How to treat a cough

Sean Parker
Consultant Respiratory Physician
North Tyneside General Hospital
@drsmparker

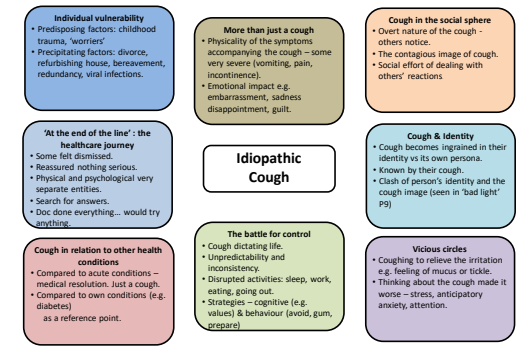
NHS
Northumbria Healthcare
NHS Foundation Trust

NHS
Northumbria Healthcare
NHS Foundation Trust

So what? It's only a cough…

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

Hulme et al ERJ Open Res 2017
Young et al Ther Adv Resp Dis 2010



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…

Common symptom in hospice palliative care. Complicates many conditions.

Lung cancer.
57% cough.
23% find it painful.
Predictor of poor QOL[2].

62% severe enough for treatment. Association with; Performance status. GI symptoms (reflux, nausea).

IPF
80% IPF patients cough. ↓QOL

Malassiotis et al Chest 2017.
Harle et al Chest 2018.
Stapleton et al Supp Care Cancer 2016.
Key et al Cough 2010

Original Article

PALLIATIVE MEDICINE

Management of chronic cough in patients receiving palliative care: Review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland

Bee Wee Oxford University Medical School and Fellow of Harris Manchester College, University of Oxford, Oxford, UK
Juliet Browning King's College London, London, UK
Astrid Adams Oxford Radcliffe Hospitals NHS Trust, Oxford, UK
Debbie Benson Wren Hallenvale Deanery, Worcester, UK
Paul Howard Sue Ryder, Berkshire West, Reading, UK
Gwen Klepping Oxford Radcliffe Hospitals NHS Trust, Oxford, UK
Alex Molassiotis School of Nursing, University of Manchester, Manchester, UK
David Taylor Buckinghamshire Hospitals NHS Trust, High Wycombe, UK

'**Despite the prevalence and distressing impact of chronic cough in patients with advanced, life-limiting illnesses, there is virtually no substantial evidence to support its management in clinical practice'**

with chronic cough. They also took into consideration convenience, toxicity and minimizing burden and harm or intervention, as well as considering the potential for disease-directed treatment and the possibility of pharmacological and co-existing benign causes of chronic cough.
Conclusions: These recommendations (Grade D) include simple linctus, therapeutic trial of sodium cromoglycate and then prescription of an opioid or opioid derivative (dextromethorphan, morphine or codeine). Further research is clearly and urgently required in this area for more effective approaches to managing cough, tested in trials that have sufficient size, power and validity.

Keywords
Antitussive agents, cough, palliative care, practice guideline, systematic review

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+

Short reports

Seven alternatives to evidence based medicine

David Isaacs, Dominic Fitzgerald

Basis of clinical practice

Basis for clinical decisions	Marker	Measuring device	Unit of measurement
Evidence	Randomised controlled trial	Meta-analysis	Odds ratio
Eminence	Radiance of white hair	Luminometer	Optical density
Vehemence	Level of stridency	Audiometer	Decibels
Eloquence (or elegance)	Smoothness of tongue or nap of suit	Teflometer	Adhesin score
Providence	Level of religious fervour	Sextant to measure angle of genuflection	International units of piety
Diffidence	Level of gloom	Nihilometer	Sighs
Nervousness	Litigation phobia level	Every conceivable test	Bank balance
Confidence*	Bravado	Sweat test	No sweat

*Applies only to surgeons.

1. Basic Science/physiology
2. Clinical approach to cough.
3. Antitussives

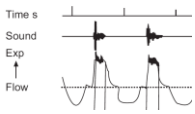
Generalised approach

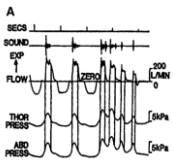
Based on what we know-try and draw out some principles that can be applied to all patients.

'Expert opinion' (Evidence grade 4…)

What is a cough? 'Cough' and 'expiratory reflex'

- "A forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound"[1].
- Physiological distinction between 'Cough' (preceded by inspiration), clear lower airway and 'Expiratory reflex' (no inspiration), prevent aspiration.
- 4 phase defensive reflex (inspiration, compressive (0.2 s), expulsive and restorative phases). May be voluntary.
- Likely complex of both in patients (they don't care which). Complex motor activity.





Widdicombe J, Fontana G. ERJ 2006; 28:10-15
Fontana G. Lung 2008; 186 (Suppl 1):S1-S4.

1. Morice AH et al ERJ 2007; 29:1256-1275

Protective reflex

NORMAL
'physiological cough'

IMPAIRED COUGH
Aspiration
Pneumonia
Elderly
EOL

ENHANCED COUGH
Unpleasant symptoms
↓QOL

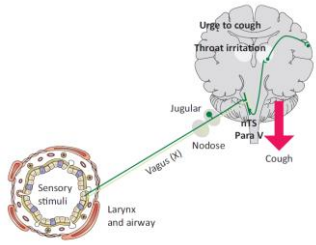
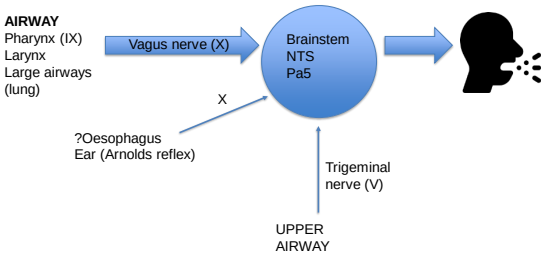


