

Cough in lung cancer

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1.

Chronic cough after lung cancer surgery

2.

**Clinical expert guideline
: UK task group + Chest**

3.

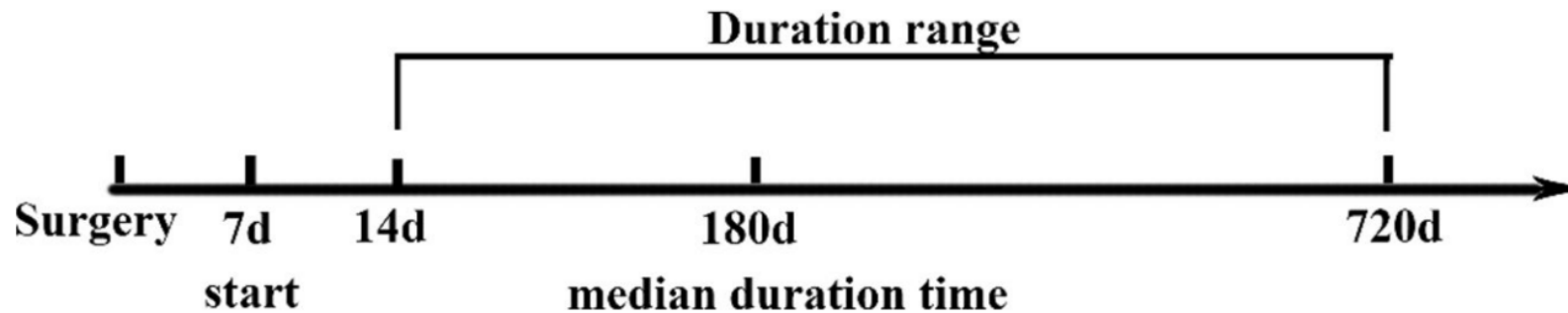
Aprepitant for Cough in Lung Cancer

Chronic cough after lung cancer surgery

Risk factors for cough after pulmonary resection

Meta-analysis (Nineteen studies with 4755 patients)

- The incidence of postoperative cough was 21.1%-55.8%.
- Peaked 30 days after discharge, and turned to mild or disappeared more than 90 days after discharge.



Tools	Items	Cough Characteristics			Impact of Cough on Quality of Life				
		Intensity	Frequency	Duration	Physical	Psychological	Social	Functional	Emotional
VAS [16]	1	+	+	-	-	-	-	-	-
CSS [17]	2	-	+	-	-	-	-	-	-
CQLQ [18]	28	-	-	-	+	+	-	+	+
LCQ [19]	19	-	-	-	+	+	+	-	-

VAS = Visual Analog Scale, CSS = Cough Symptom Score, CQLQ = Cough-Specific Quality of Life Questionnaire, LCQ = Leicester Cough Questionnaire.

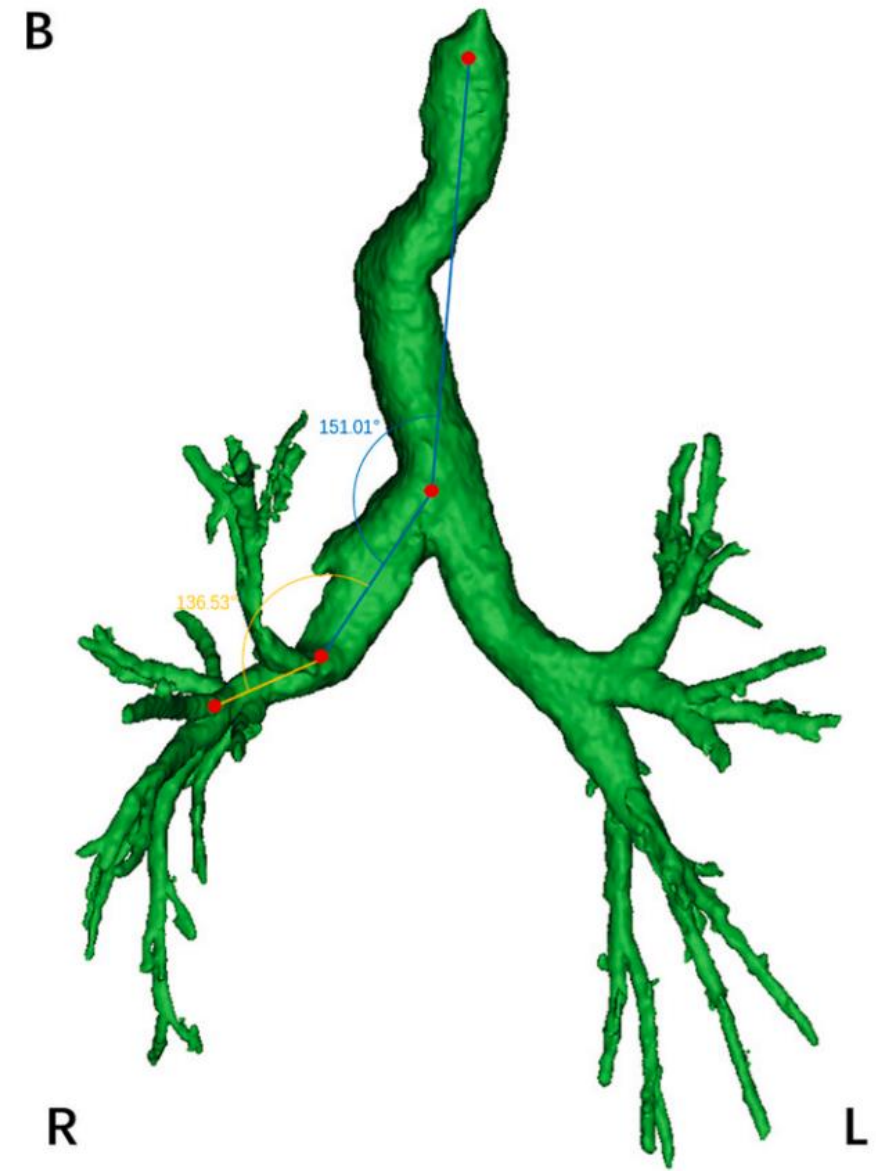
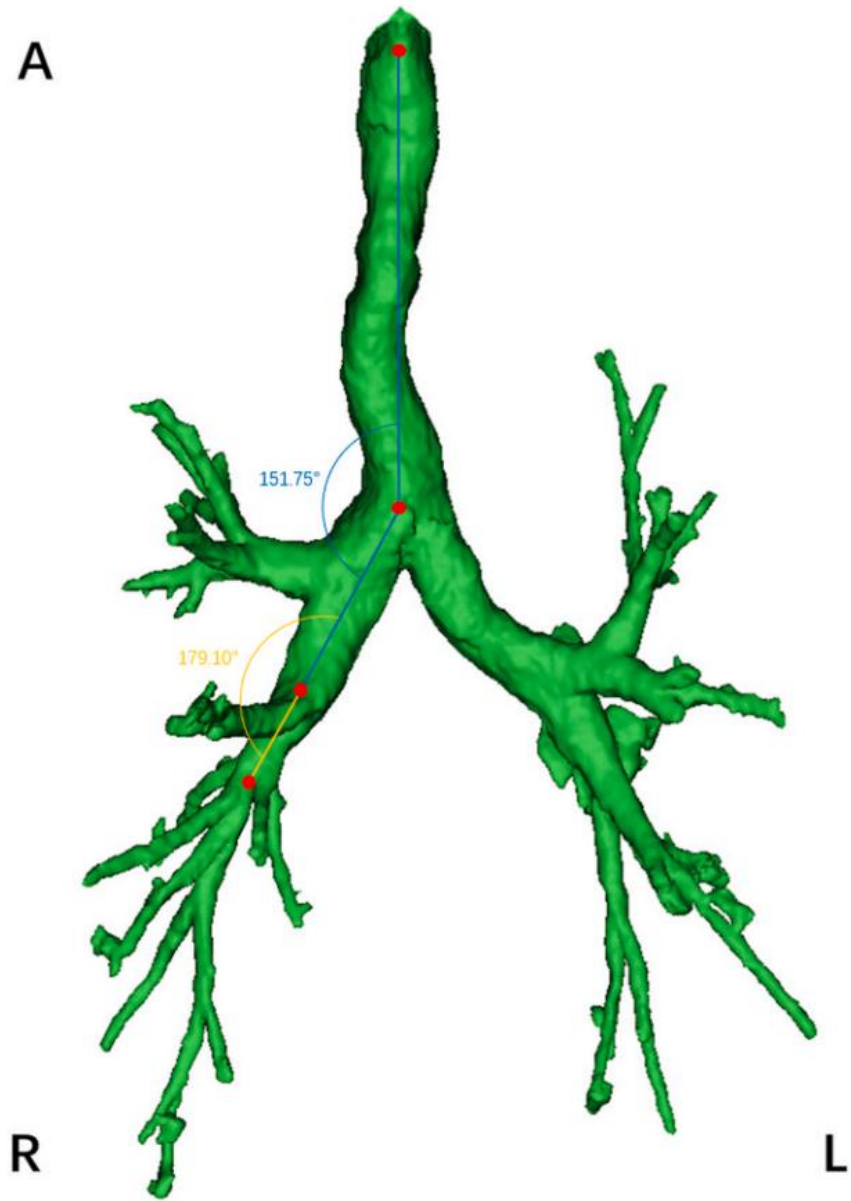
Risk factors for cough after pulmonary resection

