특발성 기침

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강혜선

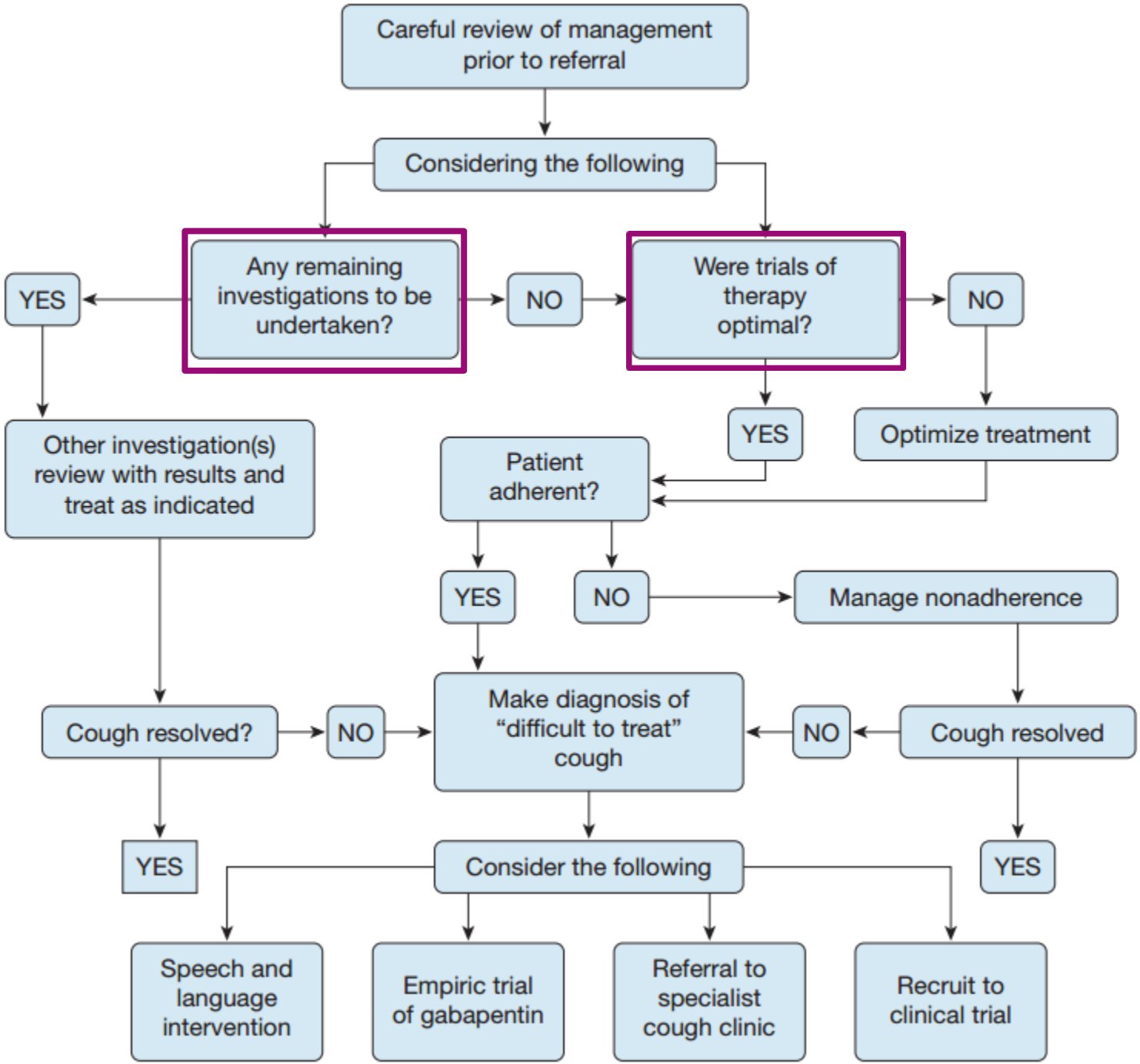
Contents

Definition

Unexplained chronic cough

- Cougn > 8 weeks
- Persists after investigagion and supervised therapeutic trials

Gipson, P. et al, Chest, 2016 149(1): 27-44.



Gipson, P. et al, Chest, 2016 149(1): 27–44.

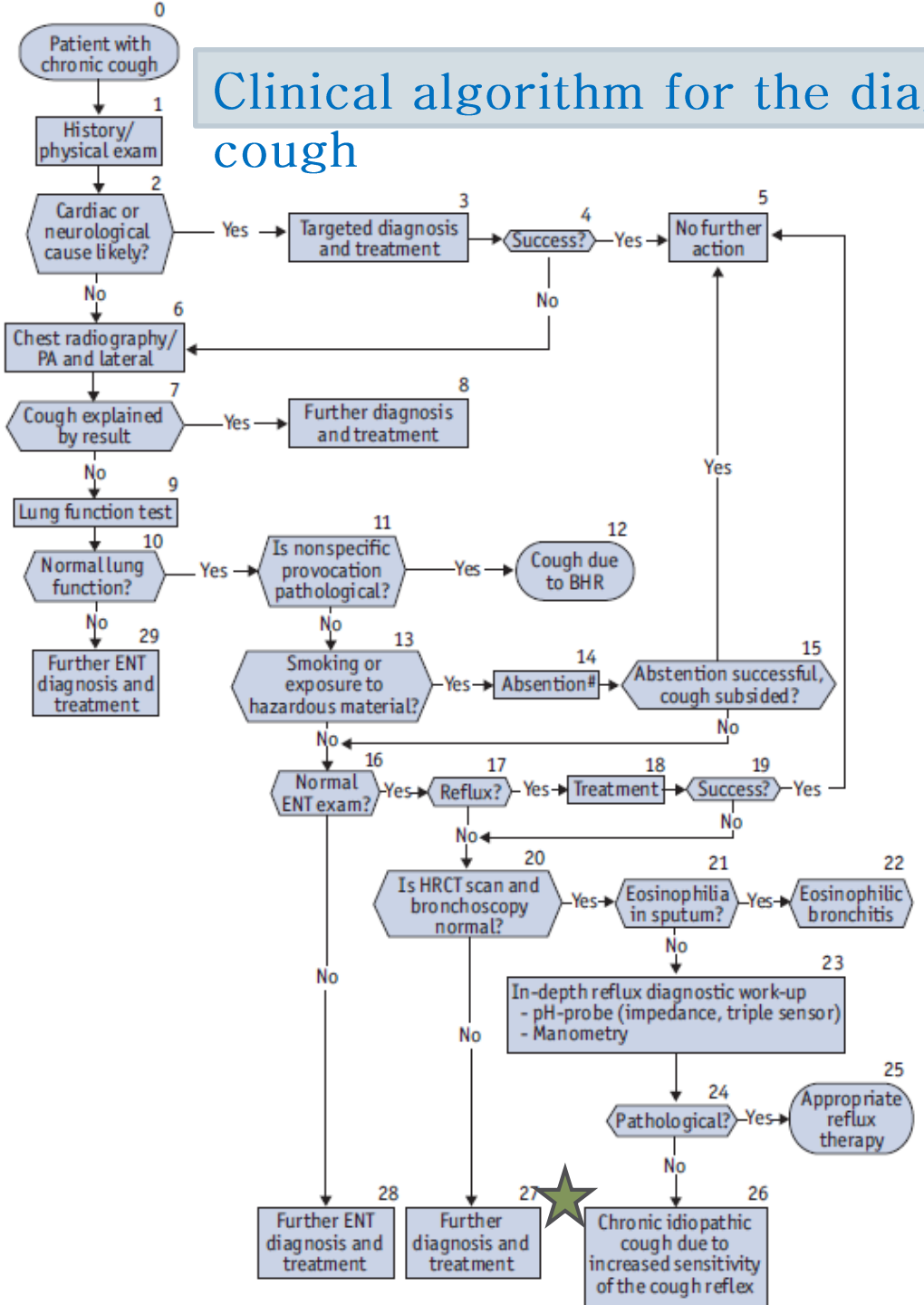
- Idiopathic
  - *Idiopatheia*
  - Disease not preceded or occasioned by another, or by any known cause
- Unexplained
  - Many conditions from unknown causes

Pratter, M.R. *Chest* 129(1 Suppl): 220s–221s.

