Interventions for cough in cancer (Review)

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[Intervention Review]

Interventions for cough in cancer

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ABSTRACT

Background

Cough is a common symptom in patients with malignancies, especially in patients with lung cancer. Cough is not well controlled in clinical practice and clinicians have few management options to treat it.

Objectives

The primary objective of this review was to determine the effectiveness of interventions, both pharmacological and non-pharmacological, (other than chemotherapy and external beam radiotherapy) in the management of cough in malignant disease (especially in lung cancer).

Search strategy

Databases searched included: The Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effectiveness (DARE) (*The Cochrane Library* issue 4, 2009); MEDLINE (1966 to May 2010); EMBASE (1980 to May 2010); CINAHL (1980 to May 2010); PSYCHINFO (1980 to May 2010); AMED (1985 to May 2010); SIGLE (1980 to May 2010); British Nursing Index (1985 to May 2010); CancerLit (1975 to May 2010). We searched for cough suppressants, antitussives and other drugs with antitussive activity as well as non-pharmacological interventions (see Appendices 1-4 for search terms).

Selection criteria

We selected randomised controlled trials (RCTs) and clinical trials (quasi-experimental trials, and trials where there is a comparison group but no mention of randomisation) in participants with primary or metastatic lung cancer or other cancers.

Data collection and analysis

Two review authors independently assessed titles and abstracts of all studies, and extracted data from all selected studies before reaching consensus. A third review author arbitrated with any disagreement. Meta-analysis was not attempted due to the heterogeneity of studies.

Main results

Seventeen studies met inclusion criteria and examined either brachytherapy, laser or photodynamic therapy (eight studies) or a variety of pharmacological therapies (nine studies). Overall, there was absence of credible evidence and the majority of studies were of low methodological quality and high risk of bias. Brachytherapy seemed to improve cough in a variety of doses in selected participants, suggesting that possibly the lowest effective dose should be used to minimise side effects. Photodynamic therapy was examined in one

study, and while improvements in cough were observed, its role over other therapies for cough is unclear. Some indication of effect was observed with morphine, codeine, dihydrocodeine, levodropropizine, sodium cromoglycate and butamirate citrate linctus (cough syrup), although all studies had significant risk of bias.

Authors' conclusions

No practice recommendations could be drawn from this review. There is an urgent need to increase the number and quality of studies evaluating the effects of interventions in the management of cough in cancer.

PLAIN LANGUAGE SUMMARY

Interventions for cough in patients with cancer

Cough is a distressing symptom in patients with cancer and difficult to manage in practice. Hence, the aim of this review is to assess and synthesise the available literature in the management of cough in cancer patients, in order to improve on practice recommendations. Studies with chemotherapy or radiotherapy were excluded. An extensive literature search yielded 17 studies for evaluation. Eight of them were about the use of brachytherapy (a technique where a radiation source is placed inside the bronchus in the lung or next to the area requiring treatment), use of laser resection or photodynamic therapy (a treatment that uses a drug plus a special type of light to kill cancer cells). Nine more studies assessed the effects of a number of different medication, including codeine and morphine. Overall, the research was of poor quality with significant methodological problems, hence no credible evidence is available in the literature to guide practice. Acknowledging these limitations, brachytherapy was found to be helpful in a variety of radiation doses in selected patients. Also some pharmacological treatments were found to be helpful particularly with regards to morphine, codeine, dihydrocodeine, levodropropizine, sodium cromoglycate and butamirate citrate linctus (a cough syrup), although all studies had significant risk of bias and some reported side effects. No practice recommendations could be drawn from this review. There is an urgent need to increase the number and quality of studies evaluating the effects of interventions in the management of cough in cancer.

BACKGROUND

Description of the condition

Cough and breathlessness are the two of the most common symptoms reported by lung cancer patients, and can be distressing to patients (Kvale 2003). Cough can be dry, or associated with sputum production (wet cough). Cough is present in more than 65% of patients with advanced lung disease, and may exacerbate breathlessness (Kvale 2006; Watson 2005). Cough in malignant disease can be the result of cancer progression with lung metastasis (spread of tumour(s)), complications from cancer, or may be treatment-related (Homsí 2001). For example, certain chemotherapeutic drugs, such as bleomycin and methotrexate, can induce cough. Some of the other key triggers for inducing cough include airway involvement, pleural effusion or pleural involvement, radiation therapy, and superior vena cava syndrome (Homsí 2001). Although the volume of literature concerning the management of breathlessness in lung cancer patients is increasing, cough has received minimal attention, despite the fact that it can be distressing, lead to decreased quality of life, and sleep disturbances (Watson

2005). This may be the case as patients find breathlessness more distressing than cough (the latter symptom being associated with smoking in the past and the stigma of such behaviour), minimal investment from the industry, limited cooperation between respiratory and oncology clinicians, and the limited management options available.

Description of the intervention

Management options for cough in malignant disease are few, and high quality evidence of effectiveness for any treatment is scarce. Lung cancer accounts for the most common diagnosis linked with cough. While surgery for early stage non-small cell lung cancer (NSCLC) may significantly improve cough, this is not an option for the majority of lung cancer patients, as they are diagnosed at an advanced stage. Palliative chemotherapy and radiation therapy can lead to improvements in a range of symptoms including cough (Numico 2001; Thatcher 1997; Vansteenkiste 2003). Pharmacological treatments are largely based on the use of antitussive drugs (cough suppressants) - opioids or non-opioids - for which

the evidence-base is minimal (Kvale 2006). Slow-release morphine has been reported to improve intractable cough, and the side effects of constipation and drowsiness from the use of morphine can be tolerated well (Chung 2008). Furthermore, Chung 2008 has also reported that some centrally acting drugs, such as paroxetine, gabapentin, carbamazepine and amitriptyline (more commonly used to treat epilepsy and mood disorders), have treated chronic cough successfully, although the evidence of their effectiveness in lung cancer-related cough is minimal. Benzonatate, clobutinol, dihydrocodeine, hydrocodone and levodropropizine may be the only antitussives studied in the context of advanced cancer (Homsí 2001), but antitussives are far from effective for managing chronic cough (Chung 2007), and better management approaches are needed for these patients.

Non-pharmacological interventions may also have a role in the management of chronic cough. Evidence is emerging for the efficacy of behavioural approaches (arising from speech pathology interventions) for treating it, though the role of such treatments is not clearly understood (Vertigan 2006). In a randomised trial of chronic cough patients, speech pathology training appeared to reduce cough significantly (Vertigan 2006). Vocal hygiene strategies have the potential to reduce cough and throat clearing in people with voice disorders, and such behavioural exercises may be useful in cancer patients who are experiencing cough, although the literature in this field is only just emerging. They can include pursed lip breathing, replacing cough with swallowing, avoiding smoking, avoiding mouth breathing, minimising the consumption of alcohol and caffeine or increasing water intake/steam inhalation. Since laryngectomy patients have also benefited from heat and moisture exchangers (Ackerstaff 2003), these studies suggest a potential role for non-pharmacological interventions in the management of chronic cough. Nevertheless, there is a lack of discussion in the literature about mechanisms by which such non-pharmacological interventions might improve cough, and, at present, our understanding in this area is minimal.

Why it is important to do this review

It is evident that cough in advanced cancer is not well controlled (Homsí 2001), and, currently, clinicians have few options to use in its management. There is an urgent need to evaluate the available evidence on the management of cough in cancer, in order to provide evidence-based recommendations for the management of this difficult symptom in clinical practice and provide some direction for future research.

OBJECTIVES

The objectives of this review are to determine the effectiveness of interventions, both pharmacological and non-pharmacological, (other than chemotherapy and external beam radiotherapy)

in the management of cough in malignant disease (especially in lung cancer) and assess any adverse effects from the use of these interventions.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs).
- Clinical trials (quasi-experimental trials, and trials where there is a comparison group but no mention of randomisation). These types of studies are included, as it is evident that few high quality RCTs have investigated the management of cough in malignant disease, and these will serve to highlight some promising treatments that will need further evaluation.

Types of participants

Adult participants (over 18 years of age) of either gender with malignant disease experiencing cough or coughing, or dry cough, or nocturnal wet cough, or wet cough in participants too weak to expectorate properly due to (primary or metastatic) lung cancer or other malignancies, including cough after insertion of a bronchial stent, in any clinical setting. Participants with malignant disease who have cough due to chest infections are excluded.

Types of interventions

Pharmacological and non-pharmacological interventions excluding chemotherapy and external beam radiotherapy.

1. Pharmacological interventions

Pharmacological interventions include any medicinal product or substance as classified by the EU directive 2001/83/EEC. These can include cough suppressants and antitussive drugs (including opioids), corticosteroids, demulcents (drugs that soothe), or nebulised local anaesthetics.

2. Non-pharmacological interventions

Non-pharmacological interventions included any invasive or non-invasive interventions that are not classified as medicinal products in the above-mentioned EU directive, and can include drainage of pleural effusions, complementary therapies (i.e. acupuncture or use of menthol and eucalyptus), brachytherapy (radiation therapy where radioactive materials are in direct contact with the tissue

being treated), photodynamic therapy (using light to kill cancer cells), physiotherapy, education, or self management. Interventions should have a comparator group (placebo, another substance or usual care).

Chemotherapy studies are excluded from this review, as there are a significant number of publications with a number of chemotherapy regimens, where symptoms and quality of life were secondary outcomes, that showed improvements in symptoms (i.e. Clegg 2001; Natalie 2004; Reck 2005; Thatcher 1997). Radiotherapy (external beam) for cough is also excluded from this review, as a Cochrane review has been published on the topic, showing it has positive effects (Lester 2006).

The review included studies from all cancers, as cough can be a symptom in non-lung primary cancers with metastatic lung disease, or in other non-lung cancers as a result of their treatment, although this is a less common occurrence.

Types of outcome measures

Primary outcomes

The primary outcome is subjective or objective improvement in cough frequency, severity, or alleviation of distress.

Secondary outcomes

Secondary outcomes include quality of life (measured by validated scales, including the EORTC-QOL-C30, FACT-G; WHOQOL scale) or symptom scores.

Search methods for identification of studies

Electronic searches

The following databases were searched:

- Databases on *The Cochrane Library*, including The Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effectiveness (DARE) (*The Cochrane Library* issue 4, 2009);
- MEDLINE (1966 to 10th of May 2010);
- EMBASE (1980 to 10th of May 2010);
- CINAHL (1980 to 10th of May 2010);
- PSYCHINFO (1980 to 10th of May 2010);
- AMED (1985 to 10th of May 2010);
- SIGLE (1980 to 10th of May 2010);
- British Nursing Index (1985 to 10th of May 2010);
- CancerLit (1975 to 10th of May 2010).