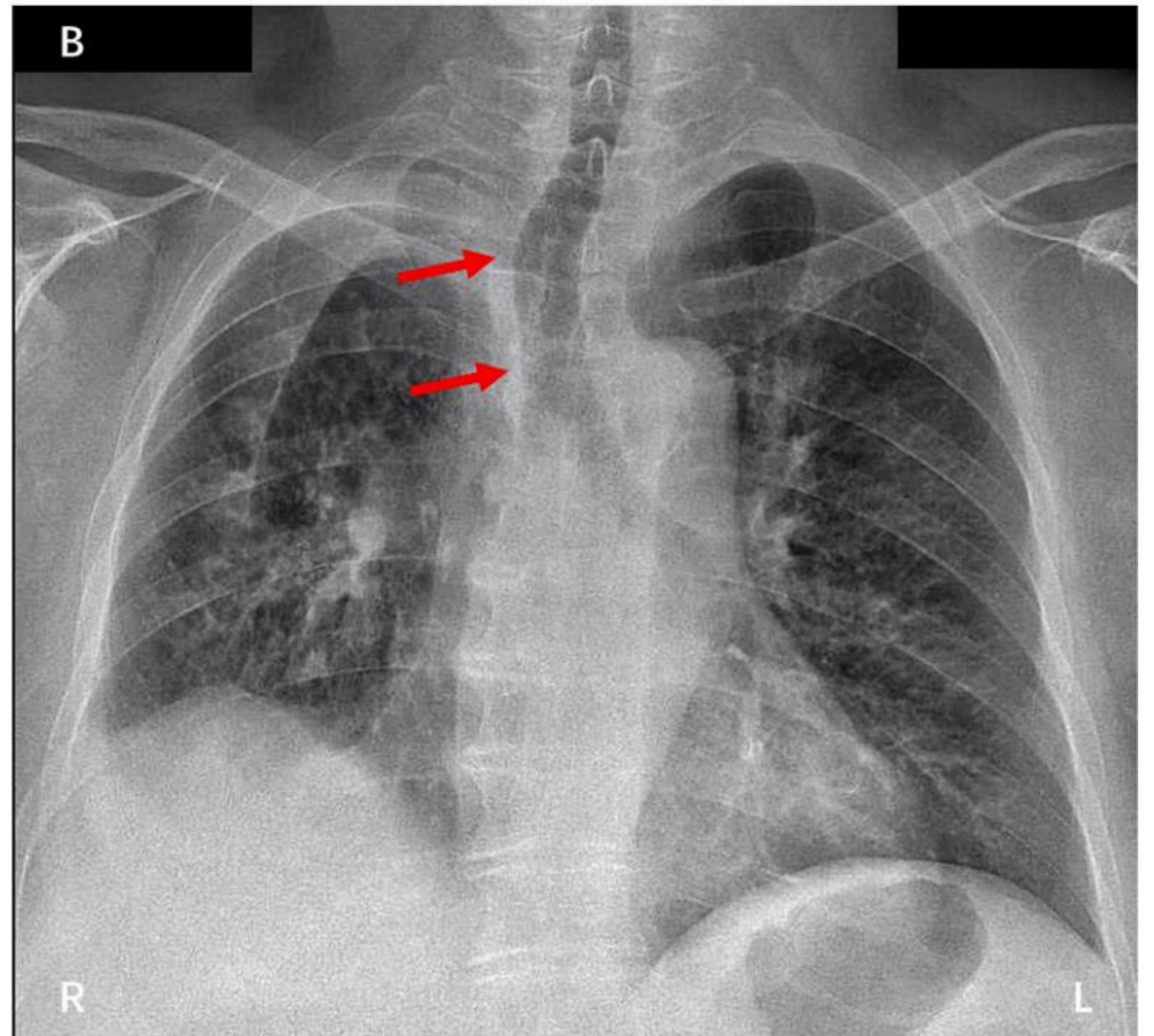
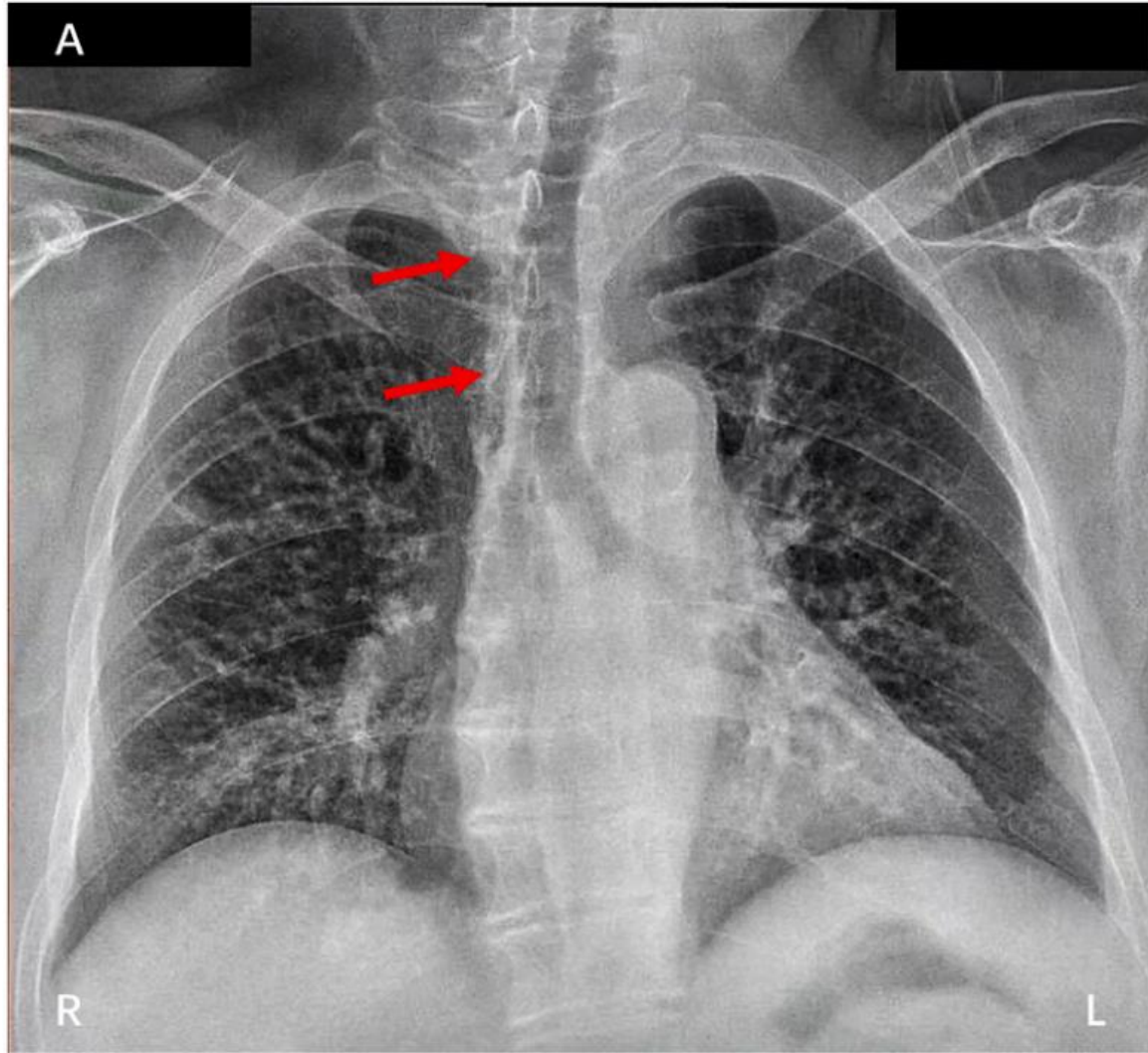
Risk factors

- Female sex [OR=1.69, 95% CI (1.07, 2.66), p=0.02]
- Preoperative cough [OR=5.96, 95% CI (2.58, 13.73), p<0.01]
- Right lobe operation [OR=2.14, 95% CI (1.44, 3.19), p<0.01]
- Lobectomy [OR=3.70, 95% CI (1.73, 7.90), p<0.01]
- Lymph node dissection
 - ① Subcarinal lymph node dissection [OR=3.45, 95% CI (1.86, 6.39), p<0.01]
 - ② Mediastinal lymph node removal [OR=3.49, 95% CI (2.07, 5.89), p<0.01]
 - ③ Peritracheal lymph node resection [OR=3.05, 95%CI (1.40,6.64), p<0.01]
- Closure of bronchial stump with stapler [OR=5.19, 95% CI (1.79, 15.07), p<0.01]
- **Postoperative acid reflux [OR=11.07, 95%CI (4.38,28.02), p<0.01].**

Risk factors for cough after pulmonary resection

- Female sex [OR=1.69, 95% CI (1.07, 2.66), p=0.02]
 - **The influence of female hormones (estrogen)**
 - Transient receptor potential (TRP) V1/A1 was higher in cough group.
 - Estrogen can affect C fiber activation by affecting TRPV1 activation/sensitization.
- Right lobe operation [OR=2.14, 95% CI (1.44, 3.19), p<0.01], Lobectomy [OR=3.70, 95% CI (1.73, 7.90), p<0.01]
 - A larger residual cavity in the thoracic cavity after surgery, which can lead to **changes in the anatomical structure** in the thoracic cavity, bronchial distortion, residual lung deformity.
- Lymph node dissection
 - The removal of lymph nodes may **damage the vagus nerve**
- Closure of bronchial stump with stapler [OR=5.19, 95% CI (1.79, 15.07), p<0.01]
 - Stapler was not conducive to the discharge of airway secretions
 - **Chronic inflammatory reaction** of the airway stump

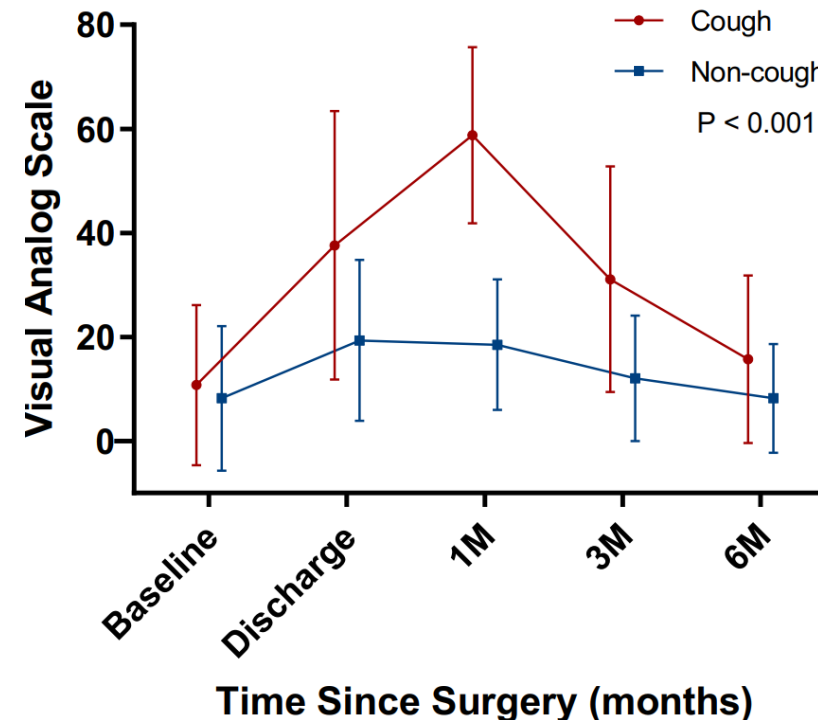
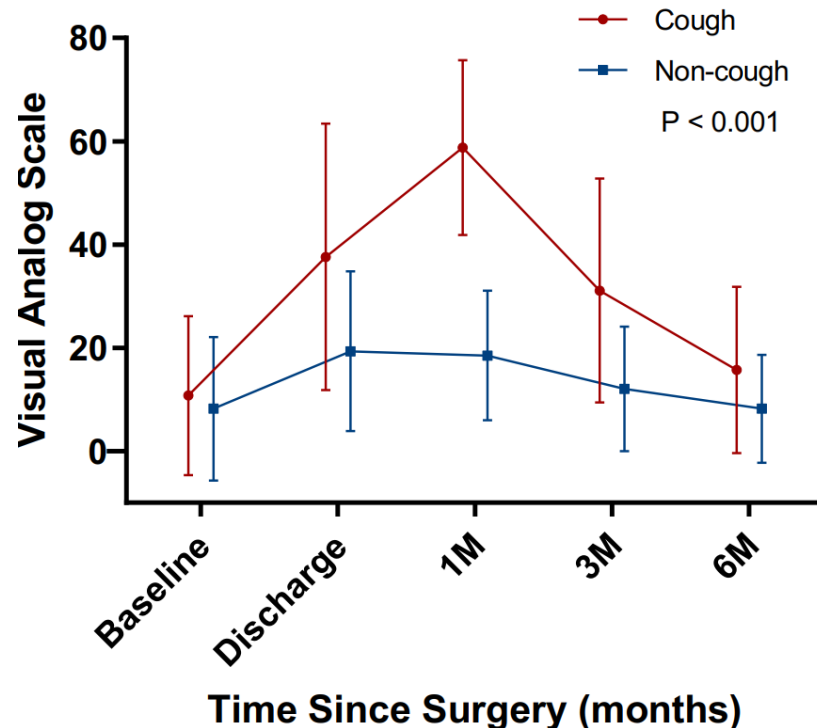




