Taming Chronic Cough

John Oppenheimer, MD
Clin Prof Med UMDNJ
Dir Research Pulm & Allergy Assoc

Educational Goals

- Following this lecture, the audience should be familiar:
  - Differential diagnosis of cough
  - Causes of chronic cough
  - Be able to effectively perform an evaluation for chronic cough
  - Be able to effectively treat chronic cough

Cough Guidelines

Diagnosis and Management of Cough Executive Summary

ACCP Evidence-Based Clinical Practice Guidelines

Richard S. Irwin, MD, FCCP, Chair;
Michael H. Baumann, MD, FCCP (HSP Liaison); Donald C. Bolser, PhD;
Louis-Philippe Boulet, MD, FCCP (CTS Representative);
Sidney S. Braman, MD, FCCP; Christopher E. Brightling, MBBS, FCCP;
Kevin K. Brown, MD, FCCP; Brendan J. Canning, PhD;
Anne B. Chang, MBBS, PhD; Peter V. Dicpinigaitis, MD, FCCP;
Ron Eccles, DSc; W. Brendle Glomb, MD, FCCP; Larry R. Goldstein, MD;
LeRoy M. Graham, MD, FCCP; Frederick E. Hargreave, MD;
Paul A. Kvale, MD, FCCP; Sandra Zelman Lewis, PhD;
F. Dennis McCool, MD, FCCP; Douglas C. McCrory, MD, MHSc;
Udaya B.S. Prakash, MD, FCCP; Melvin B. Pratter, MD, FCCP;
Mark J. Rosen, MD, FCCP;
Edward Schulman, MD, FCCP (ATS Representative);
John Jay Shannon, MD, FCCP (ACP Representative);
Carol Smith Hammond, PhD; and Susan M. Tarlo, MBBS, FCCP

Guidelines for Evaluating Chronic Cough in Pediatrics

ACCP Evidence-Based Clinical Practice Guidelines

Anne B. Chang, MBBS, PhD; and William B. Glomb, MD, FCCP

Eur Respir J 2004; 24: 481–492
DOI: 10.1183/09031936.04.00027804
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

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*

Cough

- defense mechanism
- spread infection
- one of the most common causes to see an MD*
  - *Internist's 3rd most common serious problem generating an office visit *(The Nat Amb Care Survey US 17:975. Wash, DC. Dep HEW Pub PHS 79-1787 . Vital Health Stat Series #36. 1978. Pp.4-29).*
  - **Most common reason for which patients seek medical evluation (Madison Otolaryn Clin of NA. 201043;1-13).*

Reasons Why Pts with Chronic Cough Seek MD Attention

Something's wrong	98%	108 consecutive unselected pts
Exhaustion	57%	
Self conscious	55%	
Insomnia	45%	
Life-style change	45%	
Musculoskel pain *	44%	* MS pain in 1 pt rib fx
Hoarseness	43%	
Excessive perspiration	42%	
Urinary incontinence	39%	
Dizziness	38%	
Fear of Ca	33%	
Fear of Aids or TB	28%	
Retching	21%	
Vomiting	18%	
Nausea	16%	
Anorexia	15%	
Syncope or Near Syncope	5%	

Chest 1991;99:1477-84

Cough the basics

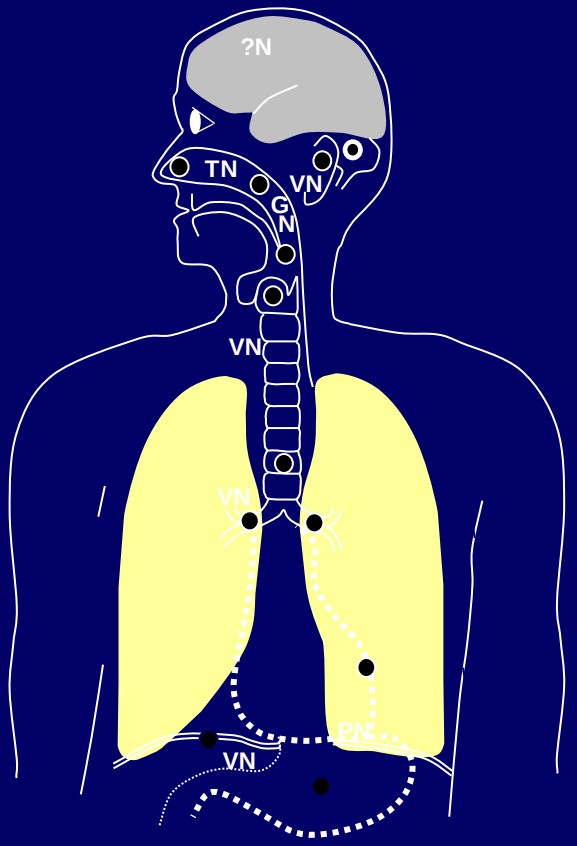
- In healthy patients:
  - mucociliary clearance is the major method to clear airway lumen.
  - cough is a reserve mechanism.
  - mucociliary clearance is 2 times that of pts with CB

- With cough:
  - healthy pts can increase clearance by 2.5%
  - CB pts can increase clearance by 20%.

Cough the basics

- Involuntary cough appears to be entirely vagally mediated

- stimulation of structures vagally innervated can result in cough.
  - oropharynx
  - larynx
  - respiratory tract
  - tympanic membrane
  - external auditory meatus



RECEPTORS

"COUGH CENTER"

GN GLOSSOPHARYNGEAL NERVE

PN PHRENIC NERVE

TN TRIGEMINAL NERVE

VN VAGUS NERVE

?N CORTCAL INPUT

Cough the basics

- Most sensitive sites to induce cough:
  - larynx
  - tracheobronchial tree
    - especially corina and bronchial branching points
  - *Note: experimentally one can't induce cough in smaller airways and the alveoli.*

Cough the basics

- Central cough receptor:
  - Theoretical has never been established anatomically integrated by medulla oblongata (brainstem)
    - afferent fibers near nucleus of the tractus solitarius
    - motor outputs in ventral receptor group.
    - Nucleus retroambiguoualis sending motoneurons to respiratory muscles
    - nucleus ambiguous to larynx and bronchial tree.
    - *most anti-tussive Rx acts centrally
      - don’t know how

Cough the basics

- Mucus secretion:
  - Afferent receptor that causes cough also result in reflex secretion of mucus from airway submucosal glands.
    - Mucus:
      - entraps inhaled particles/chemicals and allows clearance via mucociliary transport as well as cough itself
      - results in narrowing of the airway which results in increase in linear velocity of airflow which yields increase in turbulence and central implication of pollutants
      - acts as a physiochemical barrier between lamina irritants and airway wall

Cough the basics

- Respiratory muscles and cough:
  - inspiratory phase – deep inspiration
  - compressive phase - forceful expiration against a closed glottis
  - explosive phase – glottis opens and expiration accelerates (200 m/sec)
    - **expiratory respiratory muscles are the most important component of expiration of cough, as even without glottis can be effective (even with ET tube can clear secretions)**

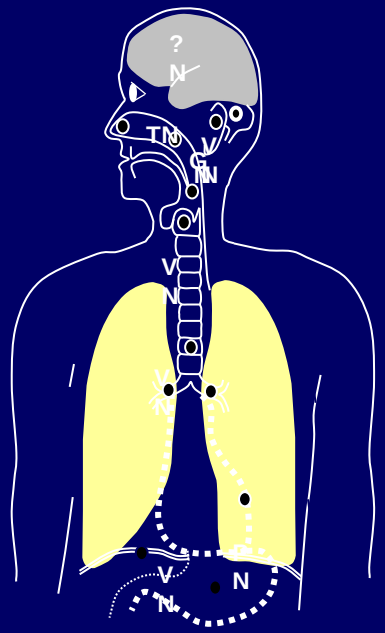
Cough the basics

- Ineffective cough results in:
  - Atelectasis
  - Pneumonia
  - Gas exchange abnormalities

Diagnostic Evaluation

Diagnostic Evaluation

- via the anatomic diagnostic protocol
  - systematic evaluation through assessing locations of afferent limb of the cough reflex



RECEPTORS

"COUGH CENTER"

