Management of refractory chronic cough

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North Tyneside General Hospital
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Typical referral

Dear Dr

Please see this 48 year old man, He developed a cough 6 months ago after a coryzal illness. He hasn’t responded to antibiotics and more recently trials of high dose PPI and a nasal spray. CXR is normal. He’s normally fit and well other than mild hypertension.

Thankyou

Not infrequent referral

Dear Dr

Please see this 56 year old female. Never smoked. PMHx hypothyroidism. She's had a cough for at least 20 years. She previously saw Dr X locally at St Elsewhere and had normal investigations and was eventually discharged as there was nothing else to do. She has also been down to another place where the cough was thought to be due to reflux. She didn't respond to various treatments including PPI, ranitidine, gaviscon, metoclopramide, domperidone, disofrol and baclofen. She had a fundoplication but the cough is no better. We have tried various things (sometimes repeatedly)over the years including steroids (oral and ICS), nasal steroids, salbutamol, codeine linctus, Amitryptilline and various OTC medicines. CXR and spirometry is normal. She's really frustrated and finds the cough embarrassing-particularly at work. She has embarrassing incontinence. Is there anything you can do to help?

Thankyou

Part of routine work for every chest physician

Often seen negatively

Patients often frustrated/anxious/negative experience of system

Not interesting

Nothing we can do-nihilism and frustration

Part

Ofter

Patie

Not i

Noth

Can make a big difference to these patients

Positive attitude to the problem (not going away…..)

Systematic approach

Knowledge of

a) How much to investigate
b) How far to go with empirical treatment trials (ie when to stop)
c) How to use antitussives (MST/gabapentin)

Availability of services to help (SALT…)

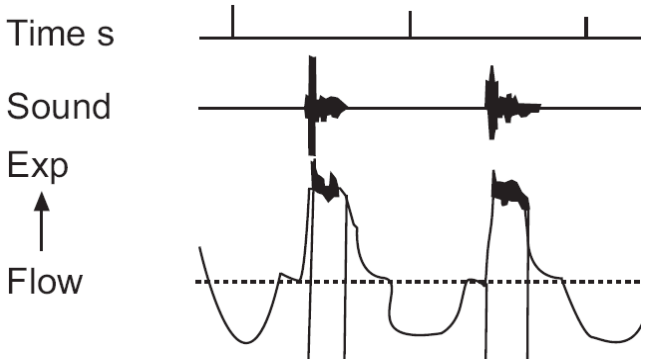
Almost all cough should be sorted in secondary care

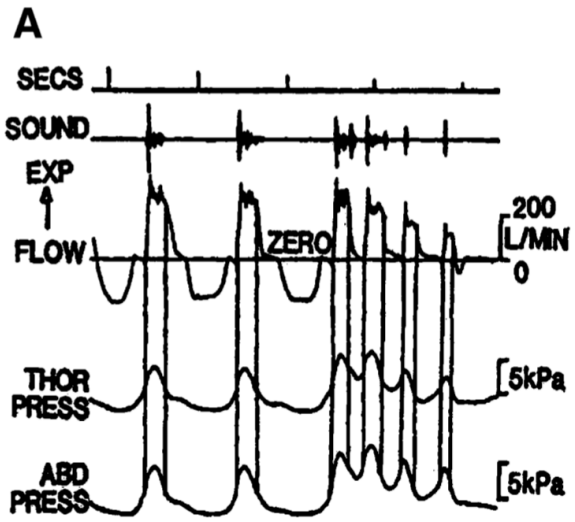
- What is a cough
- Why is cough important
- What do we know about the cough reflex
- What are the causes of chronic cough and how do we treat it?
- Antitussives
- Non pharmacological approaches

What is a cough?

What is a cough?

- “A forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound”[1].
- 4 phase defensive reflex (inspiration, compressive (0.2 s), expulsive and restorative phases). May be voluntary.





1. Morice AH et al ERJ 2007; 29:1256-1275
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3. Fontana G. Lung 2008; 186 (Suppl 1):S3–S6

Cough: A protective reflex

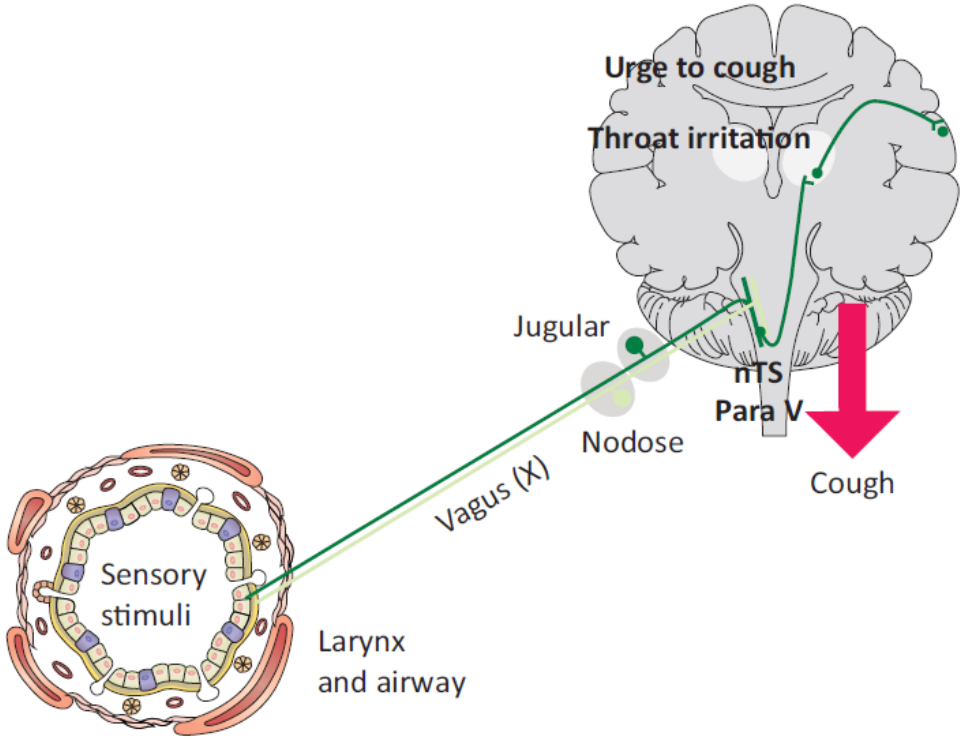


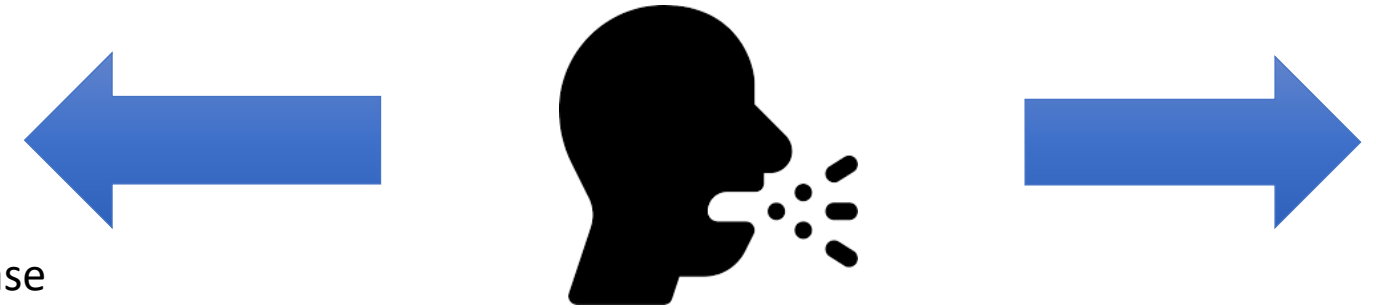
Fig 2. Schematic diagram representing the cough reflex. Vagal afferents transmit stimuli from the airways to the nucleus tractus solitarius (nTS) and paratrigeminal nucleus (Para V) in the brainstem. Neuronal signals are then transmitted to the somatosensory cortex via the thalamus causing throat irritation and urge to cough. These sensations, if great enough, lead to cough via activation of spinal motor neurons.

Satia et al Clinical Medicine 2016

Protective reflex

NORMAL
'physiological cough'

IMPAIRED COUGH
Aspiration
Pneumonia
Elderly
Neurological disease
(dementia, stroke, PD)
EOL



ENHANCED COUGH
Unpleasant symptoms
↓QOL

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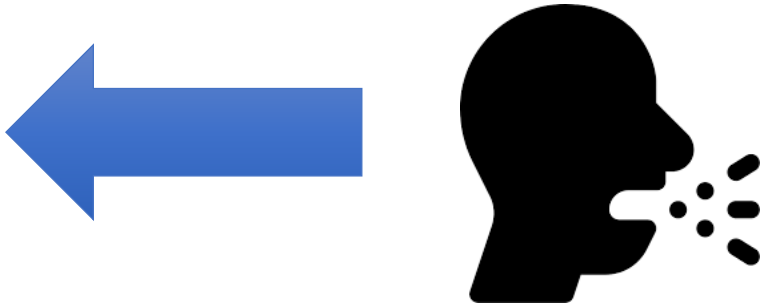

ENHANCED
COUGH
Unpleasant
symptoms
↓QOL

Acute cough

Chronic cough

Definitions; Acute or chronic cough?

Definitions

Acute cough (<3 weeks): usually infection (viral) and self limiting.

Common primary care presentation

‘Self care’-OTC medications etc

(subacute)

Chronic cough (>8 weeks): wide range of causes, not well understood.

Lung disease (asthma, COPD, lung cancer, IPF)

Extrapulmonary disease (rhinitis ? Reflux)

Smoking

Drugs eg ACEI

Refractory chronic cough: unresponsive to treatment for specific cause.

(Refractory) Unexplained chronic cough.

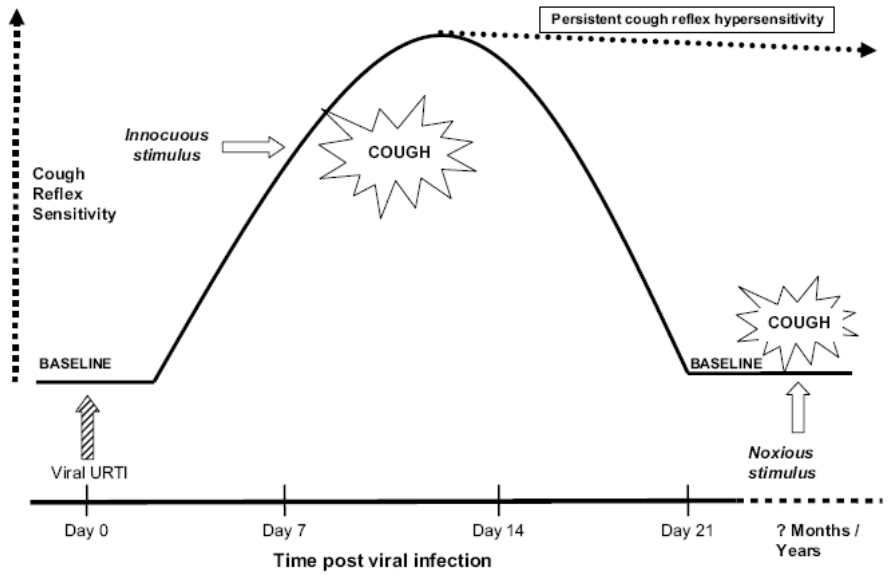

Fig. 1. Schematic of proposed changes in cough reflex sensitivity following viral upper respiratory tract infection. Following a viral infection, the cough reflex becomes hyperreactive and remains in this activated state for a variable period of time (two-three weeks) during which cough may be provoked by innocuous stimuli such as exposure to scents, aerosols and changes in air temperature. In the majority of subjects the hyperreactivity diminishes and the cough reflex responsiveness returns to its baseline state. However, in some circumstances this hypersensitized state persists long after the initial triggering event leading to a chronic cough state.

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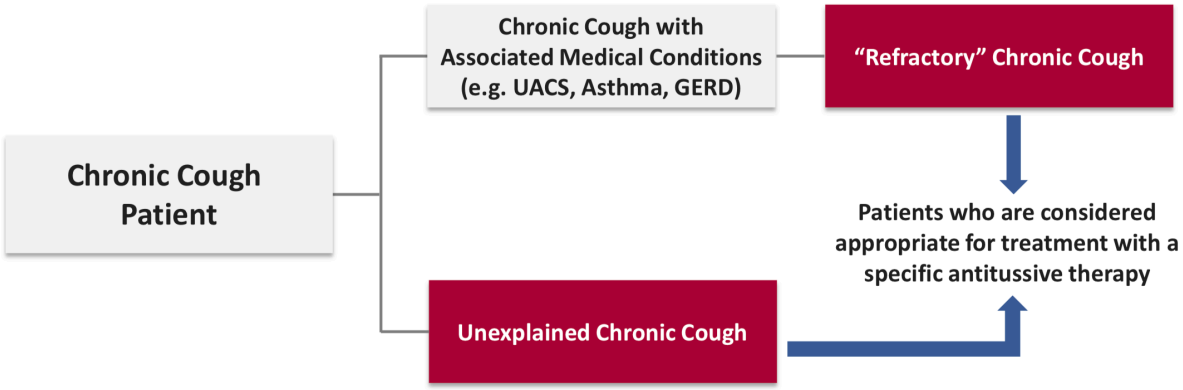

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Eg. Cough persisting in asthma

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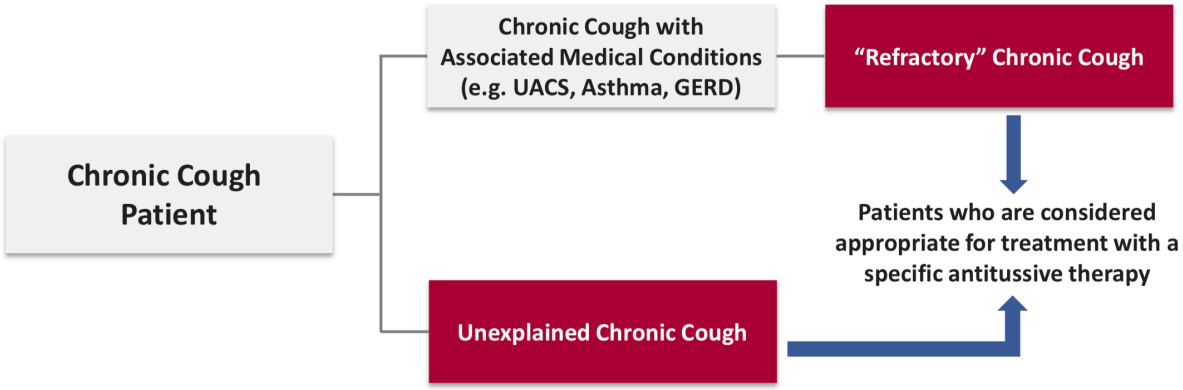

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Smoking

Drugs eg ACEI

Refractory chronic cough: unresponsive to treatment for specific cause.

Eg. Cough persisting in asthma

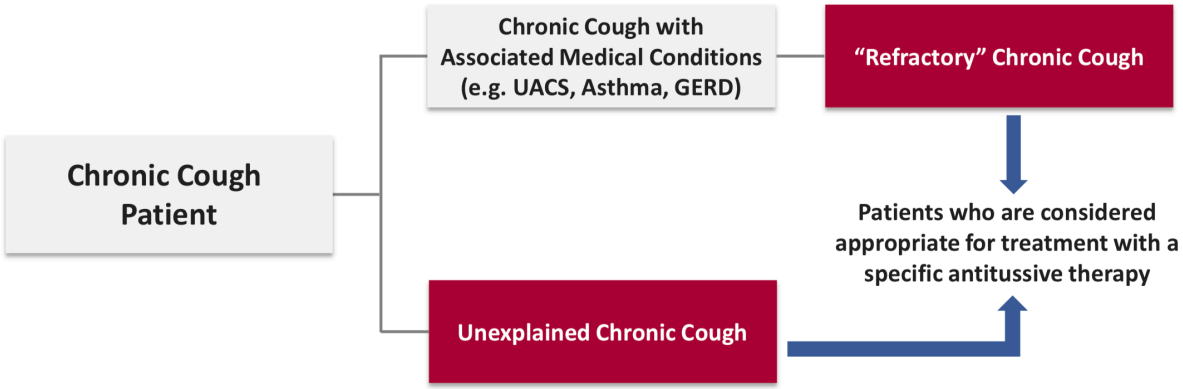
(Refractory) Unexplained chronic cough.

No cause/pathology found

(idiopathic)

Considerable overlap with 'refractory chronic cough', often effectively interchangeable.

No real agreement on definitions



Look at

McGarvey L, Gibson PG. What Is Chronic Cough? Terminology. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):1711-1714.

May help (or not..)

So what? It’s only a cough

So what? It's only a cough…

- **Reduced quality of life[1,2].**
- **Unpleasant (UTC)**
- **Associated physical symptoms** (fatigue, chest pain (rib #), incontinence, vomiting, headache)
- **Psychomorbidity** (anxiety, depression, anger, distress)
- **Social** aspects-altered/spoiled social identity. Social effort[3].)
- **Healthcare Costs**

1. Young et al Ther Adv Resp Dis 2010
2. French et al Arch Int Med 1998
3. Hulme et al ERJ Open Res 2017

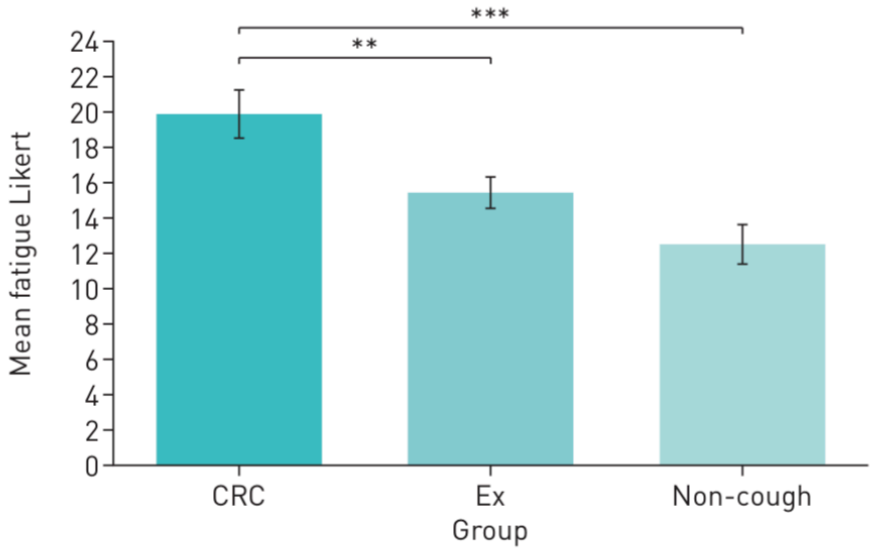
Psychopathology in patients with chronic cough

- Higher levels of depression (mild) and anxiety, fatigue and somatic physical symptoms than controls.
- Refractory cough (compared to explained cough) showed higher levels of;

Depression

Fatigue

Negative illness representations (beliefs around negative consequences, lower illness coherence and higher emotional representations).



Hulme K, Deary V, Dogan S, Parker SM. Psychological profile of individuals presenting with chronic cough. ERJ Open Res 2017; 3

Individual vulnerability

- Predisposing factors: childhood trauma, 'worriers'
- Precipitating factors: divorce, refurbishing house, bereavement, redundancy, viral infections.

More than just a cough

- Physicality of the symptoms accompanying the cough – some very severe (vomiting, pain, incontinence).
- Emotional impact e.g. embarrassment, sadness disappointment, guilt.

Cough in the social sphere

- Overt nature of the cough - others notice.
- The contagious image of cough.
- Social effort of dealing with others' reactions.

'At the end of the line' : the healthcare journey

- Some felt dismissed.
- Reassured nothing serious.
- Physical and psychological very separate entities.
- Search for answers.
- Doc done everything… would try anything.

Refractory Cough

Cough & Identity

- Cough becomes ingrained in their identity vs its own persona.
- Known by their cough.
- Clash of person's identity and the cough image (seen in 'bad light' P9)

Cough in relation to other health conditions

- Compared to acute conditions – medical resolution. Just a cough.
- Compared to own conditions (e.g. diabetes)

as a reference point.

The battle for control

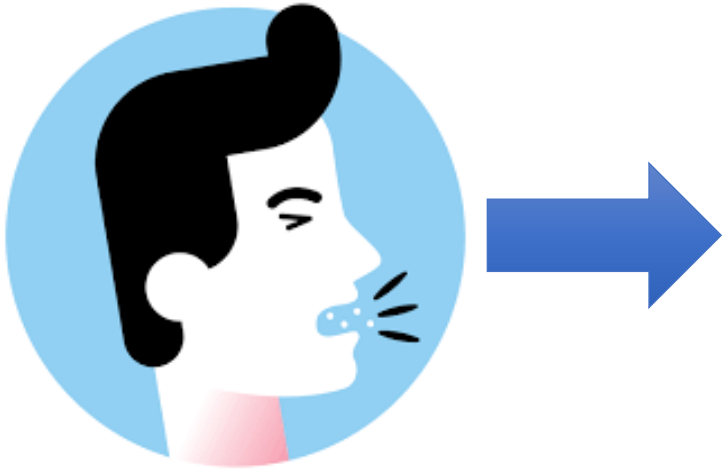
- Cough dictating life.
- Unpredictability and inconsistency.
- Disrupted activities: sleep, work, eating, going out.
- Strategies – cognitive (e.g. values) & behaviour (avoid, gum, prepare)

Vicious circles

- Coughing to relieve the irritation e.g. feeling of mucus or tickle.
- Thinking about the cough made it worse – stress, anticipatory anxiety, attention.

Hulme K, Dogan S, Parker SM, Deary V. 'Chronic cough, cause unknown': A qualitative study of patient perspectives of chronic refractory cough. J Health Psychol. 2017

So what? It's only a cough…



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Increased healthcare costs-a burden on the NHS

Increased healthcare costs in a large community sample- patients coded as having cough.

Most disparities seen in primary care

Attendance

Prescribing costs

	Chronic cough	**Acute cough, multiple events**	**Acute cough, single event**
N (%)	12,513 (8.3)	38,599 (25.7)	99,119 (66.0)
Female, N (%)	7,529 (60.2)	22,960 (59.5)	57,769 (58.3)
Age, median (IQR), years	66 (52-77)	61 (45-75)	53 (38-68)
Healthcare resource use, N (£), per person-year			
All contacts	24.7 (£3,663)	18.4 (£2,700)	12.1 (£1,326)
Inpatient admissions	1.5 (£2,306)	1.0 (£1,709)	0.5 (£694)
Outpatient attendances	5.9 (£650)	4.3 (£466)	2.8 (£306)
Primary care contacts	17.3 (£707)	13.1 (£524)	8.8 (£326)
Primary care prescriptions	81.1 (£715)	54.7 (£442)	32.9 (£252)

Birring et al ERJ 2020 (abstract)

Increased healthcare costs-a burden on the NHS

Increased healthcare costs in a large community sample

Most disparities seen in primary care

In secondary care-patients seen in cough clinic (mostly refractory chronic cough)-accrued significant costs

Cost correlated with severity

Approx £1800

- **Introduction:** Chronic cough is a common cause for medical consultations. We investigated healthcare use in chronic cough, and its relationship with symptom severity, health status, anxiety severity and objective cough frequency (CF).
- **Methods:** Prospective study of consecutive patients with chronic cough from a specialist clinic who were invited to complete cough severity visual analogue scale (VAS), cough-specific health status Leicester Cough Questionnaire (LCQ), EuroQol EQ-5D-5L, Generalised Anxiety Disorder (GAD7) and objective CF monitoring with Leicester Cough Monitor. Case notes were reviewed for cough specific healthcare use for 12 months before and after the first cough clinic consultation. Unit costs were taken from NHS reference costs or departmental data.
- **Results:** 100 participants (69% female) had chronic cough of median (IQR) duration 3 (2-10) years; mean (SD) age 58 (15) years. Associated diagnoses included refractory chronic cough (57%) and asthma (15%). Cough severity, health status, anxiety severity and CF were: median (IQR) VAS 57 (30-79) mm, mean (SD) LCQ 12 (4), EQ-5D-5L 0.846 (0.178), GAD7 2.78 (4.85), and geometric mean (SD) CF 15.3 (2.5) coughs$\cdot hr^{-1}$, respectively. Patients accrued £1,800 of costs. In univariate analysis, cost increased with duration of cough ($p=0.02$), worsening VAS ($p<0.01$), LCQ ($p<0.01$) and GAD7 ($p=0.02$), and increased CF ($p=0.04$). Cost was not associated with gender ($p=0.20$), age ($p=0.31$) or EQ-5D-5L ($p=0.64$).
- **Discussion:** Chronic cough is associated with a significant cost in a specialist cough clinic, and the cost was associated with cough-specific health status, anxiety and symptom severity. Further work should investigate other factors which may affect cost in chronic cough.

Birring et al ERJ 2020 (abstract)

Increased healthcare costs-a burden on the NHS

Increased healthcare costs in a large community sample

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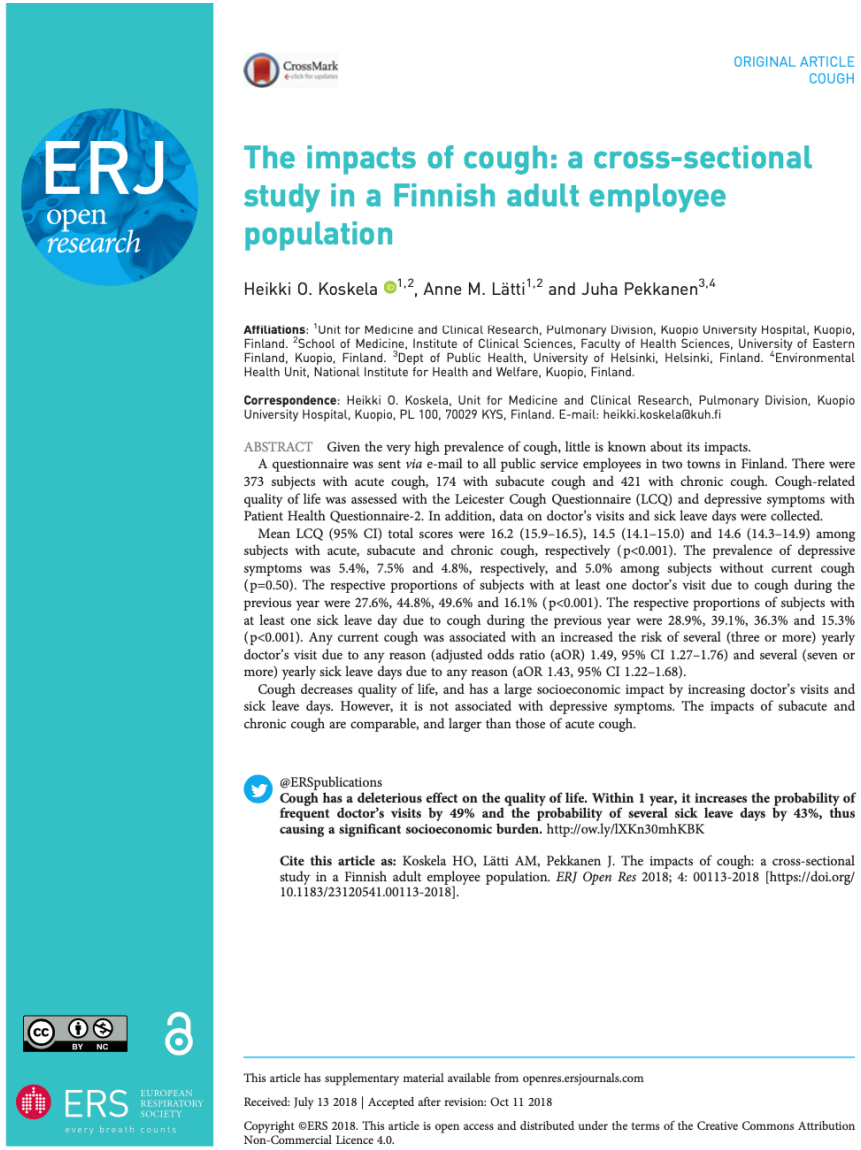
Approx £1800

More doctors visits

More absenteeism/sick leave



ERJ open research

CrossMark

ORIGINAL ARTICLE
COUGH

The impacts of cough: a cross-sectional study in a Finnish adult employee population

Heikki O. Koskela [1,2], Anne M. Lätti[1,2] and Juha Pekkanen[3,4]

Affiliations: [1]Unit for Medicine and Clinical Research, Pulmonary Division, Kuopio University Hospital, Kuopio, Finland. [2]School of Medicine, Institute of Clinical Sciences, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland. [3]Dept of Public Health, University of Helsinki, Helsinki, Finland. [4]Environmental Health Unit, National Institute for Health and Welfare, Kuopio, Finland.

Correspondence: Heikki O. Koskela, Unit for Medicine and Clinical Research, Pulmonary Division, Kuopio University Hospital, Kuopio, PL 100, 70029 KYS, Finland. E-mail: heikki.koskela@kuh.fi

ABSTRACT Given the very high prevalence of cough, little is known about its impacts.

A questionnaire was sent *via* e-mail to all public service employees in two towns in Finland. There were 373 subjects with acute cough, 174 with subacute cough and 421 with chronic cough. Cough-related quality of life was assessed with the Leicester Cough Questionnaire (LCQ) and depressive symptoms with Patient Health Questionnaire-2. In addition, data on doctor's visits and sick leave days were collected.

Mean LCQ (95% CI) total scores were 16.2 (15.9–16.5), 14.5 (14.1–15.0) and 14.6 (14.3–14.9) among subjects with acute, subacute and chronic cough, respectively ($p<0.001$). The prevalence of depressive symptoms was 5.4%, 7.5% and 4.8%, respectively, and 5.0% among subjects without current cough ($p=0.50$). The respective proportions of subjects with at least one doctor's visit due to cough during the previous year were 27.6%, 44.8%, 49.6% and 16.1% ($p<0.001$). The respective proportions of subjects with at least one sick leave day due to cough during the previous year were 28.9%, 39.1%, 36.3% and 15.3% ($p<0.001$). Any current cough was associated with an increased the risk of several (three or more) yearly doctor's visit due to any reason (adjusted odds ratio (aOR) 1.49, 95% CI 1.27–1.76) and several (seven or more) yearly sick leave days due to any reason (aOR 1.43, 95% CI 1.22–1.68).

Cough decreases quality of life, and has a large socioeconomic impact by increasing doctor's visits and sick leave days. However, it is not associated with depressive symptoms. The impacts of subacute and chronic cough are comparable, and larger than those of acute cough.

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Cough has a deleterious effect on the quality of life. Within 1 year, it increases the probability of frequent doctor's visits by 49% and the probability of several sick leave days by 43%, thus causing a significant socioeconomic burden. http://ow.ly/lXKn30mhKBK

Cite this article as: Koskela HO, Lätti AM, Pekkanen J. The impacts of cough: a cross-sectional study in a Finnish adult employee population. *ERJ Open Res* 2018; 4: 00113-2018 [https://doi.org/10.1183/23120541.00113-2018].

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every breath counts

This article has supplementary material available from openres.ersjournals.com

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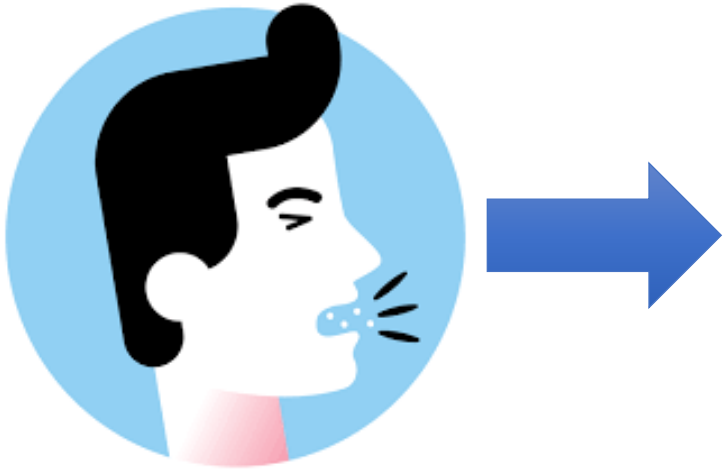
So what? It's only a cough…



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- **Associated physical symptoms** (fatigue, chest pain (rib #), incontinence, vomiting, headache)
- **Psychomorbidity** (anxiety, depression, anger, distress)
- **Social** aspects-altered/spoiled social identity. Social effort[3].)
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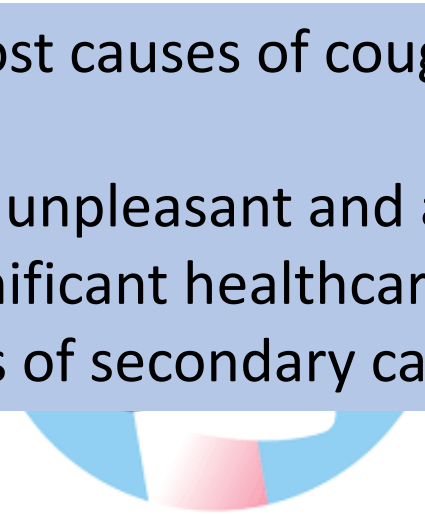
So what? It's only a cough…

- **Reduced quality of life**[1,2].
- **Unpleasant (UTC)**

Whilst most causes of cough are not life threatening;

a) it is unpleasant and associated with significant morbidity for the patient.
b) Significant healthcare costs.
c) Lots of secondary care referrals (at least 10%-sole focus)-you need to do this well.



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How does the cough reflex work?

What is a cough?

