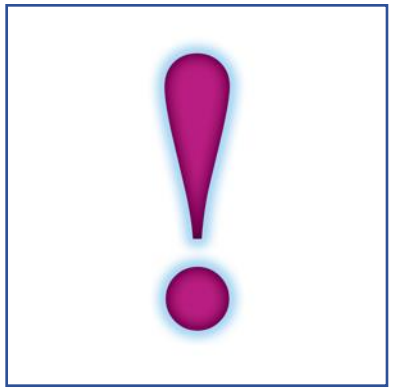
Pneumo Update Europe 2016

24-25 June, Prague

Hot Topic:
The Pain of Chronic Cough



Lorcan McGarvey, UK

Overview

- Definitions / epidemiology
- State of the Art - Common causes – guidelines and new insights
- State of the Art - Anatomy and neurophysiology
- Mechanistic insights and the pain of coughing
- State of the Art - New therapeutic targets

Definitions

- ***Acute cough*** is defined as one lasting less than three weeks

- ***Chronic cough*** is defined as one lasting greater than eight weeks

Morice, A. H., McGarvey, L. & Pavord, I. Recommendations for the management of cough in adults. Thorax 61, i1-24, (2006).

State of the Art

What are the current recommendations for evaluation of a patient with chronic cough?

- Typical patient
- Cough as an isolated problem
- Non smoker
- Normal chest radiograph
- Normal spirometry

A worldwide survey of chronic cough

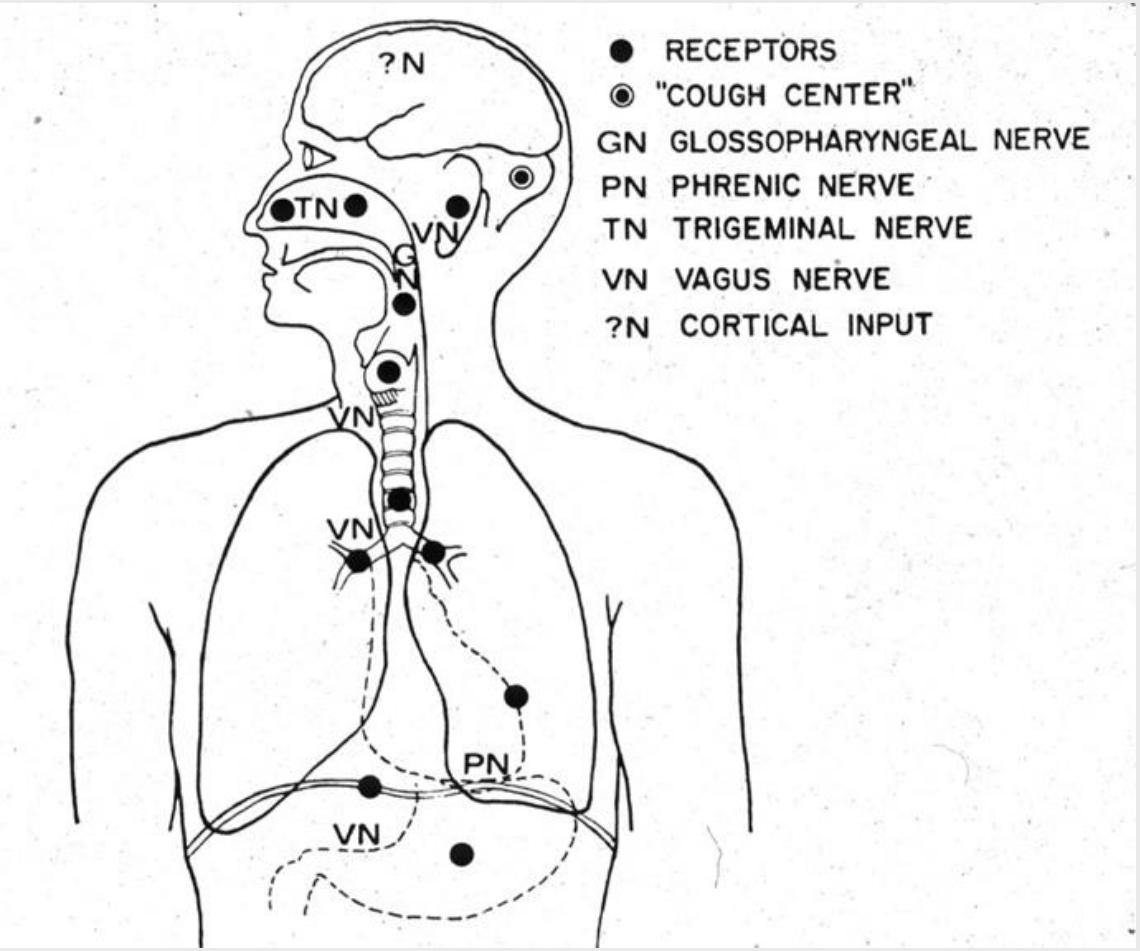
TABLE 1 Age and sex distribution of patients presenting to cough clinics within each country

Country	Totals	Age group in years										
		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	⩾100
UK n=4792												
Total		0.02	1.29	2.80	7.35	17.3	24.7	28.7	14.7	3.00	0.08	0.02
Female	65	100	53	55	61	68	65	64	65	67	75	0
Male	35	0	47	45	39	32	35	36	35	33	25	100
USA n=1000												
Total		0.00	0.40	3.00	7.40	17.20	23.9	23.2	16.6	7.40	0.90	0.00
Female	70	0	50	57	59	70	69	75	74	64	89	0
Male	30	0	50	43	41	30	31	25	26	36	11	0
Holland n=1841												
Total		0.00	1.74	2.34	7.77	15.5	26.5	26.7	15.6	3.75	0.16	0.00
Females	67	0	75	56	63	66	67	68	67	72	100	0
Males	33	0	25	44	37	34	33	32	33	28	0	0
Sweden n=389												
Total		0.00	1.29	9.77	8.48	15.9	20.8	29.3	12.6	1.80	0.00	0.00
Females	67	0	60	79	45	69	62	73	65	86	0	0
Males	33	0	40	21	55	31	38	27	35	14	0	0
South Korea n=1518												
Total		0.07	2.44	9.35	12.5	14.6	22.6	25.5	11.9	1.05	0.07	0.00
Female	69	0	35	47	63	76	75	74	67	44	100	0
Male	31	100	65	53	37	24	25	26	33	56	0	0
China n=492												
Total		0.20	2.64	16.46	27.9	24.6	14.8	8.94	3.86	0.61	0.00	0.00
Females	51	100	46	38	49	50	74	52	42	33	0	0
Male	49	0	54	62	51	50	26	48	58	67	0	0

The data are presented as percentages.

Morice AH *et al*., Eur Respir J 2014; 44: 1149-1155)

The Anatomic Diagnostic Protocol



Irwin RS *et a*l. Am Rev Respir Dis. 1981; 123: 413-7

The diagnosis and management of chronic cough

A.H. Morice and committee members

Committee members: G.A. Fontana, A.R.A. Sovijarvi, M. Pistolesi, K.F. Chung, J. Widdicombe, F. O'Connell, P. Geppetti, L. Gronke, J. De Jongste, M. Belvisi, P. Dicpinigaitis, A. Fischer, L. McGarvey, W.J. Fokkens, J. Kastelik*

Eur Respir J 2004; 24: 481–492

BTS GUIDELINES

Recommendations for the management of cough in adults

A H Morice, L McGarvey, I Pavord, on behalf of the British Thoracic Society Cough Guideline Group

Thorax 2006;**61**(Suppl I):i1–i24. doi: 10.1136/thx.2006.065144

Overview of the Management of Cough

CHEST Guideline and Expert Panel Report

Richard S. Irwin, MD, Master FCCP; Cynthia T. French, PhD, ANP-BC; Sandra Zelman Lewis, PhD; Rebecca L. Diekemper, MPH; and Philip M. Gold, MD, FCCP; on behalf of the CHEST Expert Cough Panel