GN GLOSSOPHARYNGEAL NERVE

PN PHRENIC NERVE

TN TRIGEMINAL NERVE

VN VAGUS NERVE

?N CORTCAL INPUT

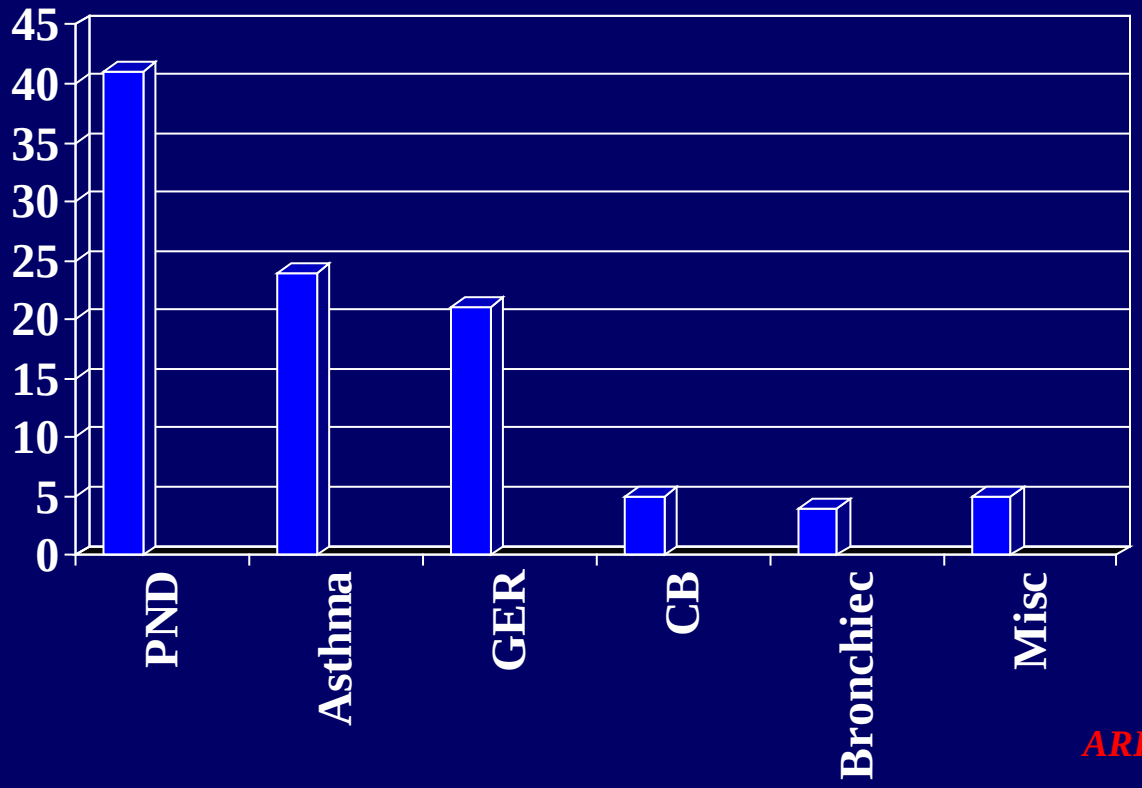
Irwin et al. Chest 2006;1-292s

The Anatomic Diagnostic Protocol - Adults

- Chronic cough => 8 weeks
  - With use of protocol in studies cause can be determined 88-100% of the time.
  - Resultant therapy with success rate of 84-98%.

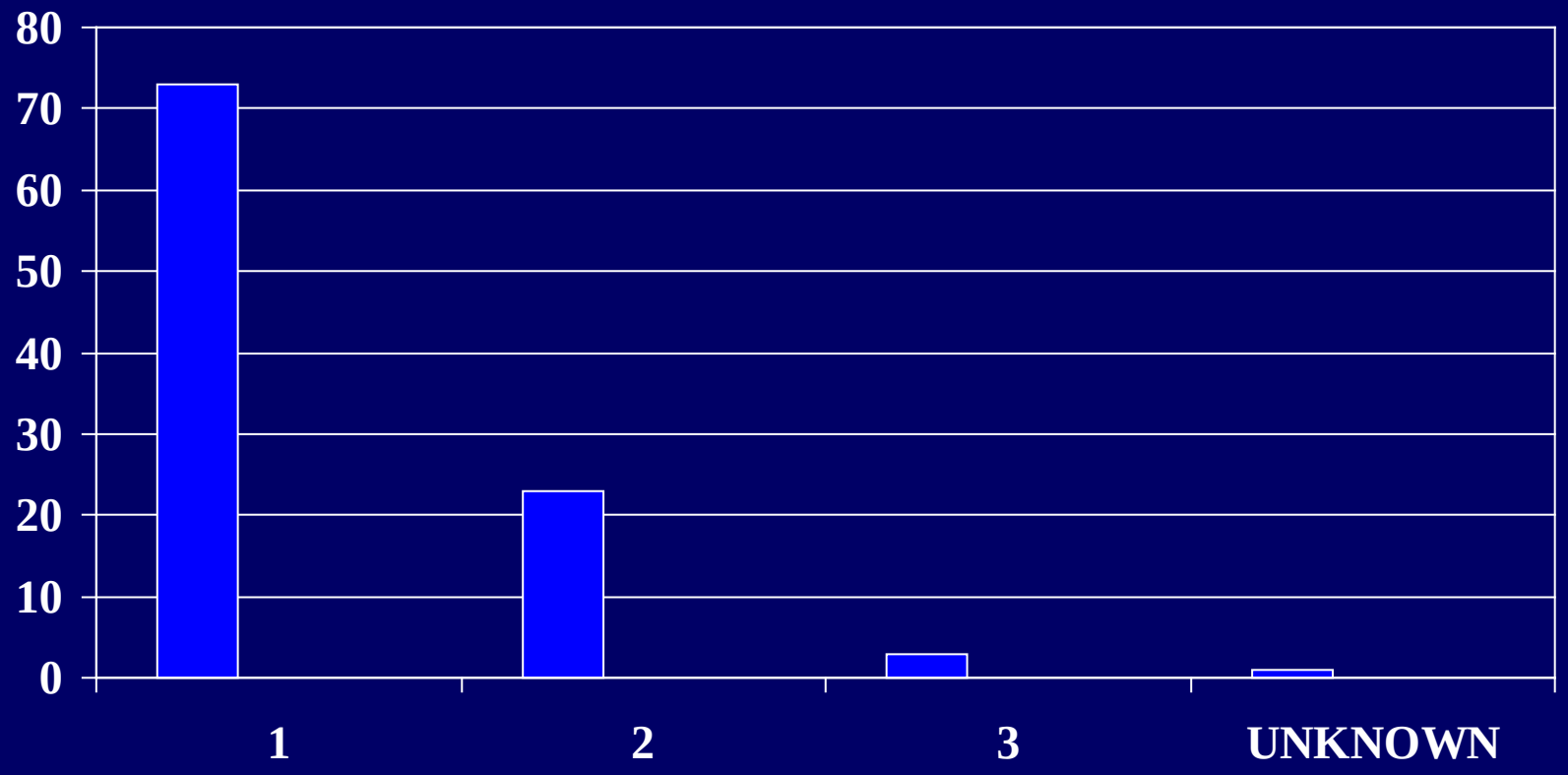
Rank Ann All 2007;98:305-13

Causes of Cough



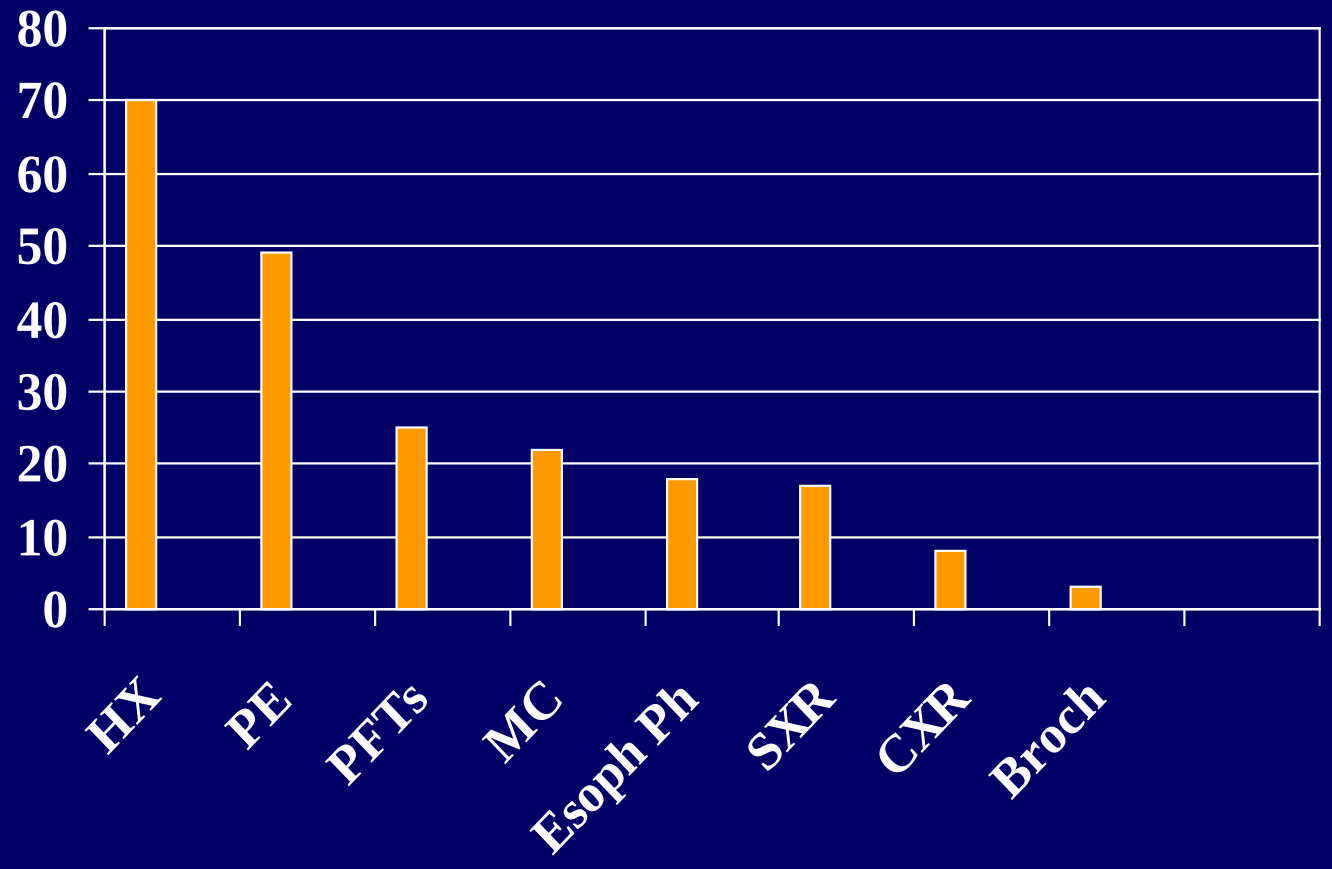
ARRD 141:640-7

Causes of cough



ARRD 141:640-7

Usefulness of Components of Cough Dx Protocol



ARRD 141:640-7

Chronic cough/UACS

- most common cause

  $\Rightarrow$ stim sensory nerves $\Rightarrow$ cough reflex

  – ***Hx:*** patient describe PND with pharyngeal irr (occ sense of foreign body).

