CHEST

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer

CHEST Guideline and Expert Panel Report

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BACKGROUND: Cough among patients with lung cancer is a common but often undertreated symptom. We used a 2015 Cochrane systematic review, among other sources of evidence, to update the recommendations and suggestions of the American College of Chest Physicians (CHEST) 2006 guideline on this topic.

METHODS: The CHEST methodologic guidelines and the Grading of Recommendations, Assessment, Development, and Evaluation framework were used. The Expert Cough Panel based their recommendations on data from the Cochrane systematic review on the topic, uncontrolled studies, case studies, and the clinical context. Final grading was reached by consensus according to the Delphi method.

RESULTS: The Cochrane systematic review identified 17 trials of primarily low-quality evidence. Such evidence was related to both nonpharmacologic (cough suppression) and pharmacologic (demulcents, opioids, peripherally acting antitussives, or local anesthetics) treatments, as well as endobronchial brachytherapy.

CONCLUSIONS: Compared with the 2006 CHEST Cough Guideline, the current recommendations and suggestions are more specific and follow a step-up approach to the management of cough among patients with lung cancer, acknowledging the low-quality evidence in the field and the urgent need to develop more effective, evidence-based interventions through high-quality research.

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ABBREVIATIONS: CHEST = American College of Chest Physicians; RCT = randomized controlled trial

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Summary of Recommendations and Suggestions

1. In adult patients with cough associated with lung cancer that persists despite cancer treatment, we suggest, as a first step, that a comprehensive assessment according to a published, evidence-based management guideline be undertaken to identify any co-existing causes linked with cough and initiate treatment accordingly (Ungraded, Consensus Based Statement).

2. In adult patients with lung cancer experiencing cough despite anticancer treatment, we suggest cough suppression exercises as alternative or additional to pharmacological therapy where such services are available (Grade 2C).

3. In adult patients with cough due to localized endobronchial disease for whom surgery, chemotherapy, or external beam radiation are not indicated, we suggest the use of endobronchial brachytherapy where such specialist facilities are available and in suitable patients (Grade 2C).

4. In adult patients with lung cancer who require a pharmacological approach for the treatment of cough, we suggest an initial trial with demulcents such as butamirate linctus (syrup) or simple linctus (syrup) or glycerin-based linctus (syrup) where available (Grade 2C).

5. In adult patients with lung cancer experiencing cough that does not respond to demulcents, we suggest pharmacological management using an opiate-derivative titrated to an acceptable side-effect profile (Grade 2C).

6. In adult patients with lung cancer experiencing opioid-resistant cough, we suggest a peripherally-acting antitussive (where available), such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate (Grade 2C).

7. In adult patients with lung cancer experiencing opioid-resistant cough that does not respond to peripheral antitussives, we suggest a trial with local anesthetics, including nebulized lidocaine/bupivacaine or benzonatate (Ungraded, Consensus Based Statement).

8. In adult patients with intractable cough due to lung cancer in whom surgery, chemotherapy, external beam radiation, brachytherapy and the previously mentioned nonpharmacological and pharmacological approaches are ineffective or not indicated, we suggest that clinicians consider performing N-of-1 randomized controlled trials to determine if any of the following drugs might be of benefit in controlling cough because none have been definitively shown to be effective nor devoid of side effects: diazepam, gabapentin, carbamazepine, baclofen, amitriptyline, thalidomide (Ungraded, Consensus Based Statement).

Cough among patients with lung cancer is a common symptom affecting 57% of them as shown in a study of 223 consecutive outpatients with lung cancer.[1] In the same study, one-half of the patients felt their cough warranted treatment, and 23% reported their cough to be painful, reporting a median visual analog scale score of 32 mm (25th-75th interquartile range, 20-51; range, 0-100; high scores = worse cough severity). Although many cancer symptoms are managed well in clinical practice, the management of cough is lagging behind, with health professionals often using inconsistent approaches to manage cough in a field with a minimal high-level evidence base.[2,3] Treatment decisions by patients are also significantly influenced by the possibility of reduction of tumor-associated symptoms, including primarily the symptoms of cough, shortness of breath, and pain.[4] Nevertheless, symptom management research in lung cancer care is fairly unbalanced, with some symptoms, including cough, receiving minimal attention in the literature.[5]

Cough is also an important determinant of quality of life. In a lung cancer study in 450 patients in the United States,[6] with samples similar to those in France and Germany (n = 613 and 600, respectively),[7] cough, alongside loss of appetite, pain, and shortness of breath, was a significant predictor of quality of life. The same set of four symptoms has been linked with significant decreases in quality of life in patients with lung cancer in another study.[8] A study about the experience of patients with lung cancer with cough clearly showed the impact from this symptom on socializing, the embarrassment from cough in public places, and the psychological effects experienced by patients.[9] It is now clear that cough has complex interrelationships with other symptoms, including breathlessness and fatigue, forming a symptom cluster,[10] suggesting the need for a more comprehensive management of this symptom.