CHEST 2014; 146(4):885-889

Asthma

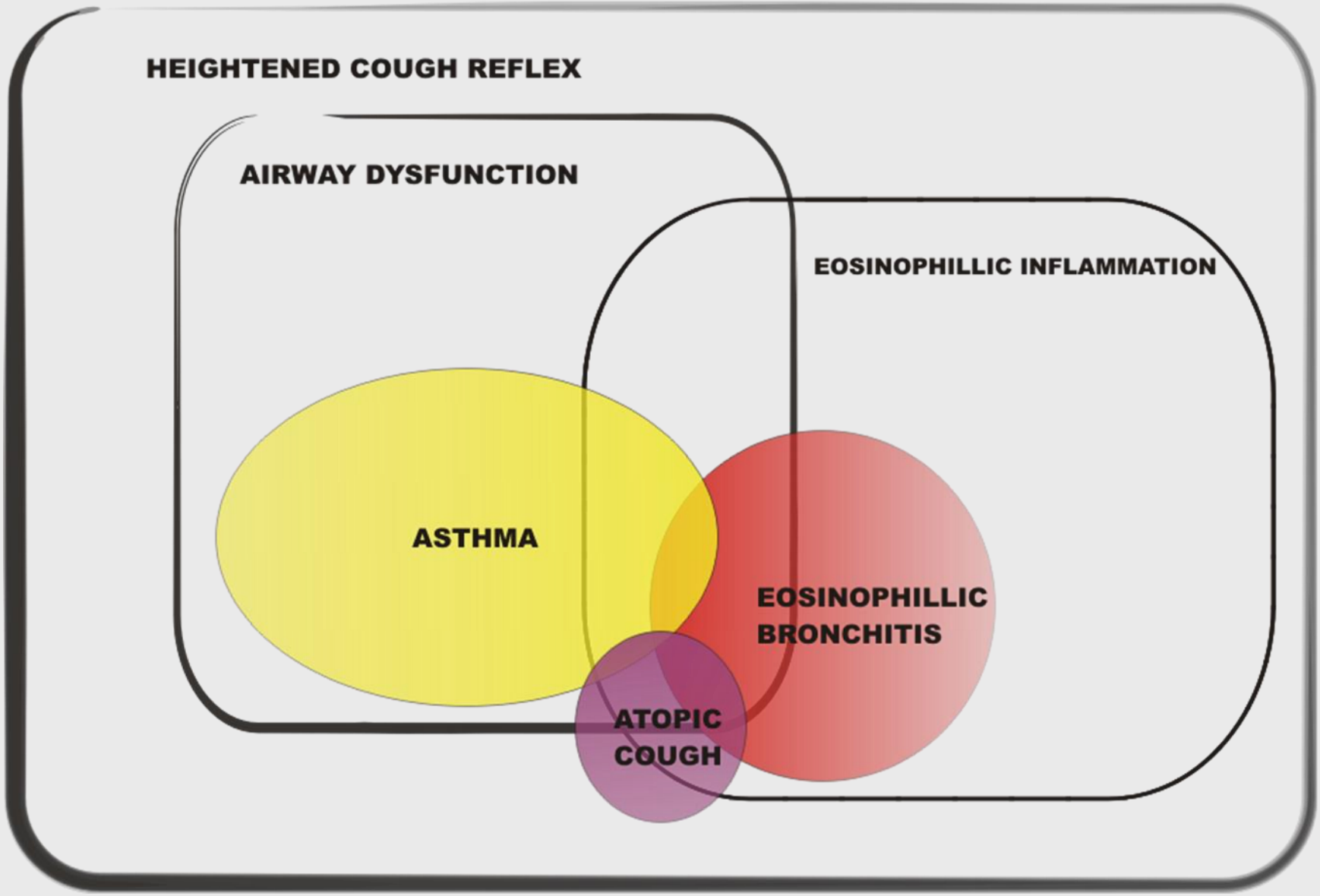

HEIGHTENED COUGH REFLEX
AIRWAY DYSFUNCTION
EOSINOPHILLIC INFLAMMATION
ASTHMA
EOSINOPHILLIC BRONCHITIS
ATOPIC COUGH

Table 1. Clinical and Pathological Features of Eosinophilic Airway Disorders

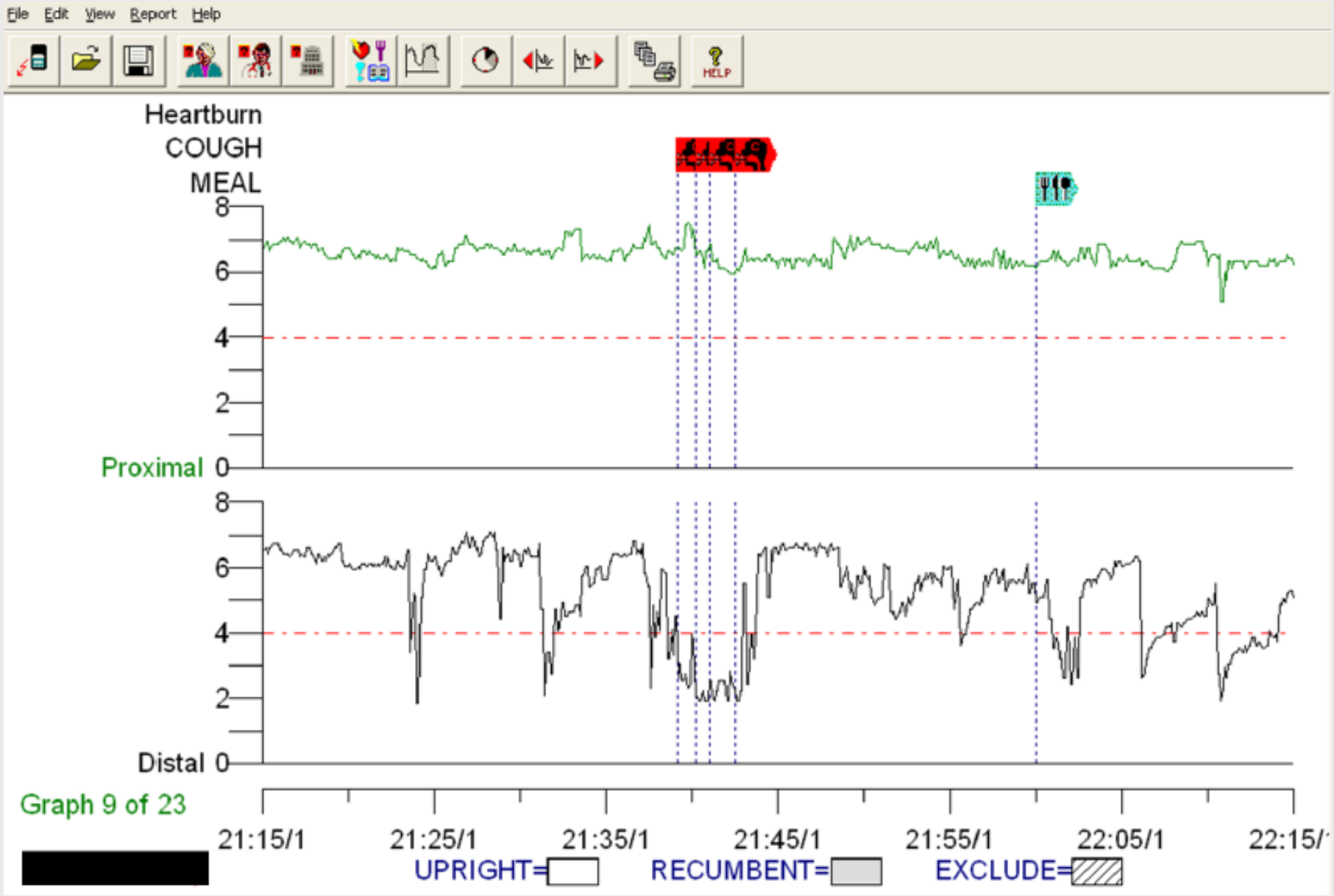
	Classic Asthma	CVA	NAEB
Symptoms	Cough, SOB, wheeze	Cough only	Cough (often with upper airway symptoms)
Atopy*	60-80%	40-80%	20-70%
Variable airflow limitation	+	±	—
AHR	+	+	—
Cough hypersensitivity	— ~↑	— ~↑	↑
Response to bronchodilator	+	+	unknown
Response to corticosteroid	+	+	+
Response to H_1 antagonists	±	±	unknown
Rapid decline of lung function	+	±	±
Progression to classic asthma	NA	30%	10%
Sputum eos↑(>3%)	usually	usually	always (by definition)
Exhaled NO	↑	↑	↑

Niimi A. Current Respiratory Medicine Reviews 2011; 7(1): 47-54

Take-Home Messages (Asthma)