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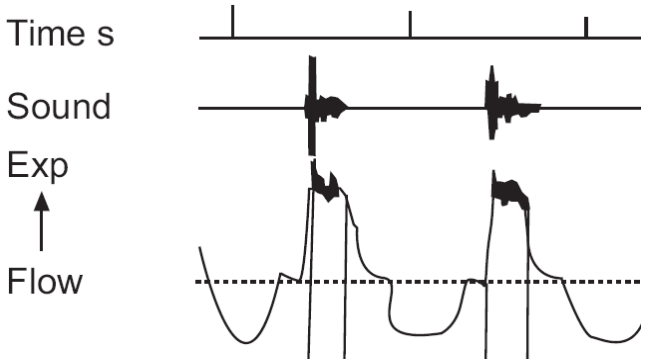
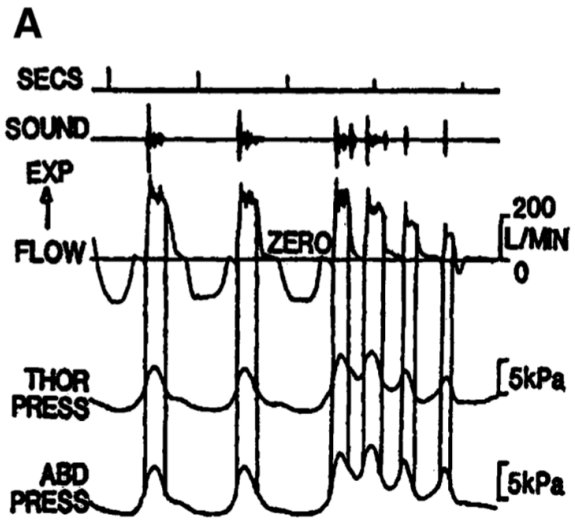
- 4 phase defensive reflex (inspiration, compressive (0.2 s), expulsive and restorative phases). May be voluntary.
- Expiratory reflex-no inspiratory phase





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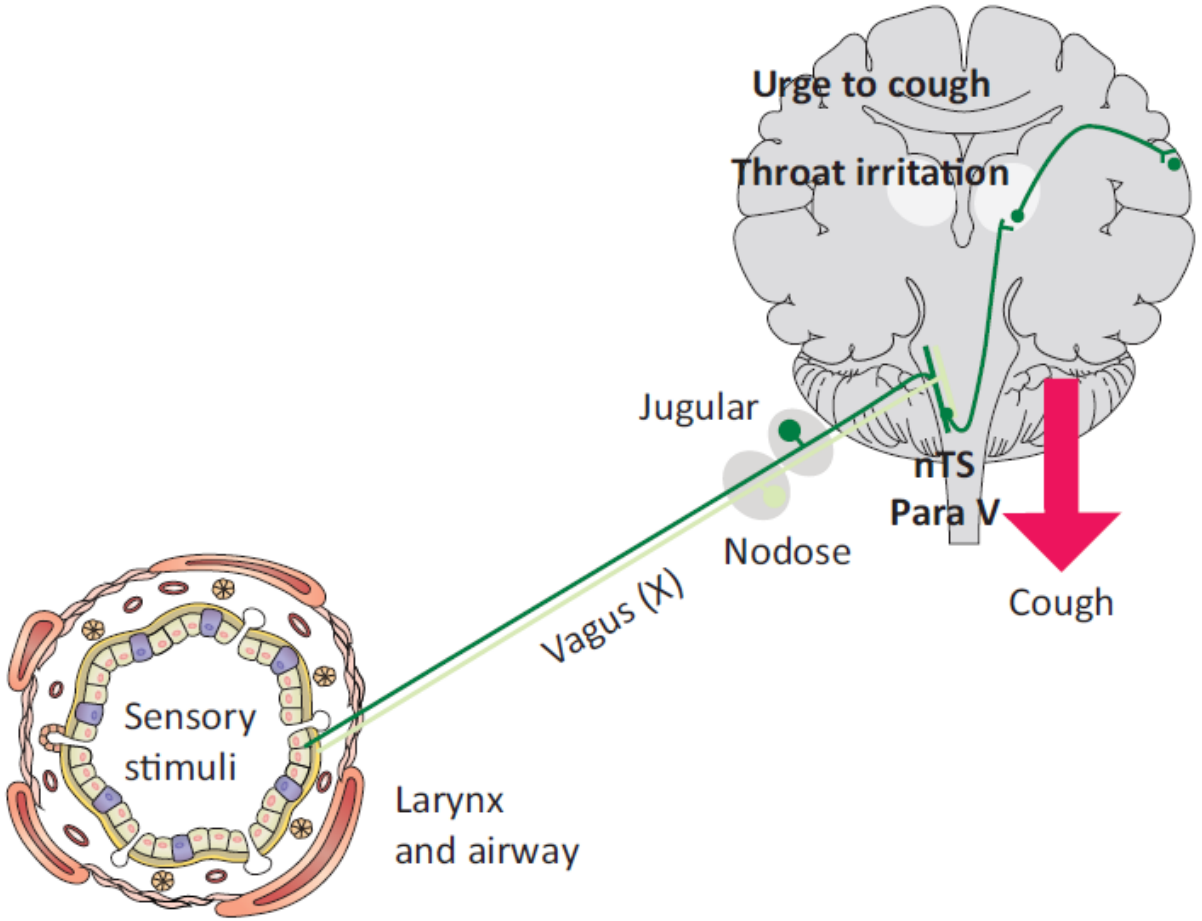

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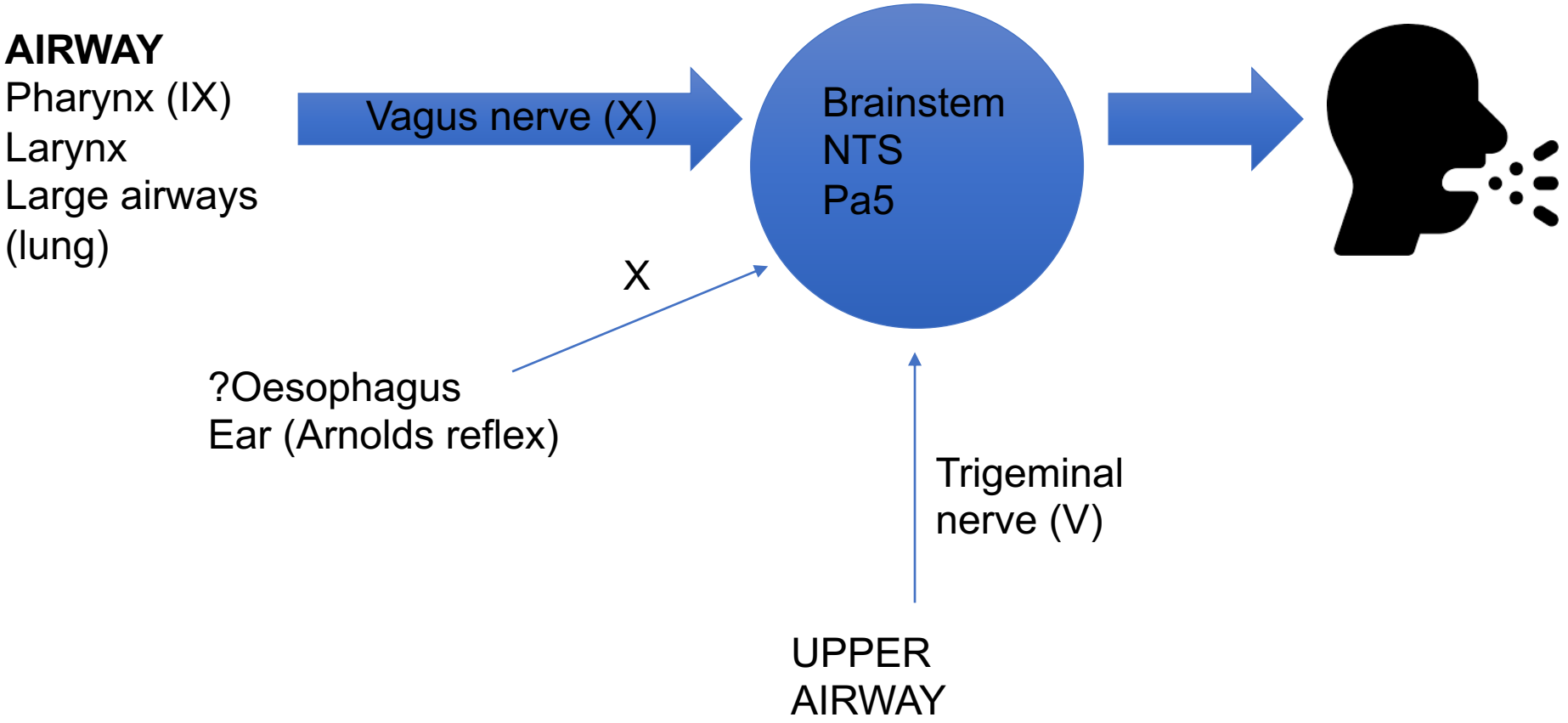
Satia et al Clinical Medicine 2016

Afferent input

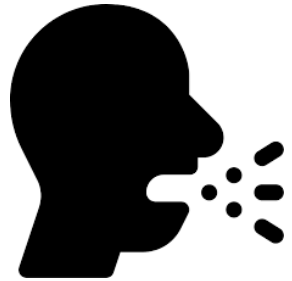


Afferent input

C fibres (slow, chemically sensitive)
TRPA1 (irritants)
TRPV1 (capsaicin)
ASIC (H+)
NK1 (Sub P)
P2X (ATP)
5HT3

AIRWAY → Vagus nerve (X) → Brainstem NTS Pa5
NK 1 (Sub P)
NMDA
Glutamate

Aδ Fibres



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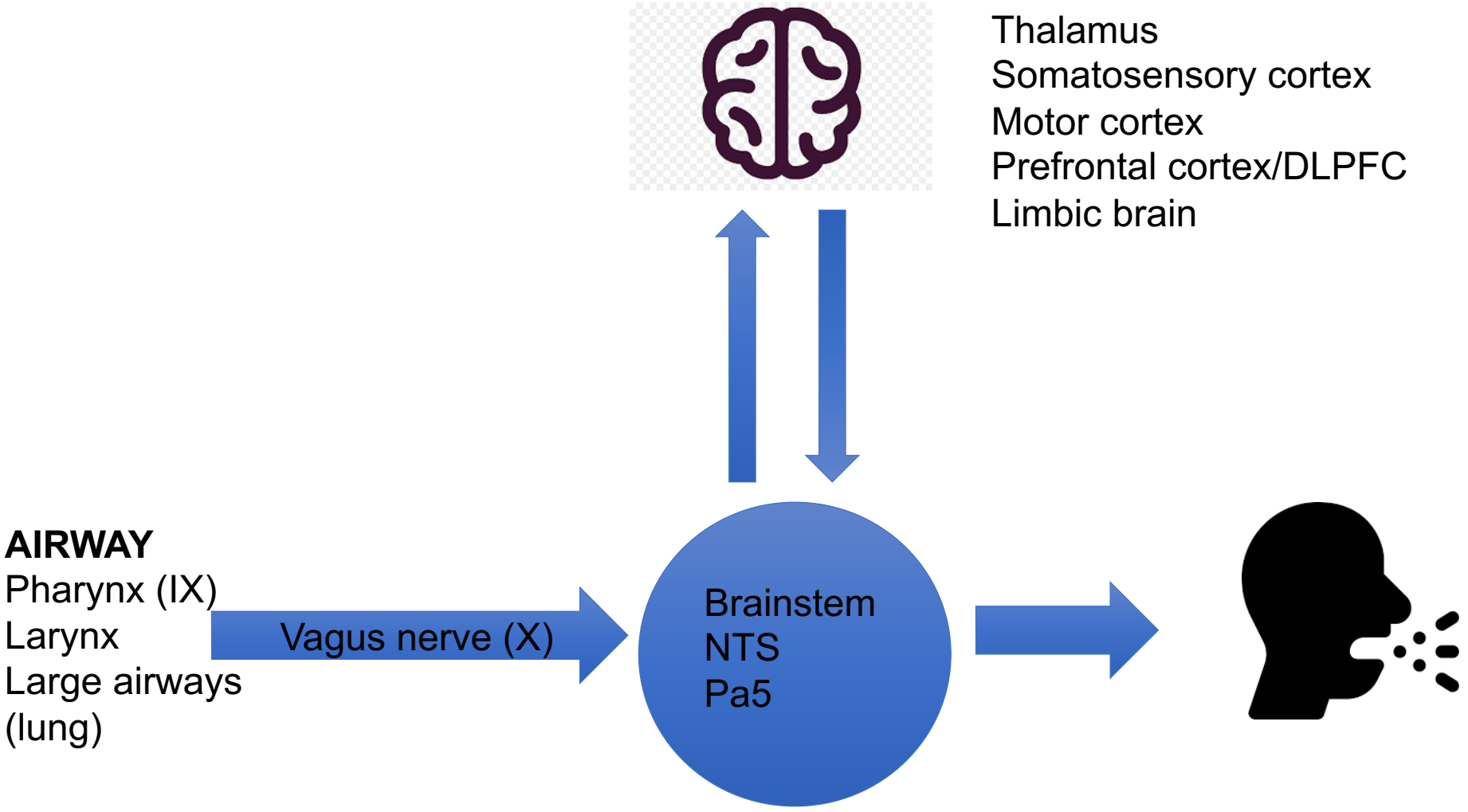
AIRWAY → Vagus nerve (X) → Brainstem
NTS
Pa5
NK 1 (Sub P)
NMDA
Glutamate → 

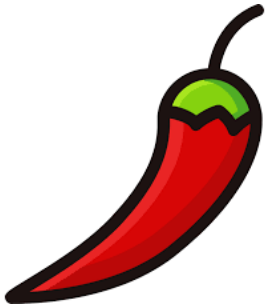


Aδ Fibres (fast, mechanically sensitive)
'cough receptors'
Punctate mechanical stimuli
ASIC
Stretch

Higher cerebral control –not just a brainstem reflex

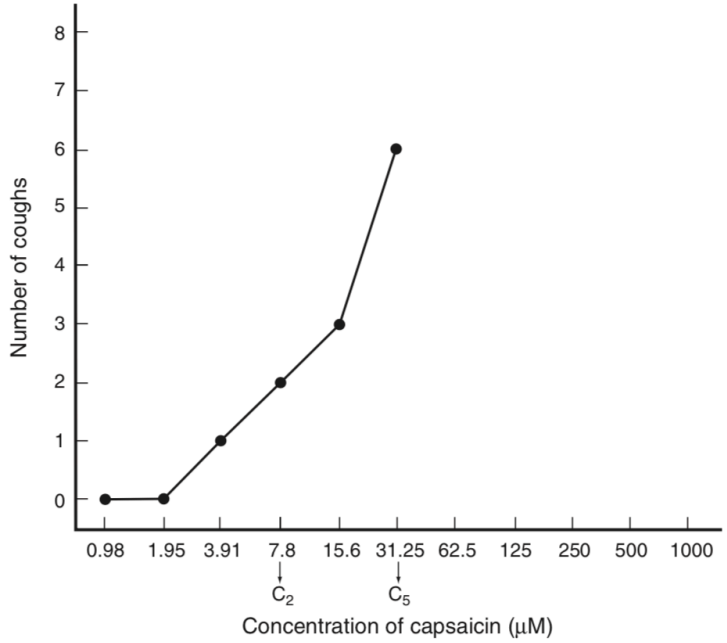


Urge to cough (UTC)- a key respiratory sensation



TRPV1 (Vagal C fibres)

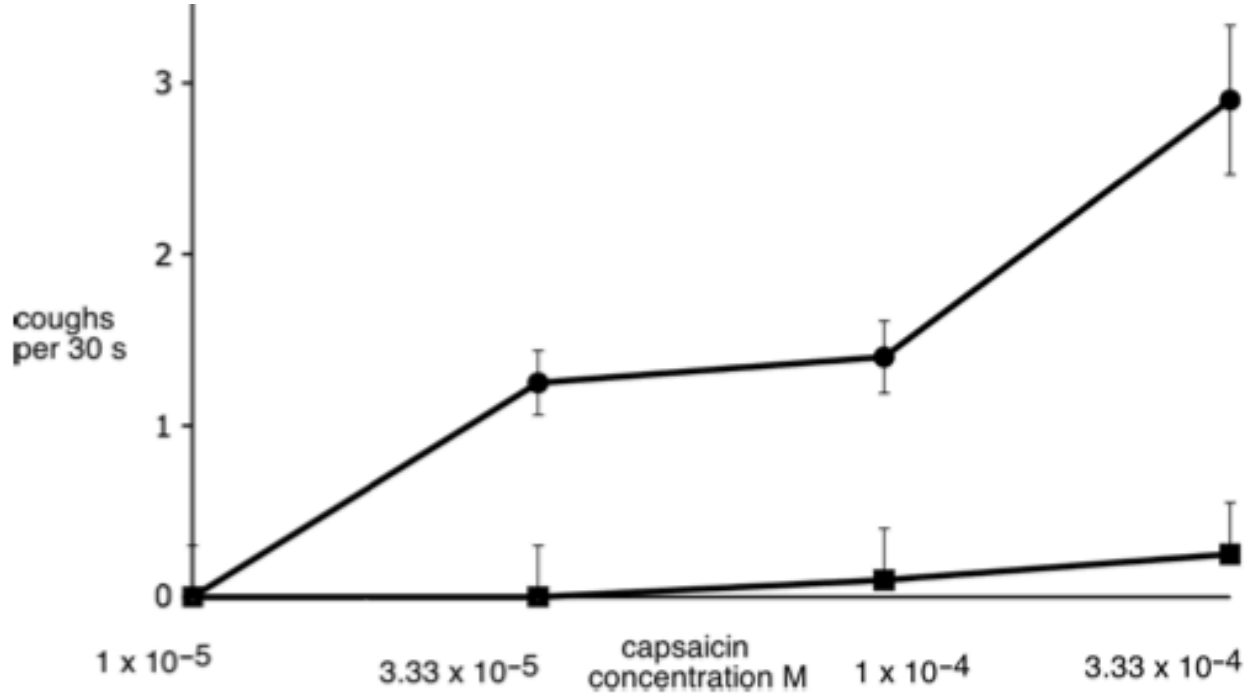
<u>Urge to Cough (UTC)</u>
Irritation/tickle/something stuck/hair in throat.
Neck-Chest



1. Davenport et al Pulm pharm ther 2007
2. Dicpinigiaitis et al Respirology 2012
3. Widdicombe Resp Physiol Neurobiol 2009
4. Woodcock et al Brit Med Bull 2010
5. Eccles Hand Exp Pharm 2009

Volitional control of cough

TRPV1 (Vagal C fibres) → Cough



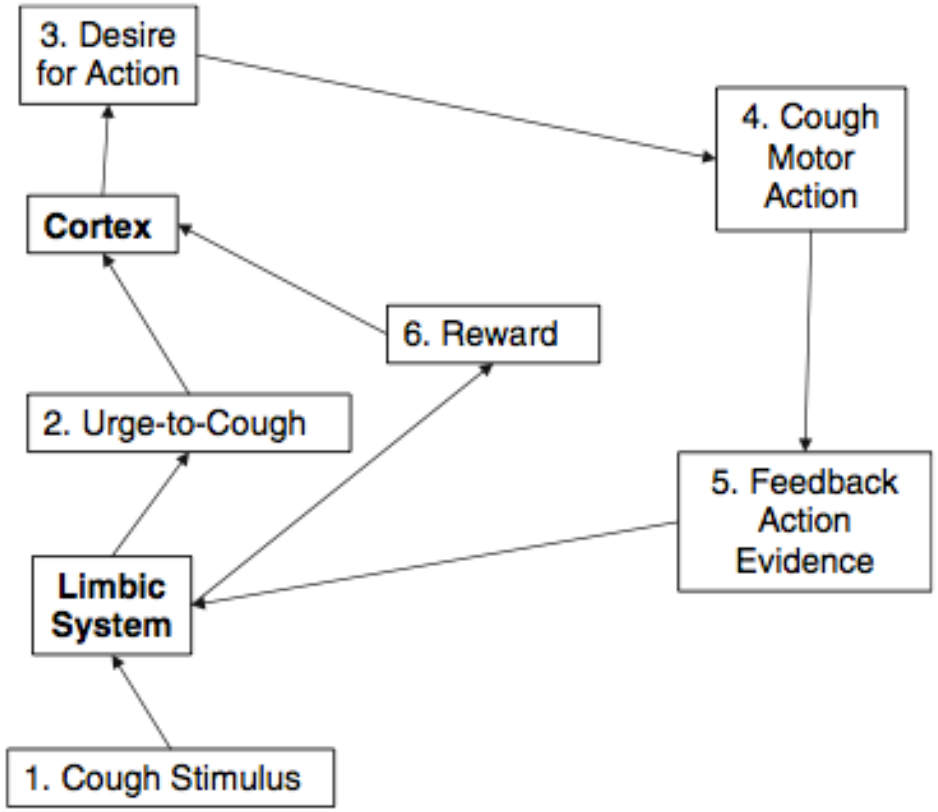
No suppression
'Allow yourself to cough if you need to..'

'Try not to cough'→ voluntary cough suppression

1. Hutchings et al Resp Med 1993
2. Hegland et al J Appl Physiol 2012

Urge to cough- a key respiratory sensation

- Interoception
- 'biological urge that is induced by stimuli that motivate the subject to protect the airway by coughing' . Often difficult to locate/describe[1].
- Affective component (perceived as unpleasant) → action that causes sensation of relief. 'Homeostatic emotion'[2].
- If coughing behaviour satisfies the urge then the UTC will be relieved, if not then the urge continues[3].
- Survival, social function?
- Often described by patients with cough[4].



1. Mazzone et al cough 2013
2. Van den Bergh Lung 2012
3. Davenport Hand Exp Pharm 2009
4. La Crette et al Thorax 2012

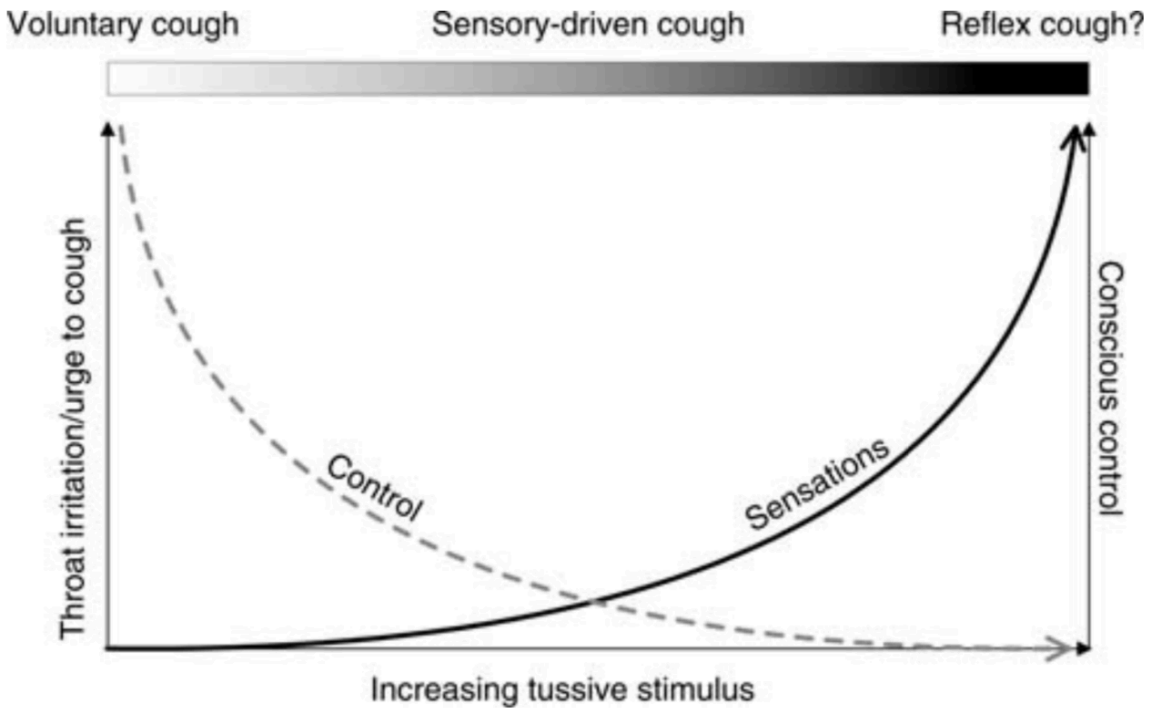


Fig. 1 Suggested relationships between voluntary coughing, sensory-driven cough and reflex cough.

Woodcock et al Brit Med Bull 2010

Higher brain control of cough-fMRI studies

Sensory discrimination (primary somatosensory cortex, anterior insula)

Spatial discrimination (posterior parietal cortex, DLPFC)

Separate areas decode stimulus intensity (anterior insula) and perception (primary SSCtx)

Cognitive component (orbitofrontal cortex, cingulate cortex, limbic system)

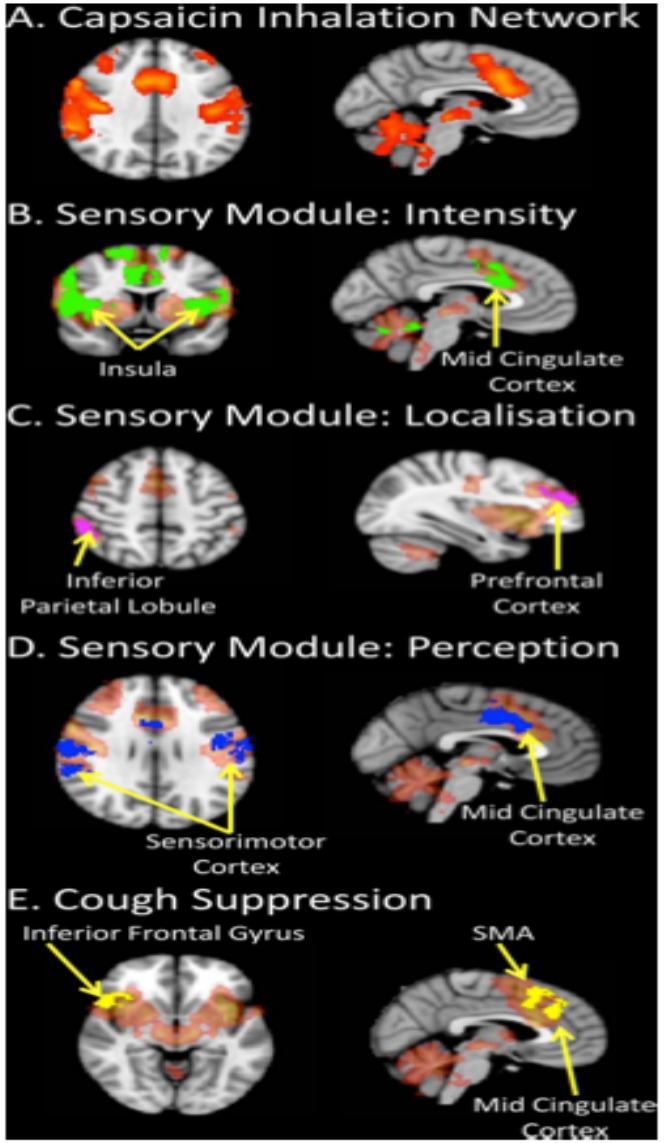
Motor

Voluntary cough (sensorimotor cortex, supplementary motor area, cerebellum)

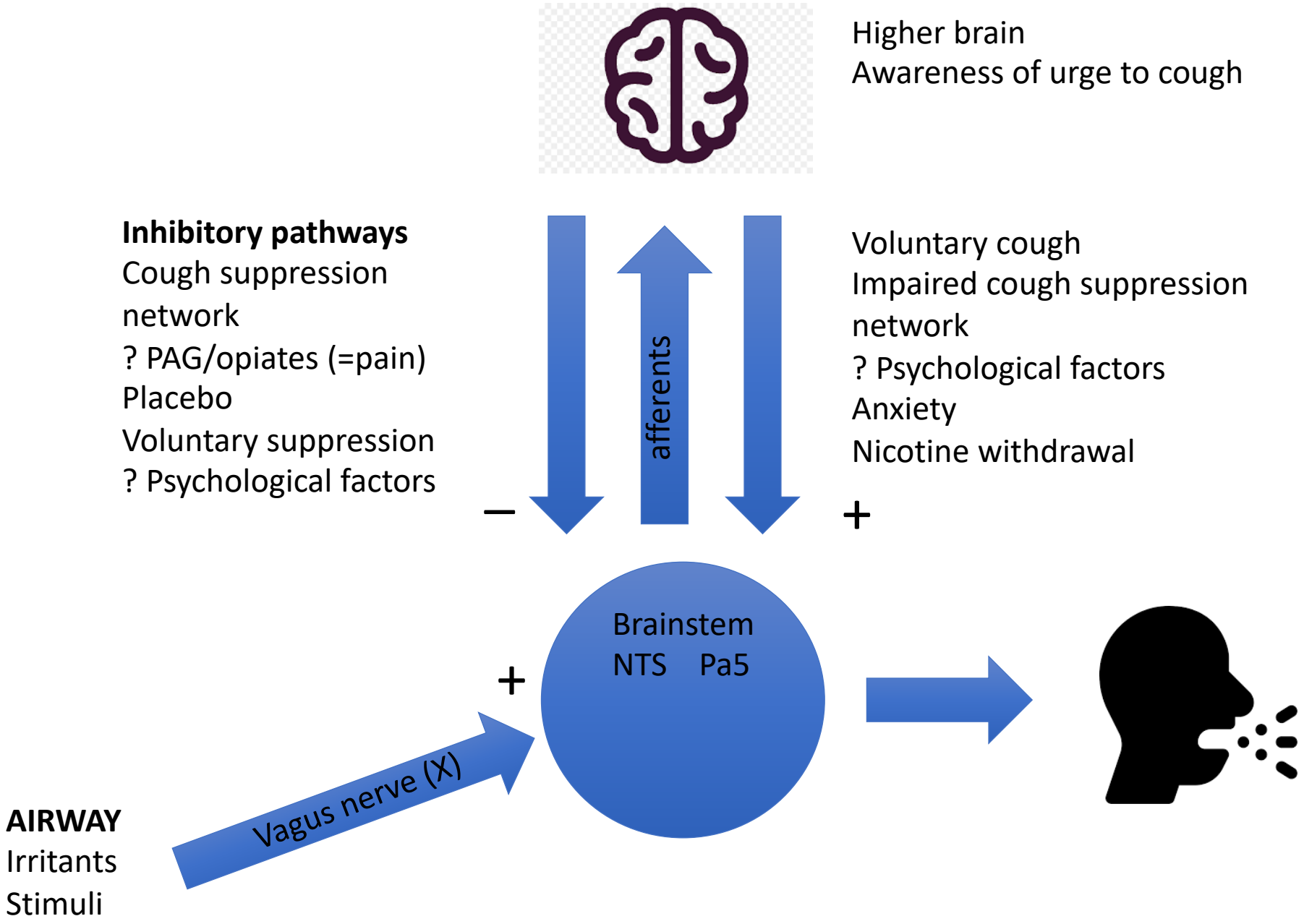
Reflex cough (post. Insula, post cingulate ctx, medulla)

Voluntary cough (motor cortex)

Suppression (anterior insula, suppl motor area, motor cingulate ctx, right inf frontal gyrus)



1. Mazzone et al Cough 2013


Higher brain
Awareness of urge to cough
Inhibitory pathways
Cough suppression network
? PAG/opiates (=pain)
Placebo
Voluntary suppression
? Psychological factors
afferents
Voluntary cough
Impaired cough suppression network
? Psychological factors
Anxiety
Nicotine withdrawal
–
+
+
Brainstem
NTS Pa5
Vagus nerve (X)
AIRWAY
Irritants
Stimuli

Chronic cough a sensory neuropathy; cough reflex hypersensitivity

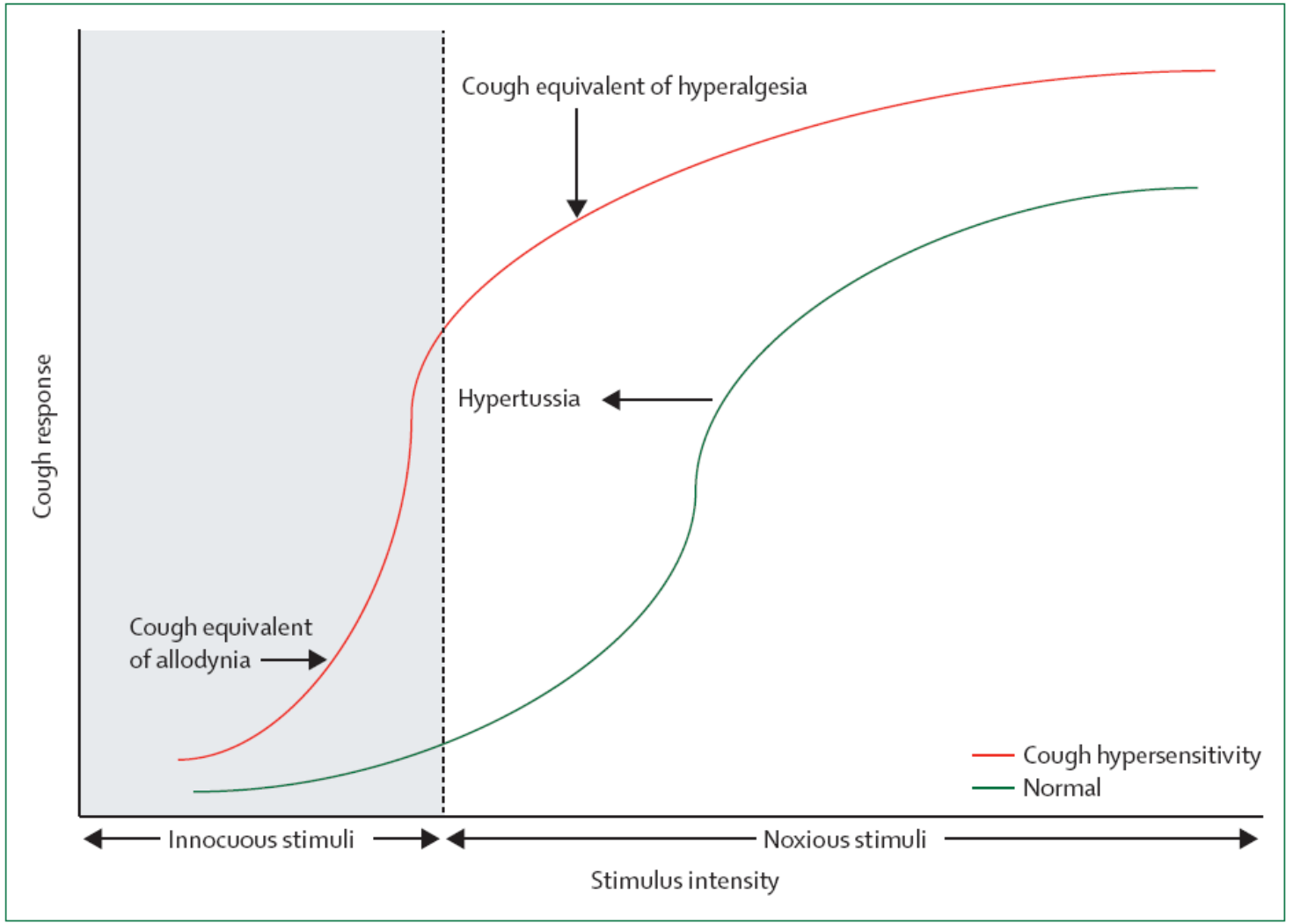


Figure 4: **Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states**

Cough hypersensitivity results in cough in response to innocuous stimuli, as in allodynia.