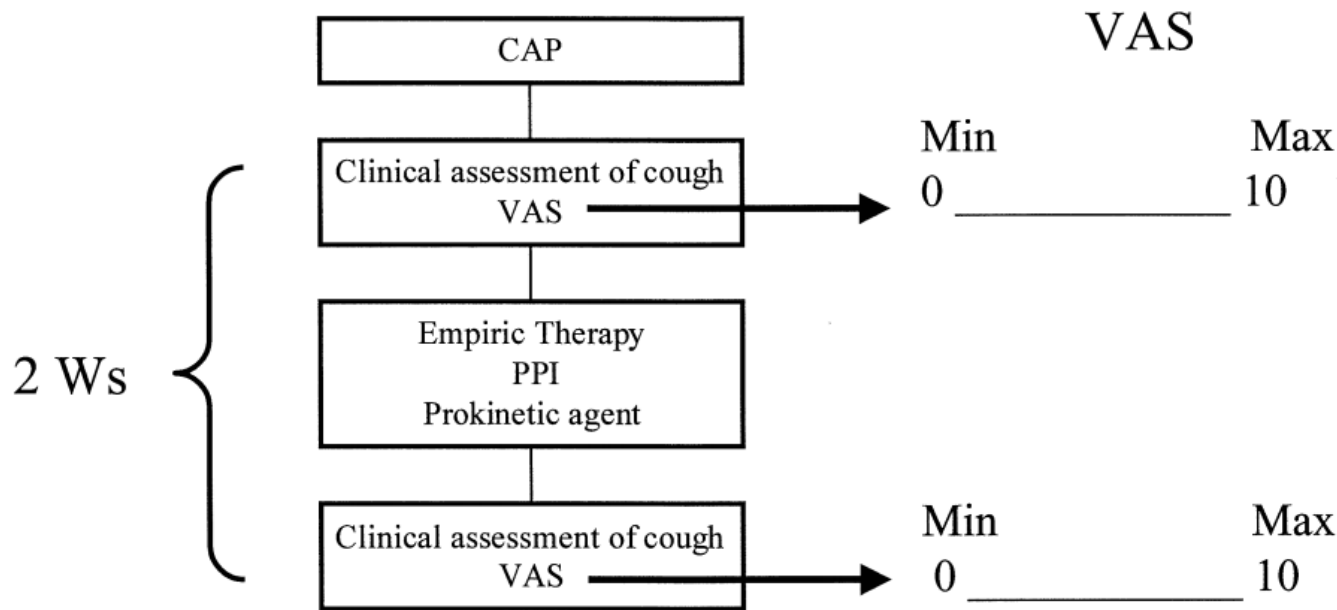
Trajectories and risk factors of persistent cough after pulmonary resection

Prospective observational study (Cough group (N=130) vs Non-cough group (N=376))

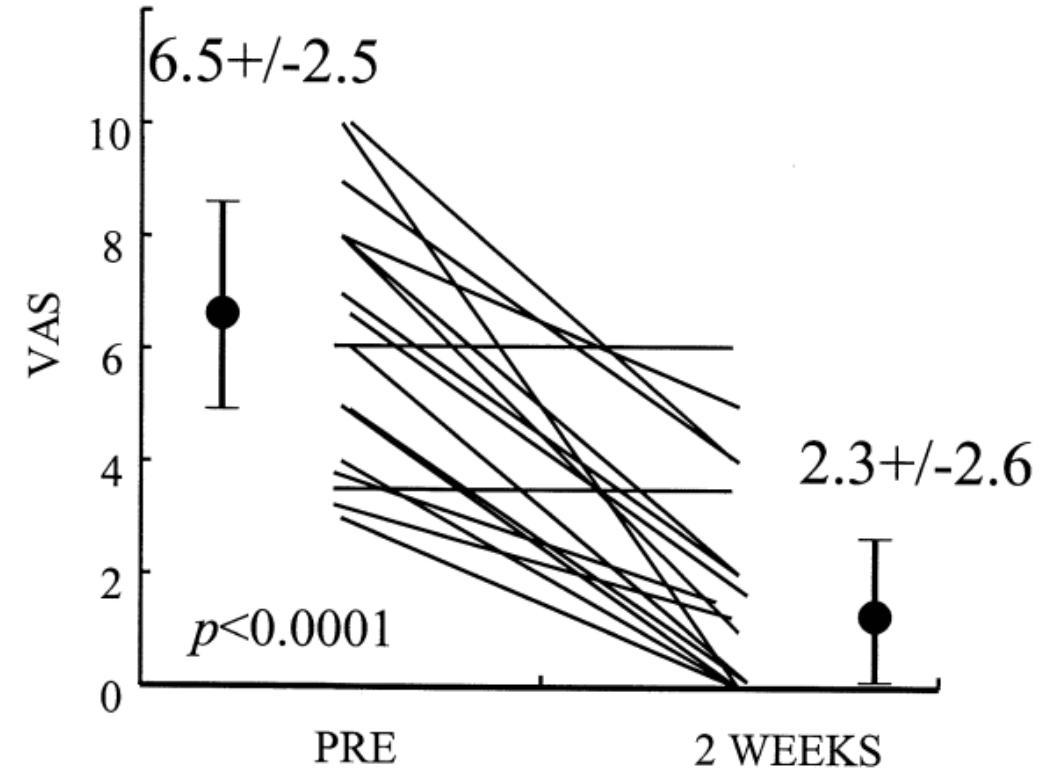
- Before surgery, at discharge, and 1, 3, and 6 months following surgery
- Multivariable regression analysis revealed that a **duration of anesthesia** exceeding 156 min (odds ratio [OR]: 1.847, 95% CI: 1.156–2.951, $p = 0.010$) and **gastroesophageal acid reflux** (OR: 3.870, 95% CI: 2.376–6.304, $p < 0.001$) were independent risk factors



Persistent Cough Following Pulmonary Resection: Observational and Empiric Study of Possible Causes



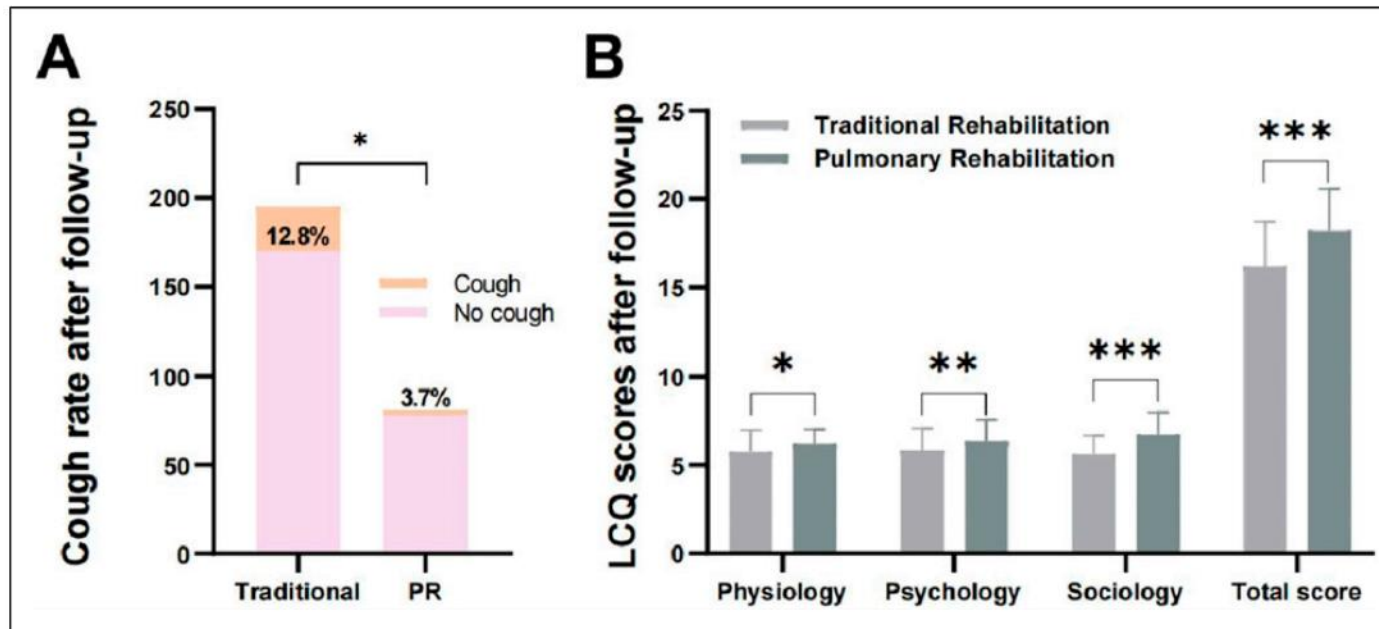
30 mg/d of Lansoprazole was used as **proton pump inhibitor** and 15 mg/d of Mosaprid in 3 doses was used as pro-kinetic agent.



Pulmonary Rehabilitation Exercises Effectively Improve Chronic Cough After Surgery for Non-small Cell Lung Cancer

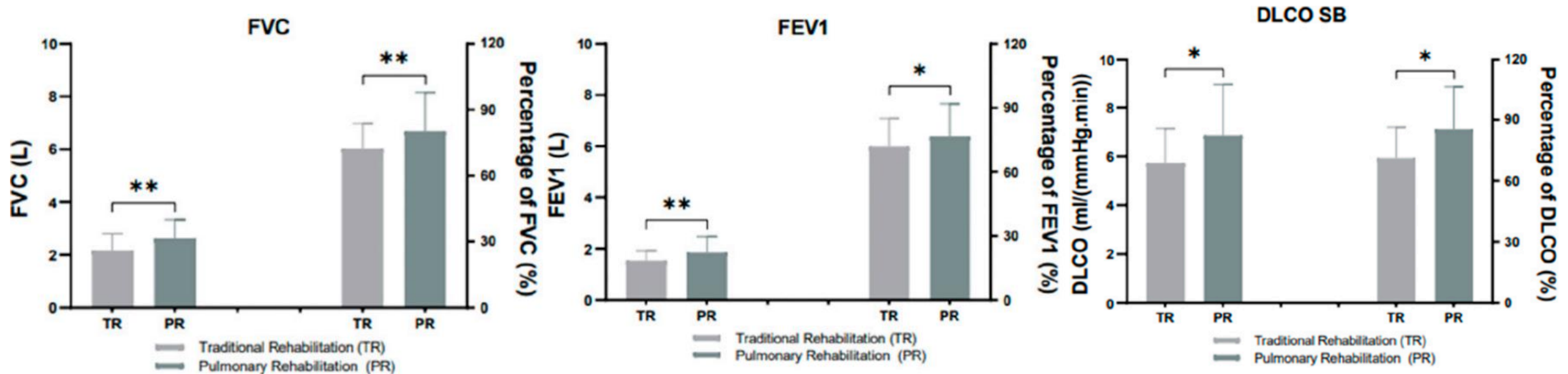
Retrospective review

- The traditional rehabilitation group (N=195) vs the pulmonary rehabilitation group (N=81)
- The pulmonary rehabilitation group continued to have (1) a lower cough incidence (3.7% vs 12.8%, $P = .022$), (2) higher LCQ scores across all dimensions: somatic ($6.19 \pm .11$ vs 5.75 ± 1.20 , $P = .035$), mental (6.37 ± 1.19 vs 5.85 ± 1.22 , $P = .002$), sociological (6.76 ± 1.22 vs 5.62 ± 1.08 , $P < .001$), and total (18.22 ± 2.37 vs 16.21 ± 2.53 , $P < .001$) at the 6-month follow-up.



