Management of chronic cough in patients receiving palliative care: Review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland

Bee Wee, Juliet Browning, Astrid Adams, Debbie Benson, Paul Howard, Gwen Klepping, Alex Molassiotis and David Taylor

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Management of chronic cough in patients receiving palliative care: Review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland

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Abstract

Background: Chronic cough is a disruptive and exhausting symptom, reported as very distressing in a quarter of those in their last year of life. Existing guidelines for management of chronic cough primarily deal with the commonest benign causes of cough: asthma; eosinophilic bronchitis; gastro-oesophageal reflux disease; rhinosinusitis.

Aim/design: To examine what literature evidence exists and formulate recommendations for managing chronic cough in patients with advanced, progressive, life-limiting illnesses.

Data sources: Electronic databases (MEDLINE, EMBASE, CINAHL, Cochrane Library, Google Scholar); hand-search; grey literature.

Results: Of 11 initially eligible studies, 5 provided evidence at level 2 or better. The small size of these studies, heterogeneity of study population and diversity of interventions and outcome measures used meant that comparison across studies and compilation of guidelines based on high-quality evidence was not possible. Pragmatic recommendations based on available evidence were formulated, drawing on the included studies and, in addition, extrapolating from two other well-designed studies involving patients with chronic cough. They also took into consideration convenience, toxicity and minimizing burden and harm of intervention, as well as considering the potential for disease-directed treatment and the possibility of pharmacological and co-existing benign causes of chronic cough.

Conclusions: These recommendations (Grade D) include simple linctus, therapeutic trial of sodium cromoglycate and then prescription of an opioid or opioid derivative (dextromethorphan, morphine or codeine). Further research is clearly and urgently required in this area for more effective approaches to managing cough, tested in trials that have sufficient size, power and validity.

Keywords

Antitussive agents, cough, palliative care, practice guideline, systematic review

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**Introduction**

Chronic cough, defined as a cough lasting more than eight weeks, is a distressing and debilitating problem. It is a presenting symptom in over 65% of people with lung cancer. It often persists, and has been reported as ‘very distressing’ in 22% of people with lung cancer and 26% of those with chronic lung disease in their last year of life.

Like pain, acute cough normally has a protective function, clearing mucus and foreign bodies from the larynx and lower respiratory tract. However, chronic cough is frequently socially disruptive and physically exhausting, and may exacerbate concurrent symptoms such as pain, breathlessness, insomnia and incontinence. Cachexia and generalized weakness, common in those near the end of life, may make the effort of coughing more exhausting and less effective.

The British Thoracic Society has produced comprehensive guidelines for the management of chronic cough, as have the European Respiratory Society and American College of Chest Physicians. All these necessarily focus on the commonest causes of chronic cough: asthma, non-asthmatic eosinophilic bronchitis, gastro-oesophageal reflux disease (GORD) and upper airways cough syndrome arising from rhinosinusitis. None of these guidelines specifically deal with the intractable cough related to advanced progressive cancer as well as non-malignant life-limiting illness. This paper reports on the findings of a task group, set up by the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland, to undertake a review of the evidence for pharmacological and non-pharmacological management of chronic cough in this group of patients and produce recommendations for clinical practice.

**Methods**

The task group was drawn from doctors, nurses and pharmacists in specialist palliative medicine and respiratory medicine. The task group met on two occasions: the first to agree a protocol for the literature review drafted by BW and JB; the second to discuss the quality of the evidence identified and to formulate recommendations relevant to the clinical practice of palliative medicine.

The inclusion criteria for studies were defined as follows.

- English language papers that reported on studies involving adults or children with advanced, progressive, life-limiting illnesses who had a chronic cough lasting more than eight weeks. Chronic obstructive pulmonary disease would be included, but not chronic cough related to asthma, eosinophilic bronchitis, GORD, chronic bronchorrhoea, trauma, congenital abnormalities, angiotensin-converting enzyme (ACE) inhibitors and opportunist infections in HIV.
- Studies using any therapeutic intervention: pharmacological or non-pharmacological agents; antitussives; disease-specific therapies.