- Cough is underestimated as a problem (Osman LM *et al*. Thorax 2001; 56:138-42, Mincheva R *et al*. Resp Res 2014; 15:79)
- Asthma/eosinophilic airway syndrome are common and generally steroid responsive
- FeNO has value in the clinic (Yi F *et al*. Chest 2016; 149(4): 1042-1051)
- Negative tests for bronchial hyper-responsiveness and eosinophilia – no steroids

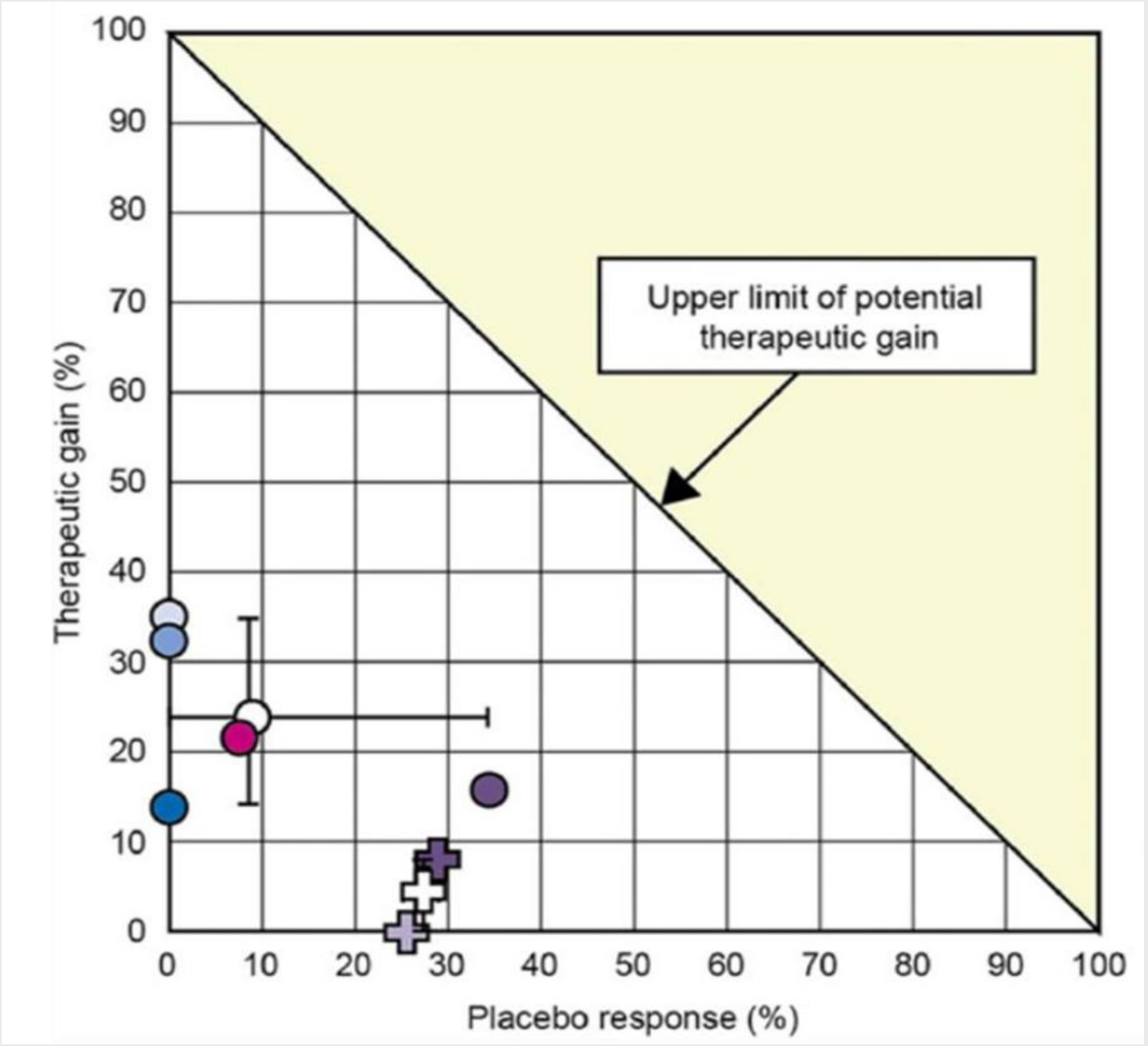
Gastro-oesophageal Reflux



Tracing from 24 hour oesophageal pH monitoring in patient with PPI responsive cough

Current position on treating acid reflux associated cough

- Diet modification to promote weight loss in overweight or obese patients
- Head of bed elevation and avoiding meals within 3 hours of bedtime;
- In patients who report heartburn and regurgitation, proton pump inhibitors, H2-receptor antagonists, alginate, or antacid therapy sufficient to control these symptoms



Kharilis PJ *et al*. Chest 2013;143(3):605-612.

Take-Home Messages (reflux)

- Lifestyle modification and treating acid reflux still likely to be effective
- In adult patients without heartburn or regurgitation, proton pump inhibitor therapy alone is unlikely to be effective
- Non acid reflux and oesophageal dysmotility are important factors
- Reconsider the use of diagnostic evaluation (oesophageal pH-metry/manometry/impedance)
- Selecting patients likely to be responsive to treatment is a key objective

Upper Airway Cough Syndrome (Post nasal drip)

Take home messages (UACS)

- Nasal symptoms common in acute cough
- Chronic cough and upper airway symptoms (post nasal drip) often co-exist
- Efficacy claims largely driven by treatment with sedating anti-histamines
- ENT specialists commonly see patients with chronic cough but don’t often refer!
- ENT specialists have made important contributions to understanding cough

Treatment of Unexplained Chronic Cough

CHEST Guideline and Expert Panel Report

Peter Gibson, MBBS; Gang Wang, MD, PhD; Lorcan McGarvey, MD; Anne E. Vertigan, PhD, MBA, BAppSc (SpPath); Kenneth W. Altman, MD, PhD; and Surinder S. Birring, MB ChB, MD; on behalf of the CHEST Expert Cough Panel

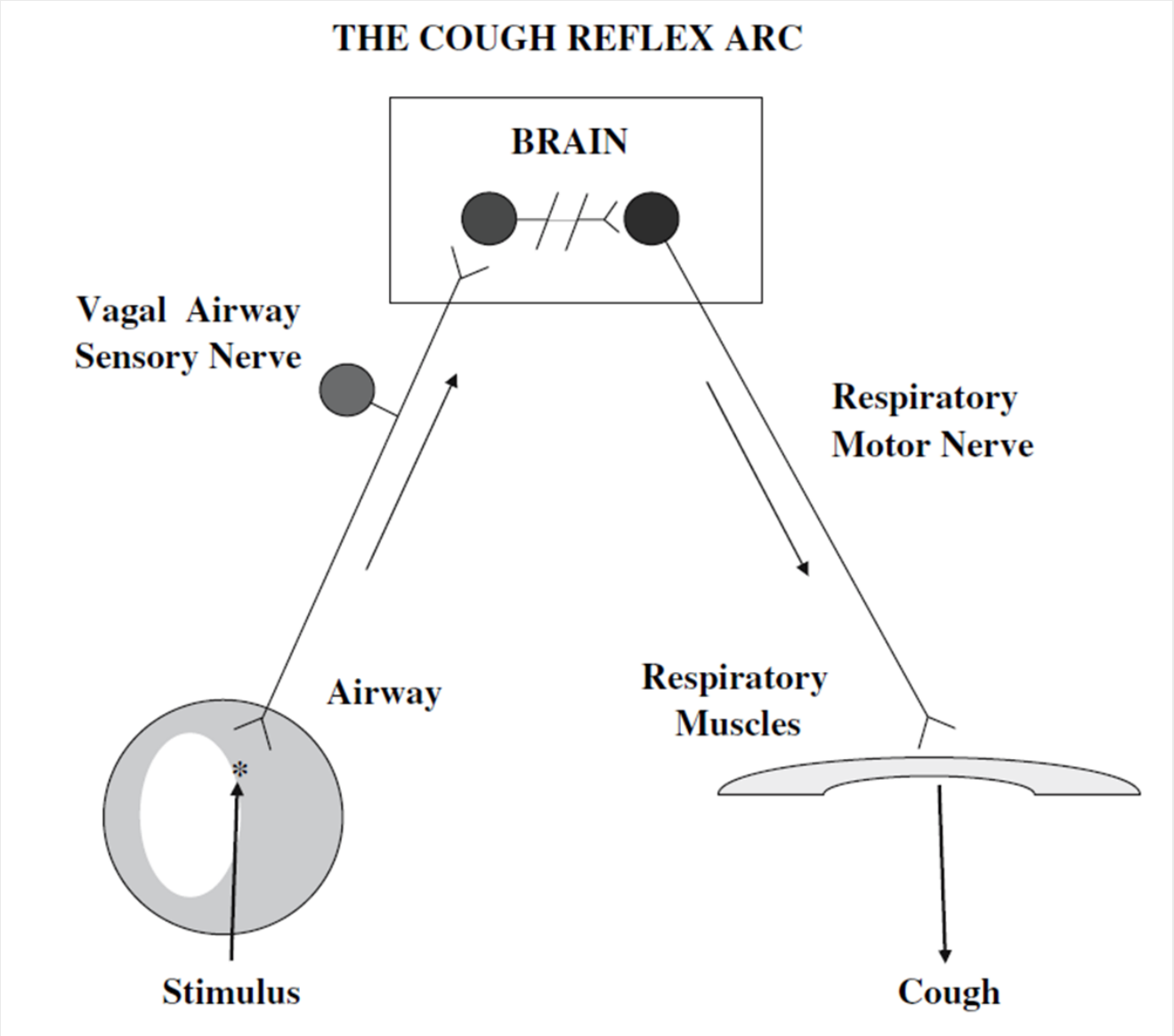
- Diagnose unexplained chronic cough (UCC) after investigation and supervised trials of therapy according to best practice guidelines
- Adult patients with UCC – suggest therapeutic trial of speech pathology
- Consider gabapentin (but assess risk/benefit)