Pulmonary Rehabilitation Exercises Effectively Improve Chronic Cough After Surgery for Non-small Cell Lung Cancer

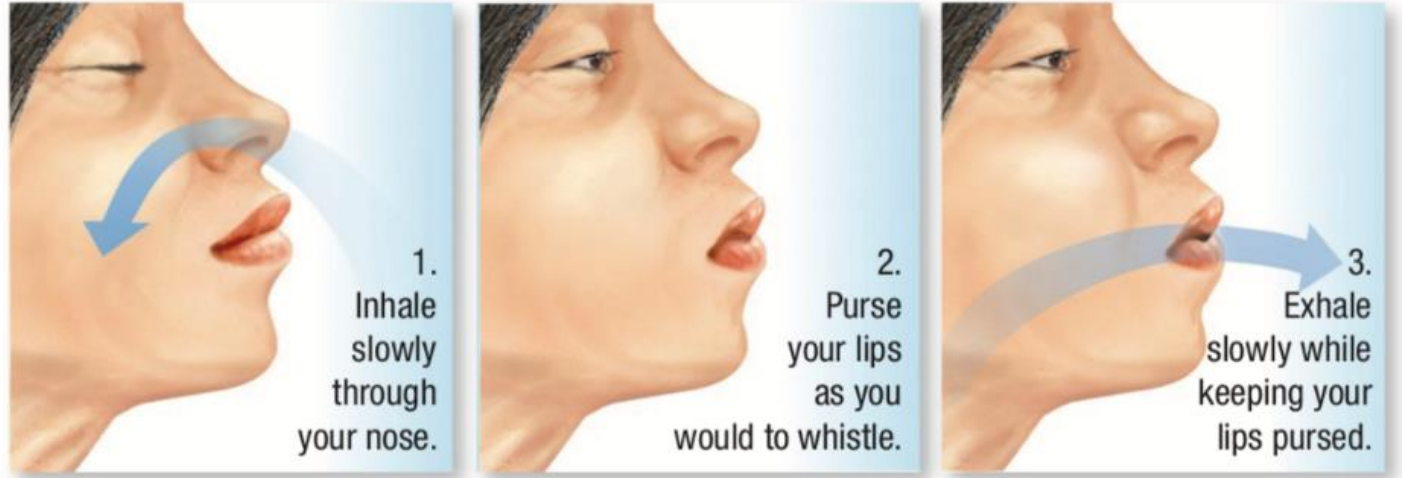
- Additionally, lung function parameters including FVC, FVC%, FEV1, FEV1%, MVV, MVV%, DLCO SB, and DLCO% were all significantly higher in the pulmonary rehabilitation group compared to the traditional group.



Hospitalisation		At Home	
Name of Exercise	Description	Name of Exercise	Description
Breathing apparatus	Adopted three-ball breathing apparatus for respiratory function exercise. 3min * 3/day	Breathing apparatus	Adopted three-ball breathing apparatus for respiratory function exercise. 5min * 3/day
Pursed lips breathing	Inhaled through the nose for 2s, followed by holding the breath for 2s, then exhaled slowly through pursed lips for 10-20s. 5-10min * 3/day.	Pursed lips breathing or deep breathing	Inhaled deeply to maximum, followed by holding the breath for 2s, then exhaled slowly for 10-20s. 10-15min * 3/day.
Coughing	Active or assisted coughing. 2min * 3/day	Coughing	Active coughing. 2min * 3/day
Expelling sputum	Manual back patting, and postural vibratory expectoration. 5min * 3/day	Stretching exercise	Including head, neck, shoulder, limb, and chest expansion exercises. 5-10min * 3/day
Stretching exercise	Including head, neck, shoulder, limb, and chest expansion exercises 3-5min * 3/day	Aerobic exercise	According to the patient's physical recovery, moderate to high intensity aerobic exercise, such as walking or jogging. 10-30min * 3/day



Three-ball breathing apparatus



Pursed lips breathing



Manual back patting



Postural vibratory expectoration

Clinical expert guideline
: UK task group + Chest

Cough in lung cancer

1. In 1997, Lee et al. performed the first survey. Among 3,794 patients, they found that **the most frequent symptom was cough (57.2%)**.

Lung Cancer 2000;30:15-22.

2. In 2005, In et al. performed the second survey.

Among the total of 8,788 patients, **they found that cough (38.1%) was still the most frequent symptom.**

Lung Cancer 2009;64:232-7.

Chronic Cough Due to Lung Tumors

- Many studies have shown that lung cancer is **the cause of chronic cough in $\leq 2\%$** of all patients who present with a chronic cough.

CHEST / 129/1/JANUARY, 2006 SUPPLEMENT

Lung cancer: clinical presentation and specialist referral time

Symptomatic pattern	All series n (%)	Diagnostic period [#] n				p-value [†]
		I	II	III	IV	
Non-symptomatic patients (incidental diagnosis)	158 (12.4)	20	51	39	48	<0.01
Symptomatic patients	1119 (87.6)	299	268	281	271	
Patients with						
Cough	639 (50.0)	184	153	160	142	<0.01
Systemic symptoms	630 (49.3)	174	153	157	146	NS
Dyspnoea	433 (33.9)	111	96	106	120	NS
Chest pain	402 (31.5)	142	105	87	68	<0.001
Bloody sputum	381 (29.8)	101	102	84	94	NS
Symptoms of local or distant dissemination	298 (23.3)	65	77	76	80	NS
Chest infection	252 (19.7)	67	60	72	53	NS
Mean number of symptoms per patient	2.38	2.82	2.78	2.64	2.59	

NS: nonsignificant. [#]: quartiles of the distribution of the dates of diagnosis (Period I: no. 319 (Jan. 1989–May 1992); Period II: no. 319 (Jun. 1992–Sep. 1995); Period III: no. 320 (Oct. 1995–May 1999); Period IV: no. 319 (Jun. 1999–Oct. 2002)); [†]: Yates corrected Chi-squared test.

Total (50.0%), I (61.5%), II (57.1%), III (56.9%), IV (52.4%)

Lung cancer: clinical presentation and specialist referral time

Symptoms	Adenocarcinoma n (%)	Squamous cell n (%)	Small cell n (%)
No symptom (casual discovery)	57 (20.6)	40 (8.1)	14 (9.7)
Cough	51 (18.4)	95 (19.2)	19 (13.2)
Bloody sputum	37 (13.4)	119 (24.0)	15 (10.4)
Dyspnoea	32 (11.6)	52 (10.5)	28 (19.4)
Chest pain	38 (13.7)	53 (10.7)	28 (19.4)
Chest infection	14 (5.1)	55 (11.1)	9 (6.3)
Systemic symptoms	24 (8.7)	51 (10.3)	11 (7.6)
Symptoms of local or distant dissemination	24 (8.7)	31 (6.3)	20 (13.9)

#: test of independence for a multi-way contingency table: Chi-squared=89.862; p=0.000.

RESEARCH ARTICLE

Open Access

A cross sectional study to determine the prevalence of cough and its impact in patients with lung cancer: a patient unmet need



Amélie Harle^{1,2*}, Alex Molassiotis³, Oliver Buffin^{4,5}, Jack Burnham^{4,6}, Jaclyn Smith^{7,8}, Janelle Yorke^{4,9} and Fiona H. Blackhall^{2,10}

57% of the patients. (Stage III~IV 87%)

Statistically significant

- **On anticancer therapy**

Statistically non-significant

- **Cancer stage, histology, age, smoking status**
- **Sex, Performance status**

Cough in Patients With Lung Cancer A Longitudinal Observational Study of Characterization and Clinical Associations



Amélie S. M. Harle, PhD; Fiona H. Blackhall, PhD; Alex Molassiotis, PhD; Janelle Yorke, PhD; Rachel Dockry, PhD; Kimberley J. Holt, MPhil; Danielle Yuill, MRes; Katie Baker, PhD; and Jaclyn A. Smith, PhD

62% of the patients. (Stage III~IV 90%)

Statistically significant

- **Performance status**
- **Female sex, asthma, GERD, Nausea**

Statistically non-significant

- **Cancer stage, histology, age, smoking status**

REVIEW

Open Access

Clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough

Alex Molassiotis^{1*}, Jaclyn A Smith², Mike I Bennett³, Fiona Blackhall⁴, David Taylor⁵, Burhan Zaveri⁶, Amelie Harle⁴, Richard Booton⁷, Elaine M Rankin⁸, Mari Lloyd-Williams⁹, Alyn H Morice¹⁰

Abstract

Background: Cough is a common and distressing symptom in lung cancer patients. The clinical management of cough in lung cancer patients is suboptimal with limited high quality research evidence available. The aim of the present paper is to present a clinical guideline developed in the UK through scrutiny of the literature and expert opinion, in order to aid decision making in clinicians and highlight good practice.

Methods: Two systematic reviews, one focusing on the management of cough in respiratory illness and one Cochrane review specifically on cancer, were conducted. Also, data from reviews, phase II trials and case studies were synthesized. A panel of experts in the field was also convened in an expert consensus meeting to make sense of the data and make clinical propositions.

Results: A pyramid of cough management was developed, starting with the treatment of reversible causes of cough/specific pathology. Initial cough management should focus on peripherally acting and intermittent treatment; more resistant symptoms require the addition of (or replacement by) centrally acting and continuous treatment. The pyramid for the symptomatic management starts from the simpler and most practical regimens (demulcents, simple linctus) to weak opioids to morphine and methadone before considering less well-researched and experimental approaches.

Conclusion: The clinical guidelines presented aim to provide a sensible clinical approach to the management of cough in lung cancer. High quality research in this field is urgently required to provide more evidence-based recommendations.

1. Introduction

Cough is a common symptom in about 23-37% of general cancer patients and 47-86% of lung cancer patients [1]. The first author's data on 100 cancer patients assessed using the Memorial Symptom Assessment Scale from the beginning of cancer treatment to 3, 6 and 12 months showed a prevalence of 42.9%, 39.2%, 35.1% and 36.1% respectively, similarly to the experience of breathlessness, although less distressing than breathlessness [2]; these numbers almost doubled in the lung cancer subgroup analysis. Despite such high prevalence, the management of cough remains suboptimal, with

little high quality evidence to guide practice. Much of the current practice on the symptomatic management of cough in lung cancer is experiential and primarily is geared around the use of oral opioids. Current guidelines on the management of cough are often broad and non-specific (suggesting difficulty in making any specific recommendations) and either focus on non-cancer respiratory illnesses with different pathophysiology from cancer-related cough, or provide broad reviews of generally poor quality studies [3-7]. Professional societies that have developed guidelines (non-cancer) include the American College of Chest Physicians (ACCP) [3,8], the European Respiratory Society (ERS) [9] and the British Thoracic Society (BTS) [7].