A scoping search using broad terms and several databases, as well as consultation with clinicians, contributed to the development of the search terms shown in Appendices 1-4. We searched for

cough suppressants, antitussives and other drugs with antitussive activity as well as non-pharmacological interventions. Please see the MEDLINE search strategy in [Appendix 1](#), which was adapted as appropriate for the other databases searched for this review (Appendices 2-4).

While we incorporated a large number of search terms in this review, we did not test the sensitivity and specificity of our search terms. As there is always the risk of overlooking when exhaustive terms are used, we re-ran the search using a shortlist of broad terms around cough and cancer through the MEDLINE database and compared the results of this search with the initial more exhaustive one. However, this search yielded no new papers. We have also searched the reference lists of reviews on cough (cancer and non-cancer focus) as well as case reports. Searching the grey literature identified no relevant theses or conference abstracts. Hence, all the above make us confident that we have not overlooked any important articles in the field.

Searching other resources

Hand searching and personal contact

The reference list of all relevant studies were checked for identification of additional studies. Hand searching further included key journals, such as *Cough*, *Lung Cancer*, *Brachytherapy*, and *Supportive Care in Cancer*. Authors of the main studies were contacted to find out about any unpublished data or grey literature. Excluded studies were documented separately in the 'Characteristics of excluded studies'. We have also communicated with key authors of cough studies in the respiratory field, who confirmed that they were not aware of other studies.

Language

There were no language restrictions.

Data collection and analysis

Selection of studies

Titles and abstracts of identified studies were reviewed by two review authors independently, as was the full text of all potentially relevant studies. Any disagreements were resolved after discussion with the rest of the review team, which consisted of five researchers.

Assessment of methodological quality

The Cochrane Risk-of-Bias tool was used to assess the methodological quality in the studies. This tool assists review authors to make a judgement (yes, no or unclear) in six areas, including

method of generating allocation sequence, allocation concealment, blinding, reporting of incomplete outcome data, selective outcome reporting and other sources of bias. Methodological quality was assessed independently by two review authors. An Oxford Quality score was assigned for each study (Jadad 1996). This is a score that runs from zero to five, with points assigned for randomisation, blinding and follow up or losses. Two review authors considered each item of the tool for each potential study, with the aim of reaching consensus agreement. Any disagreements were arbitrated by a third review author.

Data extraction

A data extraction form was designed and two review authors extracted data independently before reviewing their results to reach consensus. A third review author verified a random sample of one-quarter of the forms. Data extracted included:

- publication details,
- study aim,
- study design,
- sample size and patient characteristics,
- adverse effects reported,
- method of assessing cough,
- type of intervention,
- setting (outpatient/inpatient),
- outcome measures,
- withdrawals and dropouts,
- handling of missing data,
- study results,
- follow-up data,
- any economic data,
- any patient narrative comments.

All data extracted from the studies was entered into the RevMan 5 software.

Data analysis

The findings were interpreted within the framework of a narrative synthesis, as the studies were too heterogeneous, with regard to interventions and outcomes, to permit meta-analysis. RR and number-needed-to-treat-to-benefit (NNTs) were not used, as numerical aggregation of the data was not possible, given the broad range of the subject matter and the significant heterogeneity of material. Hence, a narrative synthesis of the interventions was used.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Please see the '[Characteristics of included studies](#)' table for full information on the included studies. Overall, the literature searches yielded 1132 studies. Studies were excluded because they were primarily case studies (n = 299) or reviews (n = 354). Other studies were excluded because the sample involved paediatric participants (n = 32) or non-cancer participants (n = 197). A further 16 studies were excluded as they were laboratory studies, 106 because they were unrelated to cough and 43 because the intervention was chemotherapy or external beam radiotherapy. Eighty-five studies were assessed in more detail by looking at the full text.

In total seventeen studies fulfilled the review's inclusion criteria, and included 1390 participants (from which 1231 were cancer patients, primarily with a diagnosis of lung cancer). The median sample size of cancer patients in these studies was 68 participants (range = 9 to 342). The reasons for exclusion of the remaining 68 studies are shown in the '[Characteristics of excluded studies](#)'. Studies included in the review were categorised into two broad areas, one reporting results from Brachytherapy, Laser therapy and Photodynamic therapy, and the other reporting results from pharmacological studies. There was no study identified that reported a non-pharmacological intervention (other than brachytherapy, laser and photodynamic therapy).

Risk of bias in included studies

The risk of bias was high in all studies, with only one study reporting randomisation ([Diaz-Jimenez 1999](#)), while the vast majority of studies were unblinded and did not report data on attrition.

Effects of interventions

A. Brachytherapy, Laser therapy and Photodynamic therapy

Eight studies were examined under this category. [Canak 2006](#) carried out a comparative study of laser resection and laser resection plus brachytherapy in 64 lung cancer patients. Cough was decreased by 25% in the former group and by 50% in the latter group, suggesting that the combined treatment was more effective for this group of primarily male and younger participants. Photodynamic therapy was tested in one study ([Diaz-Jimenez 1999](#)), showing similar results in relation to cough between the photodynamic and laser therapy groups, albeit with prolonged survival in the photodynamic group. Nevertheless, the advantage of photodynamic therapy over other available palliation approaches remains to be proven. Several studies have used a variety of endobronchial brachytherapy doses and a variety of distances from the tumour, all showing similar results and improvements in cough.

16 Gy in two fractions, 10 Gy in a single fraction or 15 Gy in a single fraction had similar outcomes (Mallick 2006). In the latter study, endobronchial symptoms were palliated and the duration of response was satisfactorily prolonged with significant improvement seen in quality of life. However, the study did not show any significant difference in the treatment arms (possibly due to the small sample); therefore the optimal dose, fractionation and combination with external radiation are still open to debate. Arm C had shorter duration of symptom palliation, though it achieved comparable rates of palliation of all symptoms and objective signs and it could be a potential treatment for patients with poor performance status. Another study compared 10 Gy in a single fraction, 14 Gy in two fractions or 15 Gy in three fractions and also found similar improvement (Muto 2000), also showing that the smallest irradiated volume and a fractionated HDRBT are associated with fewer side effects. 5 Gy (and 4 Gy for a small number of participants) were also effective in another small scale study of 30 participants (Nori 1993), showing that excellent clinical response with minimal morbidity can be achieved by reducing the dose per fraction delivered by HDR brachytherapy. 24 Gy over three fractions weekly also resulted in improvements in another small scale study, with peripheral tumours showing a better response than central tumours (Ofiara 1997). Speiser 1993 tested 10 Gy in a single fraction at 5 mm depth, 10 Gy in 10 mm depth or 7.5 Gy at 10 mm depth, all in single fractions and again found similar improvement in the three doses. The conclusion from this study was that the use of high dose rate remote afterloading brachytherapy provides excellent palliation in a group of patients where cure is either not attainable or has a low probability, and palliation should be the principle goal of therapy for patients with such intraluminal neoplastic disease. Tredaniel 1994 tested brachytherapy as the sole therapy, using 7 Gy over two or three fractions and showed that this was an effective palliation method for cough, particularly in small tumours and in limited disease. The authors concluded that effective remission of endobronchial tumours can be achieved with HDR endobronchial brachytherapy used as the sole therapy, in carefully selected patients who have small tumours, limited to bronchial lumen/wall without adjacent parenchymal extension or metastatic disease and that duration of response and survival rates are similar to those seen in conventional treatment, however, these benefits are achieved with less expense and without major complications.

The above results show that there is no standard dose of brachytherapy, as all doses resulted in similar outcomes for cough. This may indicate that the lowest dose should be preferred, as it can have a good response and a lower number of adverse reactions. The studies in this category were, however, of low quality, with five out of the seven studies receiving a '0' Jadad score and with an increased risk of bias. Often it was difficult to understand exactly what the investigators did or whether some of these were retrospective audits of treated patients presented in a research article format. Attempts to communicate with authors were difficult, as

many of these studies were old and current author details could not be located. The measurement of cough was far from perfect, with only a couple of studies using a standardised index of cough, while others examined presence of symptoms (including cough), raising questions about the reliability and validity of these assessments.

B. Pharmacological treatments

Nine studies met the inclusion criteria and were included under the category of pharmacological treatments. All but one study had a small sample size (mean = 59) and half of them included mixed samples of patients with a variety of pulmonary diseases, with lung cancer being a small proportion of these participants (data was extrapolated for cancer patients only). No studies used a validated method of measuring cough, all of them relying on patient self-reports of single-item scales assessing frequency, duration and/or intensity of cough, or on physician estimates of improvement. In some cases, reporting of data was limited and occasionally key data were not reported or were summarised under a broad comment from the investigator(s). Jadad scores were generally low (see 'Characteristics of included studies' table).

Acknowledging the above limitations and biases, the products tested included hydropropizine and oxadiazol (Boselli 1972), butamirate citrate linctus (Charpin 1990), a mixture of codeine with phenyltoloxamine and dihydrocodeine (Dotti 1970), two different Chinese herbal preparations (Koichiro 2002; Tao 2003), morphine and codeine (Kleibel 1982), levodropropizine and dihydrocodeine (Luporini 1998), sodium cromoglycate (Moroni 1996) and dihydrocodeine (Tansini 1971). The earliest study (Dotti 1970) initially assessed the tolerability of a product containing the equivalent of 30 mg codeine and 10 mg phenyltoloxamine in a mixed sample of participants with pulmonary diseases and found 'good/excellent' tolerance in all participants. The investigators then continued testing this mixture against another one that contained 5 mg dihydrocodeine, twice daily. The results suggest that the mixture containing codeine was the more effective one (Dotti 1970). While authors stated that the sample included 13 participants with lung cancer, data from only five participants could be seen in the article; the author could not be located for clarification. Another study from the early seventies assessed the effect of dihydrocodeine 10 to 20 drops t.i.d (three times daily) (25 drops = 10 mg) (N = 40, n of cancer patients = 9) and found that dihydrocodeine was more effective than placebo (Tansini 1971). The third study from the seventies (Boselli 1972) used a mixed sample of participants (n of patients with lung cancer = 12) to assess the effect of hydropropizine or oxadiazol. The results supported the effectiveness of hydropropizine, although this group of participants experienced a higher sedative effect and more, albeit mild, nausea.

