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Interventions for cough in cancer (Review)

Molassiotis A, Bailey C, Caress A, Tan JY

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[Intervention Review]

Interventions for cough in cancer

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ABSTRACT

Background

This is an updated version of the original Cochrane review first published in Issue 9, 2010 on “Interventions for cough in cancer”. 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 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 methods

For this update, we searched for relevant studies in CENTRAL and DARE (*The Cochrane Library*); MEDLINE; EMBASE; PsycINFO; AMED and CINAHL to 9 June 2014. In addition, we searched for ongoing trials via the metaRegister of controlled trials (mRCT), ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the UK Clinical Research Network Study Portfolio.

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 the titles and abstracts of all studies for inclusion, and extracted data from all included studies independently before reaching consensus. A third review author arbitrated on any disagreement. Meta-analysis was not attempted due to the heterogeneity of the studies.

Main results

For the original version of the review, 17 studies met the inclusion criteria and examined either brachytherapy, laser or photodynamic therapy (eight studies) or a variety of pharmacological therapies (nine studies). Overall, there was an absence of credible evidence and the majority of studies were of low methodological quality and at high risk of bias. Brachytherapy in a variety of doses seemed to improve cough 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 in relationship to other therapies for cough was unclear. Some indication of positive effect was observed with morphine, codeine, dihydrocodeine, levodropropizine, sodium cromoglycate

and butamirate citrate linctus (cough syrup), although all studies had significant risk of bias. For this update, we did not identify any additional trials for inclusion. Two ongoing trials were identified but no study results were available.

Authors' conclusions

No new trials were included since the publication of the original version of this review, while 11 new studies that were identified were eventually excluded from this review. Therefore, our conclusions remain unchanged. 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 for 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 is difficult to manage in practice. Hence, the aim of this review was to assess and synthesise the available literature on the management of cough in cancer patients in order to improve practice recommendations. Studies with chemotherapy or radiotherapy were excluded. An extensive literature search yielded 17 studies for evaluation. For this update, we did not identify any additional studies for inclusion. Eight of the studies were about the use of brachytherapy (a technique where a radiation source is placed inside the bronchus in the lung for lung cancer 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 studies assessed the effects of a number of different medications, including codeine and morphine. Overall, the research was of poor quality with significant methodological problems, hence no credible evidence was available in the literature to guide practice. Acknowledging these limitations, brachytherapy in a variety of radiation doses was found to be helpful in selected patients. Some pharmacological treatments were found to be helpful, in particular 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 for the management of cough in cancer.

BACKGROUND

This review is an update of a previous review first published in the Cochrane Database of Systematic Reviews, Issue 9, 2010.

Description of the condition

Cough and breathlessness are two of the most common symptoms reported by lung cancer patients, and they can be distressing to patients (Kvale 2003). Cough can either 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)), a complication of the cancer, or may be treatment-related (Homsi 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 (Homsi 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 and 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 associated stigma of such behaviour) and because of 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 is scarce for any treatment. 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 treatment options 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 reported that some centrally acting drugs, such as paroxetine, gabapentin, carbamazepine and amitriptyline (more commonly used to treat epilepsy and mood disorders), have been used to treat chronic cough successfully, although 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 (Homsi 2001), but antitussives are far from effective for managing chronic cough (Chung 2007) and better management approaches are needed for these patients.

How the intervention might work

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 cough, 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, as shown with 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. Stategies 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 or 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 (Homsi 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 to provide some direction for future research.

OBJECTIVES

The primary objective 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).

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 were included as it was evident that few high quality RCTs have investigated the management of cough in malignant disease and these studies would serve to highlight some promising treatments that need further evaluation.

Types of participants

Adult participants (over 18 years of age and of either gender) with malignant disease and experiencing cough or coughing, dry cough, 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 had cough due to chest infections were excluded.

Types of interventions

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

1. Pharmacological interventions

Pharmacological interventions included any medicinal product or substance as classified by the EU directive 2001/83/EEC. These could 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 were not classified as medicinal products in the above-mentioned EU directive, and could include drainage of pleural effusions, complementary therapies (that is 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 were excluded from this review as there are a significant number of publications with various chemotherapy regimens where symptoms and quality of life were secondary outcomes and that showed improvements in symptoms (that is Clegg 2001; Natale 2004; Reck 2005; Thatcher 1997). Radiotherapy (external beam) for cough was 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 treatment, although this is a less common occurrence.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

Secondary outcomes included quality of life (measured by validated scales, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Cancer 30 (EORTC-QOL-C30), Functional Assessment of Cancer Therapy: General (FACT-G); WHOQOL scale) or symptom scores.

Search methods for identification of studies

Electronic searches

For details of the original searches please see Appendix 1. For this update, we searched the following databases to 9 June 2014:

- CENTRAL and DARE (via *T he Cochrane Library*) (2014, Issue 5 of 12);
- MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (May 2010 to 9 June 2014);
- EMBASE (via Ovid) (May 2010 to 9 June 2014);
- PsycINFO (via Ovid) (2010 to week 1 June 2014);
- AMED (via Ovid) (2010 to June 2014);
- CINAHL (via EBSCO) (May 2010 to June 2014).

Medical subject headings (MeSH) or equivalent, key words and free words were employed for searching. Search strategies were tailored to individual databases and were adapted from those used in the original version of this review. We have been simplifying the search strategies used in this update as we felt that having an 'intervention' section in the search strategy was restricting the search too much. We did not use Open Grey, British Nursing Index and CancerLit as, based on our experience of doing the original review, there were seldom targeted trials identified in these three databases. The updated search strategies for this review are listed in Appendix 2, Appendix 3, Appendix 4, Appendix 5 and Appendix 6.

Searching other resources

Handsearching, personal contact and ongoing trials searching

For the original review and this update, the reference lists of all relevant studies were checked for identification of additional studies. Handsearching alsoincluded 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 communicated with key authors of cough studies in the respiratory field, who confirmed that they were not aware of other studies. In addition, we searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), ClinicalTrials.gov (www.clinicaltrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) and the UK Clinical Research Network Study Portfolio (http://public.ukcrn.org.uk/search/) for ongoing trials.

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.

Data extraction and management

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 (as outpatient or 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 were entered into the RevMan 5.3 software (RevMan 2014).

Assessment of risk of bias in included studies

For the original version of this review, the Cochrane risk of bias tool was used to assess the methodological quality of the studies. This tool assisted review authors to make a judgement (yes, no or unclear) in six areas, including the 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 agreement by consensus. Any disagreements were arbitrated by a third review author. For this update, two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011), with any disagreements resolved by discussion. A risk of bias table was produced for each included trial using the risk of bias tool in the RevMan 5.3 software (RevMan 2014).

We assessed the following for each of the included studies:

- random sequence generation (for checking potential selection bias);
- allocation concealment (for checking potential selection bias);
- blinding of participants and personnel (for checking potential performance bias);
- blinding of outcome assessment (for checking potential detection bias);
- incomplete outcome data (for checking potential attrition bias due to the amount, nature and handling of incomplete outcome data);
- selective reporting (for checking potential reporting bias);
- size of study (for checking potential biases confounded by small sample size);
- other bias.

Measures of treatment effect

Any related to cough, patient-reported or physiological.

Unit of analysis issues

Use of cross-over designs, repeated measures designs or cluster randomised trials was identified.

Dealing with missing data

No specific attempt was made to manage missing data, as only narrative synthesis of the identified studies was possible.

Assessment of heterogeneity

A minimal number of studies for any given intervention was found, hence no formal assessment took place.