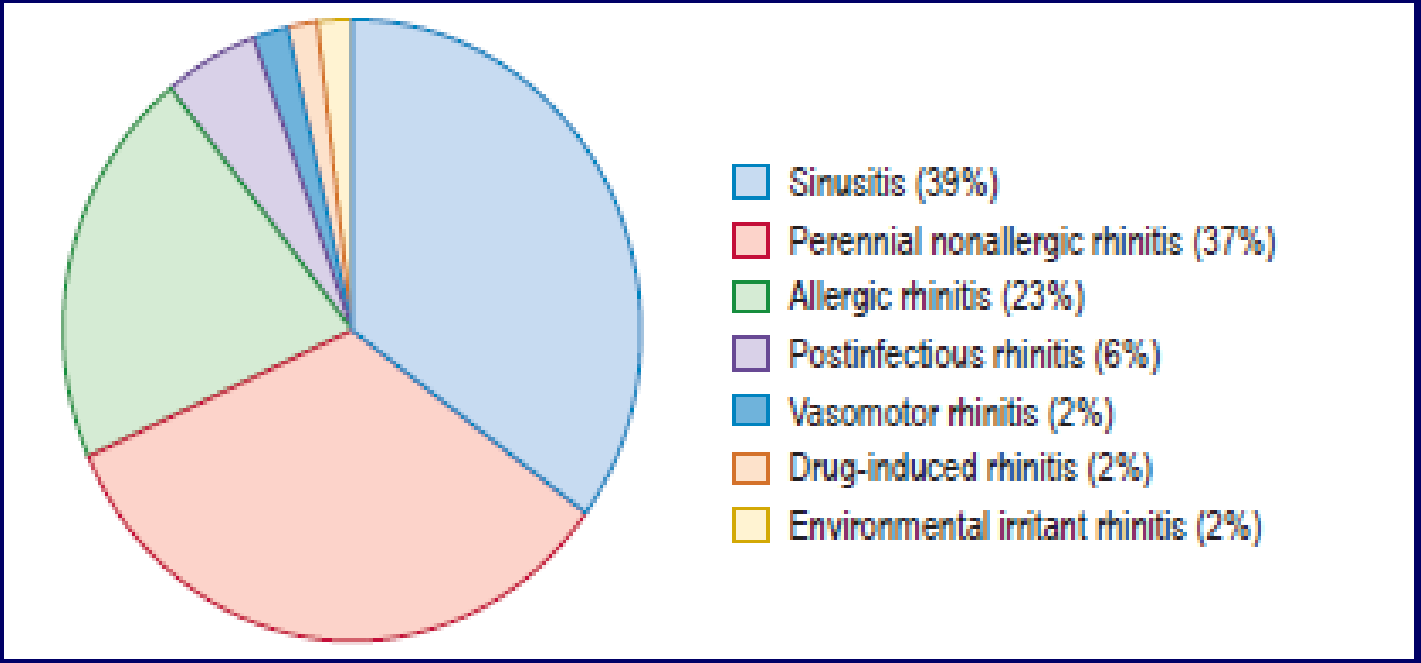
  – Consider $\propto$ AR, NARES, post infection, env irritant, VMR or sinusitis.

    - Important to remember pts may have no symptoms

  – PE*:* Posterior pharynx with mucoid secretions, cobblestone appearance of post pharynx (observe for throat clearing) Flow Volume loop with variable extrathoracic upper airway obstruction

Rank Ann All 2007;98:305-13

Relative frequencies of disorders causing UACS in patients with Chronic Cough



Middleton 8th 2014:1036

Chronic cough/ Asthma

2nd most common cause

- Inflammation ⇒ stimulation of sensory nerves ⇒ cough reflex
- In as many as 28% of asthmatics, cough may be sole symptom
  - Dispingaitis Chest 2006;129:75-9s

Hx: Wheeze, SOB, triggers

- Spiro with obstruction with reversibility

Rank Ann All 2007;98:305-13

Chronic cough/ GERD

- 3rd most common cause
  - Stimulation of afferent limb of cough reflex at the distal esophagus
- *Hx*:
  - heartburn, sour brash or regurgitation
  - 2/3 patients without symptom of GERD
- *Dx:*
  - pH probe abnl (may be seen in assoc with cough) even in absence of pt sx or therapeutic trial of PPI BID

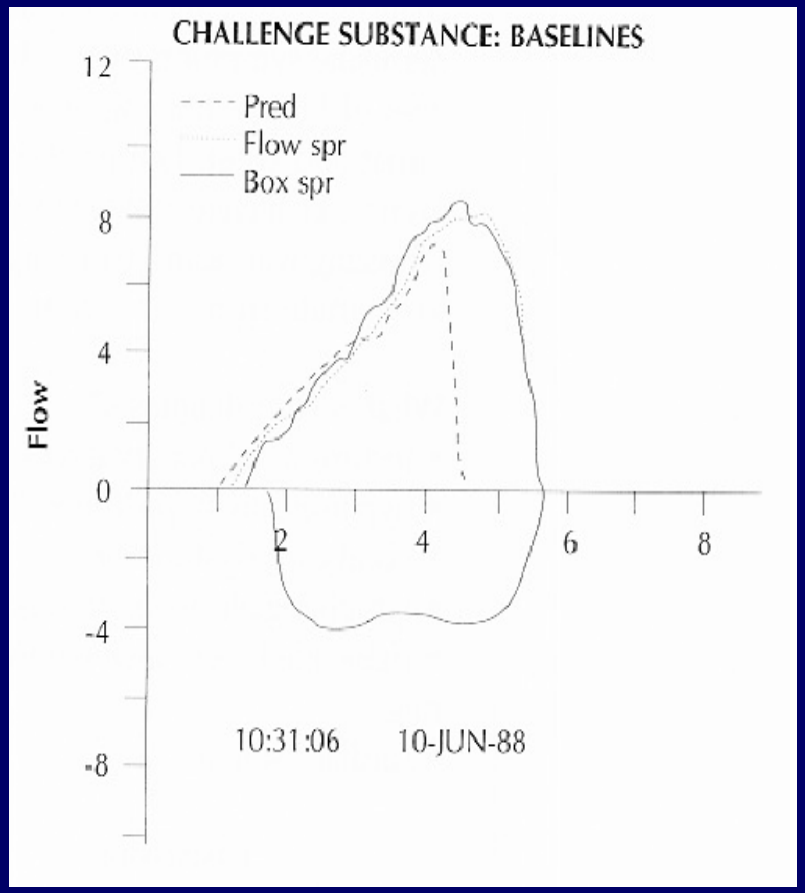
Rank Ann All 2007;98:305-13

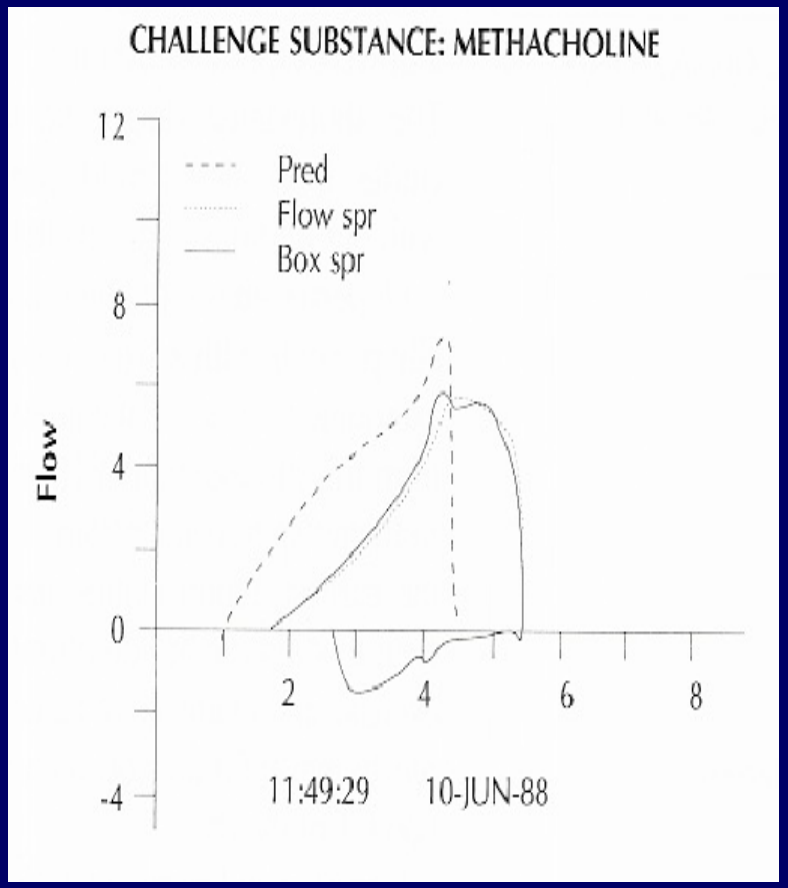
Cough the basics

- Reversible extrathoracic upper airway obstruction arises form stimulation of cough reflex in the upper respiratory tract assoc with PND +/- GERD, throat clearing or both.