Most physicians use approaches based on experience and trial and error rather than evidence, and much of the treatment of cancer-related cough is geared toward

the use of opioids. The American College of Chest Physicians (CHEST), in the past, has made an attempt to develop recommendations for the management of cough as part of a set of guidelines for a number of symptoms affecting patients with lung cancer[11,12]; however, the three recommendations presented were broad, reflecting the difficulty in making more specific recommendations. Two more guidelines have been developed, one from a UK task force evaluating research in cough management in lung cancer[13] and another focusing on chronic cough in palliative care.[14] These two guidelines have focused only on the pharmacologic management of cough. Consequently, there is a need to update and consolidate these guidelines by using current evidence and a more stringent process of evaluation of the recommendations.

In this regard, CHEST assessed the existing guidelines and an updated Cochrane systematic review[15] alongside other systematic reviews to propose an evidence-based set of specific guidelines for the symptomatic management of cough among patients with lung cancer that persists and is bothersome despite lung cancer treatment with surgery or systemic anticancer treatment such as chemotherapy or (external-beam) radiotherapy. Lung cancer treatments can also cause cough as a side effect, particularly in the context of radiation-induced fibrosis. Hence, the current guideline focuses on the management of cough beyond anticancer treatments. The specific aims of the current guidelines were to (1) evaluate the existing evidence in the management of cough related to lung cancer and (2) develop a set of recommendations and/or suggestions for the management of cough beyond initial lung cancer treatments.

Materials and Methods

The methodology of the CHEST Guideline Oversight Committee[16] was used to select the Expert Cough Panel Chair and the international panel of experts to synthesize the evidence and to develop the recommendations and suggestions that are contained within this article. In addition to the quality of the evidence, the recommendation and suggestion grading also includes a strength-of-recommendation dimension, used for all CHEST Guidelines.[16] In the context of practice recommendations, a grade 1 recommendation is a strong recommendation and applies to almost all patients, whereas a grade 2 recommendation is weak and conditional and applies to only some patients. The strength of recommendation here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Harms incorporate risks and burdens to the patients that can include convenience or lack of convenience, difficulty of administration, and invasiveness. These, in turn, impact patient preferences. The resource considerations go beyond economics and should also factor in time and other indirect costs. We have considered these parameters in determining the strength of the recommendations or suggestions and associated grades.

The findings of a Cochrane systematic review that was updated in 2015[15] were used to support the evidence-graded recommendations or suggestions. The initial Cochrane systematic review and the subsequent update were carried out by the first author (A. M.). The process of review of previous studies identified in the systematic review included assessment of the study quality or risk of bias by using the Cochrane quality assessment tool. This is a seven-item tool exploring selection-, performance-, detection-, attrition-, and reporting-related biases in a study. When the quality of studies included in the systematic review[15] were checked using the Documentation and Appraisal Review Tool tool,[17] similar results indicating poor quality of included studies were found. Because the search for articles for the Cochrane systematic review ended just before work on this guideline article began, no additional literature search took place for this article. A highly structured consensus-based Delphi approach was used to provide expert advice on all guidance statements. The total number of eligible voters for each guidance statement did not vary because none were recused from voting on any particular statements because of their potential conflicts of interest. Transparency of process was documented. Further details of the methods related to conflicts of interest and transparency have been published elsewhere.[16]

On the basis of the systematic review[15] and the Delphi method described, the lung cancer cough panel writing group developed guideline recommendations or suggestions. These then underwent review and voting by the full cough panel. For a recommendation or suggestion to be accepted, it had to be voted on by 75% of the cough panelists and achieve ratings of strongly agree or agree by 80% of the voting panelists. Agreement was achieved by 81% to 96% of those voting in the current recommendations. No panelist was excluded from voting.

Results

The recommendations and suggestions that follow are largely based on the updated Cochrane systematic review[15] that included a comprehensive search of multiple databases without language restrictions. An overview of the studies available in cough related to lung cancer is shown in Table 1, using the Grading of Recommendations, Assessment, Development, and Evaluation framework.[18] The review identified 17 studies, eight testing brachytherapy or laser or photodynamic therapy and nine testing a variety of drugs for the management of cough among patients with lung cancer. The total sample included 1,390 patients, among whom 1,231 had mostly lung cancer. If a mixed sample of patients was used, data were extracted for the cancer subsample when possible. Overall, there was absence of credible evidence, and the majority of studies were of low methodologic quality and at high risk of bias.