The two Chinese herbal studies tested the effects of two oral herbal combinations (Fei Tong in the first and TJ-29 in the second (Tao

2003; Koichiro 2002). The first study assessed the herbal combination against prednisolone and found that the herbal combinations produced better results than the steroids, while the second study, which had cough as a secondary outcome, found no difference with a historical control group (unspecified treatment). The effects of levodropropizine (equivalent dose to 75 mg) and dihydrocodeine (equivalent dose of 10 mg) were assessed in another study through patient and physician reports, and both were found to be equally effective, although the sedative effect of dihydrocodeine was higher at 22% over 8% (Luporini 1998). A morphine derivative in another study was found to be as effective as codeine capsules, although the dose for both was unclear (Kleibel 1982). In a small study of 20 participants, sodium cromoglycate (two puffs, 40 mg) was found to be more effective than placebo, however, typically needing 36 to 48 hours before any effects could be observed (Moroni 1996). The latter study, however, had too few patients to make a strong statement of the treatment effect. Also, if patients had an underlying respiratory condition (i.e. asthma) it could explain the effect of sodium cromoglycate, but this information was not collected. Finally, a study using a mixed sample of participants (N = 67, n of cancer patients = 14) tested the effects of butamirate citrate linctus against clobutinol (Charpin 1990). While the results for the whole sample were not significant between the two groups, with both groups showing improvements in the severity and frequency of cough, when the analysis was carried out for cancer patients only, a significant difference was observed in favour of butamirate linctus.

DISCUSSION

This review has shown the almost complete absence of any credible evidence in the management of cough in cancer patients. This is surprising given the high prevalence of this symptom in clinical practice; our own data on cough prevalence using the Memorial Symptom Assessment Scale in a heterogeneous sample of 100 cancer patients assessed at the beginning of treatment and 3, 6 and 12 months later showed that 42.9%, 39.2%, 35.1% and 36.1% of patients respectively complained of cough, in similar numbers to breathlessness, albeit the cough was less distressing than breathlessness; the prevalence in the lung cancer subgroup was double that of the whole sample (Molassiotis, in press). Most research was of poor quality and conducted in the 1970s. Little up-to-date evidence is available.

While the review established the overall usefulness of brachytherapy in selected populations of lung cancer patients, this is a specialised invasive intervention available only in a few specialist centres. Doses varied from study to study, although it appears that 10 Gy in a single fraction, two fractions of 7 to 8 Gy or three fractions of 5 Gy could lead to similar improvements and had a similar adverse event profile. This data concurs with another well-

conducted pre- and post-test single arm study (N=95) showing symptom improvements with brachytherapy of 7.5 Gy at 10 mm in three fractions once/week or 10 Gy twice, with cough showing complete resolution in centrally-located tumours and significant improvement in peripheral lung tumours (Celebioglu 2002). Similarly, another phase II study of three treatments with 5 Gy each showed an improvement of 42.8% (Anacak 2001) [both these two studies were excluded from our review because they were single arm studies]. Furthermore, a systematic review of high-dose rate brachytherapy in the palliation of symptoms in non-small lung cancer, primarily including single arm trials (that were excluded in the current review), confirmed that: a) for previously untreated symptomatic endobronchial non-small lung cancer, external beam radiation is more effective for palliation of symptoms (including cough) than high-dose rate endobronchial brachytherapy; and b) the evidence is inconclusive that high dose rate brachytherapy and external beam radiation provide improved relief over external radiation alone (Ung 2006).

There is an urgent need for RCTs to be conducted in this field to clarify a number of therapeutic issues, including which patients benefit more, what is the most appropriate radiation dose and what are the most effective approaches to distance. Photodynamic therapy was assessed in only one study with positive results, although its advantage over other methods of palliation is not clear. No firm conclusions could be drawn for any of the pharmacological treatments presented, although butamirate linctus, codeine (60 mg), morphine, dihydrocodeine (10 mg), cromoglycate and hydropropizine/levodropropizine seem to exercise some positive effect in cough related to lung cancer. This (variable) effect should be balanced with their potential side effects, including nausea, dizziness or diarrhoea with butamirate linctus or drowsiness, constipation, respiratory depression or dependence with opioids. The effect of sodium cromoglycate in the absence of asthma or other respiratory pathology may be limited, and this information about the sample in the study by Moroni 1996 was not reported, making this result questionable. The effects of codeine 60 mg and levodropropizine (at 60 mg, 100 mg and 200 mg t.i.d) on cough are further supported from studies in chronic cough patients (see excluded studies by Barnabe 1995; Catena 1997; Fasciolo 1994; Mathys 1983). Butamirate linctus is currently included in many over-the-counter cough preparations and common management of lung cancer-related cough in clinical practice includes codeine and morphine. It is worth noting that some of the above compounds (for example hydropropizine or oxadiazol) are not available or have limited availability in some countries. The review identified no non-pharmacological interventions.

Population

The cancer population in these studies was quite disparate in terms of tumour and disease characteristics, including stage, extent of

lung involvement, location of tumours and other concurrent (respiratory) disease that could be linked with the presence of cough. The mixed studies also included a wide variety of patients, some with tuberculosis or other respiratory illnesses. The extent of cough 'chronicity' in those samples involving patients with respiratory disease, and smoking status were not considered in any of the studies. The extremely small sample of cancer patients included in some studies makes the results little more than clinical impressions.

Assessment

None of the studies provided evidence of the reliability of the methods used to assess cough. Particularly those studies using physician estimates of improvement highlight the possibility of strong bias influencing the results. The methods used were simple, often using single-item and unvalidated scales, and these did not assess the impact of cough on the patients' daily living and quality of life. The level of measurement in most cases was nominal, providing data on outcomes that probably lacked sensitivity.

Design of studies

Most studies did not achieve a high score using the Jadad scale, with the highest score being three, and 9/17 studies receiving a score of 0. This indicates that the degree of bias in all these studies is high. The heterogeneity of the included studies and the different ways used in each study to assess cough led us to abandon the initial idea to carry out a quantitative synthesis of the data and hence only a narrative synthesis of the data was possible; this is an appropriate way of presenting aggregated data from diverse studies (Popay 2006).

AUTHORS' CONCLUSIONS

Implications for practice

No recommendations for practice could be offered from this review, as the evidence was limited and of the lowest quality. Very few treatment options have been tested even with poor quality designs, and other therapeutic interventions often used in current clinical practice (e.g. methadone linctus, lidocaine) and those that are contained in over-the-counter preparations (e.g. dextromethorphan,

simple linctus) have not been assessed as yet. Hence as far as cough management in cancer is concerned, it is clear that its evidence-based practice remains in its infancy, and that therapeutic interventions can often only be applied with little certainty about their actual benefits. Another area that is missing is a clear threshold of cough (in terms of frequency or intensity or troublesomeness) above which cough becomes a clinical problem; such a threshold can assist clinicians to make decisions about when to start an intervention (considering the side effects of the available antitussives and opioids) as well as observing clinically meaningful improvements from an intervention.

Implications for research

The results of this review show the significant research gap that exists in relation to cough management. This is common in palliative care research, with most Cochrane reviews of similar topics providing little useful data despite being well conducted (Wee, 2008) and the existence of a limited number not only of randomised trials but also good quality observational studies (Hadley, 2009). Future research should focus on developing methodologically sound and sufficiently powered studies testing pharmacological (and potentially non-pharmacological) interventions for the management of cough in cancer patients. This means that accurate and reliable assessment of cough is urgently required, and development and testing of the necessary measures is a priority. Objective cough counts could be used as an outcome measure of cough. Samples should be carefully selected to be homogeneous in a number of clinical characteristics that may be implicated in the development of cough. Studies should also assess the impact of the interventions on patients' quality of life rather than merely on frequency and/or severity of cough only. The impact of the intervention may extend to improvements in other symptoms present concurrently with cough (e.g. night time length and sleep quality, breathlessness or anxiety) and such symptoms could be used as secondary outcomes. Essentially what is needed is a higher investment in research on this distressing symptom and closer, more effective collaboration between respiratory, speech pathology and oncology clinicians and researchers to improve the management of cough in cancer patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boselli 1972

Methods	Double blind randomised controlled trial.	
Participants	Stage 1 of study (n = 31): Malignant neoplasms (including GI, renal, hepatic, pulmonary neoplasms or pleural cancer n = 12). Stage 2 of study (n = 40): various respiratory disorders (e.g. spontaneous pneumothorax, asthma, chronic bronchitis, and lung neoplasms n = 12). Unknown age and gender characteristics.	
Interventions	Intervention drug (cancer patients n = 6): 1-N-fenil-4-N-(2,3-diidrossipropil)-dietilendiamina (Hydropropizine). Control drug (cancer patients n = 6): Oxadiazol. Both solutions were prepared with identical characteristics, put in identical bottles, only identifiable by differing initials. Codes were not revealed until after the experiment was completed. No information on drug dosage.	
Outcomes	Pre-treatment: In patients where coughing fits were particularly intense, the cough had a ‘non-productive’ character which seriously impacted upon rest (n = unknown). Post treatment: Intervention drug group: 4/6 = excellent (80-100% reduction in coughing fits); 1/6 =good (60-80% reduction in coughing fits); 1/6 = moderate (40-60% reduction in coughing fits). Control drug group: 1/6 = good; 3/6 = moderate; 2/6 = none (less than 40% reduction in coughing fits). Jadad score = 3.	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Allocation concealment?	Unclear	No details provided

Canak 2006

Methods	Comparative study. No randomisation.	
Participants	<p>N = 64, histology proven lung cancer, most had grade IIIb.</p> <p>Group 1: Mean age: 57 years. Sex: M 18/F 2.</p> <p>Group 2: Mean age: 58 years. Sex: M 37/ F7.</p> <p>INCLUSION CRITERIA: Malignant central airway obstruction due to lung cancer, Karnofsky index = 50. EXCLUSION CRITERIA: patients > 70 years.</p>	

Canak 2006 (Continued)

Interventions	GROUP 1: n = 20; Laser resection only - Sharplan 3000 Nd: YAG laser, performed under GA using flexible bronchoscope via modification of Freidel's rigid bronchoscope. GROUP 2: n = 44; Laser resection as above plus HDR BT 14 Gy in 2# / weekly (7 Gy per #) at 1cm, followed by EBRT using split course, with 40 Gy in 10 fractions (2x5 fractions).	
Outcomes	Pre-treatment: all patients had cough as a symptom. Post treatment: Group 1: decrease in frequency cough = 25% (P = 0.69). Group 2: decrease in frequency cough = 50% (P ≤ 0.0005). Comparative analysis between groups showed no statistical difference though authors state figures support claims that group 2 treatment provides better cough palliation. Jadad score = 0	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Allocation by availability of treatment; Group 1 patients received laser resection only due to technical issues in radiation department.

