Medicine

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The Practical Approach to Treating Chronic Cough

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WAN

Definitions

- ***Acute cough*** is defined as one lasting <3weeks

- ***Chronic cough*** is defined as one lasting greater >8weeks

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

A worldwide survey of chronic cough

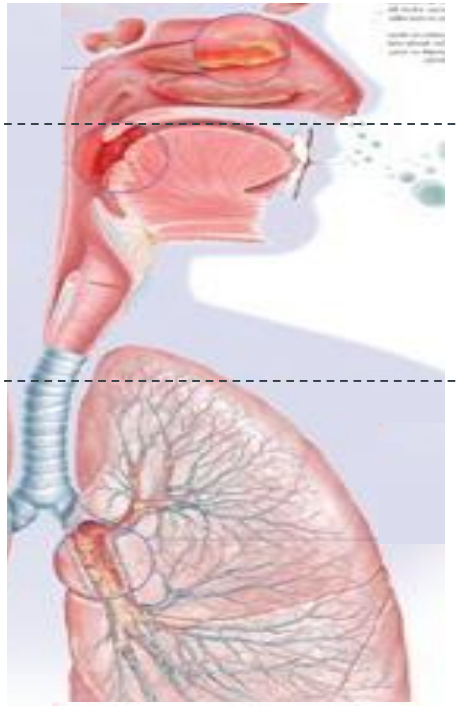
TABLE 1 Age and sex distribution of patients presenting to cough clinics within each country

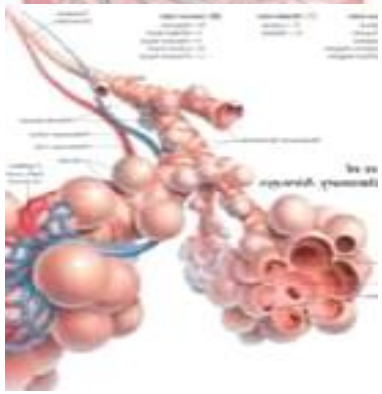
Country	Totals	Age group in years										
		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	⩾100
UK n=4792												
Total		0.02	1.29	2.80	7.35	17.3	24.7	28.7	14.7	3.00	0.08	0.02
Female	65	100	53	55	61	68	65	64	65	67	75	0
Male	35	0	47	45	39	32	35	36	35	33	25	100
USA n=1000												
Total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

The data are presented as percentages.

Eur Respir J 2014; 44: 1149–1155

Identifiable causes of cough





- Nasal
  - Rhinitis, sinusitis, polyps, post-nasal drip
- Laryngeal
  - GORD
  - Vocal cord dysfunction
  - Tumour
- Lung
  - COPD
  - Tumours
  - Bronchiectasis
  - Interstitial lung disease

Clinical presentation

- Mild, moderate or severe: score out of 10
- Daily
  - Day and night
- Periodic
- Associated symptoms
  - Loss of consciousness – Cough induced syncope
  - Incontinence
- Impact on lifestyle
  - Irritation, embarrassment, social isolation
  - Loss of employment

Assessment – not evidence based

- Primary care:
  - Staged treatment of obvious symptoms
  - Empirical treatment with nasal steroids, ICS, PPI
- Secondary care:
  - HRCT
  - Bronchoscopy

Assessment – in tertiary care

- Spirometry, DLCO and FENO
- Upper GI
  - Oesophageal manometry 24-hour pH/impedance
  - Endoscopy
  - Barium study
- HRCT
- ENT assessment:
  - Endoscopy
  - CT of the sinuses
- Speech therapist

Medical treatment of GORD

- Proton pump inhibitors (PPIs): e.g. esomeprazole
- Prokinetics
  - Domperidone
  - Cisapride
  - Azihtromycin
- Increased tone of Lower Oesophageal Sphincter (LOS)
  - Baclofen (a GABA(B) agonist) (max 20 mg tds)
  - Gabapentin

(γ-Aminobutyric acid – chief inhibitor neutrotransmiter)

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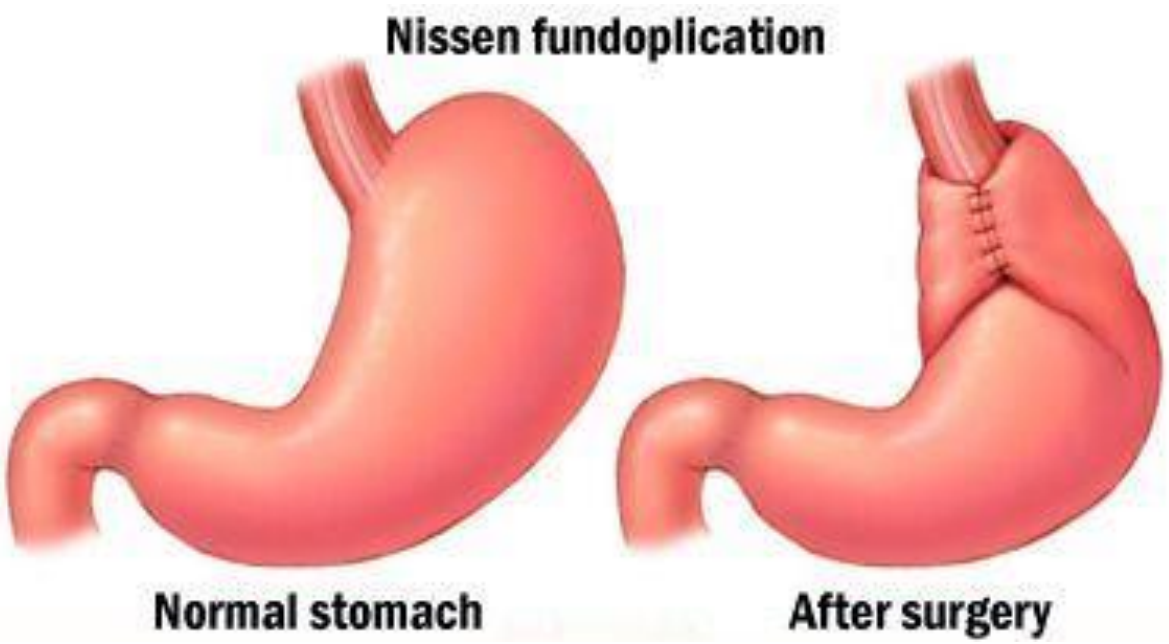
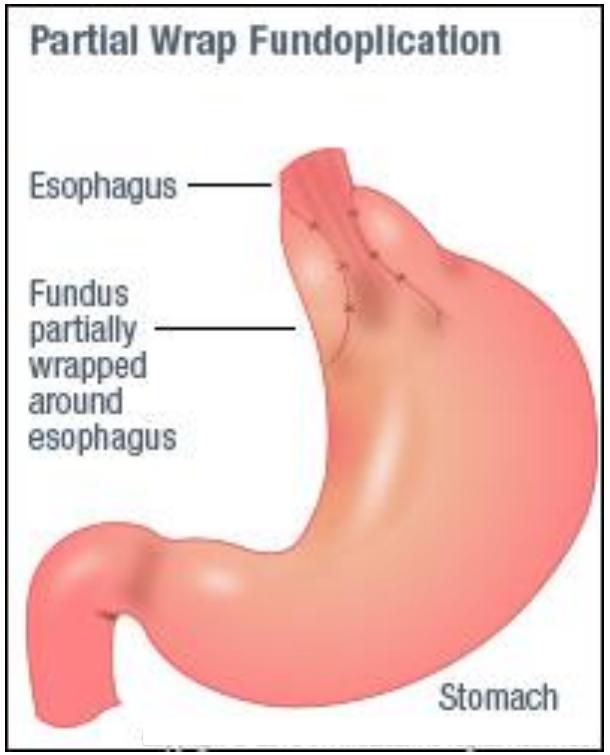
Surgical treatment of GORD





Endostim for the treatment of GORD

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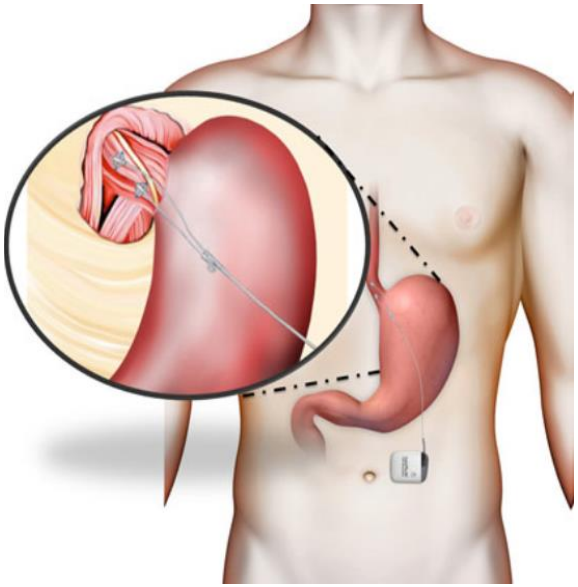
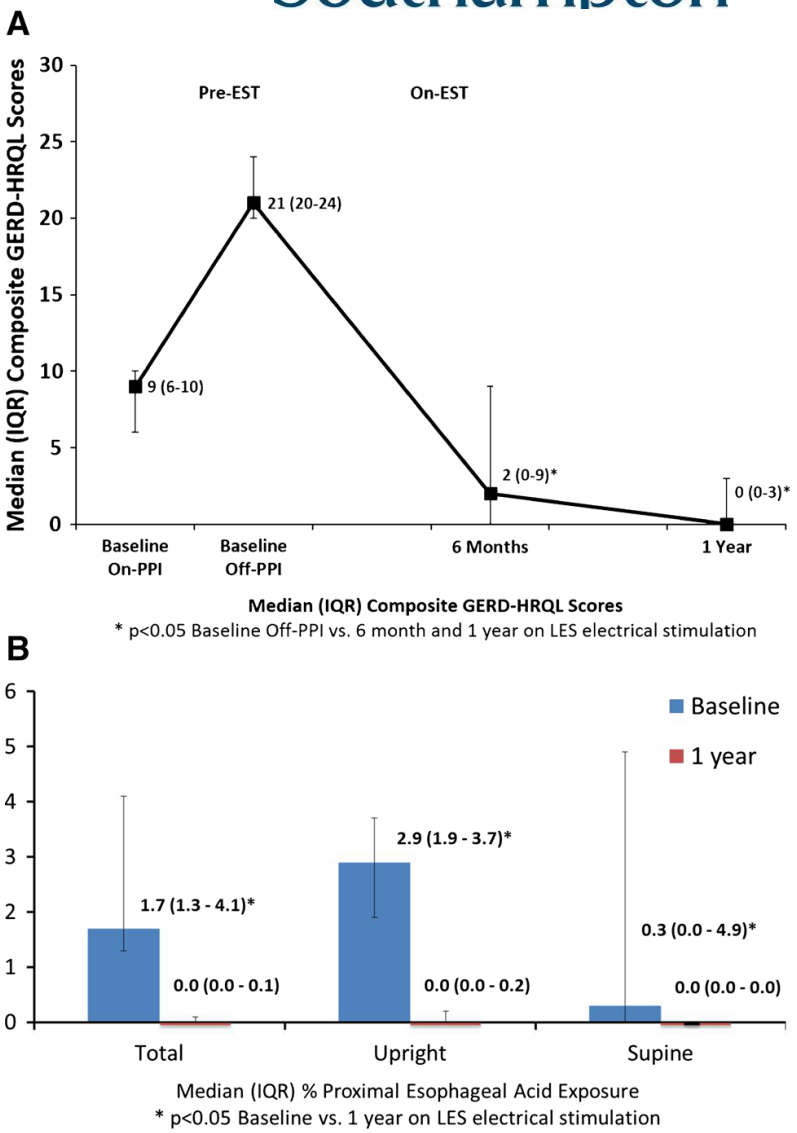




Hoppo, T. et al; Long-term results of electrical stimulation of the lower esophageal sphincter for treatment of proximal GERD ; Surg Endosc (2014) DOI 10.1007/s00464-014-3603-x

BTS GUIDELINES

Recommendations for the management of cough in adults

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

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

ERS TASK FORCE

The diagnosis and management of chronic cough

A.H. Morice and committee members

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

[Evidence-Based Medicine]

CHEST

Treatment of Unexplained Chronic Cough

CHEST Guideline and Expert Panel Report

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

Chest 2016;149:27

Unexplained (Idiopathic) Chronic Cough

Cough that persists despite appropriate investigation and treatment

- Chronic cough with no diagnosable cause (UCC)
- Explained but refractory cough
- Unexplained but refractory
- 20-42% of outpatient referrals

Chest guidelines 2016

Unexplained cough

- defined as a cough that persists >8 wk, and remains unexplained after investigation, and supervised therapeutic trial(s) conducted according to published best-practice guidelines;

- guideline/protocol based assessment process that includes objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis, or a therapeutic corticosteroid trial;

Chest 2016 guidelines

Unexplained cough –when not to treat

- In case of a negative workup for acid gastroesophageal reflux disease, proton pump inhibitor therapy should not be prescribed
- In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), inhaled corticosteroids should not be prescribed

Chest guidelines 2016

Unexplained cough – new treatments

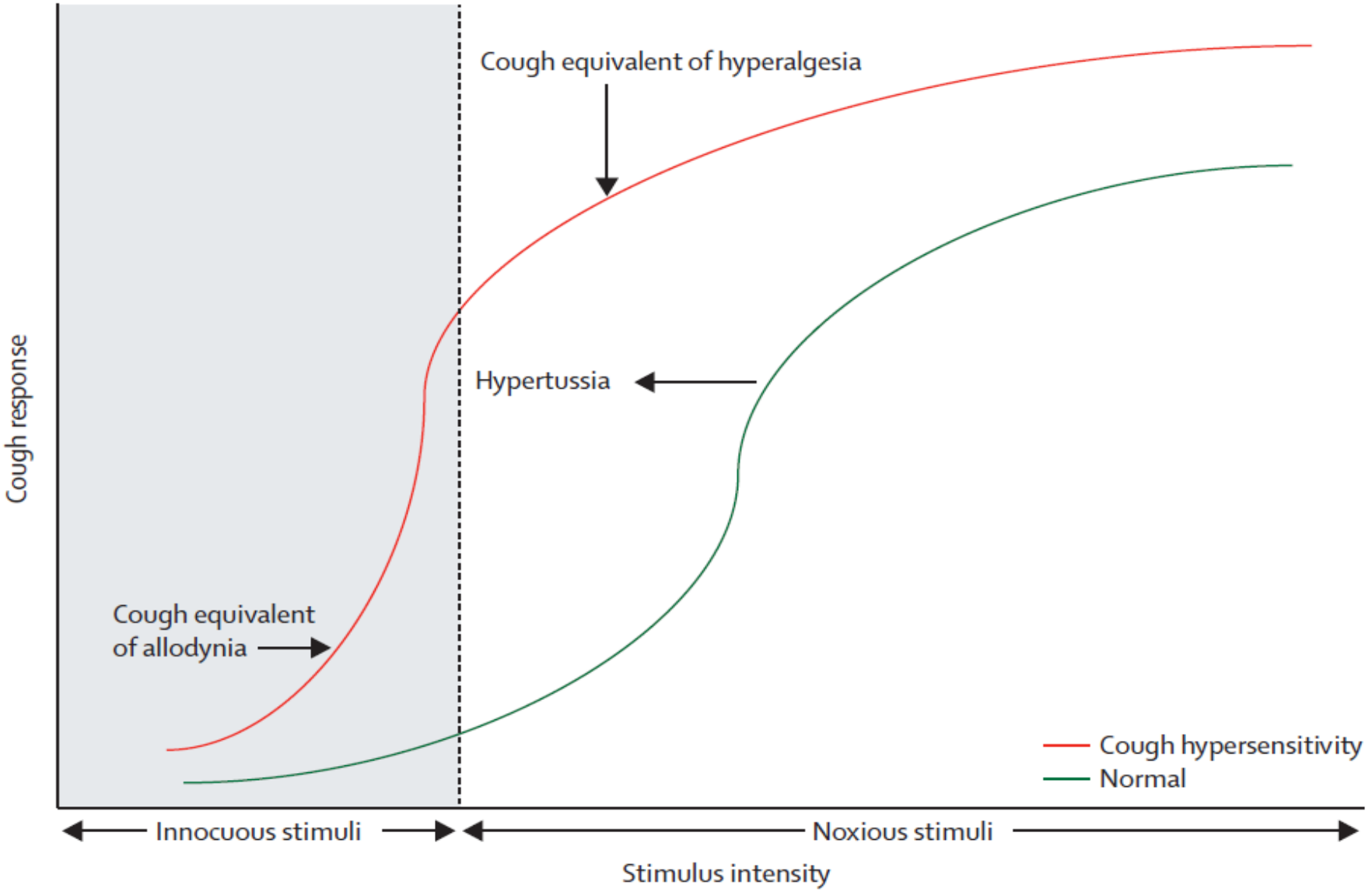
- Therapeutic trial of gabapentin
  - Discuss potential side effects and the risk-benefit profile and
  - Reassess the risk-benefit profile at 6 months before continuing the drug
- Therapeutic trial of multimodality speech pathology therapy

Chest guidelines 2016

Gabapentin

- Lipophilic analogue of the neutrotransmitter γ-aminobutyric acid
- Effective for neuropathic pain with central sensitisation
- Central sensitisation in chronic pain/cough
  - Paraesthesia (absence of stimulus)/Laryngeal paraesthesia (throat irritation/tickle)
  - Hyperalgesia (low exposure to known pain stimulus)/Hypertussia (tussive stimuli: smoke, fumes)
  - Allodynia (pain triggered by a non-painful stimulus)/Allotussia (cold air, talking)

Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states



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

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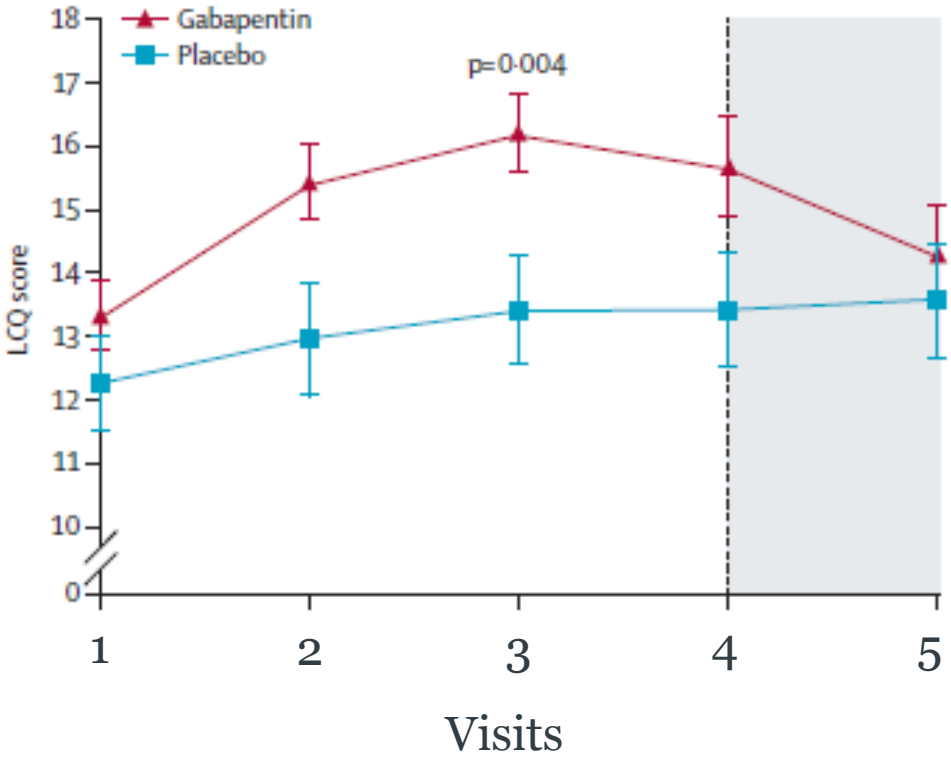
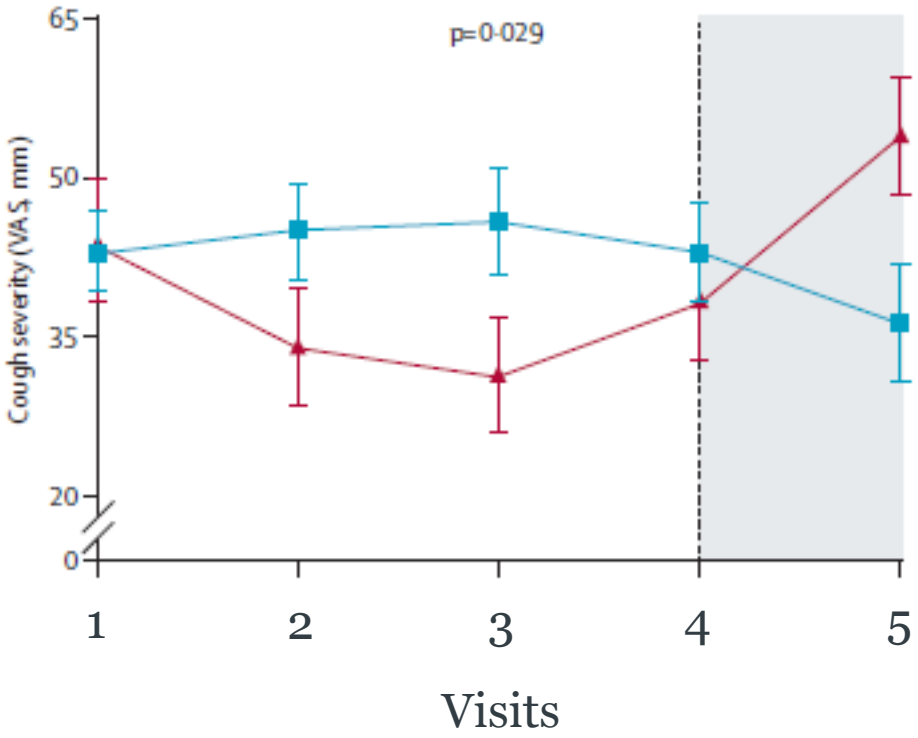
Gabapentin – 10 week RCT: up to 1800 mg





Ryan et al. Lancet 2012;380:1583

Gabapentin – side effects

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

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

Table 2: **Adverse effects**

Ryan et al. Lancet 2012;380:1583

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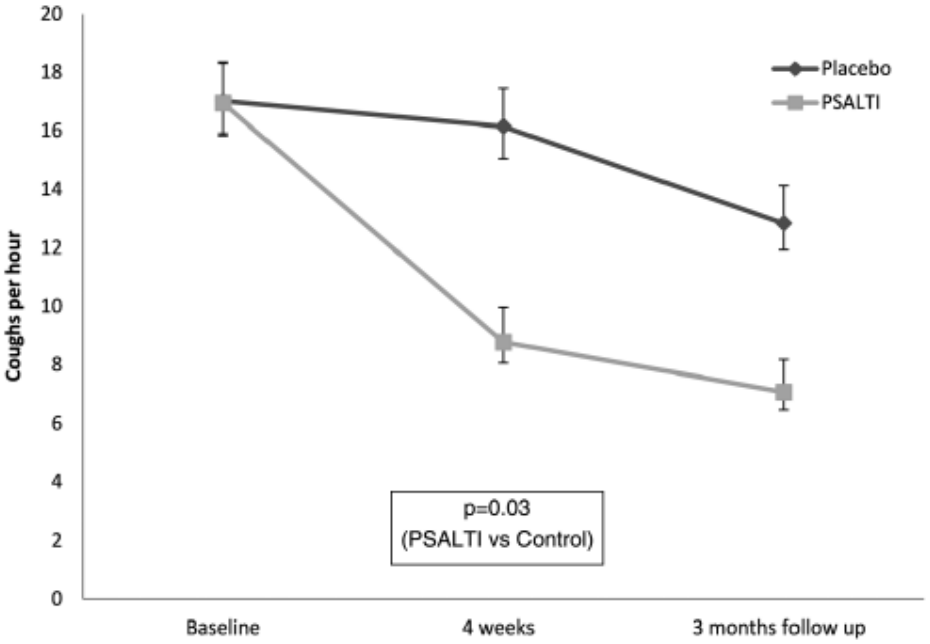
PSALTI

Table 1 PSALTI components

PSALTI component	Technique
Education	Educate patients on the cough reflex, chronic cough and cough reflex hypersensitivity. Explain the negative effects of repeated coughing. Educate patients on voluntary control of cough.
Laryngeal hygiene and hydration	Increase frequency and volume of water and non-caffeinated drinks. Reduce caffeine and alcohol intake. Promote nasal breathing.
Cough control	Teach patients to identify their cough triggers. Teach patients to use cough suppression or distraction techniques at the first sign or sensation of the need or urge to cough. These cough-suppression/distraction techniques include: forced swallowing, sipping water and sucking sweets. Teach patients breathing exercises: breathing pattern re-education promoting relaxed abdominal breathing pattern technique; pursed lip breathing to use to control cough.
Psychoeducational counselling	Motivate patients, reiterate the techniques and the aims of therapy. Behaviour modification: to try to reduce over-awareness of the need to cough. Stress and anxiety management

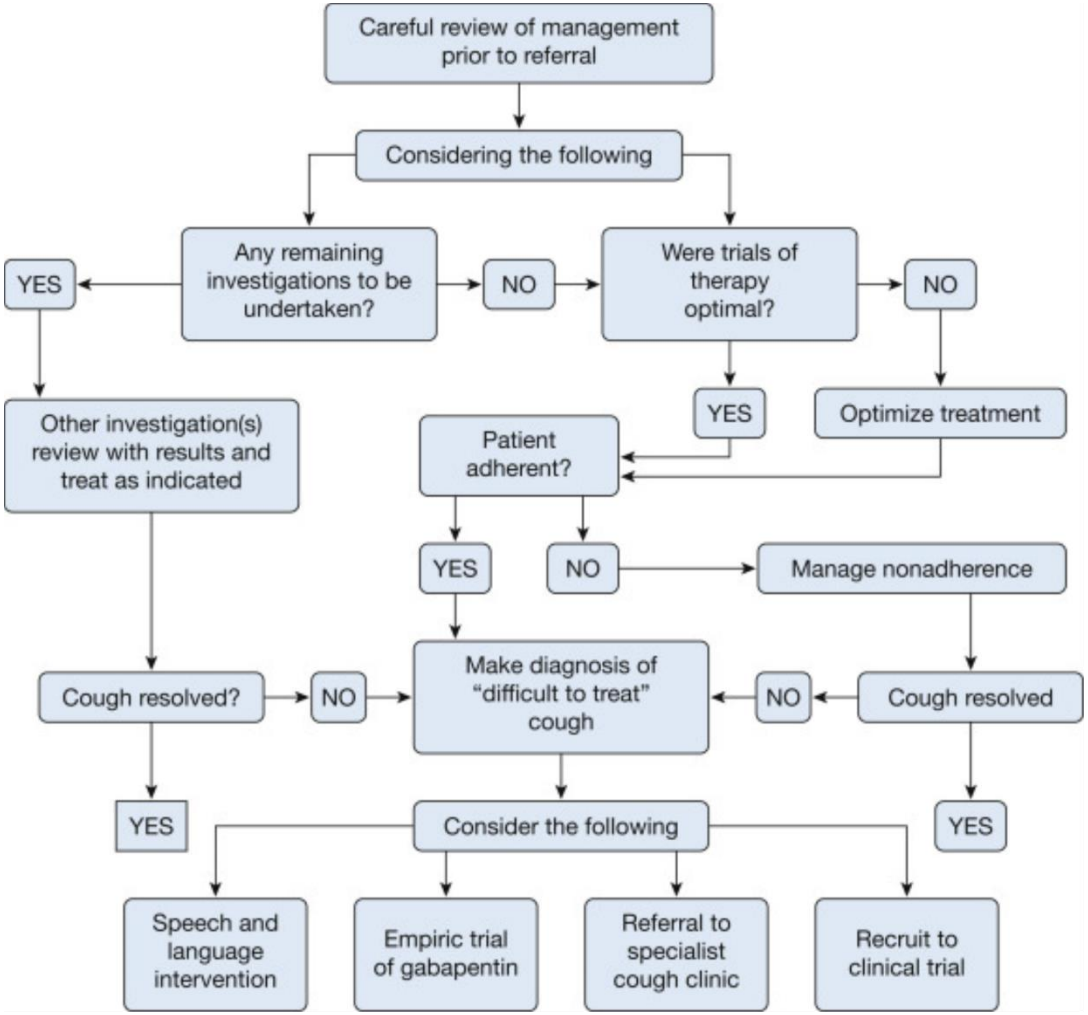
Modified from Chamberlain *et al.*[18]
PSALTI, physiotherapy, and speech and language therapy intervention.



Chamberlain et al. Thorax 2017;72:129

From: Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report

Chest. 2016;149(1):27-44. doi:10.1378/chest.15-1496

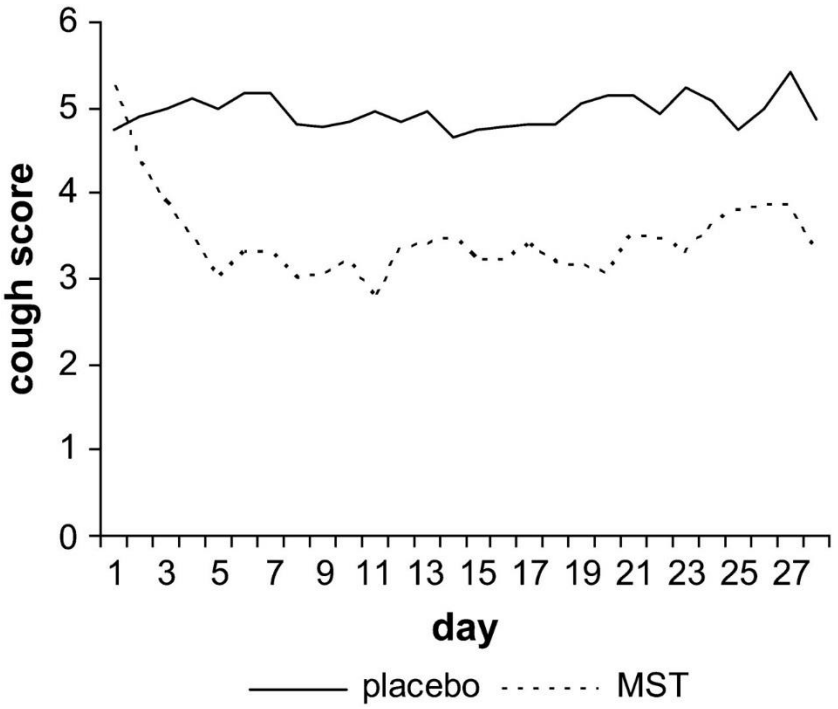


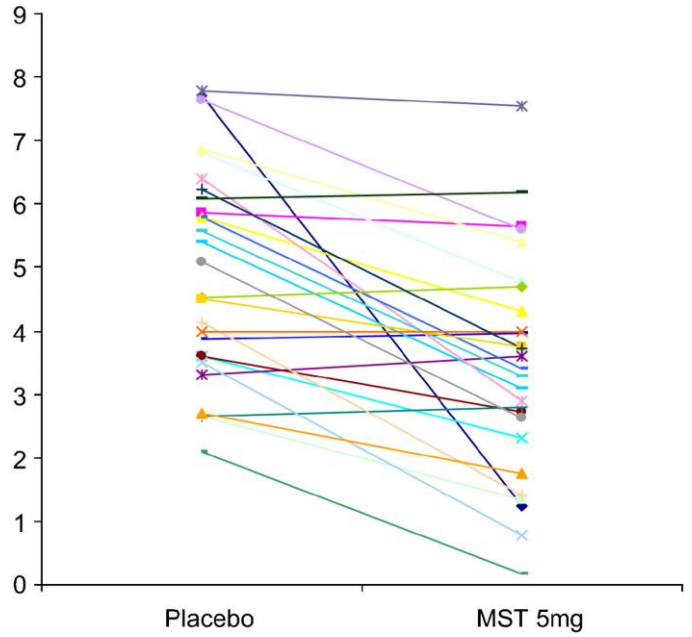
Other treatments

- Amitryptiline
- Morphine
- Potential new antitussives:
  - BW443C (μ-opioid receptor agonist)
  - SB-221122 (δ-opioid agonist)
  - Bradykinin (B2) receptor antagonists: Icatibant, HOE-140
  - Transient receptor potential vanilloid receptor-1 (Capsazepine – competitive antagonist of capsaicin)
  - P2X3 receptor antagonist

Morphine treatment of chronic cough:

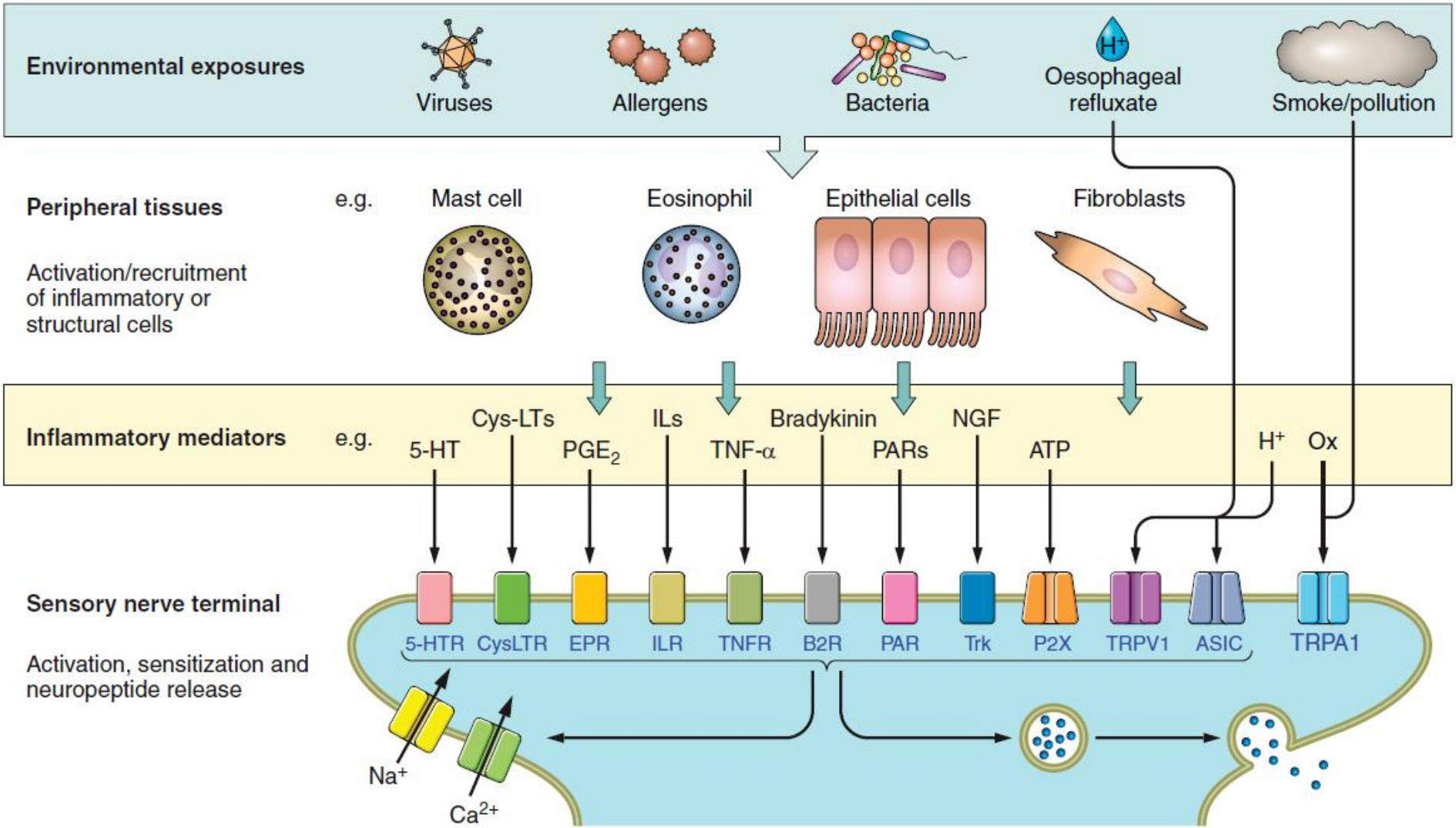
Action via μ-opioid receptors in the cough centres in the brain





Morice A et al. Am J Respir Crit Care Dis 2007;175:312 n=27 patients

Mechanisms of peripheral sensitization of airway afferent nerve fibers.



Physiol Rev 96: 975–1024, 2016

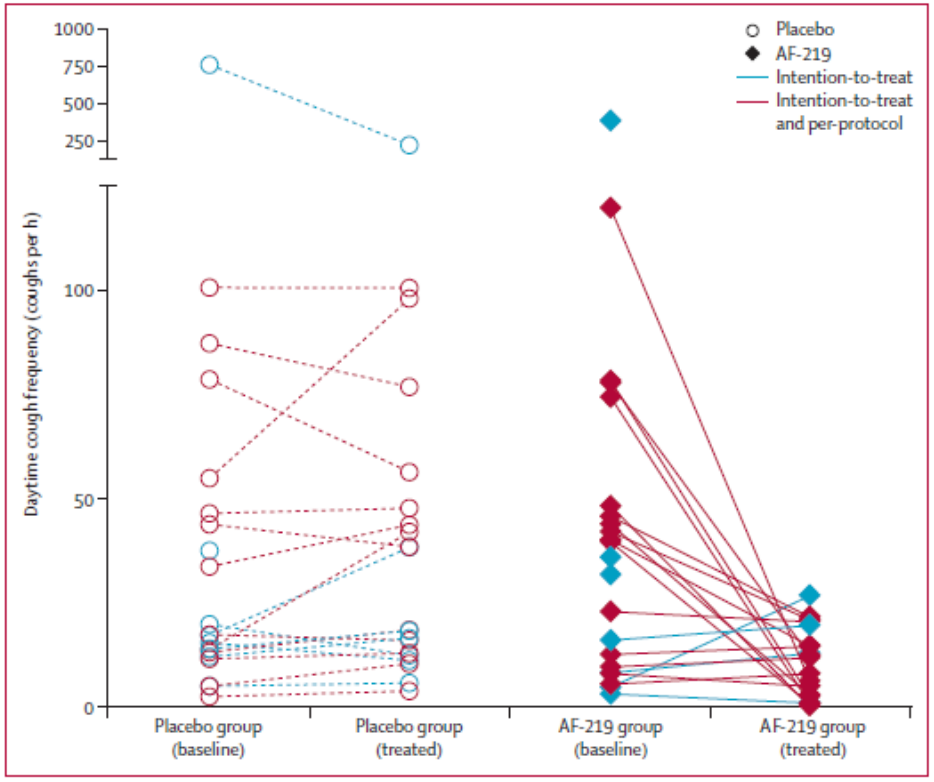
P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

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

Lancet 2015; 385: 1198–205

Summary

Background Preclinical studies suggest that P2X3 receptors are expressed by airway vagal afferent nerves and



	Placebo (n=22)	AF-219 (n=24)
Dysgeusia	0	21 (88%)
Hypogeusia*	0	13 (54%)
Nausea	1 (5%)	9 (38%)
Oropharyngeal pain	1 (5%)	5 (21%)
Headache	1 (5%)	3 (13%)
Salivary hypersecretion	1 (5%)	3 (13%)
Cough	1 (5%)	3 (13%)
Anosmia	0	2 (8%)
Constipation	0	2 (8%)
Gastro-oesophageal reflux disease	0	2 (8%)
Glossodynia	0	2 (8%)
Depressed mood	0	2 (8%)
Vision blurred	0	2 (8%)

Adverse events were classified according to MedDRA Version 14.0 and displayed by preferred term.*Reports of hypogeusia or ageusia were categorised as hypogeusia. Every patient reported at least one type of taste adverse event during AF-219 treatment.

Table 4: **Treatment-emergent adverse events reported by more than one AF-219-treated patient**

Take home message

- Assess the patient as much as possible – guided by the symptoms
- Treat the patient on the basis of symptoms and objective findings
- Refer to Southampton treatment-resistant cases:
  - Unexplained cough: morphine trial, experimental drug trials, mindfulness trial (soon to start)
  - GORD-induced cough if considered suitable for surgery
  - Last chance saloon