CHEST 2016; 149(1):27-44

Take-Home Message (Cough management protocols)

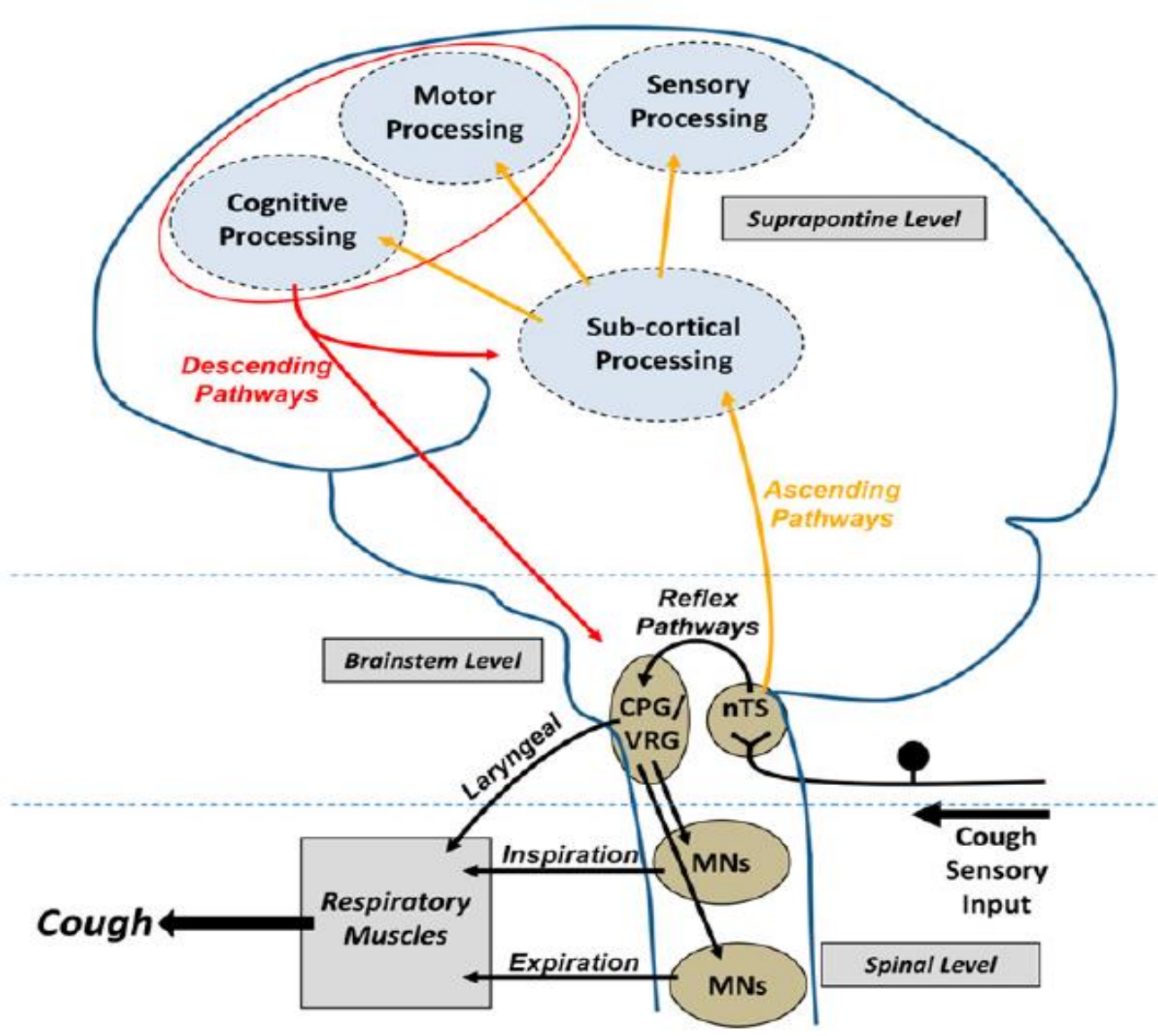
- They do work but fidelity to treatment guidelines is variable
- Despite extensive investigation and intensive trials of therapy cough is often unexplained and troublesome
- Currently we have no effective treatments

State of the Art



Canning B *et al*. ACCP Expert Cough Panel Guideline & Report. Chest 2014; 146: 1633