Chung et al Lancet 2013

Morice at al ERJ 2014

Afferent/peripheral factors

Central factors

‘Treatable traits’

Infection

ACE inhibitors

?reflux

Upper airway disease

Airway inflammation

Underlying disease eg Cancer Fibrosis

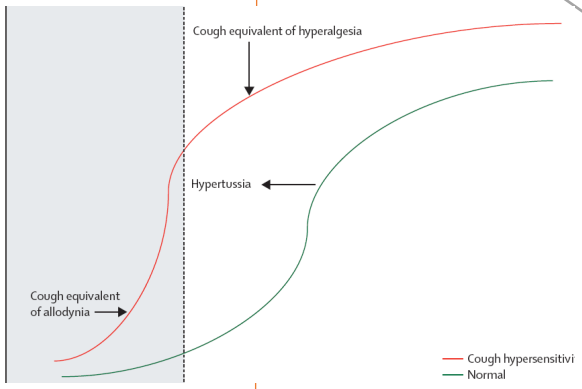
Anxiety

Psychological factors

↓central cough inhibition

Predisposition or acquired hypersensitivity

Pathological cough/ Hypertussia/ Hypersensitivity



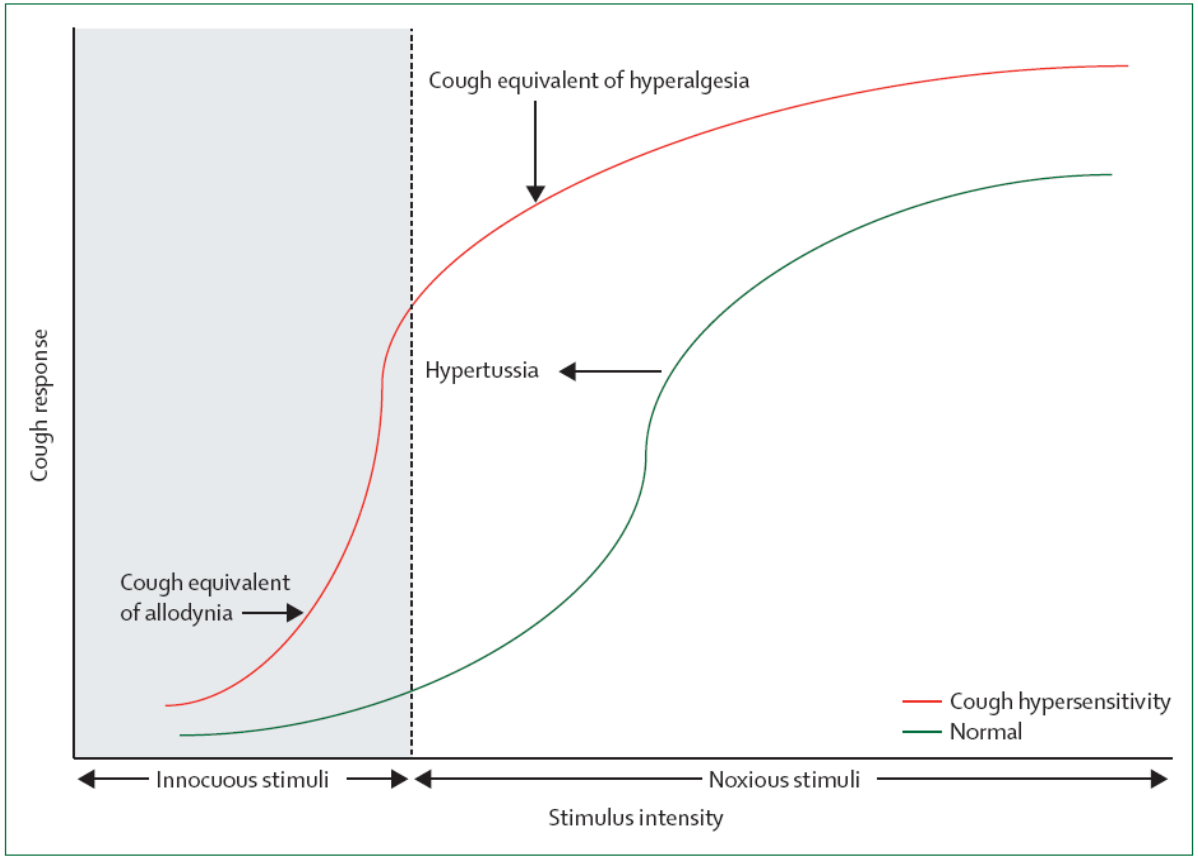
Placebo
Voluntary control

Chronic cough a sensory neuropathy; cough reflex hypersensitivity

- ‘Cough hypersensitivity syndrome’. Dysregulated sensation key mechanism underlying chronic cough, whatever the cause.
- Describes symptom complex suffered by many patients.
- Similarity with neuropathic disorders such as ‘chronic pain’.

Hypertussia (hyperalgesia)-exaggerated response to cough stimuli (smoke/odours)

Allotussia (allodynia)-response to non tussive stimuli (talk, laugh)



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Cough hypersensitivity results in cough in response to innocuous stimuli, as in allodynia.

Chung et al Lancet 2013

Morice at al ERJ 2014

What causes chronic cough and how should we treat it?

Old approach (what I was taught as an SpR…)

- Make sure there is no underlying pathology (Hx, exam, CXR, lung function)
- If nothing found then treat 3 common causes of cough sequentially (regardless of if have specific symptoms);

Asthma (trial ICS)

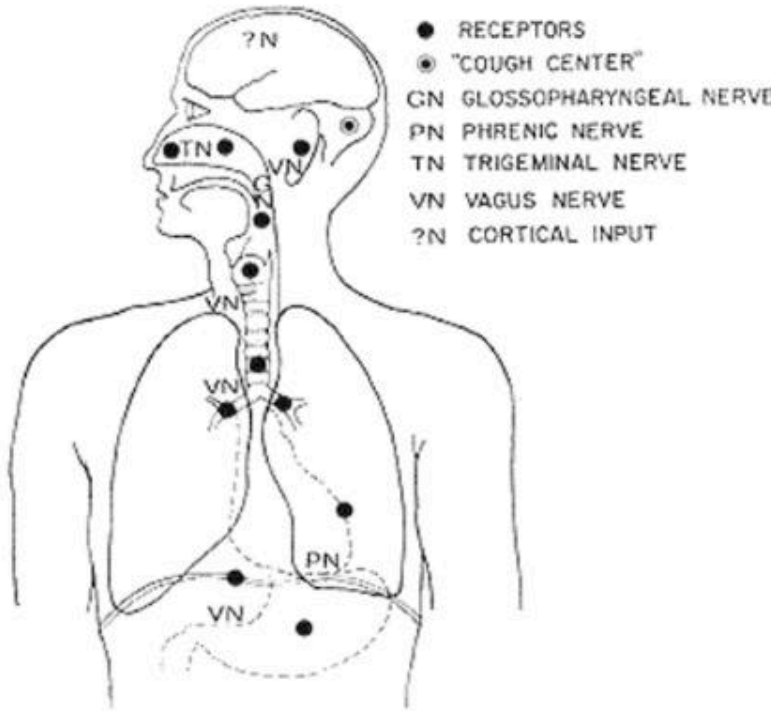
Reflux (trial PPI)

Rhinitis (trial nasal steroids)

- If that fails then patient usually dismissed ‘nothing else we can do….’

The ‘anatomical diagnostic protocol’

- **‘Anatomical diagnostic protocol’**, assumes that cough is most commonly caused by pathology affecting structures innervated by vagal sensory afferents involved in the cough reflex.
- Protocol based investigation and empirical therapy. Assumption regarding aetiology based largely on response to empirical treatment[1].
- Most common causes: ‘post nasal drip syndrome’, asthma, chronic bronchitis and gastroesophageal reflux disease (GERD) in 94%.
- Major advance on what went before it. Massively influential.
- Numerous series claimed high rates of success with empirical trials of specific treatment (up to 98%)[1,2]. Continues to be standard practice for many.



1. Irwin et al JAMA 1977. 2
2. Irwin RS et al Am Rev Resp Dis 1981

	Number (women)	Diagnosis				
		Asthma/CVA/ EB/AC	GORD	PNDS	Idiopathic	Other
USA						
Irwin[54]	102 (59)	24%	21%	41%	1%	CB (5%)
Irwin[55]	49 (27)	43%	10%	47%	0	CB (7%)
Poe[56]	139 (84)	35% (mostly CVA)	5%	26%	12%	CB (7%)
Pratter[57]	45 (28)	31%	11%	87%	0	Overlap of diagnosis with PNDS
Smyrnios[58]	71 (32)	24%	15%	40%	3%	..
Mello[59]	88 (64)	14%	40%	38%	2%	..
French[60]	39 (32)	15%	36%	40%	2%	..
Irwin[61]	24 (13)	21%	33% (rhinitis included)	33% (GORD included)	46%	..
UK						
O'Connell[62]	87 (63)	10%	32%	34%	27%	..
McGarvey[63]	43 (29)	23% (CVA)	19%	21%	19%	..
Brightling[64]	91 (NR)	31% (EB 13%)	8%	24%	7%	..
Birring[65]	236 (NR)	24%	15%	12%	26%	..
Niimi[66]	50 (39)	26%	10%	17%	40%	..
Kastelik[67]	131 (86)	24%	22%	6%	7%	Postviral (8%); bronchiectasis (8%); ILD 8%
Japan						
Fujimura[68]	176 (NR)	66% (36% asthma; 29% atopic cough)	2%	0	12%	Sinobronchial disease in 17%
Shirahata[69]	55 (NR)	42% (CVA)	0	7%	13%	31% improved on non-specific cough therapy
Brazil						

1. Chung KF, Pavord ID Lancet 2008;371:1364-74 (Review)

Causes of cough: Conventional View

ISSUES with this approach

- Based on expert opinion. Low quality evidence (2- and less).
- Not backed up by evidence from good quality trials. No RCT of this approach to managing cough. Placebo/period effects, regression to mean etc..
- Good quality trials of components of the approach contradict assumptions (PPI's!).
- Parsimonious assumption that the response to specific therapy implies causation is flawed (1st generation antihistamines and the UACS).
- Not the experience of many, often patients do not respond to treatment. No cause identified in up to 46% of patients[1].
- Differing views US vs UK.
- May be discrete entity of treatment resistant/ 'idiopathic/refractory cough' with typical phenotype.

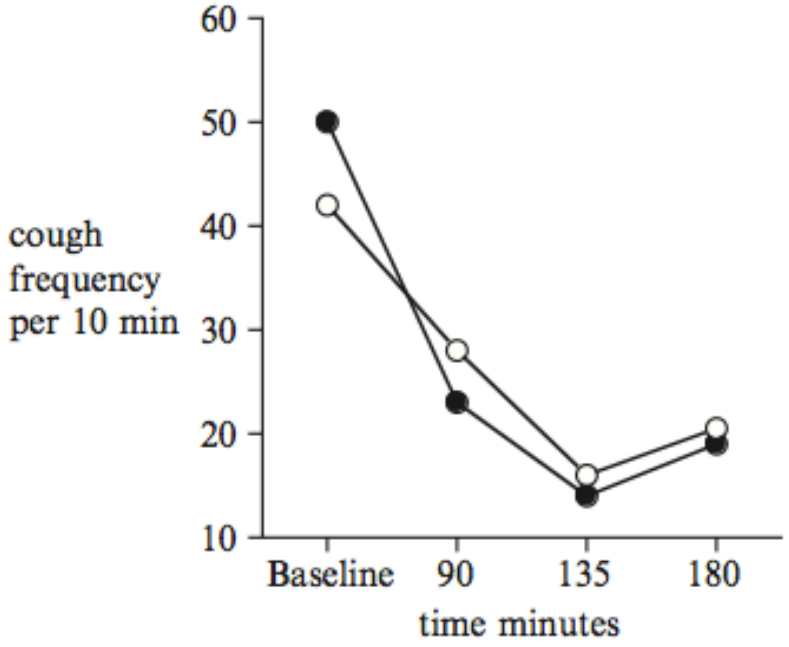


Fig. 2 Median cough frequency (per 10 min) for patients with cough associated with common cold. Immediately after the baseline measurement (0 min) patients were treated with either a single dose of 30 mg dextromethorphan powder in a hard gelatin capsule (*round symbols*, $n = 21$) or a matched placebo capsule containing lactose powder (*square symbols*, $n = 22$). (Lee et al. 2000)

1. Eccles Hand Exp Pharm 2006

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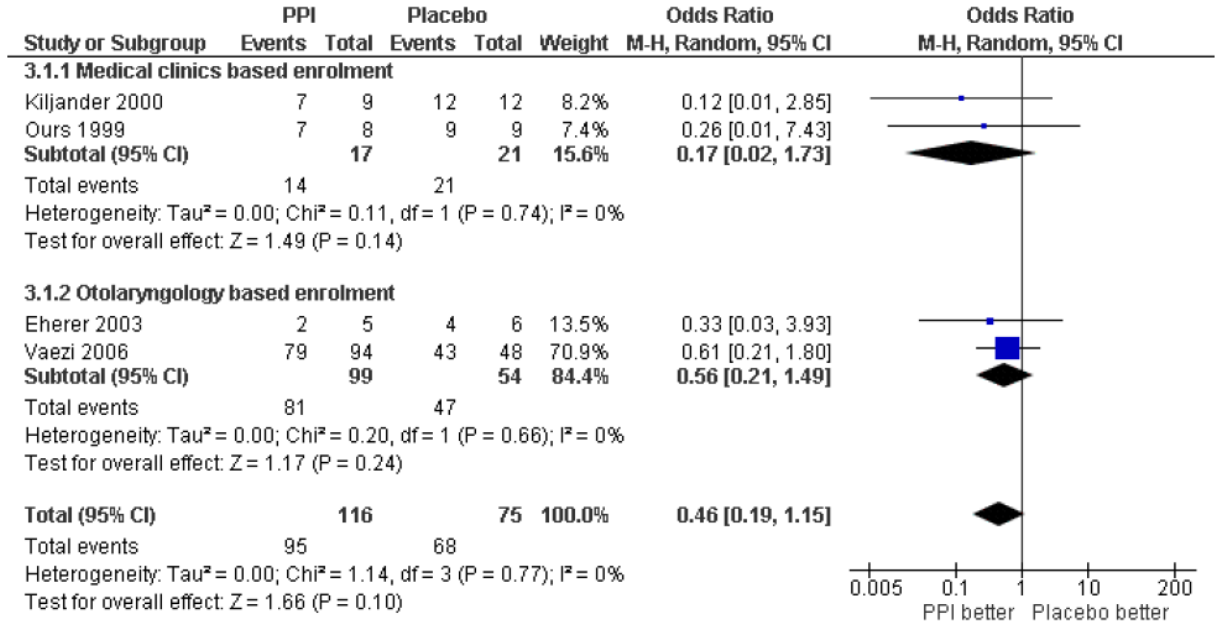
Figure 3. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.1 Clinical failures (still coughing at end of trial or reporting period).



1. Chang et al Cochrane database of systematic reviews 2011;1:CD004823 grade 1+)

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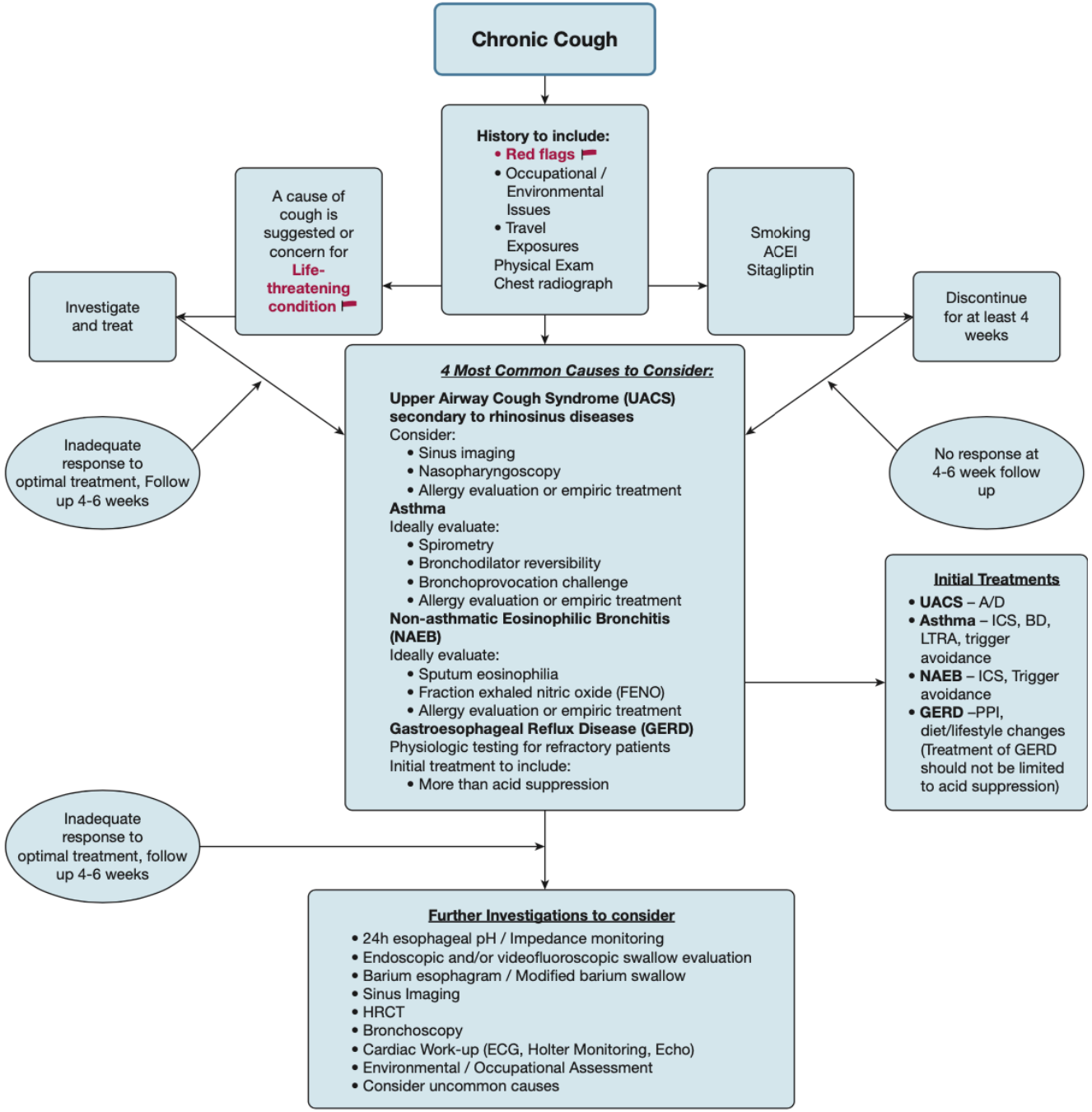

Irwin et al Chest 2018

More frequent

Less frequent

Smoking

Post infectious cough

ACEI use

Respiratory disease eg asthma/COPD/cancer/ILD etc

Rhinitis

Reflux ?

Rare causes eg OSA/earwax/big tonsils

More frequent

Less frequent

Smoking

Post infectious cough

ACEI use

Respiratory disease eg asthma/COPD/cancer/ILD etc

Rhinitis

Reflux ?

Rare causes eg OSA/earwax/big tonsils

Combination of history/exam and basic investigations (CXR/spiro)- identify treatable causes/aggravants.

'Sieving'

Link with cough less controversial

Treat specific 'traits' eg stop smoking/taking ACEI or treat asthma with ICS

Less controversial/better evidence base

Smoking

Post infectious cough

ACEI use

Respiratory disease eg asthma/COPD/cancer/ILD etc

Rhinitis

Reflux ?

Rare causes eg OSA/earwax/big tonsils

Treatment less likely to be successful-not blindly treating regardless of symptoms

Controversial
Weaker evidence base

Less controversial/better evidence base

Smoking

Post infectious cough

ACEI use

Respiratory disease eg asthma/COPD/cancer/ILD etc

Rhinitis

Reflux ?

Rare causes eg OSA/earwax/big tonsils

Cough hypersensitivity

Can be specifically addressed SALT antitussives

Controversial
Weaker evidence base

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task Force Report

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Alyn H. Morice, Eva Millqvist, Kristina Bieksiene, Surinder S. Birring, Peter Dicpinigaitis, Christian Domingo Ribas, Michele Hilton Boon, Ahmad Kantar, Kefang Lai, Lorcan McGarvey, David Rigau, Imran Satia, Jacky Smith, Woo-Jung Song, Thomy Tonia, Jan W. K. van den Berg, Mirjam J. G. van Manen, Angela Zacharasiewicz

Please cite this article as: Morice AH, Millqvist E, Bieksiene K, *et al*. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01136-2019).

CHEST

Classification of Cough as a Symptom in Adults and Management Algorithms

CHEST Guideline and Expert Panel Report

*Richard S. Irwin, MD, Master FCCP; Cynthia L. French, PhD, RN, ANP-BC, FCCP; Anne B. Chang, MBBS, PhD, MPH; Kenneth W. Altman, MD, PhD; on behalf of the CHEST Expert Cough Panel**

BACKGROUND: We performed systematic reviews using the population, intervention, comparison, outcome (PICO) format to answer the following key clinical question: Are the CHEST 2006 classifications of acute, subacute and chronic cough and associated management algorithms in adults that were based on durations of cough useful?

METHODS: We used the CHEST Expert Cough Panel's protocol for the systematic reviews and the American College of Chest Physicians (CHEST) methodological guidelines and Grading of Recommendations Assessment, Development, and Evaluation framework. Data from the systematic reviews in conjunction with patient values and preferences and the clinical context were used to form recommendations or suggestions. Delphi methodology was used to obtain the final grading.

RESULTS: With respect to acute cough (< 3 weeks), only three studies met our criteria for quality assessment, and all had a high risk of bias. As predicted by the 2006 CHEST Cough Guidelines, the most common causes were respiratory infections, most likely of viral cause, followed by exacerbations of underlying diseases such as asthma and COPD and pneumonia. The subjects resided on three continents: North America, Europe, and Asia. With respect to subacute cough (duration, 3-8 weeks), only two studies met our criteria for quality assessment, and both had a high risk of bias. As predicted by the 2006 guidelines, the most common causes were postinfectious cough and exacerbation of underlying diseases such as asthma, COPD, and upper airway cough syndrome (UACS). The subjects resided in countries in Asia. With respect to chronic cough (> 8 weeks), 11 studies met our criteria for quality assessment, and all had a high risk of bias. As predicted by the 2006 guidelines, the most common causes were UACS from rhinosinus conditions, asthma, gastroesophageal reflux disease, nonasthmatic eosinophilic bronchitis, combinations of these four conditions, and, less commonly, a variety of miscellaneous conditions and atopic cough in Asian countries. The subjects resided on four continents: North America, South America, Europe, and Asia.

CONCLUSIONS: Although the quality of evidence was low, the published literature since 2006 suggests that CHEST's 2006 Cough Guidelines and management algorithms for acute, subacute, and chronic cough in adults appeared useful in diagnosing and treating patients with cough around the globe. These same algorithms have been updated to reflect the advances in cough management as of 2017. CHEST 2018; 153(1):196-209

KEY WORDS: cough; evidence-based medicine; guidelines; management algorithms for acute, subacute, and chronic cough in adults

ABBREVIATIONS: AECOPD = acute exacerbation of COPD; CHEST = American College of Chest Physicians; PICO = population, intervention, comparator, outcome; QoL = quality of life; NAM = National Academy of Medicine; UACS = upper airway cough syndrome

AFFILIATIONS: From the UMassMemorial Medical Center (Drs Irwin and French), Worcester, MA; the Menzies School of Health Research and Respiratory Department (Dr Chang), Lady Cilento Children's Hospital, Qld Uni of Technology Queensland, Australia;

Treatable traits: toward precision medicine of chronic airway diseases

Alvar Agusti[1], Elisabeth Bel[2], Mike Thomas[3], Claus Vogelmeier[4], Guy Brusselle[5,6], Stephen Holgate[7], Marc Humbert[8], Paul Jones[9], Peter G. Gibson[10], Jørgen Vestbo[11], Richard Beasley[12] and Ian D. Pavord[13]

Affiliations: [1]Respiratory Institute, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona and CIBER Enfermedades Respiratorias (CIBERES), Spain. [2]Dept of Respiratory Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. [3]Primary Care and Population Sciences, University of Southampton, Southampton, UK. [4]Dept of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-Universität Marburg, and Member of the German Center for Lung Research (DZL), Germany. [5]Dept of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. [6]Depts of Epidemiology and Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. [7]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton General Hospital, Southampton, UK. [8]Université Paris-Sud; Service de Pneumologie, Hôpital Bicêtre (Assistance Publique-Hôpitaux de Paris); INSERM UMR_S 999, Le Kremlin-Bicêtre, France. [9]St George's University of London, London, UK. [10]Dept of Respiratory and Sleep Medicine, John Hunter Hospital, Hunter Medical Research Institute, and Priority Research Centre for Asthma and Respiratory Disease, The University of Newcastle, NSW, Australia. [11]Centre for Respiratory Medicine and Allergy, Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, Manchester, UK. [12]Medical Research Institute of New Zealand, Wellington, New Zealand. [13]Respiratory Medicine Unit, NDM Research Building, Nuffield Dept of Medicine, University of Oxford, Oxford, UK.

Correspondence: Alvar Agusti, Respiratory Institute, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain. E-mail: Alvar.Agusti@clinic.ub.es

ABSTRACT Asthma and chronic obstructive pulmonary disease (COPD) are two prevalent chronic airway diseases that have a high personal and social impact. They likely represent a continuum of different diseases that may share biological mechanisms (*i.e.* endotypes), and present similar clinical, functional, imaging and/or biological features that can be observed (*i.e.* phenotypes) which require individualised treatment. Precision medicine is defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations". In this Perspective, we propose a precision medicine strategy for chronic airway diseases in general, and asthma and COPD in particular.

@ERSpublications
A discussion of the concept of "treatable traits" as a way towards precision medicine of chronic airway diseases http://ow.ly/UbJAm

A rational approach to chronic cough (or as rational as possible given the evidence base…)

1. Is there a problem?
2. Potential removable aggravating factors (ACEI/smoke) /underlying structural lung disease (COPD, asthma, ILD etc.)
3. Evidence of active eosinophilic airway disease?
4. Any treatable aggravating factor (GERD etc, rhinitis etc)?
5. Am I doing all I can to help

Pavord and Chung Lancet 2008

All patients coming to my clinic get

- **Detailed Hx/exam**

- **Spirometry**
- **FENO**
- **CXR**
- **Routine bloods** (plus extras if needed)
- (LCQ) or VAS

They may also get

- Methacholine/mannitol
- CT/HRCT
- Bronchoscopy

Initial assessment

The history, examination, and investigations for patients with chronic cough are performed to exclude treatable traits of the disease for which directed therapy can be offered. The guideline panel placed higher value on control of any on-going pathology such as reflux or airway eosinophilia before currently available neuro-modulatory treatments are considered. A detailed history and examination should be directed to exclude malignancy, infection, foreign body inhalation or the use of an angiotensin converting enzyme (ACE) inhibitor. The impact of cough should be assessed either by recording simple measures such a cough score out of 10 or VAS or by more detailed, validated measures of cough quality of life (LCQ or CQLQ). Validated questionnaires may help to detect features of airway reflux (HARQ and RSI) and airway hypersensitivity[84].

Initial evaluation should include spirometry and a recent chest x-ray (CXR) (Good Practice Statement).

ERS guideline 2019

All patients coming to my clinic get

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Not true!

Initial evaluation should include spirometry and a recent chest x-ray (CXR) (Good Practice Statement).

ERS guideline 2019

1) Is there a problem?

- Why has patient come, is the cough a problem or concern regarding potential causes.
- Cancer is often a big concern.
- Low frequency of serious pulmonary diagnoses in patients with dry cough and normal basic investigations (spirometry, CXR, examination)[1].
- Reassurance may be all that is required.

1. Pavord and Chung Lancet 2008

2) Aggravating factors?

- **Infection**-cough reflex sensitivity enhanced post viral infection.
- Smoke (active/passive), cough is reduced to normal/near normal in ex smokers. Stop smoking.
- ACEI. Discontinue in all patients.
- Active structural respiratory disease (COPD, asthma, IPF, CCF etc..)

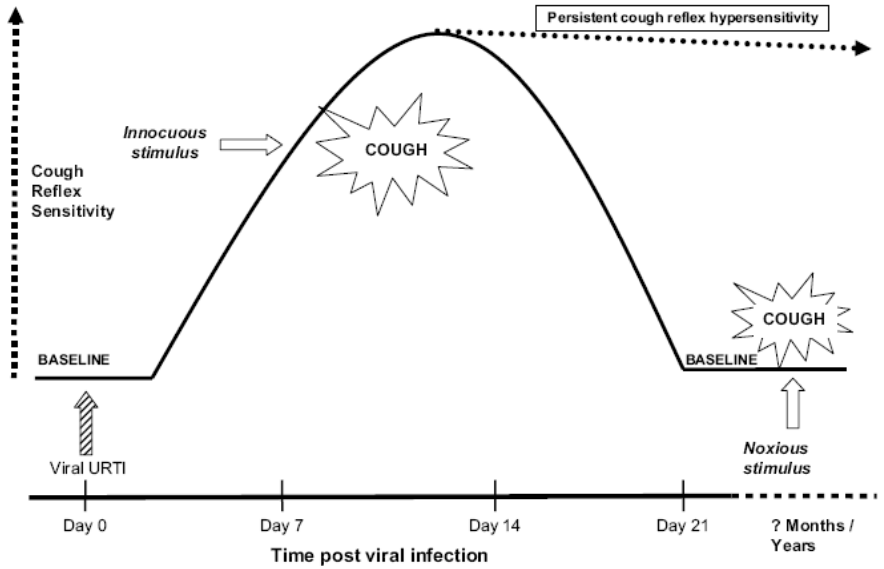
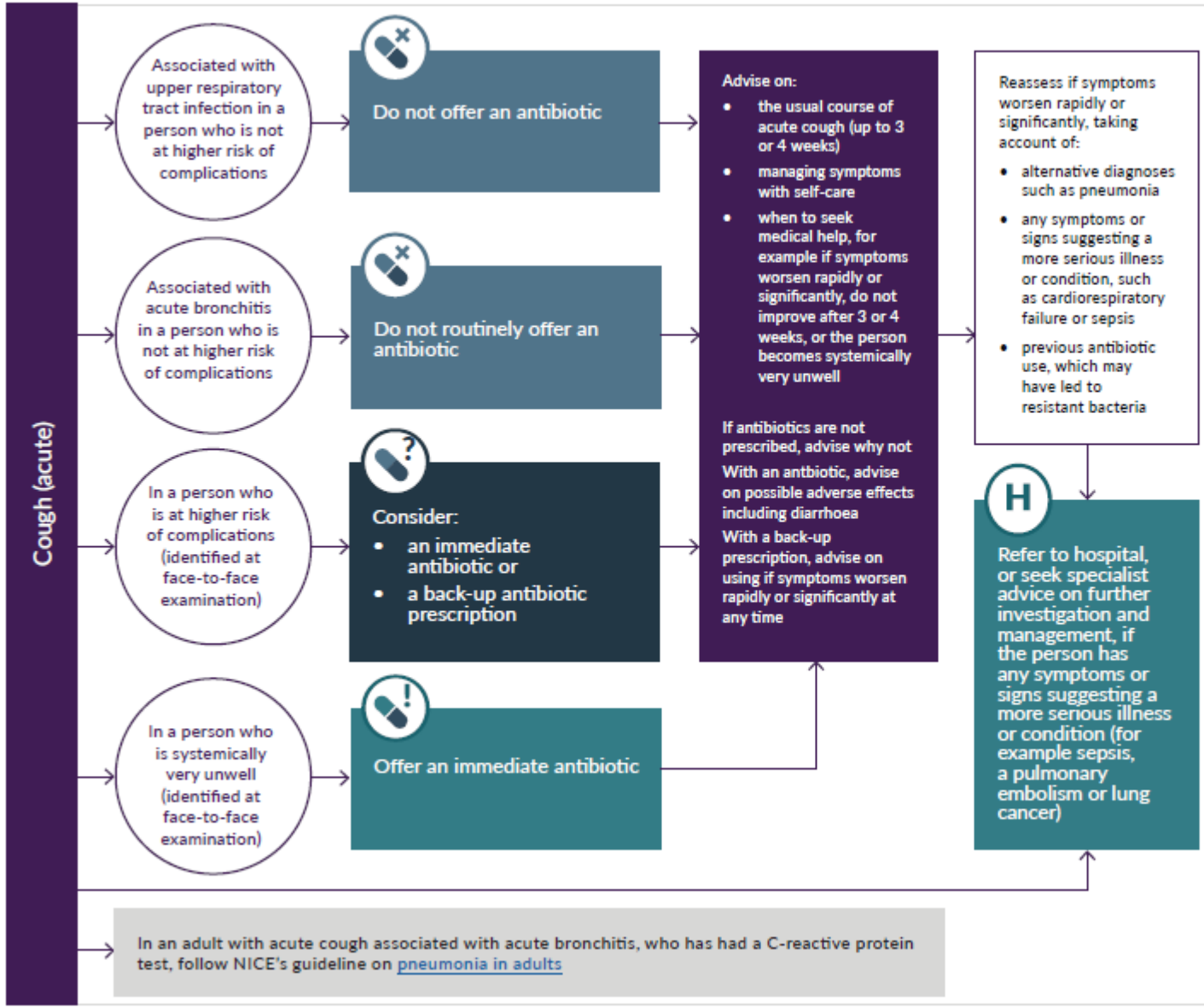


Fig. 1. Schematic of proposed changes in cough reflex sensitivity following viral upper respiratory tract infection. Following a viral infection, the cough reflex becomes hyperreactive and remains in this activated state for a variable period of time (two-three weeks) during which cough may be provoked by innocuous stimuli such as exposure to scents, aerosols and changes in air temperature. In the majority of subjects the hyperreactivity diminishes and the cough reflex responsiveness returns to its baseline state. However, in some circumstances this hypersensitized state persists long after the initial triggering event leading to a chronic cough state.