TABLE 1] Studies of Cough Management in LC

Study/Year	Design	Participants	Intervention	Outcomes	Level of Evidence/ Quality of Evidence[a]	Jadad Score
Speech therapy and cough suppression exercises						
Yorke et al[27]/2015	Feasibility RCT, unblinded	Patients with LC with breathlessness, cough, and fatigue (N = 101)	Breathing exercises, cough suppression exercises, acupressure	Clinically meaningful change (−0.86 in trial arm, −2.26 in control arm) using cough scale Symptom improvement of 7.48 in trial arm, worsening of −21.90 in control arm according to overall symptom scale	2B/low	3
Vertigan and Gibson[22]/2012	Systematic review	Chronic refractory cough (two trials)	Speech pathology training	Significant cough improvements	1 (non-LC)	…
Chamberlain et al[25]/ 2014	Systematic review	Chronic refractory cough (five trials)	Various: education, cough suppression techniques, breathing exercises, and counseling	Significant cough improvements	1 (non-LC)	…
Endobronchial BT						
Canak et al[28]/2006	Comparative study, no randomization	LC (N = 64)	Trial arm: laser resection plus HDR BT 14 Gy in two fractions at 1 cm, followed by EBRT 40 Gy in 10 fractions Control arm: laser resection only	Control arm: decrease in cough by 25% ($P = .069$) Trial arm: decrease in cough by 50% ($P < .005$) Comparative analysis in the two groups: no statistically significant difference	2C/low	0
Mallick et al[29]/2006	Prospective randomized trial	LC (squamous cell) (N = 45)	Arm 1: EBRT 30 Gy, 10 fractions in 2 wk followed by EBRT 16 Gy in two fractions Arm 2: EBRT 30 Gy, 10 fractions in 2 wk plus 10 Gy 1-cm depth in a single fraction Arm 3: 15 Gy 1-cm depth in a single fraction	No significant difference among the three arms, overall response 84.5%	2C/low	1
Muto et al[30]/2000	Comparative trial	Advanced NSCLC (N = 320)	All patients: 2 Gy per fraction for up to 50 Gy Arm 1 (n = 84): 10 Gy for a	Similar response in all three groups. For the patients treated with	2C/low	0

(Continued)

TABLE 1] *(Continued)*

Study/Year	Design	Participants	Intervention	Outcomes	Level of Evidence/ Quality of Evidence[a]	Jadad Score
			single fraction at a 1-cm depth Arm 2 (n = 47): 14 Gy for two fractions at a 1-cm depth before EBRT and after completion of EBRT Arm 3 (n = 189): 15 Gy for three factions at beginning and after 3 and after 6 wk of EBRT (arm 3a had BT 1-cm depth, arm 3b had BT 0.5-cm depth)	three fractions of HDR BT plus EBRT, a smaller number of side effects occurred, and relief from symptoms linked to bronchial obstruction and survival was similar for the three groups.		
Nori et al[31]/1993	Comparative trial	Primary or metastatic LC (N = 32)	EBRT for all 50 Gy BT regimen: 5 Gy per fraction for 28 patients; 4 Gy per fraction for four patients at a 1-cm depth	Six of seven patients with unremitting cough found cough relief in frequency and intensity > 50%; duration of response at 6 mo: 88% in arm 1 (treated by BT as a boost to primary external beam irradiation) and 70% in arm 2 (treated with BT for endobronchial recurrence after prior irradiation with external beam)	2C/low	0
Ofiara et al[32]/1997	Comparative trial, same treatment in different groups	LC, endobronchial (N = 30) Group 1 (n = 20): endoluminal disease Group 2 (n = 10): submucosal infiltration or extrinsic compression or both	8 Gy at a 1-cm depth, aim for 24 Gy in three fractions over 6 wk	Overall significant improvements Group 1: no statistically significant difference Group 2: statistically significant improvement Location: central, no statistical difference; peripheral, statistical difference	2C/low	0
Speiser and Spratling[33]/1993	Comparative trial	Endobronchial cancer (N = 342)	Arm 1 (n = 47): medium dose rate 10 Gy in a single fraction at a 5-mm depth	No between-group analysis reported. Authors noted no difference in cough palliation	2C/low	0

(Continued)