Contents

- Definition
- Diagnosis
- Clinical characateristics
- Mechanisms
- Treatment

Clinical algorithm for the diagnosis of chronic cough



P. Kardos *Breathe* 2010(7) 123-133.

Box 2 | Red flags: alarm symptoms and findings in chronic cough[65]

- Hemoptysis
- Smoker with >20 pack year smoking history
- Smoker over 45 years of age with a new cough, altered cough, or cough with voice disturbance
- Prominent dyspnea, especially at rest or at night
- Substantial sputum production: more than one tablespoon a day
- Hoarseness
- Systemic symptoms: fever, weight loss
- Complicated gastroesophageal reflux disease (GORD) symptoms associated with weight loss, anemia, overt gastrointestinal bleeding (hematemesis or melena), severe symptoms, dysphagia, odynophagia, or failure of empiric treatment for GORD
- Recurrent pneumonia
- Abnormal clinical respiratory examination
- Abnormal chest radiograph

Gibson, P. G. and A. E. Vertigan (2015). Bmj 351: h5590.

Box 3 | Remediable conditions and conditions not to be missed in patients with chronic cough[65]

Remediable conditions

Asthma	PFT c provocation, FeNO
Gastroesophageal reflux disease	EGD, pH monitoring
Obstructive sleep apnea	polysomnography
Angiotensin converting enzyme inhibitor use	History taking, avoidance
Eosinophilic bronchitis	Sputum eosinophilia,
Rhinosinusitis	FeNO

Serious cough related conditions

PNS

Cancer of the larynx, bronchus, or lung

Parenchymal lung disease: chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, bronchiectasis, sarcoidosis, pneumothorax

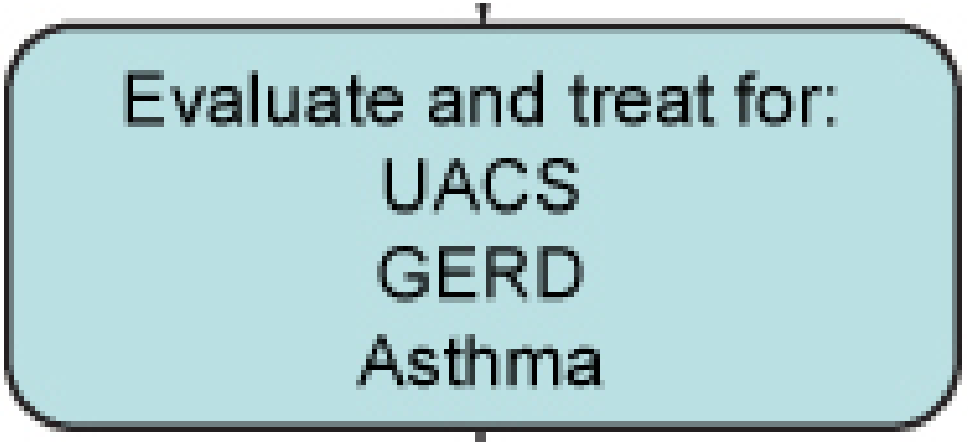
Cardiovascular disease: left ventricular failure, pulmonary embolism, aortic aneurysm

Infection: tuberculosis, lung abscess, pertussis

Gibson, P. G. and A. E. Vertigan (2015). Bmj 351: h5590.

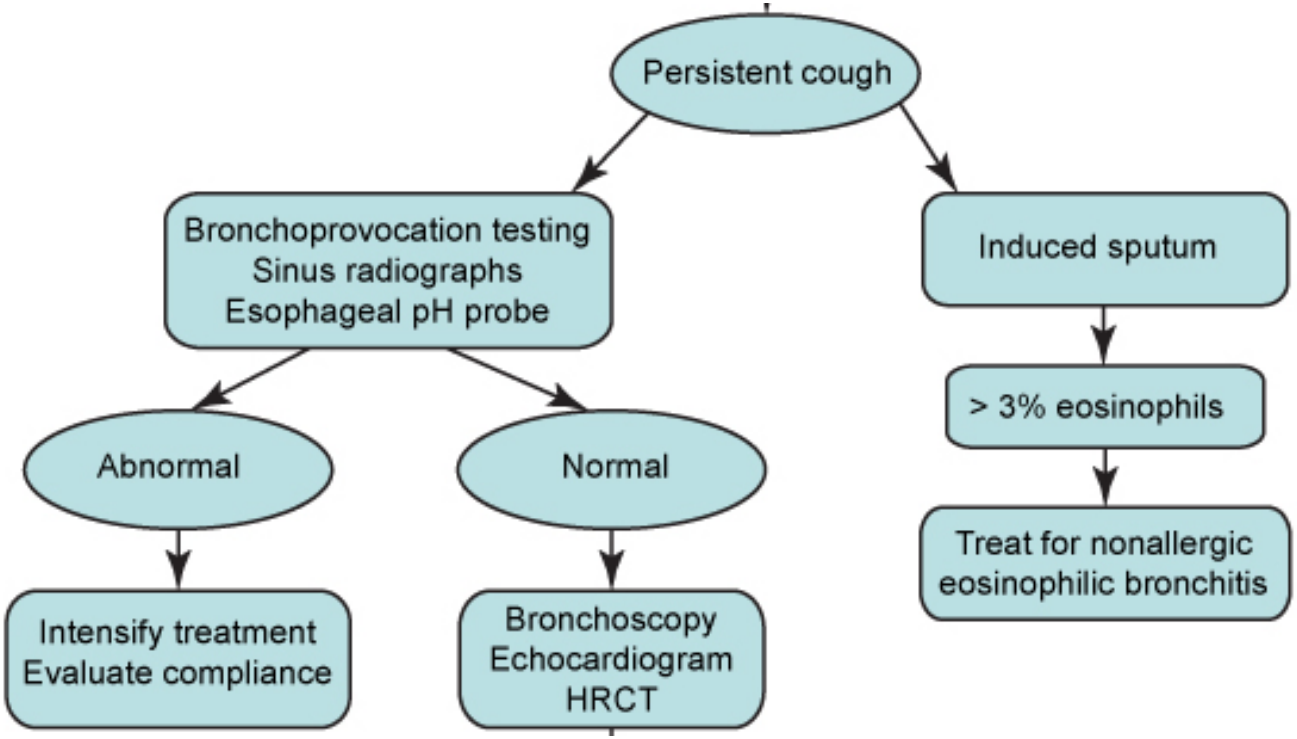
Diagnosis

- **Completion** of systemic assessment and treatment for known causes



Gipson, P. et al, Chest, 2016 149(1): 27-44.

- Other causes



  - Atopic cough, habit, non-reflux
  - Prolonged post-viral cough

- Diagnostic/treatment failure

McGarvey, L.P., Cough, 2005. 1: p.9.

Contents

- Definition
- Diagnosis
- Clinical characateristics
- Mechanisms
- Treatment

Clinical characteristics

- Persistent cough triggered by URTI
  - Ddx. Postviral cough

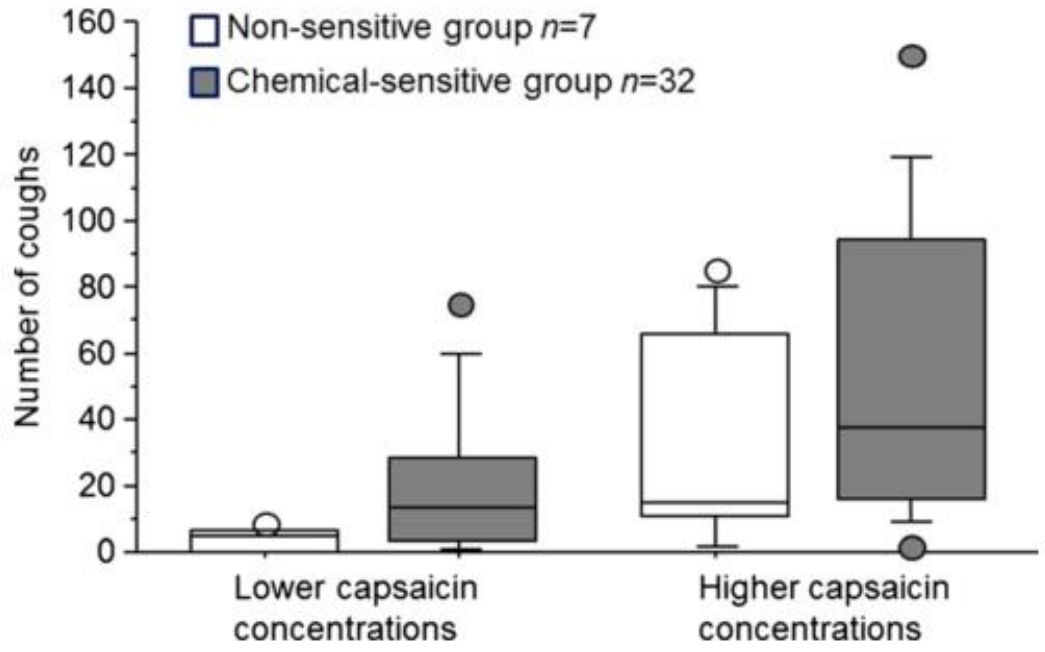
Variables	CIC	non-CIC	p Value
Median age, yr	57	58	NS
Median age at onset, yr	46.5	50	NS
Female gender, %	76	66	NS
Median duration of cough, mo	72	24	0.002
Preceded by URTI, %	48	24	0.014
Median log C5	− 0.009	0.592	0.032

Haque, R.A. et al., Chest 2005 127(5): 1710-3.