Cough (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

DRAFT August 2018



Self-care

Be aware that limited evidence suggests that the following have some benefit in relieving cough symptoms:

- honey (in people over 1 year)
- pelargonium (herbal remedy)
- cough medicines containing the expectorant guaifenesin (in people over 12 years)
- cough medicines containing the antitussive dextromethorphan (in people over 12 years and if the cough is not persistent, such as in asthma, or accompanied by excessive secretions)

Background

- Acute coughs are usually self-limiting but can last up to 3 to 4 weeks
- Usually caused by a viral upper respiratory tract infection, such as a cold or flu
- Also caused by acute bronchitis, which is usually viral but can be bacterial
- Antibiotics make little difference to how long a cough lasts

People at higher risk of complications:

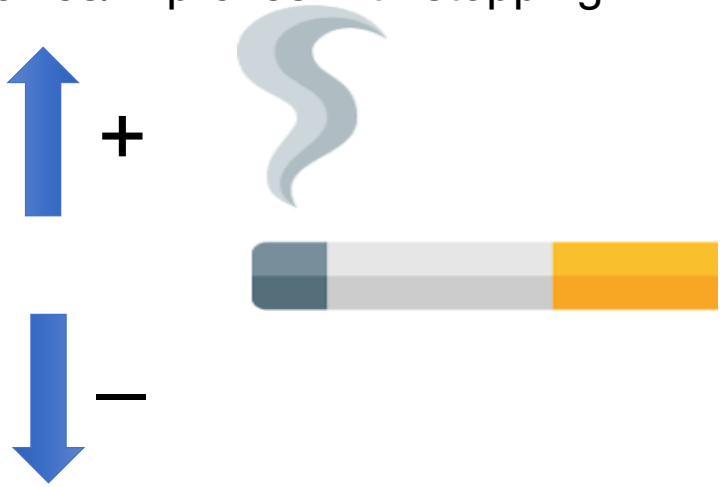
- have a pre-existing comorbidity
- are young children who were born prematurely
- are older than 65 years with 2 or more of the following, or older than 80 years with 1 or more of the following:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure
  - current use of oral corticosteroids

NICE uses 'offer' when there is more certainty of benefit and 'consider' when evidence of benefit is less clear.

2) Aggravating factors?

- Infection-cough reflex sensitivity enhanced post viral infection.
- **Smoke** (active/passive), cough is reduced to normal/near normal in ex smokers. Stop smoking.
- ACEI. Discontinue in all patients.
- Active structural respiratory disease (COPD, asthma, IPF, CCF etc..)

Smokers cough (chronic bronchitis)
Resolves/improves with stopping.



↓Cough reflex sensitivity
Voluntary inhibition of cough

Nicotine inhibits the cough reflex

Cough worsens with stopping.

Nicotine suppresses the cough reflex

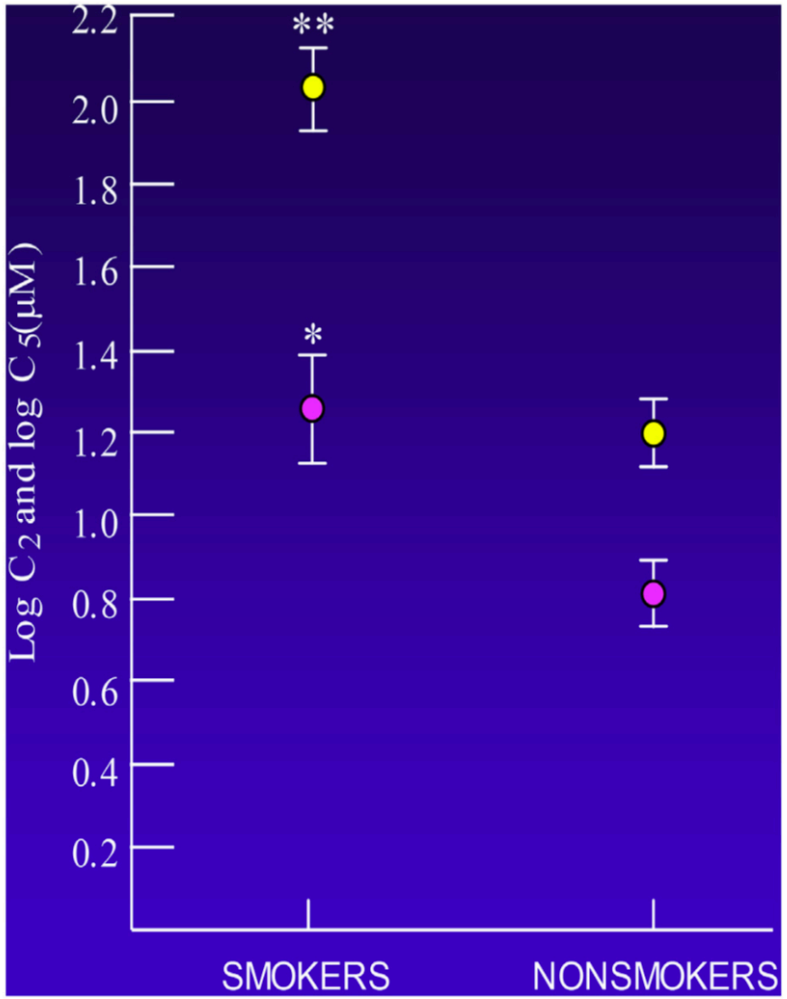


Fig. 1. Capsaicin cough challenge data in smokers and nonsmokers. Open circles represent mean log C_5; solid circles represent mean log C_2. Error bars represent ±SEM. *p = 0.004; **p < 0.000001. C_5 and C_2 represent the concentration (μM) of capsaicin inducing ≥5 and ≥ 2 coughs, respectively (from ref. [10], with permission).

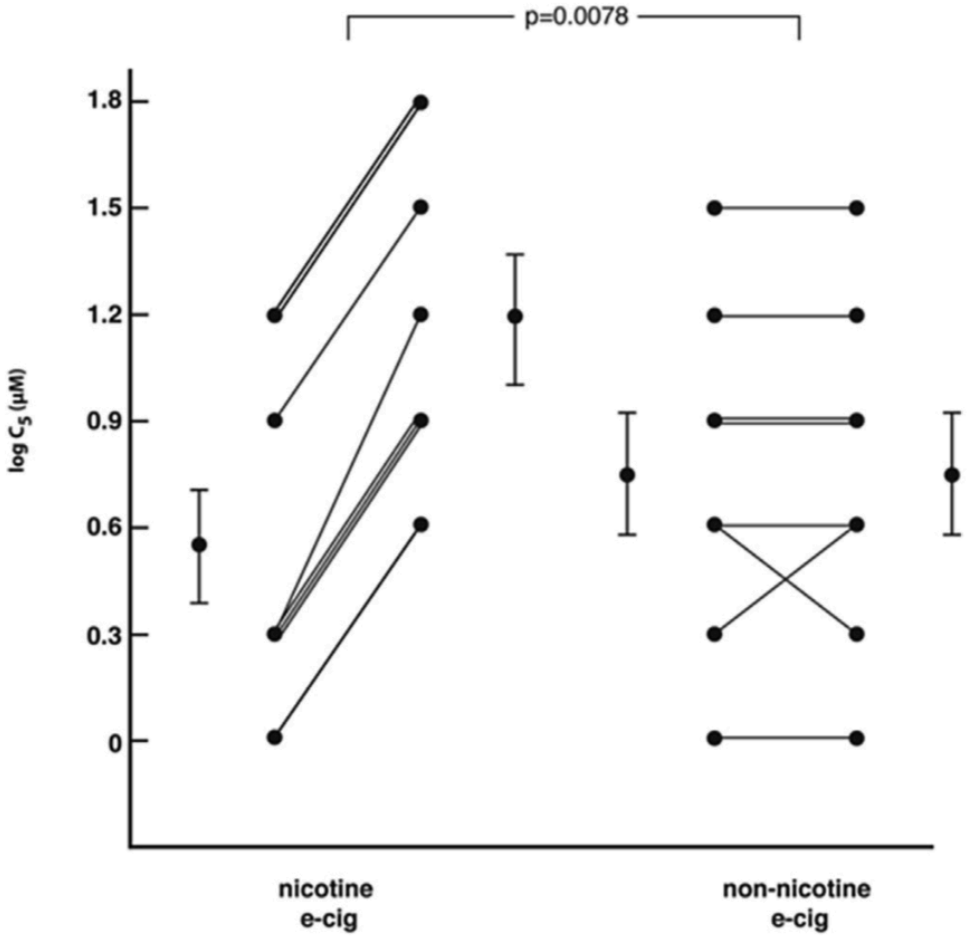


Fig. 4. Comparison of the effect of nicotine-containing and non-nicotine-containing e-cig exposure on cough reflex sensitivity (C_5) in a subgroup of 8 subjects who had demonstrated the largest increments in C_5 (greatest degree of inhibition of cough reflex sensitivity) after nicotine-containing e-cig use. The non-nicotine-containing e-cig exposure did not affect cough reflex sensitivity as did the nicotine-containing product (p = 0.0078 for difference in change in C_5) (from ref. [16] with permission).

Dicpinigiaitis Pulm pharm ther 2017

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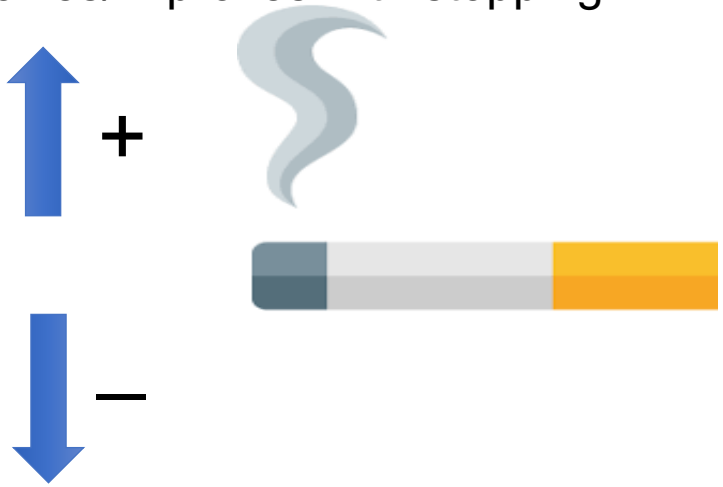

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Voluntary inhibition of cough

Nicotine inhibits the cough reflex

Cough worsens with stopping.-**NRT**

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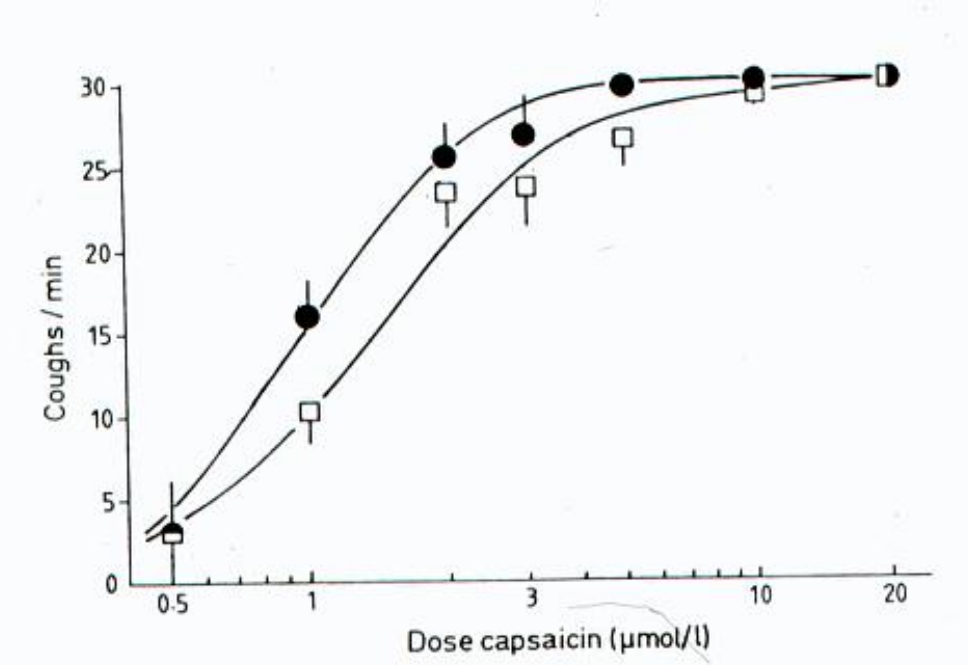

Morice AM et al
Lancet 1987;1116

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Specific disease needs specific treatment.

Low incidence serious disease in non smokers if normal examination/CXR/spirometry.

Worries re cancer-common symptom in lung cancer and CXR may be normal.

Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombo-cytosis	Abnormal spirometry	Haemoptysis	
0.40 0.3, 0.5	**0.43** 0.3, 0.6	**0.66** 0.5, 0.8	**0.82** 0.6, 1.1	**1.1** 0.8, 1.6	**0.87** 0.6, 1.3	**1.6** 0.8, 3.1	**1.6** 0.9, 2.9	**2.4** 1.4, 4.1	PPV as a single symptom
0.58 0.4, 0.8	**0.63** 0.5, 0.9	**0.79** 0.6, 1.0	**0.76** 0.6, 1.0	**1.8** 1.1, 2.9	**1.6** 0.9, 2.7	**2.0** 1.1, 3.5	**1.2** 0.6, 2.6	**2.0** 1.1, 3.5	Cough
	0.57 0.4, 0.9	**0.89** 0.6, 0.3	**0.84** 0.5, 1.3	**1.0** 0.6, 1.7	**1.2** 0.7, 2.1	**1.8**	**4.0**	**3.3**	Fatigue
		0.88	**1.2** 0.9, 1.8	**2.0** 1.2, 3.8	**2.0** 1.2, 3.8	**2.0**	**2.3**	**4.9**	Dyspnoea
			0.95 0.7, 1.4	**1.8** 1.0, 3.4	**1.8** 0.9, 3.9	**2.0**	**1.4**	**5.0**	Chest pain
				1.2 0.7, 2.3	**2.3** 1.2, 4.4	**6.1**	**1.5**	**9.2**	Loss of weight
					1.7	**0.9**	**2.7**	**>10**	Loss of appetite
							3.6	**>10**	Thrombocytosis
								>10	Abnormal spirometry
								17	Haemoptysis

Figure 2 Positive predictive values (PPVs) for lung cancer for individual risk markers and for pairs of risk markers in combination (against a background risk of 0.18%). Notes: (1) The bold figure in each cell is the PPV when both features are present and the two smaller figures represent the 95% confidence intervals for the PPV. These have not been calculated when any cell in the 2×2 table was below 10 (invariably this was because too few controls had both features). For three pairs of symptoms, no controls had the combination; while strictly speaking undefined, these PPVs must logically be very high and so they have been set as >10%. (2) The yellow shading is for pairs of symptoms with a PPV over 1%, the amber shading is when the PPV is above 2%, and the red shading is for PPVs above 5%. (3) The cells along the diagonal relate to the PPV when the same feature has been reported twice. Thus, the cough/cough intersect is the PPV for lung cancer when a patient has attended twice with cough. For a third presentation with cough the PPV was 0.77% (95% CI 0.54 to 1.1).

3) Eosinophilic airway disease?

- Around a quarter of patients
- Asthma/cough variant asthma/eosinophilic bronchitis.
- Spirometry (may be normal)
- May have serum eosinophilia (>0.3) and elevated F_ENO-low sensitivity/specificity.
- If no evidence of above, not unreasonable to use empirically.
- Trial

Oral steroids eg Prednisolone 30mg od (2/52)

Inhaled steroids 2-4/52 eg BDP 400mcg bd/ equivalent.

- Ongoing treatment with inhaled corticosteroids.
- ? Montelukast
- If you think there is airways disease then treat…..
- These conditions are treatable.

Pavord and Chung Lancet 2008

Anti-asthmatic drugs

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

We suggest a short-term ICS trial (2-4 weeks) in adult patients with chronic cough (conditional recommendation, low quality evidence).

We suggest a short-term anti-leukotriene trial (2-4 weeks) in adult patients with chronic cough, particularly in those with asthmatic cough (conditional recommendation, low quality evidence).

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ERS guideline 2019

FE_{NO}

- Indirect measure of eosinophilic airway inflammation.
- If peripheral eosinophils are elevated then eosinophils likely in airway.
- FENO <25=normal, 25-50 indeterminate, >50 highly suggestive of eosinophilia.
- Predicts steroid response
- Depends on 'cut off' point, various studies. Hahn et al: 5.8 likelihood ratio for steroid response if FENO>38[1]
- <u>Is useful but interpret with caution</u>

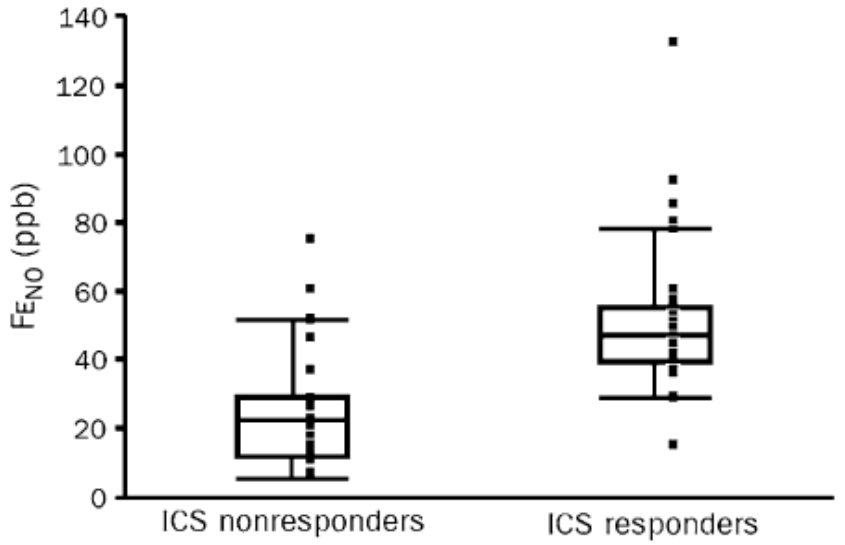

Fig. 1 Use of exhaled nitric oxide to predict response to ICS for chronic cough (reproduced with permission from [25])

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

There is a need for convenient and practical tests for predicting anti-inflammatory treatment responses in patients with chronic cough. However, there is a still lack of quality evidence. Placebo-controlled trials are warranted to assess their utility and also consensus is required on threshold levels in patients with chronic cough.

Hahn et al Mayo clinic proc 2007

ERS guideline 2019

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- Should see a convincing response if airway disease-Ongoing treatment with inhaled corticosteroids.
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ERS guideline 2019

Vague. Don't just use
If airway disease then treat specific traits
Unlikely to be beneficial if non response to ICS at decent dose

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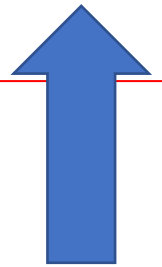

Based on 1 trial in COPD
Vague statement
Again-treat airway disease appropriately-address relevant treatable traits

4) Any other treatable aggravating factors

- GERD
- Rhinitis
- Snoring and OSA (refer).
- Tonsillar enlargement (refer).
- Infection (may take 6/12 to settle, symptomatic treatment).
- Occupational element.

'No preconceptions should exist regarding causes' here.

May be more than one aggravating factor, may need to treat all to have impact on cough.

	Eosinophilic airway diseases	Non-eosinophilic chronic cough
Age	Any	40–60 years
Sex	Equal	Female predominant
Response to corticosteroids	Good	Poor
Pathology	Eosinophilic	Non-eosinophilic
Exhaled (NO)	Raised	Low
Variable airflow obstruction	Present in asthma	Absent
Airway hyper-responsiveness	Present in asthma	Absent

NO=nitric oxide.

Table 1: **Differences between the two major types of chronic cough**

Pavord and Chung Lancet 2008

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- Gastroesophageal reflux disease/ GERD
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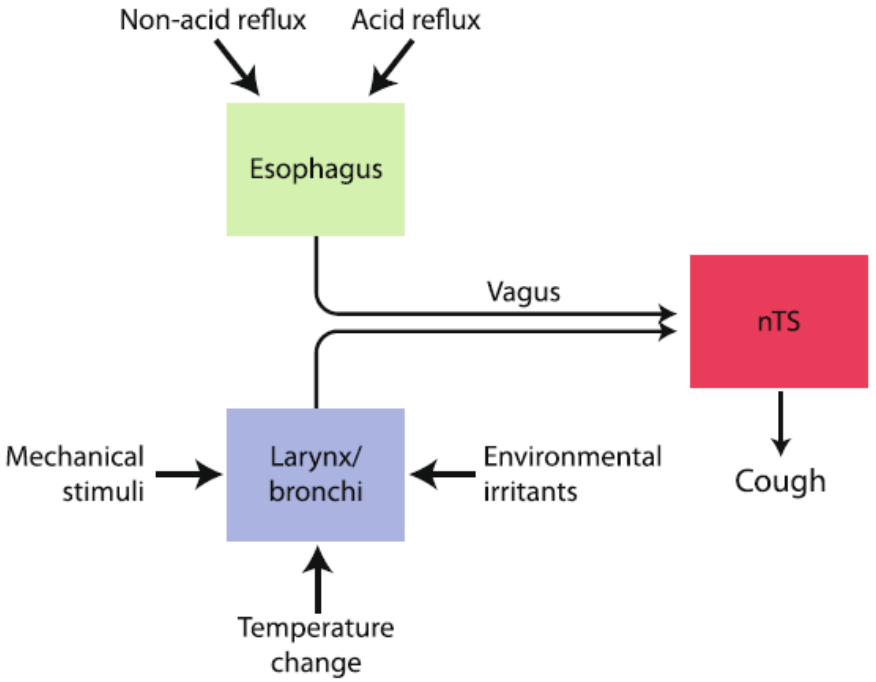

Fig. 1 Schematic showing the stimuli known to trigger coughing in patients with chronic cough and afferent vagal pathways. nTS—nucleus tractus solitarius

Pavord and Chung Lancet 2008

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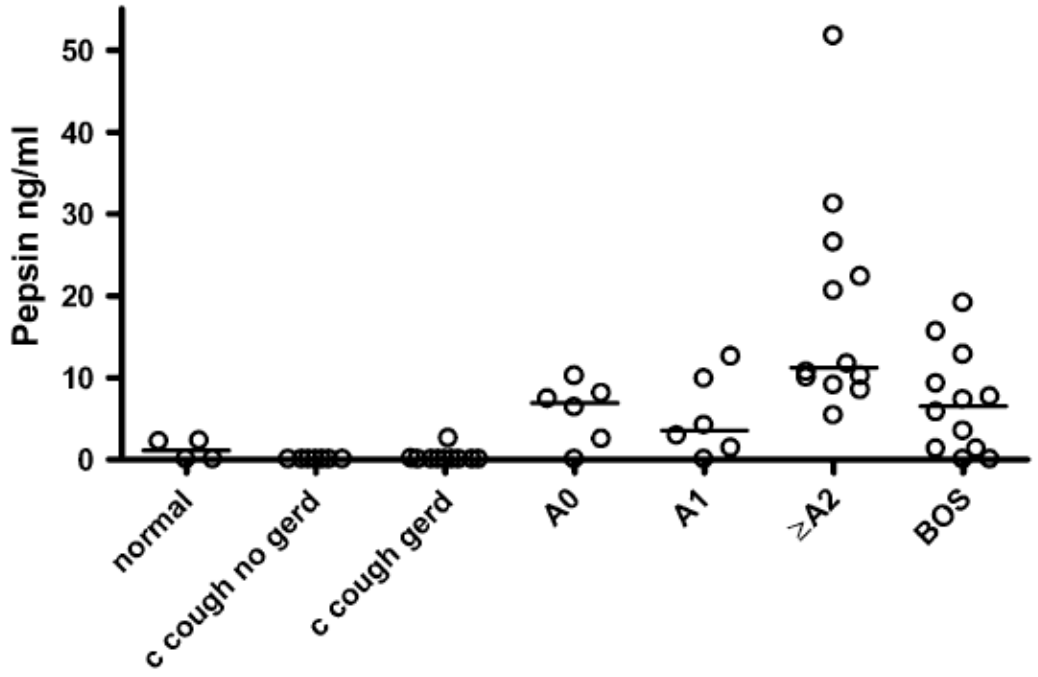
No evidence of aspiration in chronic cough



1. Stovold R et al Am J Resp Crit Care Med 2007; 175(12): 1298-303 grade 2+

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Acid instillation-may sensitise cough if pre-existing chronic cough/GERD
Studies yield different results

Table 1 Summary of cough and esophageal acid infusion studies

Study (year)	Participants	Design	Intervention	Assessment tool	Results
Irwin et al. [17] (1993)	*n*=12 reflux-related cough patients[a]	Randomized controlled, crossover, double-blind	30-min acid and saline infusion	Cough sound recordings during infusion	No difference between acid- and saline-induced cough frequency
Ing et al. [18] (1994)	*n*=22 chronic cough + reflux patients[b]	Randomized controlled, crossover, double-blind	15-min infusion with saline/0.1N HCl	Cough sound recordings during infusion	Increased cough frequency and amplitude with acid compared with saline in chronic cough group only
	n=12 healthy volunteers		*n*=7 chronic cough patients repeated procedure before and after esophageal infusion; lignocaine/ipratropium instillation/ inhalation		Cough frequency decreased with lignocaine instillation
Wu et al. [19] (2002)	*n*=7 mild persistent asthma patients with no chronic cough or symptoms of GERD EGD in all patients: no esophagitis, but no pH studies	Randomized controlled, crossover, patient blinded (researcher also blinded?)	Distal esophagus; infusion: saline/0.1N HCl over 10 min, 1 week interval (5 cm above LES)	Cough reflex sensitivity (capsaicin C3)	Decreased threshold for C3
				Spirometry	Spirometry: no change
				UE pH	No spontaneous coughing
Javorkova et al. [20••] (2008)	*n*=18 healthy volunteers *n*=9 chronic cough+ GERD patients[c] *n*=16 typical GERD patients[c]	Randomized controlled, crossover, double-blind	15-min infusions of saline vs HCl (0.1 mol/L)	Cough reflex sensitivity (capsaicin C2)	Increased sensitivity of cough reflex with acid infusion for chronic cough + GERD group only

[a] 24-h pH-metry ±barium swallow

[b] 24-h pH-metry

[c] EGD ± 24 pH-metry

EGD esophagogastroduodenoscopy; *GERD* gastroesophageal reflux disease; *LES* lower esophageal sphincter; *UE* upper esophagus

1. Stovold R et al Am J Resp Crit Care Med 2007; 175(12): 1298-303 grade 2+

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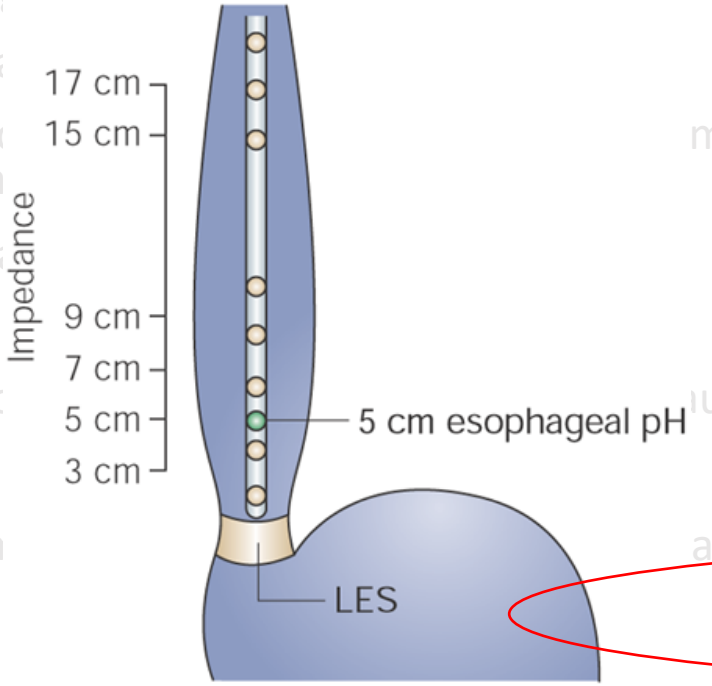
- Rhinitis
- Snorin… and OSA (refer)
- Tonsill…
- Infecti… ma… treatm…
- Occup…
- 'No prec… …us…
- May be n… …ay… treat a…



Oesophageal studies; positive symptom association for *both* reflux-cough and cough reflux

Table 2 Temporal associations between reflux and cough using objective measurements[a]

Study (year)	Participants	Esophageal monitoring	Cough monitoring	Temporal association
Sifrim et al. [33] (2005)	*n*=28 chronic cough patients (from specialist cough clinic, excluding patients with causes other than reflux)	Combined impedance/pH	Ambulatory esophageal manometry	*n*=10 (36%) positive SAP for reflux–cough (5 acid, 3 weakly acid, 2 both); *n*=6 (21%) positive SAP for cough–reflux
Blondeau et al. [32] (2007)	*n*=100 chronic cough patients (23 on PPI) (from specialist cough clinic, excluding patients with causes other than reflux)	Combined impedance/pH	Ambulatory esophageal manometry	*n*=36 (36%) positive SAP for reflux–cough (9 acid, 23 weakly acid, 4 both); *n*=42 (42%) cough–reflux events observed (SAP not calculated)
Bogte et al. [42] (2008)	*n*=55 chronic cough patients (retrospectively identified from referrals for pH-metry, excluding patients with causes other than reflux)	pH monitoring	Ambulatory esophageal manometry (*n*=14; event marking *n*=55)	*n*=11 (20%) positive SAP for reflux–cough; *n*=5 (9%) positive SAP for cough–reflux
Smith et al. [44••] (2010)	*n*=71 chronic cough patients (consecutive patients from specialist cough clinic)	Combined impedance/pH	Acoustic 24-h recording	*n*=34 (48%) positive SAP for reflux–cough; *n*=40 (56%) positive SAP for cough–reflux; *n*=23 (32%) positive SAP for both reflux–cough and cough–reflux
Kunsch et al. [45•] (2011)	*n*=25 patients with respiratory and GERD symptoms (19 chronic cough); *n*=20 healthy participants	Overnight pH and Bilitec[b]	Overnight acoustic recording	*n*=9 (47.3%) positive SAP for reflux–cough; *n*=0 positive SAP for cough–reflux

[a] All 2-min windows

[b] Medtronic (Shoreview, MN)

GERD—gastroesophageal reflux disease; PPI—proton pump inhibitor; SAP—symptom association probability

Smith et al Curr Gastroenterol Rep 2011; 13:247-256 (Review).

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- Occupational element.

'No preconceptions should exist regarding causes' here.

May be more than one aggravating factor, may need to treat all to have impact on cough.

Weak peristalsis with large breaks in 34% cough patients (12 heartburn)
Prolonged clearance of refluxed events.

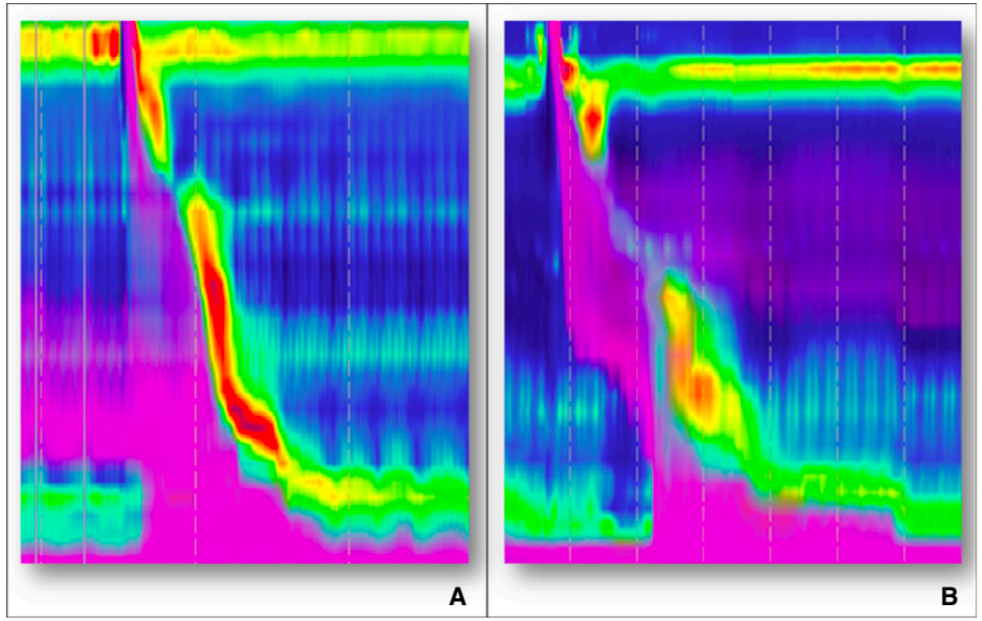

Figure 1 Example of a normal peristaltic event with complete bolus transit (A) and a peristaltic event with large break associated with escape of bolus (indicate by purple color) and thus incomplete bolus transit (B).