TABLE 1] *(Continued)*

Study/Year	Design	Participants	Intervention	Outcomes	Level of Evidence/ Quality of Evidence[a]	Jadad Score
			Arm 2 (n = 144): high dose rate 10 Gy in a single fraction at a 10-mm depth Arm 3 (n = 151): high dose rate 7.5 Gy in a single fraction at a 10-mm depth EBRT for curative intent, 60 Gy in 30 fractions; for palliative intent, 37.5 Gy in 15 fractions	with different doses used. Results showed cough decrease of 32%, 52%, 85% in the three arms, respectively.		
Trédaniel et al[34]/ 1994	Comparative trial	Malignant airway obstruction (N = 51)	14 Gy at 1-cm depth in two fractions in 2 d, 2-wk gap, repeated up to 6 wk (total dose, 42 Gy in six fractions in 6 wk) Group 1: three BT sessions; Group 2: two BT sessions and if improvement noted a third BT session administered	Overall improvement of 70% with complete or partial response in both groups	2C/low	0
Lester et al[36]/2006	Cochrane systematic review (14 trials)	NSCLC	Palliative radiotherapy regimens	Patients should be treated with short courses of palliative radiotherapy of one or two fractions.	1 (mostly poorly designed trials)	…
Pharmacologic treatments						
Charpin and Weibel[37]/1990	Double-blind randomized trial	Various pulmonary conditions (N = 67), LC subgroup (n = 14)	Treatment arm: butamirate citrate linctus (Sinecod) Control arm: clobutinol 4 mg/mL	Treatment arm: improvement in seven of seven patients Control arm: improvement in two of seven patients ($P = .026$) (but no differences in the whole sample)	2C/low	3
Dotti[40]/1970	Double-blind randomized trial	Various pulmonary conditions (N = 41), LC subgroup (n = 13)	Treatment arm: equivalent dose of 30 mg codeine base and 10 mg phenyltoloxamine base Control arm: lactose (placebo) Arm 3: dibenzonium bromide 30 mg	Better improvement in the codeine arm (unclear subgroup analysis)	2C/low	1

(Continued)

TABLE 1] *(Continued)*

Study/Year	Design	Participants	Intervention	Outcomes	Level of Evidence/ Quality of Evidence[a]	Jadad Score
Tansini and Cavallaro[41]/1971	Double-blind randomized trial	Chronic respiratory conditions and LC (N = 40)	Treatment arm: dihydrocodeine Control arm: placebo	Major improvement in the treatment arm	2C/low	2
Kleibel[42]/1982	Comparative study	Variety of cancers (N = 31)	Arm 1: a morphine derivative (no indication of dose) Arm 2: codeine based (no indication of dose)	Similar effect in both groups (but more side effects in arm 2 in 30% of patients)	2C/very low	0
Homsi et al[45]/2002	Phase II trial with dose titration	Metastatic LC or lung or pleural metastasis (N = 20)	5 mg hydrocodone administered twice daily The dose was then titrated daily (maximum: 60 mg/ 24 h), if needed, until ≥ 50% improvement of the frequency of cough was achieved and then maintained for 3 consecutive days.	19 patients had at least 50% improvement in cough frequency. The median best response was 70% improvement in cough frequency (range, 50%-90%). The median hydrocodone dose associated with the best response was 10 mg/d.	2C/low	0
Schildmann et al[46]/ 2011	Systematic review (four trials)	Cancer and other pulmonary chronic illnesses	Levodropropizine	Levodropropizine probably equally effective to dihydrocodeine or moguisteine and with possible earlier cough reductions than dextromethorphan	1 (mostly poorly designed trials)	…
Lingerfelt et al[47]/ 2007	Case studies	Palliative care	Nebulized lidocaine	Cough improvements	2C/very low	…
Doona and Walsh[48]/ 1998	Case studies	Advanced cancer	Benzonatate	Cough improvements	2C/very low	…

BT = brachytherapy; EBRT = external-beam radiation therapy; HDR = high-dose radiotherapy; LC = lung cancer; NSCLC = non-small cell lung cancer; RCT = randomized controlled trial.
[a]For grading details, see reference 18.

Evidence and Recommendations/Suggestions

Clinical research question: In adults with lung cancer experiencing cough beyond initial cancer treatments, what are the most effective pharmacologic and nonpharmacologic interventions?