Data synthesis

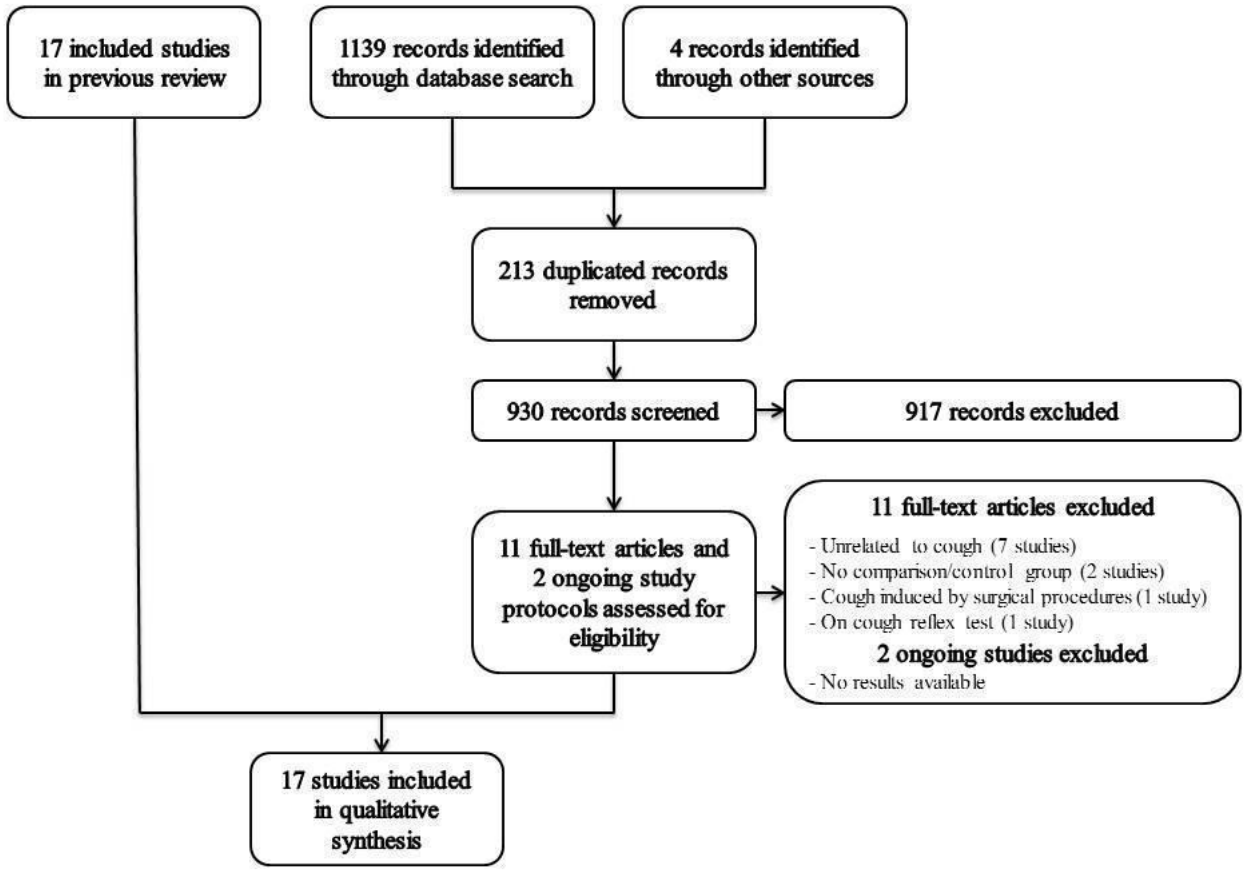
The findings were interpreted within the framework of a narrative synthesis as the studies were too heterogeneous with regard to interventions and outcomes to permit meta-analysis. The risk ratio (RR) and number needed to treat to benefit (NNTB) were not used as numerical aggregation of the data was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

RESULTS

Description of studies

The flow chart of the study selection is shown in Figure 1. Please see the 'Characteristics of included studies' table for full information on the included studies.

Figure 1. Flow chart of study selection.



Results of the search

For the original version of this review, overall the literature searches yielded 1132 studies. Studies were excluded because they were primarily case studies (n = 299), reviews (n = 354), or the randomised 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. The reasons for exclusion of the remaining 68 studies are shown in the 'Characteristics of excluded studies'.

Included studies

In total 17 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 studies included in the review were categorised into two broad areas: those reporting results from brachytherapy, laser therapy and photodynamic therapy; and those reporting results from pharmacological studies. There was no study identified that reported a non-pharmacological intervention other than brachytherapy, laser and photodynamic therapy.

For this update, a total of 1139 records were identified by searching the databases. Four ongoing studies were also found. Two hundred and thirteen duplicate records were removed and another 917 records were excluded because they were: primarily case studies (n = 42), reviews or meta-analyses (n = 116), laboratory studies (n = 6), qualitative interview (n = 1), conference abstracts (n = 4), studies involving paediatric participants (n = 35) or had non-cancer participants (n = 220), unrelated to cough (n = 173), and the study intervention was chemotherapy or external beam radiotherapy (n = 320). This updated review found no additional trials for inclusion.

Excluded studies

Two ongoing studies and 11 full-text articles were retrieved for further evaluation and all the 11 full-text papers were finally excluded in this update. Reasons for excluding these 11 trials were added to the 'Characteristics of excluded studies'. The two ongoing studies were excluded because the study results were not available. See 'Characteristics of ongoing studies' for more information.

Risk of bias in included studies

The risk of bias was high in all studies, with only one study reporting randomisation methods (Diaz-Jimenez 1999), while the vast majority of studies were unblinded and did not report data on attrition. We completed two risk of bias summary graphs for the included trials. Please see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

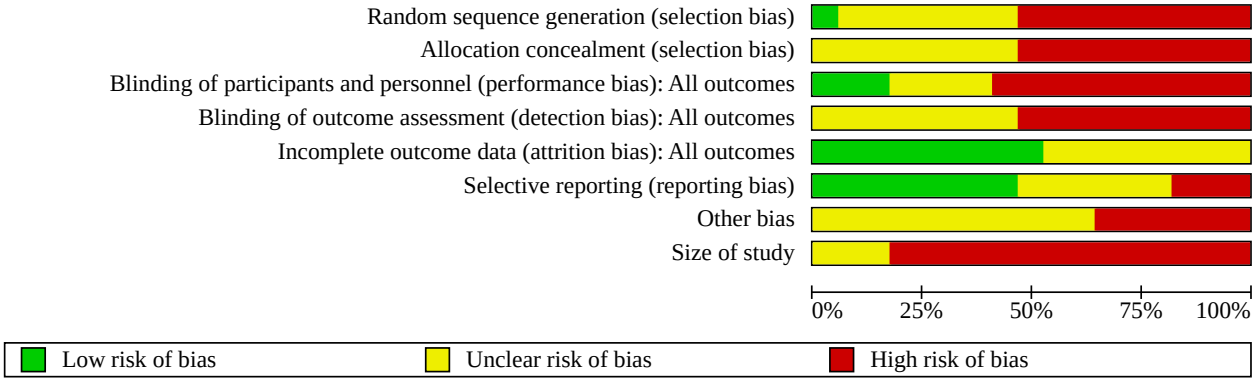
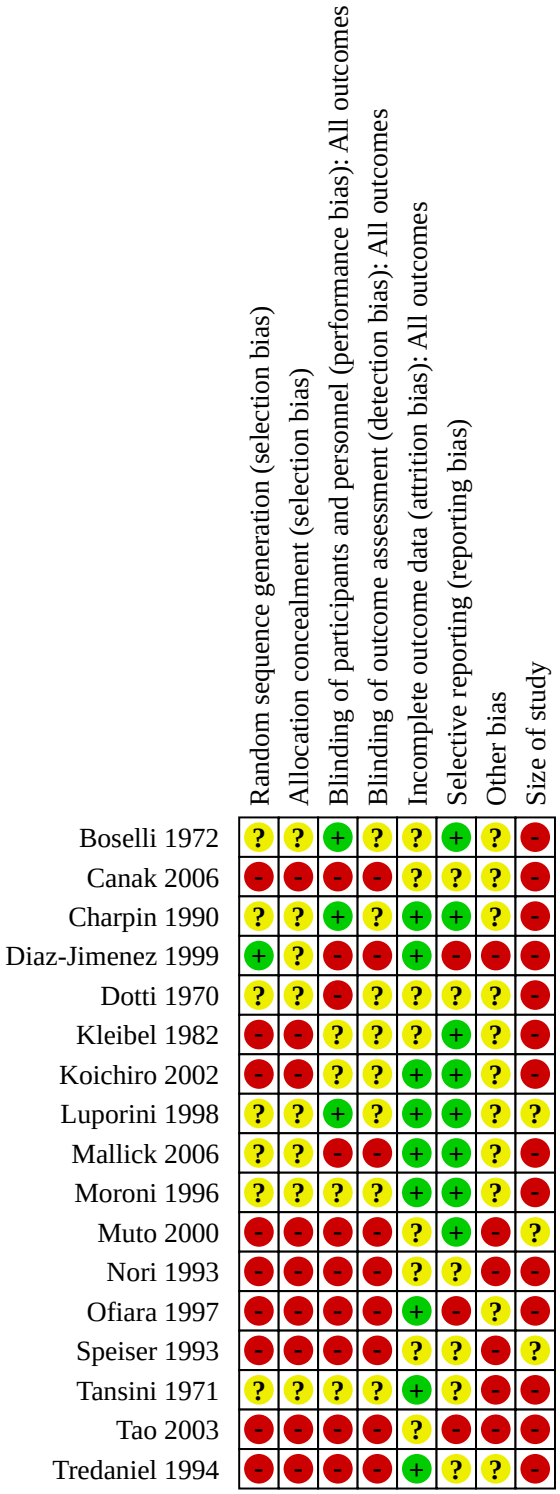


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The majority of studies (n = 9) had a high risk of selection bias, with the remaining eight having unclear risk due to insufficient information provided in the published papers.

Blinding

Three of the included studies had low performance and detection bias, while the vast majority were either at high risk (=9) or unclear risk of bias (n = 5).

Incomplete outcome data

Attrition bias was unclear in eight studies due to lack of information, while the remaining nine were at low risk of bias.

Selective reporting

Eight studies were at low risk of reporting bias, four at high risk, and the remaining five at unclear risk of bias.

Other potential sources of bias

In many studies the information was insufficient to make a judgement (n = 7) or it presented an unclear study design (n = 4). Six studies were at high risk of bias: the cough condition was not the same in the study groups in one trial; studies had uneven sample sizes between the study groups in two trials; and there were no patient characteristics reported in three studies.

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 this 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 between the treatment arms (possibly due to the small sample); therefore the optimal dose, fractionation and combination with external radiation were still open to debate. Arm C had a shorter duration of symptom palliation, though it achieved comparable rates of palliation of all symptoms and objective signs and 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 found similar improvements (Muto 2000); also showing that the smallest irradiated volume and fractionated high dose rate brachytherapy were associated with fewer side effects. A dose of 5 Gy (and 4 Gy for a small number of participants) waseffective in another small scale study of 30 participants (Nori 1993), showing that an excellent clinical response with minimal morbidity could be achieved by reducing the dose per fraction delivered by high dose rate brachytherapy. In another small scale study 24 Gy over three fractions weekly also resulted in improvements, 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 at 10 mm depth or 7.5 Gy at 10 mm depth, all in single fractions, and again found similar improvements with the three doses. The conclusion from this study was that the use of high dose rate remote afterloading brachytherapy provided excellent palliation in a group of patients where cure was either not attainable or had 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 with small tumours and limited disease. The authors concluded that effective remission of endobronchial tumours could be achieved with high dose rate endobronchial brachytherapy as the sole therapy. The patients were carefully selected, had small tumours limited to the bronchial lumen or wall without adjacent parenchymal extension or metastatic disease, and duration of response and survival rates were similar to those seen in conventional treatment; however, these benefits were achieved with less expense and without major complications.

The above results showed that there was no standard dose of brachytherapy, as all doses resulted in similar outcomes for cough. This indicated that the lowest dose should be preferred, as it had a good response and a lower number of adverse reactions. The studies in this category were of low quality however, 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 the studies were retrospective audits of treated patients presented in a research article format. Attempts to communicate with authors were made 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 the 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 n = 59) and half of them included mixed samples of patients with a variety of pulmonary diseases, with lung cancer patients being a small proportion of these participants (data were 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 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 to excellent' tolerance in all participants. The investigators then continued testing this mixture against another that contained 5 mg dihydrocodeine, twice daily. The results suggested that the mixture containing codeine was more effective (Dotti 1970). While the 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 70s assessed the effect of dihydrocodeine 10 to 20 drops 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 70s (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 high sedative effect and more, albeit mild, nausea.

The two Chinese herbal studies tested the effects of two oral herbal combinations (TJ-29 in the first study and Fei Tong in the second) (Koichiro 2002; Tao 2003). The first study, which had cough as a secondary outcome, found no difference compared with a historical control group (unspecified treatment) while the second study assessed the herbal combination against prednisolone and found that the herbal combinations produced better results than the steroids.

The effects of levodropropizine (equivalent dose 75 mg) and dihydrocodeine (equivalent dose 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% compared with 8% for levodropropizine (Luporini 1998). In another study, a morphine derivative was found to be as effective as codeine capsules, although the dose for both medications 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 participants needed 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 about the treatment effect. Also, if patients had an underlying respiratory condition (that is asthma) that 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, 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

No new trials were identified for inclusion since the publication of the original version of this review. This review has shown the almost complete absence of any credible evidence on 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, showed that 42.9%, 39.2%, 35.1% and 36.1% of patients complained of cough when assessed at the beginning of treatment and 3, 6 and 12 months later, respectively. This was 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, 2010a). Most research was of poor quality and was conducted in the 1970s. Little up-to-date evidence is available. Nevertheless, evidence from this review and other sources that included clinical expert opinion have been utilised to devise a clinical guidelines for managing cough in lung cancer (Molassiotis, 2010b). Subsequent work by Wee et al (Wee 2012) has summarised the related evidence using less stringent criteria, leading to the development of a new guideline for palliative care.

While this 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. These data concur with another well-conducted pre- and post-test single arm study (n = 95) showing symptom improvements with brachytherapy, 7.5 Gy at 10 mm in three fractions once per week or 10 Gy twice per week, with cough showing complete resolution in patients with centrally-located tumours and significant improvement in patients with peripheral lung tumours (Celebioglu 2002). Similarly, another phase II study of three treatments with 5 Gy showed an improvement of 42.8% (Anacak 2001). Both of these 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 patients with non-small lung cancer, primarily including single arm trials (excluded from 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 compared with 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 or levodropropizine seem to exercise some positive effect on cough related to lung cancer. This (variable) effect should be balanced with the 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 population was not reported in the study by Moroni 1996 , making this result questionable. The effects of codeine 60 mg and levodropropizine (at 60 mg, 100 mg and 200 mg three times daily) on cough are supported by other studies in chronic cough patients (see excluded studies Barnabe 1995; Catena 1997; Fasciolo 1994; Matthys 1983). Butamirate linctus is currently included in many over-the-counter cough preparations, and management of lung cancer-related cough commonly includes codeine and morphine in clinical practice. 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) diseases 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. In particular, 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 patients' daily living and quality of life. The level of measurement was nominal in most cases, 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 3, and 9/17 studies receiving a score of 0. This indicates that the degree of bias was high in all of these studies. The heterogeneity of the included studies and the different ways that the studies assessed 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).

Summary of main results

Brachytherapy for selected patients with lung cancer is a useful intervention for managing cough, as is external beam radiation therapy (although the latter result is based on single arm studies not included in the review). A number of pharmacological treatments, including butamirate linctus, codeine (60 mg), morphine, dihydrocodeine (10 mg), cromoglycate and hydropropizine or levodropropizine, may have a positive effect in managing cough, although the evidence is based on poorly controlled studies.

Overall completeness and applicability of evidence

The studies included in this review are methodologically weak, conducted many years ago (in some cases decades ago), with unclear information on several aspects of the study, making the available data incomplete. The evidence is extremely weak.

Quality of the evidence

Mostly studies had a high risk of bias and provided low quality evidence.

Potential biases in the review process

None.

Agreements and disagreements with other studies or reviews

None.

AUTHORS' CONCLUSIONS

Implications for practice

Since publication of the original version of this review, no new trials were identified for inclusion. No implications 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 that are often used in current clinical practice (for example methadone linctus, lidocaine) and those that are contained in over-the-counter preparations (for example dextromethorphan, simple linctus) have not been assessed as yet. Hence, as far as cough management in cancer is concerned, it is clear that evidence-based practice remains in its infancy and therapeutic interventions can be applied with little certainty about their actual benefits. Another area that is missing is a clear threshold of cough (in terms of frequency, 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 in observing clinically meaningful improvements from an intervention.

Implications for research

The results of this review update 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 with the existence of a limited number of RCTs and 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 the 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 for 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 on frequency or severity of cough only. The impact of the intervention

may extend to improvements in other symptoms that are present concurrently with cough (for example night time length and quality of sleep, 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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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boselli 1972

Study characteristics	
Methods	Double blind randomised controlled trial

Boselli 1972 *(Continued)*

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% to 100% reduction in coughing fits); 1/6 = good (60% to 80% reduction in coughing fits); 1/6 = moderate (40% to 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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both solutions were prepared with identical characteristics, put in identical bottles, only identifiable by different initials. Codes not revealed until after experiment finished."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on "Methods" were reported
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (31 in stage 1 of study, and 40 in stage 2 of study)

Canak 2006

Study characteristics	
Methods	Comparative study. No randomisation
Participants	N = 64, histology proven lung cancer, most had grade IIIb Group 1: mean age: 57 years. Sex: M 18/F 2 Group 2: mean age: 58 years. Sex: M 37/ F7 Inclusion criteria: malignant central airway obstruction due to lung cancer, Karnofsky index = 50 Exclusion criteria: patients > 70 years
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 fractions (#) weekly (7 Gy per #) at 1 cm, followed by EBRT using split course, with 40 Gy in 10 fractions (2 x 5 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	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Comparative study, no randomisation
Allocation concealment (selection bias)	High risk	Allocation by availability of treatment; Group 1 patients received laser resection only due to technical issues in radiation department
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Seems all subjects were included in analysis but insufficient information provided; outcome data for frequency of cough only given in percentages

Canak 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information provided, no information given regarding how cough or other symptoms were measured
Other bias	Unclear risk	Unclear study design, could be a retrospective study design
Size of study	High risk	Small sample size (20 and 44 in each study group respectively)

Charpin 1990

Study characteristics	
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 to 81. Sex: M18/F22. Weight, kg (mean ± SD, range): 60 ± 11, 44 to 84 Clobutinol group (n = 30): Age, years (mean ± SD, range): 55 ± 13, 24 to 79. Sex: M17/F13. Weight, kg (mean ± SD, range): 66 ± 14 (36 to 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 125 ml 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): 1 tablespoon, 3 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 to 11) Clobutinol group 7.5 ± 2.0 (3 to 10) Post-treatment Improvement of coughing frequency (patient's diary) (for cancer patients only): Butamirate citrate linctus group = 7/7, clobutinol group = 2/7 (x 2 = 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. A significant difference occurred in carcinoma patients in favour of butamirate citrate (P = 0.013) No significant difference found between groups either at end of study or during 4 days of treatment Physician's Global Opinion score:

Charpin 1990 *(Continued)*

	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
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The trial medications…were supplied in identical bottles… and labeled with a drug code and with a patient number"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seven patients were excluded from analysis with reasons, per protocol analysis conducted
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on "Methods" were reported
Other bias	Unclear risk	Statistically significant better effect was found for butamirate in cancer patients
Size of study	High risk	Small sample size (30 in each of the two study groups)

Diaz-Jimenez 1999

Study characteristics

Methods	Prospective randomised controlled trial
Participants	N = 31, NSCLC Age mean (SD) 65 (7). Sex: M (31) PDT group mean age (years) = 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

Diaz-Jimenez 1999 *(Continued)*

	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 after 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
Interventions	PDT Group: n = 14; PDT based on estimated size of tumour. Tumours were irradiated (630 nm light) via a flexible fibre optic bronchoscope 40 to 50 hours post-intravenous injection of 2 mg/kg DHE (Photofin). Two days post-treatment a bronchoscopy was performed to clean detritus. Second argon dye irradiation was performed if parts of tumour failed to show signs of necrosis 96 to 120 hours post-treatment, and if bronchoscopy revealed recurrence then patients could receive a second 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 to 6 laser photo radiations with maximum of 2 photo radiations per session. If toxic effects occurred, treatment was stopped until these resolved 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 at 2 to 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 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)
Outcomes	Pre-treatment: cough was more common in Nd-YAG laser resection group (P = 0.02) 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 improvements than did cough between 1 week and 1 month post-treatment Adverse events: 26 patients had at least one adverse event, 16 patients experienced two adverse events; cough and photosensitization was the most frequent combination. Five patients died within 2 months of last day of treatment (1 in PDT group 'probably' related to treatment) Jadad score = 2
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The groups were assigned by opening randomly ordered closed envelopes…"
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial; blinding unable to take place due to types of treatments being compared

Diaz-Jimenez 1999 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label trial; blinding unable to take place due to types of treatments being compared
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates provided with explanations
Selective reporting (reporting bias)	High risk	Karnofsky performance status during the follow-up periods not reported; no information given on how cough was measured
Other bias	High risk	Cough conditions not similar between groups at baseline (P = 0.02); prolonged survival of patients in PDT group could be due to unequal distribution of patients
Size of study	High risk	Small sample size (14 and 17 in each study group respectively)

Dotti 1970

Study characteristics	
Methods	Double blind randomised controlled trial
Participants	N = 41, various conditions: pulmonary neoplasia (n = 13); recent or chronic pulmonary TB (n = 26); bronchopulmonitis (n = 2) Part 1 (n = 26). Age range: 19 to 76 years. Sex: M22/F4 Part 2 (n = 20). Age range: 19 to 74 years (5 of these were previously treated in the first part of the study). Sex: M18/F2 Inclusion criteria: patients who had been admitted to participating hospital for persistent cough
Interventions	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 28 mg of phenyltoloxamine resinate, equal to 10 mg of phenyltoloxamine base). B = lactose (placebo); C = dibenzonium bromide 30 mg + lactose (all in capsule form) Treatment consisted of 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 a person's 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 Part 2 of study (cancer patients n = unclear): A = Codipront Bracco (as explained above) compared with dihydrocodeine with pentamethyletetratzole drops (10 g containing 1 g pentamethylene tetrazole + 0.05 g dihydrocodeine. On alternate days, these patients were given the Arm A drug in doses of 2 capsules per day (BD), and dihydrocodeine with pentamethylenetetrazole in doses of 45 drops for first 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 to good, 2/4 = doubtful; placebo 4/4 = doubtful or none; dibenzonium bromide = 1/4 moderate, 3/4 doubtful or none

Dotti 1970 *(Continued)*

	Tolerance: good to 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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding unable to take place in the second part of study as different types of preparation being tested (capsules versus drops)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided, authors state that 12 patients had pulmonary neoplasia but can only find data for 5 cancer patients
Selective reporting (reporting bias)	Unclear risk	Subjective and objective effects on frequency, duration and intensity of coughing spells were measured and reported for patients, but unable to identify 8/13 cancer patients results
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (41 in total and 13 in cancer sample size)

Kleibel 1982

Study characteristics

Methods	Comparative study
Participants	N = 31, variety of cancers (largest group was metastatic breast cancer, n = 17) Sex: M10/F21
Interventions	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: 2 x 1 daily (no indication of mg)

Kleibel 1982 *(Continued)*

	Group B (n = 10): Codipront capsules (containing codeine and silver (Ag)). Dosage 2 x 1 daily (no indication of mg)
Outcomes	Post-treatment: Time until drug effectiveness was observable: in both groups between 20 and 30 minutes; no statistical difference Duration of effectiveness: between 7 and 8 hours in both groups; no statistical difference Dorecotuss retard. Cough-free interval day 1 = 13/21 good, 5/21 moderate, 3/21 unsatisfactory Codipront. Cough-free interval day 1 = 8/10 good, 2/10 moderate Adverse events: opioid-specific side effects only in group B, with 3 patients (3/10) with constipation Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comparative study, no randomisation
Allocation concealment (selection bias)	High risk	Open label trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or exclusions reported
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the “Methods” section were reported
Other bias	Unclear risk	Unclear study design
Size of study	High risk	Small sample size (21 and 10 in each study group respectively)

Koichiro 2002

Study characteristics

Methods	Comparative study using a historical cohort as the control group. Sample from 1993 to 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

Koichiro 2002 *(Continued)*

	Control group. Mean age, range: 73.1 years, 60 to 87 Experimental group. Mean age, range: 65.7 years, 57 to 75
Interventions	Intervention group: N = 12, receiving TJ-29 (Chinese Medicine Herb, Tsumura Co Bakumondo-to; 9 g, 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-group differences were seen in relation to hoarseness of voice, xerostomia, pharyngoxerosis and cough Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comparative study using an historical cohort as the control
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts reported with reasons
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on “Methods” were reported
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (20 in total)

Luporini 1998

Study characteristics

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:

Luporini 1998 *(Continued)*

	Age, years (mean, SD): 62.9 ± 9. Sex: M59/F10. Weight, kg (mean, SD): 67 ± 11. Height, cm (mean, SD): 167 ± 7. Smokers: 10 Dihyrocodeine 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 - Levotuss, 6% oral drops, daily administered dose equal to 75 mg (25 drops) three times per day, 6 to 8 hourly intervals, for 7 days Intervention group (n = 71): dihydrocodeine rhodanate - Paracodina 1% oral drops, daily administered dose equal to 10 mg (25 drops) three times per day, 6 to 8 hourly intervals for 7 days 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
Outcomes	Pre-treatment: 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 Night awakenings (mean, SD): 1.4 ± 1.9 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 Night awakenings (mean, SD): 1.1 ± 1.5 After treatment: 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 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): levodropropizine 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 Dihydrocodeine group (n, mean, SD): Day one: 29, 1.6 ± 1.2, day three: 29, 0.6 ± 0.9, day seven: 27, 0.6 ± 1.1 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) 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) Safety, presence of somnolence: levodropropizine = 5/66 (8%; P < 0.05); dihydrocodeine = 15/69 (22%) Per protocol analysis of somnolence: Levodropropizine: 5/60 (8%; P < 0.05); dihydrocodeine: 15/63 (24%) Patients receiving concomitant medication known to induce somnolence: levodropropizine group: n = 3, dihydrocodeine group n = 4. No severe somnolence reported after treatment with either drug Other secondary safety results (e.g. BP/HR/blood results) showed no significant change in either group during treatment

Luporini 1998 *(Continued)*

	Adverse events: Levodropropizine group: n = 6 (1 death due to disease, vomiting, diarrhoea, epigastric pain). Dihydrocodeine group: n = 4 (1 death due to disease, erythema of abdomen, gastric pain, somnolence) Jadad score = 3
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To keep the two treatments indistinguishable as per the number of drops dispensed, the dose of...was slightly higher than the recommended dose…"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts explained, used per protocol analysis; small attrition rate unlikely to have a relevant impact on observed effect size
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on "Methods" were reported
Other bias	Unclear risk	Insufficient information provided
Size of study	Unclear risk	Relatively small sample size (69 and 71 in each study group respectively)

Mallick 2006

Study characteristics	
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 # (8 Gy per #) Arm B (n = 15): received EBRT to a dose of 30 Gy/10 #/2 weeks 10 Gy at 1 cm depth in 1 # (single dose)

Mallick 2006 *(Continued)*

	Arm C (n = 15): 15 Gy at 1 cm depth in 1 # (single dose), without EBRT
Outcomes	Pre-treatment: all participants had cough prior to treatment 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) Cough median time to relapse in months: overall = 5, Arm A = 4; Arm B = 7; Arm C = 4 (P = 0.09) Cough median time to progression in months: overall = 8, Arm A = 7; Arm B = NR; Arm C = NR (P = 0.77) EORTC QLQ LC-13 cough scores: Overall pre-post = 62/33* Arm A = 67/40*; Arm B = 65/36*; Arm C = 56/22* (* statistically significant difference) 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. 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 complications. 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) Jadad score = 1
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding unable to take place due to types of treatments being compared
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding unable to take place due to types of treatments being compared
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized sample included in final analysis
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on “Methods” were reported
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (15 in each of the three study groups)

Moroni 1996

Study characteristics	
Methods	Double blind placebo controlled randomised trial
Participants	N = 20, locally advanced or unresectable metastatic NSCLC Intervention group: age, years (mean, range): 65.6, 55 to 74. Sex: M8/F2 Placebo group: age, years (mean, range): 62.7, 52 to 71. Sex: M7/F3 Both groups were similar in terms of histology and previous treatment regimes Inclusion criteria: patients with locally advanced or unresectable metastatic NSCLC and irritative neoplastic cough resistant to conventional treatment
Interventions	Intervention group (n = 10): 40 mg sodium cromoglycate per day (patients instructed to inhale 2 puffs 4 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 to 75 percentile 2.3 to 3.7) Placebo group mean daily score = 3.03 (median 3.2; 25 to 75 percentile 2.3 to 3.7) Post-treatment: Cough score Sodium cromoglycate group - mean daily score = 1.6 (median 1.4; 25 to 75 percentile 1.4 to 1.8) Placebo group - mean daily score = 2.9 (median 2.9; 25 to 75 percentile 2.1 to 3.6) Cough intensity: reduction in cough intensity in sodium cromoglycate group compared to placebo was statistically significant, P < 0.001 Cough neither worsened nor remained stable in any sodium cromoglycate patient, which was different to the placebo control group Jadad score = 2
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias)	Unclear risk	"…in a double-blind trial, either inhaled sodium cromoglycate or placebo (inhaled physiological solution...)", no other information provided

Moroni 1996 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, all subjects included in the analysis
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on "Methods" were reported
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (10 in each of the two study groups)

Muto 2000

Study characteristics	
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 to IIIB, Karnofsky Performance Score > 60, expectancy of life > 6 months, presence of cough or dyspnoea or both, 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 and 6 weeks of treatment) Group C1: n = 50, dose calculated at 1 cm from central axis of the catheter of treatment Group C2: n = 139, dose calculated at 0.5 cm from the central axis
Outcomes	Pre-treatment: symptomatic response rate (presence of symptoms in percentages Group A: 92; Group B: 96; Group C1: 90; Group C2: 91 Post-treatment: symptomatic response rate (presence of symptoms during treatment and after 1 month in percentages Group A: 80/42; Group B: 82/28; Group C1: 79/12; Group C2: 83/11 Overall response rate to cough 1 month post-treatment = 77%; 82% after 6 months

Muto 2000 *(Continued)*

	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
	Severe complication: fatal haemoptysis
	Group A: 2/78; Group B: 3/46; Group C1: 2/36; Group C2: 3/120
	Complications linked to procedure of bronchoscopy
	Group A: 2/78; Group B: 2/46; Group C1: 0/36; Group C2: 3/120
	Broncho-oesophageal fistulas occurred in 1/78
	Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Subjects who were lost follow up not included in final analysis; attrition rate is 12.5% and unlikely to have influenced study results
Selective reporting (reporting bias)	Low risk	All expected outcomes listed in the section on “Methods” were reported
Other bias	High risk	No baseline comparison between study groups; no patients characteristics reported for any patients
Size of study	Unclear risk	Relatively small sample size (sample size range from 47 to 139 in the four study groups)

Nori 1993

Study characteristics

Methods	Comparative trial
Participants	N = 32, majority of patients had primary malignant neoplasm of lung (n = 30)

Nori 1993 *(Continued)*

	Age, years (median, range): 59, 49 to 80 Histology Primary malignant neoplasm of lung: n = 30; primary cervical carcinoma: n = 1; primary colon carcinoma with lung metastasis: n = 1 Group 1: all had pulmonary neoplasms IIIB (treated by BT as a boost to primary external beam irradiation) 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
Interventions	Prior treatment given: Median external beam dose prior to intraluminal treatment = 50 Gy Range, group 1 = 50 to 60 Gy, group 2 = 40 to 50 Gy Brachytherapy only performed when bronchoscopy revealed an endobronchial component of the primary or recurrent tumour Time from completion of EBRT to BT (median/average): group 1 = 7 days; group 2 = 6 months BT regimen for both groups: uniform dose of 5 Gy per # for 28 patients and 4 Gy per # for 4 patients was prescribed at 1 cm depth. Length of treatment varied from 4 to 7 cm, median length = 5 cm Majority of patients received 3 to 4 # weekly
Outcomes	Pre-intervention treatment, presenting symptoms (number/%): haemoptysis 15/47%; cough 7/22%; dyspnoea 10/31%, combination of above 25/78% 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% of group 2 patients Adverse events: treatment was well tolerated, 'minimal acute or late complications' were observed. One procedure was abandoned secondary to bleeding during the 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 Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place

Nori 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition and exclusions not reported
Selective reporting (reporting bias)	Unclear risk	Only reported 7/32 patients who had: "unremitting cough" before treatment; insufficient data given on how cough was measured
Other bias	High risk	No baseline comparison between study groups; study design unclear
Size of study	High risk	Small sample size (17 and 15 in each study group respectively)

Ofiara 1997

Study characteristics	
Methods	Comparative study using the same treatment on different disease populations
Participants	N = 30, symptomatic endobronchial bronchogenic carcinoma Patients stratified into 2 groups depending on disease type (after initial bronchoscopy) Group 1 patients (n = 20): tumour characterised by endoluminal disease Group 2 patients (n = 10): submucosal infiltration or extrinsic compression, or both Patients were also stratified according to tumour location = central (trachea or main stem bronchi, n = 10) or peripheral (lobar or segmental bronchi, n = 14) Group 1: Age, years (mean, range): 64, 33 to 73; squamous cell: 15; adenocarcinoma: 4; small cell: 1; Stage (TNM): IIIa, 9; IIIb, 8; IV, 2; small cell limited, 0; extensive, 1; initial ECOG score (SD): 1.8 (0.8) Group 2: Age, year (mean, range): 65, 44 to 80; squamous cell: 5; adenocarcinoma: 3; small cell: 2; Stage (TNM): IIIa, 3; IIIb, 4; 1V, 1; small cell limited, 1; extensive, 1; initial ECOG score (SD): 1.7 (0.9) 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
Interventions	High dose remote afterloading endobronchial irradiation and brachytherapy All patients: 8 Gy at 1 cm depth, with an aim for 24 Gy in 3 # over 6 weeks: 8 Gy per # weekly Follow-up bronchoscopy performed 4 weeks post-BT (week 8)
Outcomes	Post-treatment Overall: statistically significant improvement in cough from baseline to week 8 (11/24, P < 0.01) Group 1: no statistically significant improvement in cough was seen (6/16) Group 2: statistically significant improvement from baseline to week 8 (5/8, P < 0.05)

Ofiara 1997 *(Continued)*

	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 and 8 of study (group 1 = 2 patients; group 2 = 1 patient), attributed to progressive underlying disease Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusions reported
Selective reporting (reporting bias)	High risk	Performance status after treatment not reported
Other bias	Unclear risk	Insufficient information provided
Size of study	High risk	Small sample size (20 and 10 in each study group respectively)

Speiser 1993

Study characteristics

Methods	Comparative study - patients treated according to disease based on a protocol
Participants	N = 342, endobronchial carcinoma Age, years (mean ± SD, range): 66.6 ± 9.6 years, 31 to 90 Sex: M214/F125 (63%/37%) Histology: 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

Speiser 1993 *(Continued)*

	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 Palliative intent: primary lung carcinoma, NSCLC; T4 or M1 or both disease category; or patients with lesser 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 Recurrence: all histologies for patients who had received a prior course of curative intent radiation therapy
Interventions	Group 1 (n = 47): medium dose rate 10 Gy in 1 # (single dose) at 5 mm depth Group 2 (n = 144) high dose rate, 10 Gy in 1 # (single dose) at 10 mm depth Group 3 (n = 151): high dose rate 7.5 Gy in 1 # (single dose) at 10 mm depth Number of BT procedures per patient, N/%: 2 = 38/11; 3 = 281/82.5; 4 = 12/3.5; 5 = 4/1; 6 = 6/2 Each group was split into curative intent, palliative or recurrent and could receive the following treatment on top of the treatment described above: Curative intent - EBRT 60 Gy in 30 # (weeks 1 to 6); BT performed during weeks 1, 3, 5 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 Recurrent cancer - all patients had received a prior course of curative intent EBRT; received BT only on weeks 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	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) 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’ Cough symptom percentage of symptom index score: first brachytherapy 100; second brachytherapy 68; third brachytherapy 48; first follow-up bronchoscopy 15. Symptom index response expressed as per cent 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 Adverse events: complications arising from bronchoscopy (post-therapy) in Group 1 patients = 3%, included pneumothorax (3 patients), arrhythmia, haemoptysis, and infection. This was secondary to technique of placing catheter and was rectified, then a 0.5% complication rate reported Radiation bronchitis and stenosis: Group 1 9%; Group 2 12%; Group 3 11%. Massive haemoptysis (leading to death): 7.3% Jadad score = 0
Notes	
Risk of bias	

Speiser 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or exclusions reported
Selective reporting (reporting bias)	Unclear risk	Cough scores analysed but no between-group comparison reported
Other bias	High risk	No baseline comparison between study groups; uneven sample sizes between groups
Size of study	Unclear risk	Relatively small sample size (sample size range from 47 to 151 in the three study groups)

Tansini 1971

Study characteristics	
Methods	Double blind placebo controlled randomised trial
Participants	N = 40, mixed sample of patients with chronic respiratory disorders including lung cancer Male and female mixed sample Age, years (range): 13 to 79 Intervention group: N = 9 patients with cancer, of which 8 patients had lung cancer and 1 patient had an unknown primary with lung and brain metastases Placebo group: N = 3 with lung cancer
Interventions	Intervention group (N = 32 mixed sample, of which n = 9 cancer patients): received pentamethylentetrazol with dihydrocodeine hydrodanate (Cardazol-Paracodin). Dose = 10 to 20 drops three times daily for 7 to 18 days Placebo group (N = 8 mixed sample, of which n = 3 cancer patients): received placebo (no details). Dose = 10 to 20 drops three times daily for between 4 and 15 days

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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts, all subjects included in the analysis
Selective reporting (reporting bias)	Unclear risk	Cough frequency scores measured and reported for all study patients, but unsure who did the cough measurement (patient-report or physician-report)
Other bias	High risk	Uneven sample sizes between groups
Size of study	High risk	Small sample size (32 and 8 in each study group respectively)

Tao 2003

Study characteristics

Methods	Comparative trial
Participants	N = 45, malignant tumour patients (largest group was pulmonary carcinoma n = 19) Fei Tong liquid group (Chinese Medicine herbal combination): Age (mean, range): 56.4 years, 34 to 75. Sex: M19/F11 Control group: Age (mean, range): 60.7 years, 36 to 77. Sex: M9/F6

Tao 2003 *(Continued)*

	The two groups were comparable in age, types of tumour and radiotherapy or chemotherapy, or both, applied (P < 0.05)
Interventions	Intervention group (n = 30): Fei Tong oral liquid, 20 ml TID or Fei Tong aqueous decoction one dose a day, for 30 days as one therapeutic course Control group (n = 15): oral prednisilone, 0.5 to 1 mg/kg, per day, or IV drip of dexamethasone, 2.5 to 5 mg, once a day for one month or more
Outcomes	Pre-treatment Intervention group (± SD): cough 4.06 (± 2.27); control group: cough 3.40 (± 1.68) After treatment Intervention group (± SD): cough 1.50 (± 1.68, P < 0.01); control group: cough 3.53 (± 2.07) Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	No details provided, probably not done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding unable to take place
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding unable to take place
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition data reported, results only briefly presented
Selective reporting (reporting bias)	High risk	“Drumstick finger” not reported in results; no information given on how cough was measured
Other bias	High risk	Uneven sample sizes between groups; unclear study design
Size of study	High risk	Small sample size (30 and 15 in each study group respectively)

Tredaniel 1994

Study characteristics	
Methods	Comparative trial

Tredaniel 1994 *(Continued)*

Participants	N = 51, malignant airway obstruction Group 1 (presenting only with endobronchial disease): Age, year (mean, SD): 62.3, 8.3; Karnofsky Index (mean, SD) 85.9, 11.5 Previous surgery: 15; previous radiotherapy: 16; previous chemotherapy: 8; chronic respiratory failure: 3; relapse from previously treated tumour or second primary lung tumour: 26 Group 2 (presenting with extraluminal extension of disease): Age, year (mean, SD): 64.7, 10.5; Karnofsky Index (mean, SD): 72, 13.6 Chronic respiratory failure: 1; previous surgery: 8; previous radiotherapy: 16; previous chemotherapy: 7; endobronchial tumour with endothoracic extraluminal dissemination: 15; peripheral metastases: 7 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
Interventions	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) Group 1: 3 BT treatment sessions were planned. 26 patients received 6 #; 1 received 5 # (last not performed after side effects after fifth treatment); 2 received 4 # (1 refused last #; 1 died in between receiving second and third #) Group 2: 2 BT # were performed, and if a good response was noted, patients received a third #; 9 patients received 3 #; 10 received 2 #; 3 received 1 # (due to significant clinical deterioration)
Outcomes	Pre-treatment: 14 patients in group 1 did not suffer from functional symptoms (including cough) Post-treatment: 46 patients were available for histologic analysis at 2 months Symptomatic relief of symptoms: Symptoms unable to be assessed for 7 patients as they lived too far away (3 in group 1; 4 in group 2) 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% 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 and 5 months following treatment. Radiation bronchitis in 7 patients (3 group 1, 4 group 2) Transient fever and chills in 2 patients, 24 hrs post-procedure 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)

Tredaniel 1994 *(Continued)*

	Jadad score = 0
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not used (comparative study, no randomisation)
Allocation concealment (selection bias)	High risk	Not used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding took place
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding took place
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of dropouts reported, small dropout rates unlikely to have effects on outcomes
Selective reporting (reporting bias)	Unclear risk	No information given on how cough was measured; not all patients available for symptom analysis
Other bias	Unclear risk	Unclear regarding study design
Size of study	High risk	Small sample size (29 and 22 in each study group respectively)

#: 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
Bini 1971	No comparison/control group
Blaszczyk 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	Restrospective 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

Study	Reason for exclusion
Han 2007	Retrospective study
Hendrickson 2012	Studies unrelated to cough, cough was drug-related adverse event
Homsi 2000	No comparison/control group
Homsi 2002	No comparison/control group; phase II trial
Huang 2010	Surgical procedure focused on refractory cough induced by radical systematic mediastinal lymphadenectomy
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
Li 2012	Retrospective study, 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
Navigante 2010	Studies unrelated to cough, cough was drug-related adverse event
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
Radbruch 2012	Studies unrelated to cough, cough was related to subjective nasal assessment

Study	Reason for exclusion
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
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
Solomayer 2012	Studies unrelated to cough, cough was drug-related adverse event
Spasova 2001	Retrospective study
Speiser 1990	No comparison/control group
Speiser 1995	Review article
Spitz 2012	Studies unrelated to cough, cough was drug-related adverse event
Taulelle 1996	No comparison/control group
Taulelle 1998	No comparison/control group
Taylor 2010	Studies unrelated to cough, cough was related to subjective nasal assessment
von Gunten 2005	Review article
Vucicevic 1999	No comparison/control group
Xu 2011	No comparison/control group
Yamada 2012	Study focused on cough reflex test, not on cough symptoms
Yokomise 1998	Case study
Zajac 1993	No comparison/control group
Zonder 2012	Phase I trial, studies unrelated to cough, cough was drug-related adverse event
Zylicz 2004	review article

Characteristics of ongoing studies *[ordered by study ID]*

Harle 2013

Study name	Aprepitant for the treatment of cough in lung cancer
Methods	Randomised single arm placebo controlled cross-over study
Participants	Inclusion criteria: 1. Patients willing and able to give consent for participation in the trial 2. Male or female aged 18 years or above 3. WHO PS 02 4. Diagnosed with lung cancer 5. Able and willing to participate in and comply with the trial schedule 6. Persistent cough ≥ 4 weeks 7. Not on anticancer therapy 8. No anticancer therapy planned to commence for the duration of the trial participation Exclusion criteria: 1. Received anticancer therapy within 4 weeks of trial entry 2. Receiving aprepitant therapy 3. Presence of a RTI within last 4 weeks 4. Previous adverse event to aprepitant 5. Presence of constipation grade 2 or above (CTCAE v4) 6. Scheduled elective surgery or other procedures requiring sedation or general anaesthesia during trial period 7. Potentially fertile women of childbearing age 8. Currently participating in another research trial involving an investigational product 9. Any other significant disease or disorder which, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or affect the patient?s ability to participate in the trial
Interventions	Aprepitant, patients will receive 3 days treatment with aprepitant or placebo at standard doses: 125 mg D1, 80 mg D2 and 80 mg D3 followed by 3 days washout period and 3 further days of aprepitant or placebo at standard doses
Outcomes	Primary outcome: Daytime ambulatory cough monitoring; timepoint(s): baseline, D3 and D9 Secondary outcomes: 1. Biomarker analysis; timepoint(s): Day 3 and Day 9 2. Cough Severity Visual Analogue Scale score; timepoint(s): baseline, Day 3 and Day 9 3. Manchester Cough in Lung Cancer Scale score; timepoint(s): baseline, Day 3 and Day 9
Starting date	01/04/2013
Contact information	Dr Amelie Harle Department of Medical Oncology 550 Wilmslow Road Manchester M20 4BX United Kingdom