Fig 2. Schematic diagram representing the cough reflex. Vagal afferents transmit stimuli from the airways to the nucleus tractus solitarius (nTS) and paratrigeminal nucleus (Para V) in the brainstem. Neuronal signals are then transmitted to the somatosensory cortex via the thalamus causing throat irritation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

Satia et al Clinical Medicine 2016

Afferent input



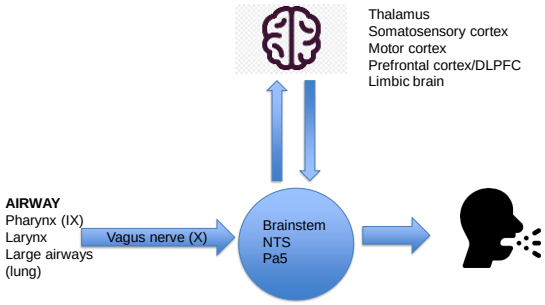
Afferent input

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

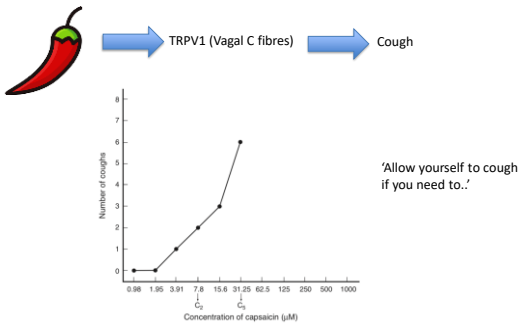
AIRWAY → Vagus nerve (X) → Brainstem NTS Pa5 (NK 1 (Sub P), NMDA, Glutamate)

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

Higher cerebral control –not just a brainstem reflex



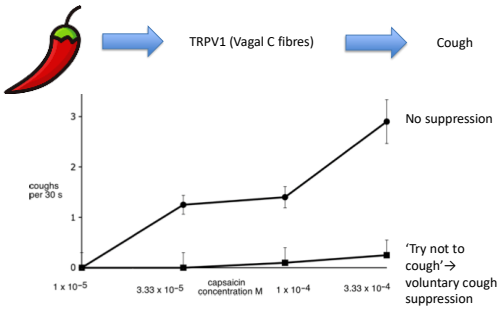
Capsaicin cough challenge



'Allow yourself to cough if you need to..'

Dicpinigaitis Hand exp pharm 2009

Volitional control of cough

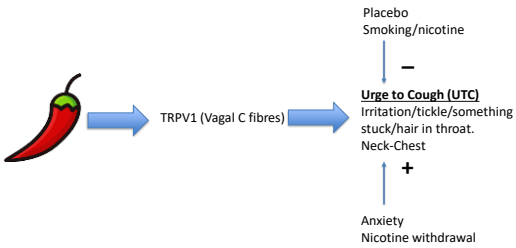


No suppression

'Try not to cough'→ voluntary cough suppression

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

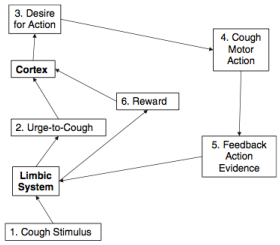
Urge to cough (UTC)- a key respiratory sensation



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

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

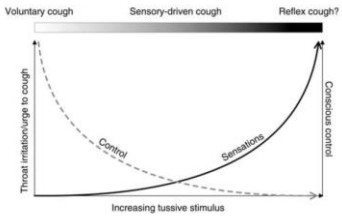


Fig. 1 Suggested relationships between voluntary coughing, sensory-driven cough and reflex cough.

Woodcock et al Brit Med Bull 2010

Higher brain control of cough-fMRI studies

- Cough not simply a brainstem reflex…
- Neural activation is seen[1] with capsaicin cough challenge:

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)

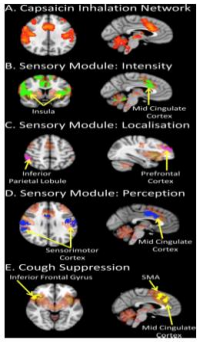
Motor
Voluntary cough (sensorimotor cortex, supplementary motor area, cerebellum)

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

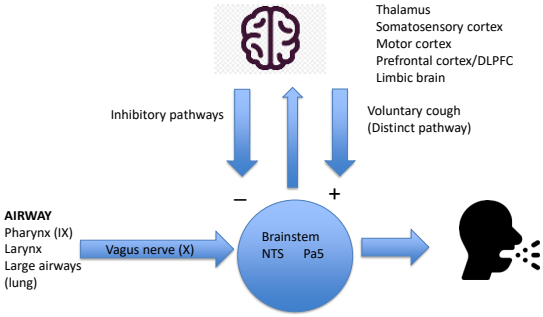
Voluntary cough (motor cortex)

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

1. Mazzone et al Cough 2013



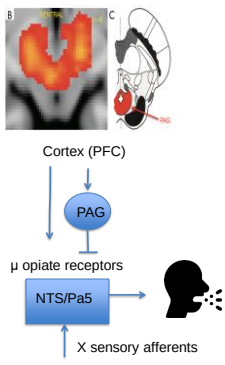
Higher cerebral control of cough



Descending inhibitory control-similar to pain.

- Elevated activity in peri-acqueductal grey matter (PAG), n. cunieformis, raphe nucleus in chronic cough/hypersensitivity.
- Endogenous 'analgesia' system. Stimulation of PAG induces deep analgesia. Endogenous opiates (μ receptors).
- PAG integrates sensory and cortical information. Matches behavioural response to competing demands.
- Very similar pattern of activation seen in chronic pain.
- Role in cough not entirely clear as yet.

McGovern et al J Thor Dis 2017
Ando et al Thorax 2016



The placebo effect and cough

- Placebo-major part of response to many cough medicines[1].
- Complex psychological factors.
- Opioid–ergic mechanisms involving the pre frontal 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].