Rank Ann All 2007;98:305-13

Flow Volume loops are helpful





Oppenheimer, Nelson MD Air Currents, Fall 1992, Vol 1, No.1

Chronic cough/ ACE inhib

- ⇒accumulation bradykinin or substance P ⇒ ↑ sens of cough reflex (Bradykinin, ? Subs P inactivated by ACEI)?

- ***Hx:***
  - nonproductive/irritating/tickling cough +/- sensation of something in the throat
    - **Class effect <u>not</u> dose related**
    - **Freq. 0.2%-33%**
    - **Overall ∝ 2%**
    - **May take wks to months and even yrs for onset**

- ***Dx:*** confirm resolution with D/C (usu 1-2 mo)

Rank Ann All 2007;98:305-13

Chronic Cough/ACE inhib

- Mechanism uncertain, believed by be caused by inhibiting the degradation of inflammatory mediators in the airway which upregulate the sensitivity of vagal afferents inducing cough
  - Birring AJRCCM 2011;183:708-15
- May be switched to and ARB, as not associated with chronic cough
  - Lacourciere J Hypertension 1994;12:1387-93
- For patients who need to continue and ACE some literature that adding nifedipine may aid
  - Madison Asthma and Rhinitis 2nd ed 2000:1282-302

Chronic Cough/Misc.

- <6% causes
  - Bronchogenic CA
  - Metastatic CA
  - Sarcoid
  - Left Vent failure
  - Aspiration ∝ Zenkers Diverticulum
  - Eosinophilic bronchitis

Rank Ann All 2007;98:305-13

Chronic Cough/Unusual Causes

- Irritation of tympanic membrane (hair, TE tubes)
- Gilles de la Tourette's syn
- Neurolemmoma of vagus nerve in neck
- Endobronhial suture
- Esophageal cyst
- Pertusis
- Psychogenic cough

  ⇒ **consider only after all other possibilities excluded**

Rank Ann All 2007;98:305-13

Chronic Cough Rx

- Specific Anti-tussive therapy:

  PND/AR:

  - env control
  - drying H-1 antag
  - nasal steroids
  - IT

Rank Ann All 2007;98:305-13

Chronic Cough Rx

- Specific Anti-tussive therapy:

  PND/sinusitis:

  - antibiotics (consider 6-8 wks)
  - decongestant
  - nasal steroid/OCS

Rank Ann All 2007;98:305-13

Rx Asthma

- A talk in itself
- Controller Rx ICS/LTM etc.

Rank Ann All 2007;98:305-13

GERD and Cough

- Caused by irritation of the vagus fibers
  - Are sensitive to acid as well as nonacid volume reflux

- Dx is very challenging as no currently available tests are highly predictive
  - Barium swallow without aid
  - Nl endoscopy or pH probe does not exclude reflux
  - ACCP and BTS guidelines suggest empiric dietary manipulation and BID PPI
    - Diet changes, limit ETOH, elevation of HOB, wt loss, sleep apnea evaluation

Rank Ann All 2007;98:305-13

GERD Rx

Search methods

- Searched the Cochrane Airways Group Specialised Register, the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, review articles and reference lists of relevant articles.

Selection criteria

- All randomized controlled trials (RCTs) on GERD treatment for cough in children and adults without primary lung disease.

Data collection and analysis

- Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information.

Chang Cochrane 2010

GERD Rx

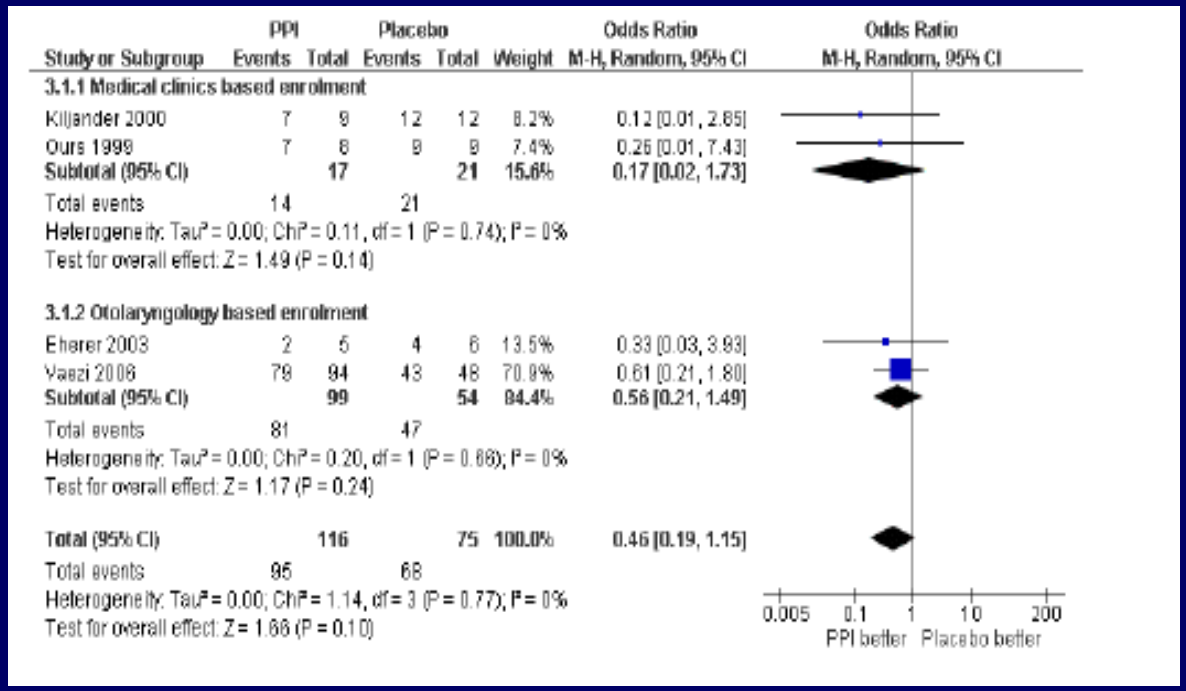
- Analysed nine adult studies comparing PPI (two to three months) to placebo for various outcomes in the meta-analysis

- Found a significant improvement in change of cough scores at end of intervention (two to three months) in those receiving PPI (standardized mean difference -0.41; 95% CI -0.75 to -0.07) using generic inverse variance analysis on cross-over trials.

- Two studies reported improvement in cough after five days to two weeks of treatment.

Chang Cochrane 2010

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).



Chang Cochrane 2010

GERD and Cough

- In those that fail PPI and prokinetic agent consider (NERD):
  - RLG
  - pH probe
  - Impedance testing via GI consult

  - Antireflux surgery should be considered in patients with continued sx and objective evidence of reflux – failing maximal medical Rx
    - *Evidence regarding fundoplication for GERD induced cough is lacking*

Rank Ann All 2007;98:305-13

Chronic Cough Unexplained

- New guidelines recommend this term instead of idiopathic
- Mechanism uncertain
  - Possibly caused by heightened cough reflex
  - Sensitivity such that factors triggering are too subtle to determine

Rank Ann All 2007;98:305-13
Gibson Chest 2016;149:27-44

Unexplained cough

- With use of diagnostic and treatment protocols in cough have led to management in approximately 93% of patients with chronic cough.
- A percentage of patients however continue to suffer from chronic cough with no obvious cause or treatable trigger (+*)
- QOL decrement is similar to severe COPD (^)
- This stresses the need for symptomatic treatment

+ Kastclik ERJ 2005;25:235-43
*Pratter Chest 2006;129:s222-31
^French Arch Int Med 158;1657-61