Charpin 1990

Methods	Double blind randomised controlled trial	
Participants	N = 67, various conditions: carcinoma (N = 14), acute and chronic bronchopneumonopathies (N = 22), pulmonary tuberculosis and haemoptysis (N = 12), other aetiology (N = 12). Butamirate Citrate group (n = 30). Age, years (mean, ± SD, range) 58 ± 18, 19-81. Sex: M18/F22. Weight, Kg (mean, ± SD, range): 60 ± 11, 44-84. Clobutinol group (n = 30): Age, years (mean, ± SD, range): 55 ± 13 24-79. Sex: M17/F13. Weight, Kg (mean, ± SD, range): 66 ± 14 (36-92).	
Interventions	Intervention 1: (n = 7 carcinoma patients) Butamirate Citrate Linctus (Butamirate citrate 1.29 mg/ml, Zyma). Intervention 2: (n = 7 carcinoma patients) Silomat Syrup (Clobutinol 4 mg/ml, Boehringer, Ingelheim). Supplied in identical bottles of 125ml each, labelled with a drug code and patient number (patients were given 2 bottles of medicine each for the duration of study). Dosage and delivery (for both medicines): One tablespoon, three times daily, to be taken 0.5 hrs before meals for a total of five days).	
Outcomes	Pre treatment: Total cough score (sum of severity for day and night, and frequency) mean, ± SD (range) (for cancer patients only): Butamirate citrate group 7.1 ± 1.9 (4-11). Clobutinol group 7.5 ± 2.0 (3-10). Post treatment:	

Charpin 1990 (Continued)

	<p>Improvement of coughing frequency (patient's diary) (for cancer patients only): Butamirate Citrate Linctus group = 7/7, Clobutinol group =2/7, (x2 = 4.97, P = 0.026). No significant difference between groups detected globally for the whole sample. Total efficacy score (patient's diary): Highly significant improvements (P < 0.001) were found within both groups. Significant difference occurred in carcinoma patients in favour of Butamirate Citrate (P = 0.013).</p> <p>No significant difference found between groups either at end of study or during 4 days of treatment.</p> <p>Physician's Global Opinion score: Significant difference occurred in carcinoma patients in favour of Butamirate Citrate (P = 0.026). No significant difference between groups was found for the whole sample. Adverse events: 7 patients in each group complained of side effects (mainly nausea and drowsiness) though not severe enough to interrupt treatment. Jadad score = 3</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	No details provided

Diaz-Jimenez 1999

Methods	Prospective randomised controlled trial
Participants	<p>N = 31, NSCLC. Age mean (SD) 65 (7). Sex: M (31). PDT group mean age = 67; Nd-YAG group mean age = 64. Presence of contralateral pulmonary metastases and dyspnoea on minimal effort similar in both groups. PDT group contained fewer patients with advanced disease. Previous treatment: 5 patients had previously received treatment for lung cancer (3 in PDT group received external radiotherapy, 1 in Nd-YAG laser group received chemotherapy+radiotherapy, 1 in Nd-YAG laser group underwent exploratory thoracotomy - no tumour resection performed). Periods from last treatment were 11, 41, 114 weeks for radiotherapy patients and 40 weeks from last chemotherapy. INCLUSION CRITERIA: > 18 years, biopsy proven or recurrent inoperable NSCLC with totally or partially obstructive endobronchial lesions with or without extrabronchial tumour; clinical evidence of airway obstruction, Karnofsky index ≥ 40, able to tolerate bronchoscopy procedures, ≥ 4 weeks post last chemotherapy, ≥ 3 weeks post radiation dose. EXCLUSION CRITERIA: patients previously treated with PDT or Nd: YAG laser, patients who had tracheal lesions that compromised both main bronchi, brain metastasis, bone pain due to skeletal metastasis, pneumonectomy, tumours eroding or invading great vessels, haematoporphyrin hypersensitivity, low leukocyte count, low platelet count, renal failure, liver dysfunction.</p>
Interventions	<p>PDT Group: n = 14; PDT based on estimated size of tumour. Tumours were irradiated (630-nm light) via a flexible fibre optic bronchoscope 40-50 hours post IV injection of 2mg/kg DHE (Photofin). Two days post treatment a bronchoscopy was performed to clean detritus. 2nd argon dye irradiation was performed if parts of tumour failed to show signs of necrosis 96-120 hours post treatment, and if bronchoscopy</p>

Diaz-Jimenez 1999 (Continued)

	<p>revealed recurrence, then patients could receive a 2nd session of PDT, with the same dose of DHE followed by laser photo radiation. Patient could receive a maximum of three doses of DHE at 1-6 laser photo radiation with max of 2 photo radiations per session. If toxic effects occurred, treatment was stopped until these resolved.</p> <p>Nd-YAG laser group: n = 17; Bronchoscopy performed using a rigid bronchoscope and standard techniques under GA. Nd-YAG resection was performed. Bronchoscopy was repeated 2-4 days until considered further treatment would not give additional benefit. If symptoms worsened or recurred and tumour regrowth was confirmed, further Nd-YAG laser treatment was indicated.</p> <p>Control bronchoscopy performed on all patients 1 week post PDT, every month for 3 months and at 6 and 12 months (and at 18 months if possible thereafter).</p>	
Outcomes	<p>Pre-treatment: Cough was more common in Nd-YAG laser resection group (P = 0.02).</p> <p>Post treatment: Improvement of symptoms was similar in both groups. Symptoms (including cough) improved 1 week post treatment; dyspnoea, haemoptysis and sputum production showed greater improvement than did cough between 1 week and 1 month post treatment.</p> <p>Adverse events: 26 patients had at least one adverse event, 16 patients experienced two adverse events; cough and photosensitization was the most frequent combination. 5 patients died with 2 months of last day of treatment (1 in PDT group ‘probably’ related to treatment).</p> <p>Jadad score = 2</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Allocation concealment?	Yes	Probably done but not mentioned in the paper

Dotti 1970

Methods	Double blind randomised controlled trial	
Participants	<p>N = 41, various conditions: <i>Pulmonary Neoplasia</i> (n = 13); Recent or Chronic Pulmonary TB (n = 26); Bronchopulmonitis (n = 2).</p> <p>Part 1 (n = 26). Age range: 19-76. Sex: M22/F4.</p> <p>Part 2 (n = 20). Age range: 19-74 (5 of these were previously treated in the first part of the study). Sex: M18/F2.</p> <p>INCLUSION CRITERIA: patients who had been admitted to participating hospital for persistent cough.</p>	
Interventions	<p>Part 1 of study (cancer patients n = unclear): A = Codipront Bracco (capsule containing 172 mg Codeine resinate, equal to 30 mg of codeine base, and 28mg of phenyltoloxamine resinate, equal to 10mg of phenyltoloxamine base). B = lactose (placebo); C = dibenzonium bromide 30mg + lactose (All in capsule form).</p> <p>Treatment consisted in the administration, on alternate days, of a different treatment arm, according to a pre-established schedule. In all cases, patients were started with type A, followed by B and C. Maximum dose was 2 capsules per day (BID), except if weight was >75 kg, then 3 capsules per day were given. Treatment continued for a minimum of 6 days to a maximum of 20 days.</p> <p>Part 2 of study (cancer patients n = unclear): A = Codipront Bracco (as explained above) compared with</p>	

Dotti 1970 (Continued)

	Dihydrocodeine with pentamethyletetrazole drops (10 g containing 1 g pentamethylene tetrazole + 0.05 g dihydrocodeine. On alternate days, these patients were given Arm A drug in doses of 2 capsules per day (BD), and dihydrocodeine with pentamethylenetetrazole in doses of 45 drops for 1 st 2 days and 30 drops the last 2 days (consistent duration of treatment = 8 days).	
Outcomes	Although authors state there were 13 patients included with pulmonary neoplasia, only results for 5 patients could be found within the paper. Part 1 of study (for cancer patients only): (4 patients). Therapeutic results: Codipront Bracco 2/4 = excellent /good, 2/4 = doubtful; Placebo 4/4 = doubtful/none; Dibenzonium Bromide = 1/4 moderate, 3/4 doubtful/none. Tolerance: good/excellent for all medications. Part 2 of study (for cancer patients only): (1 patient). Antitussive effect: DP Drops = moderate; Codipront Bracco = Good. Tolerance: excellent for both medications. Jadad score = 1	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Nio details provided

Kleibel 1982

Methods	Comparative study	
Participants	N = 31, variety of cancers (largest group was metastatic breast cancer, n = 17) Sex: M10/F21	
Interventions	<p>Group A (n = 21): Dorecotuss retard (Dr. Rentschler Arzneimittel GmbH, Laupheim), a synthetic Morphine-derivative, without acting centrally, thus regulating the cough with, reportedly, no central side-effects. Dosage: 2x1 daily (no indication of mg).</p> <p>Group B (n = 10): Codipront capsules (containing codeine/Ag). Dosage 2x1 daily (no indication of mg).</p>	
Outcomes	<p>Post treatment:</p> <p>Time until drug effectiveness was observable: in both groups between 20 and 30 minutes; no statistical difference.</p> <p>Duration of effectiveness: between 7 and 8 hours in both groups; no statistical difference.</p> <p>Dorecotuss ret. Cough-free interval day 1= 13/21 good, 5/21 moderate, 3/21 unsatisfactory.</p> <p>Codipront. Cough-free interval day 1= 8/10 good, 2/10 moderate.</p> <p>Adverse events: Opioid-specific side effects only in group B, with 3 patients (3/10) with constipation.</p> <p>Jadad score = 0</p>	
Notes		

Kleibel 1982 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Open label trial

Koichiro 2002

Methods	Comparative study using a historical cohort as the control group. Sample from 1993-1996 is the historical control group and from 1997 to 1999 is the experimental group.
Participants	N = 20, early laryngeal carcinoma patients receiving radiotherapy. All patients were male. Control group. Mean age, range: 73.1, 60-87. Experimental group. Mean age, range: 65.7, 57-75.
Interventions	Intervention group: N=12, receiving TJ-29 (Chinese Medicine Herb, Tsumura Co.'s Bakumondo-to; 9 gr, three times daily before meals. Control group: (unclear) no treatment
Outcomes	While the TJ-29 was able to reduce the severity of mucositis induced by radiotherapy as well as the severity of sore throat (P = 0.0023), no between-groups differences were seen in relation to hoarseness of voice, xerostomia, pharyngoxerosis and cough. Jadad score = 0
Notes	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	No details provided