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Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer

CHEST Guideline and Expert Panel Report



Alex Molassiotis, RN, PhD; Jaclyn A. Smith, MBChB, PhD; Peter Mazzone, MD, MPH; Fiona Blackhall, MD, PhD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel

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. CHEST 2017; 151(4):861-874

KEY WORDS: cough; evidence-based medicine; guidelines; lung cancer

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

AFFILIATIONS: From the School of Nursing (Dr Molassiotis), The Hong Kong Polytechnic University, Hong Kong, China; the Centre for Respiratory Medicine and Allergy (Dr Smith), University of Manchester and University Hospital of South Manchester, Manchester, England; the Respiratory Institute (Dr Mazzone), Cleveland Clinic, Cleveland, OH; the Department of Medical Oncology (Dr Blackhall), Christie Hospital NHS Trust, Manchester, England; and the University of Massachusetts Medical School (Dr Irwin), Worcester, MA.

DISCLAIMER: American College of Chest Physician guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which

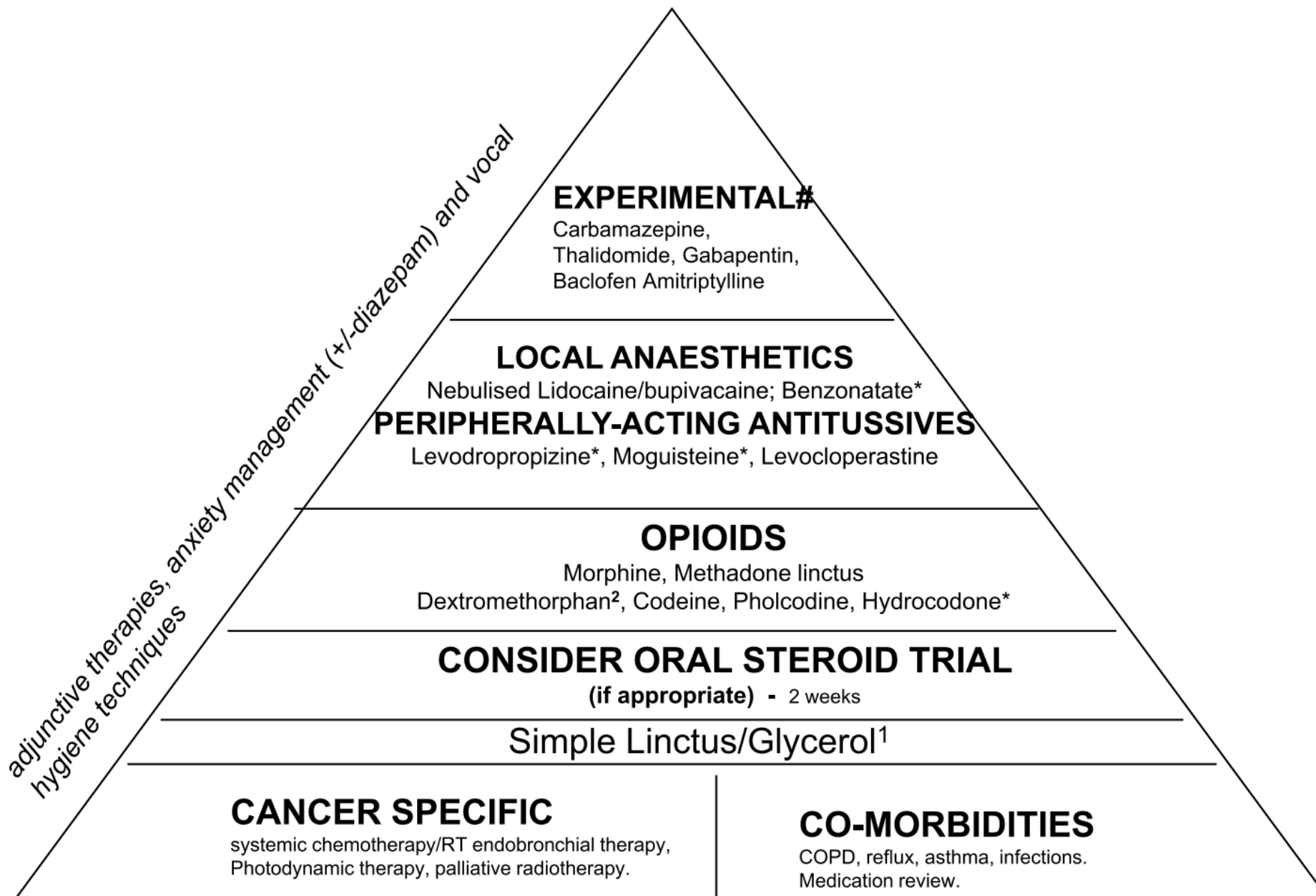
always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at <http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/CHEST-Guidelines>.

FUNDING/SUPPORT: CHEST was the sole supporter of these guidelines, this article, and the innovations addressed within.

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DOI: <http://dx.doi.org/10.1016/j.chest.2016.12.028>





Butamirate linctus syrup



Simple linctus syrup



Glycerin-based linctus syrup

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).**



Dextromethorphan
종합 감기약 주성분, 단독약 X



Codein



Cough sy

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).



Levodropropizine



Benzonatate

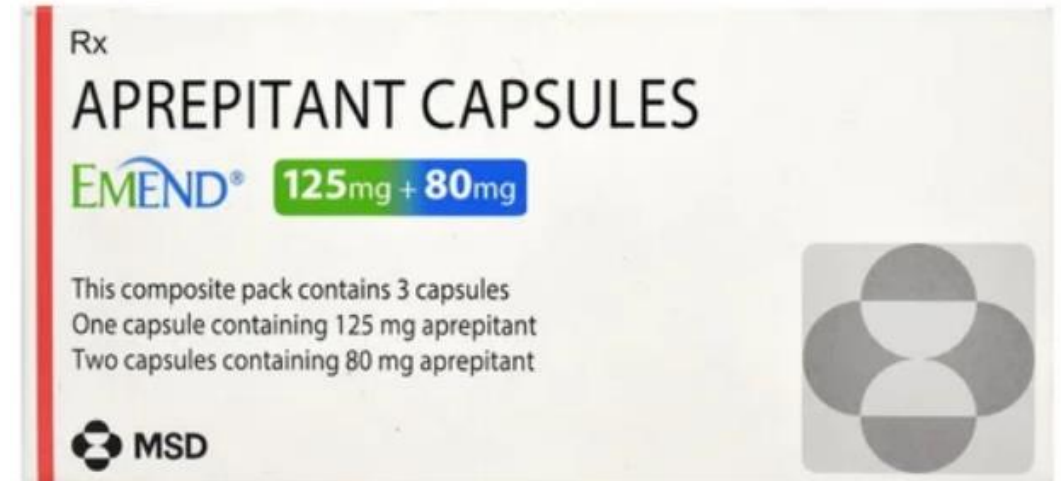
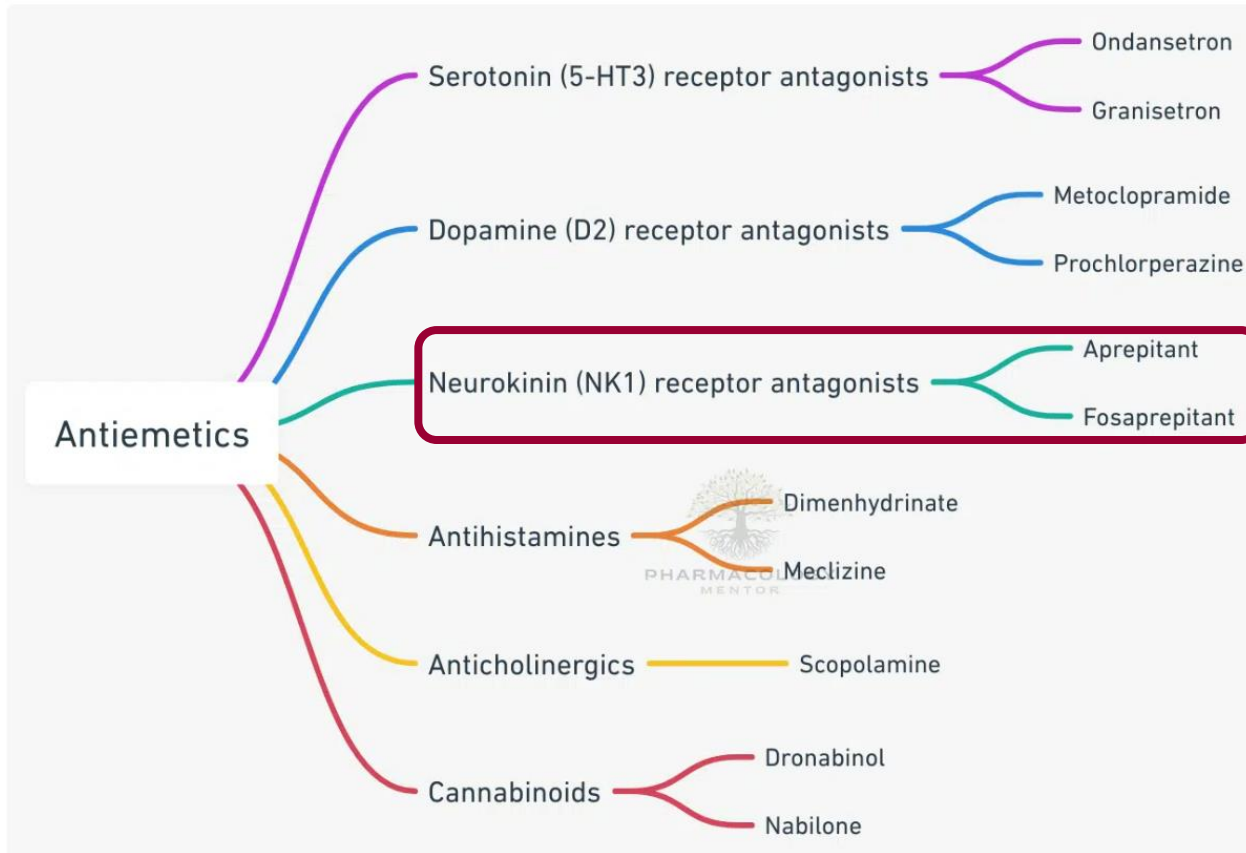


Levocloperastine

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)

Aprepitant for Cough in Lung Cancer

Aprepitant [Emend]