- Persistent cough triggered by URTI
- Heightened cough sensitivity
  - Allotussia / hypertussia

Haque, R.A. et al., Chest 2005 127(5): 1710-3.

- Persistent cough triggered by URTI
- Heightened cough sensitivity



Ternesten-Hasseus, E.. Et al., Cough, 2013. 9(1): p.5.

	Number (% female)	Mean age (SD) (years)	Median cough duration (range) (months)
O'Connell F *et al* [14]	16(81%)	51(31–70)*	72 (12–240)
McGarvey L *et al* [15]	8(75%)	46(8)	19 (6–36)
Forsythe P *et al* [30]	6(66%)	47(13)	72(2–240)
Jatakanon A *et al* [31]	10(50%)	60(4)	60 (18)^
Birring SS et al [32]	25(72%)	55(3)	12 (7–360)
Chaudhuri R *et al* [33]	6(60%)	58(9)	14(19)^
Haque R *et al* [16]	31(76%)	57(32–81)*	72 (8–324)*

- Heightened cough sensitivity
- Female predominance

Health seeking behavior

Sex hormone - peri- or post menopausal

McGarvey, L.P. *Cough* 2005 1:9.

Clinical characteristics

- Persistent cough triggered by URTI
- Heightened cough sensitivity
  - Allotussia / hypertussia
- Female predominance
  - Hormone / organ specific autoimmune disease

McGarvey, L.P. *Cough* 2005 1:9.

	Controls (no.)	Cases (no.)
	$n = 65$	$n = 22$
Autoimmune disorder		
Hypothyroidism	2	5
Hyperthyroidism	3	0
Diabetes mellitus type1	2	3
Pernicious anaemia	0	2
Celiac disease	1	1
Vitiligo and premature menopause	0	1
Vitiligo and chronic autoimmune hepatitis	0	1
Addison's disease	0	0
Inflammatory bowel disease	0	0
Alopecia	0	0
Total	8	13**
	$n = 24$	$n = 15$
Autoantibodies		
Thyroid peroxidase	0	4
Parietal cell	1	1
Endomysial	1	1
Islet cell	1	0
Adrenal	0	0
Total	3	6*

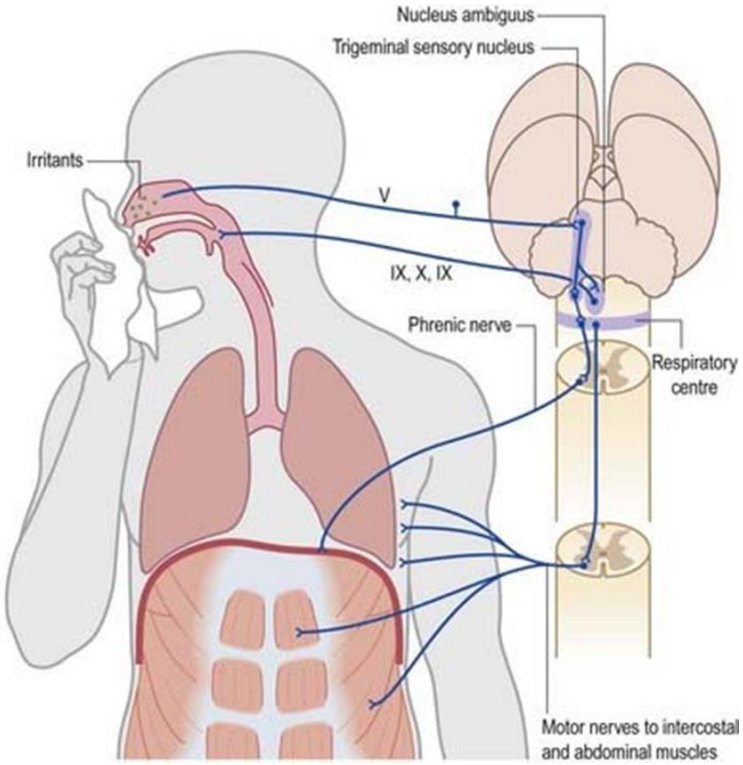
Birring, S.S., et al., Respir med, 2004. 98(3): p. 242-6.

Contents

- Definition
- Diagnosis
- Clinical characateristics
- **Pathogenesis**
- Treatment

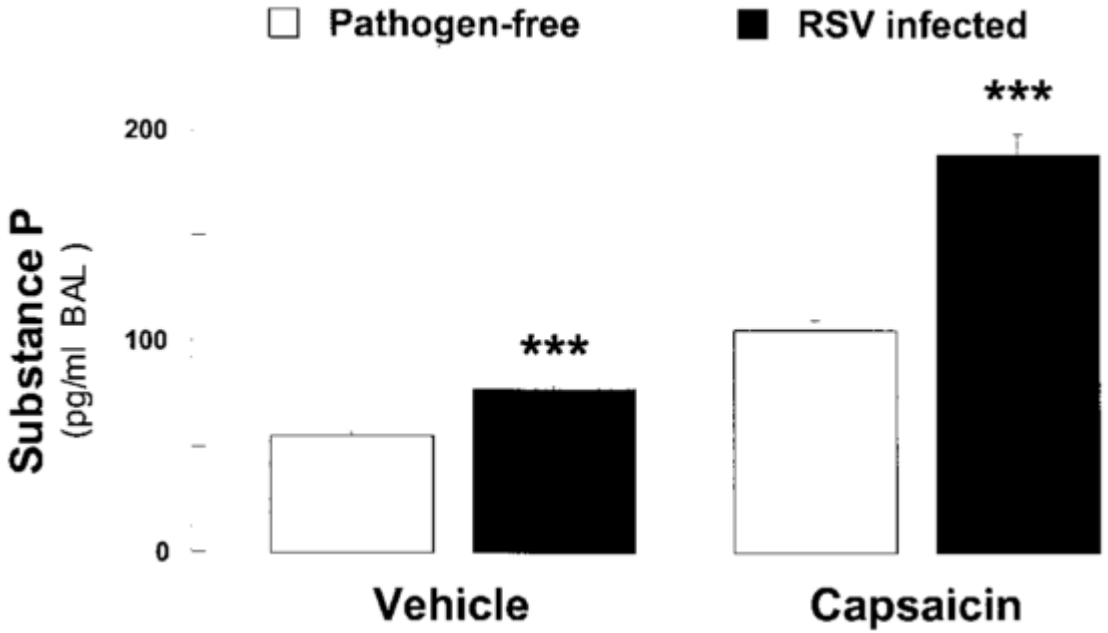
Pathogenesis

- Heightened cough reflex sensitivity
  1. Peripheral sensitization
  2. Central sensitization
  3. Airway lymphocytosi
  4. Sex-hormones