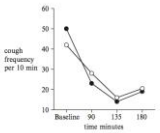
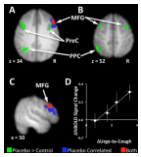


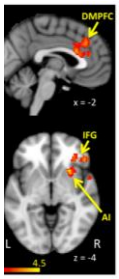
Fig. 2 Median cough frequency (per 10 min) for patients with cough associated with common cold. Immediately after the baseline measurement (0 min) patients were treated with either a single dose of 30 mg dextromethorphan powder in a hard gelatin capsule (*round symbols*, n = 21) or a matched placebo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

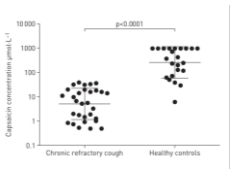


1. Eccles Hand exp pharm 2009
2. Leech et al Chest 2012
3. Van den bergh Lung 2012

Diminished central cough suppression network in chronic refractory cough

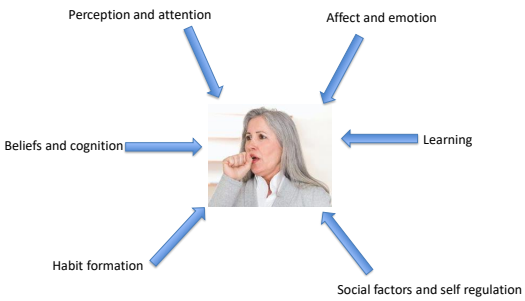
DMPFC
Anterior mid cingulate cortex
Right inferior frontal gyrus
Right anterior insula



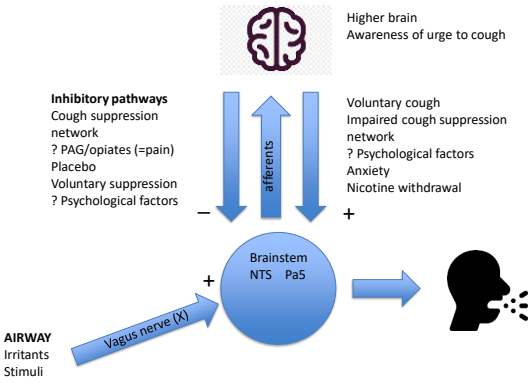


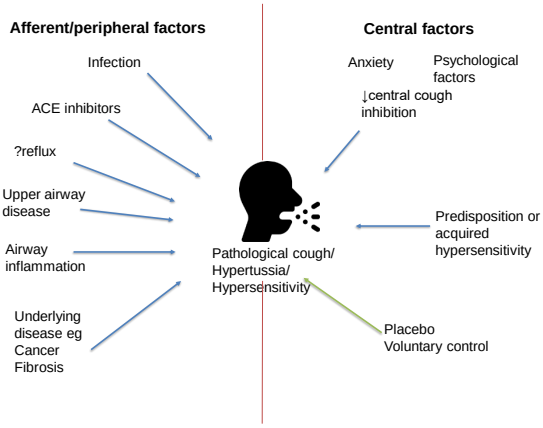
Ando et al Thorax 2016
Cho et al ERJ 2019

Possible psychological factors



Van den Bergh Lung 2012





Cough hypersensitivity

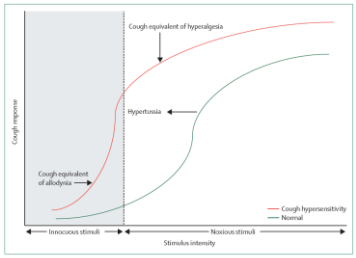


Figure 4: Relation between stimulus intensity and cough response in cough hypersensitivity, and parallel with abnormal pain states
Cough hypersensitivity results in cough in response to innocuous stimuli, as in allodynia.

Chung et al Lancet 2013

How do we help our patients who complain of cough?

1) Ineffective cough or overactive cough?

2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression

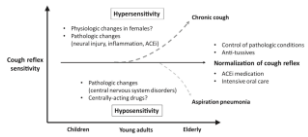
1) Ineffective cough or overactive cough?

2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression



Won et al Resp Phys Neurobiol 2018

Cough ↓ with;
Stroke
Dementia
Parkinsons disease

How to improve cough reflex?
Palliative care?
ACEI
'Oral care'
Capsaicin?
Physiotherapy

1) Ineffective cough or overactive cough?

2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression

Dry/non productive→ suppression

Infection →antibiotics/clearance

Blood→ address cause

Thick sputum →mucolytics/nebulized saline/clearance techniques

Weak cough→ physio/clearance/oral care

1) Ineffective cough or overactive cough?

2) Productive?

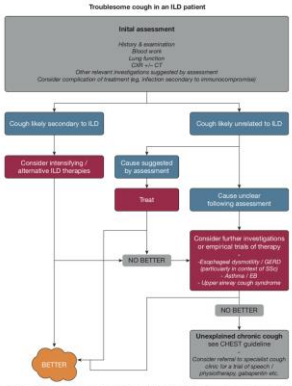
3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression

COUGH CATEGORY	DIFFERENTIAL
Noncancerous state	Neuromuscular pathology[a] • Multiple sclerosis • Amyotrophic lateral sclerosis • Hereditary ataxia • Late-stage dementia (irrespective of type) • Cerebrovascular disease
	Immunocompromised host[a] • Prolonged neutropenia • Organ transplant recipients • HIV infected (with CD4 lymphocyte count at < 200 cells/μL)
	End-stage heart failure End-stage respiratory failure End-stage kidney failure
Cancerous state	
• Directly caused by cancer	Pulmonary parenchymal involvement (primary or secondary Lymphangitic carcinomatosis Intrinsic or extrinsic airway obstruction by tumour Pleural effusion Pleural tumour (primary or implant) Multiple tumour microemboli Pulmonary leukostasis Superior vena cava syndrome
• Indirectly caused by cancer	Anorexia–cachexia syndrome Pulmonary aspiration Pulmonary embolus Paraneoplastic syndrome Radiotherapy sequelae Chemotherapy induced (eg, bleomycin, cyclophosphamide) Chemotherapy-induced cardiomyopathy (eg, adriamycin)
Unrelated to primary disease[a] (Chronic[a])	Upper airway cough syndrome[b] Asthma Gastroesophageal reflux disease Chronic bronchitis Bronchiectasis

Bonneau Can Fam Phys 2009



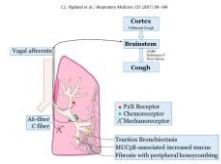
Birring et al Chest 2018

Figure 2 – A proposed algorithm detailing a management approach to troublesome cough in an interstitial lung disease (ILD) patient. CXR = chest radiograph, EB = eosinophilic bronchitis, GERD = gastro-esophageal reflux disease, SSc = systemic sclerosis.