The primary outcomes of interest were disappearance of the cough and/or objective or subjective change in the cough pattern (e.g. intensity or frequency). Secondary outcomes included change in quality of life resulting from change in symptoms associated with cough, number of different types of interventions needed to achieve a reduction in cough intensity and/or frequency and number of times an intervention had to be repeated to achieve or maintain a reduction in cough intensity and/or frequency.

Search terms used were ‘palliative’ (and a variety of terms relating to ‘palliative’) in combination with ‘antitussive’, ‘cough suppression’ and a range of therapies, for example, corticosteroids, codeine and opioids. Only papers published in English were included. A full list of the search terms is available in the appendix. Five electronic databases were searched: MEDLINE 1966–2010; EMBASE 1980–2010; CINAHL 1982–2010; Cochrane Library; Google Scholar. The reference lists of all relevant studies and reviews were hand-searched for additional studies. Investigators known to be conducting research in this area were asked for information relating to grey literature, including conference abstracts, theses and publications in non-indexed journals.

The literature search was conducted by JB, then the abstract of each potentially relevant paper independently screened by JB and one other member of the task group. Papers were excluded at this point if they clearly did not fit the inclusion criteria. The rest were read in full and recorded on a data extraction form, designed by BW and JB and based on the Critical Appraisal Skills Programme (CASP) tools. Information extracted from each paper included characteristics of trial participants (including age, diagnosis, stage and severity of disease), details of intervention (including dose, duration, frequency and whether or not there was placebo control), study design and type of outcome measure (including change or disappearance of cough frequency or severity, change in quality of life reported and number and times an intervention was required). If there was disagreement about eligibility between two reviewers and this could not be resolved following discussion, those papers would be brought to the final meeting of the task group for a wider discussion. The Cochrane Collaboration’s tool for assessing risk of bias would be used to evaluate bias within individual studies. A meta-analysis of the data would be carried out if the quality and size of studies identified allowed but it was acknowledged, from the start of this process, that this was unlikely, so the methodology for a meta-analysis was not explicitly set out at that point.

A qualitative summary of each of the included studies was prepared for consideration at the final meeting of the
task group, where the risk of bias within and across studies would be discussed. The grading system developed by the Scottish Intercollegiate Guidelines Network (SIGN) was used to allow recommendations to be graded according to the strength of the evidence⁷ (see Box 1 for SIGN grading) and formulated for clinical practice.

**Box 1. SIGN Guidelines.**⁷

**Levels of evidence:**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+++</td>
<td>High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case control or cohort studies, or high-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2−</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

**Grade of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review or RCT rated as 1+++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including of studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+++ or 1-</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including of studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
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</table>

**Results**

Sixty studies were identified; 11 were accepted for consideration (see Figure 1).

The remaining papers were reviews or unrelated to advanced, life-limiting illnesses. The details of the 11 studies assessed for eligibility are set out in Table 1.⁸⁻¹⁸

Of these, only five provided levels of evidence of 2 or above; the remainder were case reports or case series. There were three randomized controlled trials: Moroni et al.⁸ compared inhaled sodium cromoglycate with placebo; Matthys et al.⁹ used a cross-over design to compare dextromethorphan hydrobromide, codeine phosphate and placebo; Sevelius et al.¹⁰ gave his subjects different doses of codeine (7.5, 15, 30 or 60 mg) or placebo as a single daily dose on four consecutive days. Moroni et al.⁸ found sodium cromoglycate to be significantly more effective than placebo in reducing cough intensity. In Matthys et al.’s study,⁹ dextromethorphan was found to be more effective at reducing cough intensity than codeine (non-significant), and both were significantly more effective than placebo. Dextromethorphan was significantly preferred by patients. Sevelius et al.¹⁰ found an average reduction in six-hour post-codeine treatment cough counts of between 29% and 67%, compared to placebo, with a significant dose–response relationship. However, there was no relationship between the dose of codeine and patients’ evaluations of its effectiveness. All three studies were small, ranging from 12 to 20 in each and there was no power calculation reported.
<table>
<thead>
<tr>
<th>Lead author (year)</th>
<th>Type of study</th>
<th>Level of evidence (as per SIGN Guidelines)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Tools used</th>
<th>Risk of bias</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moroni (1996)</td>
<td>RCT (double-blind)</td>
<td>1 -</td>
<td>n = 20 non-small cell lung cancer Age: 52–74</td>
<td>Sodium cromoglycate vs. placebo</td>
<td>Cough reported on 0–4 scale daily (unvalidated)</td>
<td>Randomization procedure, allocation concealment and blinding procedures not clearly reported; outcome data adequately reported</td>
<td>Statistically significant reduction in cough scale with sodium cromoglycate ($p &lt; 0.001$)</td>
</tr>
<tr>
<td>Mathys (1983)</td>
<td>Randomized double-blinded cross-over trial</td>
<td>1 -</td>
<td>n = 16 pulmonary TB, bronchial carcinoma or obstructive lung disease Age: 25–74</td>
<td>Dextromethorphan vs. codeine vs. placebo (3 consecutive nights per arm of intervention)</td>
<td>Pressure transducer measured frequency &amp; amplitude on a 0–10 scale</td>
<td>Randomization procedure described – sequences of Latin square design; allocation concealment not clearly described; blinding procedure and outcome data adequately described</td>
<td>Dextromethorphan &amp; codeine both significantly more effective than placebo ($p &lt; 0.0001$) Dextromethorphan more effective than codeine (non-significant) Dextromethorphan significantly preferred by patients ($p &lt; 0.001$)</td>
</tr>
<tr>
<td>Sevelius (1971)</td>
<td>Randomized cross-over trial (double-blind)</td>
<td>1 -</td>
<td>n = 12 emphysema, chronic bronchitis, arteriosclerotic heart disease &amp; congestive heart failure (CHF) Age: 47–78</td>
<td>Codeine (7.5, 15, 30 or 60 mg) or lactose placebo: a different intervention administered as single daily dose on each of 4 consecutive days</td>
<td>Objective cough count using microphone &amp; recording system; patients’ subjective evaluations of effectiveness of each medication using a graded multiple choice questionnaire (daily)</td>
<td>Randomization method not explicitly reported but described as ‘pre-arranged’; incomplete block design used; blinding and outcome data adequately described</td>
<td>Cough counts reduced at all 4 doses of codeine: statistically significant difference between different doses and from placebo ($p &lt; 0.005$) Percentage reduction: 29% for 7.5 mg, 42% for 15 mg, 56% for 30 mg, 67% for 60 mg codeine</td>
</tr>
<tr>
<td>Homsi (2002)</td>
<td>Uncontrolled trial: Phase II study</td>
<td>2 -</td>
<td>n = 20 advanced cancer duration of cough: 2 days–3 years Median age: 63</td>
<td>Hydrocodone with dose titration</td>
<td>Assessed by phone call or bedside interview each day; last assessment 2 days after response (unvalidated)</td>
<td>Outcome data reported</td>
<td>Reduction in cough frequency (at least 50% improvement) in 19 (95%) Median best response = 70%</td>
</tr>
<tr>
<td>Lead author (year)</td>
<td>Type of study Level of evidence (as per SIGN Guidelines)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Tools used</td>
<td>Risk of bias</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Luporini (1998)</td>
<td>Uncontrolled randomized trial (double-blind)</td>
<td>n = 140 Primary lung cancer or metastatic cancer of the lungs</td>
<td>Levodropropizine vs. dihydrocodeine</td>
<td>Cough severity graded by patients &amp; investigators on a 0–5 scale (unvalidated) Recorded number of night awakenings due to cough</td>
<td>Randomization procedure and allocation concealment not clearly reported; outcome data adequately reported</td>
<td>Cough severity significantly reduced (p &lt; 0.05) in both groups (by approx. 2 points each). Number of night awakenings significantly decreased (p &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Burns (2000)</td>
<td>Case report</td>
<td>n = 1 Age: 76, male, metastatic malignant melanoma</td>
<td>Nebulized lidocaine &amp; transdermal scopolamine</td>
<td>Not stated</td>
<td>N/A</td>
<td>Patients' cough was reported to be considerably improved &amp; remained well controlled until death</td>
<td></td>
</tr>
<tr>
<td>Doona (1998)</td>
<td>Case report</td>
<td>n = 3 Adeno-carcinoma, non-small cell carcinoma, renal cell carcinoma</td>
<td>Benzonatate</td>
<td>Observation (unvalidated)</td>
<td>N/A</td>
<td>Cough resolved in all 3 cases</td>
<td></td>
</tr>
<tr>
<td>Estfan (2008)</td>
<td>Case report</td>
<td>n = 1 Age: 24, female; renal cell carcinoma</td>
<td>Oral diazepam (given for anxiety – coincidental report cough improvement)</td>
<td>Patient's description &amp; use of rescue hydrocodone for cough (unvalidated)</td>
<td>N/A</td>
<td>Improvement in cough, cough stopped over a 2-day period &amp; she did not use any rescue hydrocodone</td>
<td></td>
</tr>
<tr>
<td>Lingerfelt (2007)</td>
<td>Case report</td>
<td>n = 4 Carcinoma or CHF &amp; pulmonary hypertension</td>
<td>Nebulized lidocaine</td>
<td>Cough severity evaluated using the Edmonton Symptom Assessment System Index before &amp; after treatment</td>
<td>N/A</td>
<td>Improvement was seen in 2 out of 4 patients</td>
<td></td>
</tr>
<tr>
<td>Stein (1997)</td>
<td>Case report</td>
<td>n = 1 Age: 83, female Breast carcinoma with lung metastases</td>
<td>Nebulized morphine</td>
<td>Observation (unvalidated)</td>
<td>N/A</td>
<td>Cough resolved</td>
<td></td>
</tr>
<tr>
<td>Yoneda (1997)</td>
<td>Case report</td>
<td>n = 1 Age: 59, male Squamous cell carcinoma of proximal oesophagus</td>
<td>Insertion of stent placed across the gross area of tumour in case of oesophageal-bronchial fistula</td>
<td>Observation (unvalidated)</td>
<td>N/A</td>
<td>Cough resolved</td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial

Table 1. (Continued)
Table 2. Recommendations (Grade D).7

1. Consider whether there is potential for disease-directed treatment, e.g. chemotherapy, radiotherapy, corticosteroids, laser therapy, etc.
2. Review medications and consider whether appropriate to discontinue those which might be exacerbating cough, e.g. ACE inhibitors.
3. Consider the likelihood of co-existing benign causes of chronic cough, e.g. asthma, non-asthmatic eosinophilic bronchitis, gastro-oesophageal reflux disease (GORD) and upper airways cough syndrome arising from rhinosinusitis. Remember that presentations may be atypical, e.g. asthmatic cough without wheeze or reflux cough which is not acidic.
4. Prescribe simple linctus: a demulcent cough preparation for which there is no empirical evidence but it is simple and safe.
5. Therapeutic trial of sodium cromoglycate: evidence from one small randomized controlled trial (RCT)8 but relatively safe. Main limitation is the need to be able to use an inhaler device.
6. Prescribe an opioid or opioid derivative:
   a. Dextromethorphan: weak evidence6 but low toxicity and can be purchased in many countries without a medical prescription.
   b. Morphine: most recent evidence suggests significant benefit over placebo17 but this was in patients without significant lung disease. Start with 5 mg modified release morphine 12 hourly (or equivalent) unless patient is already on morphine for other reasons, then titrate upwards.
   c. Codeine: historical evidence weak and most recent evidence suggests no benefit over placebo,20 although this was in chronic obstructive pulmonary disease (COPD) patients with stable disease; probably should not choose this over the dextromethorphan or morphine.

Moroni et al.’s study9 had a relatively homogenous population: patients with locally advanced or unresectable metastatic non-small cell lung cancer. Patients with different respiratory and cardiac conditions were included in the other studies.

Two studies were considered to offer evidence at level 2. In an uncontrolled phase II study, Homsi et al.11 demonstrated a reduction in cough frequency with hydrocodone in patients with advanced cancer. In a much larger but uncontrolled study, Luporini et al.12 showed a significant reduction in cough severity in patients with primary or secondary lung cancer using either levodropropizine or dihydrocodeine. Reports of adverse effects were similar in both groups but the percentage of patients experiencing somnolence in those taking levodropropizine was significantly lower than those on dihydrocodeine.

