Complete Summary

GUIDELINE TITLE

The management of dyspnea in cancer patients: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Viola R, Kiteley C, Lloyd N, Mackay JA, Wilson J, Wong R, Supportive Care Guidelines Group. The management of dyspnea in cancer patients: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Nov 6. 46 p. (Evidence-based series; no. 13-5). [64 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Dyspnea experienced during advanced cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology
Pharmacology
Pulmonary Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the evidence regarding the effectiveness of agents in four specific pharmacologic classes (opioids, phenothiazines, benzodiazepines, and systemic corticosteroids) for relieving dyspnea experienced by advanced cancer patients when the underlying cause of the dyspnea is not treatable or its specific treatment does not relieve the dyspnea

TARGET POPULATION

Adult, advanced cancer patients with dyspnea from any cause

Note: In general, for the purposes of this guideline, cancer is considered advanced when it has spread beyond the organ in which it started and is not curable.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Opioids
    - Systemic opioids by oral and parenteral routes
    - Nebulized morphine (recommended against)
2. Non-opioids
    - Phenothiazines
        - Oral promethazine
        - Parenteral promethazine (recommended against)
        - Prochlorperazine (not recommended)
        - Chlorpromazine and methotrimeprazine (no trials available to support or refute use)
    - Systemic corticosteroids (no trials available to support or refute use)
    - Benzodiazepines (not recommended)

MAJOR OUTCOMES CONSIDERED

Primary outcome of interest:

Dyspnea

Other outcomes of interest:

- Exercise tolerance
- Quality of life
- Symptomatic adverse effects
- Indicators of adverse effects, including forced expiratory volume in one second, oxygen saturation, and carbon dioxide tension

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (1966 to July, week 1, 2006), EMBASE (1980 through 2006, week 27), CINAHL (1982 through July, week 1 2006), HealthSTAR (1975 through May 2006), DARE (2006, 2nd Quarter), and the Cochrane Library (2006, Issue 2) databases were searched. Relevant articles were identified by combining the Medical subject heading (MeSH) "dyspnea" with each of the following phrases used as text words: "breathlessness", "shortness of breath", "respiratory distress", "breath and shortness", "breath and difficult". These terms were then combined with the following MeSH terms and with various text words for pharmacological agents: "narcotics", "analgesics, opioid", "phenothiazines", "antipsychotic agents, phenothiazine", "benzodiazepines", "chlordiazepoxide", "clorazepate dipotassium", "estazolam", "medazepam", "midazolam", "triazolam", "benzazepines" "anti-anxiety agents", "benzodiazepine", "adrenal cortex hormones", "hydrocortisone", "cortisone", "betamethasone", "dexamethasone", "prednisolone", "methylprednisolone", "triamcinolone", "prednisone", "fludrocortisone". These terms were then combined with the search terms for the following study designs and publication types: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, comparative studies, case-control studies, cohort studies, and cross-sectional studies. In addition, abstracts published in the conference proceedings of the American Society of Clinical Oncology (1995-2006) were searched for reports of new or ongoing trials. The reference lists from relevant articles were searched for additional trials, as were the reference lists from a sample of relevant review articles. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines.

Study Selection Criteria

Inclusion Criteria

Due to the lack of trials examining solely palliative care cancer populations, the inclusion criteria were expanded to include non-cancer patient populations. Articles were selected for inclusion in this systematic review of the evidence if they met all of the following criteria:

1. The study population included adult patients with any advanced disease experiencing dyspnea where the underlying cause of the dyspnea was not treatable or its specific treatment did not relieve the dyspnea.
2. One or more of the interventions included an opioid, phenothiazine, or benzodiazepine, administered by any route, or a systemic corticosteroid.
3. One of the outcomes reported was dyspnea as measured by visual analogue scale (VAS), Borg score, or some other patient-reported scale. Other outcomes of interest were exercise tolerance, quality of life (QOL), arterial oxygen saturation (SaO_2), measures of respiratory depression, forced expiratory volume in 1 second (FEV_1) and symptomatic adverse effects.
4. The article was a systematic review, meta-analysis, evidence-based practice guideline, or a fully published or abstract report of a randomized or non-randomized controlled study. Comparative studies, including prospective and retrospective cohort, case control, and cross sectional studies were eligible for inclusion.