Almansa et al Neurogastroenterol Motil 2015

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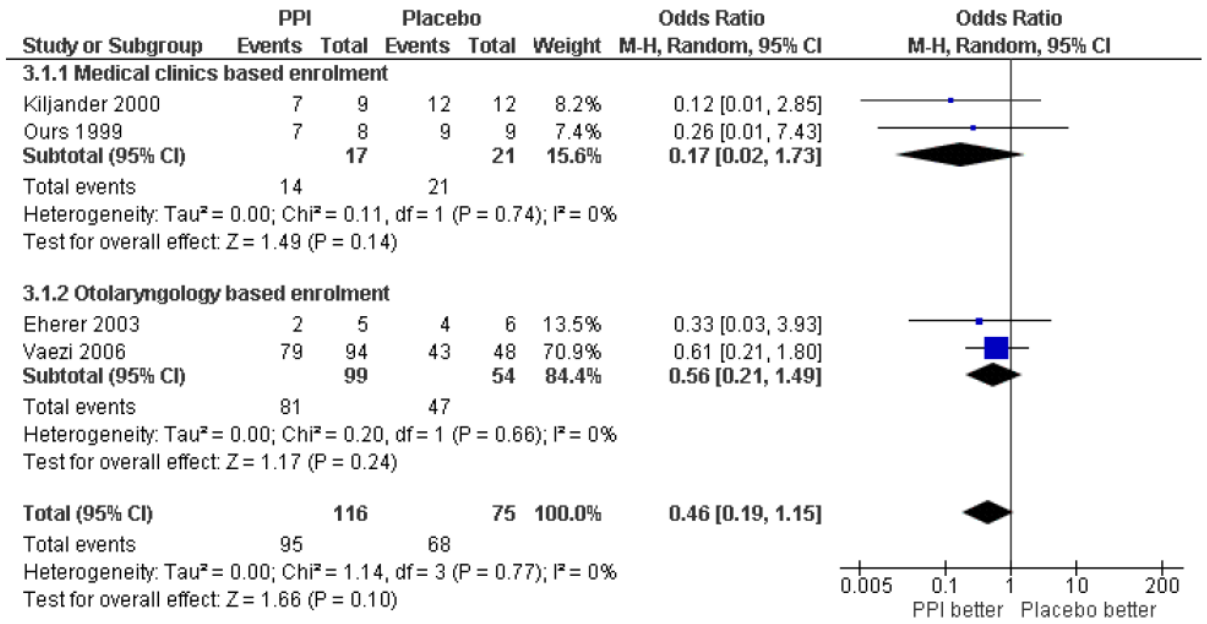
Figure 3. Forest plot of comparison: 2 PPI versus placebo (> 18 years), outcome: 2.1 Clinical failures (still coughing at end of trial or reporting period).



Pavord and Chung Lancet 2008
Chang et al Cochrane database of systematic reviews 2011;1:CD004823 grade 1+

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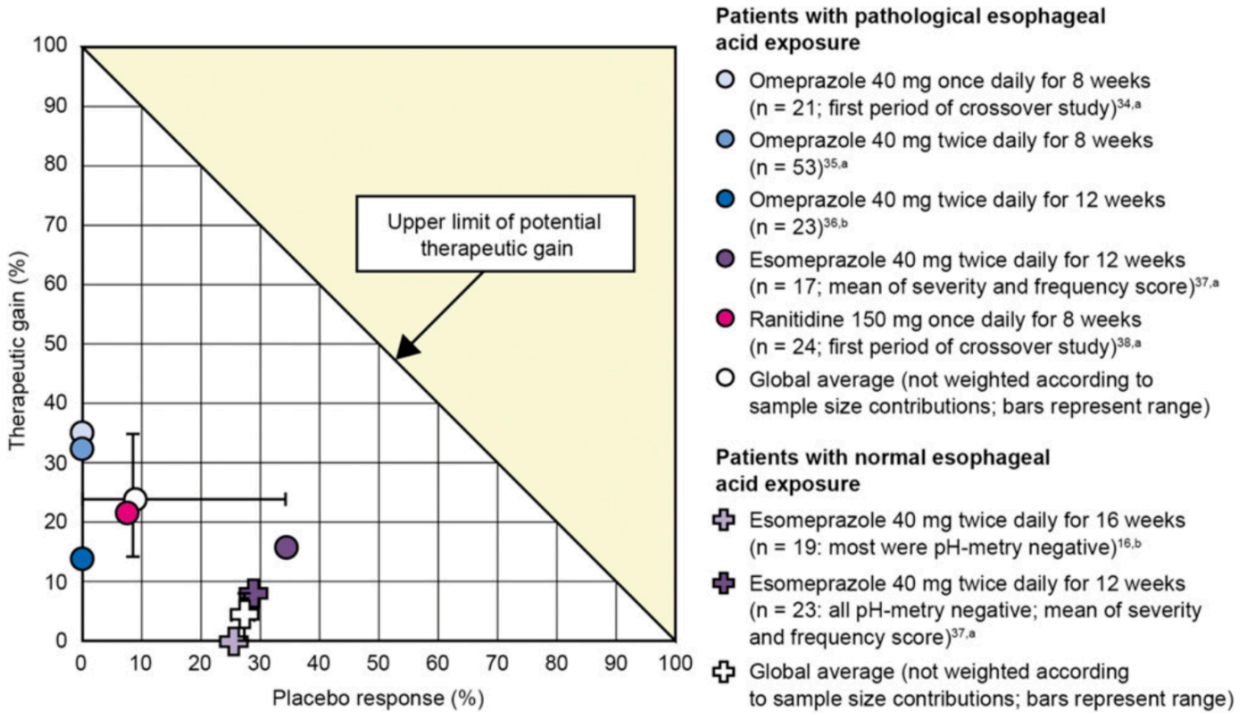

FIGURE 2. Calculated therapeutic gain for datasets derived from patients with pathologic esophageal acid exposure and populations including patients with normal esophageal acid exposure. [a]Percentage change in symptom score; [b]Percentage change in proportion of responders.

Pavord and Chung Lancet 2008
Kahrilas et al 2016

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Don't prescribe PPI's for cough unless clear peptic symptoms.

No prokinetics unless otherwise indicated.

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Pavord and Chung Lancet 2008

Anti-acids

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

We suggest that clinicians do not routinely prescribe anti-acid drugs in adult patients with chronic cough (conditional recommendation, low quality evidence).

Drugs with promotility activity

Question 5: Should drugs with promotility activity be used to treat patients with chronic cough?

There is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A one month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship. (conditional recommendation, low quality evidence).

No RCTs have been undertaken with pro-motility agents, such as baclofen, metoclopramide or domperidone, in patients with chronic cough. There are three RCTs with macrolides with pro-motility activity in adult patients with chronic cough. One study of patients with COPD GOLD stage $\geq$ 2 and chronic productive cough demonstrated a significant benefit of a 12-week low dose azithromycin (250 mg three times a week) over placebo for improving cough-specific quality of life (LCQ; MD 1.3; 95% CI 0.3 to 2.3; p=0.01)[119]. Adverse events were not significantly different. In two other trials of patients with unexplained cough or treatment-resistant cough, low-dose macrolide treatments (erythromycin 250 mg daily for 12 weeks or azithromycin 250 mg three times a week for 8 weeks) did not provide significant benefits over placebo for objective cough frequency, cough severity or cough-specific quality of life[120, 121].

ERS guideline 2019

4) Any other treatable aggravating factors

- Gastroesophageal reflux diseasae/ GERD

Don't prescribe PPI's for cough unless clear peptic symptoms.

No prokinetics unless otherwise indicated.

- Again-getting confused
- Considers macrolides as prokinetic
- Not mentioning anti-inflammatory properties
- Role in certain phenotypes airways disease—treat as appropriate (treatable traits)
- Prokinetic activity less clear
- If ? Reflux and no response to PPI then get studies/refer

Pavord and Chung Lancet 2008

Anti-acids

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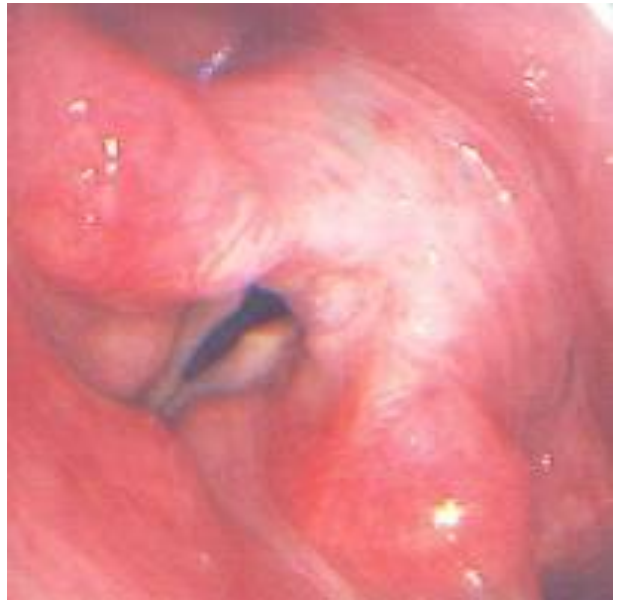
ERS guideline 2019

4) Any other treatable aggravating factors

- GERD
- Rhinitis/postnasal drip/upper airways cough
- Drip-back of throat, throat clearing, nasal discharge/stuffiness common. Rarely any objective pathology[2].
- Cough reflex sensitised by nasal stimulation (guinea pig model, capsaicin, allergic rhinitis)-central sensitisation.
- Limited effect of treatments, no double blind RCT evidence of beneficial treatment.
- **Empirical trial nasal steroid eg nasonex 100mcg od or equivalent. ? Role of antihistamine. If nasal symptoms.**
- **ENT review? Speech therapy?**
- Snoring and OSA (refer).
- Tonsillar enlargement (refer).
- Infection (may take 6/12 to settle, symptomatic treatment).
- Occupational element.

'No preconceptions should exist regarding causes' here.

May be more than one aggravating factor, may need to treat all to have impact on cough.



The upper airways

In patients who report upper airway symptoms fibre optic laryngoscopy may be performed. The larynx is commonly found to be red and inflamed. However, the test has poor sensitivity and specificity. In select patients, laryngoscopy may be useful in identifying inducible laryngeal obstruction (ILO) associated with cough, and this may help plan the need for future cough control therapy[99]. Rhinoscopy may be helpful in identifying polyps and clearing mucus from blocked sinuses in patients with recurrent sinus and nasal inflammation, but routine laryngoscopy, rhinoscopy or CT sinuses is not advised as nasal findings are not directly associated with cough[100, 101].

ERS guideline 2019

1. Pratter et al Ann Int Med 1993
2. Cathcart and Wilson IJCP 2011

4) Any other treatable aggravating factors

- GERD
- Rhinitis
- Snoring and OSA.
- Tonsillar enlargement.
- Infection (may take 6/12 to settle, symptomatic treatment).
- Occupational element (asthma, bottle factory, food processing)

‘No preconceptions should exist regarding causes’ here.

May be more than one aggravating factor, may need to treat all to have impact on cough.

	Eosinophilic airway diseases	Non-eosinophilic chronic cough
Age	Any	40–60 years
Sex	Equal	Female predominant
Response to corticosteroids	Good	Poor
Pathology	Eosinophilic	Non-eosinophilic
Exhaled (NO)	Raised	Low
Variable airflow obstruction	Present in asthma	Absent
Airway hyper-responsiveness	Present in asthma	Absent

NO=nitric oxide.

Table 1: **Differences between the two major types of chronic cough**

Pavord and Chung Lancet 2008

Chronic refractory/unexplained cough

- Only diagnosed after thorough investigation and failed trials of appropriate empirical therapy[1].
- 7-46%, overall around 20% patients in cough clinics[2].
- Middle aged females. Post menopause.
- Organ specific AI disease. IBS. Low grade lymphocytic airway inflammation[3]
- **Cough reflex hypersensitivity[4]**.
- Impaired ability to suppress cough[5].
- Capsaicin may differentiate health/disease Emax/ED50 (4 doubling doses capsaicin)[6]
- Treatment resistant. Impaired QOL. Anxiety/depression. Social stigma.

Table 3—*Comparison of Characteristics of CIC and Non-CIC Patients

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

*NS = not significant.

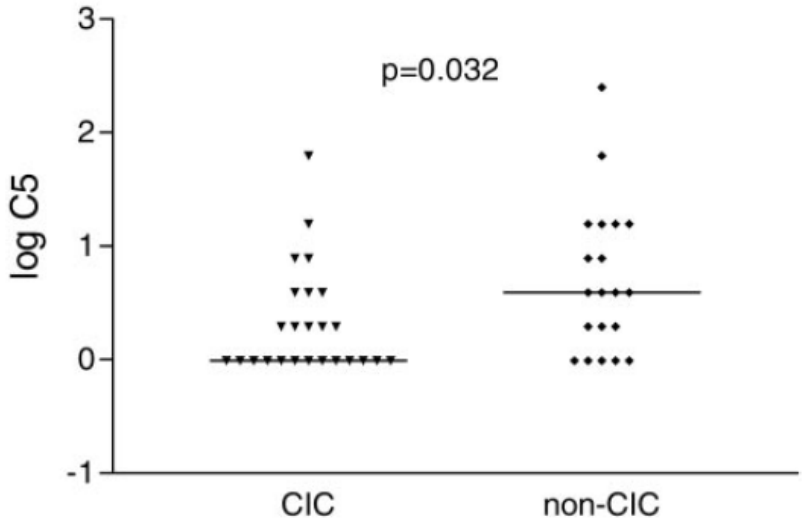


FIGURE 3. Comparison of capsaicin sensitivity between CIC and non-CIC patients.

1. Haque et al Chest 2005
2. Chung KF, Pavord ID Lancet 2008
3. Birring Pulm Pharm Ther 2011
4. Ando et al Thorax 2016
5. Cho et al ERJ 2019
6. Holt et al ERJ 2020

Cough reflex sensitivity in chronic refractory/unexplained cough

- Increased Neuronal density in airways in patients with chronic cough.[1]
- Cough reflex hypersensitivity (Emax/ED50) [2]
- Diminished central cough suppression network [3,4]

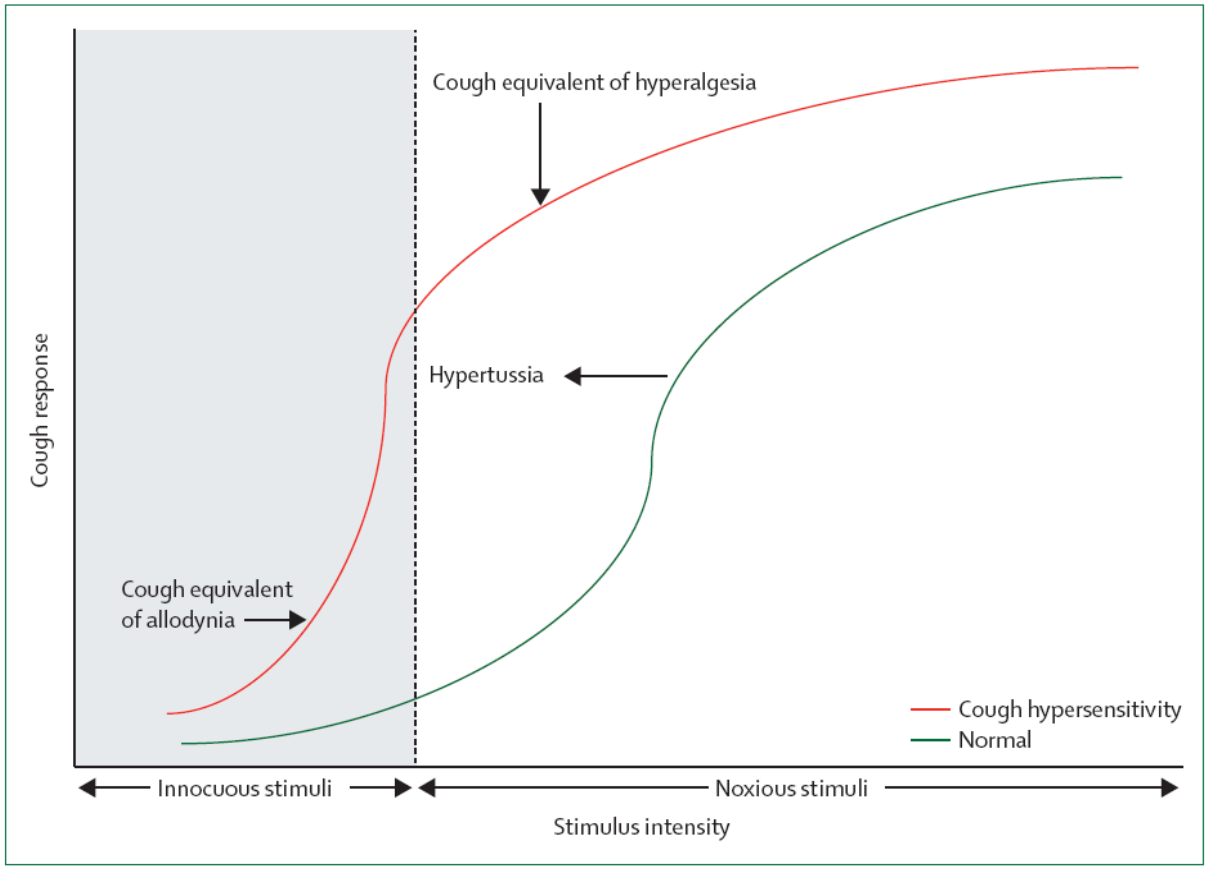


Figure 4: **Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states**
Cough hypersensitivity results in cough in response to innocuous stimuli, as in allodynia.

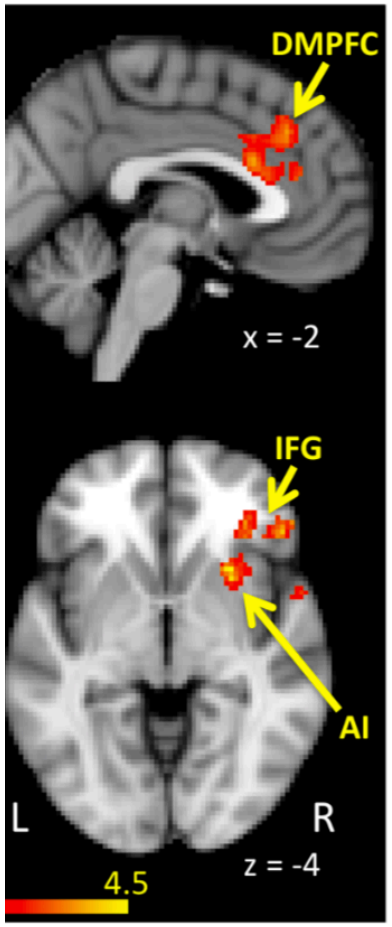
Chung et al Lancet 2013

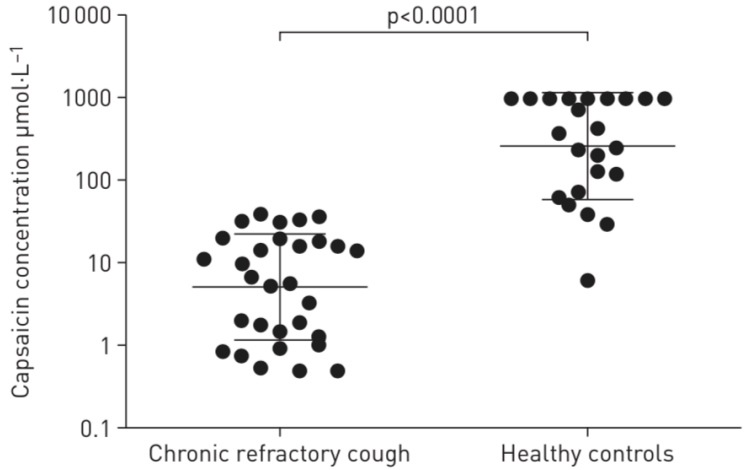
1. Shapiro et al AJRCCM 2020
2. Holt et al ERJ 2020
3. Ando et al Thorax 2016
4. Cho et al ERJ 2019

Diminished central cough suppression network in chronic refractory cough

DMPFC
Anterior mid cingulate cortex
Right inferior frontal gyrus
Right anterior insula

Issue may be reduced ability to suppress cough





Ando et al Thorax 2016
Cho et al ERJ 2019

Chronic refractory/unexplained cough

- Only diagnosed after thorough investigation and failed trials of appropriate empirical therapy[1].
- Ensure adequate trials of standard treatments, Through investigation, adherence.[4] Explanation and reassurance. Most coughs get better and are not associated with significant pathology.
- 7-46%, overall around 20% patients in cough clinics[2].
- Middle aged females. Post menopause.
- Organ specific AI disease. IBS. Low grade lymphocytic airway inflammation[3]
- Cough reflex hypersensitivity[4].
- Impaired ability to suppress cough[5].
- Treatment resistant. Impaired QOL.
- Evidence based treatments

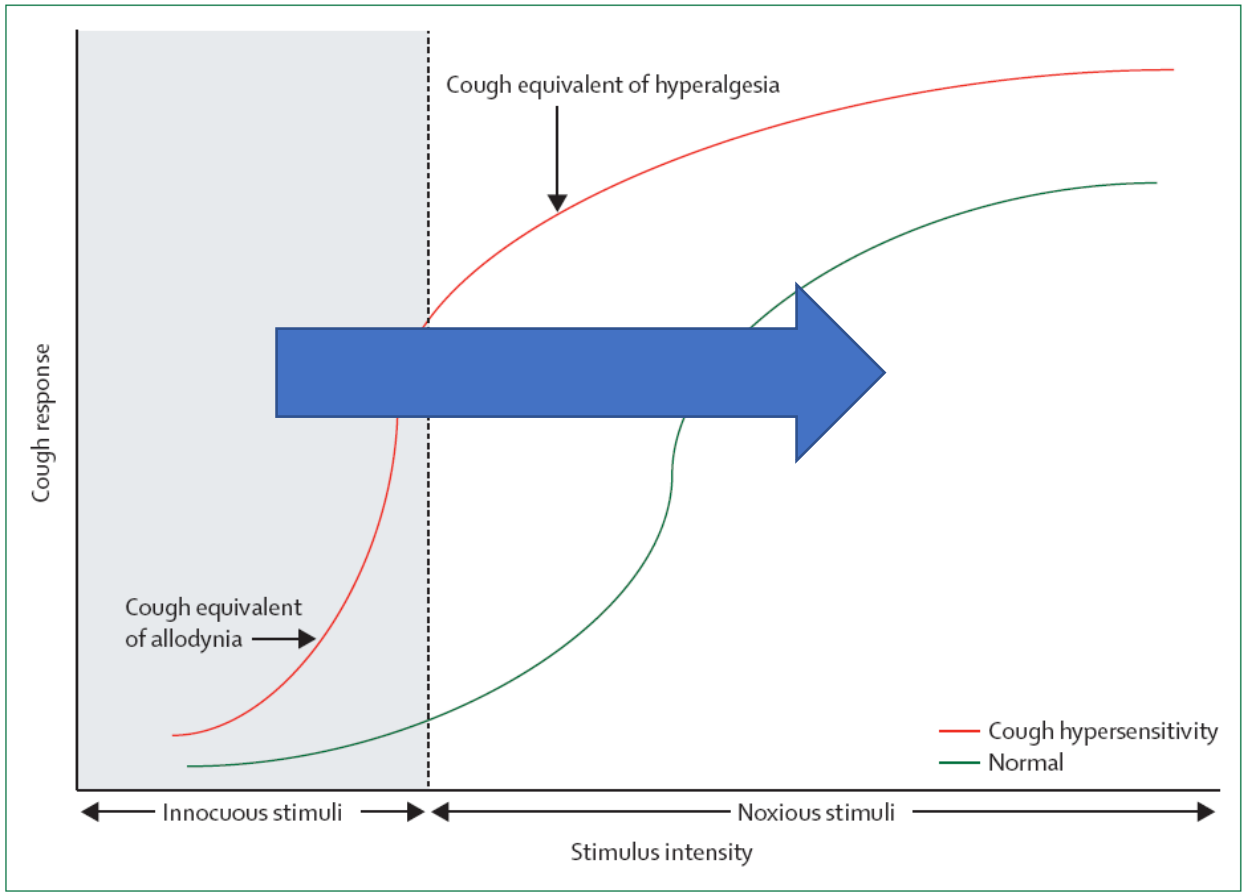
Low dose MST

Gabapentin (pregabalin, amitryptilline)

Non pharmacological cough suppression therapy

Novel agents (P2X3 blockers)

Treatment to desensitize/normalize cough reflex



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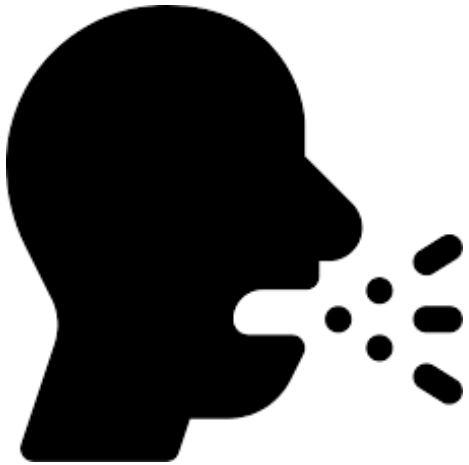
Antitussives



Cough suppressants/antitussives

Honey-Ancient Egyptians (and NICE!)

Opiates

Huge OTC market $9.5billion/year in the USA.

Common physical properties

Very weak evidence base, many no better than placebo[1]

Last licensed drug 1960's (dextromethorphan)

1. Smith et al Cochrane 2014

Cough treatments often no better than placebo..

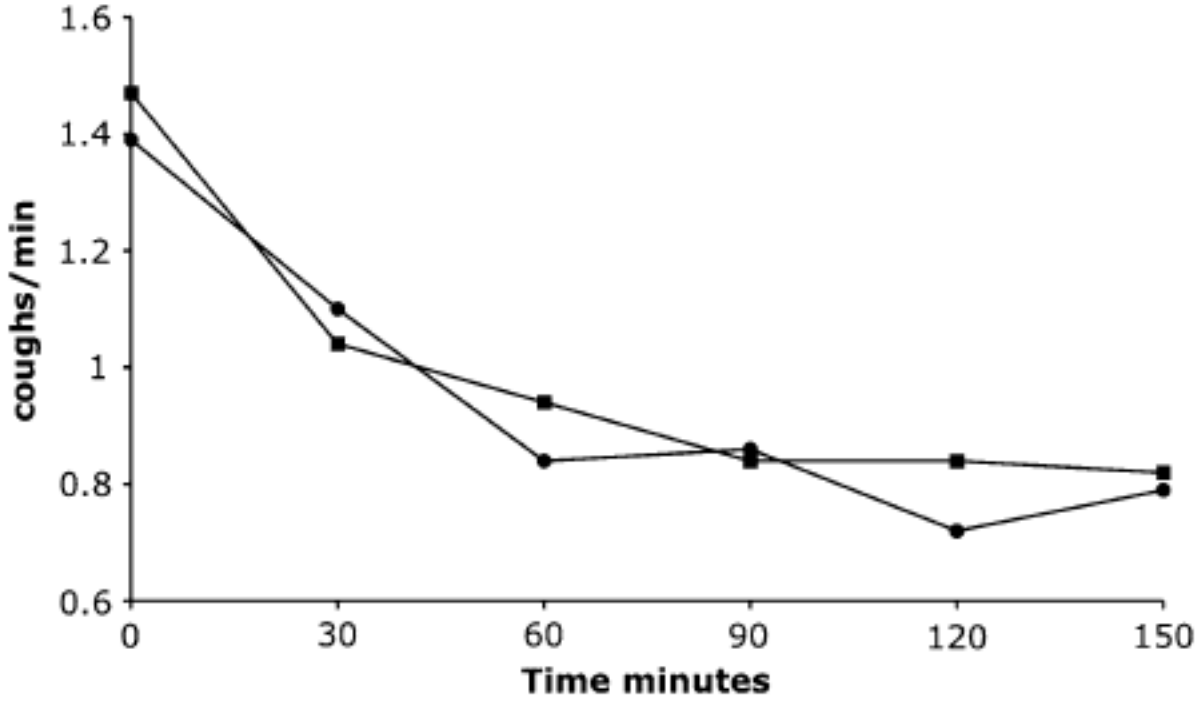


Fig. 1 Mean cough frequency before and after treatment with a single dose of codeine syrup B.P. (30 mg) in subjects with cough associated with acute upper respiratory tract infection. *Square symbols* indicate codeine syrup ($n = 46$) and *round symbols* indicate placebo syrup ($n = 45$) (redrawn from [1])

Eccles Lung 2010
Eccles et al J Clin Pharm 1992

Patients do benefit however..

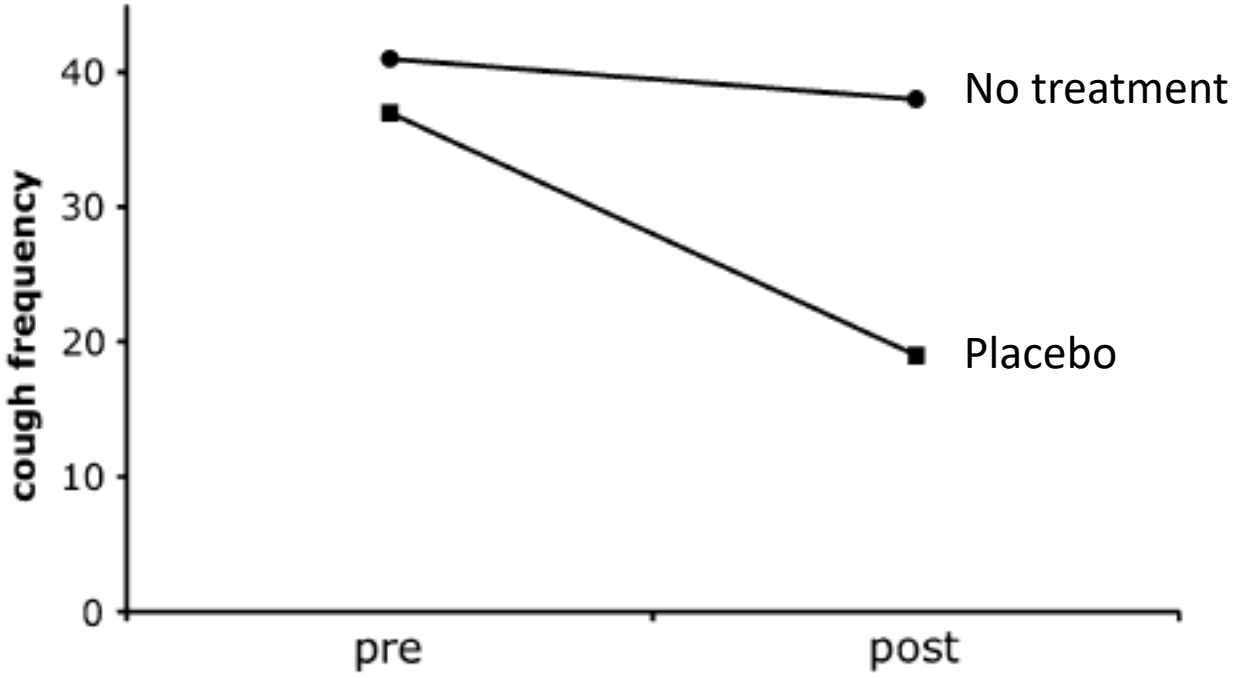
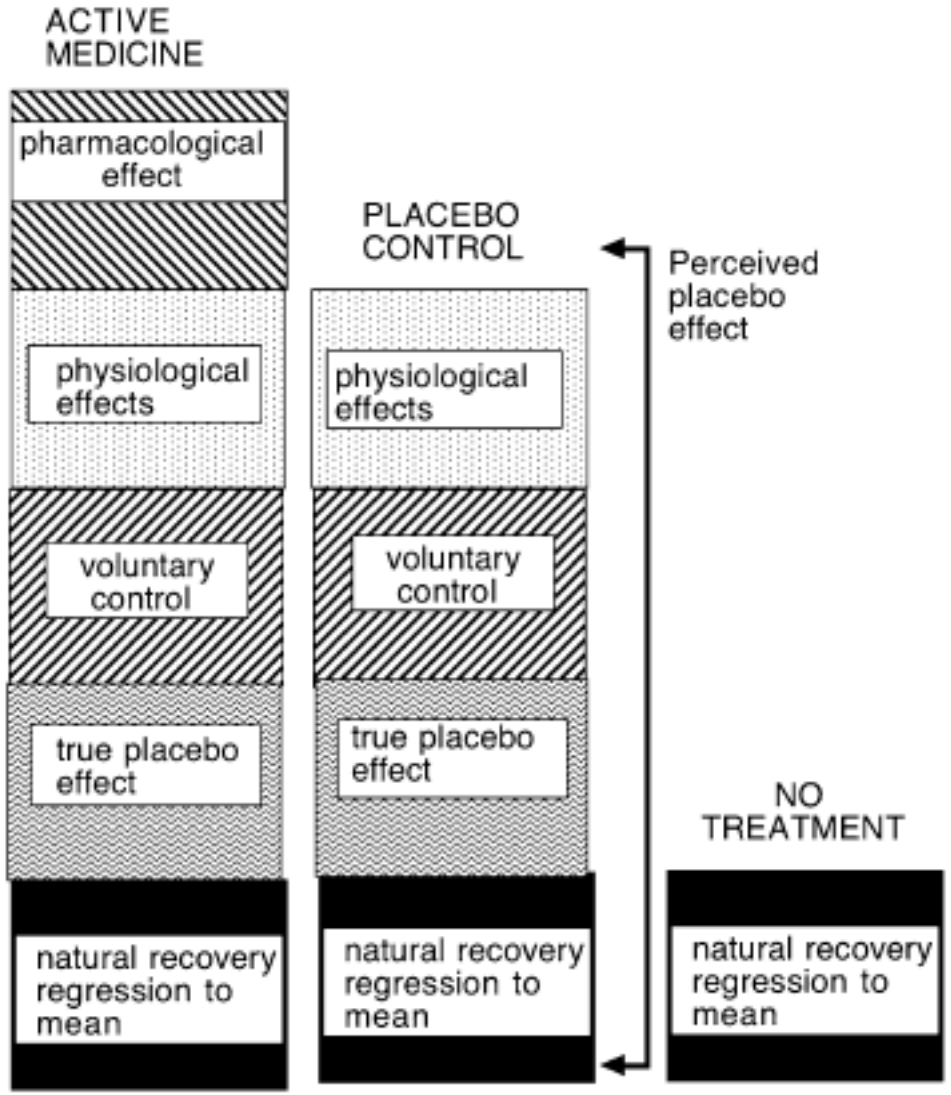


Fig. 3 Median cough frequency (per 15 min) pre-treatment and post-treatment. *Round symbols* represent the no treatment group and *triangular symbols* the placebo treatment group (redrawn from [18])

Eccles Lung 2010
Lee et al Psychosom Med 2005

How does cough medicine work

RCT intended to identify ‘pharmacological effect’
Differentiate from placebo (and other effects)



Eccles Lung 2010

‘Physiological effect’: Simple linctus/syrups/honey

- Physical properties of syrup ? 85% of cough medicine action[1].
- Glycerol (lemon, honey)
- Sapid
- Mechanism

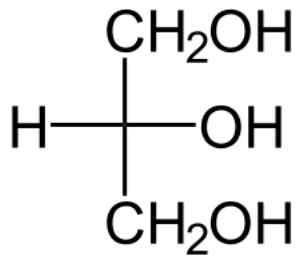
Placebo

‘Physiological’ effect

Demulcent effect (soothing); coat and lubricate pharyngeal surface

Lubrication

Sweetness ‘Honey probably relieves cough symptoms to a greater extent than no treatment, …. or placebo[2]’



1. Eccles and Mallefet Pharmacy 2017
2. Oduwole et al Cochrane database Syst Rev 2018

Physiological effect

1. ‘demulcent effect’ (soothing..), trigger salivation, increased airway secretions, lubrication.
2. Effect of substance on cough reflex (direct inhibition, endogenous opiates?)
3. Patient made aware of treatment by its sensory effects.