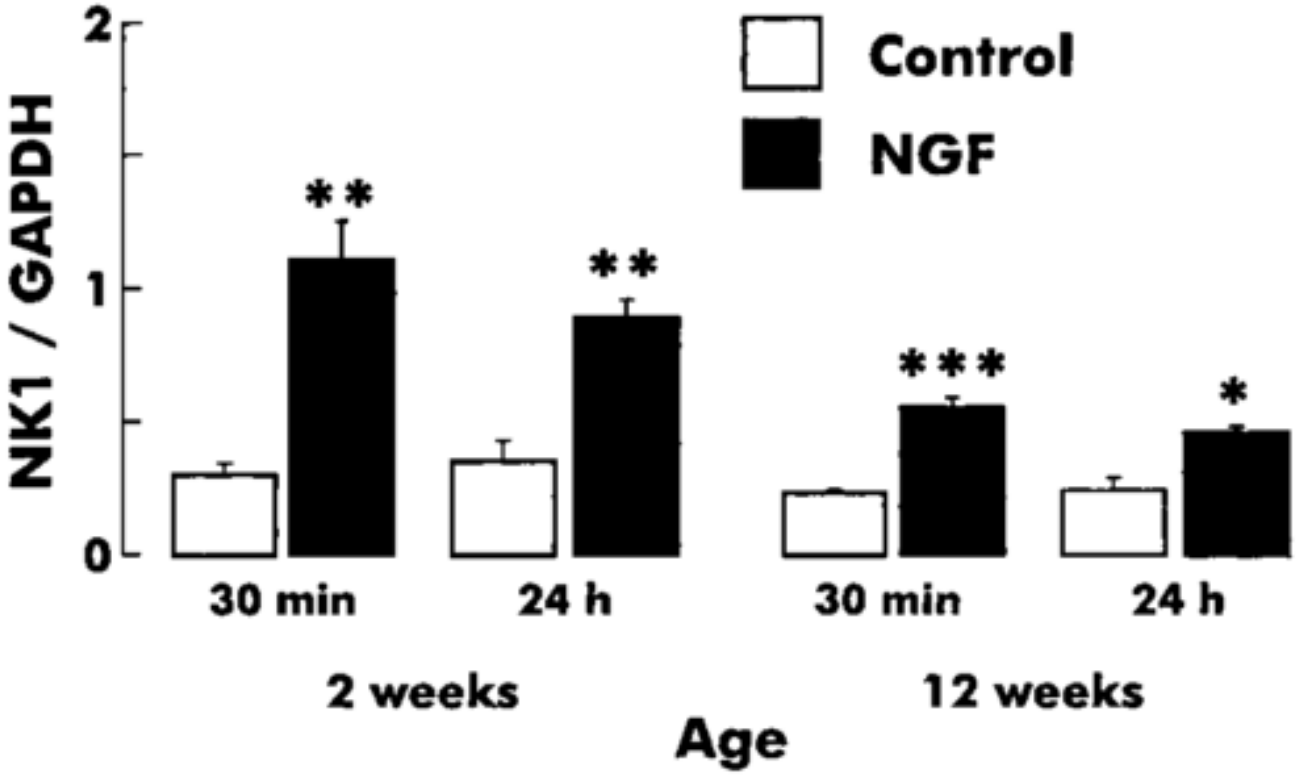
Peripheral sensitization

- Effects of viruses on cough sensitivity



BAL samples obtained 30d after RSV inoculation

Piedimonte, G. et al, Pediatr Res, 2004. 55(4): p. 657-65.

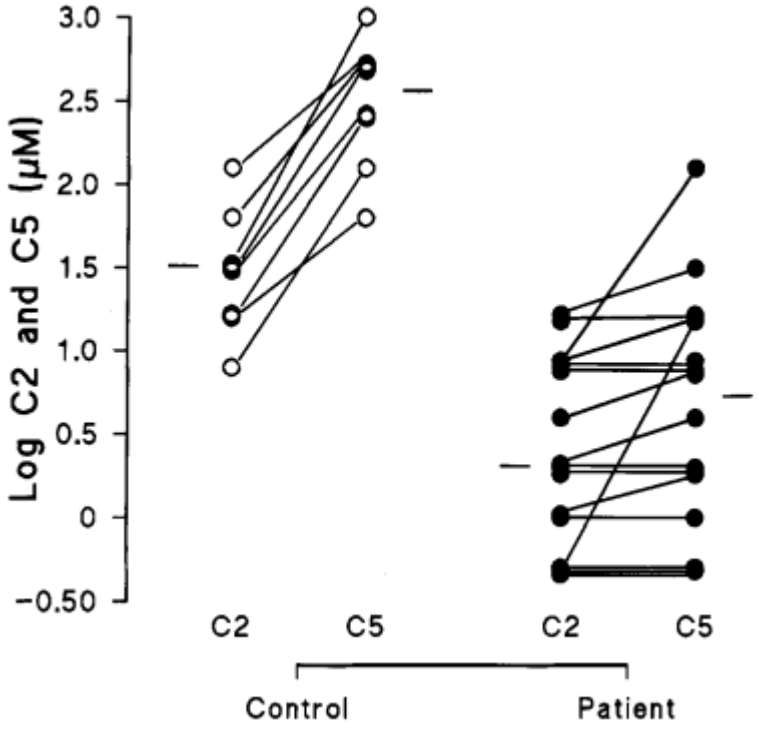


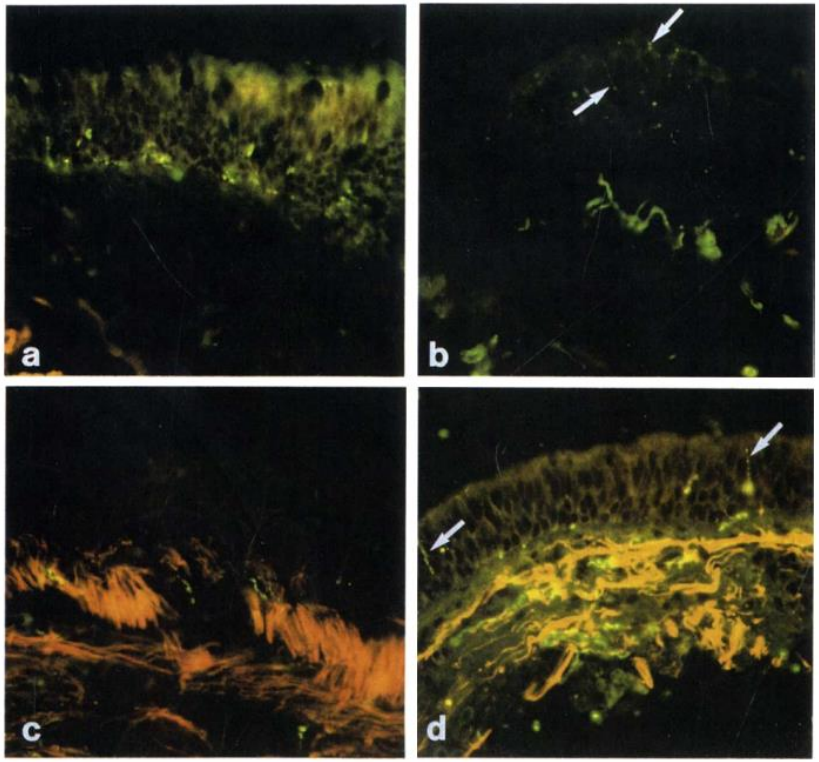
Hu C et al, Am J Physiol Lung Cell Mol Physiol 2002 283(2): | 494-502

Abnormal Intraepithelial Airway Nerves in Persistent Unexplained Cough?

FINBARR O'CONNELL, DAVID R. SPRINGALL, ANITA MORADOGHLI-HAFTVANI, TOMAS KRAUSZ, DEBORAH PRICE, RICHARD W. FULLER, JULIA M. POLAK, and NEIL B. PRIDE

Departments of Clinical Pharmacology, Histochemistry, Histopathology, Medical Physics, and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London, United Kingdom.



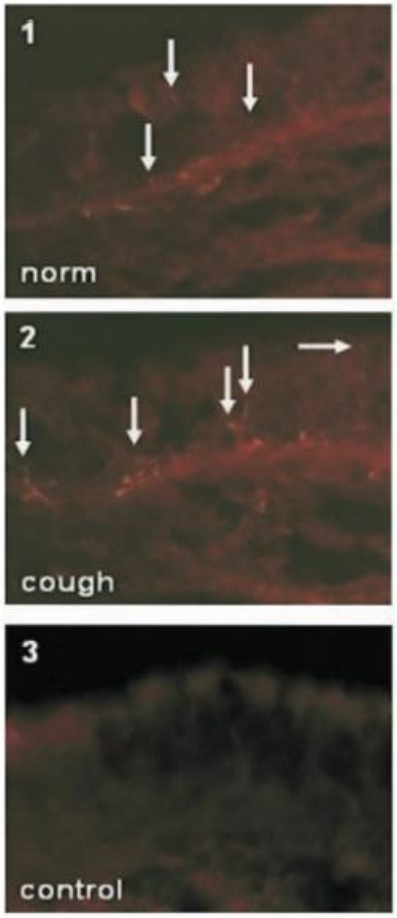


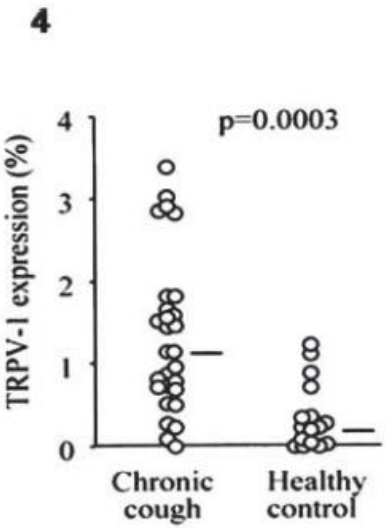
O' Connell, F. et al., Am J Respir Crit Care Med, 1995: 152(6 Pt 1): 2068-75.