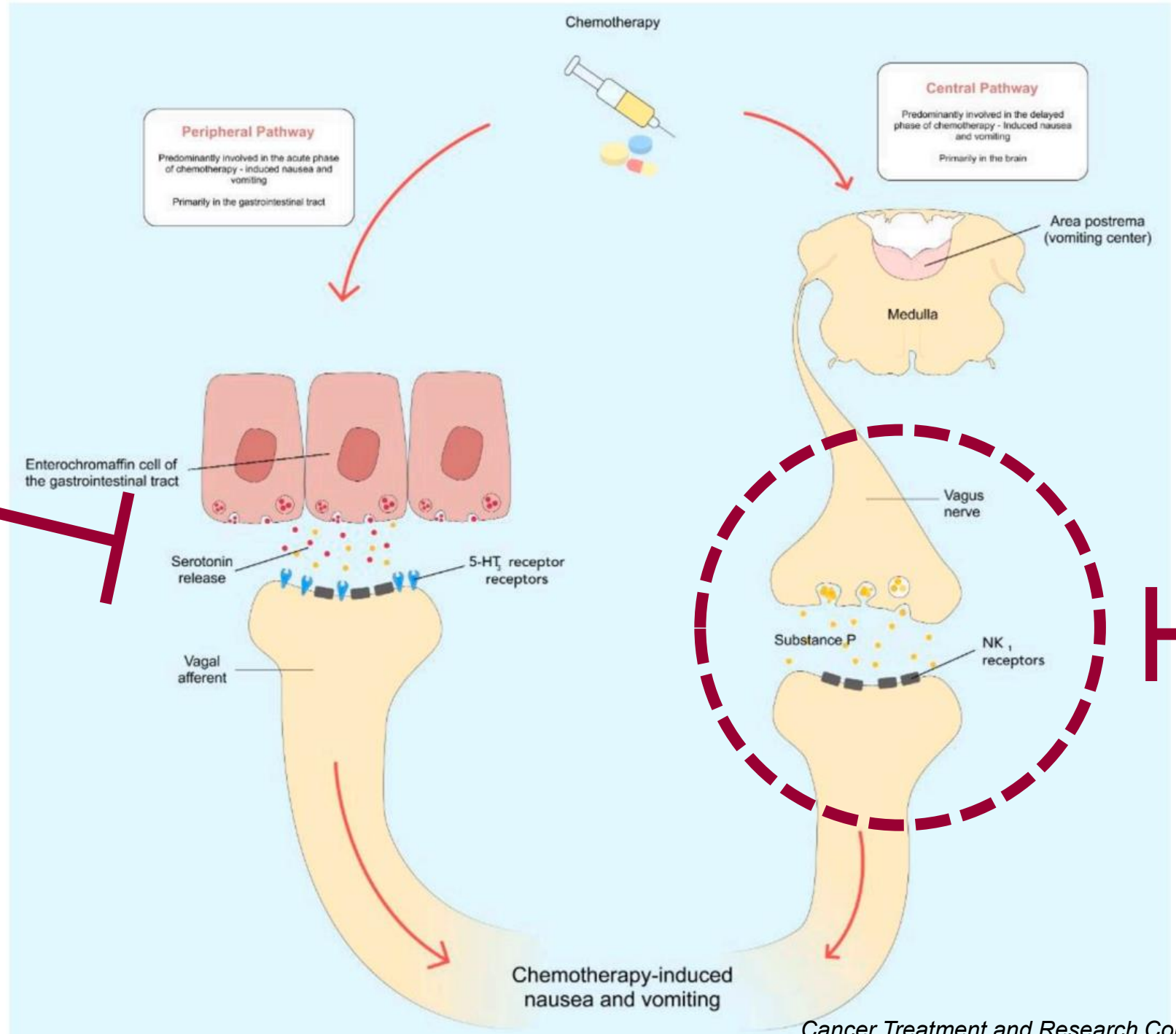


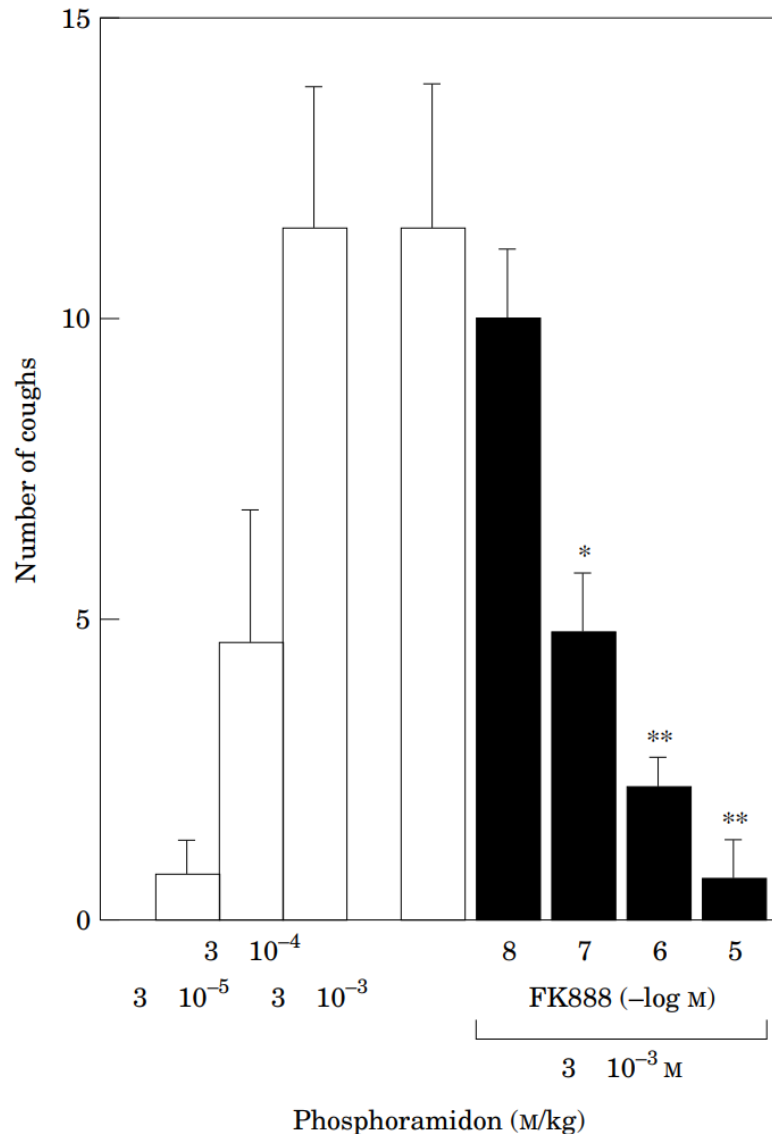
Selective NK1 receptor antagonist

5-HT₃ receptor antagonist



NK1 receptor antagonist





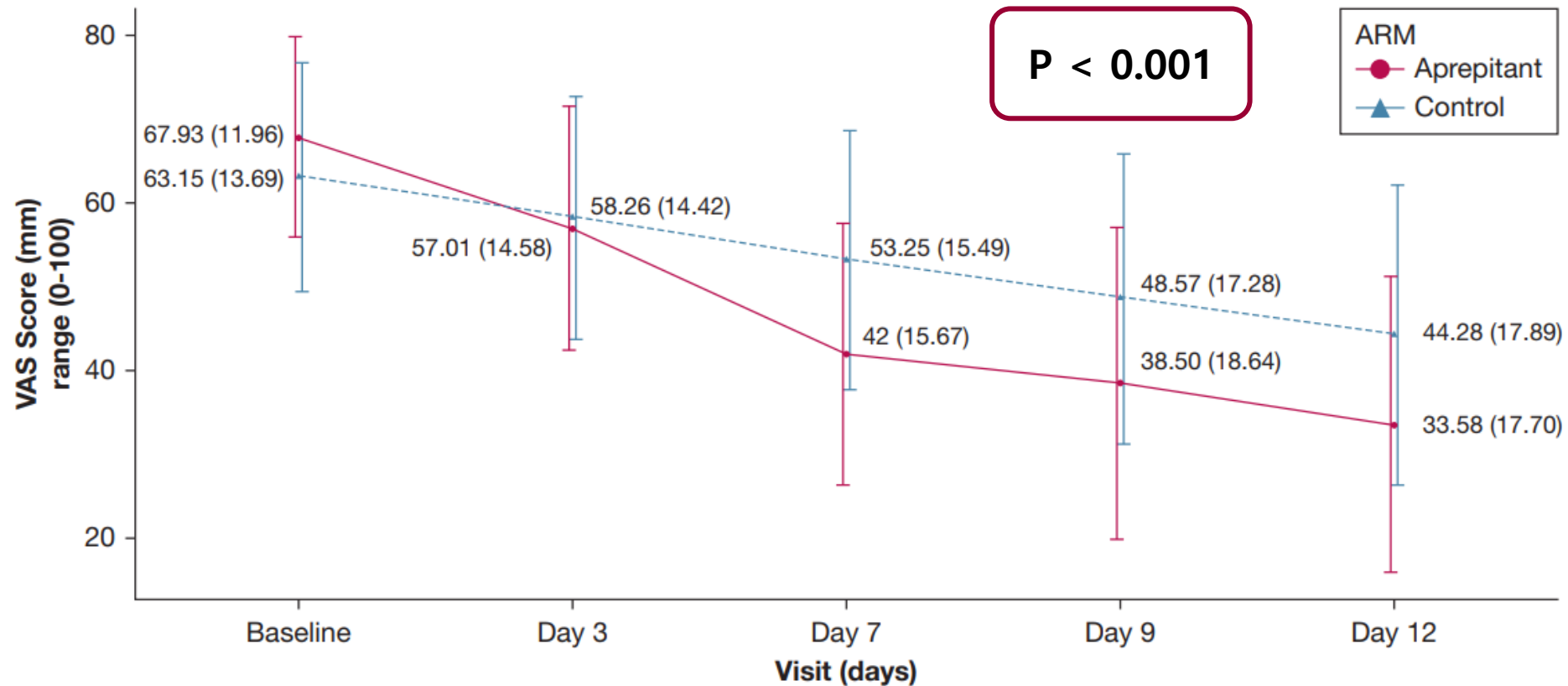
Substance P pig model

- Intraperitoneal injection of phosphoramidon caused dose-dependent increases in the number of coughs in awake guinea-pigs.
- FK888 (NK1 receptor antagonist)
- Opinion
 - A. In humans, aerosols of SP did not cause cough in normal subjects, suggesting that **damaged epithelium may facilitate the penetration of Substance P.**
 - B. Substance P does not cause bronchoconstriction either by intra-venous infusion or by inhalation in normal subjects

A Randomized Trial (1:1 = Aprepitant (N=64) vs Control (N=64))