Luporini 1998

Methods	Double blind randomised controlled trial
Participants	N = 140, Primary lung cancer (n = 107), metastatic lung cancer (n = 29), other cancers (n = 4). Levodropropizine Group: Age, years (mean, SD): 62.9 ± 9. Sex: M59/F10. Weight, Kg (mean, SD): 67 ± 11. Height, cm (mean, SD): 167 ± 7. Smokers: 10. Dihydrocodeine Group: Age, years (mean, SD): 64 ± 10. Sex: M48/F23. Weight, Kg (mean, SD): 64 ± 10. Height, cm (mean, SD): 166 ± 8. Smokers: 10.
Interventions	Intervention group (n = 69): Levodropropizine <i>Levotuss</i> , 6% oral drops: daily administered dose equal to 75mg (25 drops) three times per day, 6-8hourly intervals, for 7 days. Intervention group (n = 71) Dihydrocodeine rhodanate - <i>Paracodina</i> 1% oral drops: daily administered

	dose equal to 10 mg (25 drops), three times per day, 6-8 hourly intervals for 7 days. <i>Note: usual recommended dose of Levodropropizine is 60 mg t.i.d - but higher dose dispensed to keep the two treatments indistinguishable as per number of drops administered.</i>	
Outcomes	<p>Pre treatment:</p> <p>Levodropropizine group: Cough symptom duration days (mean, SD): 65.1 ± 96.7; Cough severity score, patient (mean, SD): 3.7 ± 0.6; Cough severity score, investigator (mean, SD): 3.8 ± 0.7.</p> <p>Night awakenings (mean, SD): 1.4 ± 1.9.</p> <p>Dihydrocodeine group: Cough symptom duration, days (mean, SD): 40.5 ± 41.7; Cough severity score, (patient mean, SD): 3.7 ± 0.6; Cough severity score, (investigator mean, SD): 3.8 ± 0.7;</p> <p>Night awakenings (mean, SD): 1.1 ± 1.5</p> <p>After treatment:</p> <p>Efficacy: Cough severity was significantly reduced (p<0.05) in both groups, effect increased with time. Time profile of cough improvement was similar with both treatments.</p> <p>The trend in cough severity, judged by investigators: both treatments produced a similar and significant decrease in cough scores (P < 0.05) with no significant difference between treatments; this confirmed the patients' subjective evaluations. Number of awakenings during the night (in patients with at least one night wake up at baseline): Levodrop group (n, mean, SD): Day one: 34, 2.4 ± 2.6, Day three: 34, 1.4 ± 1.7, Day seven: 30, 1.2 ± 1.7</p> <p>Dihydrocodeine group (n, mean, SD):</p> <p>Day one: 29, 1.6 ± 1.2, Day three: 29, 0.6 ± 0.9, Day seven: 27, 0.6 ± 1.1.</p> <p>Final estimate of antitussive efficacy of Levodropropizine: (judged by patients and investigator): worsening of cough (n = 0), no change in cough (n = 0), improvement in cough; n = 30 (patient perception) n = 33 (investigator perception) and disappearance of cough; n = 5 (patient perception) n = 3 (investigator perception).</p> <p>Final estimate of antitussive efficacy of Dihydrocodeine: (judged by patients and investigator): worsening of cough (n = 0); no change in cough (n = 0); improvement in cough n = 31 (patient perception) n = 34 (investigator perception) and disappearance of cough; n = 5 (patient perception) n = 3 (investigator perception).</p> <p>Safety: presence of somnolence: Levodropropizine = 5/66 (8%; P < 0.05). Dihydrocodeine = 15/69 (22%)</p> <p>.</p> <p>Per protocol analysis of somnolence:</p> <p>Levodropropizine: 5/60 (8%; P < 0.05); Dihydrocodeine: 15/63 (24%)</p> <p>Patients receiving concomitant medication known to induce somnolence: Levodrop group: n = 3 Dihydrocodeine group n = 4. No severe somnolence reported after treatment with either drug.</p> <p>Other secondary safety results (e.g. BP/HR/blood results) showed no significant change in either group during treatment.</p> <p>Adverse events:</p> <p>Levodrop group: n = 6 (1 death due to disease, vomiting, diarrhoea, epigastric pain). Dihydrodrop group: n = 4 (1 death due to disease, erythema of abdomen, gastric pain, somnolence).</p> <p>Jadad score = 3</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	No details provided

Mallick 2006

Methods	Prospective Randomised trial.	
Participants	N = 45, Squamous cell carcinoma (89%). Arm A: mean age: 68.9 years, Sex: M15/F0 Arm B: mean age: 63.1 years. Sex: M14/F1 Arm C: mean age: 61.5 years, Sex: M14/F1	
Interventions	Arm A (n = 15): received EBRT to a dose of 30 Gy/10#/2 weeks + EBBT 16 Gy in 2# (8Gy per #) Arm B (n = 15): received EBRT to a dose of 30 Gy/10#/2 weeks 10 Gy at 1cm depth in 1# (single dose) Arm C (n = 15): 15Gy at 1cm depth in 1# (single dose), without EBRT	
Outcomes	<p>Pre treatment: All participants had cough prior to treatment.</p> <p>Post treatment: Cough response - Overall response rate = 84.5%. No significant difference found between 3 treatment arms: Arm A = 12/15; Arm B = 13/15; Arm C = 13/15 (P = 0.844).</p> <p>Cough median time to relapse in months: Overall = 5, Arm A = 4; Arm B = 7; Arm C = 4 (P = 0.09).</p> <p>Cough median time to progression in months: overall = 8, Arm A = 7; Arm B = NR; Arm C = NR (P = 0.77).</p> <p>EORTC QLQ LC-13 Cough scores:</p> <p>Overall pre/post = 62/33*</p> <p>Arm A = 67/40*; Arm B = 65/36*; Arm C = 56/22*</p> <p>(* statistically significant difference)</p> <p>Adverse Events: Authors viewed treatment morbidity as low. According to RTOG acute morbidity criteria, acute grade 1 odynophagia (painful swallowing) was seen in 14/45 patients (31.1%), all occurring during the first month and resolving spontaneously within a few weeks.</p> <p>Transient increase in cough was seen in 12 patients (26.7%) immediately after the bronchoscopy procedure, but resolved in all within 72 hours. No grade 2 or grade 4 acute complication. One patient (in Arm C) died of fatal haemoptysis at 7 months, due to significant residual disease. 3/45 patients developed features of post-radiation fibrosis, without evidence of disease progression (only 1 symptomatic of fibrosis).</p> <p>Jadad score = 1</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	Insufficient information provided

Moroni 1996

Methods	Double-blind placebo-controlled randomised trial	
Participants	<p>N = 20, locally advanced or unresectable metastatic NSCLC.</p> <p>Intervention group: Age, years (mean, range): 65.6, 55-74. Sex: M8/F2.</p> <p>Placebo group: Age, years (mean, range): 62.7, 52-71. Sex: M7/F3.</p> <p>Both groups were similar in terms of histology and previous treatment regimes.</p> <p>INCLUSION CRITERIA: patients with locally advanced or unresectable metastatic NSCLC and irritative neoplastic cough resistant to conventional treatment.</p>	

Moroni 1996 (Continued)

Interventions	Intervention group (n = 10): 40mg Sodium Cromoglycate per day (patients instructed to inhale 2 puffs four scheduled times per day), for 2 weeks. Placebo group (n = 10): inhaled physiological solution.	
Outcomes	Pre treatment: cough score (3 days run in period): Sodium cromoglycate group - mean daily score = 3.1 (median:3.2; 25-75 percentile: 2.3-3.7); Placebo group mean daily score = 3.03 (median 3.2; 25-75 percentile: 2.3-3.7). Post treatment: Cough score: Sodium cromoglycate group - mean daily score = 1.6 (median 1.4; 25-75 percentile: 1.4-1.8). Placebo group -mean daily score = 2.9 (median 2.9; 25-75 percentile: 2.1-3.6). Cough intensity: reduction in cough intensity in sodium cromoglycate group compared to placebo was ‘statistically significant - < 0.001’. Cough neither worsened nor remained stable in any sodium cromoglycate patient, which was different to placebo control group. Jadad score = 2	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Allocation concealment?	Unclear	No details provided

Muto 2000

Methods	Comparative trial	
Participants	N = 320, Advanced (IIA-IIIB) non-small cell lung cancer. No patient characteristics reported. Inclusion criteria: Biopsy proven non small cell cancers, stage IIIA-IIIB, Karnofsky Performance Score > 60, expectancy of life > 6 months, presence of cough and /or dyspnoea, haemoptysis, obstructive pneumonia; no chemotherapy before or during treatment.	
Interventions	All patients received 2 Gy per #/daily for up to 50 Gy. Group A: n = 84, single fraction BT, dose = 10 Gy at 1 cm depth. In 75/84 single catheter HDRBT was used, in 9/84 2 catheters used - treatment in group A performed before starting EBRT. Group B: n = 47, 14 Gy in 2 # (7 Gy/#) at 1 cm (41 patients with single catheter HDRBT and 6 with double catheter) received treatment before the first EBRT and after the last EBRT treatment. Group C: n = 189, 15 Gy in 3# (5 Gy/#) (170 received single catheter HDRBT, 19 treated with 2 catheters for all fractions). Patients treated every 15 fractions of EBRT (day before the beginning of EBRT, after 3 & 6 weeks of treatment). Group C1: n = 50, dose calculated at 1cm from central axis of the catheter of treatment. Group C2: n = 139, dose calculated at 0.5cm from the central axis.	

Muto 2000 (Continued)

Outcomes	<p>Pre treatment: Symptomatic response rate (presence of symptoms in %): Group A: 92; Group B: 96; Group C1: 90; Group C2: 91.</p> <p>Post treatment: Symptomatic response rate (presence of symptoms during treatment/after 1 month in %): Group A: 80/42; Group B: 82/28; Group C1: 79/12; Group C2: 83/11.</p> <p>Overall response rate to cough 1 month post treatment = 77%; 82% post 6 months.</p> <p>Adverse events: Radiation bronchitis (found at 6-month bronchoscopy): Group A 61/78; Group B 22/46; Group C1 8/36; Group C2 19/120.</p> <p>Severe complication: fatal haemoptysis: Group A 2/78; Group B 3/46; Group C1 2/36; Group C2 3/120.</p> <p>Complications linked to procedure of bronchoscopy: Group A 2/78; Group B 2/46; Group C1 0/36; Group C2 3/120.</p> <p>Broncho - oesophageal fistulas occurred in 1/78.</p> <p>Jadad score = 0</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Not used

Nori 1993

Methods	Comparative trial	
Participants	<p>N = 32, majority of patients had primary malignant neoplasm of lung (n = 30)</p> <p>Age, years (median, range): 59, 49-80.</p> <p>Histology:</p> <p>Primary malignant neoplasm of lung: n = 30; Primary cervical carcinoma: n = 1; Primary colon carcinoma with lung metastasis: n = 1.</p> <p>Group 1: All had Pulmonary neoplasms IIIB (treated by BT as a boost to primary external beam irradiation)</p> <p>Group 2: Pulmonary neoplasms (All stage IIIB), n = 13; Other cancers (All stage III) n = 2. All were treated with BT for endobronchial recurrence after prior irradiation with external beam.</p>	
Interventions	<p>Prior treatment given:</p> <p>Median external beam dose prior to intraluminal treatment = 50 Gy.</p> <p>Range, group 1 = 50-60 Gy, group 2 = 40 to 50 Gy.</p> <p>Brachytherapy only performed when bronchoscopy revealed an endobronchial component of the primary or recurrent tumour.</p> <p>Time from completion of EBRT to BT (median/average): group 1 = 7 days; group 2 = 6 months.</p> <p>BT regimen for both groups: uniform dose of 5Gy per # for 28 patients and 4 Gy per # for 4 patients was prescribed at 1 cm depth. Length of treatment varied from 4-7 cm, median length = 5 cm.</p> <p>Majority of patients received 3-4#/weekly.</p>	