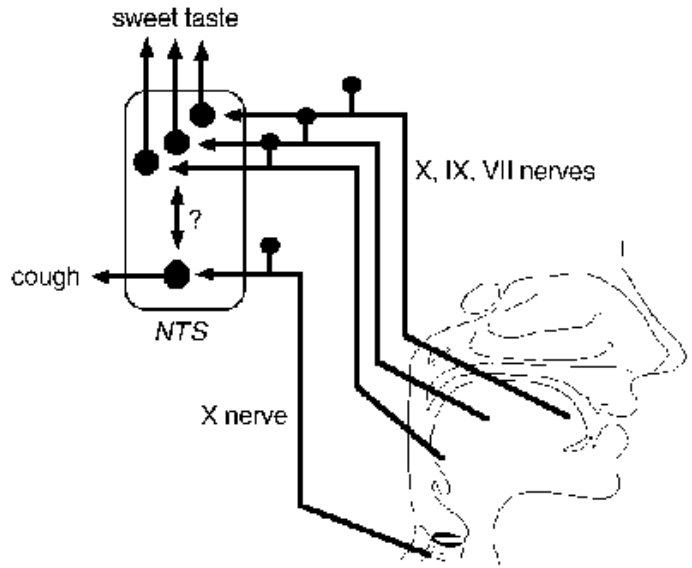
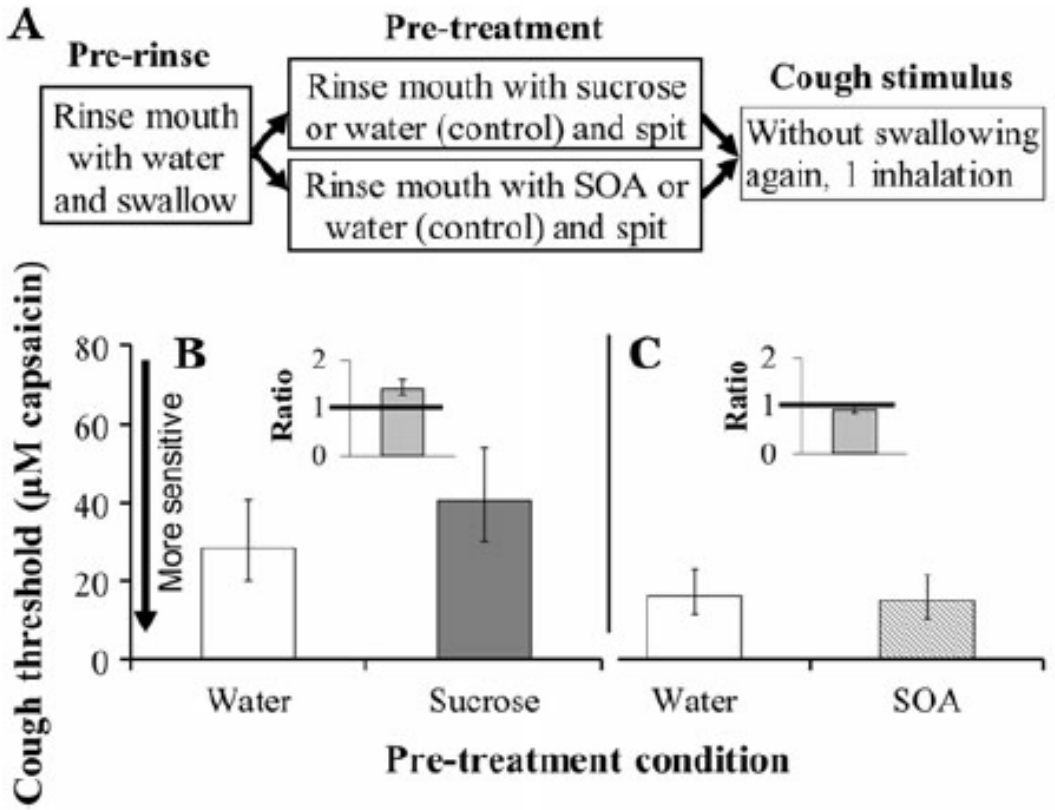


Fig. 3. Gustatory effects on cough. Gustation is mediated by branches of the VII (facial) IX (glossopharyngeal) and X (vagus) cranial nerves that supply the taste buds of the tongue. These gustatory fibres relay in the nucleus of the tractus solitarius (NTS) that also serves as the first relay for the X cranial nerves that mediate the cough reflex. It is possible that there may be some interaction between gustatory and cough pathways that influences the cough reflex, perhaps by modulating the production of endogenous opioids.

Eccles Resp Phys Neurobiol 2006

Sweet taste suppresses cough reflex



Wise et al Lung 2014

The placebo effect and cough

- Placebo-major part of response to many cough medicines[1].
- Complex psychological factors.
- Opioid–ergic mechanisms involving the prefrontal cortex (and other brain areas) and downstream circuits. Similar to activations seen in placebo pain studies.
- Placebo shown to reduce capsaicin induced urge to cough[2].
- Example of a higher cortical process that influences cough[3].

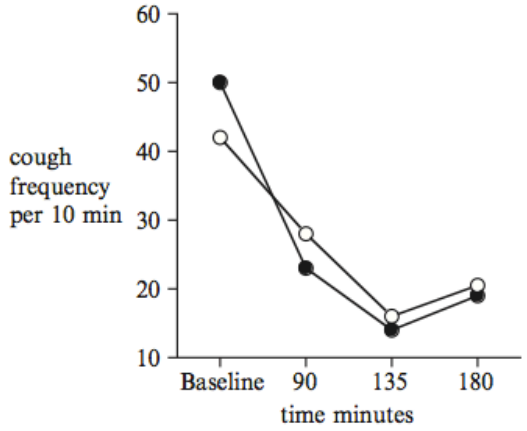
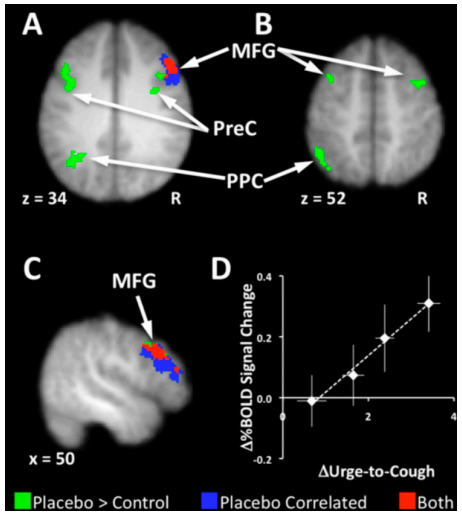
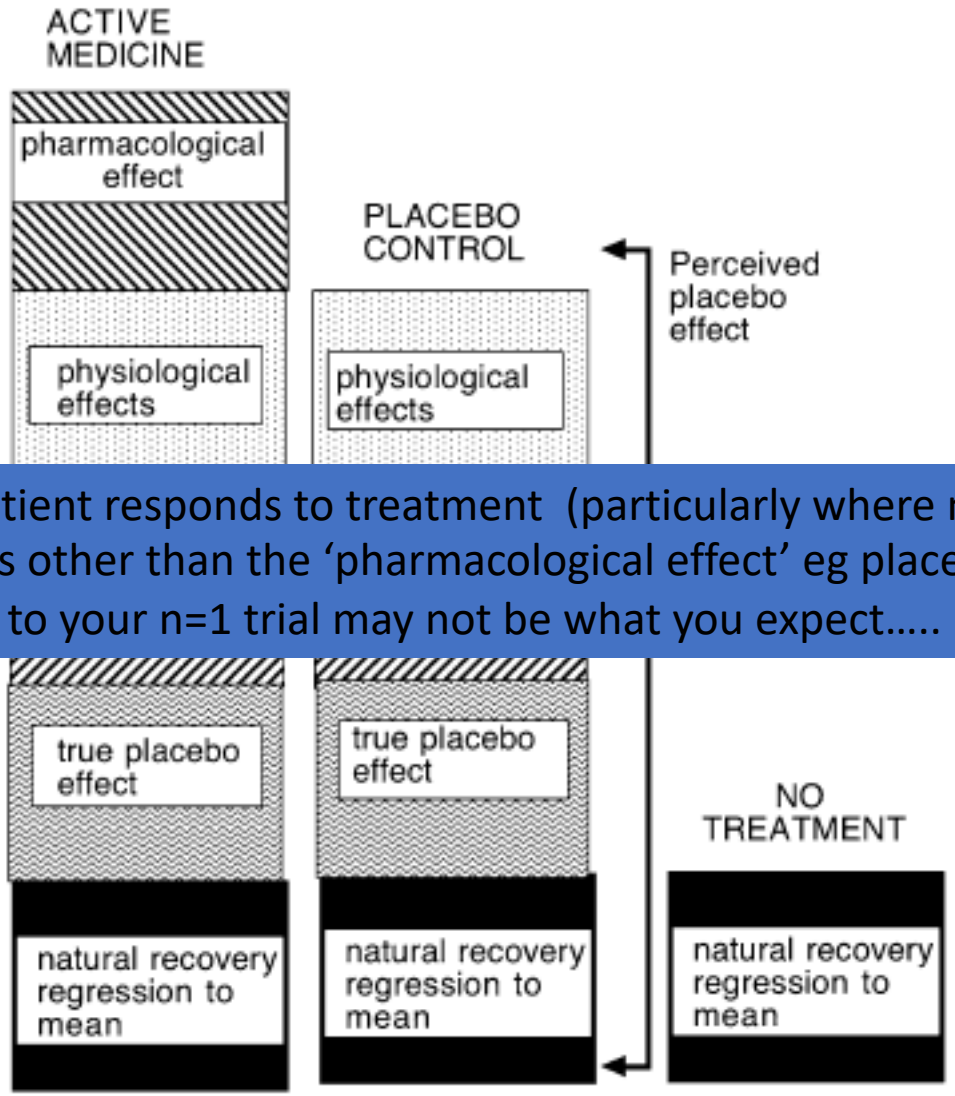


Fig. 2 Median cough frequency (per 10 min) for patients with cough associated with common cold. Immediately after the baseline measurement (0 min) patients were treated with either a single dose of 30 mg dextromethorphan powder in a hard gelatin capsule (*round symbols*, $n = 21$) or a matched placebo capsule containing lactose powder (*square symbols*, $n = 22$). (Lee et al. 2000)



1. Eccles Hand exp pharm 2009
2. Leech et al Chest 2012
3. Van den bergh Lung 2012

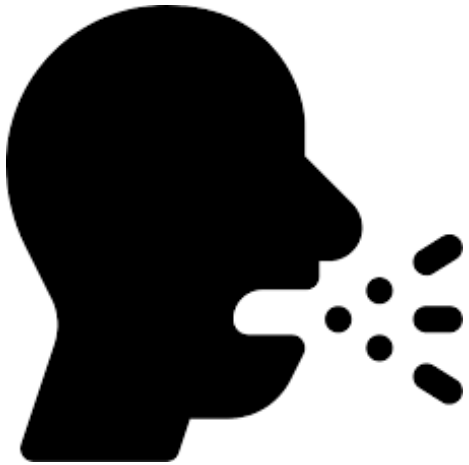
How does cough medicine work



Bear in mind reason why patient responds to treatment (particularly where no good RCT evidence exists) may be due to factors other than the 'pharmacological effect' eg placebo, physiological effects……positive response to your n=1 trial may not be what you expect…..

Eccles Lung 2010

‘Old’ antitussives



Opiates: Codeine

- Weak opiate. Unpredictable pharmacokinetics
- No benefit over placebo in 2 reasonable quality placebo controlled trials looking at acute cough in URTI[1,2].
- No benefit over placebo in COPD[3].
- Would advise against using. Probably not an effective antitussive.

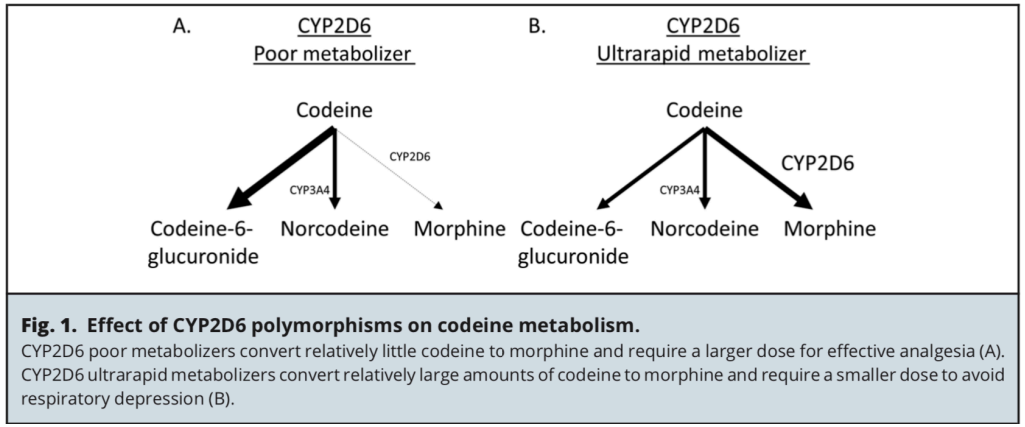
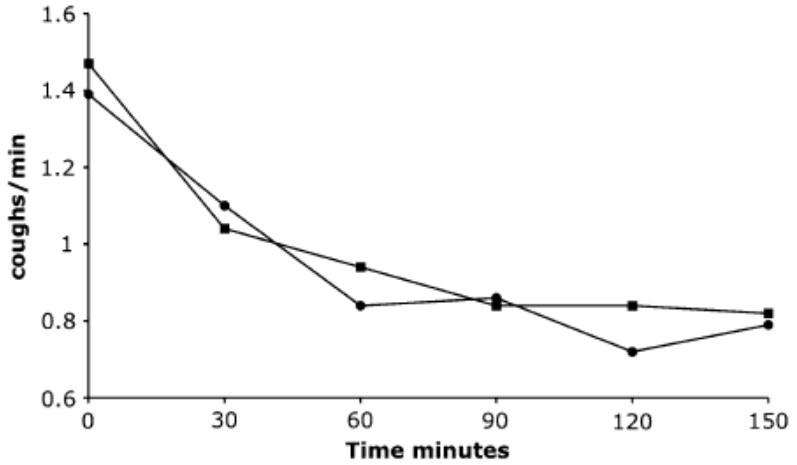


Fig. 1. Effect of CYP2D6 polymorphisms on codeine metabolism.
CYP2D6 poor metabolizers convert relatively little codeine to morphine and require a larger dose for effective analgesia (A). CYP2D6 ultrarapid metabolizers convert relatively large amounts of codeine to morphine and require a smaller dose to avoid respiratory depression (B).

Nerez and Gonzalez J App Lab Med 2017



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1. Eccles J Clin Pharm Ther 1992
2. Freestone J Pharmacy Pharmacol
3. Smith et al JACI 2006

Opiates: Morphine

- RCT in refractory cough[1]. MST 5-10mg bd.

Improved QOL at 4 weeks.

Not all patients respond (approx. 6/10)

Side effects (constipation, drowsiness) in 40%.

- Study of 'responders'[2].

71% reduction in cough frequency (similar improvement in QOL)

For those who respond, **morphine is a good antitussive.**

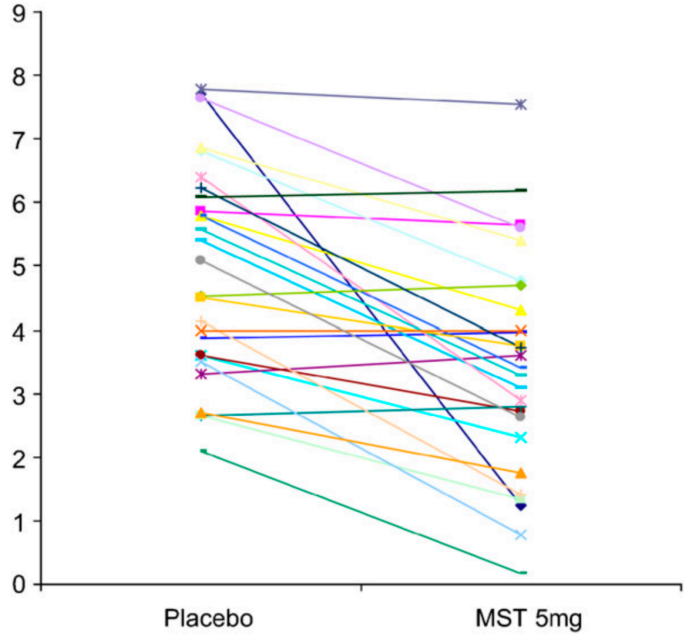


Figure 1. Daily cough severity scores on a scale of 0 to 9. MST = slow-release morphine sulfate.

We recommend a trial of low dose slow release morphine (5-10 mg bd) in adult patients with chronic refractory cough (strong recommendation, moderate quality evidence).

ERS guideline 2019

1. Morice et al AJRCCM 2007
2. Al-Shekly et al Thorax 2017
3. An et al J Pall Medicine 2015

Neuromodulators: Gabapentin/Pregabalin

- Mechanism unclear.

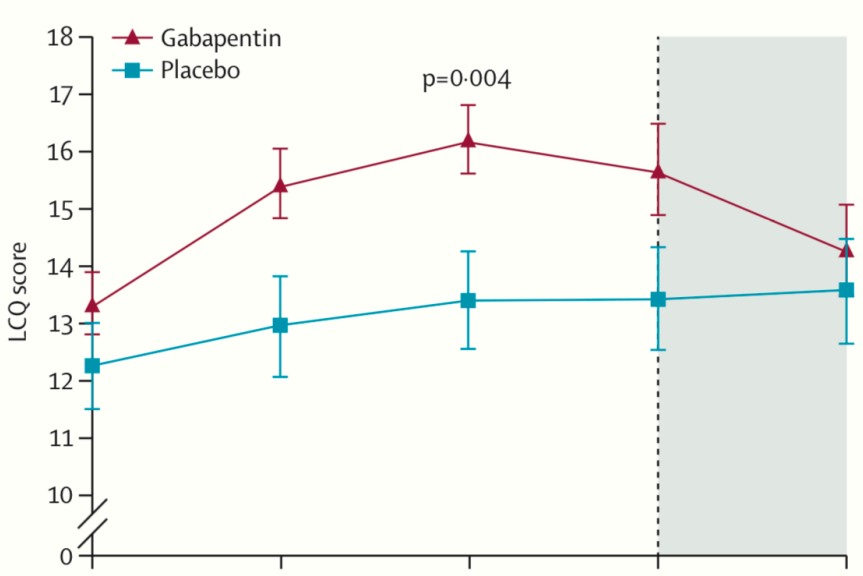
Central. Not GABA!

Blocks nociception.

$\alpha 2\boldsymbol{\delta}$ subunit presynaptic calcium channels?

NMDA ?

- Refractory cough. RCT. Modest improvement in QOL and ↓cough frequency[1].
- Improved response when combined with speech therapy treatment[2].
- Significant side effects (nausea, fatigue, lethargy, dry mouth, dizziness).
- Careful dosing e.g. starting at very low doses e.g. 100mg od and titrating up[3].
- Pregabalin and Amitryptilline-less evidence.

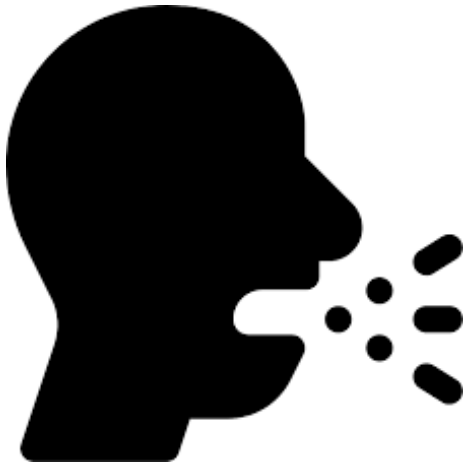


We suggest a trial of gabapentin or pregabalin in adults with chronic refractory cough (conditional recommendation, low quality evidence).

ERS guideline 2019

1. Ryan et al Lancet 2012
2. Vertigan et al Chest 2016
3. Gibson and Vertigan Pulm Pharm Ther 2015

‘New’ antitussives



Novel antitussives-drugs in development

J ALLERGY CLIN IMMUNOL PRACT
VOLUME 7, NUMBER 6

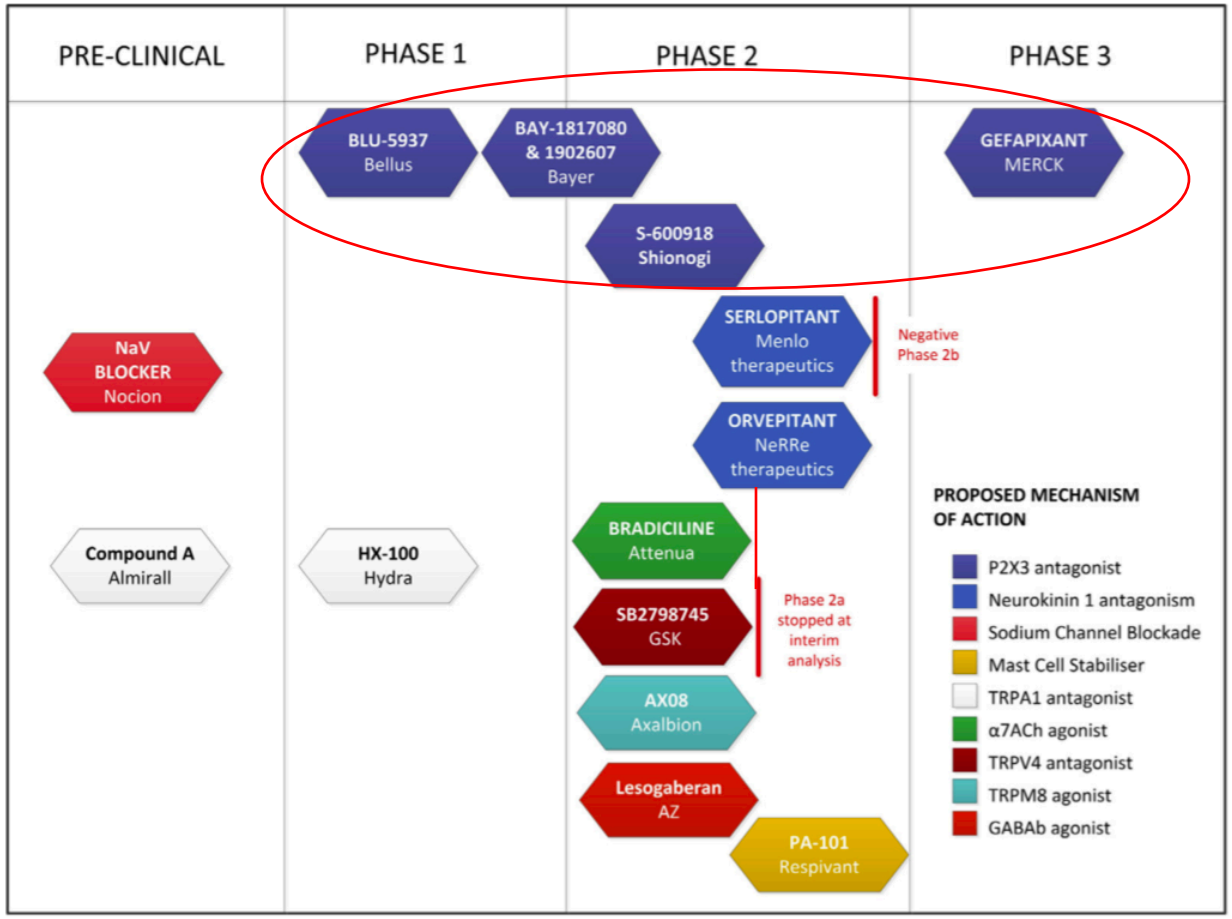


FIGURE 3. Current stages of development of agents for the treatment of chronic coughing. *NaV*, Voltage-gated sodium; *TRPA1*, transient receptor ankyrin 1; *TRPM8*, transient receptor potential melastatin 8; *TRPV4*, transient receptor vannilloid-4.

All trials of TRP antagonists negative (TRPV1, TRPA1, TRPV4)

? TRPM8 result (Axalbion).

NK1 antagonists 2 negative trials. Orvepitant-?phase 3 trial-2b-efficacy in high frequency coughers

NAChR antagonist trial (Bradanicline) negative

<u>Main area of interest/efficacy is P2X3 antagonists</u>

Novel antitussives: P2X receptor antagonists

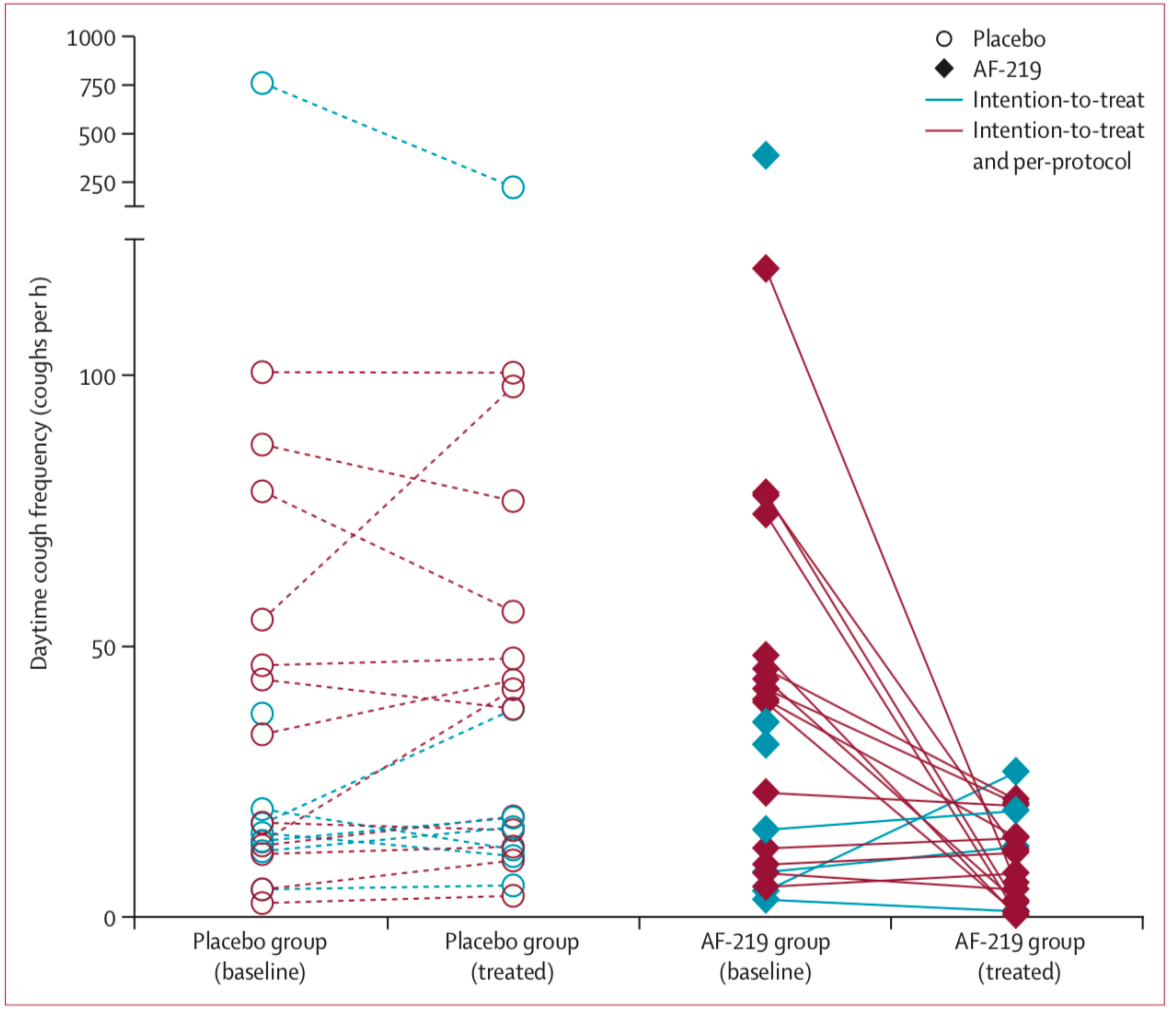


***Figure 2*: Changes in objective daytime cough frequency from baseline to end of the treatment period**
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al Lancet 2014

P2X receptors

P2X receptors

Ion channels on airway sensory nerves (vagal C fibres)

Purinergic-ATP sensitive

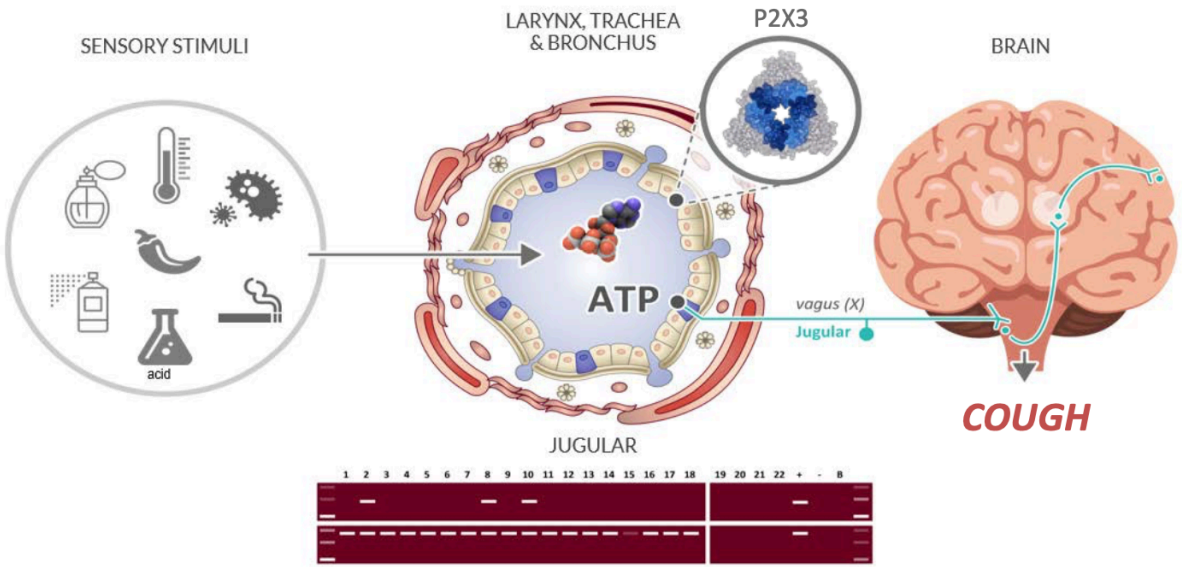
ATP released in response to cellular stress

2 main subtypes

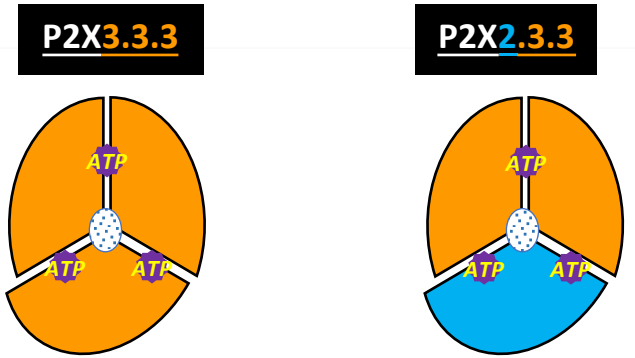
P2X2/3 (taste side effects)

? P2X3 more important for cough

P2X3 is a rational target to treat cough hypersensitivity in refractory/unexplained chronic cough



Kwong et al 2008 AJP Lung cell Mol Physiol 295 L858-65



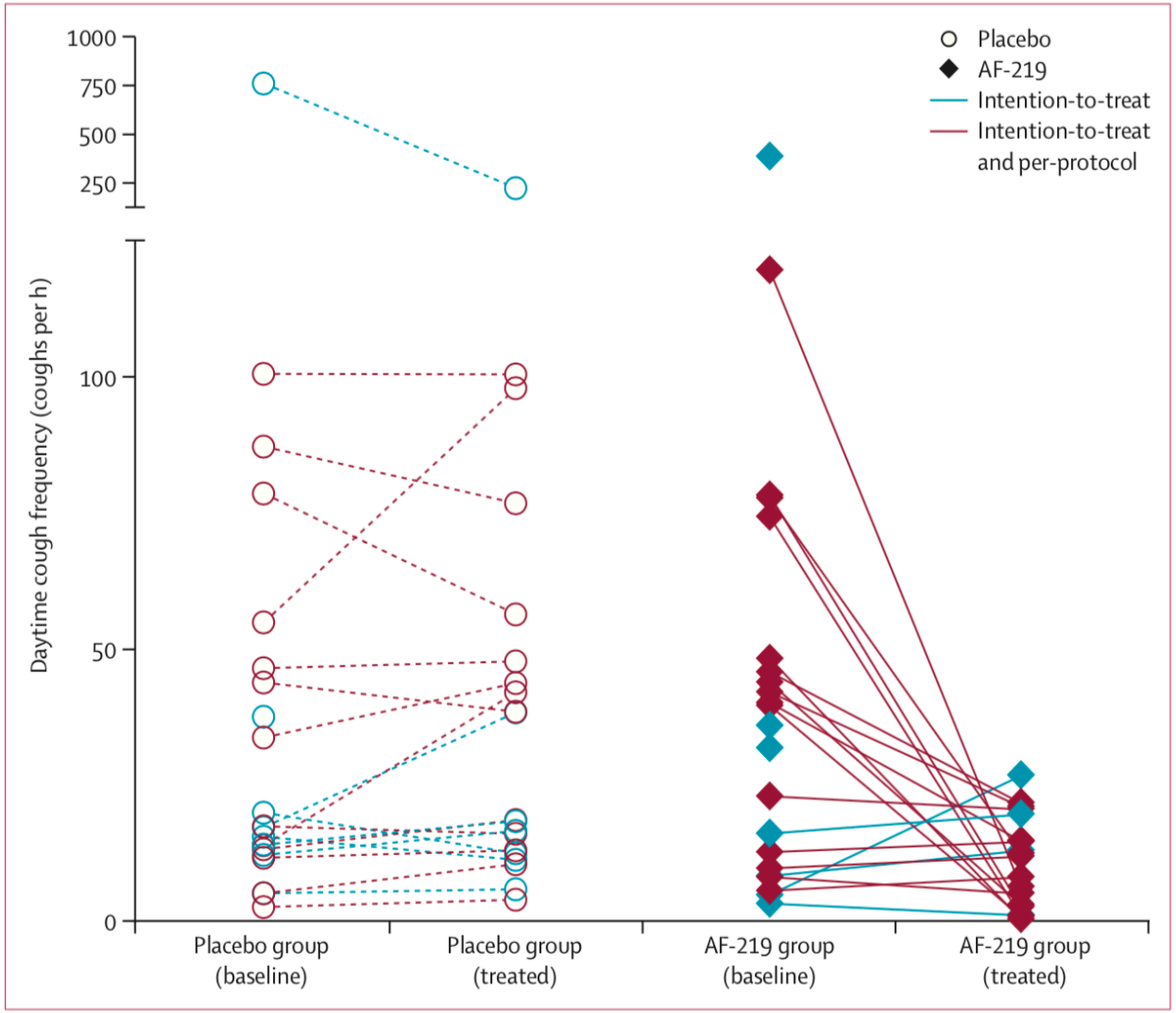
P2X3 receptor antagonists

- AF219/**MK7624/Gefapixant.**
- RCT. 2 week crossover design. 75 % reduction in cough frequency cf. placebo. Similar response for other measures (QOL, VAS, UTC)[1].

Not all patients respond.

Side effects-taste disturbance in 100% of patients at study dose (600mg).

Less selective P2X antagonist (P2X2/3 and P2X3)



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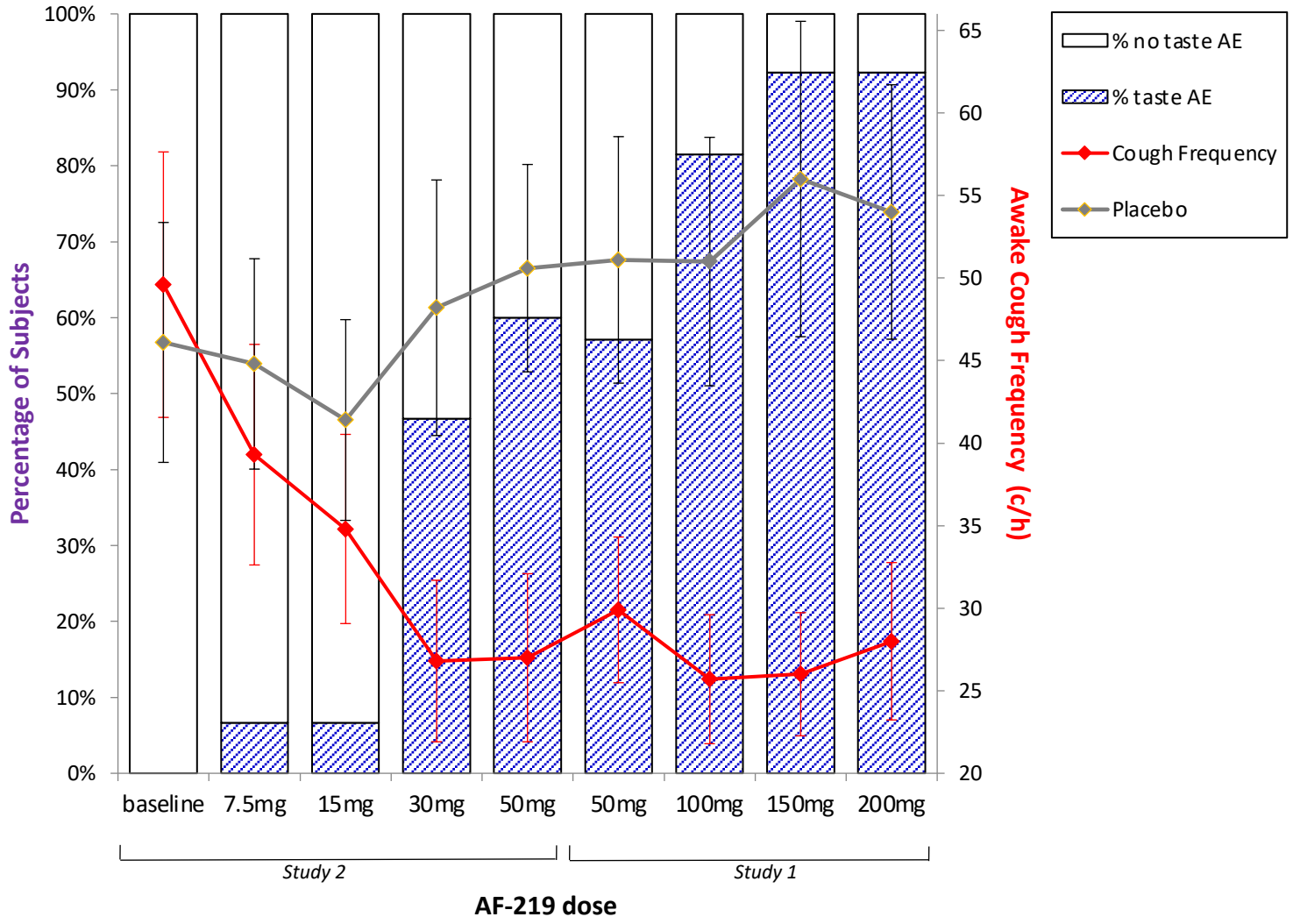
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al Lancet 2014

Phase 2b Study :Efficacy Maintained at Lower Doses with Improved Tolerability

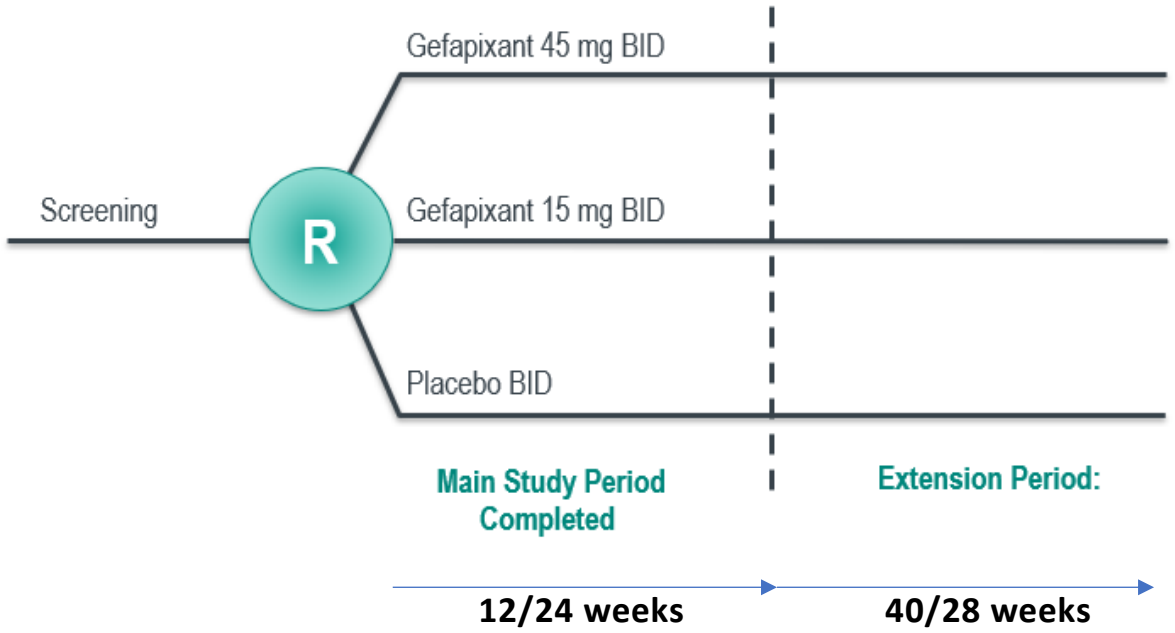


Smith et al Lancet 2020

Two Phase 3 Randomized Clinical Trials of Gefapixant, a P2X3 Receptor Antagonist, in Refractory or Unexplained Chronic Cough

STUDY DESIGN

- Two randomised, double-blind, placebo-controlled, 12-month phase III pivotal trials (COUGH-1; N = 730 and COUGH-2; N = 1,314)
- Conducted to assess the efficacy and tolerability of gefapixant (MK-7264) in subjects with refractory chronic cough (RCC) or unexplained chronic cough (UCC)
- Adults (≥18 yo) diagnosed with chronic cough (either RCC or UCC according to ACCP guidelines) for ≥1 year



McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

EFFICACY ENDPOINTS FOR THE PRIMARY ANALYSES

COUGH-1	COUGH-2
Primary efficacy endpoint	**Primary efficacy endpoint**
1. 24-hour cough frequency over 12 weeks	1. 24-hour cough frequency over 24 weeks
Key secondary efficacy endpoints	**Key secondary efficacy endpoints**
2. Awake cough frequency over 12 weeks	2. Awake cough frequency over 24 weeks
	3. Proportion of participants with a ≥1.3-point increase from baseline in LCQ total score over 24 weeks
3. Proportion of participants with a ≥30 mm reduction from baseline in 24-hour cough frequency over 12 weeks	4. Proportion of participants with a ≥30 mm reduction from baseline in 24-hour cough frequency over 24 weeks

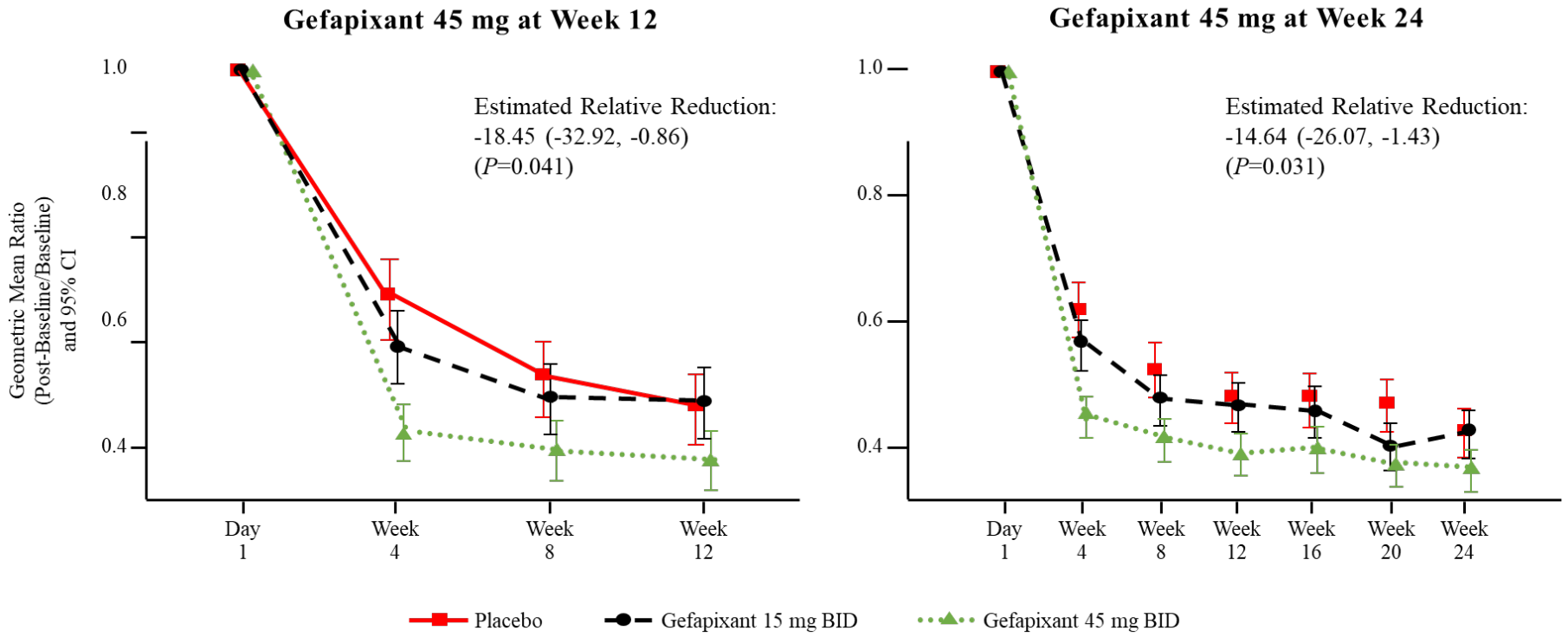
Objective cough frequency (coughs per hour) was counted using an ambulatory recording device (VitaloJAK™, Vitalograph Ltd); digital recordings were processed by Vitalograph.

McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

24-HOUR COUGH FREQUENCY OVER TIME: RATIO OF POST-BASELINE/BASELINE

COUGH-1 AND COUGH-2: MAIN PERIOD
GEOMETRIC MEAN RATIO (MODEL-BASED) AND 95% CI
FULL ANALYSIS SET

Gefapixant 45 mg BID demonstrated a significant reduction in 24h cough frequency compared to placebo in both COUGH-1 and COUGH-2.
Gefapixant 15 mg BID did not demonstrate a reduction in cough frequency when compared to placebo.



McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

Secondary Endpoint
LCQ total score at week 24:responder analysis (≥1.3-Point Increase from baseline)
COUGH-2 (P030): MAIN PERIOD
Full Analysis Set

Treatment	N	Week-24 Responders	
		n	%
Placebo	353	243	68.8
Gefapixant 15 mg BID	351	263	74.5
Gefapixant 45 mg BID	342	262	76.6

Treatment	Responders (model-based[#])				
	N*	%	Estimated difference vs Placebo	Odds Ratio vs Placebo (95% CI)	P-value
Placebo	406	70.6	--	--	--
Gefapixant 15 mg BID	404	76.1	5.55	1.33 (0.96, 1.84)	0.085
Gefapixant 45 mg BID	399	77.7	6.58	1.41 (1.01, 1.96)	0.042

[#]Logistic Regression Model

[*]N = Subjects with available data at week 24; N* = Subjects included in the analysis.

McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

AE Summary

COUGH-1 (P027): Main Period (Weeks 0 to 12)

All Subjects as Treated

	Placebo N = 243	Gefapixant 15 mg N = 244	Gefapixant 45 mg N = 243
Any AE	128 (52.7)	136 (55.7)	183 (75.3)
Serious AE	5 (2.1)	7 (2.9)	7 (2.9)
AEs Related to Treatment	32 (13.2)	46 (18.9)	152 (62.6)
Taste-related AEs[a]	8 (3.3)	26 (10.7)[b]	141 (58.0)[b]

[a]Taste-related AEs included ageusia, hypergeusia, hypogeusia, and taste disorder; difference in % vs. placebo for taste-related AEs were tested for significance

[b]P≤0.001 vs. placebo

There were two deaths (one in each study with one occurring on placebo and one on 15 mg); neither was considered to be related to treatment

McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

AE Summary

COUGH-2 (P030): Main Period (Weeks 0 to 24)

All Subjects as Treated

	Placebo N = 433	Gefapixant 15 mg N = 441	Gefapixant 45 mg N = 440
Any AE	314 (72.5)	347 (78.7)	383 (87.0)
Serious AE	16 (3.7)	13 (2.9)	14 (3.2)
AEs Related to Treatment	88 (20.3)	138 (31.3)	311 (70.7)
Taste-related AEs[a]	36 (8.3)	86 (19.5)[b]	302 (68.6)[b]

[a]Taste-related AEs included ageusia, hypergeusia, hypogeusia, and taste disorder; difference in % vs. placebo for taste-related AEs were tested for significance

[b]P≤0.001 vs. placebo

There were two deaths (one in each study with one occurring on placebo and one on 15 mg); neither was considered to be related to treatment

McGarvey L, Birring S, Morice A, *et al*. Two Phase 3 randomized clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough (COUGH-1 and COUGH-2). Presented at: European Respiratory Society (virtual); September 7, 2020; Vienna, Austria.

P2X antagonist development

- Merck (**Gefapixant**). Phase 3 studies (cough 1 and cough 2) positive. Working towards licensing.

More P2X3 selective molecules-less taste SE's

- Bellus **BLU 5937**. Selective P2X3. Further phase 2b dosing studies 2021 (NTGH)
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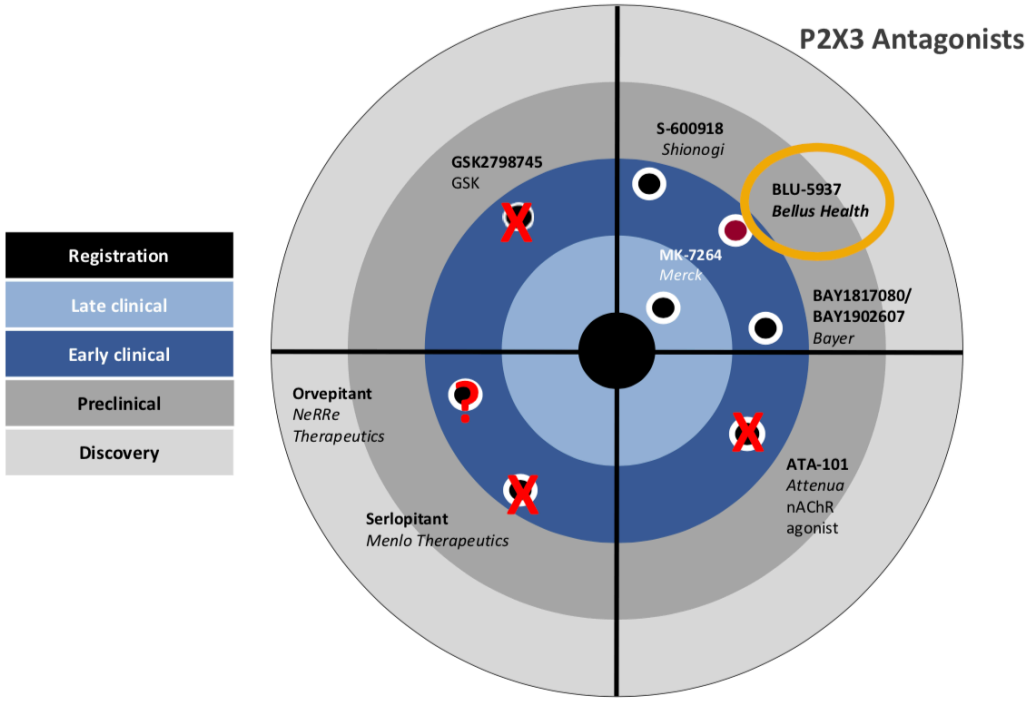
- Bayer 's **BAY1817080** & **BAY1902607.** Phase 2a studies complete. Further studies dosing phase 2b studies BAY1817080 'eliapixant' 2020/2021. (NTGH)



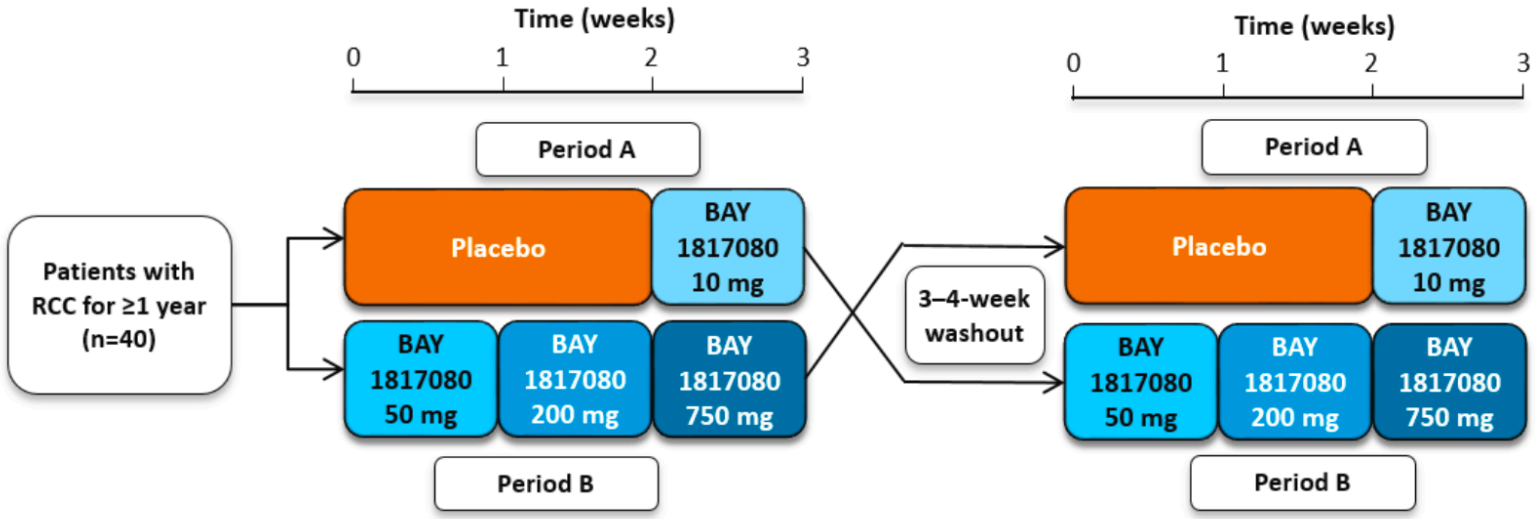
RCT BAY 1817080 vs placebo

Double blind randomized parallel group study.

Patients with RCC

Primary: 24 hr cough frequency

Secondary; VAS, LCQ

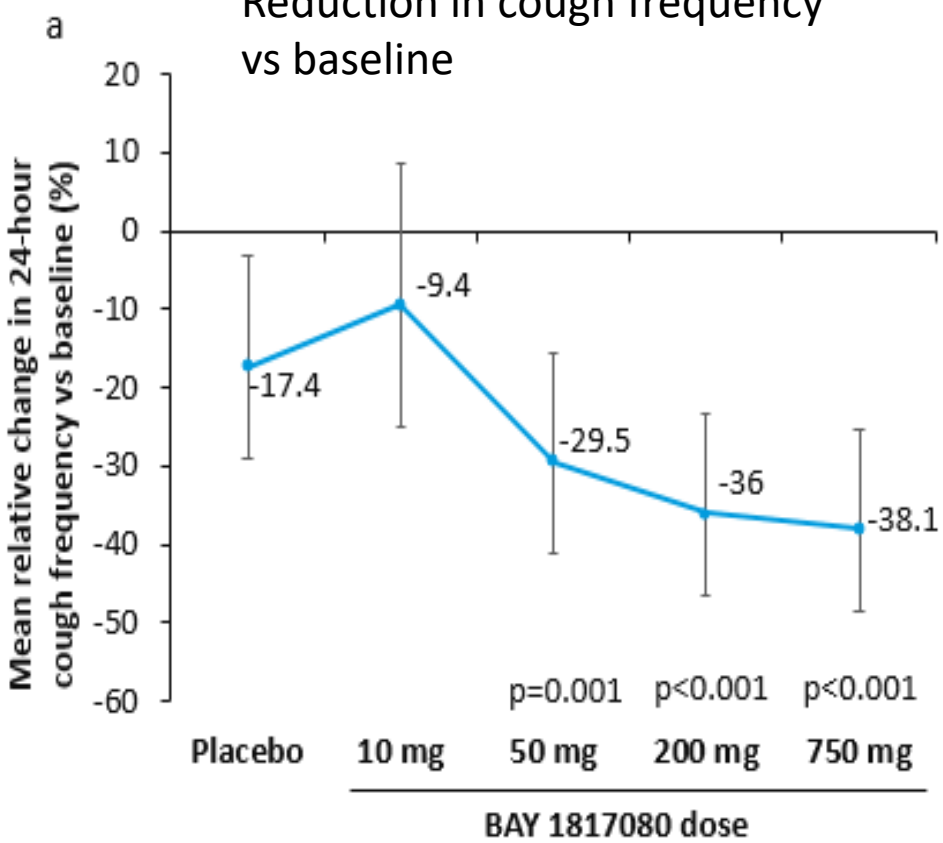


RCC, refractory chronic cough

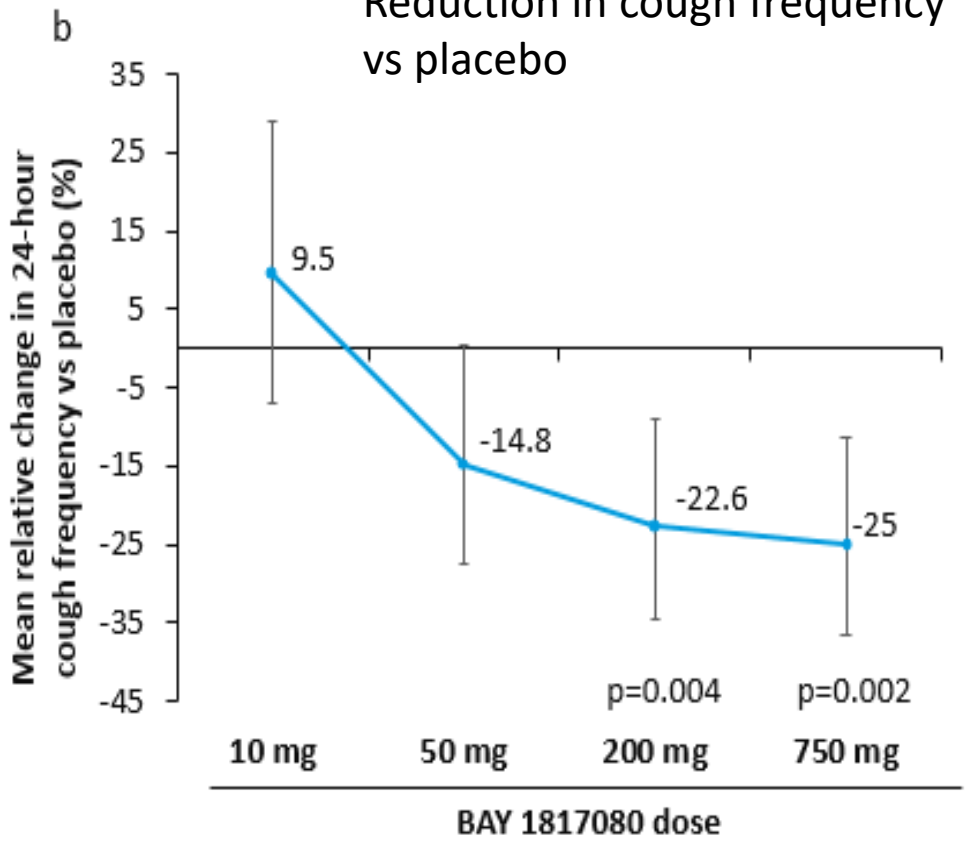
Figure 1. Study design (Part 2)

RCT BAY 1817080

Reduction in cough frequency vs baseline

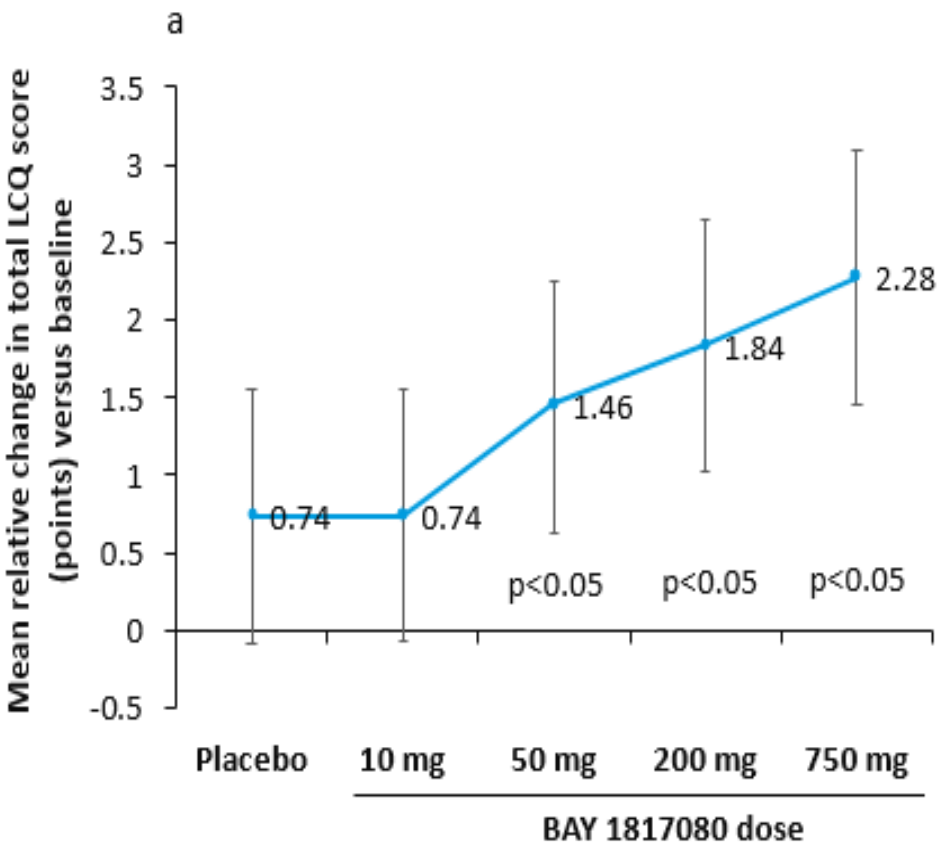


Reduction in cough frequency vs placebo

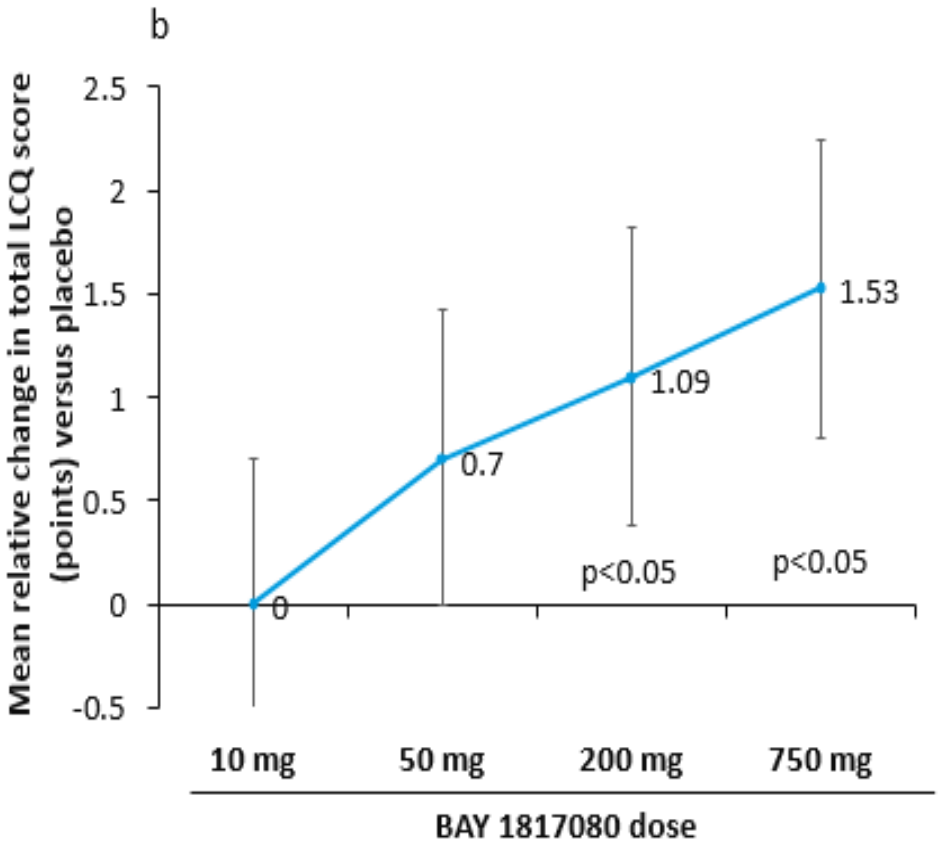


RCT BAY 1817080

Improved QOL (LCQ) vs baseline



Improved QOL (LCQ) vs placebo



RCT BAY 1817080 vs placebo

Note low rate taste SE's

Table 3. Safety summary

Share the document

AE, n (%)	Placebo (n=40)	BAY 1817080				All treatments n=40
		10 mg n=39	50 mg n=39	200 mg n=39	750 mg n=39	
Any AE	26 (65)	17 (44)	19 (49)	18 (46)	16 (41)	37 (93)
Any SAE	1 (3)[a]	0	0	0	0	1 (3)[a]
AEs reported in ≥10% of patients overall (not including taste-related events)						
Headache	6 (15)	2 (5)	5 (13)	3 (8)	1 (3)	15 (38)
Fatigue	4 (10)	1 (3)	2 (5)	1 (3)	1 (3)	8 (20)
Diarrhea	2 (5)	1 (3)	2 (5)	2 (5)	1 (3)	7 (18)
Nasopharyngitis	2 (5)	2 (5)	2 (5)	0	1 (3)	6 (15)
Cough	3 (8)	2 (5)	0	2 (5)	1 (3)	5 (13)
Dizziness	2 (5)	1 (3)	1 (3)	0	1 (3)	5 (13)
Upper respiratory tract infection	1 (3)	3 (8)	0	1 (3)	1 (3)	5 (13)
Oropharyngeal pain	0	0	2 (5)	2 (5)	0	4 (10)
Nausea	1 (3)	1 (3)	1 (3)	1 (3)	0	4 (10)
Taste-related AEs[b]						
Dysgeusia	1 (3)	0	4 (10)	4 (10)	3 (8)	9 (23)
Hypogeusia	0	0	0	1 (3)	0	1 (3)
Ageusia	0	0	0	1 (3)	0	1 (3)

P2X antagonist development

- Merck (**Gefapixant**). Phase 3 studies (cough 1 and cough 2) positive. Working towards licensing.