Summary of trials in IPF-related cough.

Author/year	Study design	Intervention	Outcomes
Hope-Gill et al. [28] 2003	Observational 10 IPF, 10 healthy controls. 6 IPF patients with cough received the intervention	**Prednisolone** 40-60 mg for ≥ 4 weeks	Patients with IPF needed significantly lower concentrations of capsaicin to induce 2 and 5 coughs than the control group. IPF subjects who received prednisolone had a decrease in cough sensitivity and VAS after treatment.
Lutheuer et al. [29] 2011	Observational proof of concept study n = 12	**Interferon alpha** 150IU tds for ≥ 1 year	6 of the 12 IPF patients included reported chronic cough and of these 5 had a significant improvement in LCQ score
Horton et al. [30] 2012	Double-blind placebo-controlled cross over n = 24	**Thalidomide** 50-100 mg od for 12 weeks	CQLQ 11.4 point reduction with thalidomide compared to placebo. Significant improvement in cough VAS and SGRQ. Side effects from thalidomide common, though no dose reductions or withdrawals secondary to AE.
Birring et al. [31] 2017	Multi-centre double blind placebo controlled crossover trial n = 24	Nebulised **sodium cromoglycate** 40 mg tds for 14 days	31% reduction in daytime and 24-h objective cough frequency compared to placebo. Improvement in LCQ with treatment, but not statistically significant

Opiates
Neuromodulators
Non Pharmacological CST



Myall et al Pulm Pharm Ther 2019

Lung cancer

- Thorough assessment.

Look for cause
Cancer related
Other pathology

- Treat the cancer (surgery, chemotherapy, radiotherapy, ?brachytherapy)
- Antitussives (very little evidence)

Linctus
Steroids
Opiates
Neuromodulators
Lidocaine
Non Pharmacological
Rest..

TABLE 2] Causes of Cough Among Patients With Cancer[a]

Pleural disease-effusion, tumor
Lung parenchyma infiltration
Major airway or endobronchial tumor
Cough after radiation or after chemotherapy
COPD; chronic bronchitis
Bronchiectasis
Pericardial effusion
Upper airway cough syndrome due to a variety of rhinosinus conditions
Gastroesophageal reflux disease
Asthma
Lymphangitis carcinomatosis
Chest infection
Microembolism
Tracheoesophageal fistula
Vocal cord paralysis
Congestive heart failure
Postinfectious cough
Eosinophilic bronchitis
Angiotensin-converting enzyme inhibitor

[a]Reviewed in Tse.[2]

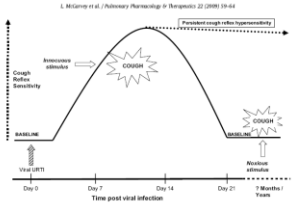
Malassiotis et al Chest 2017

1) Ineffective cough or overactive cough?

2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI



5) Cough not improving or specific treatment not possible→cough suppression

1) Ineffective cough or overactive cough?

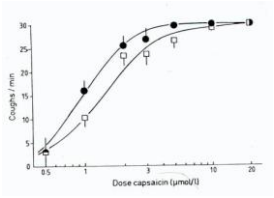
2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression

Morice et al Lancet 1987



ACE Inhibitors
Enhance cough reflex sensitivity.
Afferent sensitisation
Onset hours-months
Resolves slowly (90% in 1/12, may take up to 6/12), improvement variable.

Stop in <u>all</u> patients with cough.
A2 receptor blockers replace and well tolerated.

1) Ineffective cough or overactive cough?

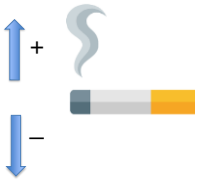
2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→cough suppression

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



↓Cough reflex sensitivity
Voluntary inhibition of cough

Nicotine inhibits the cough reflex

Cough worsens with stopping.

α7 nicotine receptor (drug target)

Dicpinigaitis 2018

1) Ineffective cough or overactive cough?

2) Productive?

3) Is there a specific cause?→Treat
Related to underlying problem?
Co-morbidity?
Look for 'treatable traits'

4) Any aggravants?
Smoking, Infection, ACEI

5) Cough not improving or specific treatment not possible→ cough suppression

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]

1. Smith et al Cochrane 2014

Cough treatments often no better than placebo..

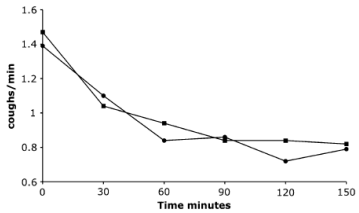


Fig. 1 Mean cough frequency before and after treatment with a single dose of codeine syrup B.P. (30 mg) in subjects with cough associated with acute upper respiratory tract infection. *Square symbols* indicate codeine syrup ($n = 46$) and *round symbols* indicate placebo syrup ($n = 45$) (redrawn from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

Eccles Lung 2010
Eccles et al J Clin Pharm 1992

Patients do benefit however..