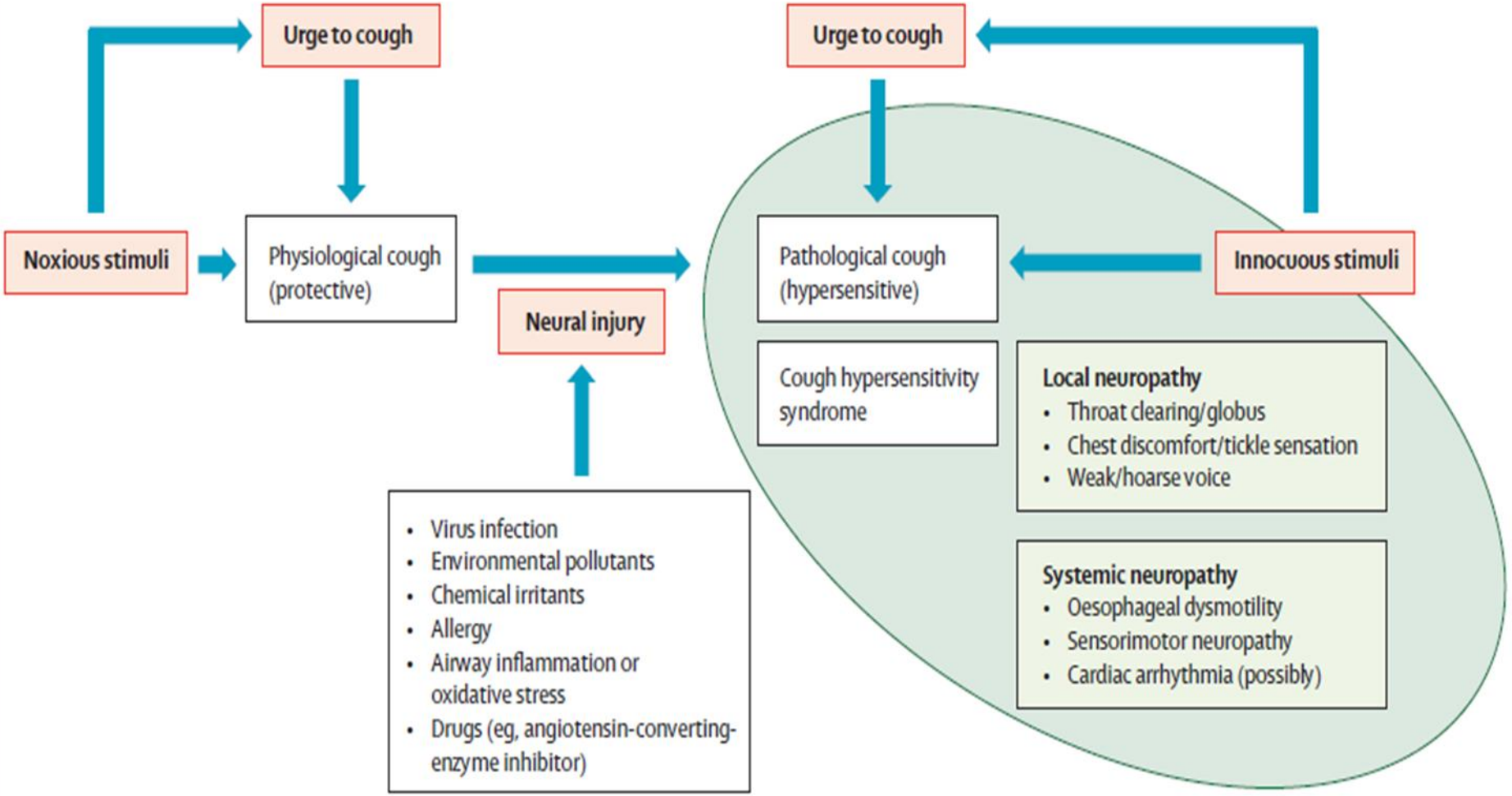
State of the Art



Canning B *et al*. ACCP Expert Cough Panel Guideline & Report. Chest 2014; 146: 1633

Chronic cough as a neuropathic disorder

Kian Fan Chung, Lorcan McGarvey, Stuart B Mazzone



Chung KF, McGarvey L, Mazzone S. Lancet Respiratory Medicine 2013; 1(5): 414-22

Clinical features of the urge-to-cough in patients with chronic cough

Emma Hilton [a,b], Paul Marsden [a,c], Andrew Thurston [a,b], Stephen Kennedy [b,c], Samantha Decalmer [a,d], Jaclyn A. Smith [a,b,*]

Respiratory Medicine (2015) 109, 701–707

Triggers

Smoky atmospheres (79%)

Talking (72%)

Cold temperatures (67%)

Dry atmospheres (66%)

Perfume smells (61%)

Chronic cough as a neuropathic disorder

Kian Fan Chung, Lorcan McGarvey, Stuart B Mazzone

Lancet Respir Med 2013;
1: 414–22

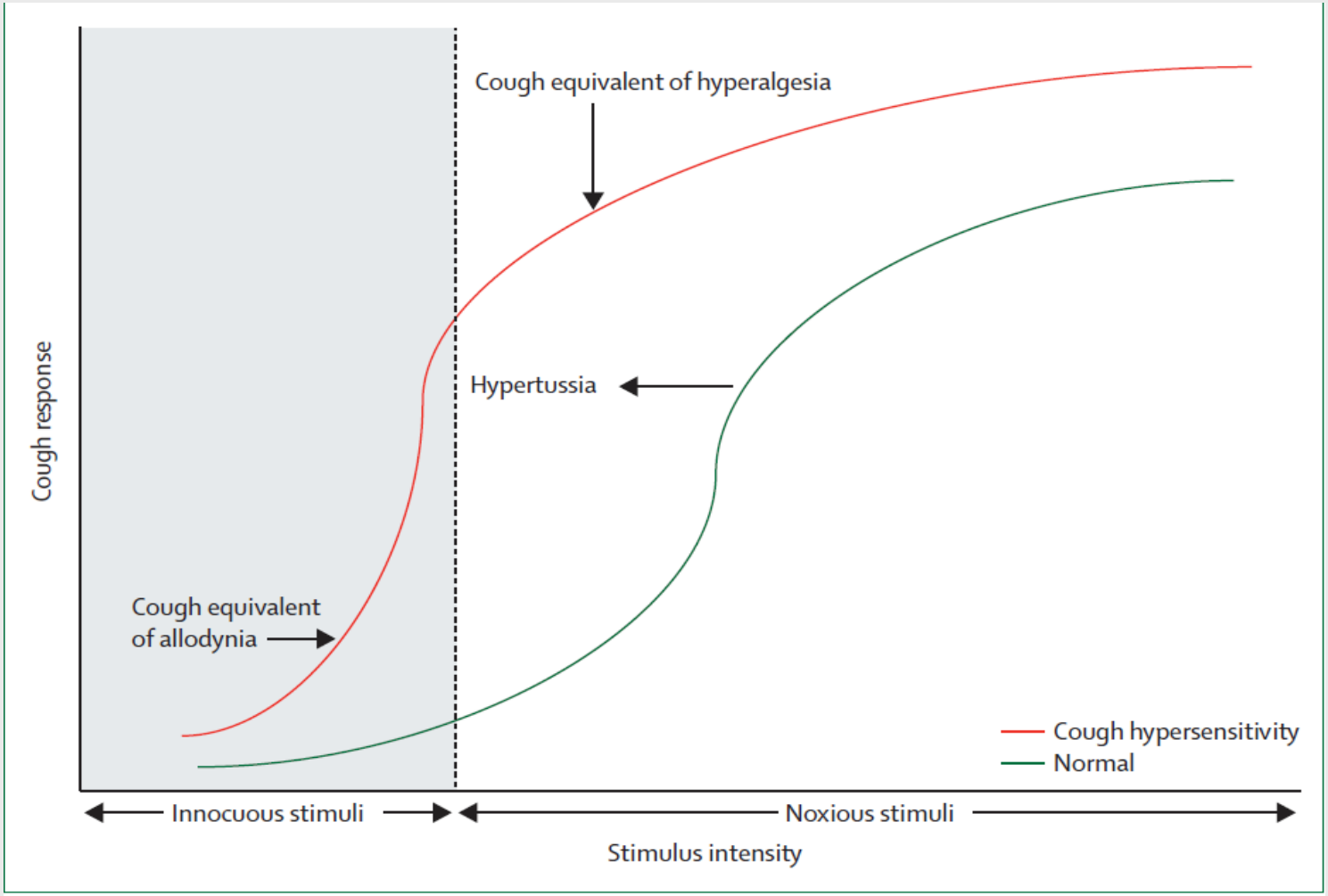
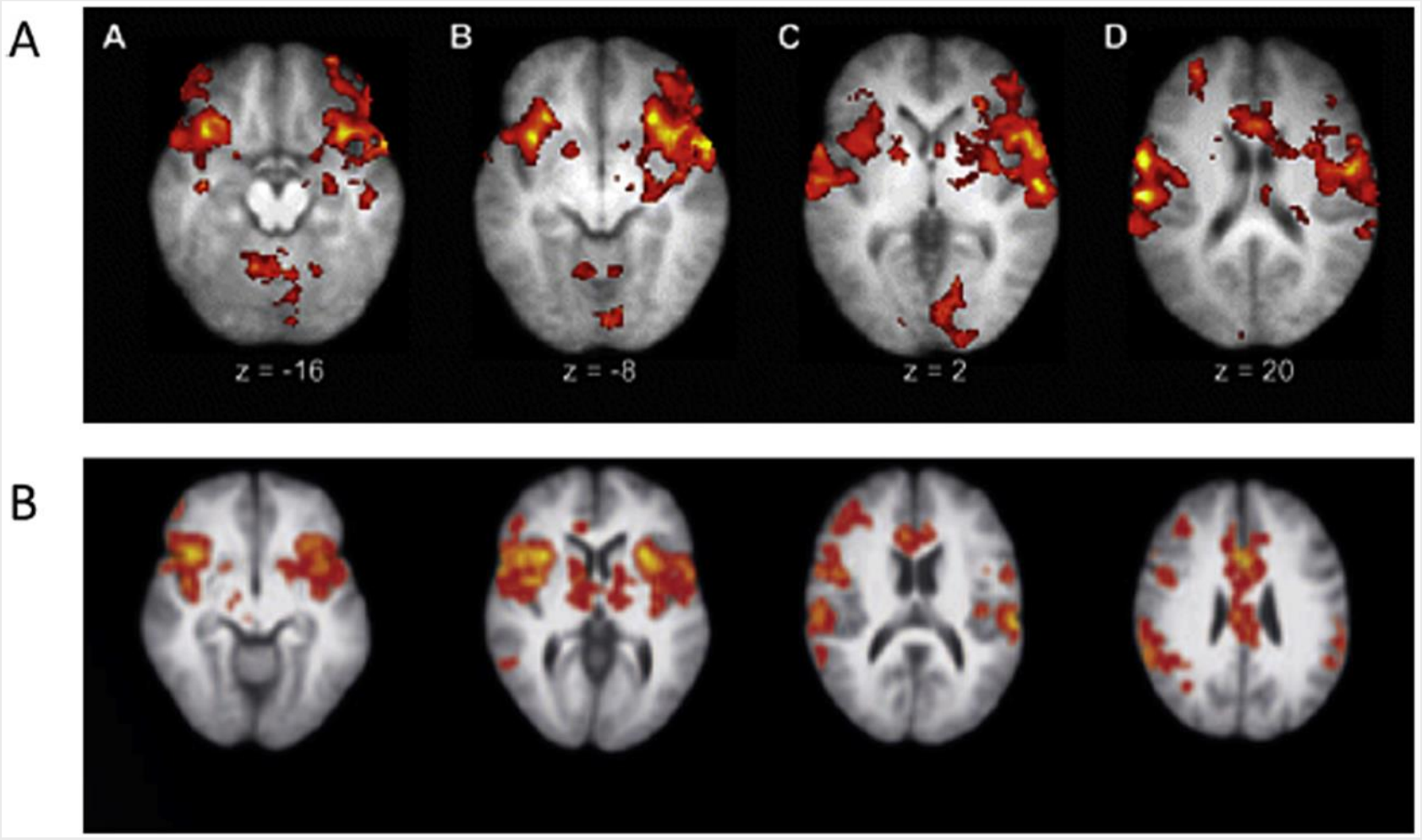