Exclusion Criteria

Articles reporting studies of the management of dyspnea by treating specific underlying causes, such as by radiotherapy, chemotherapy, drainage of pleural fluid or treatment of bronchospasm, were excluded.

1. Studies of systemic corticosteroids in non-cancer populations were excluded since the mechanisms of action of these agents in those populations are unlikely to be generalizable to cancer patients.
2. Since translation resources were not available, articles in languages other than English were not included in the review nor searched for systematically.
3. Letters, comments and editorials were not considered.
4. Redundant publications of the same study were excluded. The most complete report of such a study was included, or the earliest report if the publications were identical.

NUMBER OF SOURCE DOCUMENTS

The evidence identified included two evidence-based practice guidelines, three systematic reviews, 23 fully published randomized controlled trials (RCTs), two abstracts of RCTs, and three fully published non-randomized trials.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The results of the opioid trials were not pooled for several reasons. There was significant heterogeneity between the trials (use of different measurement instruments, assessment situations, study populations, treatments, and treatment administration routes). In addition, the trials did not consistently report the type of data required for pooling continuous variables from crossover trials - paired analyses with means and standard deviations on the same measure. Although standardized mean differences for different measures could be combined, this method is questionable for combining post-treatment outcomes with change from baseline outcomes. The limited number of trials identified that evaluated benzodiazepines and phenothiazines precluded the pooling of data from trials assessing these interventions.

Randomized and Non-randomized Trials

Study Quality

Study quality was formally assessed using the Jadad et al scale, where each trial is assigned a score out of five based on the appropriateness of the methods of randomization and blinding and whether a statement on withdrawals was included. One physician and one or two methodologists independently evaluated each study. Discrepancies were discussed among the reviewers, and consensus was reached.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Supportive Care Guidelines Group (SCGG) Consensus

The draft evidence-based series report was reviewed by the 24 members of the SCGG in May 2006. Among the four members that provided additional comments on the report, there were two substantive suggestions.

One member indicated that it may be helpful to provide a definition of 'advanced cancer' in the report. However, the cancer trials included in this evidence-based series did not all specify cancer stage and since cancer staging varies by disease site, it was felt that a more specific definition of advanced cancer by the SCGG may be challenging. The American Cancer Society description of advanced cancer as "cancer that has grown beyond the organ where it first started" and that generally is not curable was considered sufficient and was added to the *Introduction* section of the *Systematic Review*.

Another SCGG member questioned whether benzodiazepines suppress anxiety associated with dyspnea and suggested they might be useful for such anxiety but not dyspnea. The evaluation of symptom clusters in cancer is a growing area of research and it is acknowledged that anxiety can occur along with dyspnea in cancer patients. Benzodiazepines may be a treatment option for anxiety in those circumstances and a statement to this effect has been added to the *Discussion* in Section 2 of the original guideline document; however, treatments for cancer-related anxiety have not been systematically reviewed in this report.

During final approval of the report by the SCGG in November 2006, two additional concerns were raised: one related to the possible association between systemic opioids and respiratory depression; the other involved the recommendation regarding promethazine, suggesting it be changed to recommend against the use of that drug because of the potential for local tissue toxicity with intramuscular or intravenous use.

Although the effect of opioids on measures of respiratory drive was statistically significant in a few studies, the differences were small from a clinical perspective and several studies did not detect an effect. Therefore, the report was revised to acknowledge that the clinical impact of opioids on respiratory measures was limited.

With regard to the promethazine recommendation, there is some evidence to suggest that the oral form of this drug may have a role in the management of dyspnea in cancer patients, although it is acknowledged that parenteral use is of concern. Therefore, the recommendation in favour of oral promethazine was retained, with a further recommendation that promethazine should not be used parenterally.

There was an additional suggestion to reorder the recommendations into groupings of "therapies recommended" and "therapies not recommended". The potential value of presenting recommendations in that format was acknowledged; however, given the range of drugs considered in the report, it was felt that the current emphasis on providing recommendations by drug class may be most useful overall.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Supportive Care Guidelines Group (SCGG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC).

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of the original guideline document and the review and approval of the report by the PEBC Report Approval Panel, the SCGG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Methods

Feedback was obtained through a survey of 165 practitioners in Ontario, including 61 palliative care physicians, 31 respirologists, 8 family physicians, 20 nurses, 15 medical oncologists, 15 radiation oncologists, and 15 surgeons. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was distributed by mail (47 practitioners) or electronically (118 practitioners) during the last week of June, 2006. Follow-up reminders were sent at 2-3 weeks (post card or e-mail reminder) and four weeks (complete package mailed again or e-mail reminder). The SCGG reviewed the results of the survey.

This report reflects the integration of feedback obtained through the external review process with final approval given by the SCGG and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Opioids

- Systemic opioids, by the oral or parenteral routes, can be used to manage dyspnea in advanced cancer patients.
- Nebulized morphine should not be used to treat dyspnea.

Phenothiazines, Benzodiazepines, and Systemic Corticosteroids

- Oral promethazine may be used to manage dyspnea, as a second-line agent if systemic opioids cannot be used or in addition to systemic opioids. Promethazine must not be used parenterally.
- Prochlorperazine is not recommended as a therapy for managing dyspnea.
- No comparative trials are available to support or refute the use of other phenothiazines, such as chlorpromazine and methotrimeprazine, for managing dyspnea.
- Benzodiazepines are not recommended for managing dyspnea.

- No comparative trials are available to support or refute the use of systemic corticosteroids for managing dyspnea in advanced cancer patients.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by evidence-based practice guidelines, systematic reviews, randomized controlled trials (RCTs), two abstracts of RCTs, and three fully published non-randomized trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Opioids

A systematic review included a meta-analysis of nebulized opioids and systemic opioids for treating dyspnea and concluded that oral and parenteral opioids could be used to treat dyspnea ($p=0.0006$), while the use of nebulized opioids could not be supported ($p=0.31$).

Systemic Morphine

- Four randomized studies of systemic opioids involved only cancer patients. Two studies of 9 and 10 patients compared systemic morphine to placebo and found a significant benefit of morphine for treating dyspnea. One study compared two systemic morphine doses for relieving dyspnea in 33 patients and reported no difference between doses. A single-blind study involving 101 patients compared the combination of morphine and the benzodiazepine midazolam to each agent alone and observed no significant differences in dyspnea intensity. In that same study, a significantly higher proportion of patients reported dyspnea relief at 24 hours with the combined treatment compared with morphine or midazolam alone, while at 48 hours the difference remained significant between only the combination and midazolam alone.
- The largest placebo-controlled study of systemic morphine, involving 48 participants (38 were evaluable), showed a benefit on dyspnea compared to placebo in a mixed population**,** but four other small systemic morphine studies in non-cancer patients were negative.

Systemic Dihydrocodeine

Systemic dihydrocodeine was found to be significantly more beneficial in reducing breathlessness compared to placebo in three trials involving non-cancer patients. The only other trial evaluating systemic dihydrocodeine found a dyspnea benefit

halfway into an exercise test, but the benefit was not maintained at peak exercise.

POTENTIAL HARMS

Symptomatic adverse effects of drowsiness, nausea and vomiting, and constipation were frequently reported in the opioid trials. Four studies showed no systemic opioid effects on measures of ventilation while three other studies reported clinically small, statistically significant effects. In two of these studies, respiratory rate was slightly lower with systemic opioids compared with placebo, and in two studies, carbon dioxide saturation was higher with systemic opioids compared with placebo or on pre-post testing.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- In cancer patients, dyspnea may co-exist with symptoms such as anxiety and panic. Treatment of co-existing symptoms was not considered in this guideline, although this may involve the use of some of the agents reviewed in this guideline.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Viola R, Kiteley C, Lloyd N, Mackay JA, Wilson J, Wong R, Supportive Care Guidelines Group. The management of dyspnea in cancer patients: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Nov 6. 46 p. (Evidence-based series; no. 13-5). [64 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Nov

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Supportive Care Guidelines Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Supportive Care Guidelines Group (SCGG) were asked to disclose any potential conflicts of interest and declared there were none.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

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