Summary of the Evidence and Interpretation

For patients with lung cancer experiencing cough, its control often depends on the treatment of the cancer, treatment of associated comorbidities, and antitussive therapy. The cancer and noncancer-related causes of cough may include a direct effect of the tumor mass (eg, infiltration or obstruction), pleural or pericardial effusion, atelectasis, infections, gastroesophageal reflux disease, pulmonary emboli, exacerbation of coexisting COPD or congestive heart failure, esophagorespiratory fistulas, lymphangitic carcinomatosis, superior vena cava syndrome, or treatment-induced cough due to radiotherapy or (more rarely) chemotherapy.[12,19] Such causes of cough, for example, may be treated with oncological treatment of cancer, pleural drainage (if pleural effusion exists), antibiotics (when an infection is present), or steroid therapy in cases of COPD or asthma. Physicians should also differentiate between productive and nonproductive cough, where the aim of treatment is different (eg, using mucolytics in productive cough vs suppressing nonproductive cough), as suppression of cough is not always the aim of treating cough among patients with lung cancer. Nevertheless, many patients with lung cancer report typically a dry tickling cough with mechanical and environmental triggers.[9]

Therefore, on the basis of the variety of causes linked with cough among patients with lung cancer, it is essential to start the management of cough with a comprehensive assessment, first targeting the treatable causes of cough (Table 2).[20] A comprehensive list of suggestions, not necessarily evidence based, is available through the British Thoracic Society[21] and the ACCP guidelines on chronic cough due to lung tumors.[11]

1. In adult patients with cough associated with lung cancer that persists despite cancer treatment, we suggest, as a first step, that a comprehensive assessment according to a published, evidence-based management guideline be undertaken to identify any co-existing causes linked with cough and initiate treatment accordingly (Ungraded, Consensus Based Statement).

TABLE 2] Causes of Cough Among Patients With Cancer[a]

Pleural disease-effusion, tumor
Lung parenchyma infiltration
Major airway or endobronchial tumor
Cough after radiation or after chemotherapy
COPD; chronic bronchitis
Bronchiectasis
Pericardial effusion
Upper airway cough syndrome due to a variety of rhinosinus conditions
Gastroesophageal reflux disease
Asthma
Lymphangitis carcinomatosis
Chest infection
Microembolism
Tracheoesophageal fistula
Vocal cord paralysis
Congestive heart failure
Postinfectious cough
Eosinophilic bronchitis
Angiotensin-converting enzyme inhibitor

[a]Reviewed in Tse.[20]

Summary of the Evidence and Interpretation

Vertigan and Gibson[22] reviewed the work done in chronic refractory cough and the role of speech pathology and cough suppression interventions that consist of education, strategies to control cough, vocal hygiene training, and psychoeducation. Results presented in a review of a single trial of patients with respiratory diseases[23] showed that 88% of patients improved their cough in the speech pathology group vs 14% in the control group. In a systematic review of cough management trials in respiratory diseases other than lung cancer, cough suppression interventions also showed promising results.[24] The same is further supported by another systematic review of five trials in refractory chronic cough[25] in which a package of cough suppression exercises given over three to four sessions was linked with significant improvements in cough frequency, cough severity, and cough-related quality of life. Cough suppression exercises refer to a number of approaches, including education, identifying cough triggers, cough suppression techniques (ie, pursed lip breathing, swallowing, sipping water), improvements in laryngeal and vocal hygiene and hydration, breathing exercises, and counseling.[26]

In a more recent feasibility trial in 101 patients with lung cancer experiencing a respiratory distress symptom cluster (breathlessness, cough, fatigue), participants found benefit from an intervention package educating them on how to manage this symptom cluster with specific nonpharmacologic approaches, including cough suppression techniques and diaphragmatic breathing.[27] A large trial to test this feasibility trial further is now ongoing in the United Kingdom. Speech pathology training is minimally used in current health care settings primarily because of limited availability of speech therapy services. However, the use of broader cough suppression exercises may be an area to enhance in future provision of care and identify further roles for speech therapists and respiratory physiotherapists in clinical practice, if results from future trials in lung cancer are consistently positive.

2. In adult patients with lung cancer experiencing cough despite anticancer treatment, we suggest cough suppression exercises as alternative or additional to pharmacological therapy where such services are available (Grade 2C).

Summary of Evidence and Interpretation

Endobronchial brachytherapy in a variety of doses seemed to improve cough in selected participants, suggesting that possibly the lowest effective dose should be used to minimize side effects.[15] The studies reviewed[28-34] were all uncontrolled comparative trials (mostly prospective ones), although it would have been unethical to carry out randomized trials with such a treatment approach. Photodynamic therapy was examined in one study,[35] and, although improvements in cough were observed, its role in relation to other therapies for cough was unclear. When brachytherapy is indicated but not locally available, patients should be transferred to a facility where it is available. Endobronchial brachytherapy should be considered particularly for patients with small or endobronchial tumors or limited disease or in whom the tumor has extended into the large airways; otherwise, external-beam radiotherapy (or a combination of the two) may be more effective.