Nori 1993 (Continued)

Outcomes	<p>Pre intervention treatment: Presenting symptoms (number/%): haemoptysis 15/47%; cough 7/22%; dyspnoea 10/31%, combination of above 25/78%.</p> <p>Post intervention treatment: 6 out of the 7 patients with unremitting cough, found reduction in frequency and intensity by > 50%. Generally, duration of response to treatment was maintained for at least the first 6 months of follow-up in 15/17 (88%) group 1 patients, and in 70% group 2 patients.</p> <p>Adverse events: Treatment was well tolerated, ‘minimal acute or late complications’ were observed. One procedure was abandoned secondary to bleeding during initial bronchoscopy; two patients needed extended monitoring due to cardiac abnormalities. No difference in rate of complications between the two groups. One patient in group 1 had persistent cough requiring conservative treatment. No association between location of recurrence and incidence of complications.</p> <p>Jadad score = 0</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Allocation concealment?	No	Not used

Ofiara 1997

Methods	Comparative study using same treatment upon different disease population	
Participants	<p>N = 30, Symptomatic endobronchial bronchogenic carcinoma.</p> <p>Patients stratified into 2 groups depending on disease type (after initial bronchoscopy):</p> <p>Group 1 patients (n = 20): tumour characterised by endoluminal disease.</p> <p>Group 2 patients (n = 10): sub mucosal infiltration and/or extrinsic compression.</p> <p>Patients were also stratified according to tumour location = central (trachea or main stem bronchi, n = 10) or peripheral (lobar or segmental bronchi, n = 14).</p> <p>Group 1:</p> <p>Age, years (mean, range): 64, 33-73; Squamous cell: 15;</p> <p>Adenocarcinoma: 4; Small cell: 1; Stage (TNM): IIIa: 9; IIIb: 8; IV: 2; Small cell Limited: 0; Extensive: 1;</p> <p>Initial ECOG score (SD): 1.8 (0.8).</p> <p>Group 2:</p> <p>Age, year (mean, range): 65, 44-80; Squamous cell: 5; Adenocarcinoma: 3; Small cell: 2; Stage (TNM): IIIa: 3; IIIb: 4; IV: 1; Small cell Limited: 1; Extensive: 1; Initial ECOG score (SD): 1.7 (0.9).</p> <p>All patients had completed external radiation at least 1 month prior to entry into the study; both groups were similar in the interval between completion of external radiation and commencement of brachytherapy. Also, similar in terms of external radiation dose given and number of catheters placed per session.</p>	
Interventions	<p>High-dose remote afterloading endobronchial irradiation and brachytherapy.</p> <p>All patients: 8 Gy at 1 cm depth, with an aim for 24 Gy in 3# over 6 weeks: 8 Gy per #/weekly.</p> <p>Follow up bronchoscopy performed 4 weeks post BT (week 8).</p>	
Outcomes	<p>Post treatment:</p> <p>Overall: statistically significant improvement in cough from baseline to week 8 (11/24, P < 0.01).</p> <p>Group 1: no statistically significant improvement in cough was seen (6/16).</p>	

Ofiara 1997 (Continued)

	Group 2: statistically significant improvement from baseline to week 8 (5/8, P < 0.05). Location: central: no statistically significant improvement in cough (3/10); peripheral: statistically significant improvement in cough seen (8/14, P < 0.05). Adverse events: 3 patients died between weeks 4-8 of study (group 1 = 2 patients; group 2 = 1 patient), attributed to progressive underlying disease. Jadad score = 0	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	Not used

Speiser 1993

Methods	Comparative study - patients treated according to disease on a protocol.	
Participants	<p>N = 342, Endobronchial carcinoma</p> <p>Age, years (mean, SD, range): 66.6, $\pm$ 9.6 years, 31-90 years.</p> <p>Sex: M214/F125 (63%/37%)</p> <p>Histology:</p> <p>Squamous cell 49%; large cell undifferentiated 16%; adenocarcinoma 14%, small cell undifferentiated 11%; others 10%. Each group was divided into curative (20%), palliative (48%) and recurrent (32%) patients and treated with appropriate protocols.</p> <p>INCLUSION CRITERIA: Curative intent: inoperable NSCLC, received no prior radiation, T1, 2, 3, NO 1, 2, 3, and MO categories, ECOG performance status 2; weight loss less than 10% body weight for 6 months of pre diagnosis weight.</p> <p>Palliative intent: primary lung carcinoma, NSCLC; who were T4 and/or M1 disease category; or patients with less stage disease but a host performance status of H3 or H4, who had lost > 10% body weight in 6 months of pre diagnosis weight and who were ineligible for curative intent treatment. Also included patients with SCLC with significant respiratory distress and patients with non lung primaries metastatic to the endobronchial mucosa, or lung primaries with intrapulmonic spread.</p> <p>Recurrence: all histologies for patients who had received a prior course of curative intent radiation therapy.</p>	
Interventions	<p>Group 1 (n = 47): medium dose rate 10 Gy in 1# (single dose) at 5 mm depth.</p> <p>Group 2 (n = 144) high dose rate, 10 Gy in 1# (single dose) at 10 mm depth.</p> <p>Group 3 (n = 151): high dose rate 7.5 Gy in 1# (single dose) at 10 mm depth.</p> <p>Number of BT procedures per patient, N/%:</p> <p>2 = 38/11; 3 = 281/82.5; 4 = 12/3.5; 5 = 4/1; 6 = 6/2.</p> <p>Each group was split into curative intent, palliative or recurrent and could receive the following treatment on top of the treatment described above:</p> <p>Curative intent - EBRT 60 Gy in 30# (weeks 1-6); BT performed during weeks 1, 3, 5.</p> <p>Palliative intent - EBRT 25 Gy per # for total of 37.5 Gy in 15# for patients who had primary lung cancer or non oat cell histology; BT given weeks 1,2,3. For patients who did not have primary lung cancer or had oat cell histology concurrent chemotherapy could be given.</p> <p>Recurrent cancer- all patients had received prior course of curative intent EBRT; received BT only weeks</p>	

Speiser 1993 (Continued)

	1, 2, 3. EBRT was used concurrently for all patients treated in the curative intent arm; 43% in the palliative arm; 5% received additional radiation for metastatic disease at some point post entry to study. Some patients who had highly obstructing lesions (n = unknown) received laser therapy immediately prior to BT (within 24 hours).	
Outcomes	<p>Pre treatment: 99% patients had cough prior to intervention based on patient history (only patient not to report cough had a brain injury affecting short term memory and in reality had a cough, but could not remember cough episodes).</p> <p>Post treatment: No report of between group analysis for the symptom of cough; authors state within paper ‘the results of palliation cannot be shown to be significantly different with different dose used’.</p> <p>Cough symptom % of symptom index score: 1st brachytherapy 100; 2nd brachytherapy 68; 3rd brachytherapy 48; 1st follow up bronchoscopy 15.</p> <p>Symptom index response expressed as percent of weighted index at each brachytherapy and first follow up. Bronchoscopy (scores are weighted and normalised to 100% for the first score). Results show a 32%, 52%, and 85% decrease in cough respectively.</p> <p>Adverse events: complications arising from bronchoscopy (post therapy) in Group 1 patients = 3%, included pneumothorax (3 patients), arrhythmia, haemoptysis, and infection. Secondary to technique of placing catheter and was rectified, then a 0.5% complication rate reported. Radiation bronchitis and stenosis:</p> <p>Group 1 9%; Group 2 12%; Group 3 11%. Massive haemoptysis (leading to death): 7.3%.</p> <p>Jadad score = 0</p>	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Allocation concealment?	No	Not used

Tansini 1971

Methods	Double blind placebo controlled randomised trial	
Participants	<p>N = 40, mixed sample of patients with chronic respiratory disorders including lung cancer.</p> <p>Male and Female mixed sample.</p> <p>Age, years (range): 13-79</p> <p>Intervention group:</p> <p>N = 9 patients with cancer, of which, 8 patients had lung cancer and 1 patient had unknown primary with lung and brain metastases.</p> <p>Placebo group:</p> <p>N = 3 with lung cancer.</p>	
Interventions	<p>Intervention group (N = 32 mixed sample, of which n=9 cancer patients): received pentamethylentetrazol with dihydrocodeine hydrodantate (Cardazol-Paracodin). Dose = 10-20 drops, T.I.D. for 7-18 days.</p> <p>Placebo group (N = 8 mixed sample, of which n = 3 cancer patients): received Placebo (no details). Dose = 10-20 drops, T.I.D. for between 4-15 days.</p>	

Tansini 1971 (Continued)

Outcomes	Post treatment: Intervention arm - total disappearance of cough in 3 cancer patients; notable improvement in 4 cancer patients, moderate lowering of cough in 2 cancer patients; no change in 0 cancer patients. Control arm -total disappearance of cough in 0 cancer patients; notable improvement in 1 cancer patient; moderate lowering of cough in 0 cancer patients; no change in 2 cancer patients. Jadad score = 2	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	No details provided

Tao 2003

Methods	Comparative trial	
Participants	N = 45, Malignant tumour patients (largest group was pulmonary carcinoma n = 19). Fei Tong Liquid group (Chinese Medicinal herbal combination): Age (mean, range): 56.4, 34-75; Sex: M19/F11. Control Group: Age (mean, range): 60.7, 36-77; Sex: M9/F6. The two groups were comparable in age, types of tumour & radiotherapy and/or chemotherapy applied (P < 0.05).	
Interventions	Intervention group (n = 30): Fei Tong Oral Liquid, 20 ml t.i.d. or Fei Tong aqueous decoction one dose a day, for 30 days as one therapeutic course. Control group (n = 15): oral Prednisilone, 0.5-1 mg/kg, per day, or I.V. drip of Dexamethasone, 2.5-5 mg, once a day for one month or more.	
Outcomes	Pre treatment: ($\pm$ s) Intervention group: Cough 4.06 (+/- 2.27); Control group: Cough 3.40 (+/- 1.68). After treatment: ($\pm$ s) Intervention Group: Cough 1.50 (+/- 1.68, p<0.01); Control group: Cough 3.53 (+/- 2.07). Jadad score = 0	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	No	No details provided, probably not done