Figure 4: **Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states**

The PAIN of CHRONIC COUGH

CAPSAICIN INHALATION



NOXIOUS HEAT APPLED TO HAND

J. O'Neill et al. / Pulmonary Pharmacology & Therapeutics 26 (2013) 476–485

Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control

- Midbrain activity appears in hyperalgesic pain states, which suggests a common mechanism for increased pain and cough sensitivity, while decreased medial prefrontal responses in patients indicates a failure of this key component of the cough-suppression network.

Ando A *et al*. Thorax 2016; 71: 323-329

Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control

What is the bottom line?

- Using functional brain imaging, patients with cough hypersensitivity showed activation in the midbrain during airways irritation that does not occur in healthy people, whereas healthy people showed activation in the medial prefrontal cortex that is absent in the patients.

Ando A *et al*. Thorax 2016; 71: 323-329

Expert opinion on the cough hypersensitivity syndrome in respiratory medicine

Alyn H. Morice[1], Eva Millqvist[2], Maria G. Belvisi[3], Kristina Bieksiene[4], Surinder S. Birring[5], Kian Fan Chung[6], Roberto W. Dal Negro[7], Peter Dicpinigaitis[8], Ahmad Kantar[9], Lorcan P. McGarvey[10], Adalberto Pacheco[11], Raimundas Sakalauskas[4] and Jaclyn A. Smith[12]

Cough hypersensitivity syndrome

Question 1

Cough hypersensitivity syndrome (CHS) is a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure

A+	Agree strongly	14
A	Agree with minor reservations	25
A-	Agree with major reservations	4
D-	Disagree with major reservations	0
D	Disagree with minor reservations	0
D+	Disagree strongly	1

Eur Respir J 2014; 44: 1132-1148

Expert opinion on the cough hypersensitivity syndrome in respiratory medicine

Alyn H. Morice[1], Eva Millqvist[2], Maria G. Belvisi[3], Kristina Bieksiene[4], Surinder S. Birring[5], Kian Fan Chung[6], Roberto W. Dal Negro[7], Peter Dicpinigaitis[8], Ahmad Kantar[9], Lorcan P. McGarvey[10], Adalberto Pacheco[11], Raimundas Sakalauskas[4] and Jaclyn A. Smith[12]

Question 2

CHS may mimic or coexist with other pulmonary or extrapulmonary disease

A+	Agree strongly	23
A	Agree with minor reservations	13
A-	Agree with major reservations	6
D-	Disagree with major reservations	1
D	Disagree with minor reservations	1
D+	Disagree strongly	0

Eur Respir J 2014; 44: 1132-1148

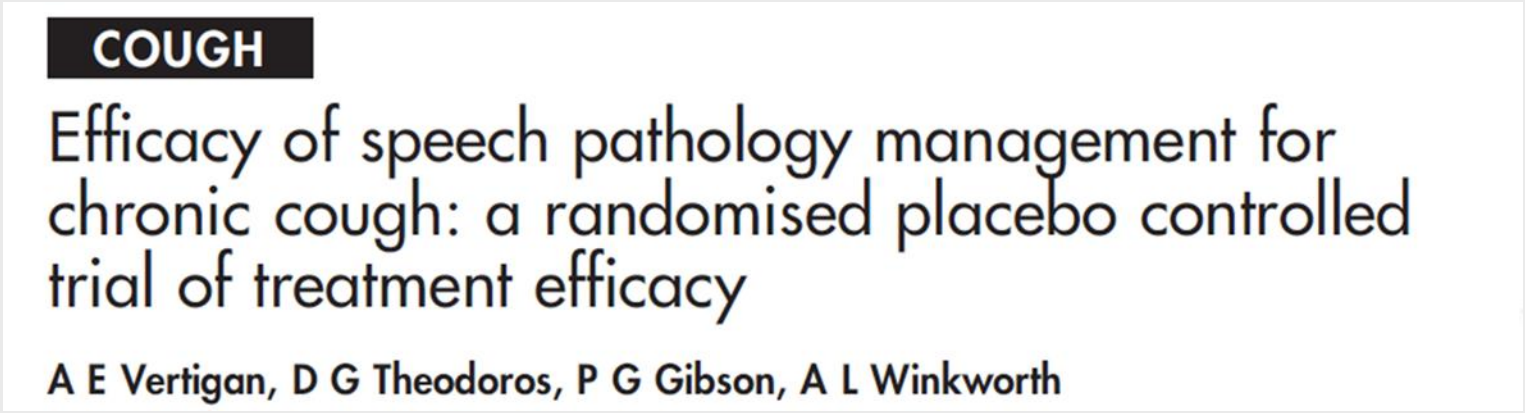
Treating Unexplained Chronic Cough - State of the Art

Opiate Therapy in Chronic Cough

Alyn H. Morice[1], Madhav S. Menon[1], Siobhan A. Mulrennan[1], Caroline F. Everett[1], Caroline Wright[1], Jennifer Jackson[1], and Rachel Thompson[1]

- 27 patients (18 female, mean age 55y) with UCC
- DBRCT 5mg BD slow release morphine
- 40% reduction in cough VAS c/w placebo ($p<0.01$)
- Significant improvement (3.2 points) in Leicester Cough Questionnaire c/w placebo ($p<0.01$)
- No change in citric acid sensitivity
- 2/3 opted to increase to 10mg BD

Am J Respir Crit Care Med Vol 175.pp 312-315, 2007



- 87 patients (64 female, mean age 59y)
- Single blind RCT of 4 specifically detailed 30 min speech pathology sessions versus placebo (healthy lifestyle education)
- Significant reduction in cough scores, QoL with SLT c/w placebo at 2 month follow up

AE Vertigan, DG Theodoros, PG Gibson, AL Winkworth, Thorax 2006;61:1065-1069. doi: 10.1136/thx.2006.064337

Table 2 Examples of strategies in the treatment programme

Component	Example
Education	No physiological benefit from cough; capacity for voluntary cough control
Strategies to reduce cough	Identify warning signs for cough and replace with modified swallow technique, pursed lip breathing exercise, or relaxed throat breath
Reduce laryngeal irritation	Increase hydration, decrease exposure to irritating stimuli
Psycho-educational counselling	Internalising locus of control; acceptance that treatment is hard work; setting realistic goals

Thorax 2006;61:1065-1069. doi: 10.1136/thx.2006.064337

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

Nicole M Ryan, Surinder S Birring, Peter G Gibson

Lancet 2012; 380: 1583–89

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

Anne Vertigan, et al., CHEST 2016; 149(3): 639-648

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

Gibson PG, Wang G, McGarvey L *et a*l. Expert Panel Report Chest 2016; 149(1): 27-44