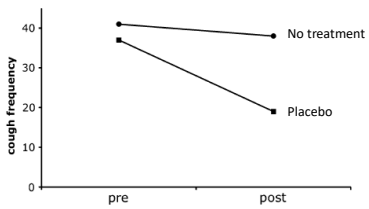
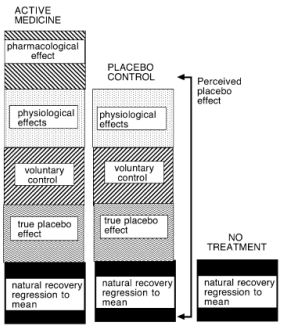


Fig. 3 Median cough frequency (per 15 min) pre-treatment and post-treatment. *Round symbols* represent the no treatment group and *triangular symbols* the placebo treatment group (redrawn from [18])

Eccles Lung 2010
Lee et al Psychosom Med 2005

How does cough medicine work



Eccles Lung 2010

Simple linctus/syrups/honey

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

Placebo

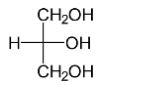
'Physiological' effect

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.

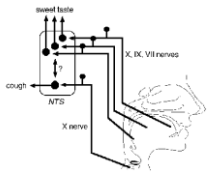
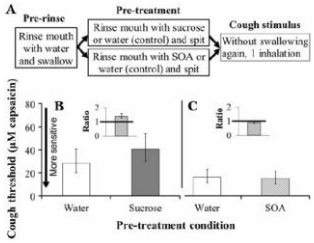


Fig. 3. Gustatory effects on cough. Gustation is mediated by branches of the VII (facial) IX (glossopharyngeal) and X (vagus) cranial nerves that supply the taste buds of the tongue. These gustatory fibres relay in the nucleus of the tractus solitarius (NTS) that also serves as the first relay for the 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.

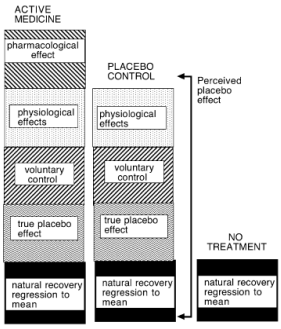
Eccles Resp Phys Neurobiol 2006

Sweet taste suppresses cough reflex



Wise et al Lung 2014

How does cough medicine work



Eccles Lung 2010

What can we use to treat the cough?

1. OTC medicine
Simple Linctus. Honey.
Dextromethorphan
Guaifenesin
Mucolytics
Antihistamines
Menthol
Herbal/complementary
2. Prescription medicines
Opiates; Codeine, Morphine
Neuromodulators; Gabapentin/pregabalin
Lidocaine (nebulised)
3. Novel Antitussives in development
4. Non Pharmacological Cough Suppression/Control therapy

What can we use to treat the cough?

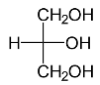
1. OTC medicine
Simple Linctus. Honey.
Dextromethorphan
Guaifenesin
Mucolytics
Antihistamines
Menthol
Herbal/complementary
2. Prescription medicines
Opiates; Codeine, Morphine
Neuromodulators; Gabapentin/pregabalin
Lidocaine (nebulised)
3. Novel Antitussives in development
4. Non Pharmacological Cough Suppression/Control therapy

Simple linctus/syrups/honey

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

Placebo
'Physiological' effect
Demulcent effect (soothing); coat and lubricate pharyngeal surface
Lubrication
Sweetness

- Some weak evidence that honey may be beneficial;
- 'Honey probably relieves cough symptoms to a greater extent than no treatment, …. or placebo[2]'



Eccles and Mallefet Pharmacy 2017
Oduwole et al nCochrane database Syst Rev 2018

Dextromethorphan

- **Dextromethorphan**.
- Mechanism

Central action
Active metabolite dextrorphan
NMDA, σ-1, nAChR, 5HT.

- Reduces cough reflex sensitivity in experimental studies.
- Conflicting studies in acute cough. Meta analysis suggests effectiveness but poor quality studies.
- Dextromethorphan; mild stimulant→intoxication (hallucinations)→dissociative out of body state. Not addictive.

Dicpinigaitis et al Pharm rev 2014
Burns and Boyer Subst abuse rehabilitation 2013

Guaifenesin

Guaifenesin:

•Only FDA approved 'expectorant'.

•Orally administered, short half life, bd dosing. Safe.

•Mechanism

Cholinergic mechanism?

No evidence alters ciliary motility/mucociliary clearance.

•Conflicting studies, data quality low. No RCT.

•NICE approve (?)

Bolser chest 2006
Malesker et al Chest 2017

Mucolytics

- Carbocisteine, N-acetyl cysteine, bromhexine.
- COPD-good evidence.
- Alters balance of sialo- and fucomucins-restores viscoelastic properties.
- Very limited evidence of efficacy in cough.
- ACCP unable to make recommendation.
- NICE not recommended
- Not antitussive as such but can help with thick sputum.

Bolser chest 2006
Dicpinigaitis et al Pharm rev 2014
Maleker Chest 2017
NICE Acute cough 2018

Antihistamines/decongestants

- H1 blockers. First generation antihistamines. Dexbrompheniramine, brompheniramine, desloratidine, promethazine
- Mechanism

Unclear. Penetrate CNS

Sedating

Side effects

Effects on cough not seen with non sedating 2nd generation antihistamines

- Used a lot in the USA
- Not readily available in UK
- Very little evidence, no good quality trials[1].

1. Dicpinigaitis et al Pharm rev 2014

Menthol

- Peppermint plant *Mentha avrensis.*
- Mechanism

TRPM8 receptor peripheral sensory nerves (TRPM8 + V afferents in nasal mucosa, activation reduces cough sensitivity).

Temperature receptor (cooling)

? Central mechanism

- Soothes URT in viral infections
- No clinical trials yet!
- Ongoing studies. Ax8 (Axalbion) in Refractory Chronic Cough.

1. Dicpinigaitis et al Pharm rev 2014

Complimentary and alternative therapies

- Wide range of complimentary/herbal treatments.
- Possible genuine pharmacological effects.
- Non pharmacological effects (placebo, physiological etc.)
- No good quality trials.
- Massage, meditation, osteopathy, reflexology-'no convincing evidence of effectiveness'.
- Pelargonium ? NICE recommend.
- Probably harmless but difficult to recommend any of these.

Table 1 Some herbal treatments for cough

Species	Common name	'Pure extract'	Action(s)	Refs
Adhatoda vasica	Malabar nut	Vasicine	Bronchodilator Expectorant Bitter	Dhuley (1999) Blumenthal (2000)
Allium sativum	Garlic	Allicin	Antibacterial	Adeleye and Opiah (2003) Bielory (2004)
Carum copticum	Ajwain	Carvacrol	Bronchodilator	Boukhatly et al. (1998, 2005)
		Thymol	Vasodilator Antihistamine	
Crocus sativus	Saffron	Safranal	Anti-inflammatory	Hosseinzadeh and Ghenaati (2006) Duke and Ayensu (1985)
Fritillaria spp.	Bèimǔ Snake's head	Alkaloids	Anti-inflammatory Expectorant Antibacterial	Saliba et al. (2004) Jiang et al. (2005) Lin et al. (2007)
Glaucium flavum		Glaucine	Antitussive Bronchodilator	Nosalova et al. (1999) Dorcks et al. (1981)
Glycyrrhizae glabrae, radix	Licorice	Liquiritin Glycyrrhizinate	Anti-cAMP	Kamei et al. (2003) Bielory (2004)
Panax quinquefolium	Ginseng	Ginsenoside	Anticoxidant Antibacterial	Bielory et al. (2004) McElhaney (2006)
Pinene spp.	Pine oil	Pinene Sobrerol	Expectorant	Medici et al. (1985) Blumenthal (2002)
Piper longum	Pepper	Piperine	Spicy	Bielory et al. (2004) Zimere (2004)
Theobroma cocoa	Chocolate Cocoa	Theobromine Epicatechin	Bronchodilator	Usmani et al. (2004) Santos et al. (1993)
Sesamum Indicum	Sesame oil	Omega 9 Sesamin	Bronchodilator Mucolytic Surfactant	Alkoshemi et al. (2002) Saleh et al. (2006)
Zingiber Officinale	Ginger	Sesquit Phenols	Anti-inflammatory	Thomas et al. (2007) Hoffman (2007)

The list is selected, somewhat arbitrarily, to give examples of herbs popular in the treatment of cough, especially in western countries. Those detailed in the text are not included. For much longer lists see Blumenthal (2000), Fetrow and Avila (2001), Skidmore-Roth (2001), and Zimere (2001, 2002).

Widdicombe and Ernst Pharm ther cough 2009

What can we use to treat the cough?

1. OTC medicine

Simple Linctus. Honey.

Dextromethorphan

Guaifenesin

Mucolytics

Antihistamines

Menthol

Herbal/complementary

2. Prescription medicines

Opiates; Codeine, Morphine

Neuromodulators; Gabapentin/pregabalin

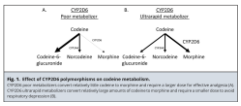
Lidocaine (nebulised)

3. Novel Antitussives in development

4. Non Pharmacological Cough Suppression/Control therapy

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.



Nerez and Gonzalez J App Lab Med 2017

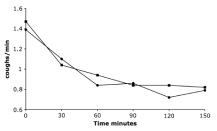


Fig. 1 Mean cough frequency before and after treatment with a single dose of codeine syrup B.P. (30 mg) in subjects with cough associated with acute upper respiratory tract infection. *Square symbols* indicate codeine syrup ($n = 46$) and *round symbols* indicate placebo syrup ($n = 45$) (redrawn from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

1. Eccles J Clin pharm ther 1992
2. Freestone J Pharmacy pharmacol
3. Smith et al J all clin imm 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.**

- Mechanism

Unknown

Central mechanism of action (descending pathways from cortex/thalamus to PAG/nucleus cunieformis.

? Placebo pathways

Lung opioid receptor? PNEC's/c fibres.

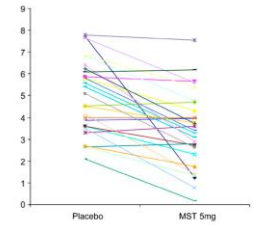


Figure 1. Daily cough severity scores on a scale of 0 to 9. MST = slow-release morphine sulfate.

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

Neuromodulators: Gabapentin/Pregabalin

- Mechanism unclear.

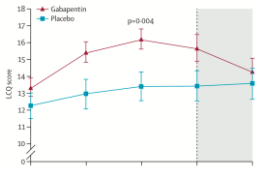
Central. Not GABA!

Blocks nociception.

$\alpha 2\delta$ 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].
- Case reports in cancer related cough.
- ACCP recommend trial in ILD
- 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.



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

Lidocaine

- No good quality evidence to support the use of lidocaine.
- A number of uncontrolled trials/case series/reports and 1 small clinical trial.
- Na_v channel blocker-inhibits conduction of nerve impulses.
- Usually a last resort.
- 1ml lidocaine 1% solution diluted to 4ml with normal saline. Nebulised (air). 4-6 hourly. Can increase dose
- Bitter taste. Oropharyngeal numbness. Bronchospasm if asthma. Drowsiness, twitching, convulsions, arrhythmia, agitation.

Slaton et al Ann Pharmacotherapy 2013
Truesdale et al Am J Hosp Pall Care 2013
Palliativemedsinfo.olh.ie (lidocaine dosing)

What can we use to treat the cough?

1. OTC medicine
Simple Linctus. Honey.
Dextromethorphan
Guaifenesin
Mucolytics
Antihistamines
Menthol
Herbal/complementary
2. Prescription medicines
Opiates; Codeine, Morphine
Neuromodulators; Gabapentin/pregabalin
Lidocaine (nebulised)
3. Novel Antitussives in development
4. Non Pharmacological Cough Suppression/Control therapy

Novel antitussives: P2X receptor antagonists

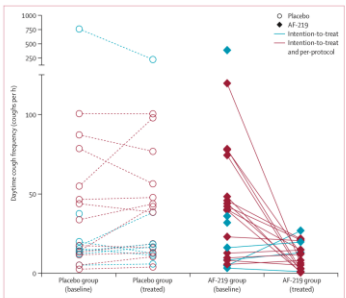


Figure 2: **Changes in objective daytime cough frequency from baseline to end of the treatment period**
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al Lancet 2014

P2X receptor antagonists

- P2X3 receptor antagonist. AF219/**MK7624/Gefapixant.**
- Antagonises ATP mediated neurotransmission.
- Vagal C fibres. Jugular and nodose ganglia.
- 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).

Abdulqawi et al Lancet 2014

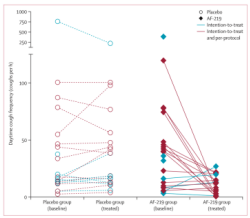
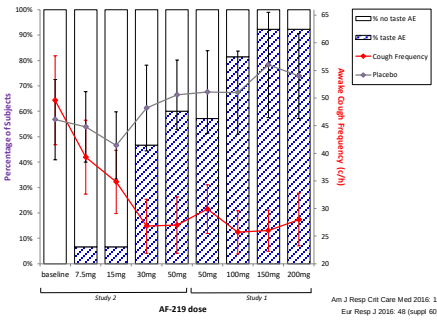


Figure 2: Changes in objective daytime cough frequency from baseline to end of the treatment period
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Human taste bud innervation

Tizzano et al Chemical Senses, 2015, Vol 40, 655–660

Efficacy Maintained at Lower Doses with Improved Tolerability



Am J Resp Crit Care Med 2016: 193 A6524
Eur Resp J 2016: 48 (suppl 60) OA1976

Adverse Events

Preferred Term	7.5 mg (N=63)	20 mg (N=63)	50 mg (N=63)	Total (N=189)	Placebo (N=63)
Dysgeusia	6 (9.5%)	21 (33.3%)	30 (47.6%)	57 (30.2%)	3 (4.8%)
Hypogeusia	0	11 (17.5%)	15 (23.8%)	26 (13.8%)	1 (1.6%)
Headache	4 (6.3%)	12 (19.0%)	4 (6.3%)	20 (10.6%)	3 (4.8%)
Upper Respiratory Tract Infection	5 (7.9%)	9 (14.3%)	6 (9.5%)	20 (10.6%)	2 (3.2%)
Ageusia	0	3 (4.8%)	13 (20.6%)	16 (8.5%)	1 (1.6%)
Paraesthesia Oral	4 (6.3%)	5 (7.9%)	4 (6.3%)	13 (6.9%)	5 (7.9%)
Cough	2 (3.2%)	5 (7.9%)	5 (7.9%)	12 (6.3%)	2 (3.2%)
Hypoaesthesia Oral	2 (3.2%)	4 (6.3%)	5 (7.9%)	11 (5.8%)	3 (4.8%)
Nausea	0	4 (6.3%)	6 (9.5%)	10 (5.3%)	0
Urinary Tract Infection	3 (4.8%)	5 (7.9%)	2 (3.2%)	10 (5.3%)	2 (3.2%)
Dry Mouth	2 (3.2%)	3 (4.8%)	3 (4.8%)	8 (4.2%)	6 (9.5%)

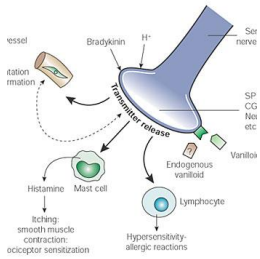
Novel antitussives: NK-1 antagonism.

- Mechanism

Tachykinins. Neuropeptides; substance P (NK-1), NK A (NK-2), NK B (NK-2)
NK-1 antagonism to Substance P (central and peripheral)
Neuropeptides produced by Vagal C fibres. Released in airways or centrally (NTS).
Peripheral release →'neurogenic inflammation' in airways (vascular leak, bronchoconstriction, inflammatory cell recruitment, mucus secretion).

Are these agents useful in cough? We don't know yet, perhaps not?

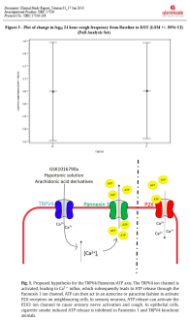
- RCT aprepitant (NK1 antagonist) in lung cancer, reduction in cough frequency.[1].
- Volcano 1. RCT orvepitant (NK1 antagonist) in refractory cough. Small trial. Reduction cough frequency (26%) at week 4, improvements in VAS and QOL[2].
- Volcano 2 phase 2b (orvepitant) awaited.
- Menlo (serlopitant) Negative trial.



1. Harle et al JCO abstract 2015
2. Smith et al AJRCCM abstract 2017
3. Szallasi and Blumberg (illustration)

Novel antitussives: TRP channel antagonists

- Family of sensory receptors. Airway and sensory nerves.
- Capsaicin activates TRPV1
- Lots of excitement but studies in CRC disappointing so far.
- RCT TRPA1 antagonist (Glenmark, unpublished) negative trial but sub optimal trial protocol.
- RCT TRPV1 antagonist (GSK SB 705498) no effect on cough frequency or QOL.[1]
- RCT TRPV4 antagonist (GSK2798745)-negative trial.[2].

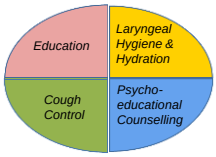


1 Khalid et al JACI 2014
2 Ludbrok at el 2019

What can we use to treat the cough?