In addition, two other studies were considered even though they did not meet the criteria for included studies.19,20 The first recruited from a regional cough clinic but excluded patients with significant lung disease; the second involved patients with chronic obstructive pulmonary disease who had stable disease. However, both merited consideration for two main reasons: (a) both were randomized double-blind placebo-controlled studies using morphine19 or codeine,20 which are widely used in palliative medicine; and (b) these patients had chronic idiopathic cough and, arguably, it might be reasonable to extrapolate these responses to patients with advanced cancer where reversible causes had already been managed. In the first study, 27 patients were randomized to slow-release morphine sulphate 5 mg twice daily for four weeks or placebo and outcomes were measured using the Leicester Cough Questionnaire. Those on the active arm showed a highly significant reduction (p < 0.01) by 40% in daily cough scores compared to baseline, whereas those on placebo showed no discernible difference from their baseline. The reduction in mean daily cough scores began in less than a week. The second was a cross-over study involving 21 patients given codeine phosphate 60 mg or matched placebo in random order, at the start of each cough recording (0 and 12 hours), between 7 and 10 days apart. Outcomes were measured using ambulatory cough recording, cough symptom score and visual analogue scale. There was no significant difference between codeine and placebo using any of these outcome measures.

Discussion

This review has yielded disappointingly little evidence, both in quantity and in quality, to support robust guidelines for the management of chronic cough in advanced, progressive disease. The three controlled randomized trials were small, involving a total of less than 50 patients between them. The patient population, interventions and outcome measures were so diverse that no attempt could be made at drawing valid conclusions across studies. It was clear that, at best, only Grade D recommendations could be formulated.

One limitation of this review was the restriction of the search to papers published in the English language only. In addition, the papers reviewed contained limited experimental and patient data, with incomplete and unclear reporting, making it difficult to evaluate the risk of bias within studies.

There was a clearly significant reduction in cough with sodium cromoglycate compared to placebo, but the sample size was small and the outcome measure used was an unvalidated tool. The evidence remains contradictory with respect to the efficacy of codeine phosphate. Sevelius et al.’s10 study showed a dose-related response to the drug compared to placebo, but Smith et al.20 showed no significant difference between codeine and placebo, using three different outcome measures, even at a dose of 60 mg, which was the same as the highest dose used in Sevelius et al.’s study.
In the light of such limited evidence, the task group agreed that other considerations, such as convenience, toxicity and minimizing the burden and harm of any intervention, had to be included when formulating recommendations for clinical practice. Although this carries a risk of introducing bias, we felt that, in our discussions, this was moderated by the multidisciplinary composition of the task group, its collective clinical experience and our intention to make the evidence and our decisions sufficiently explicit that the readers could draw their own conclusions. We also felt that such recommendations, with all their caveats, should be more helpful to the clinician than simply pointing out the lack of evidence in this area of care. The recommendations are set out in Table 2.

Conclusions

Despite the prevalence and distressing impact of chronic cough in patients with advanced, life-limiting illnesses, there is virtually no substantial evidence to support its management in clinical practice. In this paper, we have set out the findings of our literature review and formulated recommendations as best we can, based on what little evidence there is and our clinical judgement and experience. These are broadly consistent with other recent publications on cough in people with cancer\(^2\)\(^3\)\(^4\) and provide a useful current position for treating the symptom of chronic cough in patients with advanced cancer and non-malignant life-limiting conditions.

Further evidence is clearly required. It should be possible to develop robust studies using methodologies that have already been developed and tried in other patient populations. However, further research in this patient population is needed, in particular to test interventions for alleviating cough frequency, intensity and/or impact in the palliative care group.

Acknowledgements

We would like to acknowledge the constructive comments about this paper and its recommendations provided by Professor Alyn Morice and members of the Association for Palliative Medicine (APM) Science Committee.

1. BW and JB drafted protocol.
2. JB conducted literature search and prepared summary of studies.
3. JB, DB, AA, AM, DT, PH, GK and BW evaluated papers.
4. BW prepared the first draft of paper and all commented.

Conflict of interest statement

None declared.