Tredaniel 1994

Methods	Comparative trial
Participants	<p>N = 51, Malignant airway obstruction</p> <p>Group 1 (presenting only with endobronchial disease):</p> <p>Age, year (mean, SD): 62.3, 8.3; Karnofsky Index (mean, SD) 85.9, 11.5;</p> <p>Previous surgery: 15; Previous radiotherapy: 16; Previous chemotherapy: 8; Chronic respiratory failure: 3; Relapse from previously treated tumour/2nd primary lung tumour: 26</p> <p>Group 2 (presenting with extraluminal extension of disease):</p> <p>Age, year (mean, SD): 64.7, 10.5; Karnofsky Index (mean, SD): 72, 13.6</p> <p>Chronic respiratory failure: 1; Previous surgery: 8</p> <p>Previous radiotherapy: 16; Previous chemotherapy: 7; Endobronchial tumour with endothoracic extraluminal dissemination: 15; Peripheral metastases: 7</p> <p>INCLUSION CRITERIA (for treatment): histologic evidence of endobronchial visible carcinoma; Karnofsky Performance Status > 50; fit enough to undergo several flexible bronchoscopies; expected survival of > 2 months.</p>
Interventions	<p>Treated according to protocol: based on 14 Gy at 1 cm depth in 2# in 2 days (7 Gy/#) two week gap, repeated up to 6# (total dose = 42 Gy in 6# in 6 weeks).</p> <p>Group 1:</p> <p>3 BT treatment sessions were planned. 26 patients received 6#; 1 received 5# (last not performed after side effects post 5th treatment); 2 received 4# (1 refused last #; 1 died in between receiving 2nd/3rd #).</p> <p>Group 2:</p> <p>2 BT # were performed, and if a good response was noted, patients received a 3rd #. 9 patients received 3 #; 10 received 2 #; 3 received 1 # (due to significant clinical deterioration).</p>
Outcomes	<p>Pre treatment:</p> <p>14 patients in group 1 did not suffer from functional symptoms (including cough).</p> <p>Post treatment:</p> <p>46 patients were available for histologic analysis at 2 months:</p> <p>Symptomatic relief of symptoms:</p> <p>Symptoms unable to be assessed for 7 patients as they lived too far away (3 in group 1; 4 in group 2):</p> <p>Group 1: 14 patients who initially experienced no functional symptoms remained asymptomatic. Overall scores (group 1 and group 2): 21/30 (70%) achieved complete or partial relief of symptoms. Response for cough and haemoptysis was 85% - dyspnoea only 55%.</p> <p>Adverse events: fatal pulmonary haemorrhage in 5 patients (10%); 4/5 had been previously treated with external radiation > 55 Gy, all presented with endobronchial evidence of local recurrence at time of death. Difficult to separate the relative contribution of treatment and local recurrence to this fatal complication. Fatal massive bronchorrhea in 2 patients 6 & 5 months following treatment. Radiation bronchitis in 7 patients (3 group 1, 4 group 2) .</p> <p>Transient fever and chills in 2 patients, 24 hrs post procedure.</p> <p>Main side effect was pleuritic pain induced in 'many patients' during procedure, but relieved and did not stop treatment. Abundant bronchial secretions in 3 patients (requiring new bronchoscopy for aspiration, but did not prevent treatment).</p> <p>Jadad score=0</p>
Notes	
<i>Risk of bias</i>	

Tredaniel 1994 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	No	Not used

Legend for Characteristics of Included Studies:

#: fraction

BID: latin (bis in die) meaning two times per day

BT: brachytherapy

EBBT: endobronchial brachytherapy

EBRT: external beam radiotherapy

ECOG: Eastern Cooperative Oncology Group Performance Status

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer 30

EORTC LC-13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer-13

GA: general anaesthetic

HDR: high dose radiotherapy

HDR-BT: high dose rate brachytherapy

IV: intravenous

M (0, 1, 2, 3): metastases

N0: nodules 0

Nd: YAG: neodymium yttrium aluminium garnet

NR: median not reached

NSCLC: non-small cell lung cancer

PDT: photodynamic therapy

RCT: randomised controlled trial

SCLC: small cell lung cancer

T (1, 2, 3): tumour

TID: latin (ter in die) meaning three times per day

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anacak 2001	No comparison/control group
Azzopardi 1964	Unable to locate from British Library
Barnabe 1995	Mixed sample, unable to extrapolate cancer patient data
Baroncelli 1964	No comparison/control group
Bedwinek 1992	No comparison/control group
Bickert 1967	Case study

(Continued)

Bini 1971	No comparison/control group
Błaszczak 2005	No comparison/control group
Bonneau 2009	Review article
Castro 1990	Case study
Catena 1997	Not with cancer patients
Celebioglu 2002	No comparison/control group
Chang 1994	Retrospective study
Corsa 1997	No comparison/control group
Cwiertka 2003	Retrospective analysis of case notes; also brachytherapy is used in combination with radiotherapy and chemotherapy, reporting only overall combined results
Doona 1998	Case study
Dudgeon 1996	Case study
Escobar-Sacristan 2004	No comparison/control group
Estfan 2008	Review article
Fasciolo 1994	Mixed sample
Gallagher 1997	Case study
Gejerman 2002	No comparison/control group
Gerhard 1973	No comparison/control group
Gollins 1994	Retrospective study
Gollins 1996	Retrospective study; no focus in cough
Hagen 1991	Management guidelines
Han 2007	Retrospective study
Homsí 2000	No comparison/control group
Homsí 2002	No comparison/control group; phase II trial

(Continued)

Jae Youn 1998	No comparison/control group
Kleibel 1980	Testing a cough assessment method rather than a cough intervention
Kleibel 1981	Not a trial, summary of findings
Koster 1970	No comparison/control group
Kubaszewska 2008	No comparison/control group
Lingerfelt 2007	Case study
Lo 1992	Case study
Louie 1992	Case study
Marchioni 1990	No comparison/control group
Matthys 1983	Focus is not on cancer patients
McCaughan 1986	No comparison/control group
McCaughan 1999	Retrospective study
Mehta 1989	No comparison/control group
Moghissi 1997	No comparison/control group
Muers 1993	Study assessing symptoms in general
Ornadel 1997	No comparison/control group
Ozkok 2008	No comparison/control group
Piacenza 1967	Summary of results/advice presented-not reporting a trial
Quantrill 2000	No comparison/control group
Raju 1993	No comparison/control group
Roach 1990	No comparison/control group
Ruffini 1957	Unable to locate from British Library
Scarda 2007	No comparison/control group

(Continued)

Schray 1985a	No comparison/control group
Schray 1985b	No comparison/control group
Schray 1988	No comparison/control group
Seagren 1985	No comparison/control group
Sharma 2002	Unable to locate from British Library
Skowronek 2006	Review article
Spasova 2001	Retrospective study
Speiser 1990	No comparison/control group
Speiser 1995	Review article
Taulelle 1996	No comparison/control group
Taulelle 1998	No comparison/control group
von Gunten 2005	Review article
Vucicevic 1999	No comparison/control group
Yokomise 1998	Case study
Zajac 1993	No comparison/control group
Zylicz 2004	review article

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. MEDLINE search strategy

The MEDLINE search strategy below was used and adapted as appropriate for the other databases:

1. cough.mp.
2. exp cough
3. or/ 1-2
4. exp lung neoplasms OR lung neoplasms.mp.
5. mesothelioma.mp.
6. exp respiratory tract neoplasms OR respiratory tract neoplasm.mp.
7. lung metastas*.mp.
8. lung cancer.mp.
9. lung adj3 carcinom*
10. or/4-9
11. exp carcinoma OR carcinoma.mp.
12. exp neoplasms OR neoplasm.mp.
13. or/11-12
14. advanced adj3 disease*
15. advanced adj3 cancer*
16. terminal* adj3 ill*
17. Or/14-16
18. Or/ 10/ 13/17
19. cough suppressants.mp.
20. nebuli?ed saline.mp.
21. protussive.mp.
22. exp antitussive OR antitussive.mp.
23. demulcent.mp.
24. opioid*.mp.
25. opiate*.mp.
26. aromatic inhalations.mp.
27. codeine.mp.
28. morphine.mp.
29. nebuli?ed local an?esthetic.mp.
30. nebuli?ed an?esthetic.mp.
31. exp lidocaine OR lidocaine.mp.
32. exp bupivacaine OR bupivacaine.mp.
33. sodium cromoglycate.mp.
34. exp Cromolyn Sodium
35. levodropropizine.mp.
36. dihydrocod?ine.mp.
37. benzonatate.mp.
38. simple linctus.mp.
39. pholcod?ine.mp.
40. dextromethorphan.mp.

41. benzoin tincture.mp.
42. menthol.mp.
43. eucalyptus.mp.
44. inhalation.mp.
45. corticosteroids.mp.
46. steroids.mp.
47. nebuli?ed furosemide.mp.
48. nebuli?ed sodium chloride.mp.
49. exp methadone OR methadone.mp.
50. exp diazepam OR diazepam.mp.
51. diamorphine.mp.
52. beclomethasone.mp.
53. levocloperastine.mp.
54. exp pholcod?ine OR pholcod?ine.mp.
55. exp guaifenesin OR guaifenesin.mp.
56. hydrocodone.mp.
57. clobutinol.mp.
58. baclofen.mp.
59. moguisteine.mp.
60. paroxetine.mp.
61. garbapentin.mp.
62. carbamazepine.mp.
63. exp amitryptiline OR amitryptiline.mp.
64. exp nursing care OR nursing care.mp.
65. nursing intervention*.mp.
66. exp physical therap*.mp.
67. physiotherapy*.mp.
68. exp complementary therapies
69. complementary therap*.mp.
70. alternative therap*.mp.
71. alternative medicine*.mp.
72. acupuncture.mp.
73. acupressure.mp.
74. non-pharmacological intervention*.mp.
75. photodynamic therap*.mp.
76. PDT.mp.
77. brachytherapy.mp.
78. education.mp.
79. patient education.mp.
80. exp self care OR self care.mp.
81. or/18-80
82. 3 AND 18 AND 81

Appendix 2. DARE & CENTRAL search strategy

1. cough.mp. [mp=title, full text, keywords]
2. carcinoma.mp. [mp=title, full text, keywords]
3. cancer.mp. [mp=title, full text, keywords]
4. neoplasm*.mp. [mp=title, full text, keywords]
5. metastas*.mp. [mp=title, full text, keywords]
6. advanced disease.mp. [mp=title, full text, keywords]
7. mesothelioma.mp. [mp=title, full text, keywords]
8. 6 or 4 or 3 or 7 or 2 or 5
9. 8 and 1