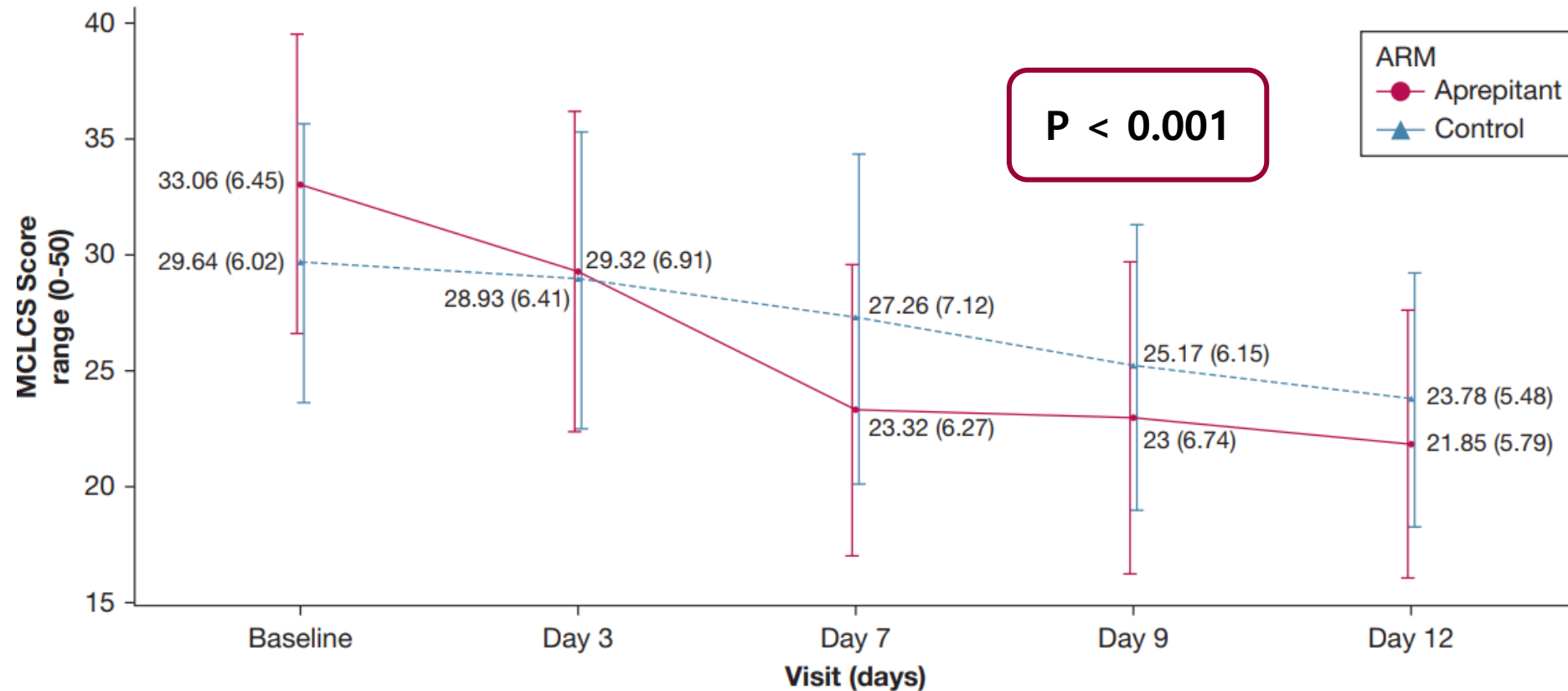
- **Advanced lung cancer (Stage IV (88%), III (12%)) and cough lasting over 2 weeks despite a cough suppressant.**
 - **Never smoker (61 ~67%), Former smoker (30~36%), COPD or asthma (3~6%)**
- **Aprepitant 125 mg (Day 1) – Aprepitant 80mg (Day 2~7) - Stop**
- **Primary end point : subjective cough improvement on day 9**
 - **The Visual Analog Scale (VAS) and Manchester Cough in Lung Cancer Scale (MCLCS).**
- **Secondary end point**
 - ① **Quality of life (QoL) as measured by the European Organization for Research and Treatment of Cancer (EORTC)**
 - ② **Adverse events**

Primary end point : subjective cough improvement on day 9



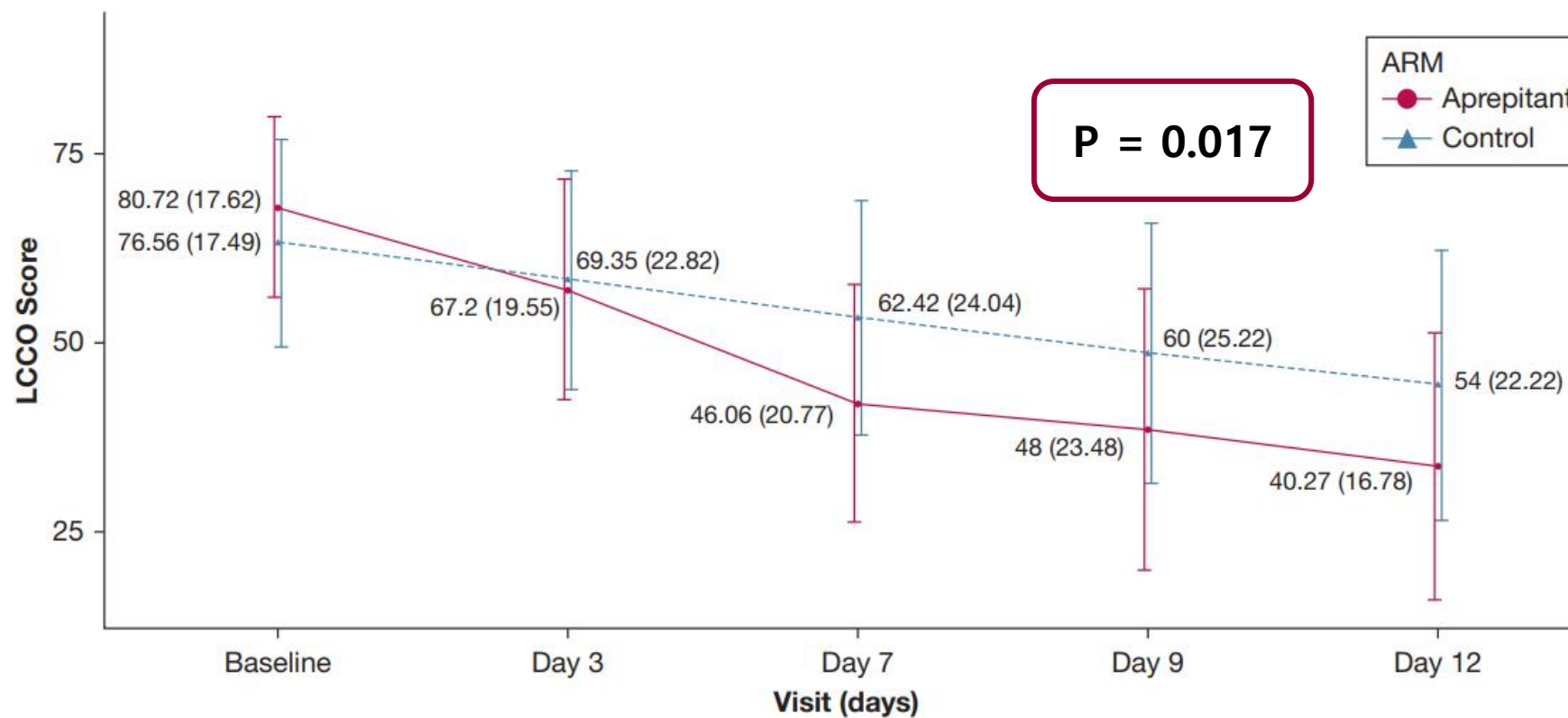
- The decrease in the cough parameters occurred as early as day 3
- The patients continued to experience a sustained antitussive effect up to day 12, that is, even after stopping aprepitant.

Primary end point : subjective cough improvement on day 9



- The decrease in the cough parameters occurred as early as day 3
- The patients continued to experience a sustained antitussive effect up to day 12, that is, even after stopping aprepitant.

Secondary end point : Quality of life (QoL) and adverse events



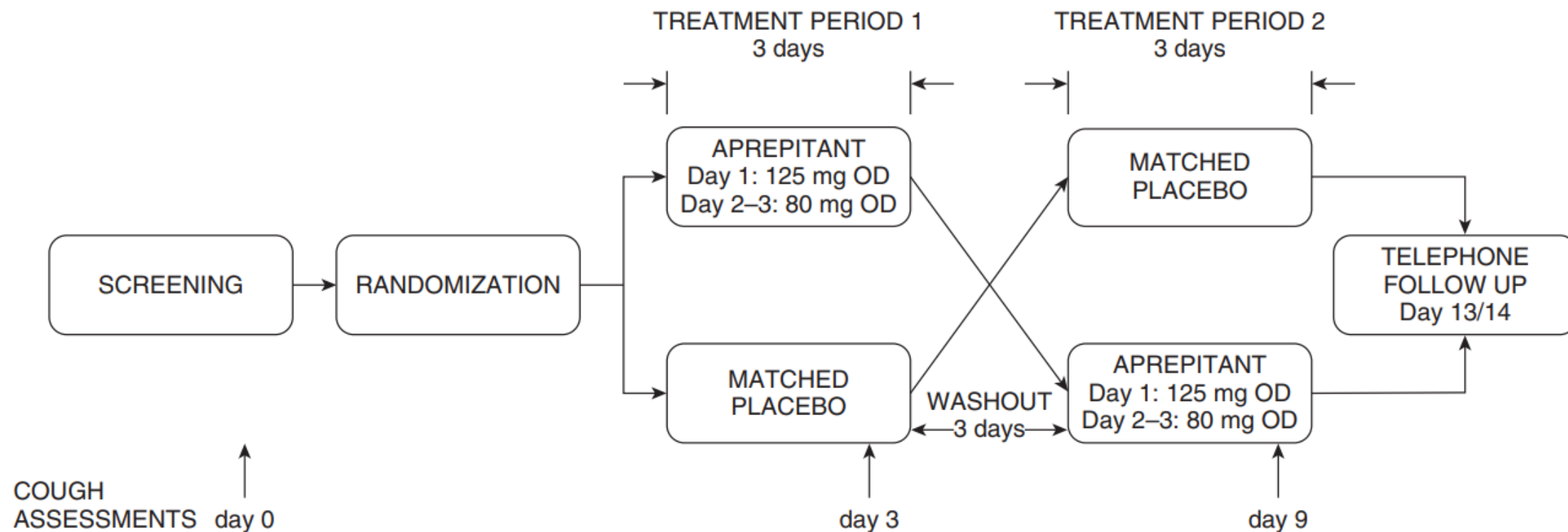
- Overall QoL was not significantly different between the two arms; however, aprepitant led to a significant improvement in the cough-specific QoL domain
- There was no increase in > grade 3 adverse events from aprepitant (No dose reduction or medication hold)

Aprepitant for Cough in Lung Cancer A Randomized Placebo-controlled Trial and Mechanistic Insights

Randomized double-blind crossover trial (N=19)

- **Advanced lung cancer (Stage IV (50%), III (50%)) and cough lasting over 4 weeks despite a cough suppressant.**
 - **Current smoker (25%), Former smoker (70%), COPD (30%)**
- **A standard antiemetic aprepitant therapy (125mg (Day 1) – 80mg (Day 2-3))**
- **Primary end point (Screening and Day 3)**
 - **Cough frequency collected using a cough monitoring device (VitaloJAK; Vitalograph Ltd.); awake/sleep/24-hour**
- **Secondary end point**
 - ① **The Visual Analog Scale (VAS) and Manchester Cough in Lung Cancer Scale (MCLCS).**
 - ② **Quality of life (QoL) as measured by the European Organization for Research and Treatment of Cancer (EORTC)**
 - ③ **Adverse events**

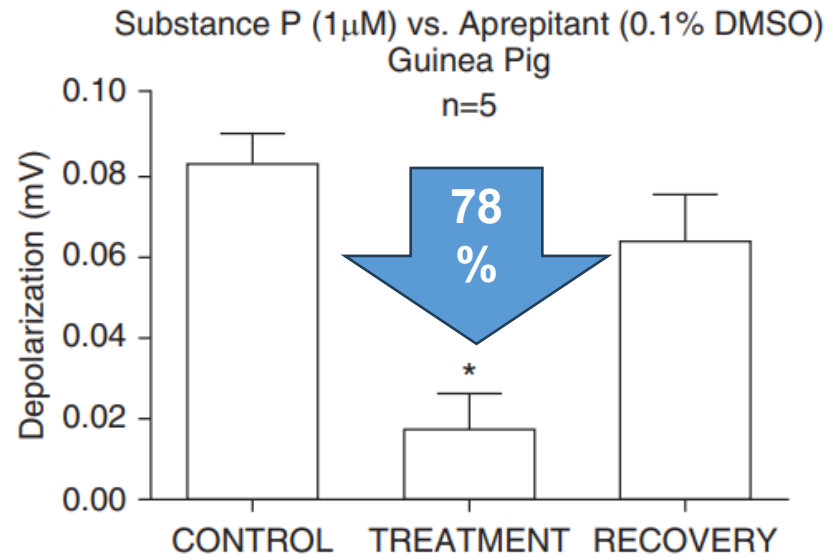
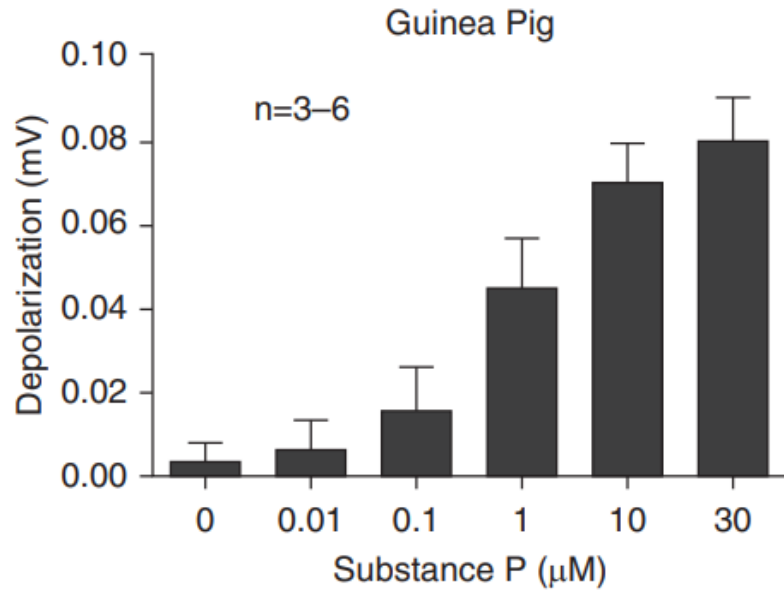
Aprepitant for Cough in Lung Cancer A Randomized Placebo-controlled Trial and Mechanistic Insights



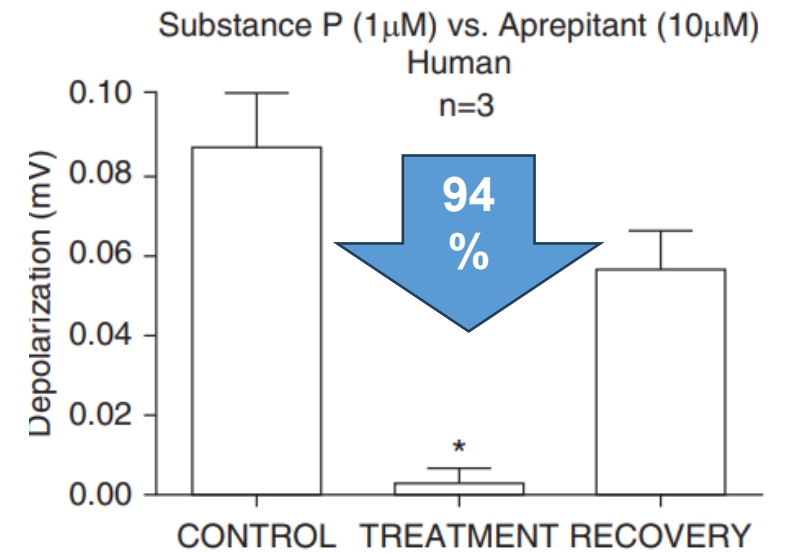
Primary and secondary end point

	Screening	Aprepitant	Placebo	Placebo-adjusted Effect of Aprepitant	P Value
Awake cough frequency					
Geometric mean (95% CI), c/h	16.3 (9.7 to 27.1)	12.1 (7.9 to 18.4)	16.1 (11.3 to 23.0)	-22.2% (-37.7 to -2.8)	0.026
Patients in analysis	19	18	19	—	
Sleep cough frequency					
Median (IQR), c/h	4.6 (1.9 to 10.0)	2.2 (0.5 to 5.4)	5.3 (1.8 to 13.0)	-59.8% (-86.0 to 15.1)	0.081
Patients in analysis	19	18	19	—	
24 h cough frequency					
Geometric mean (95% CI), c/h	12.6 (7.8 to 20.4)	9.1 (6.0 to 13.9)	13.4 (9.6 to 18.7)	-30.3% (-44.3 to -12.7)	0.002
Patients in analysis	19	18	19	—	
Cough severity VAS					
Mean score (95% CI), mm	54.5 (45.3 to 63.7)	39.6 (32.3 to 46.8)	49.6 (43.6 to 55.7)	-9.5 (-15.4 to -3.5)	0.002
Patients in analysis	19	18	19	—	
Cough impact MCLCS					
Mean score (95% CI)	24.8 (22.1 to 27.5)	19.1 (17.1 to 21.1)	21.3 (19.6 to 23.0)	-2.0 (-3.2 to -0.9)	0.001
Patients in analysis	19	18	19	—	
Item 31 EORTC QLQ-C30 + LC13					
Mean score (95% CI)	2.8 (2.6 to 3.1)	2.4 (2.1 to 2.6)	2.6 (2.3 to 2.8)	0.2 (0.0 to 0.4)	0.016
Patients in analysis	19	18	19	—	

Preclinical studies



P = 0.0145

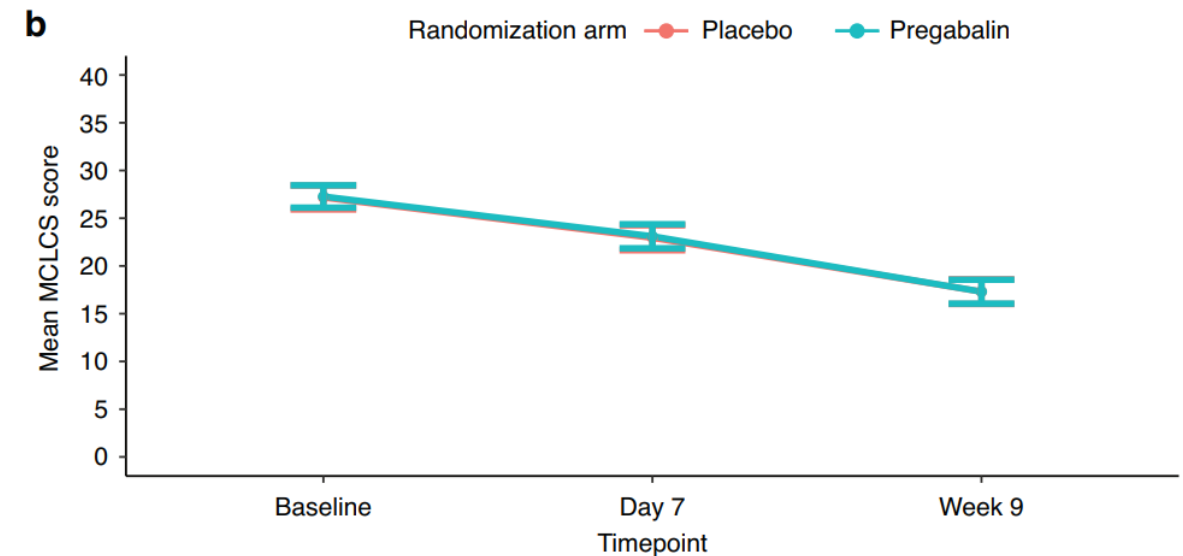
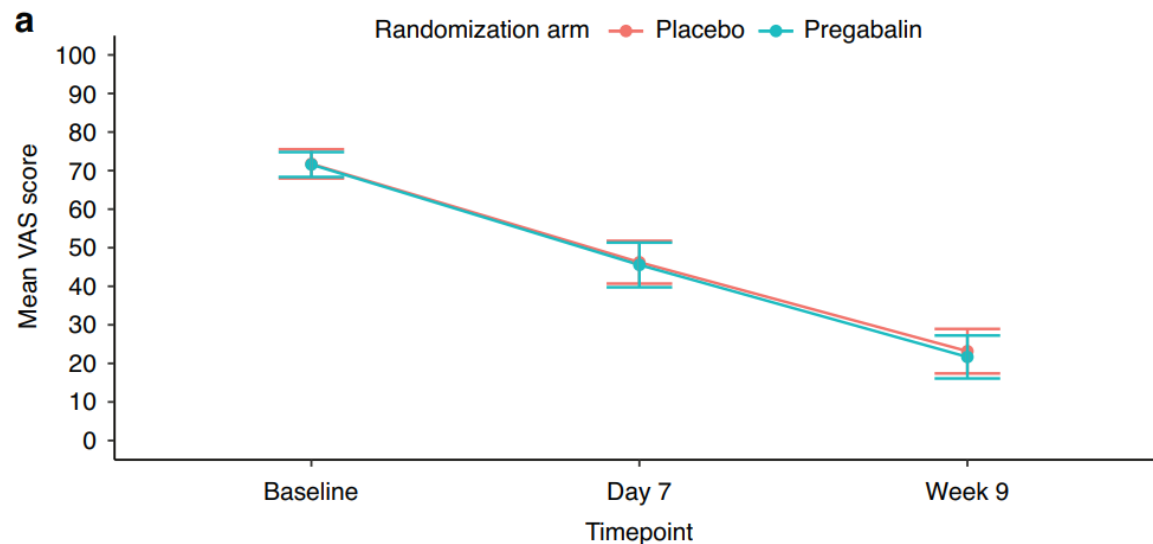


P = 0.0145

Pregabalin for chronic cough due to lung cancer: randomized, double-blind, placebo-controlled trial

Randomized double-blind placebo-controlled study (Pregabalin 300mg (N=83) vs placebo (N=83) for 9 weeks)

- Similar to the mechanism of glutamate receptor antagonists like dextromethorphan
- Primary endpoint was the change in cough severity as measured by the difference in VAS scores.
- **Pregabalin does not significantly decrease cough in patients with lung cancer.**
- **Systemic cancer-directed therapy is the most effective antitussive.**



Conclusion

Chronic cough after lung cancer surgery

- ① **Risk factors** : Female sex, Preoperative cough, Right lobe operation, Lobectomy, Lymph node dissection, Closure of bronchial stump with stapler, Postoperative acid reflux
- ② **Proton pump inhibitors** can improve symptom
- ③ **Pulmonary Rehabilitation** Exercises Effectively Improve Chronic Cough After Surgery

The management of cough in lung cancer

- ① **On-cancer treatment**
- ② Simple linctus – Opiate derivative - Peripherally acting antitussive – Clinical trial

Conclusion

Aprepitant represents a new therapeutic option for patients with advanced lung cancer and cough that is not controlled by standard cough medications.

Pregabalin does not significantly decrease cough in patients with lung cancer.

Cough has not received the same attention as other cancer symptoms, more clinical and research attention in this debilitating symptom is necessary.

감사합니다