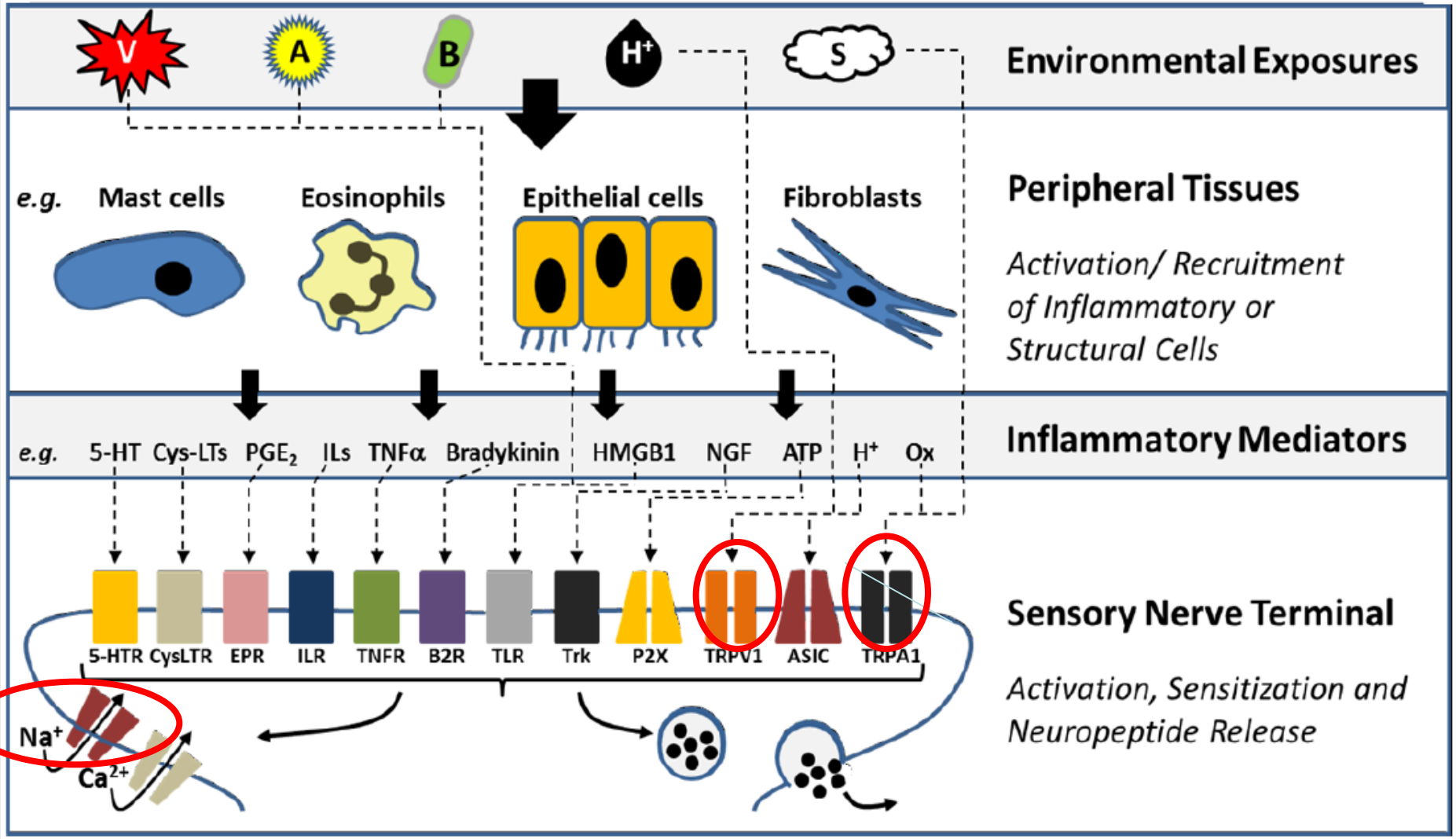
Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial.

Horton MR, Santopietro V, Mathew L, Horton KM, Polito AJ, Liu MC, Danoff SK, Lechtzin N

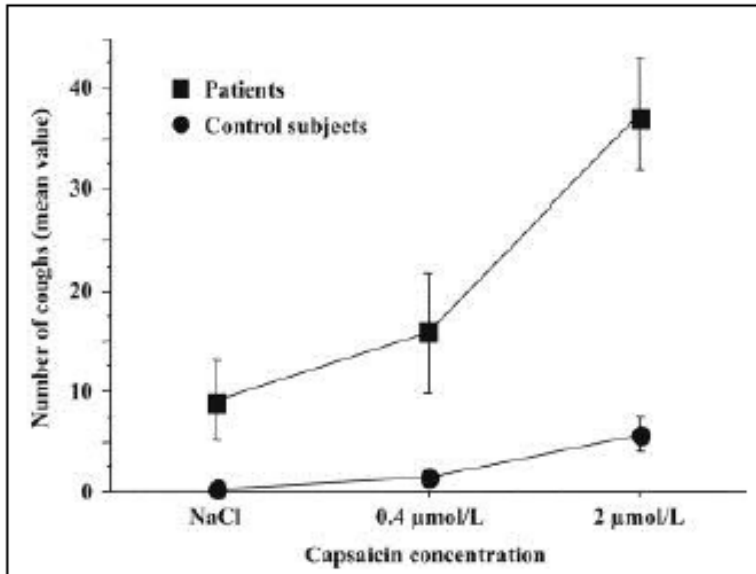
- CQLQ scores significantly improved with thalidomide. On average difference versus placebo was a decline of 11.4 points (P<0.001).
- Significantly improved scores on the visual analogue scale of cough severity, (average difference versus placebo of minus 31.2 points (P<0.001).
- 74% of thalidomide patients and 22% of placebo patients reported adverse events (Constipation, dizziness, and malaise) - more frequent with thalidomide.
- Despite adverse events, all patients requested continuation of thalidomide at the end of the study.

Ann Intern Med. 2012;157(6):398-406

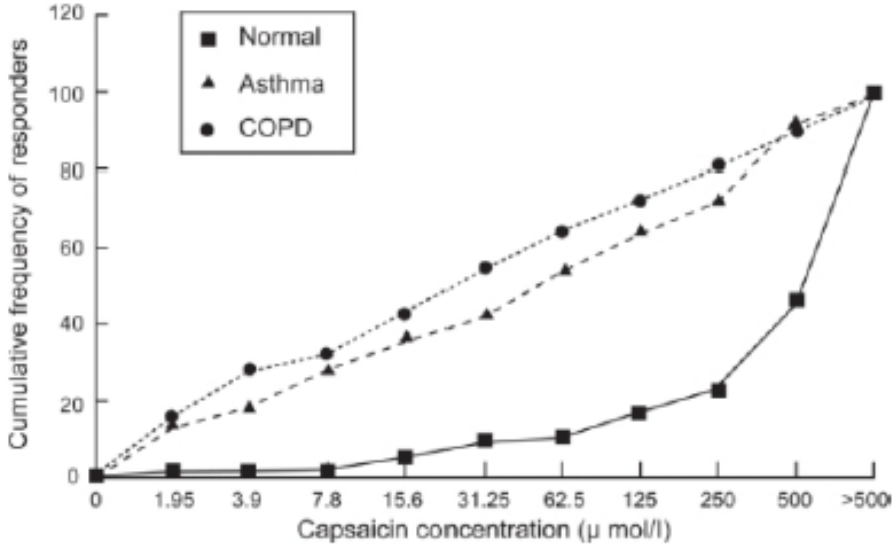
Neuro-immune interactions drive peripheral sensitization in chronic cough.