Appendix 3. CINAHL search strategy

CINAHL search strategy

1. cough.mp. [mp=title, subject heading word, abstract, instrumentation]
2. lung neoplasm*.mp. [mp=title, subject heading word, abstract, instrumentation]
3. exp Lung Neoplasms/
4. 2 or 3
5. mesothelioma.mp. [mp=title, subject heading word, abstract, instrumentation]
6. exp MESOTHELIOMA/
7. 6 or 5
8. exp Respiratory Tract Neoplasms/
9. lung metastas*.mp. [mp=title, subject heading word, abstract, instrumentation]
10. (lung adj3 carcinom*).mp. [mp=title, subject heading word, abstract, instrumentation]
11. 8 or 4 or 7 or 10 or 9
12. carcinoma.mp. [mp=title, subject heading word, abstract, instrumentation]
13. exp CARCINOMA/
14. 13 or 12
15. neoplasm*.mp. [mp=title, subject heading word, abstract, instrumentation]
16. exp NEOPLASMS/
17. 16 or 15
18. 17 or 14
19. (advanced adj3 disease*).mp. [mp=title, subject heading word, abstract, instrumentation]
20. (advanced adj3 cancer*).mp. [mp=title, subject heading word, abstract, instrumentation]
21. (terminal adj3 ill*).mp. [mp=title, subject heading word, abstract, instrumentation]
22. 21 or 19 or 20
23. 22 or 11 or 18
24. cough suppressants.mp. [mp=title, subject heading word, abstract, instrumentation]
25. nebuliz?ed saline.mp. [mp=title, subject heading word, abstract, instrumentation]
26. protussive.mp. [mp=title, subject heading word, abstract, instrumentation]
27. antitussive.mp. [mp=title, subject heading word, abstract, instrumentation]
28. exp Antitussive Agents/
29. 27 or 28
30. demulcent.mp. [mp=title, subject heading word, abstract, instrumentation]
31. opioid*.mp. [mp=title, subject heading word, abstract, instrumentation]
32. opiate*.mp. [mp=title, subject heading word, abstract, instrumentation]
33. codeine.mp. [mp=title, subject heading word, abstract, instrumentation]
34. exp CODEINE/
35. 33 or 34
36. morphine.mp. [mp=title, subject heading word, abstract, instrumentation]
37. exp MORPHINE/

38. 36 or 37
39. lignocaine.mp. [mp=title, subject heading word, abstract, instrumentation]
40. lidocaine.mp. [mp=title, subject heading word, abstract, instrumentation]
41. bupivacaine.mp. [mp=title, subject heading word, abstract, instrumentation]
42. exp Cromolyn Sodium/
43. dihydrocod?ine.mp. [mp=title, subject heading word, abstract, instrumentation]
44. benzonatate.mp. [mp=title, subject heading word, abstract, instrumentation]
45. simple linctus.mp. [mp=title, subject heading word, abstract, instrumentation]
46. pholcod?ine.mp. [mp=title, subject heading word, abstract, instrumentation]
47. dextromethorphan.mp. [mp=title, subject heading word, abstract, instrumentation]
48. menthol.mp. [mp=title, subject heading word, abstract, instrumentation]
49. eucalyptus.mp. [mp=title, subject heading word, abstract, instrumentation]
50. inhalation*.mp. [mp=title, subject heading word, abstract, instrumentation]
51. corticosteroids.mp. [mp=title, subject heading word, abstract, instrumentation]
52. steroids.mp. [mp=title, subject heading word, abstract, instrumentation]
53. exp STEROIDS/
54. 52 or 53
55. nebuli?ed furosemide.mp. [mp=title, subject heading word, abstract, instrumentation]
56. methadone.mp. [mp=title, subject heading word, abstract, instrumentation]
57. diazepam.mp. [mp=title, subject heading word, abstract, instrumentation]
58. diamorphine.mp. [mp=title, subject heading word, abstract, instrumentation]
59. beclomethasone.mp. [mp=title, subject heading word, abstract, instrumentation]
60. pholcod?ine.mp. [mp=title, subject heading word, abstract, instrumentation]
61. guaifenesin.mp. [mp=title, subject heading word, abstract, instrumentation]
62. hydrocodone.mp. [mp=title, subject heading word, abstract, instrumentation]
63. clobutinol.mp. [mp=title, subject heading word, abstract, instrumentation]
64. baclofen.mp. [mp=title, subject heading word, abstract, instrumentation]
65. moguisteine.mp. [mp=title, subject heading word, abstract, instrumentation]
66. paroxetine.mp. [mp=title, subject heading word, abstract, instrumentation]
67. carbamazepine.mp. [mp=title, subject heading word, abstract, instrumentation]
68. amitryptiline.mp. [mp=title, subject heading word, abstract, instrumentation]
69. exp Amitriptyline/
70. 69 or 68
71. nursing care.mp. [mp=title, subject heading word, abstract, instrumentation]
72. exp Nursing Care/
73. 72 or 71
74. nursing intervention*.mp. [mp=title, subject heading word, abstract, instrumentation]
75. physical therap*.mp. [mp=title, subject heading word, abstract, instrumentation]
76. exp Physical Therapy/
77. 75 or 76
78. physiotherap*.mp. [mp=title, subject heading word, abstract, instrumentation]
79. complimentary therap*.mp. [mp=title, subject heading word, abstract, instrumentation]
80. alternative therap*.mp. [mp=title, subject heading word, abstract, instrumentation]
81. exp Alternative Therapies/
82. 81 or 80
83. acupuncture.mp. [mp=title, subject heading word, abstract, instrumentation]
84. exp ACUPUNCTURE/
85. 84 or 83
86. acupressure.mp. [mp=title, subject heading word, abstract, instrumentation]
87. exp ACUPRESSURE/
88. 87 or 86
89. non-pharmacological intervention*.mp. [mp=title, subject heading word, abstract, instrumentation]
90. photodynamic therap*.mp. [mp=title, subject heading word, abstract, instrumentation]

91. PDT.mp. [mp=title, subject heading word, abstract, instrumentation]
92. brachytherapy.mp. [mp=title, subject heading word, abstract, instrumentation]
93. education.mp. [mp=title, subject heading word, abstract, instrumentation]
94. exp EDUCATION/
95. 93 or 94
96. patient education.mp. [mp=title, subject heading word, abstract, instrumentation]
97. exp Patient Education/
98. 97 or 96
99. self care.mp. [mp=title, subject heading word, abstract, instrumentation]
100. exp Self Care/
101. 99 or 100
102. 67 or 32 or 90 or 63 or 70 or 26 or 88 or 30 or 44 or 82 or 55 or 74 or 25 or 95 or 57 or 40 or 61 or 92 or 59 or 49 or 89 or 24 or 31 or 35 or 91 or 78 or 79 or 48 or 42 or 77 or 46 or 65 or 29 or 50 or 85 or 39 or 64 or 51 or 41 or 58 or 47 or 38 or 98 or 60 or 56 or 101 or 73 or 66 or 45 or 43 or 62 or 54
103. 1 and 102 and 23

Appendix 4. EMBASE search strategy

1. cough.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2. exp Coughing/
3. 1 or 2
4. lung neoplasm.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
5. exp Lung Tumor/
6. lung tumo?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. mesothelioma.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8. exp Respiratory Tract Tumor/
9. respiratory tract tumor*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10. 8 or 9
11. respiratory tract neoplasm*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
12. lung metastas*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
13. lung cancer.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
14. exp Lung Cancer/
15. 13 or 14
16. (lung adj3 carcinoma*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17. 6 or 11 or 7 or 12 or 15 or 4 or 16 or 10 or 5
18. carcinoma.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
19. exp CARCINOMA/
20. 18 or 19
21. (advanced adj3 cancer*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
22. (advanced adj3 disease*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

23. (terminal* adj3 ill*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
24. 22 or 21 or 23 or 20
25. cough suppressant*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
26. nebuli?ed saline.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
27. protussive.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
28. antitussive.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
29. exp Antitussive Agent/
30. 28 or 29
31. demulcent.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
32. opioid*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
33. opiate*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
34. cod?ine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
35. morphine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
36. lidocaine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
37. lignocaine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
38. bupivacaine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
39. sodium cromoglycate.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
40. exp Cromoglycate Disodium/
41. 39 or 40
42. levodropropizine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
43. exp Levdropropizine/
44. 42 or 43
45. dihydrocodeine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
46. benzonatate.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
47. simple linctus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
48. pholcod?ine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
49. dextromethorphan.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
50. benzoin tincture.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
51. exp Benzoin/
52. 50 or 51
53. menthol.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

54. eucalyptus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
55. inhalation.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
56. corticosteroids.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
57. exp CORTICOSTEROID/ or exp CORTICOSTEROID DERIVATIVE/ or exp CORTICOSTEROID THERAPY/
58. 57 or 56
59. exp Steroid/
60. steroid*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
61. 59 or 60
62. nebuli?ed furoseamide.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
63. nebuli?ed sodium chloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
64. Methadone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
65. diazepam.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
66. diamorphine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
67. beclomethasone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
68. exp Beclometasone/
69. 67 or 68
70. levocloperastine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
71. guaifenesin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
72. hydrocodone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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79. amitryptiline.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
80. exp Amitriptyline/
81. 80 or 79
82. nursing care.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
83. exp Nursing Care/
84. 83 or 82

85. nursing intervention*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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88. exp PHYSIOTHERAPY/
89. 87 or 88
90. complimentary therap*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
91. exp Alternative Medicine/
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93. exp ACUPUNCTURE/
94. 92 or 93
95. acupressure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
96. exp ACUPRESSURE/
97. 95 or 96
98. non-pharmacological intervention*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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101. brachytherapy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
102. exp BRACHYTHERAPY/
103. 102 or 101
104. education.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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108. 106 or 107
109. 33 or 32 or 90 or 63 or 71 or 70 or 26 or 99 or 72 or 30 or 100 or 44 or 55 or 84 or 74 or 25 or 27 or 75 or 61 or 108 or 69 or 103 or 49 or 89 or 31 or 104 or 35 or 53 or 91 or 78 or 48 or 77 or 46 or 105 or 65 or 85 or 36 or 64 or 97 or 94 or 41 or 58 or 47 or 81 or 38 or 52 or 98 or 34 or 73 or 45 or 37 or 66 or 86 or 76 or 62 or 54
110. 24 or 17 or 20
111. 109 and 3 and 110

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CONTRIBUTIONS OF AUTHORS

AM: review lead, developed search strategy, oversaw the review, assisted in data extraction, wrote final report. Responsible for any updates of this review.

AC, CB, JB: refined search strategy, selected relevant papers for review, assessed studies, assisted in writing final report.

LB: retrieved articles, carried out literature searches, extracted data, assisted in writing final report.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES