of treatment.

The section on the treatment of cancer-related pain is an update of the management of cancer-related pain (see Other Publications of Related Interest no.1). The specific objectives were as follows.

1. To determine the relative efficacy of current analgesics for cancer pain.

2. To determine whether different formulations and routes of administration are associated with different patient preferences or efficacy rates.

3. To determine the relative analgesic efficacy of palliative pharmacological and non-pharmacological cytotoxic or cytostatic therapy.

4. To determine the relative efficacy of current adjuvant physical or psychological treatments.

5. To determine the relative efficacy of current invasive surgical and nonsurgical treatments.

6. To evaluate the effectiveness of treatments for cancer-related pain associated with oral mucositis post-herpetic neuralgia.

Searching
Separate searches were performed for each area: cancer-related pain, depression and fatigue.

For cancer-related pain, an updated search was performed in MEDLINE, Cancerlit and the Cochrane Controlled Trials Register from December 1998 to June 2001 for English language studies (see Other Publications of Related Interest no.1). Additional studies were sought by checking the bibliographies of meta-analyses and selected review articles, and by consulting technical experts. Studies were excluded if they were in the previous report.

For cancer-related depression, PubMed, CINAHL and BIOSIS Previews were searched for English language studies; the search terms were provided. Additional studies were sought by checking the bibliographies of review articles and pertinent book chapters.

For cancer-related fatigue, MEDLINE, EMBASE, PsycINFO, BIOSIS Previews, NTIS, CINAHL and AMED were searched for English Language studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Existing meta-analyses were utilised in the review where available.

Specific interventions included in the review
Cancer-related pain.

Studies evaluating the relative efficacy of analgesics, the efficacy of adjuvant analgesics alone or as co-analgesics with opioids, palliative pharmacological (chemotherapy, bisphosphates or calcitonin) and non-pharmacological cytotoxic or...
static (radiation therapy or radionuclide) therapy, and adjuvant physical (reflexology and acupuncture) or psychological (cognitive-behavioural) treatments were eligible for inclusion. The dosage, duration, and route of administration of the treatment varied considerably between the included studies. Further details were provided in the report.

Cancer-related depression.

The inclusion criteria were not explicit. It appears that studies evaluating psychopharmacologic or alternative and complementary treatments, or meta-analyses of psychosocial interventions were eligible for inclusion. The psychopharmacologic treatments evaluated in the included studies were thioridazine, imipramine, methylprednisolone, mianserin, mazindol, alprazolam versus progressive muscle relaxation, amitriptyline, fluoxetine, desipramine, trazodone, clorazepate and paroxetine.

Cancer-related fatigue.

The inclusion criteria were not explicit. Studies evaluating support groups, psychotherapy relaxation therapy, exercise, massage, aerobic exercise, coping strategies, walking programmes and epoetin-alpha were evaluated in the included studies.

Participants included in the review
Studies of patients with a diagnosis of cancer who suffered pain, depression (major depressive disorder), or fatigue due to the cancer or its treatment were eligible for inclusion. Studies of patients with acute post-surgical pain were excluded. No restrictions were imposed on age, gender or ethnicity of the patients, the advancement (stage) of the cancer, or the presence of metastases.

Outcomes assessed in the review
The inclusion criteria were not explicit. The included studies reported a variety of outcome measures including pain relief and quality of life. Further details were given in the report.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies for inclusion. It was not stated whether the reviewers were blinded, or how any disagreements were resolved (see Other Publications of Related Interest no.1).

Assessment of study quality
The validity of each included study was assessed by assigning a grade according to the likelihood for bias in the internal validity and external validity, and the study size and, for cancer-related pain, the size of the treatment effect. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The data were extracted by one reviewer and checked by a second. It was not stated whether the reviewers were blinded, or how any disagreements were resolved.

For studies evaluating cancer-related pain, the data were used to derive a magnitude of effect for the difference between the control and experimental groups. For pain-related outcomes that used a visual analogue scale (VAS), the effect size assigned ranged from a large difference in effect (greater than 20 mm change on 0 to 100 mm VAS between control and experimental group) to no difference in effect (0 to 4 mm change on 0 to 100 mm VAS between control and experimental group). For studies that evaluated drug consumption, pain relief, and quality of life indices, pain management experts assigned an effect size ranging from large beneficial effect to no beneficial effect.

For studies evaluating cancer-related depression and fatigue, the results and effect between the control and experimental groups were extracted as reported in each of the included studies.

Methods of synthesis
How were the studies combined?
The studies were tabulated and presented in a narrative synthesis according to the different treatments evaluated in the included studies.

How were differences between studies investigated?
Information on the treatment type, study quality, results and effect of each included study were tabulated and compared.

Results of the review
Thirty-four RCTs for cancer-related pain, 12 RCTs and 3 meta-analyses for cancer-related depression, and 10 RCTs for cancer-related fatigue were included in the review. The total number of participants was unclear.

Only the main results are presented herein. Further analyses of cancer-related pain, depression and fatigue, and methodological quality are available in the full report.