More P2X3 selective molecules-less taste SE's

- Bellus **BLU 5937**. Selective P2X3. Further phase 2b dosing studies 2021 (NTGH)
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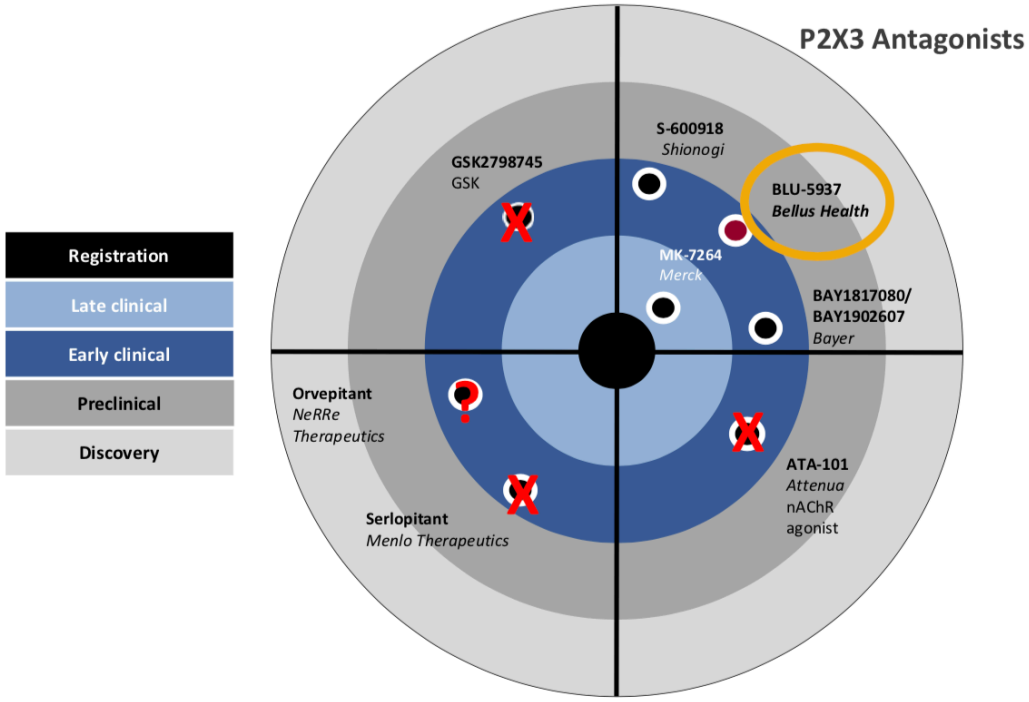
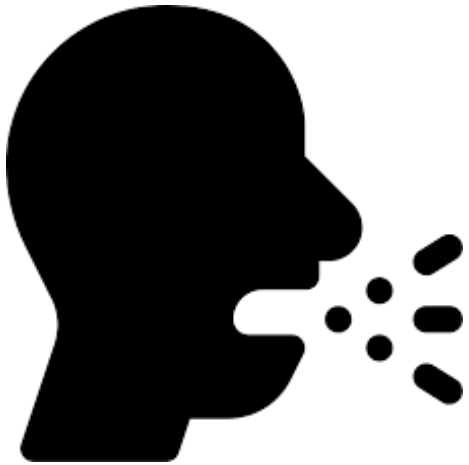


Non pharmacological cough control therapy

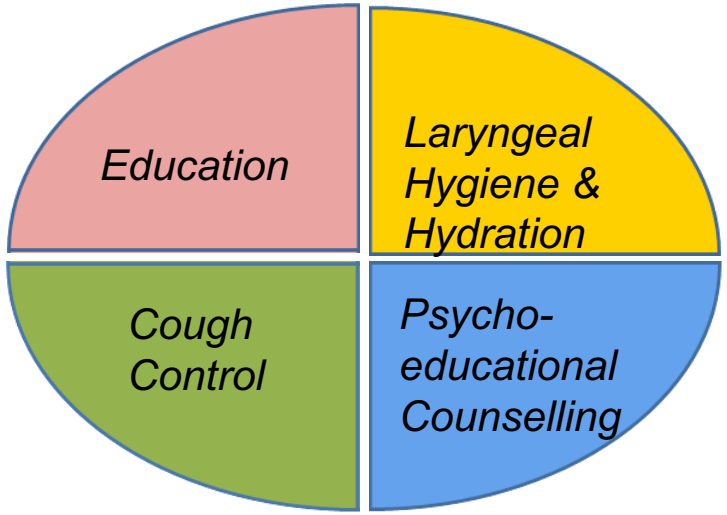


Non-pharmacological Cough Suppression Therapy (CST)

Complex Intervention
Best delivered by voice therapists
Emerging ‘respiratory SALT’ subspeciality.

Essential part of respiratory MDT.

Not a tertiary service-should be embedded in all 2ary care respiratory departments-need for service development.



Cough control therapy; complex intervention

Table 3
Non-pharmacological interventions' treatment components.
Modified from Ref. [14].

Non-pharmacological component	Technique
Education	Educate patients on cough: the anatomy of the reflex, that the cough reflex is both an involuntary and voluntary reflex, what chronic cough is and current understanding of how it can develop including the role of repeated irritation of vocal folds through repeated coughing as well as cough reflex hypersensitivity. Explain the negative effects of repeated coughing and throat clearing. Explain the aims and benefits of non-pharmacological interventions.
Vocal/Laryngeal hygiene and hydration	Increase frequency and volume of water and non-caffeinated drinks (at least 2 L a day) Reduce caffeine and alcohol intake Promote nasal breathing – nasal douching may be recommended to help nasal breathing if patient is congested. Nasal steam inhalation may be recommended to help humidification of the vocal tract.
Cough control/suppression techniques	Teach patients to identify their cough triggers so they are able to use cough suppression or distraction techniques at the first sign or sensation of the need or urge to cough. Cough suppression/distraction techniques include: forced/dry swallow, sipping water, chewing gum or sucking non-medicated sweets or lollies over a short period of time. Breathing pattern re-education promoting a relaxed abdominal breathing pattern technique whilst inhaling through the nose. May include PVFM release breathing, Cough Control Breathing and purse lip breathing
Psycho-educational counselling	Behaviour modification: to try to reduce over-awareness of the need to cough and facilitate individuals' internalisation of control over their cough. Motivate patients, reiterate the techniques and the aims of therapy Stress and anxiety management

PVFM - Paradoxical vocal fold movement.

Chamberlain Mitchell et al Pulm Pharm Ther 2019

COUGH

Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy

A E Vertigan, D G Theodoros, P G Gibson, A L Winkworth

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

See end of article for authors' affiliations

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Background: Chronic cough that persists despite medical treatment may respond to speech pathology intervention, but the efficacy of such treatment has not been investigated in prospective randomised trials. The aim of this study was to determine the efficacy of a speech pathology intervention programme for chronic cough.
Methods: A single blind, randomised, placebo controlled trial was conducted in 87 patients with chronic cough that persisted despite medical treatment. Patients were randomly allocated to receive either a specifically designed speech pathology intervention or a placebo intervention. Participants in both groups attended four intervention sessions with a qualified speech pathologist.
Results: Participants in the treatment group had a significant reduction in cough (8.9 to 4.6, $p<0.001$), breathing (7.9 to 4.7, $p<0.001$), voice (7.3 to 4.6, $p<0.001$) upper airway (8.9 to 5.9, $p<0.001$) symptom scores and limitation (2.3 to 1.6, $p<0.001$) ratings following intervention. There was also a significant reduction in breathing (6.8 to 5.6, $p=0.047$), cough (7.6 to 6.3, $p=0.014$), and limitation (2.3 to 2.0, $p=0.038$) scores in the placebo group, but the degree of improvement was significantly less than in the treatment group ($p<0.01$). Clinical judgement of outcome indicated successful ratings in 88% of participants in the treatment group compared with 14% in the placebo group ($p<0.001$).
Conclusion: Speech pathology is an effective management intervention for chronic cough which may be a viable alternative for patients who do not respond to medical treatment.

Chronic cough is a common problem that has an impact on resource utilisation and quality of life. It can persist despite medical treatment based on the anatomical diagnostic protocol in 12–42% of cases.[1–5] There is emerging evidence for the efficacy of behavioural approaches for the treatment for chronic cough arising from speech pathology intervention,[6–10] but the role of these treatments is not universally understood in either the medical or speech pathology communities. The efficacy of speech pathology management has yet to be evaluated before it can be recognised as a viable treatment option and incorporated into protocols for the management of chronic cough.

While chronic cough is considered an entity within respiratory medicine, chronic coughing and throat clearing might be conceptualised differently in the fields of otolaryngology and speech pathology. In some voice disorders, coughing and throat clearing are considered to be phonotraumatic or vocally abusive behaviours that have contributed to, exacerbated, or perpetuated the voice disorder. These behaviours may be considered habitual and targeted in treatment programmes for voice disorders. Vocal hygiene education for hyperfunctional voice disorders includes strategies to reduce coughing and throat clearing in individuals with voice disorders and has been found to improve voice quality.[11 12] However, these treatment programmes have not been systematically applied to persons with chronic cough.

Although preliminary research into behavioural management for chronic cough indicates that this form of intervention might be a feasible treatment option, the efficacy of these treatment approaches has not been systematically investigated, making it difficult to draw firm conclusions about their potential benefits. Reports of speech pathology management for chronic cough are limited by small subject numbers, lack of comparison groups, limited standardised prospective and objective measures for voice, and the lack of prospective and randomised trials.[8] Few studies of speech pathology management for chronic cough have explored treatment description and efficacy in detail.

The aim of the current study was to determine the efficacy of a speech pathology management programme for chronic cough by a prospective randomised trial of behavioural intervention. It was hypothesised that persons with chronic cough will have greater improvement in clinical outcome and symptom ratings following a speech pathology intervention than with a placebo intervention. In order to test this hypothesis, this study proposed to determine (1) whether individuals with chronic cough who received direct speech pathology intervention had a significant improvement in symptom ratings and clinical outcome; and (2) whether the extent of the change in symptom ratings was significantly different between individuals who received active treatment and those given a placebo intervention.

METHODS

A single blind, randomised, placebo controlled trial was conducted to examine the efficacy of speech pathology treatment for chronic cough. Participants were randomised to receive either Speech Pathology Evaluation and Intervention for CHronic Cough (SPEICH-C) (treatment) or an equivalent course of healthy lifestyle education (placebo). Symptom profiles were compared before and after intervention for the treatment and placebo groups along with clinical judgements of the outcome of intervention. The study was

Abbreviations: ACE, angiotensin converting enzyme; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GER, gastro-oesophageal reflux; PNDS, postnasal drip syndrome

Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial

Sarah A F Chamberlain Mitchell,[1,2] Rachel Garrod,[3] Lynne Clark,[4] Abdel Douiri,[5,6] Sean M Parker,[7] Jenny Ellis,[7] Stephen J Fowler,[8] Siobhan Ludlow,[9] James H Hull,[10] Kian Fan Chung,[10] Kai K Lee,[1] H Bellas,[11] Anand Pandyan,[2] Surinder S Birring[1]

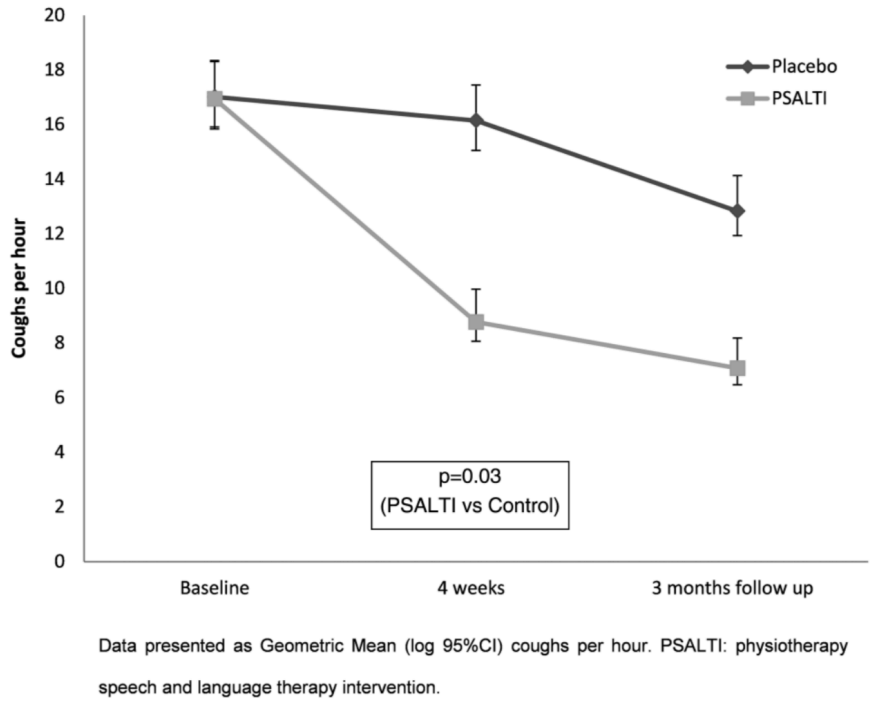


Figure 2 Change in objective cough frequency in physiotherapy, and speech and language therapy intervention (PSALTI) and control groups.

Chamberlain Mitchell et al Thorax 2017

Cochrane Library

Cochrane Database of Systematic Reviews

Authors' conclusions

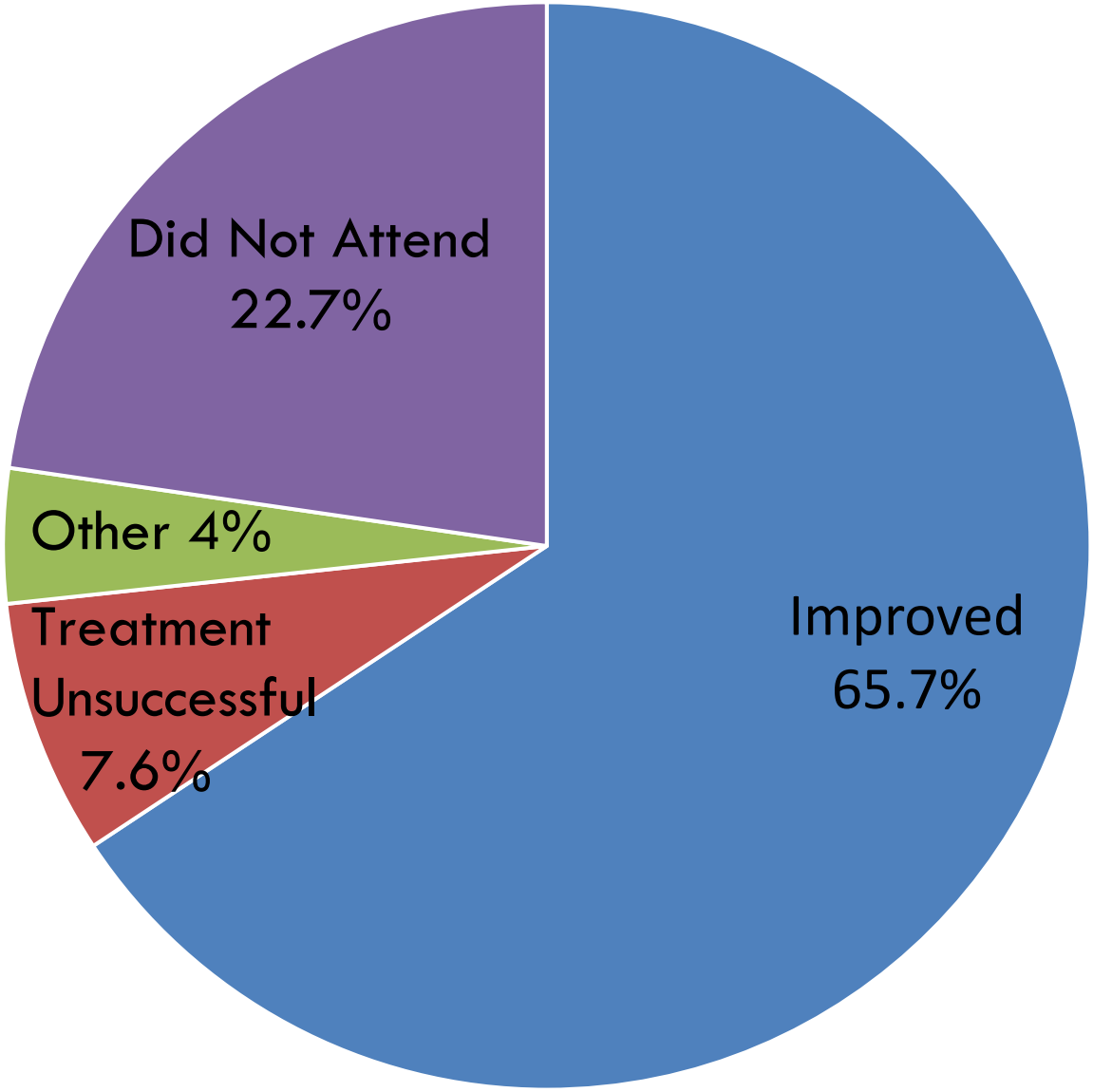
The paucity of data in this review highlights the need for more controlled trial data examining the efficacy of SLT interventions in the management of UCC. Although a large number of studies were found in the initial search as per protocol, we could include only two studies in the review. In addition, this review highlights that endpoints vary between published studies.

The improvements in HRQoL (LCQ) and reduction in 24-hour cough frequency seen with the PSALTI intervention were statistically significant but short-lived, with the between-group difference lasting up to four weeks only. Further studies are required to replicate these findings and to investigate the effects of SLT interventions over time. It is clear that SLT interventions vary between studies. Further research is needed to understand which aspects of SLT interventions are most effective in reducing cough (both objective cough frequency and subjective measures of cough) and improving HRQoL. We consider these endpoints to be clinically important. It is also important for future studies to report information on adverse events.

Because of the paucity of data, we can draw no robust conclusions regarding the efficacy of SLT interventions for improving outcomes in unexplained chronic cough. Our review identifies the need for further high-quality research, with comparable endpoints to inform robust conclusions.

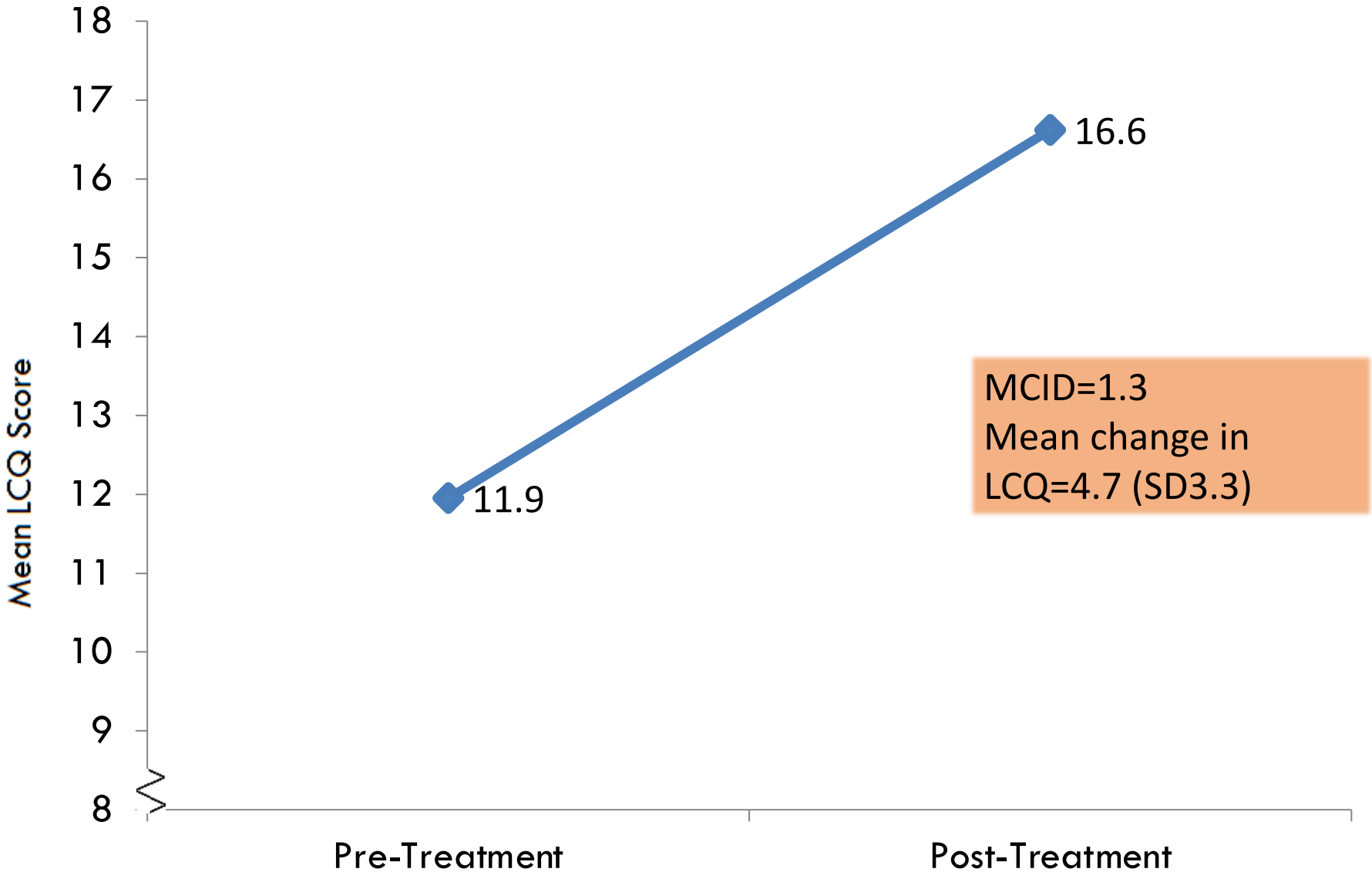
Slinger C, Mehdi SB, Milan SJ, Dodd S, Matthews J, Vyas A, Marsden PA.
Speech and language therapy for management of chronic cough.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD013067.
DOI: 10.1002/14651858.CD013067.pub2.

Subjective Outcomes following CST (n=228)



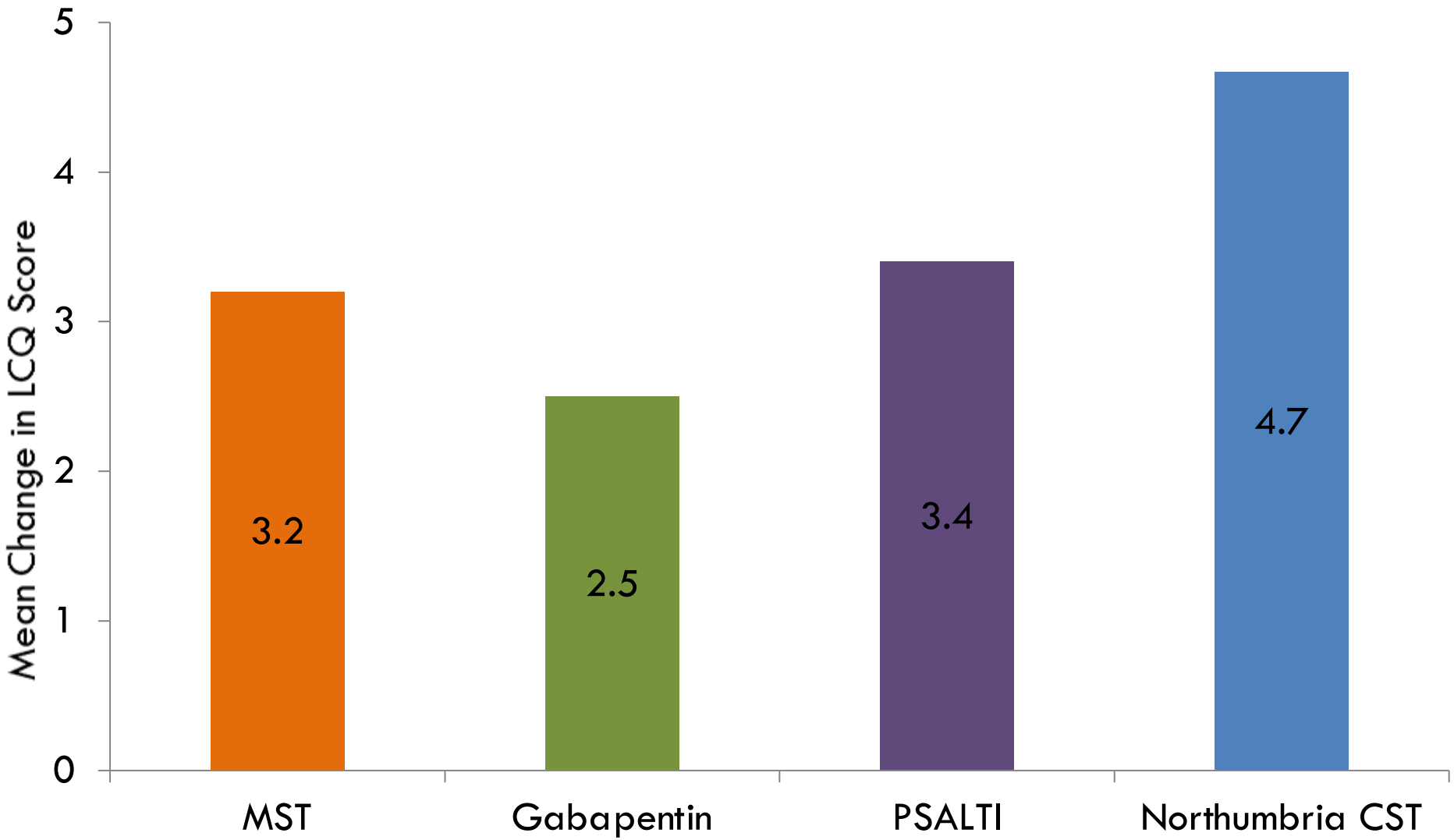
Mohammed S, Steer J, Ellis J, Parker SM. ERJ Open 2020.

Improvement in quality of life post CST



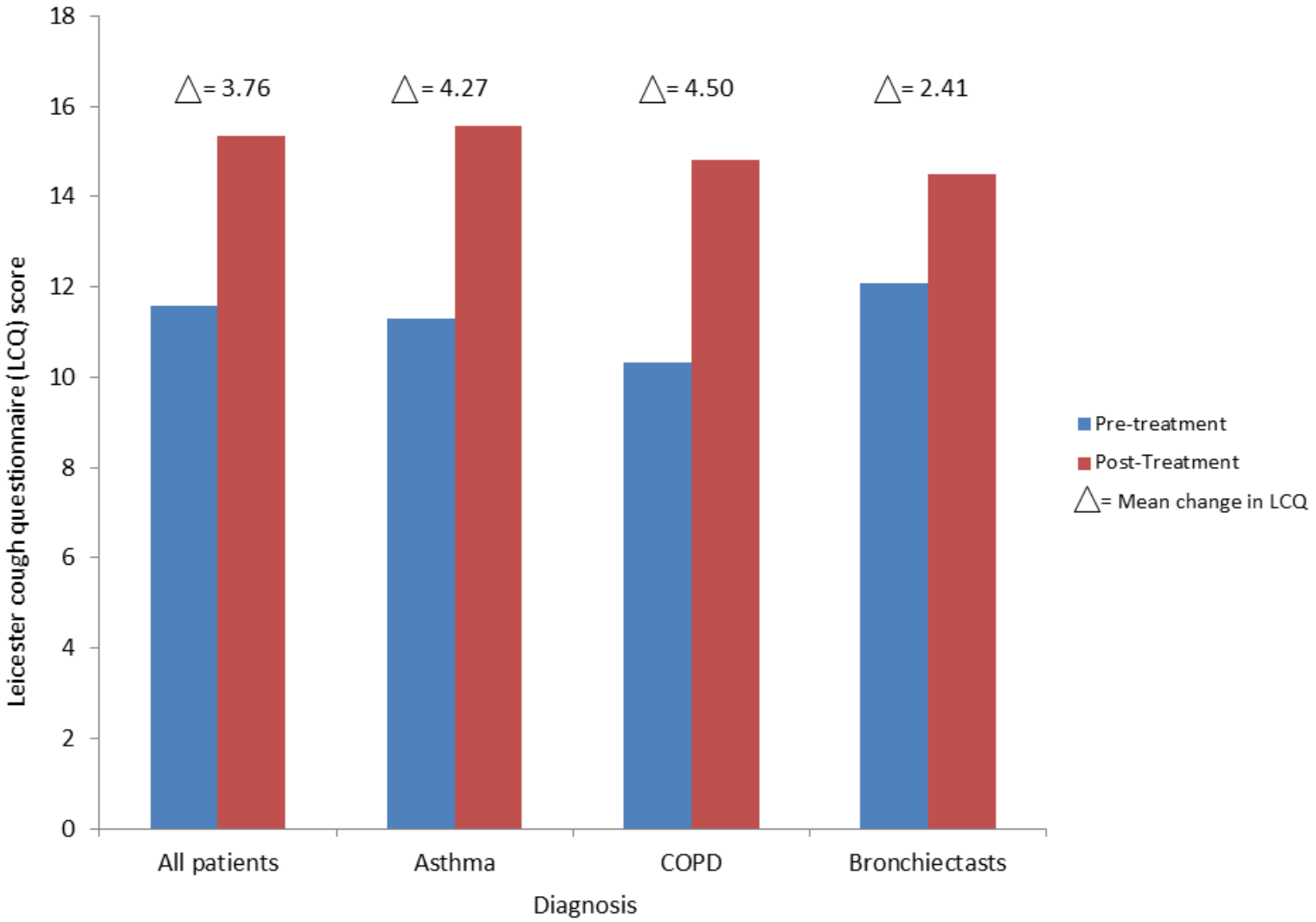
Mohammed S, Steer J, Ellis J, Parker SM. ERJ Open 2020.

CST compares favourably to other treatments



Morice et al. Am J Respir Crit Care Med 2007; 175: 312-315 Ryan et al. Lancet 2012; 380:1583-1589 Chamberlain Mitchell et al. Thorax 2017; 72: 129-136 Mohammed et al Thorax 2018

CST is useful in non CRC



Mohammed S, Steer J, Ellis J, Parker SM. ERJ Open 2020.

1 hour ★★★★★(275) GPs,GP trainees

More

Primary care symptoms: Chronic cough in an adult

Start module Add to portfolio

Respiratory consultant Dr Sean Parker guides you through the process of assessing and managing an adult patient who presents with chronic cough in primary care, including questions to ask the patient, the most likely causes, recommended investigations, initial management options, and when to refer.

This module forms part of the following courses:

- Common respiratory conditions

Learning outcomes

After completing this module, you should know:

- What questions to ask an adult patient presenting with a chronic cough

Any Questions?

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