1. OTC medicine
Simple Linctus. Honey.
Dextromethorphan
Guaifenesin
Mucolytics
Antihistamines
Menthol
Herbal/complementary
2. Prescription medicines
Opiates; Codeine, Morphine
Neuromodulators; Gabapentin/pregabalin
Lidocaine (nebulised)
3. Novel Antitussives in development
4. Non Pharmacological Cough Suppression/Control therapy

Non-pharmacological Cough Suppression Therapy (CST)



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.

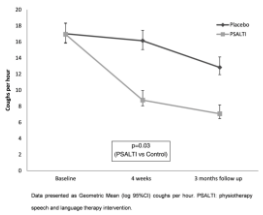
31

Chamberlain Mitchell et al Pulm Pharm Ther 2019

ORIGINAL ARTICLE

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]

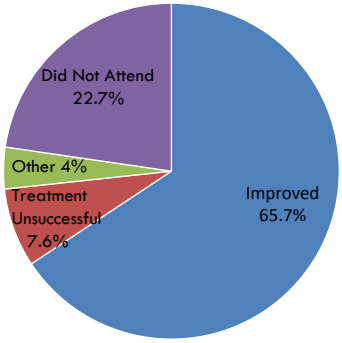


Data presented as Geometric Mean (log 95%CI) coughs per hour. PSALTI: physiotherapy speech and language therapy intervention.

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

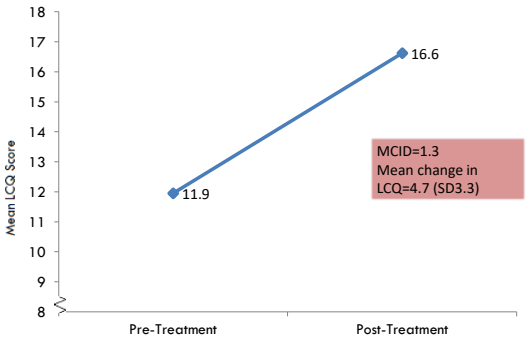
Chamberlain et al Thorax 2017

Subjective Outcomes following CST



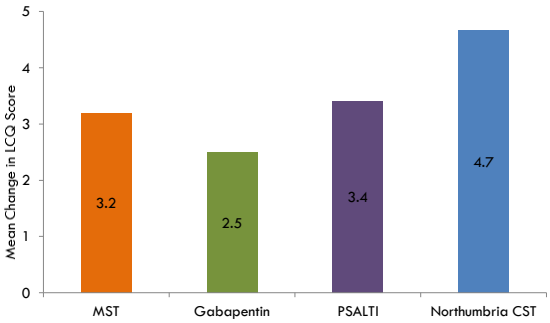
Mohammed S, Steer J, Ellis J, Kellet L, Parker SM. Thorax 2017 BTS abstract.

Improvement in Mean LCQ post CST



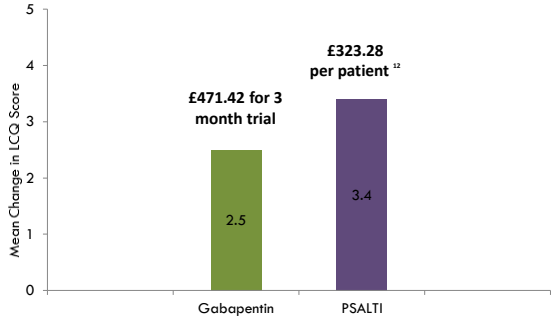
Mohammed S, Steer J, Ellis J, Kellet L, Parker SM. Thorax 2017 BTS abstract.

CST compares favourably to other treatments



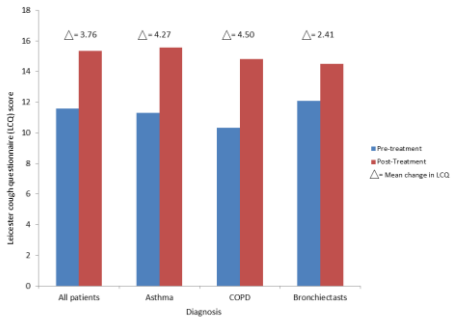
Morice et al. Am J Respir Crit Care Med 2007; 175: 312-315 Ryan et al. Lancet 2012; 380:1583-1589 Chamberlain Mitchell et al. Thorax 2017; 72: 129-136 Mohammed et al Thorax 2018

CST compares favourably to gabapentin (Mean Change in LCQ Score & Cost)



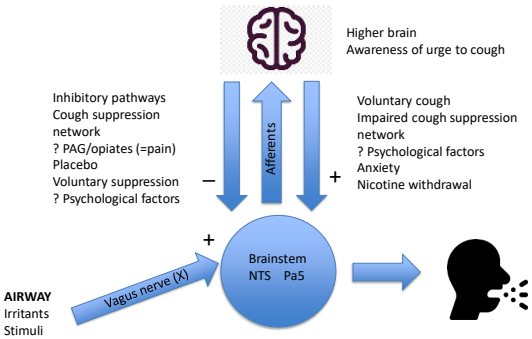
Birring et al., Pulmonary Pharmacology & Therapeutics 2017

CST is useful in non CRC



Mohammed S, Steer J, Ellis J, Kellet L, Kurji Smith N, Parker SM. Thorax 2018 BTS abstract.

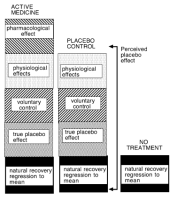
Summary 1: The cough reflex is complex…



Summary 2: Systematic assessment

1. Ineffective or overactive cough?
2. Productive?
3. Specific cause/'treatable traits' →treat.
4. Aggravants?
5. Cough suppression.

Summary 3: Cough suppression



- Simple measures (linctus/OTC)
- Non pharmacological cough suppression therapy (?)
- (P2X blockers Gefapixant)
- Opiates (morphine)
- Neuromodulators (gabapentin/pregabalin)
- Other stuff (lidocaine, steroids etc)

Any Questions?

Northumbria Healthcare NHS Foundation Trust

Sean Parker
Consultant Respiratory Physician
North Tyneside General Hospital
@drsmparker