Cancer-related pain.
The studies did not differentiate the relative efficacy of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) administered through various routes to patients with mild, moderate or severe cancer-related pain. An opioid dose-sparing effect was observed through the co-administration of NSAIDs; however, there was no consistent reduction in the side-effects. There was insufficient evidence to determine the relative efficacy of different NSAIDs, and no significant difference in analgesic benefit between NSAIDs and ‘weak’ opioids was found. Preliminary evidence suggested that oral transmucosal fentanyl citrate was superior to placebo in the treatment of breakthrough pain. No studies were found that evaluated the analgesic efficacy of NSAIDs selective for the cyclooxygenase-2 isozyme in the treatment of cancer pain.

There was no evidence of a difference in analgesic efficacy, side-effects or patient preference between different modes of administration or formulations.

Biphosphonates and radiation therapy were shown to be effective in reducing bone pain in patients receiving concurrent tumour-directed therapy. There was no real evidence of a benefit of chemotherapeutic or hormone therapy regimens.

Cognitive-behavioural treatment was shown to be effective in the treatment of cancer-related pain. In addition, hypnosis demonstrated beneficial results when used in adults and also to treat procedural and mucositis-related pain. No difference in effect was found in studies evaluating reflexology or acupuncture.

The use of neurolytic celiac plexus block was associated with pain relief in pancreatic and other visceral cancers. There was insufficient evidence to determine the effectiveness of spinally administered opioids or other agents, or ablative neurosurgical therapies such as cordotomy or rhizotomy. Cancer-related depression.

Each included study that evaluated the effectiveness of an antidepressant, conforming to usual practice, for greater than 4 weeks demonstrated significant improvements in depressive symptoms. Selective serotonin re-uptake inhibitors and tricyclic antidepressants were shown to be effective. In addition, the atypical antidepressants mianserin and trazodone demonstrated significant improvements in depressive symptoms.

Psychosocial interventions, including behavioural and cognitive counselling, psychoeducation and social support, demonstrated a mild to moderate effect in the treatment and/or prevention of depressive symptoms in patients with cancer (see Other Publications of Related Interest nos.2-3).

No controlled studies evaluating the efficacy of alternative or complementary therapy in the treatment of depression in cancer patients were found.

Cancer-related fatigue. The use of epoetin-alpha for chemotherapy-related anaemia significantly improved quality of life and fatigue in patients with cancer. Exercise programmes were shown to provide some improvement in fatigue in patients receiving radiation therapy; however, this was less clear in patients undergoing peripheral blood cell
transplantation. Psychosocial interventions also showed some benefit.

**Authors' conclusions**
The authors stated that pain, depressive symptoms and fatigue are prevalent among patients with cancer, and that efficacious treatment options are available. However, the paucity of rigorous evaluations of such treatments precludes the selection of optimum treatment regimens. The treatment of cancer-related fatigue is complicated by the need to establish factors that contribute towards the condition that can be successfully treated.

**CRD commentary**
The review addressed a broad range of questions encompassing the three cancer symptoms and several treatment alternatives. This contributed to the lack of explicit inclusion criteria for the outcomes, patient populations and interventions. In addition, it was implied that the review was restricted to RCTs but, when numerous studies were identified, published meta-analyses or studies of lower methodological quality were presented. The authors used procedures to minimise bias when selecting studies for inclusion and protected against errors in the data extraction process. However, these were not detailed in the current report, instead the reader was referred to the original report. The search for studies was extensive and sought to identify unpublished studies, although there was great potential for language bias since the data had to be published in the English language.

The presentation of the results in a narrative summary was appropriate, owing to the heterogeneity of the included studies, and study quality was assessed systematically. The summary of the data was limited and most of the studies were just described with a synthesis presented in the conclusions. The review offers an objective summary of the evidence pertaining to the treatment of cancer-related pain, depression and fatigue, and the recommendations for future research have been based on the evidence presented.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice. Instead, it was proposed that user organisations use the report as a basis for developing clinical guidelines.

Research: The authors stated that for pain, depression and fatigue, there is need for research in paediatric populations. The authors provided the following summaries for directions of future research.

**Cancer-related pain.**
Further methodologically robust studies with a greater number of patients and of longer duration are required, with cancer pain relief as the primary outcome. These studies should investigate the influence of age, gender, race, psychosocial context and cultural issues on pain relief. Further research is required to ascertain the most effective combination of drug and non-drug interventions. In addition, the route of administration needs to be assessed with regards to patient preference, comparative efficacy, and the use of initial or secondary agents or a combination. Systematic reviews of the best available evidence are required until the larger trials are accomplished.

**Cancer-related depression.**
The use of newer antidepressants and complementary and alternative treatments for depression co-morbid with cancer needs to be evaluated in studies of a minimum 6-week duration. The effectiveness of psychostimulants needs to be established for the treatment of depression, and further research is required to determine the role of antidepressants for the prevention of depression. Additional systematic reviews are required to evaluate the effectiveness of psychosocial therapy specifically for the treatment of depressive symptoms.

**Cancer-related fatigue.**
Additional studies are required to determine the effectiveness of educational programmes, psychosocial interventions and stimulant medications for the treatment of fatigue. Further observational and laboratory-based research is required to identify targets for interventions.
Funding
Agency for Healthcare Research and Quality, contract number 290-97-0019.

Bibliographic details

Original Paper URL
http://www.ahrq.gov/clinic/epcsums/csympsum.htm

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Depression /therapy; Fatigue /therapy; Neoplasms /psychology; Pain /therapy; Pain Measurement

AccessionNumber
12003008332

Date bibliographic record published
31/07/2004

Date abstract record published
31/07/2004

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.