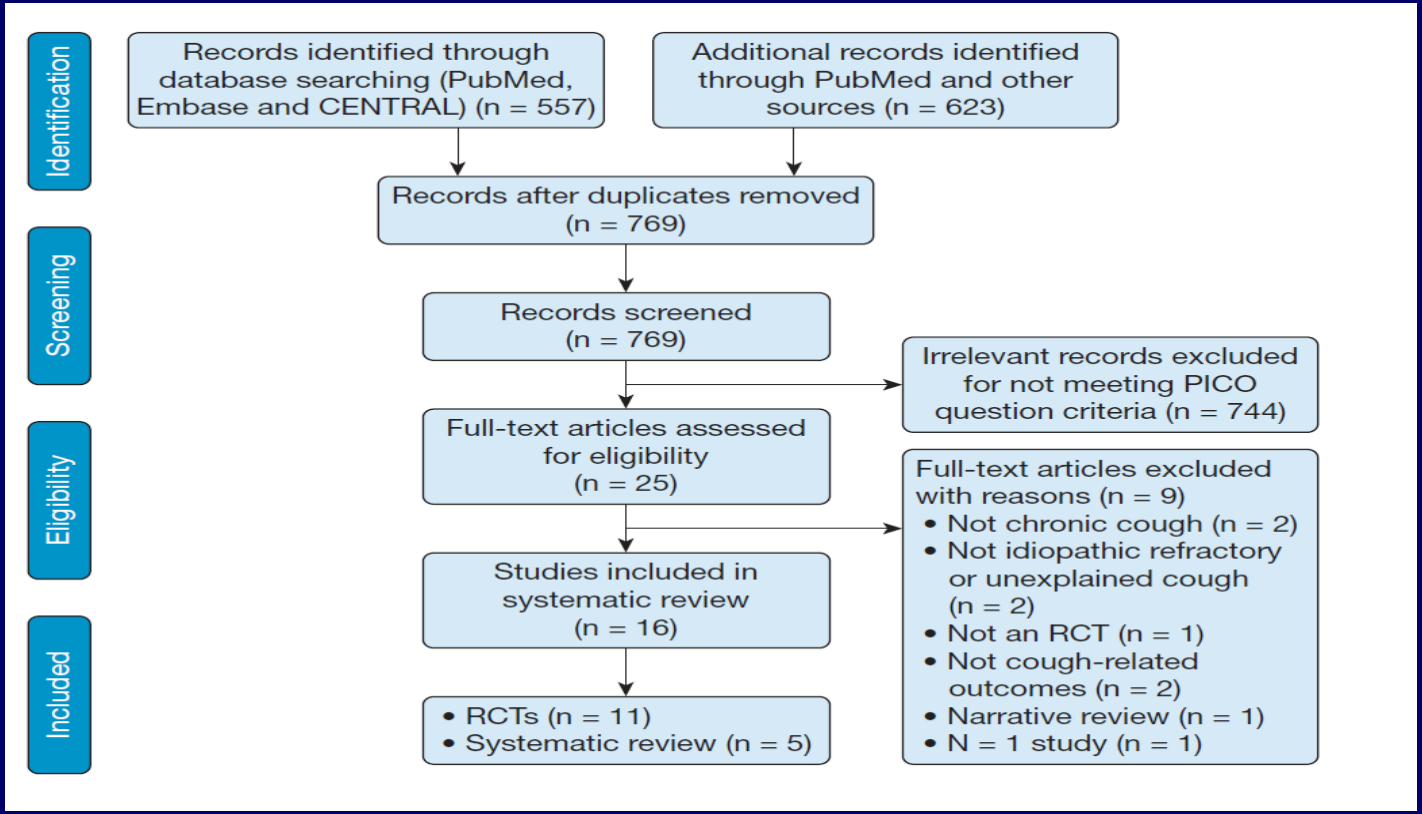
Treatment of Unexplained Chronic Cough
CHEST Guideline and Expert Panel Report

TABLE 1 Eligibility Criteria

Criteria	Study Requirements
Inclusion	English-language publication
	Population
	a. Chronic cough: duration > 8 wk
	b. Age > 12 y
	c. Unexplained or refractory or idiopathic or intractable. Patients were required to have an assessment for associated diseases that could cause chronic cough (eg, chronic lung disease) and diseases commonly associated with cough (eg, asthma, rhinosinusitis, GERD, ACEI use). The assessment could involve physician assessment; relevant investigations that were negative, leading to a diagnosis of unexplained or idiopathic cough; or relevant treatment trials that were negative or the cough was refractory to the treatment trial, leading to a diagnosis of refractory cough or intractable cough
Intervention	Treatment: any pharmacologic or nonpharmacologic intervention
Comparison/control	Randomized controlled trial or controlled clinical trial or a systematic review
Outcome	Cough severity or frequency or quality of life

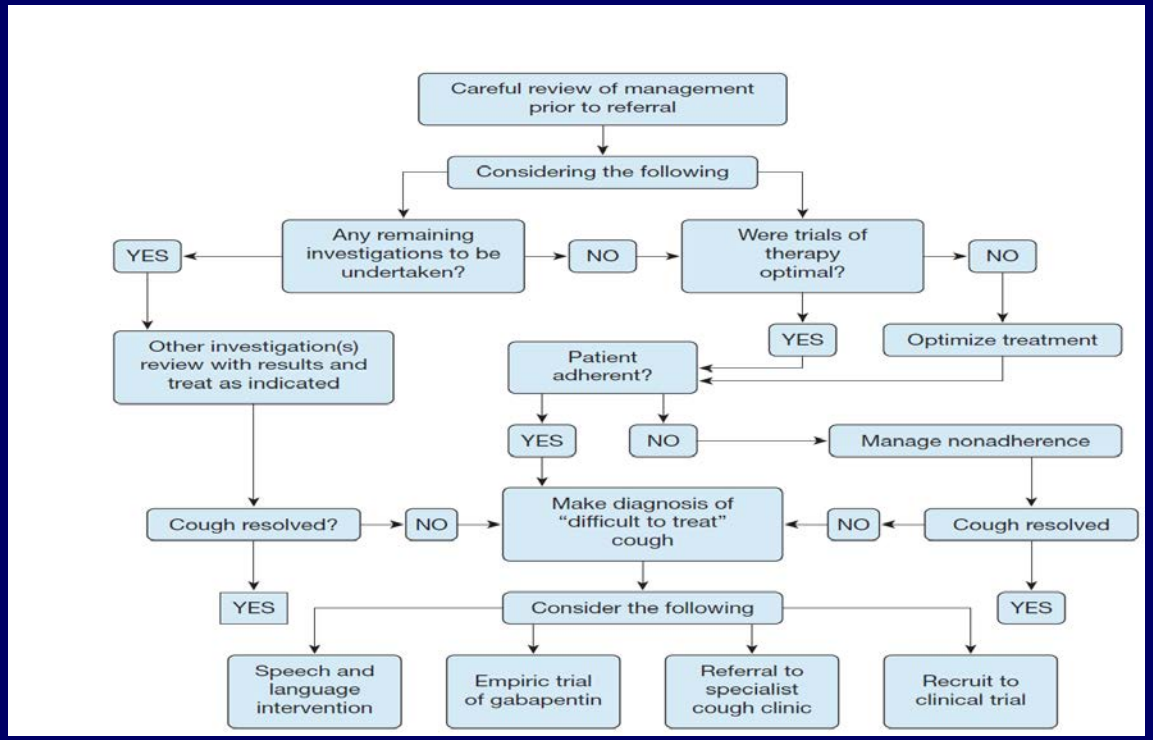
Gibson Chest 2016;149:27-44

Treatment of Unexplained Chronic Cough
CHEST Guideline and Expert Panel Report



Gibson Chest 2016;149:27-44

Proposed algorithm for managing “difficult to treat cough”



Gibson Chest 2016;149:27-44

Neuromodulatory agents

- Initial panel vote 75% in favor of weak recommendation for gabapentin and morphine(80% approval score needed to pass).
- Voting panelists suggesting split into two separate recommendations
- Gabapentin recommendation passed -90%
- Morphine failed
  - initial 71% with revote
  - change in wording to include “close follow up” failed 75%

Gibson Chest 2016;149:27-44

Neuromodulatory agents

- Gabapentin side effects no statistical difference from Pbo
- Morphine – patients dropped out due to side effects
  - Constipation – 40%
  - Drowsiness – 25%

Gibson Chest 2016;149:27-44

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

- **Background**
  - originally developed for the treatment of epilepsy and currently is also used to relieve neuropathic pain.
- **Methods**
  - This randomized, double-blind, placebo-controlled trial was undertaken at an outpatient clinic in Australia.
  - Adults with refractory chronic cough (>8 weeks' duration) without active respiratory disease or infection were randomly assigned to receive gabapentin (maximum tolerable daily dose of 1800 mg) or matching placebo for10 weeks.
  - The primary endpoint was change in cough-specific quality of life (Leicester cough questionnaire [LCQ] score) from baseline to 8 weeks of treatment.

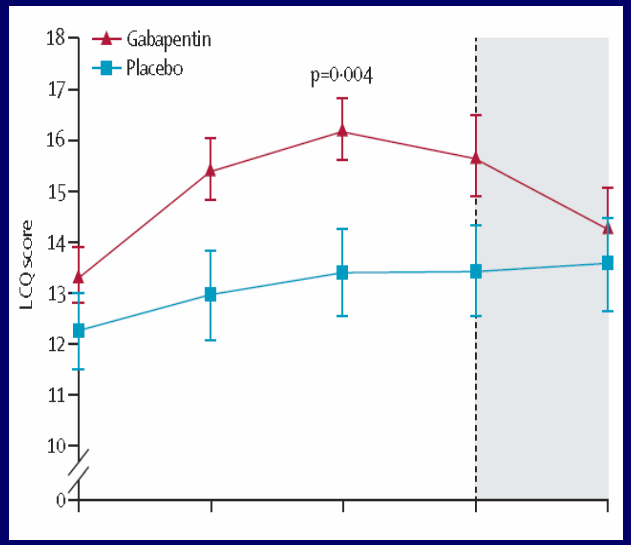
Ryan Lancet 2012;380:1583-9

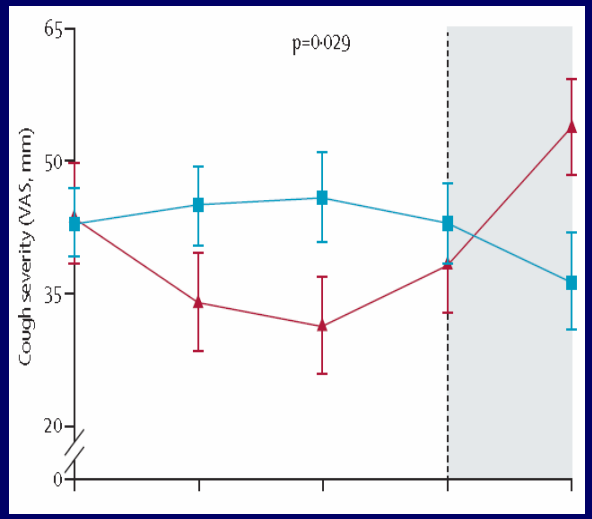
Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

- Findings
  - 62 patients were randomly assigned to gabepentin (n=32) or placebo (n=30) and ten patients withdrew before the study end.
  - Gabapentin significantly improved cough-specific quality of life compared with placebo (between group difference in LCQ score during treatment period 1·80, 95% CI 0·56–3·04; p=0·004; number needed to treat of 3·58).
  - Side-effects occurred in ten patients (31%) given gabapentin (the most common being nausea and fatigue) and three (10%) given placebo.

Ryan Lancet 2012;380:1583-9

Mean efficacy variables gabapentin vs. Pbo





- Interpretation
  - The treatment of refractory chronic cough with gabapentin is both effective and well tolerated.
  - These positive effects suggest that central reflex sensitization is a relevant mechanism in refractory chronic cough.

Ryan Lancet 2012;380:1583-9

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

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

***Table 2*: Adverse effects**

Ryan Lancet 2012;380:1583-9

ACCP recommendation

- In adult patients with unexplained chronic cough, we suggest a therapeutic trial of gabapentin as long as the potential side effects and the risk-benefit profile are discussed with patients before use of the medication, and there is a reassessment of the risk-benefit profile at 6 months before continuing the drug (Grade 2C).

Gibson Chest 2016;149:27-44

ACCP Remarks:

- Because health-related quality of life of some patients can be so adversely impacted by their unexplained chronic cough, and because gabapentin has been associated with improvement in quality of life in a randomized controlled clinical trial, the CHEST Cough Expert Panel believes that the potential benefits in some patients outweigh the potential side effects.

- With respect to dosing, patients who have no contraindications to gabapentin can be prescribed a dose escalation schedule:
  - beginning at 300 mg once a day;
  - additional doses can be added each day as tolerated up to a maximum tolerable daily dose of 1,800 mg a day in two divided doses.

Gibson Chest 2016;149:27-44

A Randomized Controlled Trial to Assess the Effect of Lidocaine Administered via Throat Spray and Nebulization in Patients with Refractory Chronic Cough

OBJECTIVE:

- To investigate the efficacy of nebulized lidocaine and lidocaine throat spray versus matched placebos in RCC.

METHODS:

- This was a randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover study, comparing the effect of single doses of nebulized lidocaine with lidocaine delivered by a throat spray and matched placebo.
- The primary end point was cough frequency over the 10 hours following Rx
- Secondary end points were visual analog scale scores for urge-to-cough and cough severity; an exploratory analysis evaluated hourly cough rates up to 5 hours after treatment.

Abdulqawi JACI in Practice 2021;9:1640-7

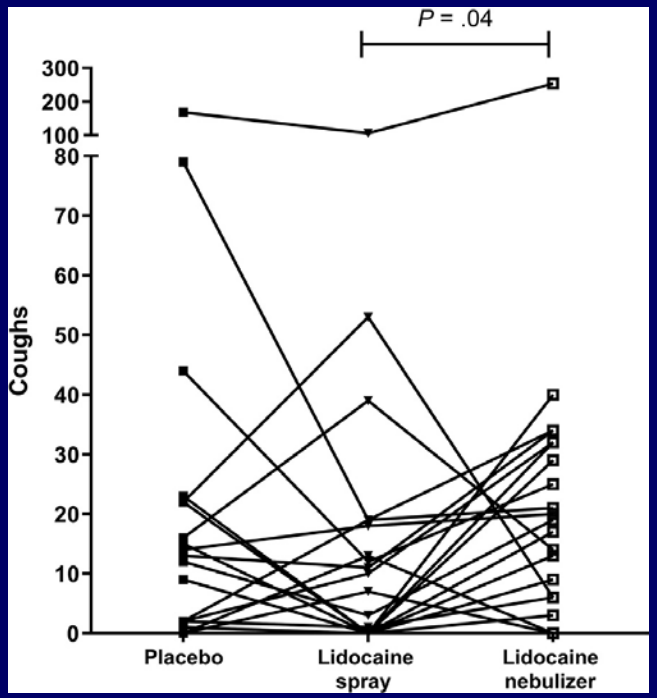
A Randomized Controlled Trial to Assess the Effect of Lidocaine Administered via Throat Spray and Nebulization in Patients with Refractory Chronic Cough

Results:

- Lidocaine throat spray, but not nebulized lidocaine, significantly reduced 10-hour cough frequency as compared with placebo (throat spray, 22.6 coughs/h; nebulization, 26.9 coughs/h; and placebos, 27.6 coughs/h; P =.04,).
- Lidocaine throat spray showed the greatest effect on cough compared with placebo in the first hour after administration (31.7 coughs/h vs 74.2 coughs/h; P= .004).
- Both nebulizer and spray treatments significantly alleviated urge-to-cough and cough severity visual analog scale scores compared with placebo (P < .05).
- There were no serious adverse events associated with lidocaine therapy.

Abdulqawi JACI in Practice 2021;9:1640-7

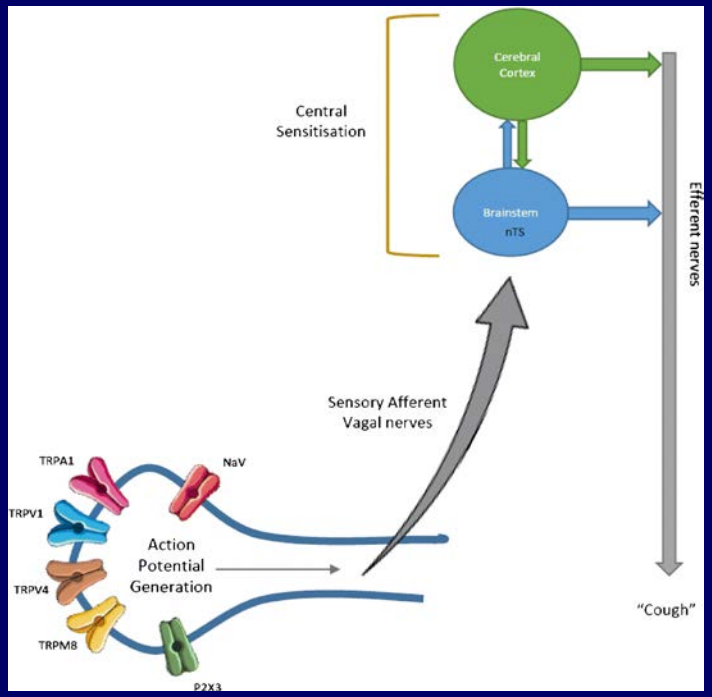
FIGURE 5. Cough counts during the nebulization period.



Why did spray work better than nebulization???
Coughing during nebulization will have reduced deposition/increased clearance of the aerosolized particles,[40] thus decreasing the dose delivered to the throat and lower airways.

Abdulqawi JACI in Practice 2021;9:1640-7

P2X3 and Cough



- Preclinical studies suggest that P2X3 receptors are expressed by airway vagal afferent nerves and contribute to the hypersensitization of sensory neurons.
- P2X3 receptors could mediate sensitization of the cough reflex, leading to chronic cough.

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

Methods

- Performed a double-blind, placebo-controlled, two-period,

crossover study at one UK center investigate the efficacy of a first-in-class oral P2X3 antagonist, AF-219 in chronic refractory cough.

- Randomly assigned patients with refractory chronic cough to AF219, 600 mg twice a day, or to placebo (1:1), and then, after a 2-week washout, assigned patients to receive the other treatment.
- Assessed daytime cough frequency (primary endpoint) at baseline and after 2 weeks of treatment using 24 h ambulatory cough recordings.

Abdulqawi Lancet 2015; 385: 1198–205

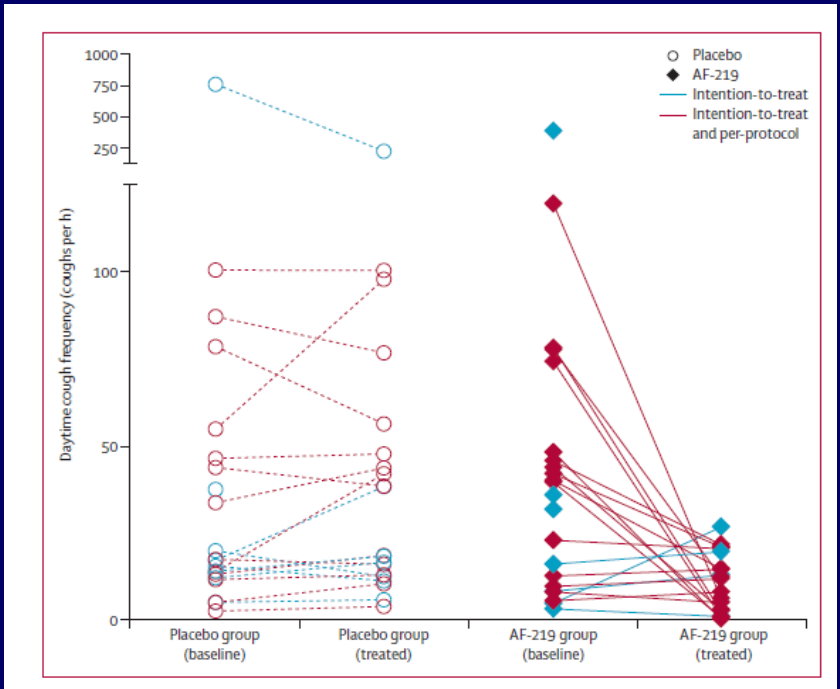
P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

- 24 patients (mean age 54·5 years; SD 11·1).
- In the observed case analysis, cough frequency was reduced by 75% when patients were allocated to AF-219 compared when allocated to placebo (p=0·0003).
- Daytime cough frequency fell from a mean:
  - 37 coughs per h to 11 coughs per h after AF-219 treatment versus
  - 65 coughs per h to 44 coughs per h after placebo.

- Six patients withdrew before the end of the study because of taste disturbances, which were reported by all patients taking AF-219.

Abdulqawi Lancet 2015; 385: 1198–205

Figure 2: Changes in objective daytime cough frequency from baseline to end of the treatment period



- 24 patients (mean age 54·5 years).

In the observed case analysis, cough frequency was reduced by 75% when patients were allocated to AF-219 compared when allocated to placebo (p=0·0003).

- Daytime cough frequency fell from a mean:

  37 coughs per h to 11 coughs per h after AF-219 treatment versus

  65 coughs per h to 44 coughs per h after placebo.

- 6 patients withdrew before the end of the study because of taste disturbances, which were reported by all patients taking AF-219.

Abdulqawi Lancet 2015; 385: 1198–205

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

	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.

Abdulqawi Lancet 2015; 385: 1198–205

Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial

Methods

- 12-week, phase 2b, randomized, double-blind, placebo-controlled study in patients with refractory chronic cough or unexplained chronic cough aged 18–80 years in the UK and the USA.
- Eligible patients had:
  - refractory or unexplained chronic cough lasting 1 year or longer,
  - no radiographic chest abnormality,
  - 40 mm or more on a 100-mm cough severity visual analogue scale at enrolment.
- Patients were randomly assigned to receive placebo or one of three doses (7·5 mg, 20 mg, or 50 mg) of oral gefapixant BID, for 84 days

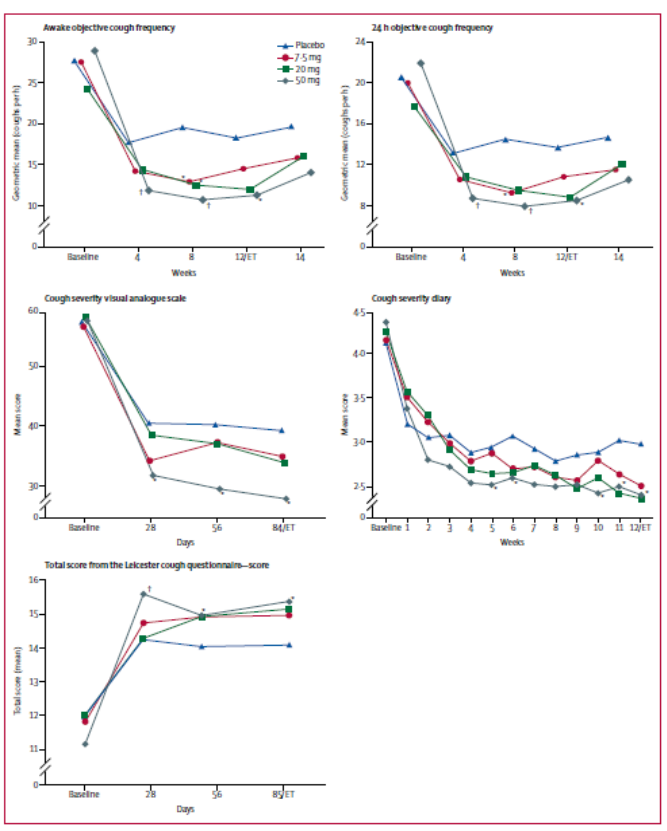
Smith Lancet Resp Med 2020;8:775-85

Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial

- The primary endpoint was placebo-adjusted change from baseline in awake cough frequency after 12 weeks, assessed in the full analysis set, which is a subset of the intention-to-treat population.
- Adverse events were monitored and safety was evaluated in all patients receiving one or more doses of study drug.
- 253 patients were randomly assigned to BID:
  - placebo (n=63),
  - gefapixant 7·5 mg (n=64),
  - gefapixant 20 mg (n=63),
  - gefapixant 50 mg (n=63).
- The mean age of patients was 60·2 (SD 9·9) years and 193 (76%) were women.

Smith Lancet Resp Med 2020;8:775-85

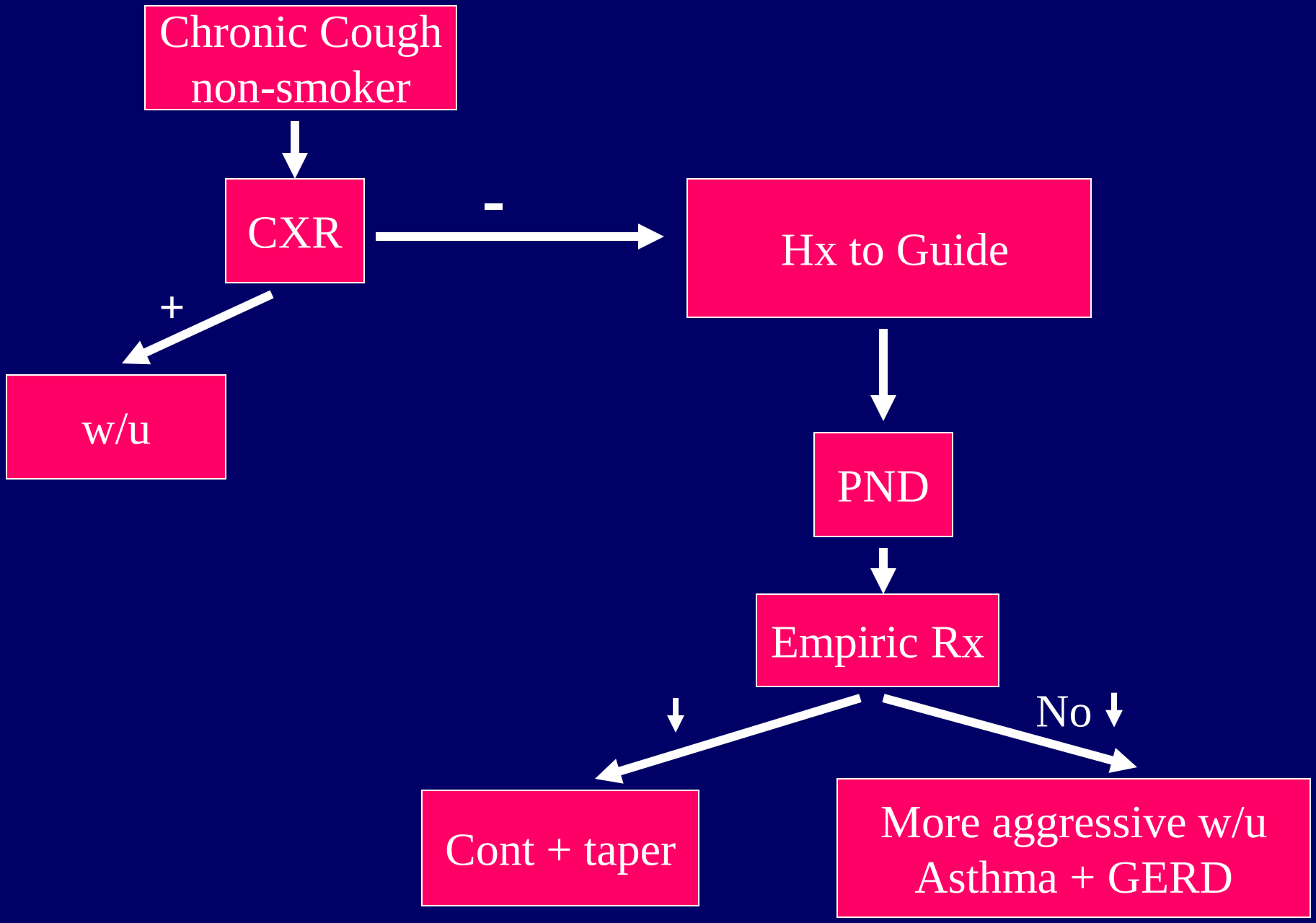
Figure 3: Efficacy measurements over time for gefapixant versus placebo in the full analysis set



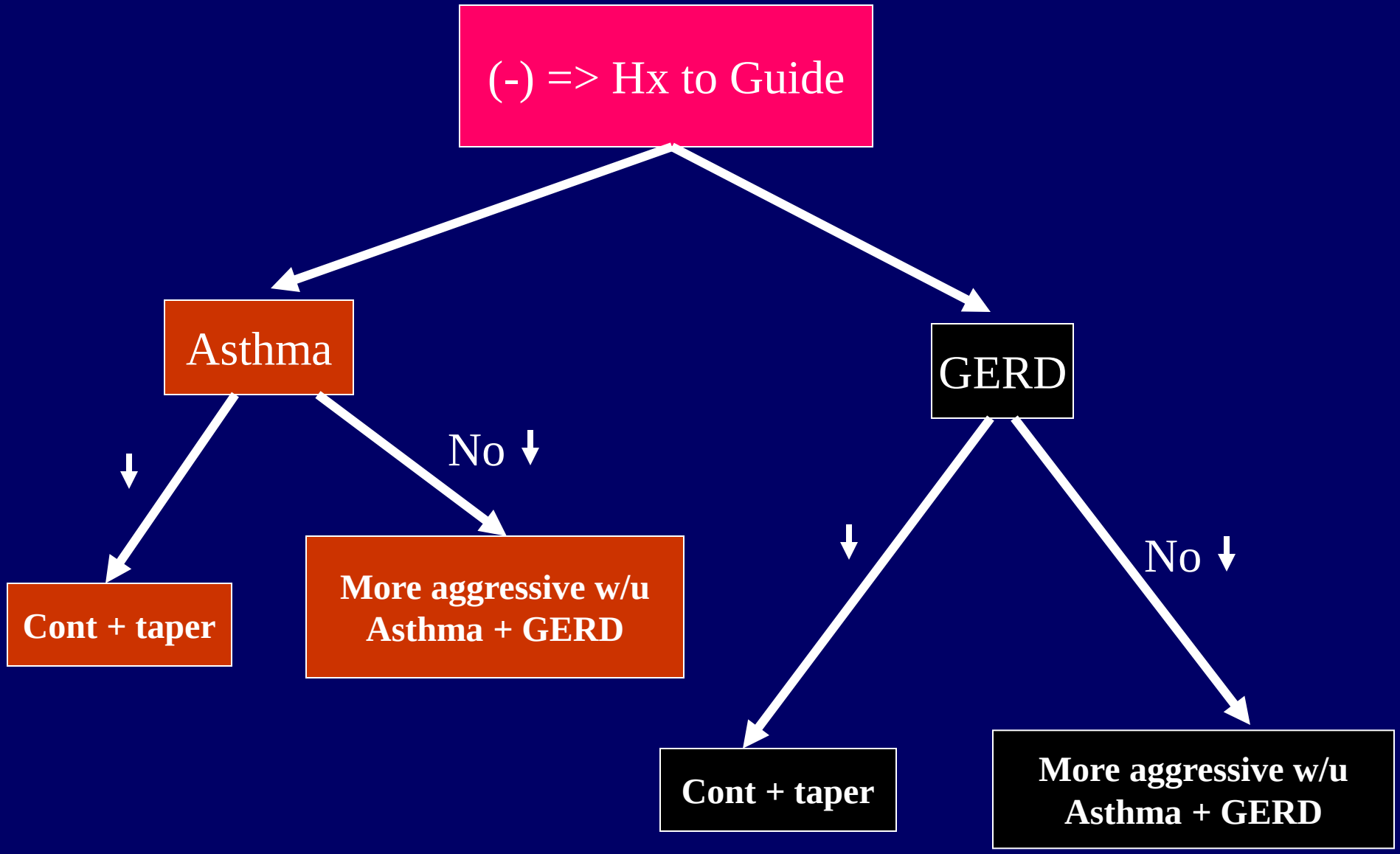
- At 12 weeks, patients' geometric mean awake cough frequency was:
  - 18·2 coughs per h with placebo,
  - 14·5 coughs per h with 7·5 mg gefapixant,
  - 12·0 coughs per h with 20 mg gefapixant
  - 11·3 coughs per h with 50 mg gefapixant.
- Estimated percentage change relative to placebo was:
  - –22·0% (p=0·097) with 7·5 mg gefapixant
  - –22·2% (p=0·093) with 20 mg gefapixant
  - –37·0% (p=0·0027) with 50 mg gefapixant.
- Dysgeusia was the most common adverse event, occurring in:
  - three (5%) patients given placebo,
  - six (10%) given 7·5 mg gefapixant,
  - 21 (33%) given 20 mg gefapixant,
  - 30 (48%) given 50 mg gefapixant.

Smith Lancet Resp Med 2020;8:775-85

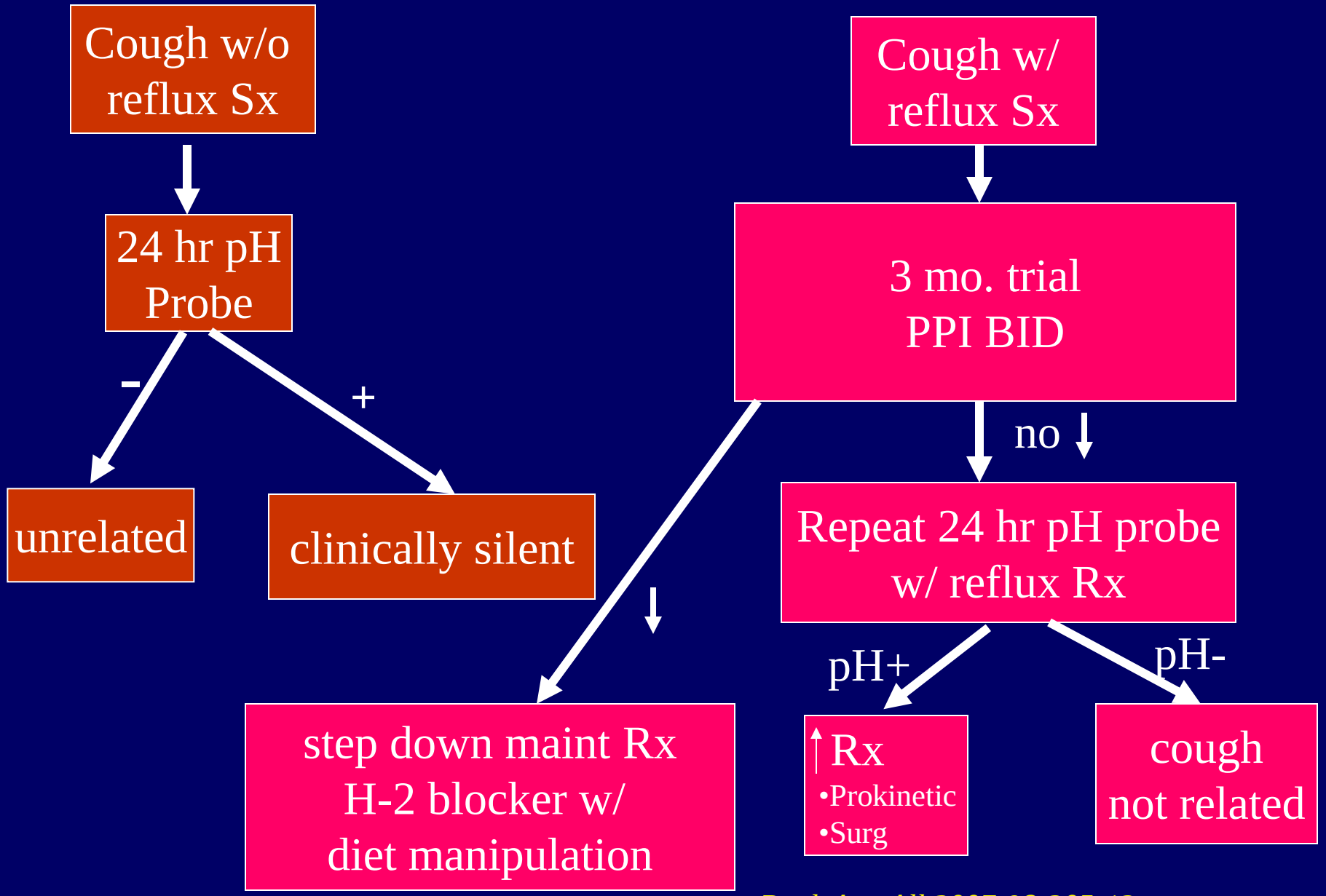
How Do we put all of this Together



Rank Ann All 2007;98:305-13



Rank Ann All 2007;98:305-13



Rank Ann All 2007;98:305-13

Chronic Cough Unexplained

- NERD
- Speech therapy
- Local anesthetics
- Gabapentin
- Hopefully future options – P2X3 blockers?