In using endobronchial brachytherapy, we suggest the lowest dose and fractionated schedule (eg, a single fraction of 10 Gy, two fractions of 7-8 Gy, or three fractions of 5 Gy), as this approach is linked with a good response and a lower number of side effects. It is worth noting that external-beam radiation of one or two fractions can also improve thoracic symptoms, as shown in a systematic review,[36] and this approach should be considered if facilities for endobronchial brachytherapy are not available. Nevertheless, as endobronchial brachytherapy can also be associated with significant risk of hemoptysis and other complications, depending on the type of lesion and the area of application, a pharmacologic therapy trial may be more appropriate to start with.

3. In adult patients with cough due to localized endobronchial disease for whom surgery, chemotherapy, or external beam radiation are not indicated, we suggest the use of endobronchial brachytherapy where such specialist facilities are available and in suitable patients (Grade 2C).

Summary of Evidence and Interpretation

It may be appropriate to start pharmacologic treatment at the same time with the previous two recommendations, especially if the cough is severe. This takes into consideration the fact that such specialist services may not be widely available, and, if they are, there are practical considerations in their delivery and their effect may not be immediate. The majority of trials reviewed in the Cochrane systematic review[15] referred to a variety of pharmacologic approaches. All of them had a high risk of bias. There was one double-blind randomized trial suggesting significant improvements in cough management from the use of butamirate citrate linctus (Sinecod syrup)[37] only in the subgroup of patients with lung cancer (n = 14). In the general respiratory disease field, there were also two additional trials on glycerol-based cough syrups,[38,39] also showing cough decreases, and this may also be appropriate treatment for patients with lung cancer. There is a variety of these cough syrups on the market, sold over the counter, including Sinecod; Benylin Tickly Coughs; Benylin Dry Coughs; Actifed Multi-Action Dry Coughs; Meltus Dry Coughs; Robitussin for dry coughs; Day & Night Nurse (GSK); and others (some of them are not available in the United States and some other countries). Many of them include dextromethorphan in variable concentrations, and the Day & Night Nurse also includes pholcodine. Because of their low cost, some evidence of effect, and low side effect profile, this approach could be tried initially, although for patients with profound cough, demulcents may be less effective, particularly as some over-the-counter preparations contain active drugs at subthreshold therapeutic levels.

When patients do not respond to this approach, opioids should be considered next. Opioids are the drugs that have most evidence in the management of cough among patients with lung cancer, albeit of low methodologic

quality, and they are perhaps not as effective as physicians would ideally like. In the Cochrane systematic review,[15] there was a double-blind randomized trial with positive results from using codeine 30 mg twice a day with phenyltoloxamine 10 mg[40]; one with dihydrocodeine,[41] and one comparing morphine with codeine.[42] However, there have been a number of case reports providing some evidence of the beneficial effect of morphine, methadone, pholcodine, and hydromorphone, summarized in a scholarly review,[43] and a phase II trial using hydrocodone.[44,45] For patients with lung cancer experiencing cough for whom treatment with an opioid derivative is indicated, we suggest pholcodine or hydrocodone (where available) or dihydrocodeine or morphine. Codeine is less preferred (despite being the most researched drug in this field) because of its greater side effect profile compared with those of other opioids, as commented on by many experts (personal communication with palliative medicine experts). Morphine should be used if the cough is not suppressed by other opioid derivatives or other means, including other centrally acting antitussives such as dextromethorphan. The patient's previous exposure to opioids will dictate the initial starting dose.

Many patients with advanced lung cancer may already be receiving opiates for other symptoms (eg, pain or breathlessness). If patients are already receiving morphine, sometimes increasing the dose by 20% may be helpful, although this is based on experience rather than any evidence. For patients with lung cancer who are experiencing nonspecific cough and who are in the palliative stage of their illness, we suggest a bedtime dose of codeine/pholcodine or morphine, as this approach may help suppress cough and induce an undisturbed sleep, although again there is no evidence for this (but physicians invariably use this approach).

Among peripherally acting antitussives, levodropropizine is probably equally effective to dihydrocodeine or moguisteine and with possible earlier cough reductions than with dextromethorphan. This was suggested by a systematic review of four trials (two randomized trials testing levodropropizine against dihydrocodeine and moguisteine and two nonrandomized placebo-controlled studies, all with important limitations and high risk of bias).[46] The major methodologic limitations of the studies reviewed make these results less convincing, and further research is necessary before any concrete conclusions are derived. Because some of these drugs are not available in many countries, the choice of treatment may be dictated primarily by availability rather than pharmacologic parameters.

Local anesthetics, such as nebulized lidocaine, have been suggested to be helpful in case studies[47,48] and are commonly used in palliative care for intractable cough that has not responded to any other approaches. This is also supported by findings from a systematic review of cough management approaches.[24] Hence, we suggest that such local anesthetics be tried when other pharmacologic approaches have failed to manage cough among patients with lung cancer. As local anesthetics can increase the risk of aspiration, which can be prevalent in frail patients with cancer, aspiration risk should be assessed prior to the use of this type of treatment for cough.

Doses used in the medications mentioned earlier vary from country to country. Table 3, shown originally in a previous cough guideline,[13] provides indicative doses.

TABLE 3] Indicative Doses for Antitussives, Demulcents, and Topical Anesthetics[a]

Medication	Dosage
Simple linctus	5 mL tid or qid
Dextromethorphan	10-15 mg tid or qid (10-30 mg in some publications, maximum dose of 120 mg/d)
Codeine	30-60 mg qid
Pholcodine	10 mL qid
Morphine (Oramorph)	5 mg (single-dose trial of Oramorph; if effective 5-10 mg slow-release morphine bid)
Diamorphine	5-10 mg subcutaneously/24 hrs
Methadone linctus	Single dose 2 mg (2 mL of 1 mg/mL solution)
Dihydrocodeine[b]	10 mg tid
Hydrocodone	5 mg bid
Inhaled cromoglycate	10 mg qid
Levodropropizine[b]	75 mg tid
Moguisteine[b]	100-200 mg tid
Levocloperastine[b]	20 mg tid
Nebulized lidocaine[c]	5 mL of 0.2 tid
Nebulized bupivacaine[c]	5 mL of 0.25% tid
Benzonatate[b]	100-200 mg qid
Prednisolone	30 mg daily for 2 wk

[a]Adapted from Molassiotis et al.[13]
[b]Not available in several countries.
[c]Avoid food and drink for at least 1 h; first dose as inpatient in case of reflex bronchospasm.

4. In adult patients with lung cancer who require a pharmacological approach for the treatment of cough, we suggest an initial trial with demulcents such as butamirate linctus (syrup) or simple linctus (syrup) or glycerol-based linctus (syrup) where available (Grade 2C).

5. In adult patients with lung cancer experiencing cough that does not respond to demulcents, we suggest pharmacological management using an opiate-derivative titrated to an acceptable side-effect profile (Grade 2C).

6. In adult patients with lung cancer experiencing opioid-resistant cough, we suggest a peripherally-acting antitussive (where available), such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate (Grade 2C).

7. In adult patients with lung cancer experiencing opioid-resistant cough that does not respond to peripheral antitussives, we suggest a trial with local anesthetics, including nebulized lidocaine/bupivacaine or benzonatate (Ungraded, Consensus Based Statement).

As the evidence described earlier is of generally low quality and the level of confidence is fairly low, it is likely that, despite best efforts as provided according to the previous recommendations, some patients will not respond to the suggested treatment. Physicians need to be aware that these cough management strategies, although based on the available evidence, are not necessarily optimal or effective enough, and discretion in their use should be exercised. The duration of treatment is an issue to consider, too: Although the evidence for this is minimal, if a short course of treatment does not lead to improvements, the treatment should be discontinued and another approach should be tried. Hence, ongoing research on the unmet need for better antitussive approaches in the lung cancer population is urgently needed. In managing cough among patients with lung cancer, who also often have advanced cancer, controlling cough and providing cough-free periods is highly important for patients from a quality-of-life perspective. In these cases, other experimental approaches may be used and trialed. We have examples in the literature of case studies in which physicians have used gamma aminobutyric acid agonists (such as baclofen),[21] diazepam,[19] paroxetine (in concomitant pruritus and cough),[49] amitriptyline,[50] gabapentin,[50,51] carbamazepine,[50] and thalidomide,[52] although many of these refer to chronic cough or cough in respiratory diseases other than cancer and could be tried in the lung cancer setting in an N-of-1 trial.