Increased Expression of Transient Receptor Potential Vanilloid-1 in Airway Nerves of Chronic Cough

David A. Groneberg, Akio Niimi, Q. Thai Dinh, Borja Cosio, Mark Hew, Axel Fischer, and K. Fan Chung

Division of Allergy Research, Department of Pediatric Pneumology and Immunology, Charité Faculty of Medicine, Humboldt-Universität zu Berlin, Berlin, Germany; and Thoracic Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom





David A.G. et al, Am J Respir Crit Care Med, 2004 170:1276–1280

Central sensitization

- Neuropathic cough : ‘urge to cough’

Table 1 | Comparison of features of chronic pain and chronic refractory cough[46]

Neuropathic pain			Neuropathic cough		
Concept	Definition/description	Example	Concept	Definition/description	Example
Paresthesia	Abnormal sensation	Tingling sensation in the skin	Laryngeal paresthesia or hypersensitivity	Abnormal sensation in the throat	Tickle or itch in throat
Hyperalgesia	Increased response to a stimulus that is normally painful but at a reduced threshold	Increased pain response to a needle prick	Hypertussia	Increased cough response to a tussigenic stimulus	Fumes, smoke, aspirate
Allodynia	Pain in response to a stimulus that does not normally produce pain, such as a mechanical or thermal stimulus	Pain in response to touch	Allotussia	Cough in response to a non-tussigenic stimulus	Thermal, vocalisation, exercise

Neuromodulator : treatment response

Vertigan AE et al, J Med Speech language patho 2007;15:189-206

Airway inflammation

Noneosinophilic CD4 Lymphocytic Airway Inflammation in Menopausal Women With Chronic Dry Cough*

Ester Mund, MD; Birger Christensson, MD, PhD;
Reidar Grönneberg, MD, PhD; and Kjell Larsson, MD, PhD, FCCP

Variables	CD3+	CD4+	CD8+	Activated T Lymphocytes HLA-DR$^+$	CD4+ CD8+‡
Dry cough	92 (84–95)	73 (69–83)	15 (9–21)	57 (38–60)	91 (81–99)
Productive cough	76 (73–88)	41 (33–54)	27 (16–37)	20 (15–26)	75 (60–81)
Control	86 (80–90)	72 (59–74)	16 (12–17)	20 (15–30)	87 (71–89)
p Values†					
Dry cough vs control	NS	NS	NS	< 0.001	NS
Productive cough vs control	NS	< 0.001	0.005	NS	0.048
Dry cough vs productive cough	0.004	< 0.0001	0.007	< 0.0001	0.003

Mund, E. et al, Chest, 2005 127(5): 1714–21.

COUGH

Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis

S S Birring, C E Brightling, F A Symon, S G Barlow, A J Wardlaw, I D Pavord

Table 2 Sputum and BAL fluid differential cell counts (%)

	Normal	Idiopathic cough	Explained cough
Induced sputum			
Lymphocytes	0.5 (0–9.8)	0.7 (0–5.8)	0.1 (0–1.3)
Eosinophil	0.5 (0–2.0)	0.2 (0–0.8)	3.8 (0–68)
Neutrophil	56 (38–84)	50 (15–81)	56 (11–88)
Macrophage	42 (12–51)	47 (17–82)	27 (1–86)
Epithelial cell	2.5 (0.8–15.1)	1.8 (0–19.8)	3.4 (0–10.8)
Squamous contamination	4 (0–15)	8 (0–35)	6 (0–16)
Viability	55 (20–81)	65 (23–87)	52 (34–83)
Total cell count $\times 10^6$/ml	1.6 (0.3–3.6)	0.9 (0.2–3.8)	1.4 (0.2–12)
BAL fluid			
Lymphocytes	6.3 (1.4–14.7)	10.0 (1.3–47)***	5.2 (2.2–28.2)
Total lymphocyte count ($\times 10^6$)	0.5 (0–1.9)	0.9 (0.2–7.1)**	0.3 (0.1–2.2)
Eosinophil	0.3 (0–2.5)	0.2 (0–1.8)	1.5 (0–13)*
Neutrophil	9 (0–24)	5 (0–33)	5 (0–19)
Macrophage	77 (43–91)	78 (47–88)	81 (38–89)
Epithelial cell	7 (2–26)	5 (1–17)	5 (2–33)
Viability	71 (45–85)	69 (19–88)	65 (25–95)
Recovery (%)	24 (8–38)	28 (15–39)	26 (19–40)
Total cell count $\times 10^6$/ml	7.0 (0.8–48)	7.5 (3.1–22.9)	5.4 (4.0–8.5)

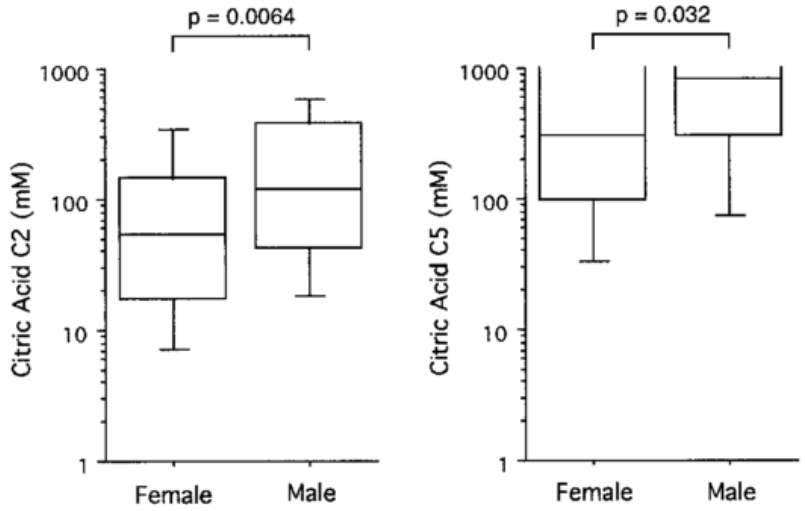
Data are expressed as median (range).
*p = 0.03, **p = 0.003, ***p = 0.002 (Kruskal-Wallis test).

Birring, SS et al, Thorax 2003 58(12): 1066–70.

Sex-hormone

Sex-related Differences in Cough Reflex Sensitivity in Patients with Chronic Cough

Jack A. Kastelik, Rachel H. Thompson, Imran Aziz, Josephine C. Ojoo, Anthony E. Redington, and Alyn H. Morice



Kastelik, J.A., et al., Am J Respir Crit Care Med, 2002. 166(7): p. 961-4.