Funding

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References


**Appendix: search strategy**

**Databases searched:**
- MEDLINE 1966–May 2010
- EMBASE 1980–May 2010
- CINAHL 1982–May 2010
- Cochrane Library
- Google Scholar

**Search terms:**

#1 – Palliative care AND close death AND near death AND terminal care AND hospice care AND terminally ill AND advanced-stage cancer

#1 AND cough AND Dextromethorphan
#1 AND cough AND Hydrocodone
#1 AND cough AND dihydrocodeine
#1 AND cough AND codeine
#1 AND cough AND morphine sulphate
#1 AND cough AND antitussive drugs
#1 AND cough AND levodropropizine
#1 AND cough AND cllobutinol
#1 AND cough AND cannaboid agonist
#1 AND cough AND GABA agonist
#1 AND cough AND menthol
#1 AND cough AND antihistamines
#1 AND cough AND vanillloid antagonist
#1 AND cough AND potassium opener
#1 AND cough AND sodium cromoglycate
#1 AND cough AND benzonatate
#1 AND cough AND (lidocaine OR lignocaine OR bupivacaaine OR local anaesthesia OR local anaesthetics)
#1 AND cough AND neurokinin antagonists
#1 AND cough AND protussives
#1 AND cough AND nebulised saline
#1 AND cough AND guaifenesin
#1 AND cough AND carbocisteine
#1 AND cough AND placebo
#1 AND cough AND re-positioning
#1 AND cough AND suction
#1 AND cough AND physical therapy

#1 AND cough AND humidity
#1 AND cough AND antitussive
#1 AND cough AND antitussive
#1 AND cough AND physiotherapy

#2 Palliat* AND close death OR near death OR hospice OR terminal* OR advanced cancer OR end PRE/1 of PRE/1 life OR end-stage

#2 AND (cough OR bronchhhoea) AND proton-pump inhibitors
#2 AND (cough OR bronchhorrhea) AND corticosteroids
#2 AND (cough OR bronchhorrhoea) AND centrally acting antitussives
#2 AND (cough OR bronchhorrhoea) AND dextromethorphan
#2 AND (cough OR bronchhorrhoea) AND hydrocodone
#2 AND (cough OR bronchhorrhoea) AND codeine
#2 AND (cough OR bronchhorrhoea) AND opioids
#2 AND (cough OR bronchhorrhoea) AND levodropropizine
#2 AND (cough OR bronchhorrhoea) AND cllobutinol
#2 AND (cough OR bronchhorrhoea) AND cannaboid receptor agonists
#2 AND (cough OR bronchhorrhoea) AND GABA receptor agonist
#2 AND (cough OR bronchhorrhoea) AND menthol
#2 AND (cough OR bronchhorrhoea) AND antihistamine
#2 AND (cough OR bronchhorrhoea) AND dextromethorphan

#2 AND (cough OR bronchhorrhoea) AND SSRIs
#2 AND (cough OR bronchhorrhoea) AND transient receptor potential vanilloid 1 receptor antagonist
#2 AND (cough OR bronchhorrhoea) AND potassium channel openers
#2 AND (cough OR bronchhorrhoea) AND peripherally acting antitussives
#2 AND (cough OR bronchhorrhoea) AND sodium cromoglycate

#2 AND (cough OR bronchhorrhoea) AND benzonatate
#2 AND (cough OR bronchhorrhoea) AND local anaesthetics
#2 AND (cough OR bronchhorrhoea) AND bupivacaine
#2 AND (cough OR bronchhorrhoea) AND lidocaine
#2 AND (cough OR bronchhorrhoea) AND neurokinin antagonists
#2 AND (cough OR bronchhorrhoea) AND mucolytics
#2 AND (cough OR bronchhorrhoea) AND nebulised saline
#2 AND (cough OR bronchhorrhoea) AND guaifenesin
#2 AND (cough OR bronchhorrhoea) AND carbocisteine
#2 AND (cough OR bronchhorrhoea) AND mecyxten
#2 AND (cough OR bronchhorrhoea) AND complementary therapy
#2 AND (cough OR bronchhorrhoea) AND placebo
#2 AND (cough OR bronchhorrhoea) AND re-positioning
#2 AND (cough OR bronchhorrhoea) AND suction
#2 AND (cough OR bronchhorrhoea) AND physical therapy
#2 AND (cough OR bronchhorrhoea) AND humidity