On occasion, complications of coughing[53] may be debilitating and not responsive to any medications. In such circumstances, physicians may consider trying other medications even when treatment decisions cannot be based on existing evidence. In such cases, single case experiments, also referred to as "N-of-1 randomized controlled trials (RCTs),"[54] should be considered because N-of-1 RCTs are the most rigorous design for establishing efficacy of treatment in individual patients.[54] The key elements in performing such trials are (1) obtaining informed consent, (2) randomizing two treatments (eg, active therapy or placebo or alternative therapy) determined by random allocation preferably with crossover, (3) double blinding, and (4) measuring a cough outcome important to the patient.[54] Because ethical issues of N-of-1 RCTs are different than those of standard RCTs involving other patients, institutional review board approval and informed written consent may not be necessary. However, consultation with the institutional review board and reading more about how to set up an N-of-1 RCT program are advised prior to starting such a program.[54] Also, the costs of preparing the placebo should be considered because it may be a barrier to developing the program. N-of-1 RCTs with placebo control groups may not be practical in a private or clinical setting, in which case an unblended N-of-1 trial, although less scientifically rigorous and robust, may be an alternative approach.

8. In adult patients with intractable cough due to lung cancer in whom surgery, chemotherapy, external beam radiation, brachytherapy and the previously mentioned nonpharmacological and pharmacological approaches are ineffective or not indicated, we suggest that clinicians consider performing N-of-1 randomized controlled trials to determine if any of the following drugs might be of benefit in controlling cough because none have been definitively shown to be effective nor devoid of side effects: diazepam, gabapentin, carbamazepine, baclofen, amitriptyline, thalidomide (Ungraded, Consensus Based Statement).

Areas of Future Research

In the field of cough management for patients with lung cancer, in which the evidence base is minimal and highly at risk of bias because of serious methodologic problems, there is an urgent need to invest more on research and

focus on building a stronger evidence base. Suggested research endeavors include the following:

- Focus on the development of nonpharmacologic approaches for managing cough as part of symptom clusters, providing a more comprehensive and holistic approach to symptom management.
- As all the areas of recommendations and suggestions in this guideline are weak ones, they need more concrete evidence through appropriately controlled randomized trials with adequately powered sample sizes, careful selection of patients with similar characteristics, and use of validated outcome measures. Medications that have several positive trials or strong positive indications in the wider field of respiratory disease and chronic cough (eg, levocloperastine) should be tried in lung cancer populations where available. More definitive answers are needed about the use of opioids in managing cough among patients with lung cancer (eg, which one to use, what the starting dose should be, what the most effective dose is, what the duration of treatment should be, what happens when a patient is already receiving opioids). In 2015, a single-arm double-blind crossover trial using a neurokinin-1 receptor antagonist (aprepitant) showed significant reductions in cough counts and reported cough severity in a small sample of patients with lung cancer,[55] and this is a pathway that may be a key component of cough mechanisms in lung cancer that should be further evaluated. The latter trial was reported only as a meeting abstract at this time, so it is not used in the main evidence base for our recommendations.
- The range of cough syrups sold over the counter should be a focus in future research in patients with lung cancer, as they contain substances such as dextromethorphan, glycerol, antihistamines, and guaifenesin that, if found effective, would be cost-effective approaches with minimal side effect burdens.
- Future research should benefit from using validated patient reported outcomes or cough counting (subjective and objective measures) in a relevant lung cancer population. At this time, there is only one cough-related quality-of-life scale specifically developed for patients with lung cancer,[56] and its use should be considered in future trials, alongside simple visual analog scales and more objective measures of cough counts. Symptom burden may be another appropriate outcome measure in trials of managing cough alongside other symptoms in patients with lung cancer.
- As a significant percentage of patients with lung cancer have (diagnosed or undiagnosed) COPD, a focus of future research should also be to assess the role of bronchodilator therapy (and/or inhaled corticosteroids) for patients with lung cancer and COPD. At present, it is currently unclear whether these therapies are effective for cough among patients with COPD without lung cancer. In the same mode, other patient comorbidities (eg, gastroesophageal reflux disease) can be considered as the focus of treatment.
- An area that we should explore more concretely is the role of smoking cessation in the symptomatic relief of cough. A large trial of smoking cessation peridiagnosis with lung cancer has shown that patients who quit smoking had a survival advantage (28 vs 18 mo) over those who did not.[57] There may well be a role for this approach in reducing respiratory symptoms in lung cancer, and this needs to be explored.
- There is also no information in the literature about cough and hemoptysis, an area that warrants more research, and the role of local treatments such as brachytherapy or tranexamic acid, and so on.

Conclusions

Compared with the 2006 CHEST Cough Guidelines, the current recommendations and suggestions are based on a Cochrane systematic review,[15] are more specific, and follow a step-up approach to the management of cough among patients with lung cancer, acknowledging the low quality evidence in the field and the urgent need for developing a more concrete evidence base through high-quality research. The strength of recommendations and suggestions made in this guideline clearly show that research in this symptom management field is lagging behind research in other symptoms in oncology. This article has also identified gaps in our knowledge and areas for future research.

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