Cough Hypersensitivity Syndrome



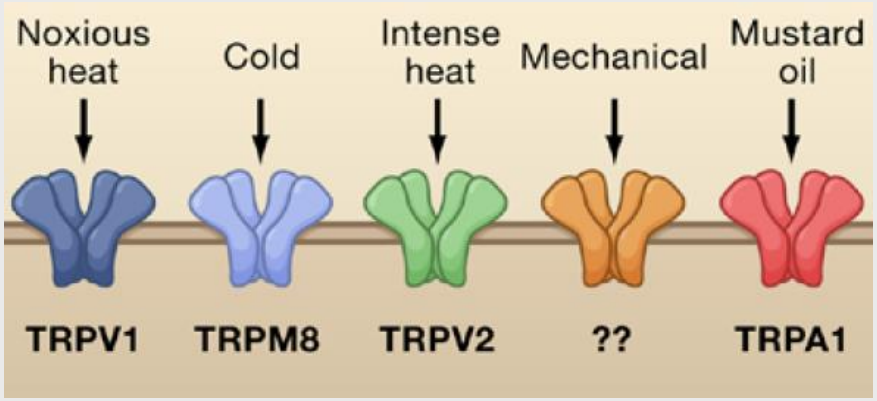
Millqvist et al., *Pulm Pharmacol Ther*, 2008



Doherty et al. *Thorax* 2000

TRP channel activation

A



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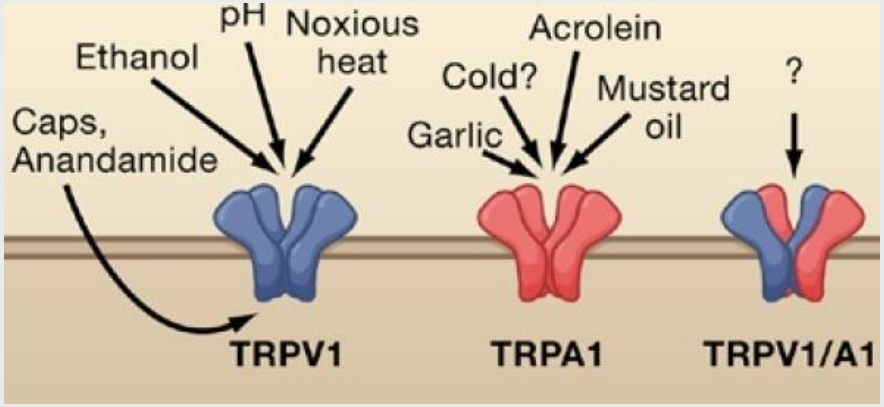
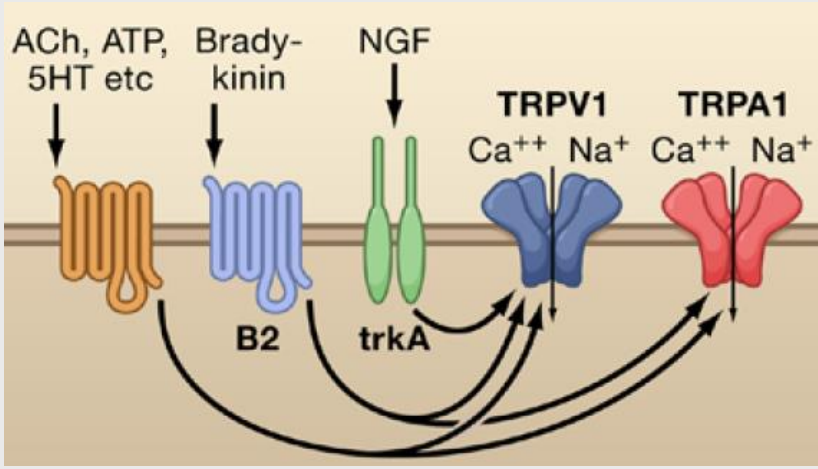




C

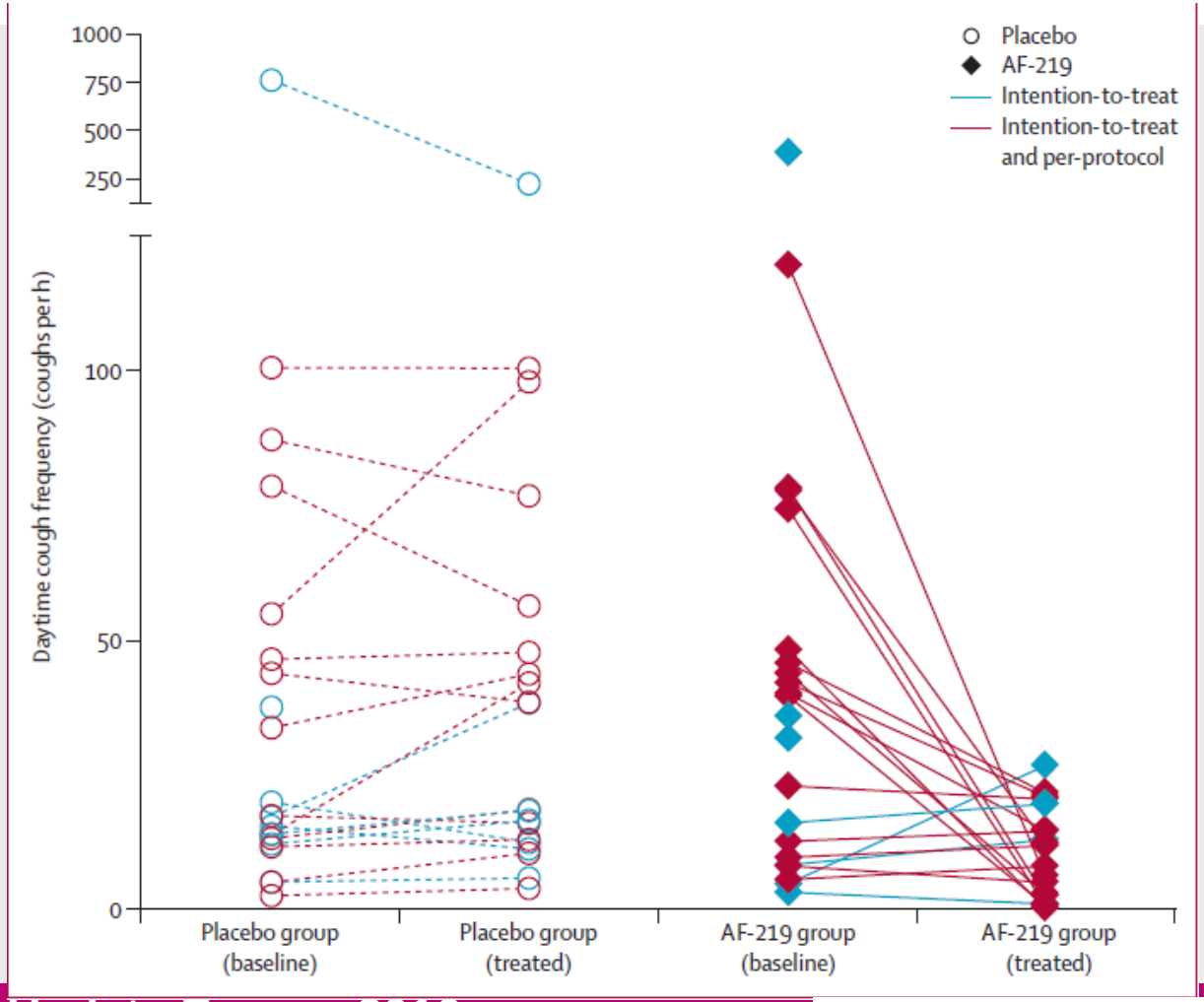
Adapted from McMahon *et al*. Cell 2006

TRP channels: The story so far

- Promising preclinical data – TRPV1 knock out animals
- Promising early clinical data (especially in pain)
- Early clinical (FTIH) and PoC studies suggest safety issues in particular hyperthermia, and temperature perception.
- TRPA1 antagonist and TRPV1 antagonist POC studies completed

P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

Rayid Abdulqawi, Rachel Dockry, Kimberley Holt, Gary Layton, Bruce G McCarthy, Anthony P Ford, Jaclyn A Smith



www.thelancet.com Published online November 25, 2014

Conclusions

- Cough is a significant health care problem
- Need to rethink our approach to cough as a clinical problem
- Real progress in understand the underlying mechanisms of clinical cough
- Collaboration with clinicians, scientists and industry is required
- The future is bright

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List of Abbreviations

ACCP – American College of Chest Physicians

AHR – Airway Hyperresponsiveness

CQLQ – Cough Quality of Life Questionnaire

DBRCT – Double Blind Randomised Conrolled Trial

FeNO – Fractional exhaled Nitric Oxide

FTIH – First Time in Humans

H2 – Histamine-2 receptor

LCQ – Leicester Cough Questionnaire

PoC – Proof of Concept

PPI – Proton pump inhibitor

TRP – Transient receptor potential

UCC – Unexplained Chronic Cough

VAS - Visual Analogue Scale