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Treatment

- Nonpharmacologic therapies
- Inhaled corticosteroids
- Neuromodulatory therapies
- Other therapies

Speech pathology therapy

Education

Cough can be triggered by irritation

Cough is not always necessary

Cough has limited physiological benefit in this condition

Cough is under automatic and voluntary control

Symptom control techniques

Cough suppression swallow

Cough control breathing

Paradoxical vocal fold movement release breathing

Release of laryngeal constriction

Reducing laryngeal irritation

Behavioral management of reflux

Reduce phonotraumatic behaviors

Hydration

Minimize exposure to irritating substances

Psychoeducational counseling

Treatment is hard work

Setting realistic goals

Vertigan AE et al, J Med Speech Language Patho 2007;15:189-206

Table 4 Comparison of mean (SD) pre- and post-intervention symptom scores and degree of change for participants in the treatment and placebo groups

Score	Group	Pre	Post	Difference	95% CI	p value
Total	Treatment†	35.4 (16.0)	22.7 (18.0)	12.7 (12.7)	9.0 to 16.1	<0.001*
	Placebo†	29.9 (13.5)	28.8 (16.5)	2.9 (12.5)	−0.7 to 6.5	0.170
	Difference‡			8.5 (13.9)	4.7 to 14.9	<0.001*
Breathing	Treatment†	7.9 (4.1)	5.0 (4.2)	2.9 (3.6)	1.8 to 3.9	<0.001*
	Placebo†	6.6 (4.7)	5.5 (3.5)	1.1 (3.4)	0.1 to 2.0	0.004*
	Difference‡			2.2 (3.7)	0.4 to 3.2	<0.001*
Cough	Treatment†	8.8 (2.8)	4.9 (3.0)	3.9 (3.2)	3.0 to 4.9	<0.001*
	Placebo†	7.5 (3.6)	6.3 (3.5)	1.2 (3.4)	0.3 to 2.2	<0.001*
	Difference‡			2.8 (3.6)	1.3 to 4.0	0.003*
Voice	Treatment†	7.2 (6.0)	4.7 (5.2)	2.5 (4.3)	1.2 to 3.7	<0.001*
	Placebo†	6.5 (4.6)	6.2 (5.0)	0.3 (4.1)	−0.9 to 1.5	0.959
	Difference‡			1.5 (4.5)	0.5 to 3.9	0.005*
Upper airway	Treatment†	9.2 (6.6)	6.5 (6.3)	2.7 (4.7)	1.4 to 4.1	<0.001*
	Placebo†	7.4 (4.9)	7.4 (5.5)	0.1 (4.1)	−1.1 to 1.2	0.946
	Difference‡			1.5 (4.8)	0.9 to 4.4	0.002*
Limitation	Treatment†	2.3 (1.2)	1.6 (1.0)	0.7 (1.1)	0.4 to 1.0	<0.001*
	Placebo†	2.2 (1.1)	2.0 (1.0)	0.3 (0.9)	0.0 to 0.6	0.038*
	Difference‡			0.5 (1.0)	0.0 to 0.8	0.011*

†Calculated using Wilcoxon signed rank test.
‡Calculated using Mann-Whitney U test.

Inhaled corticosteroid

- No beneficial effects
  - Nonasthmatic, noneosinophilic subjects
  - Negative test for BHR and eosinophilia

Pizzichini MM et al, Can Respir J 1999 6(4):323-30.

Neuromodulatory therapies

- Act on neural sensitization

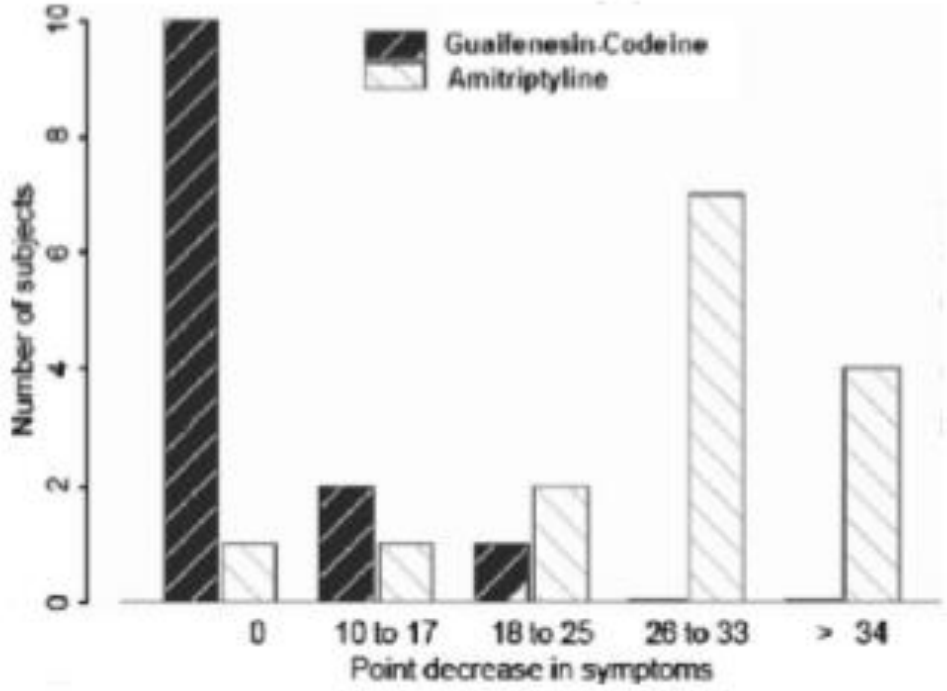
Table 2 | Effects of neuromodulator drugs on cough quality of life*

Study	Tool used	Drug	Change in score from baseline (points)
Jeyakumar et al[53]	CQLQ	Amitriptyline	24.53
		Guaifenesin-codeine	2.92
Morice et al[52]	LCQ†	Morphine	3.2
		Placebo	1.2
Ryan et al[49]	LCQ†	Gabapentin	2.5
		Placebo	1.1
Vertigan et al[51]	LCQ†	Pregabalin‡	6.6
		Placebo‡	3.3

Gipson, P. et al, Bmj 2015 351:h5590.

The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Effectiveness of Amitriptyline Versus Cough Suppressants in the Treatment of Chronic Cough Resulting From Postviral Vagal Neuropathy

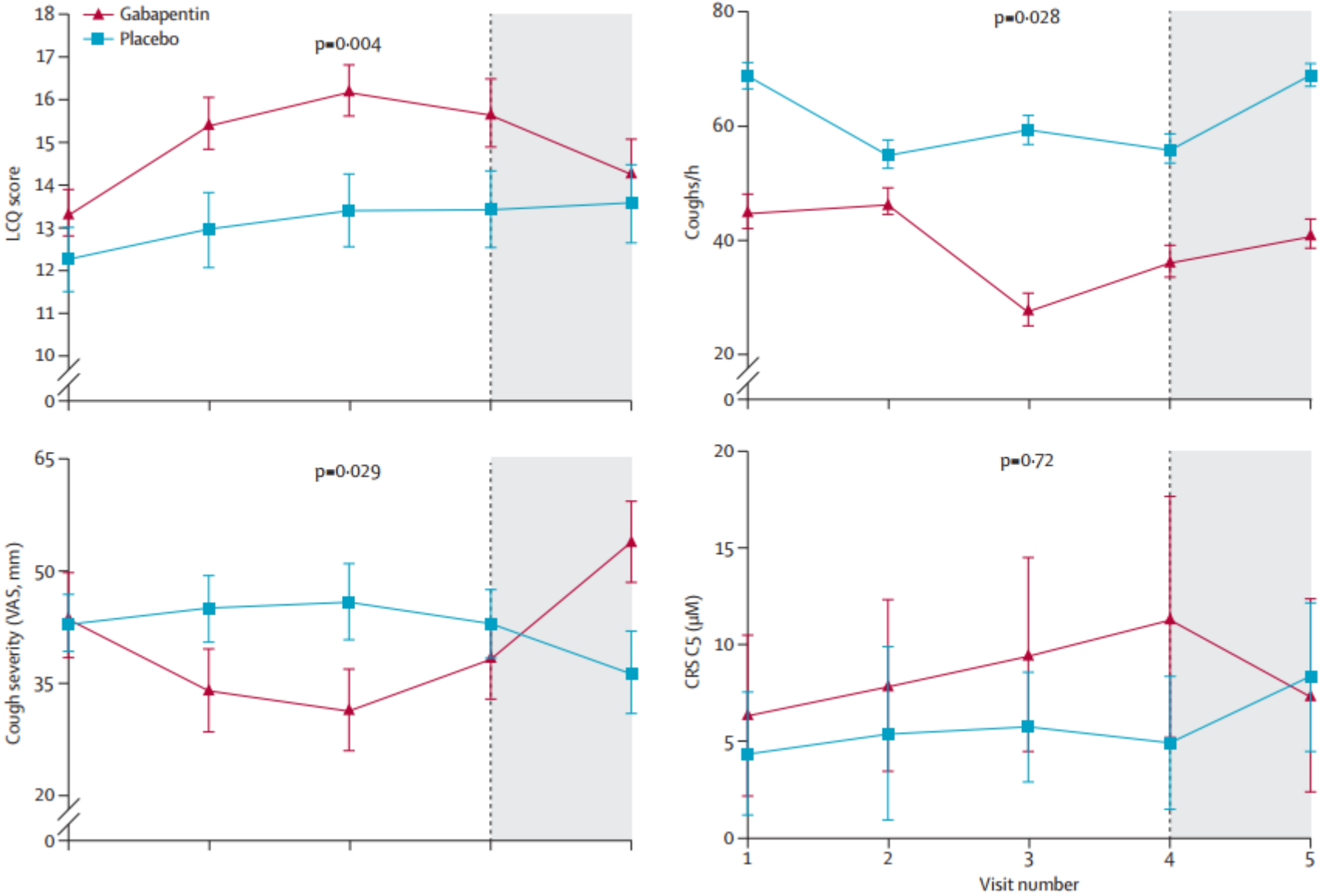


Jeyakumar A. et al, Laryngoscope 2006 116(12):2108-12.

Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

Nicole M Ryan, Surinder S Birring, Peter G Gibson

Ryan NM et al, Lancet 2012 380(9853):1583–9.



	Gabapentin (n=17)	Placebo (n=6)
Blurred vision	1 (6%)	0
Depression	0	1* (17%)
Disorientation, confusion	2 (12%)	0
Dizziness	3 (18%)	1 (17%)
Dry or very dry mouth	2 (12%)	1 (17%)
Fatigue	3 (18%)	1 (17%)
Headache	1 (6%)	0
Memory loss	1 (6%)	0
Nausea, stomach pain	4 (24%)	2 (33%)

Data are number of events (%). n=total number of events associated with study drug. *Possible comorbidity (present before study).

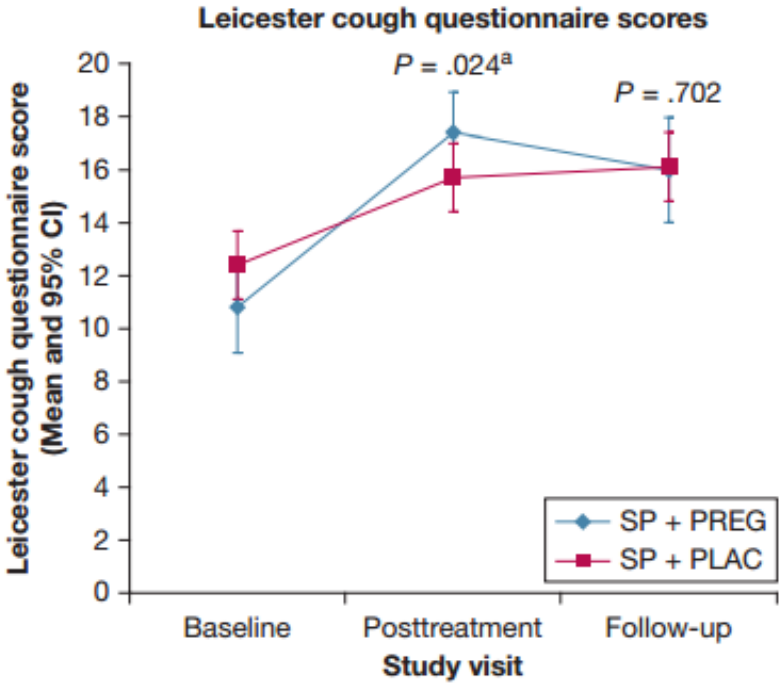
***Table 2:* Adverse effects**

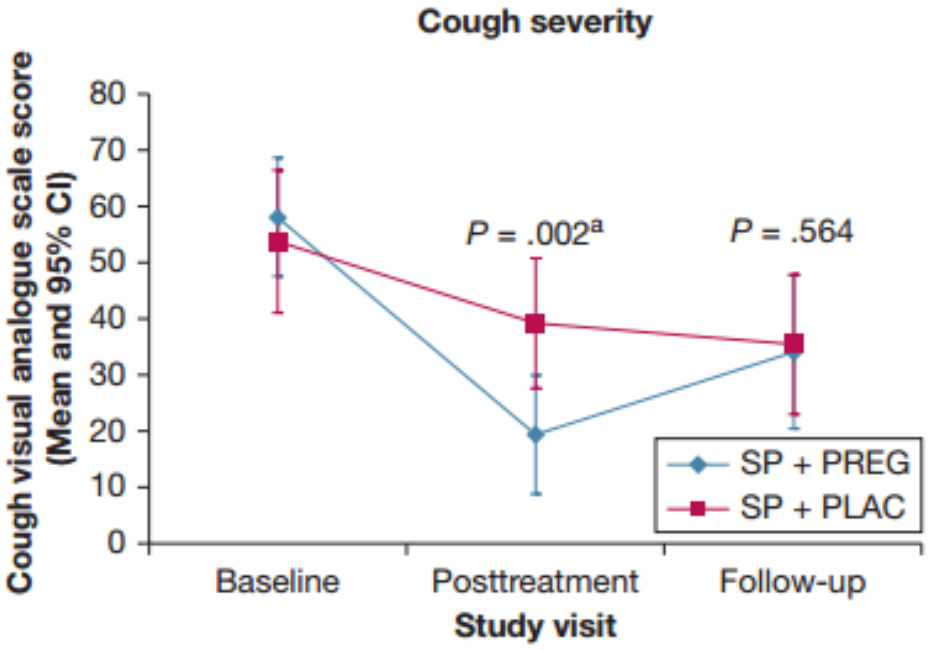
Ryan NM et al, Lancet 2012 380(9853):1583–9.

Combination therapy

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial





Vertigan AE et al, Chest 2016:149(3):639-48.

Esomeprazole

Randomised clinical trial: high-dose acid suppression for chronic cough – a double-blind, placebo-controlled study

N. J. Shaheen*,†, S. D. Crockett†, S. D. Bright*,†, R. D. Madanick*,†, R. Buckmire‡, M. Couch‡, E. S. Dellon*,†, J. A. Galanko†, G. Sharpless†, D. R. Morgan†, M. B. Spacek*,†, P. Heidt-Davis*,† & D. Henke§

Table 3 | Comparison of primary and secondary outcomes between treatment groups

	PPI (n = 22)				Placebo (n = 18)				
Outcome	Baseline	End	Change	P*	Baseline	End	Change	P*	P†
CQLQ	52.9 (12.0)	43.0 (14.3)	9.8 (12.2)	0.001	58.2 (11.8)	52.3 (12.8)	5.9 (11.1)	0.04	0.3
Cough Severity Score	2.9 (0.8)	1.9 (0.9)	1.0 (1.3)	0.002	2.8 (0.7)	2.0 (1.0)	0.8 (1.2)	0.009	0.7
Cough Frequency Score	6.2 (1.8)	3.0 (1.8)	3.2 (2.4)	<0.0001	6.8 (2.0)	4.5 (2.5)	2.3 (2.7)	0.002	0.3
Reflux Finding Score	7.6 (2.2)	6.9 (2.2)	0.6 (2.0)	0.2	8.3 (2.6)	8.2 (3.6)	0.1 (2.9)	0.9	0.5

Shaheen NJ et al, Aliment Pharmacol Ther 2011 33(2): 225–34.

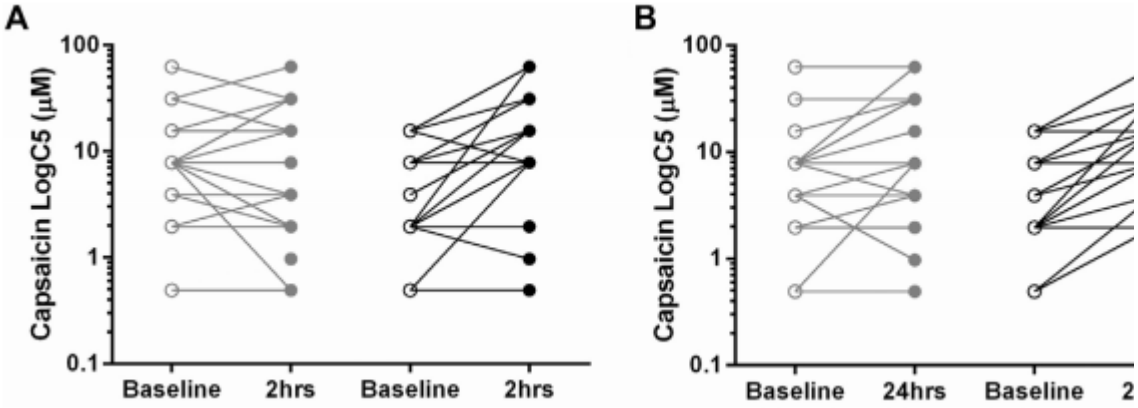
Erythromycin

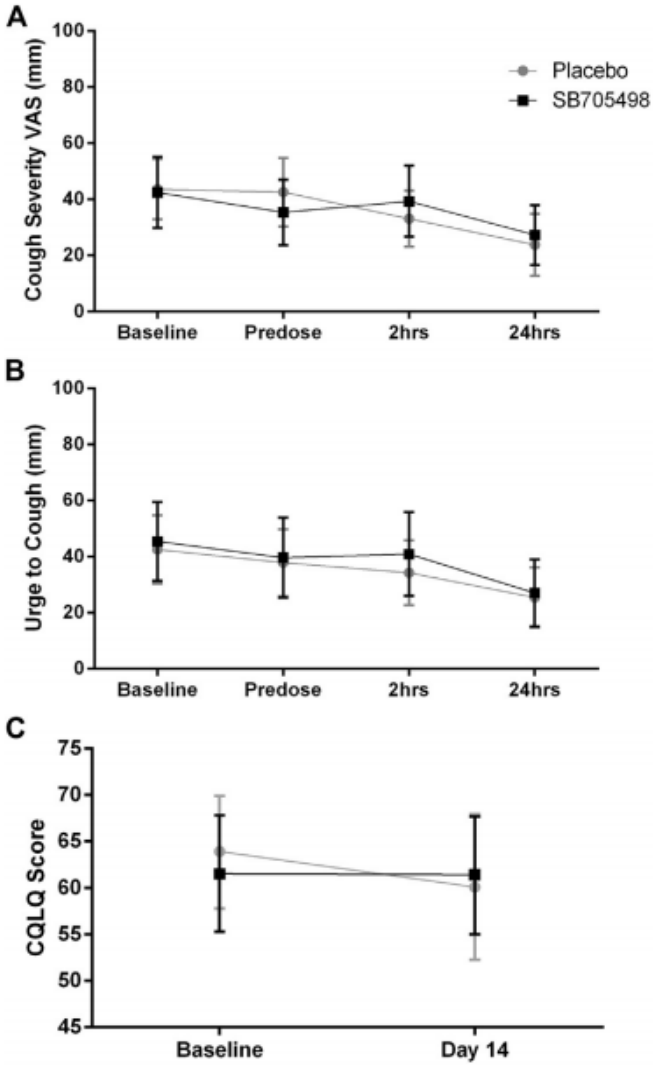
Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial

	Change from baseline to 3 months		
	Placebo	Erythromycin	Difference (95% CI)
*Coughs/24 h	0.73 (0.66)	0.67 (0.29)	1.1 (0.7 to 1.5)
Sputum neutrophils (%)	+6.6 (23)	−10.2 (33)	16.8 (1.6 to 32.1)
*C2 (μmol/l)	1.1 (0.4)	1.6 (0.06)	0.7 (0.4 to 1.3)
*C5 (μmol/l)	1.2 (0.13)	0.9 (0.25)	1.3 (0.9 to 2.0)
VAS (mm)	+2 (29)	−12 (33)	10 (−11 to 33)
LCQ	+1.8 (3.8)	+1.8 (3.8)	0 (−2 to 2)
*CFU/ml	1.17 (0.56)	0.65 (0.69)	1.8 (0.6 to 5.8)
*Sputum IL-8 (ng/ml)	2.14 (0.69)	0.75 (0.23)	2.9 (0.8 to 9.5)

Yousaf N et al, Thorax 2010 65(12):1107-10.

TRPV1 antagonists





Khalid S et al., J Allergy Clin Immunol 2014 134(1):56-

Long term outcomes

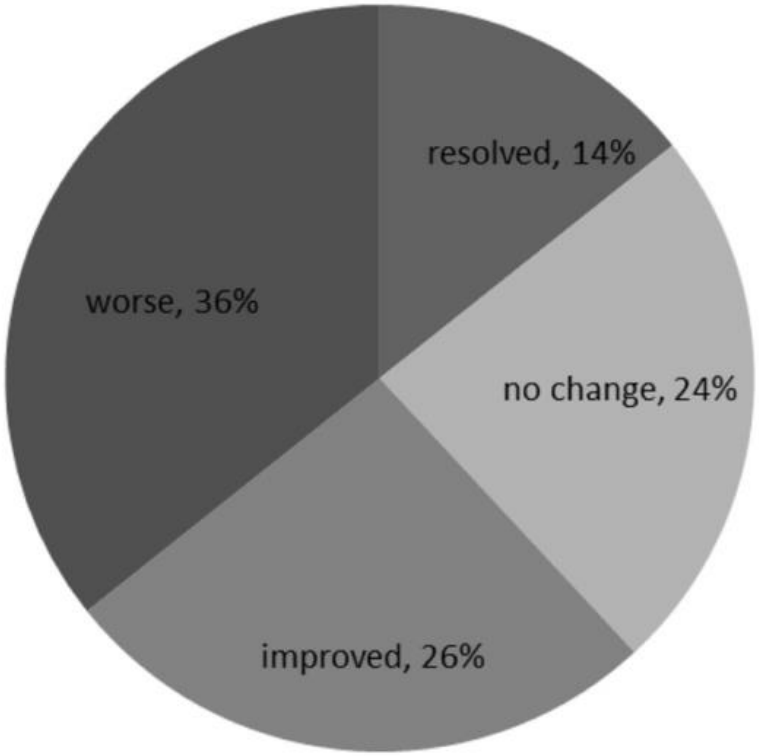


Figure 1 Change in cough as measured by a cough VAS over a 7–10 year period.

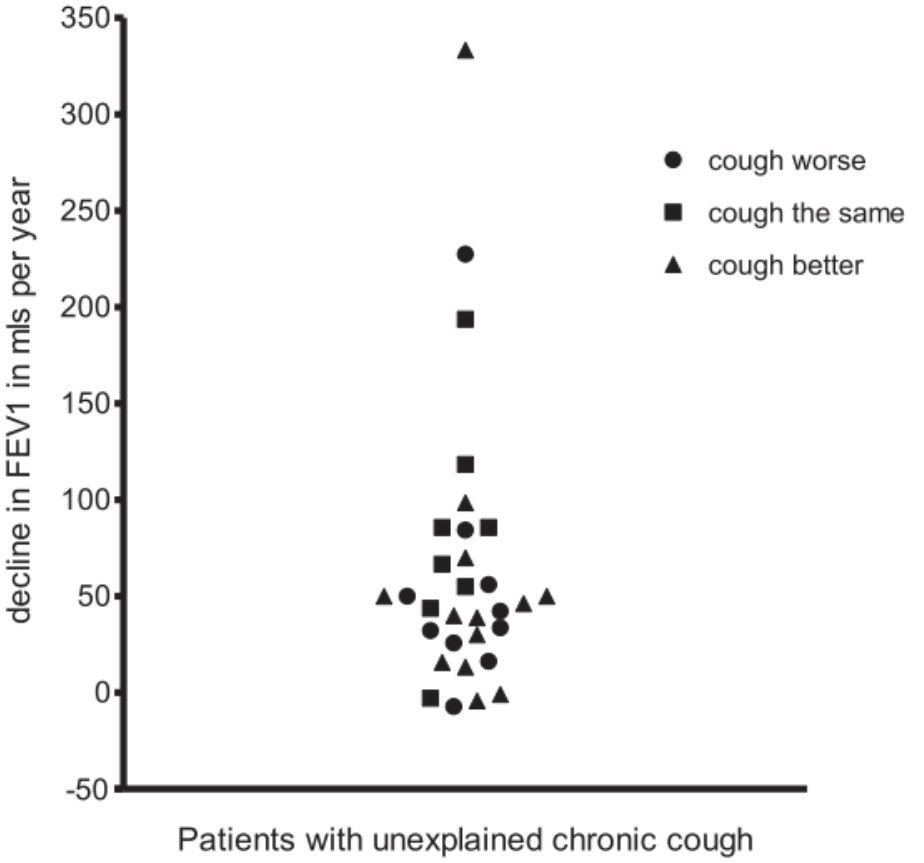


Figure 3 Annual rate of FEV_1 decline.

Yousaf, N., et al., Respir Med, 2013. 107(3): p. 408–12.

Take home message

- chronic unexplained cough
  - Persisted cough (>8 wks) after investigation and treatment trials for known causes
  - Triggered by URTI / female dominance
  - Cough reflex hypersensitivity
  - Treatment
    - Speech pathology management / neuromodulator
    - Negative test : PPI, inhaled corticosteroid is not indicated

경청해 주셔서
고맙습니다