Harle 2013 *(Continued)*

	Amelie.Harle@christie.nhs.uk
Notes	Trial ID: ISRCTN16200035, DOI 10.1186/ISRCTN16200035

Yorke 2012

Study name	Feasibility trial of a respiratory symptom intervention
Methods	Feasibility pilot randomised trial
Participants	Main inclusion criteria: 1. Diagnosed with primary or secondary LC 2. Suffering from refractory breathlessness or cough or fatigue 3. In the presence of COPD, in stable condition 4. Karnofsky score > 50% 5. Expected prognosis of at least 3 months 6. 18 plus years 7. Able to give informed consent
Interventions	A non-pharmacological self-mamagement symptom intervention focusing on the management of the respiratory distress symptom cluster (breathlessness, cough, fatigue) in lung cancer
Outcomes	Assessments were carried out at trial enrollment and at weeks 4, 8 and 12 post-intervention or enrolment Assessments included: Spirometry The modified Borg Scale (mBorg) Perceived severity of breathlessness (average and 'worst' over the past 24 h, and "now") and distress caused by breathlessness will be measured using 0 to 10 numerical rating scales anchored as follows: 0 = no breathlessness or no distress due to the breathlessness and 10 = worst imaginable breathlessness or distress due to breathlessness. Using the same approach, patients' ability to cope with breathlessness and satisfaction with the management of their breathlessness was assessed The Chronic Respiratory Disease Questionnaire-short form Hospital Anxiety and Depression Scale (HADS)
Starting date	01/10/2012
Contact information	Mrs June Warden University of Manchester School of Nursing, Midwifery and Social Work The University of Manchester Jean McFarlane Building

Yorke 2012 *(Continued)*

	University Place Oxford Road Manchester M13 9PL UNITED KINGDOM Tel: 0161 306 7887 june.warden@manchester.ac.uk
Notes	Trial ID: ISRCTN 13173844

APPENDICES

Appendix 1. 2010 searches

For the original version of the review, the following databases were searched:

- databases in *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* 2009, Issue 4, 2009);
- MEDLINE (1966 to 10 May 2010);
- EMBASE (1980 to 10 May 2010);
- CINAHL (1980 to 10 May 2010);
- PsycINFO (1980 to 10 May 2010);
- AMED (1985 to 10 May 2010);
- SIGLE (renamed as Open Grey) (1980 to 10 May 2010);
- British Nursing Index (1985 to 10 May 2010);
- CancerLit (1975 to 10 May 2010).

A scoping search was adopted in the original version of the review using broad terms and several databases, as well as consultation with clinicians, contributed to the development of the search terms shown in Appendices 1 to 4. We searched for cough suppressants, antitussives and other drugs with antitussive activity as well as non-pharmacological interventions.

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.

MEDLINE

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

CENTRAL and DARE

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 2. Updated search strategy for CENTRAL and DARE (the Cochrane Library)

#1 MeSH descriptor: [Cough] this term only

#2 cough*:ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Neoplasms] explode all trees

#5 (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 #3 and #6 Publication Year from 2010 to 2014

Appendix 3. Updated search strategy for MEDLINE (via Ovid)

1. Cough/

2. (cough* or coughing).tw.

3. or/1-2

4. exp Neoplasms/

5. (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.

6. 4 or 5

7. 3 and 6

8. (201005* or 201006* or 201007* or 201008* or 201009* or 201010* or 201011* or 201012* or 2011* or 2012* or 2013* or 2014*).ed.

9. 7 and 8

10. randomized controlled trial.pt.

11. controlled clinical trial.pt.

12. randomized.ab.

13. placebo.ab.

14. drug therapy.fs.

15. randomly.ab.

16. trial.ab.

17. or/10-16

18. exp animals/ not humans.sh.

19. 17 not 18

20. 9 and 19

Appendix 4. Updated search strategy for EMBASE (via Ovid)

1. Cough/

2. (cough* or coughing).tw.

3. or/1-2

4. exp Neoplasms/

5. (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.

6. 4 or 5

7. 3 and 6

8. (201005* or 201006* or 201007* or 201008* or 201009* or 201010* or 201011* or 201012* or 2011* or 2012* or 2013* or 2014*).dd.

9. 7 and 8

10. random$.tw.

11. factorial$.tw.

12. crossover$.tw.

13. cross over$.tw.

14. cross-over$.tw.

15. placebo$.tw.

16. (doubl$ adj blind$).tw.

17. (singl$ adj blind$).tw.

18. assign$.tw.

19. allocat$.tw.

20. volunteer$.tw.

21. Crossover Procedure/

22. double-blind procedure.tw.

23. Randomized Controlled Trial/

24. Single Blind Procedure/

25. or/10-24

26. (animal/ or nonhuman/) not human/

27. 25 not 26

28. 9 and 27

Appendix 5. Updated search strategy for PsycINFO (via Ovid)

1. (cough* or coughing).tw.

2. exp Neoplasms/

3. (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.

4. 2 or 3

5. 1 and 4

6. clinical trials/

7. (randomis* or randomiz*).tw.

8. (random$ adj3 (allocat$ or assign$)).tw.

9. ((clinic$ or control$) adj trial$).tw.

10. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

11. (crossover$ or "cross over$").tw.

12. random sampling/

13. Experiment Controls/

14. Placebo/

15. placebo$.tw.

16. exp program evaluation/

17. treatment effectiveness evaluation/

18. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.

19. or/6-18

20. 5 and 19

21. limit 20 to yr="2010 -Current"

Appendix 6. Updated search strategy for AMED (via Ovid)

1. exp Neoplasms/

2. (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or nonhodgkin$ or adenocarcinoma$ or leuk?emia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$ or myeloma$ or oncolog$).tw.

3. 1 or 2

4. cough/

5. (cough* or coughing).tw.

6. 4 or 5

7. 3 and 6

8. limit 7 to yr="2010 -Current"

WHAT'S NEW

Date	Event	Description
1 June 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 9, 2010

Date	Event	Description
13 May 2015	Review declared as stable	This review will be assessed for further updating in 2020.
25 February 2015	New citation required but conclusions have not changed	No new studies were identified for inclusion, while 11 new studies that were identified were eventually excluded from this review.
25 February 2015	New search has been performed	This is an updated version of the original Cochrane review first published in Issue 9, 2010.
12 October 2010	Amended	Some references revised.

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. Carried out update of review, edited the update and assessed studies through the new risk of bias tables and figures.

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

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

JYT: supported the update of the review, searched the literature, reviewed studies, carried out risk of bias assessment, assisted in writing the updates in the final report.

DECLARATIONS OF INTEREST

AM: no relevant conflicts of interest to declare.

CB: no relevant conflicts of interest to declare.

AC: no relevant conflicts of interest to declare.

JYT: no relevant conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Breathlessness Research Charitable Trust, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

A restricted search in May 2020 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Antitussive Agents [therapeutic use]; Brachytherapy [methods]; Cough [etiology] [*therapy]; Drugs, Chinese Herbal [therapeutic use]; Laser Therapy [methods]; Neoplasms [*complications] [therapy]; Photochemotherapy [methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans