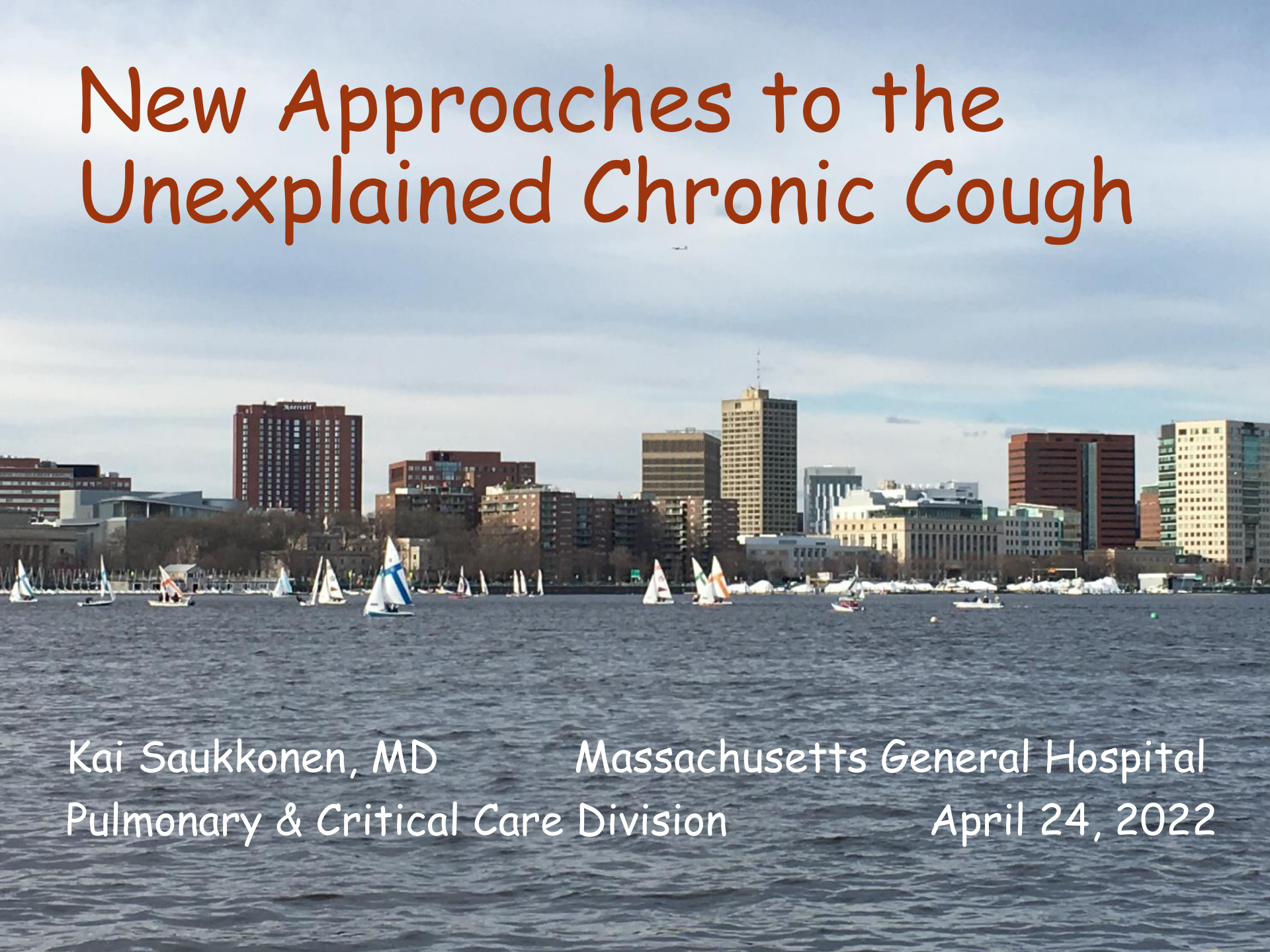
New Approaches to the Unexplained Chronic Cough



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April 24, 2022

Disclosures

- Some off-label uses of medications are mentioned.
- No financial disclosures

Learning Objectives: Chronic cough (1)

- Definition and Pathophysiology
- Differential diagnosis
- History
- Physical Exam
- Laboratory evaluation

Learning Objectives: Chronic cough (2)

- Treatment
- Speech pathology
- Cough hypersensitivity
  - Pathophysiology
  - New drugs for cough hypersensitivity
- Take home points

Chronic cough: Definition

- Cough that lasts more than 8 weeks

The *unexplained* chronic cough

- *Unexplained*, rather than *idiopathic*
- **Patient**: history, adherence
- **Doctor**: history, differential diagnosis, investigation

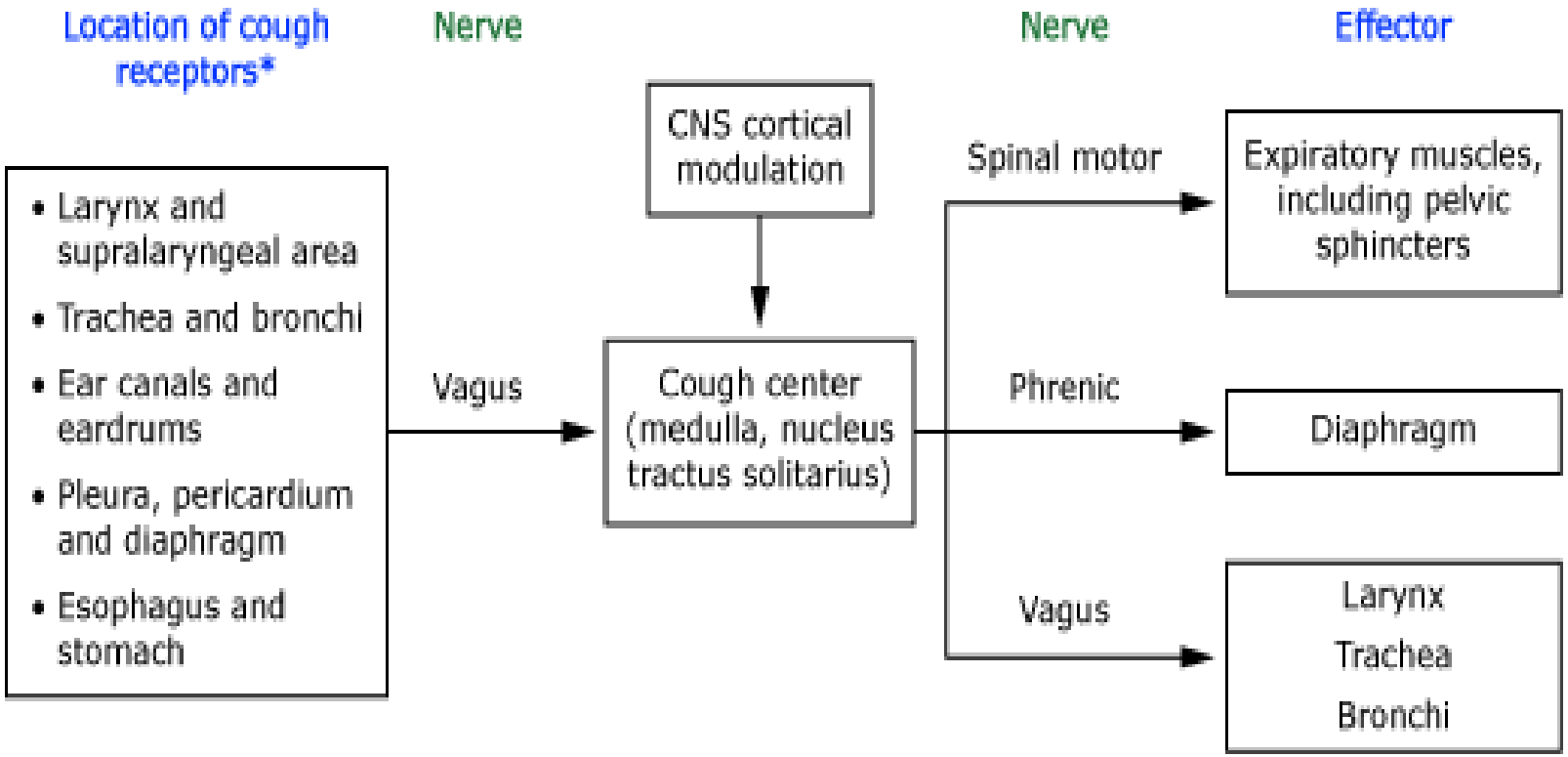
Cough: Overview

- Most common cause for visit to doctor's office (30 million visits a year)

Cough: Overview

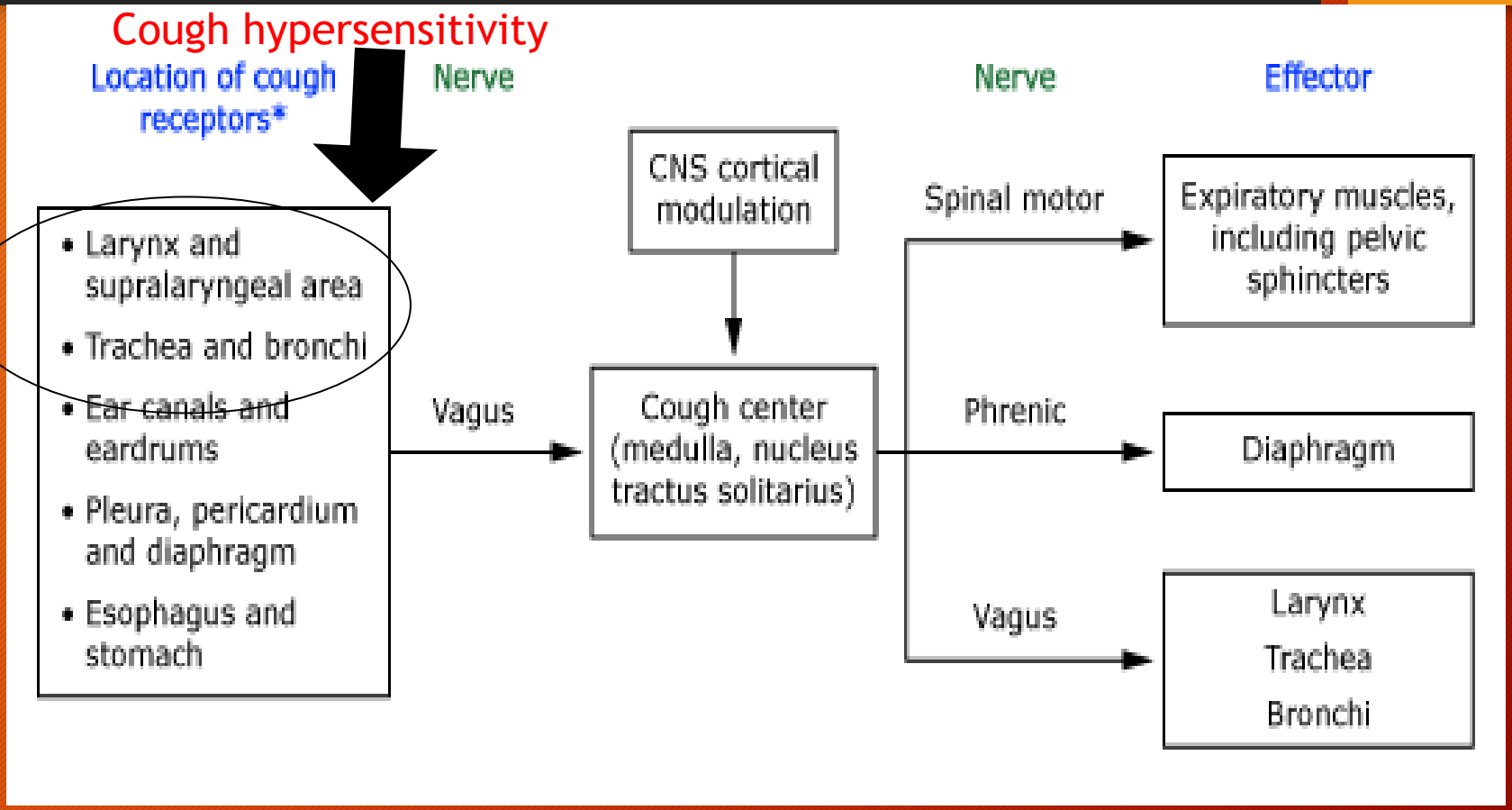
- Complications:
  - Syncope
  - Insomnia
  - Emesis
  - Subconjunctival hemorrhage
  - Fecal/urinary incontinence
  - Social embarrassment
  - Hernia
  - Rib fracture
  - Revenue lost

The Cough Reflex



UpToDate

The Cough Reflex



UpToDate

Chronic cough

- Definition
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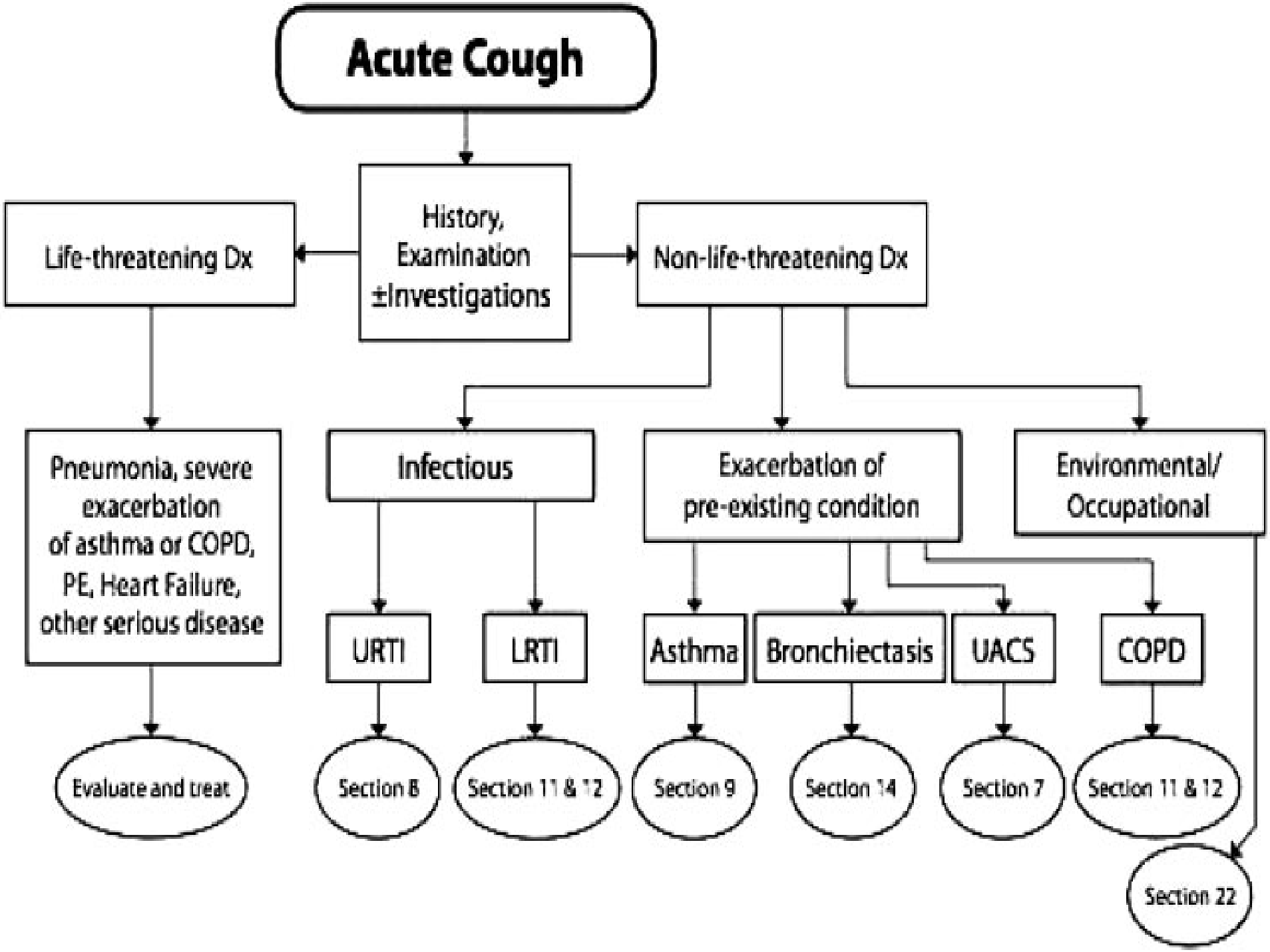
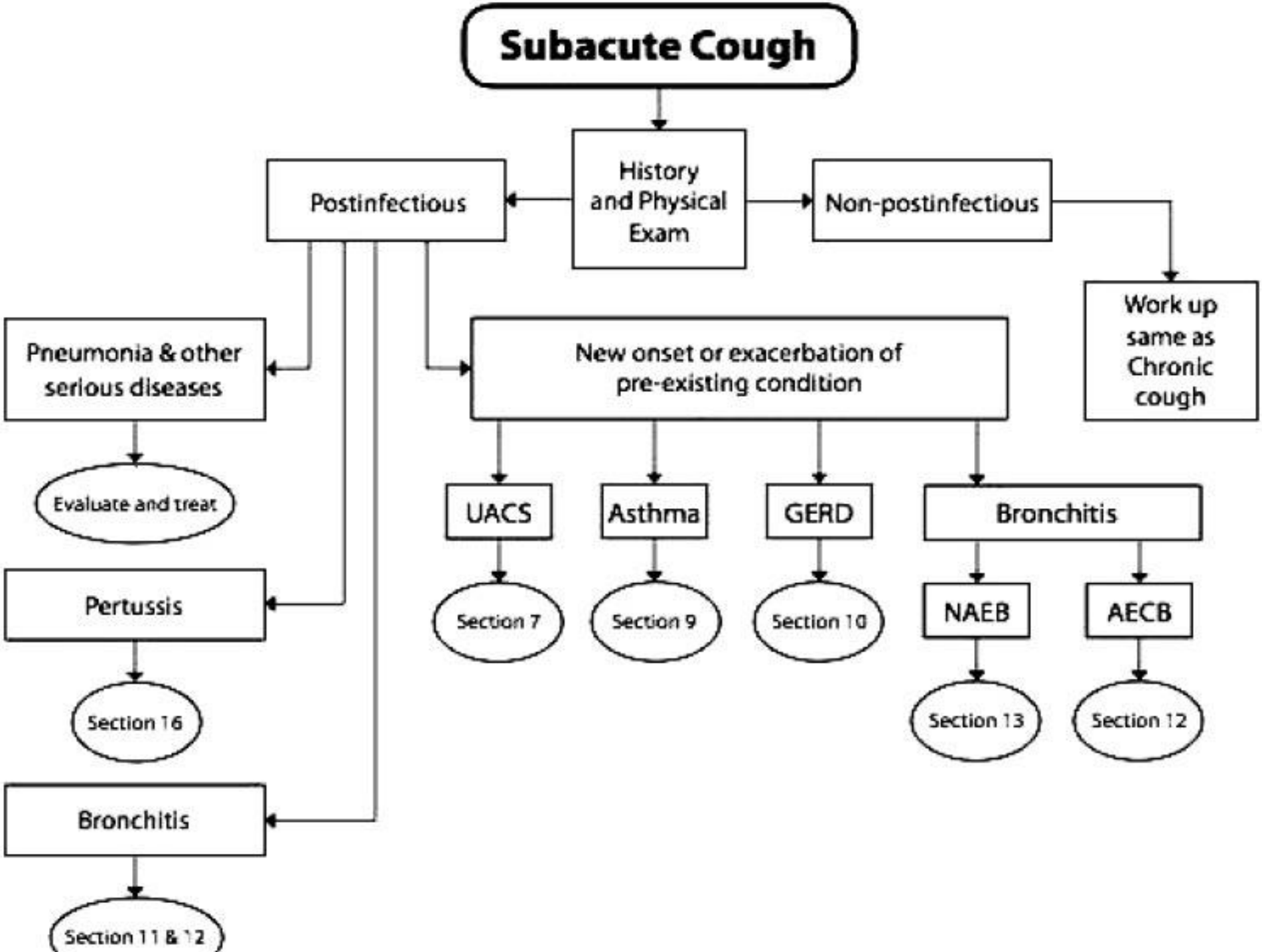
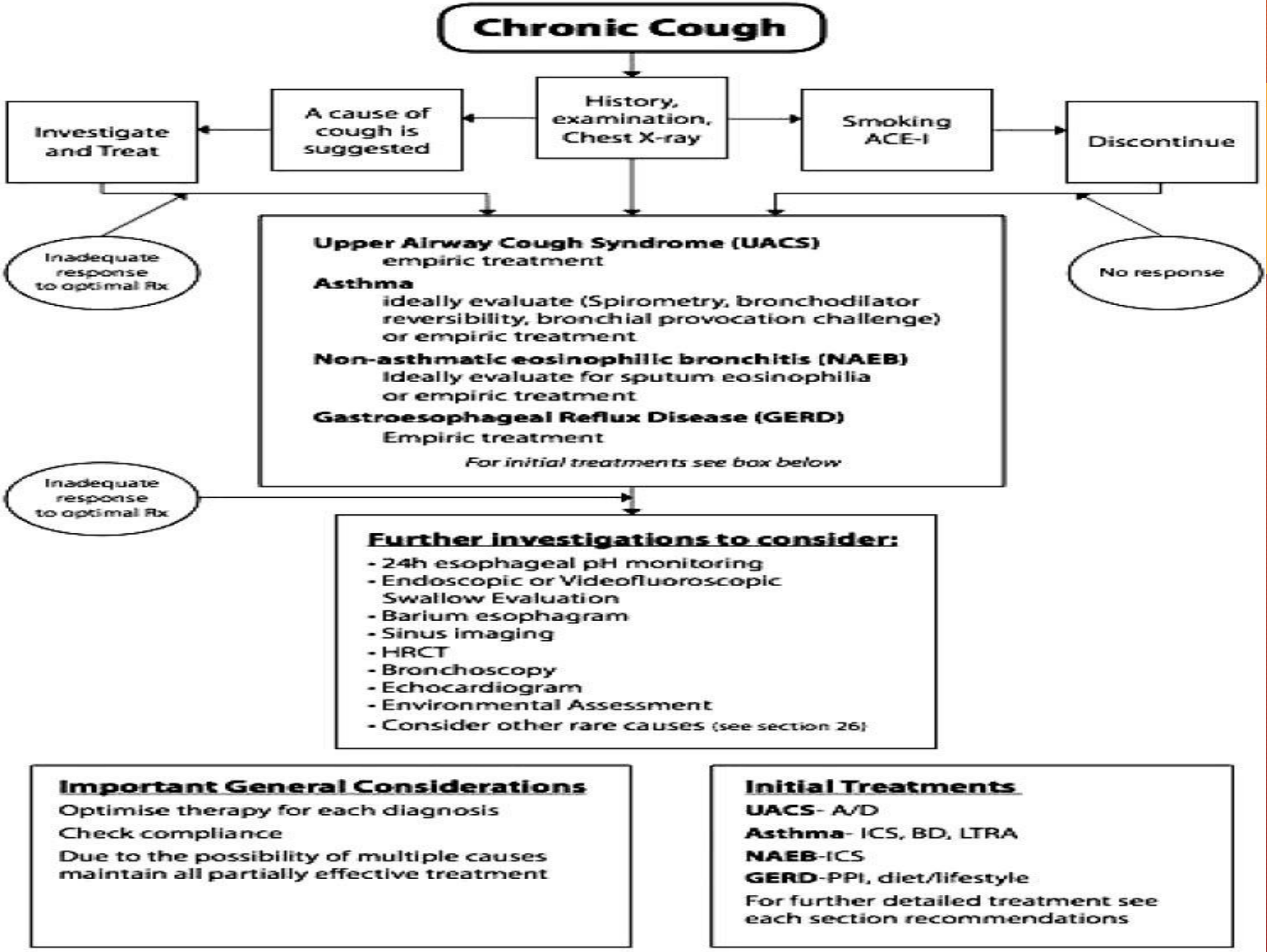
ACCP cough guidelines

- Acute cough
- Subacute cough
- Chronic cough

Diagnosis and Management of Cough
ACCP Evidence-Based Clinical Practice Guidelines
Chest 2006


Acute Cough
History, Examination ±Investigations
Life-threatening Dx
Non-life-threatening Dx
Pneumonia, severe exacerbation of asthma or COPD, PE, Heart Failure, other serious disease
Infectious
Exacerbation of pre-existing condition
Environmental/ Occupational
URTI
LRTI
Asthma
Bronchiectasis
UACS
COPD
Evaluate and treat
Section 8
Section 11 & 12
Section 9
Section 14
Section 7
Section 11 & 12
Section 22


Subacute Cough
History and Physical Exam
Postinfectious
Non-postinfectious
Work up same as Chronic cough
Pneumonia & other serious diseases
Evaluate and treat
Pertussis
Section 16
Bronchitis
Section 11 & 12
New onset or exacerbation of pre-existing condition
UACS
Section 7
Asthma
Section 9
GERD
Section 10
Bronchitis
NAEB
Section 13
AECB
Section 12


Chronic Cough
History, examination, Chest X-ray
A cause of cough is suggested
Investigate and Treat
Smoking ACE-I
Discontinue
Inadequate response to optimal Rx
No response
Upper Airway Cough Syndrome (UACS)
empiric treatment
Asthma
ideally evaluate (Spirometry, bronchodilator reversibility, bronchial provocation challenge) or empiric treatment
Non-asthmatic eosinophilic bronchitis (NAEB)
Ideally evaluate for sputum eosinophilia or empiric treatment
Gastroesophageal Reflux Disease (GERD)
Empiric treatment
For initial treatments see box below
Inadequate response to optimal Rx
Further investigations to consider:
- 24h esophageal pH monitoring
- Endoscopic or Videofluoroscopic Swallow Evaluation
- Barium esophagram
- Sinus imaging
- HRCT
- Bronchoscopy
- Echocardiogram
- Environmental Assessment
- Consider other rare causes (see section 26)
Important General Considerations
Optimise therapy for each diagnosis
Check compliance
Due to the possibility of multiple causes maintain all partially effective treatment
Initial Treatments
UACS- A/D
Asthma- ICS, BD, LTRA
NAEB-ICS
GERD-PPI, diet/lifestyle
For further detailed treatment see each section recommendations

Chronic cough

- Definition
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Taking the History

- “Just listen to your patient,
  he is telling you the diagnosis.”
  --Osler

BMJ 2000;321:1087

Taking the History

- “How can I help you?”
- “Tell me your story.”
- “How did you end up seeing a lung doctor?”
- Listen for more than 20 seconds.
- Clarify.

Taking the History

- If you don’t ask, they may not tell you.
- Leave no relevant question unasked.

Taking the History

- How did it start?
- Have you had this before?
- What makes it better? Worse?
- What have you tried?
- Related to eating, exercise, environment, etc?
- Smoker?
- Is the cough productive?

Taking the History

- Is it really a cough?
- Or throat-clearing?
- Or snorting?
- Or a nervous tic?

Box 2 | Red flags: alarm symptoms and findings in chronic cough[65]

- Hemoptysis
- Smoker with >20 pack year smoking history
- Smoker over 45 years of age with a new cough, altered cough, or cough with voice disturbance
- Prominent dyspnea, especially at rest or at night
- Substantial sputum production: more than one tablespoon a day
- Hoarseness
- Systemic symptoms: fever, weight loss
- Complicated gastroesophageal reflux disease (GORD) symptoms associated with weight loss, anemia, overt gastrointestinal bleeding (hematemesis or melena), severe symptoms, dysphagia, odynophagia, or failure of empiric treatment for GORD
- Recurrent pneumonia
- Abnormal clinical respiratory examination
- Abnormal chest radiograph

Gibson 2015

Box 3 | Remediable conditions and conditions not to be missed in patients with chronic cough[65]

Remediable conditions

Asthma

Gastroesophageal reflux disease

Obstructive sleep apnea

Angiotensin converting enzyme inhibitor use

Eosinophilic bronchitis

Rhinosinusitis

Serious cough related conditions

Cancer of the larynx, bronchus, or lung

Parenchymal lung disease: chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, bronchiectasis, sarcoidosis, pneumothorax

Cardiovascular disease: left ventricular failure, pulmonary embolism, aortic aneurysm

Infection: tuberculosis, lung abscess, pertussis

Gibson 2015

Ask about specific SINUS symptoms

- Post nasal drip
- Mucus dripping in the back
- Tickle in the throat
- Something in the back of the throat
- History of sinus infections or surgery
- History of sinus headaches

Use sterile water to mix solution for sinus irrigation

Primary Amebic Meningoencephalitis Deaths Associated With Sinus Irrigation Using Contaminated Tap Water

Jonathan S. Yoder,[1] Susanne Straif-Bourgeois,[4] Sharon L. Roy,[1] Thomas A. Moore,[5] Govinda S. Visvesvara,[1] Raoult C. Ratard,[4] Vincent R. Hill,[1] Jon D. Wilson,[6] Andrea J. Linscott,[5] Ron Crager,[7] Natalia A. Kozak,[2] Rama Sriram,[1] Jothikumar Narayanan,[1] Bonnie Mull,[1] Amy M. Kahler,[1] Chandra Schneeberger,[1] Alexandre J. da Silva,[3] Mahendra Poudel,[5] Katherine L. Baumgarten,[5] Lihua Xiao,[1] and Michael J. Beach[1]

CID 2012:55 (1 November) • e79

Ask about specific REFLUX symptoms

- Heartburn, “agida”, chest pain/pressure
- Regurgitation, especially when bending over
- Bad taste in the back of the mouth
- Symptoms after going to bed, especially after a large meal.
- Symptoms worse after gaining weight.

Chronic cough

- Definition
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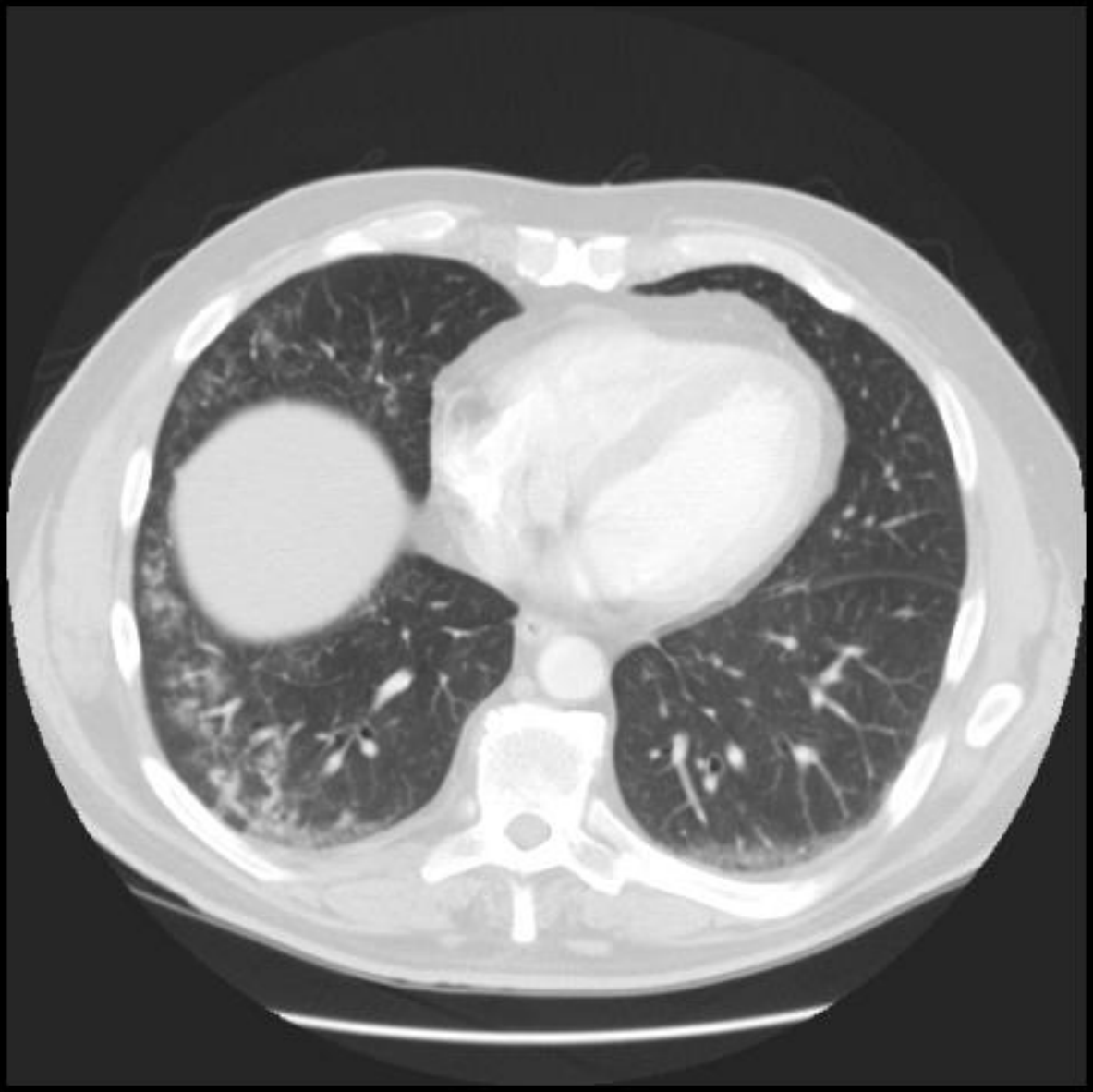
- Take home points

Chronic cough: Physical exam

- Vital signs
- Coughing now? At rest, or with walking?
- Demonstrate the cough.
- Stridor, distress, dyspnea
- Clubbing, edema, rash
- Murmur, gallop, rales, wheezes, rhonchi
- Throat clearing, swallowing mucus

50M with cough

- SOB
- Fever
- Rash



Diagnosis?

- Dermatomyositis with Bronchiolitis Obliterans Organizing Pneumonia
- Look at the whole patient.

35 M chronic cough

- Diagnosed with asthma
- No relief from the usual interventions
- Cough and associated dyspnea are so debilitating that he’s gained 100 lbs while working as a policeman.


L
PA

Diagnosis?

- Endobronchial carcinoid

Diagnosis?

- Endobronchial carcinoid
- Symptoms resolved once tumor cored out and then resected.

Diagnosis?

- Endobronchial carcinoid
- Symptoms resolved once tumor cored out and then resected.
- Question the diagnosis.

40F with polymyositis and mixed connective tissue disease

- Sent by rheumatologist because of cough for six weeks.
- She has interstitial lung disease. Is it time to escalate immunosuppression?
- No postnasal drip or reflux symptoms.

Spirometry at BTPS

ATS ✔ — Pre Bronchodilator — ✔ Post Bronchodilato

		Actual	Predicted	% Pred	CI Range				Actual	% Pred	% Change
FEV!	L	1.46	2.60	56	2.04	3.16	A	M	1.58	61	8
FVC	L	1.97	3.01	65	2.33	3.69	A	m	2.03	67	3
FEV! / FVC	%	74	86	86	77	----	A		78	91	5
FEF@%_&%	L/s	1.06	3.18	33	1.82	4.54			----	----	----
PEFR	L/s	4.90	5.71	86	2.86	8.56			5.97	105	22
FIVC	L	1.87	3.01	62	2.33	3.69			2.00	66	7

Plethysmography

ATS ✔ — Pre Bronchodilator

		Actual	Predicted	% Pred	CI Range			
TLC	L	3.45	4.39	79	3.31	5.47	N	
FRC	L	2.15	2.41	89	1.35	3.47	N	
ERV	L	0.67	1.03	65	----	----		
RV	L	1.48	1.38	107	0.61	2.15	N	
RV/TLC	%	43	31	139	22	40	A	
VC	L	1.97	3.01	65	2.33	3.69		

Resistance

Raw	cmH2O/L/s	3.43	< = 2.80		----	----	A	
sGaw	L/s/cmH2O	0.14	> = 0.12		----	----	N	

Diffusion

ATS ⊘ — Pre Bronchodilator

		Actual	Predicted	% Pred	CI Range			
DLCO	mL/min/mmHg	12.57	22.14	57	15.64	28.64		
DLCO [Hb]	mL/min/mmHg	13.59	22.14	61	15.64	28.64	A	m
Hb	g/dl	11.2	13.4	----	12.0	16.0		
VA [BTPS]	L	2.78	4.43	63	4.35	4.51		
DLCO/VA	mL/min/mmHg/L	4.89	5.53	88	4.21	6.85	N	

Diagnosis?

- Had been started on lisinopril two months earlier.
- Cough resolved, off ACE-I.
- Did not need therapy for ILD.

Diagnosis?

- Had been started on lisinopril two months earlier.
- Cough resolved, off ACE-I.
- Did not need therapy for ILD.
- Beware of misdirection.

62 F with cough for a year

- 62 F
- Cough for a year
- CXR with hint of vertical linear RLL atelectasis
- CT confirmed same minimal linear atelectasis

62 F with cough for a year

- What happened a year ago?

62 F with cough for a year

- What happened a year ago?
- Surgery for cervical epidural abscess.

Diagnosis?

- Bronchoscopy showed a foreign body (piece of chicken) in RLL.

Diagnosis?

- Bronchoscopy showed a foreign body (piece of chicken) in RLL.
- Cough resolved once the foreign body was removed.

77 F with cough for 1½ years

- Started a year and a half ago
- Smoked a pack a day for 5-10 years, quit 50 years ago
- Constant postnasal drip.
- No heartburn.
- Mild to moderate obstruction on PFT's
- CXR unremarkable

77 F with cough for 1½ years

- Dry cough
- Getting worse
- Has to sit up at night
- Only Ricola and water help, but only for a few minutes.

77 F with cough for 1½ years

- Changed lisinopril to another BP medicine
- Tried nasal steroids
- Tried Advair
- Tried proton pump inhibitors
- Saw Primary Care
- Saw ENT
- Saw Pulmonary

77 F with cough for 1½ years

- “They said there’s nothing more they could do.”

-- The Patient

77 F with cough for 1½ years

- “There’s always something you can do.*”

-- Kai Saukkonen, MD

*That doesn’t mean you have to do it.

Diagnosis?

- She had been changed from Zestril (lisinopril) to Vasotec (enalapril).

Diagnosis?

- She had been changed from Zestril (lisinopril) to Vasotec (enalapril).
- She stopped her Vasotec.
- Her cough went away.

Diagnosis?

- She had been changed from Zestril (lisinopril) to Vasotec (enalapril).
- She stopped her Vasotec.
- Her cough went away.
- Cough due to Angiotensin Converting Enzyme inhibitor

Chronic cough

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Chronic cough: Laboratory evaluation

- Pulmonary Function Testing
- Chest x-ray
- Chest CT scan routine, high resolution
- Barium swallow
- Video swallow study (formerly modified barium swallow)
- Bronchoscopy
- pH probe
- Manometry

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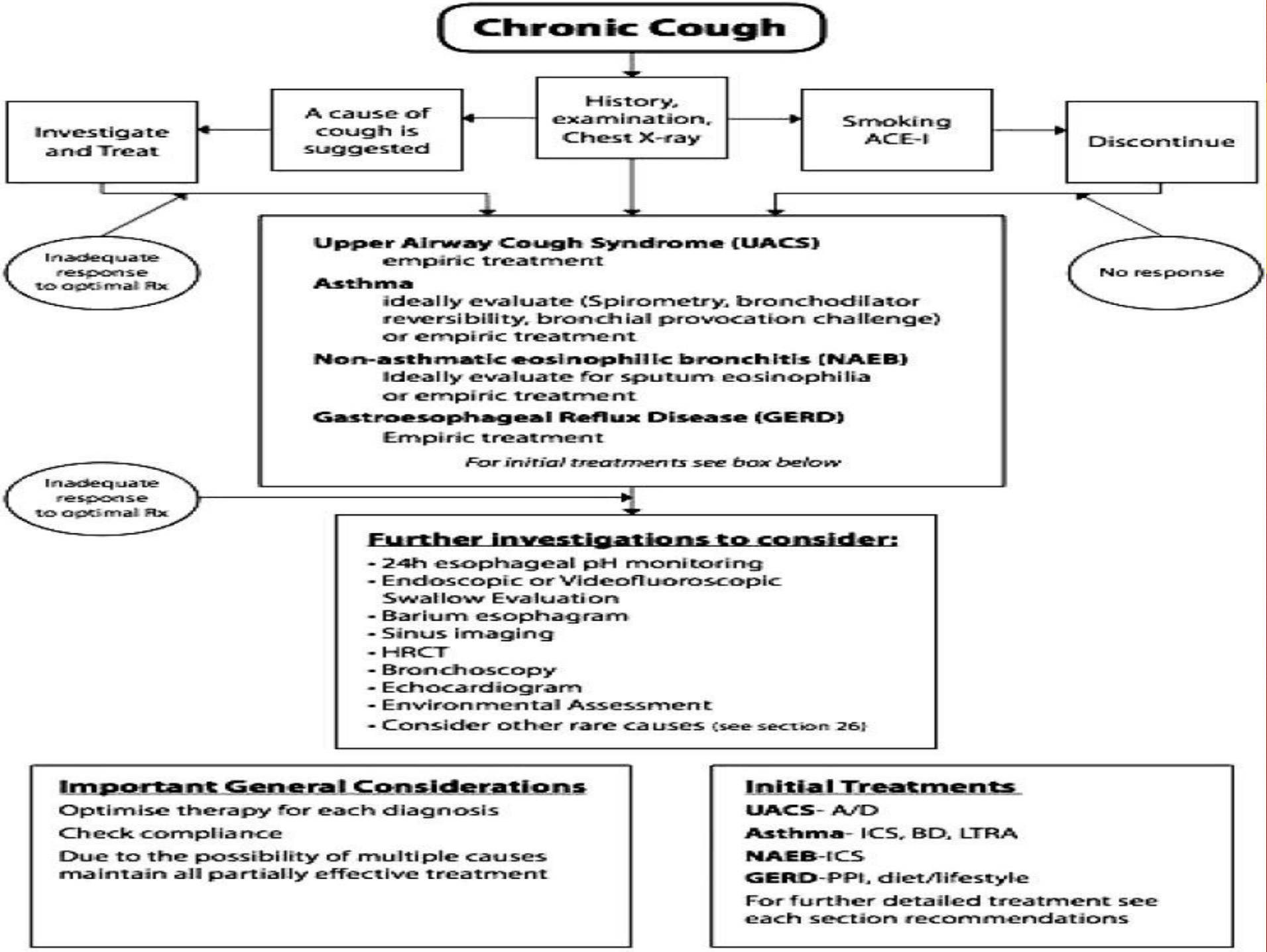
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Symptom control

Table 1. Commonly used therapies available in the United States for symptomatic treatment of chronic cough

Broad Category	Medication/Therapy Class	Therapy Name
Nonspecific pharmacological antitussives (cough suppressants)	Anesthetics	Benzonatate
	Opiates	Codeine, hydrocodone
	Other	Dextromethorphan
Nonpharmacological antitussives	Foods	Honey, tea, lemon, liquor
	Psychological	Cognitive behavioral therapy
	Alternative	Acupuncture, tai chi, yoga, meditation
	Multidimensional	Speech therapy
Protussives	Expectorants	Guaifenesin
	Mucolytic or mucus modifying	Acetylcysteine, dornase alfa inhaled
Nonpharmacological protussives	Physical	Chest physical therapy

Assessment and Management of Chronic Cough. Comparative Effectiveness Review No. 100, Agency for Healthcare Research and Quality, 2013 (total of 256 pages)

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Speech Pathology for Cough

- Education
- Cough control techniques
- Vocal hygiene training
- Psychoeducational counseling

- *Patient needs to be motivated.*

Vertigan, 2011

Table 2. Mechanism of speech pathology treatment

Component	Examples	Mechanism
Education	No physiological benefit to cough, negative side-effects of cough, capacity for voluntary control of cough	Improve adherence
		Increase acceptance of a behavioural approach
	Cough can be suppressed despite irritating sensation	Reduce deliberate coughing
Cough suppression strategies	Identify UTC and substitute competing response	Improve awareness and voluntary control over cough
	Cough suppression swallow	Vocal fold adduction replaces cough but without causing laryngeal irritation
	Cough control breathing	Mimics fast airflow through larynx but moves point of constriction from larynx to the lips. Creates positive pressure in oral cavity to prevent vocal folds closing
	Release of laryngeal constriction	Retracts false vocal folds and improves voluntary control of laryngeal posture during breathing and phonation
	Relaxed throat breathing	Treats underlying vocal cord dysfunction
Vocal hygiene training	Behavioural management of reflux	Reduce reflux events
	Increased systemic and surface hydration	Reduced phonation threshold pressure, improve wound healing, reduce risk of injury
	Reduce exposure to irritating substances	Reduce exposure to triggers
	Reduce phonotraumatic behaviours, e.g. hard glottal attack, laryngeal constriction, hyperadduction	Reduced vocal fold impact stress; Reduced laryngeal constriction; reduced laryngeal inflammation (Verdolini)
Psychoeducational counselling	Supportive counselling, motivational interviewing, validate concerns	Increase acceptance of a behavioural approach
		Increase motivation
		Reduce anxiety
	Manage emotion as a trigger for cough	

UTC, urge to cough.

Gibson et al, 2014

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

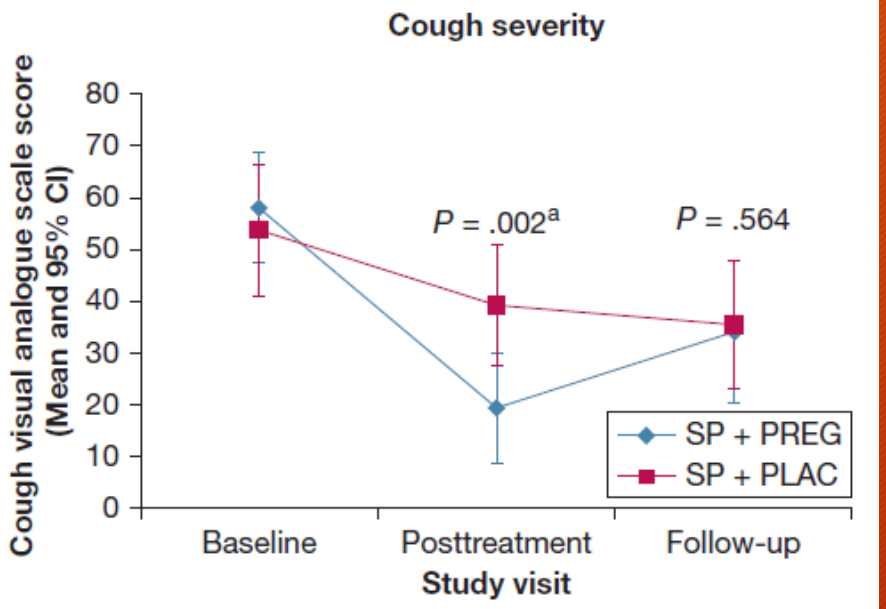

Figure 4 – *Mean (95% CI) cough severity visual analog scale by visit and treatment group. See Figure 1 and 2 legends for expansion of abbreviations.* [a]*P* < .05.

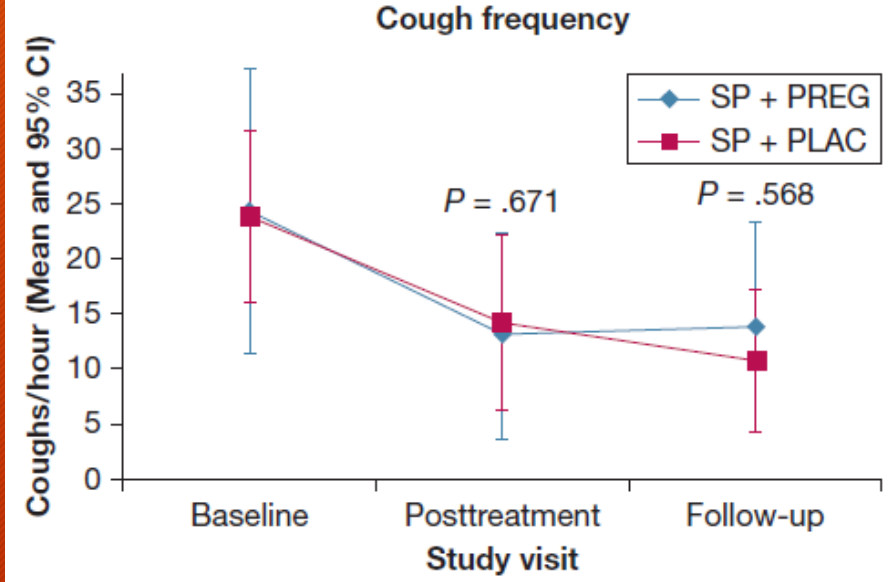

Figure 5 – *Mean (95% CI) objective cough frequency by visit and treatment group using the 24-hour ambulatory cough monitoring with the Leicester Cough Monitor. See Figure 1 and 2 legends for expansion of abbreviations.*

Vertigan, Chest 2016

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Cough Hypersensitivity

- "The cardinal feature of chronic cough is persistent upregulation the cough reflex, which may be driven by complex interactions between biologic, neurologic, immunologic, genetic, comorbid, and environmental factors."

Song, 2014

Neuropathic cough is like neuropathic pain.

Table 1 | Comparison of features of chronic pain and chronic refractory cough[46]

Neuropathic pain		
Concept	Definition/description	Example
Paresthesia	Abnormal sensation	Tingling sensation in the skin
Hyperalgesia	Increased response to a stimulus that is normally painful but at a reduced threshold	Increased pain response to a needle prick
Allodynia	Pain in response to a stimulus that does not normally produce pain, such as a mechanical or thermal stimulus	Pain in response to touch

Neuropathic cough		
Concept	Definition/description	Example
Laryngeal paresthesia or hypersensitivity	Abnormal sensation in the throat	Tickle or itch in throat
Hypertussia	Increased cough response to a tussigenic stimulus	Fumes, smoke, aspirate
Allotussia	Cough in response to a non-tussigenic stimulus	Thermal, vocalisation, exercise

Gibson 2015

Cough Hypersensitivity (umbrella term like COPD)

- Reflux
- Asthma
- Rhinitis
- Eosinophilic bronchitis

- **There is a major impact on quality of life, which is underappreciated.**

Morice opinion 2014

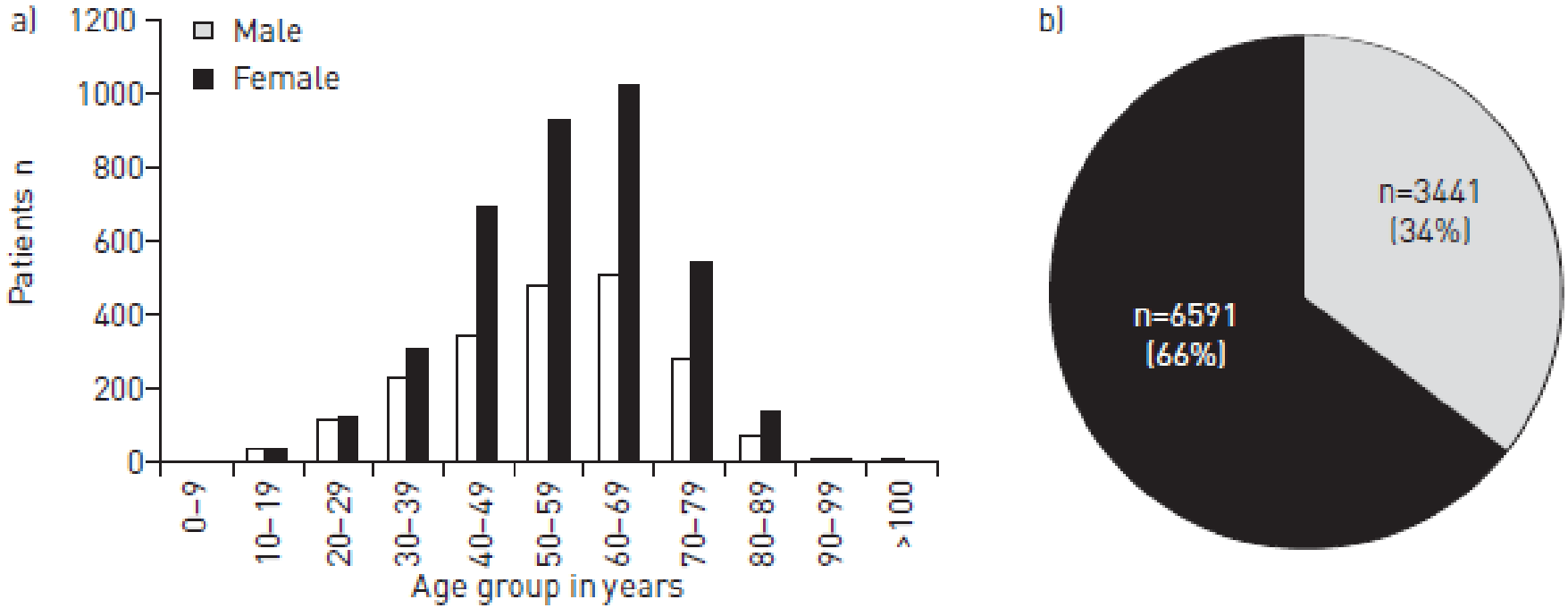


FIGURE 1 Age and sex distribution of all the patients presenting to the clinics.

Morice survey, 2014

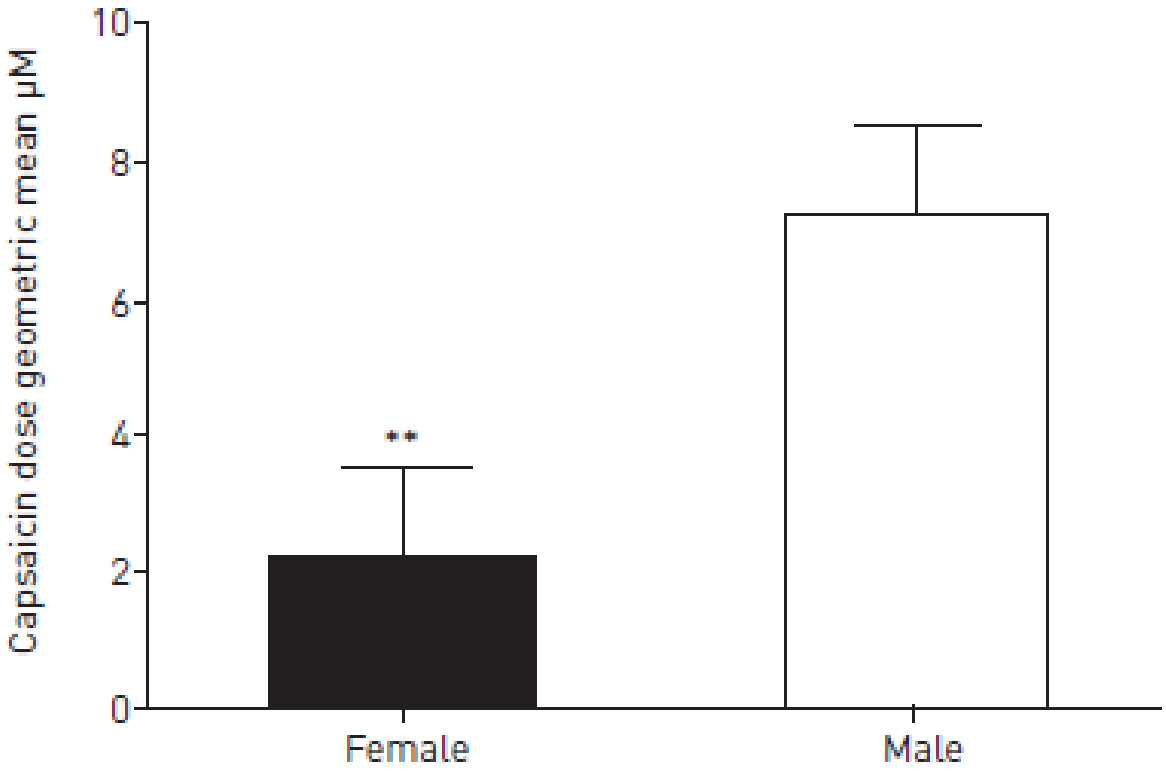


FIGURE 2 The maximum dose of capsaicin that could be inhaled without coughing was measured for a group of young, healthy females (n=10) and males (n=10). The geometric mean of the tolerable dose was significantly lower in females, the t-test with 18 degrees of freedom was 2.9. **: $p<0.01$.

Morice survey2014

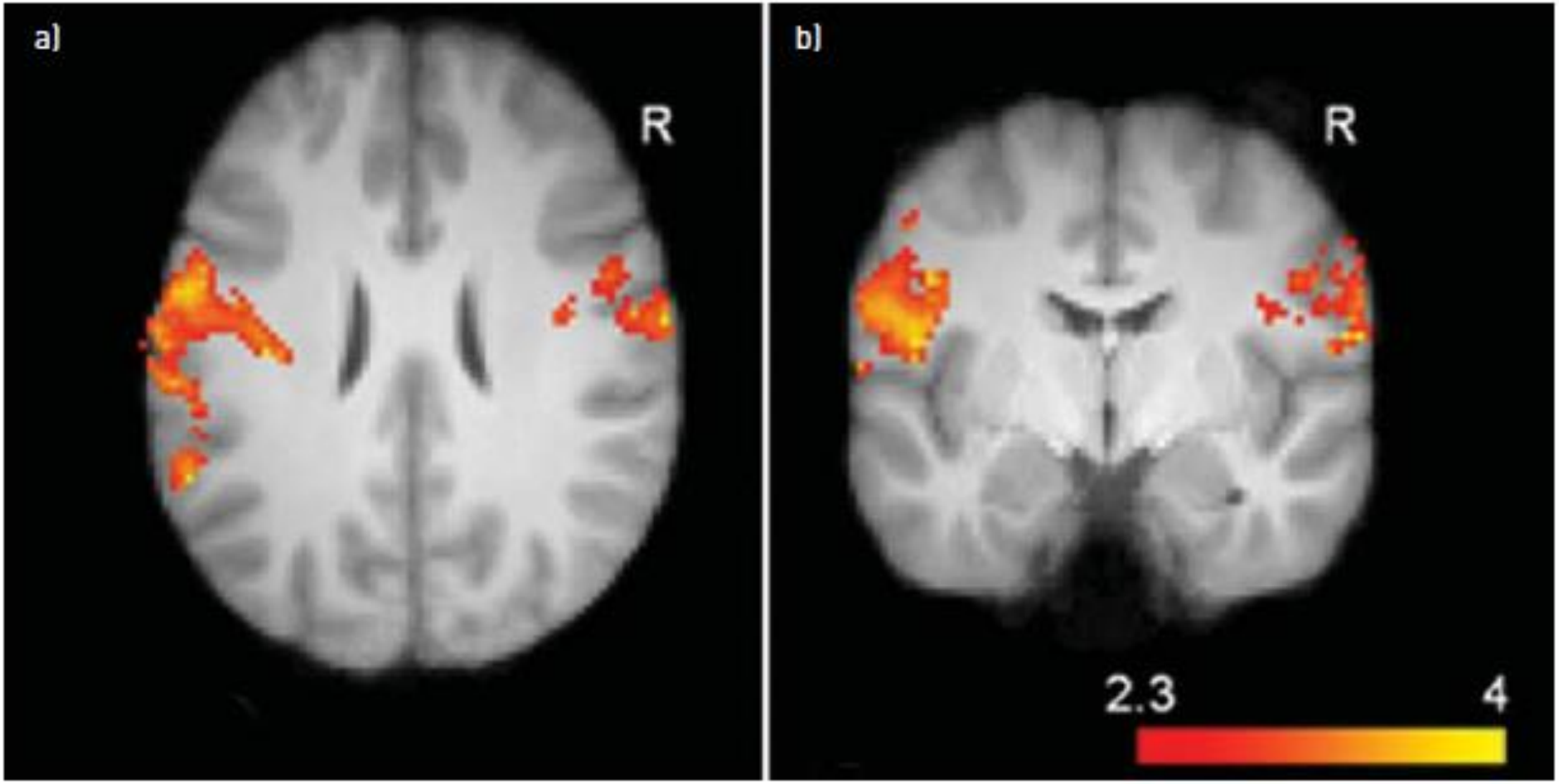


FIGURE 3 Regional brain responses in axial and coronal views during inhalation of the tolerable dose of capsaicin. These functional brain images show the location of the activations that were significantly different in young healthy females compared to males. a) The region of somatosensory cortex showing sex-related differences was located at the lower part of the central sulcus, seen here in axial view 26 mm above the anterior commissure. b) The lower part of the central sulcus ends above the lateral sulcus, which can be seen in this coronal slice, 6 mm behind the anterior commissure, as a darker horizontal line below the rendered activations in both hemispheres. This lower part of the somatosensory cortex receives afferent inputs from the airways.

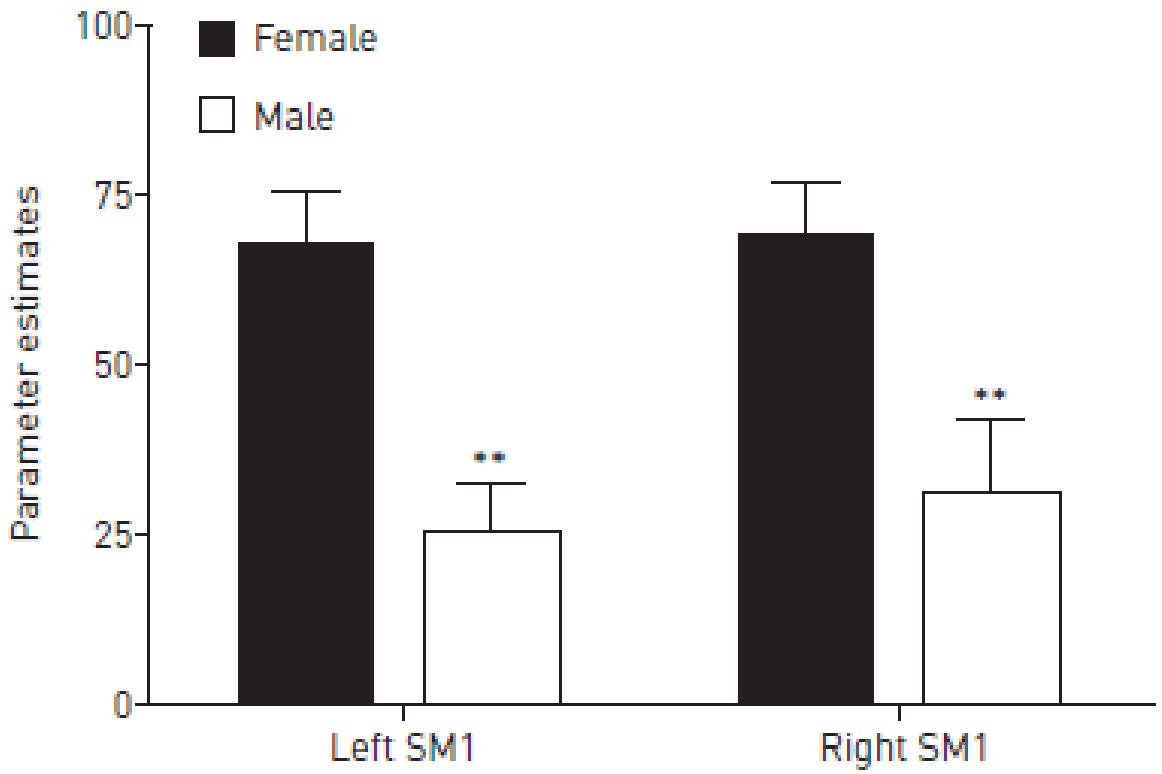


FIGURE 4 Quantification of the size of the regional responses in the right and left primary somatosensory cortices (SM1) of females and males, as represented by mean parameter estimates. Activations were significantly greater in the females compared to the males in the left and the right hemispheres. **: $p<0.01$.

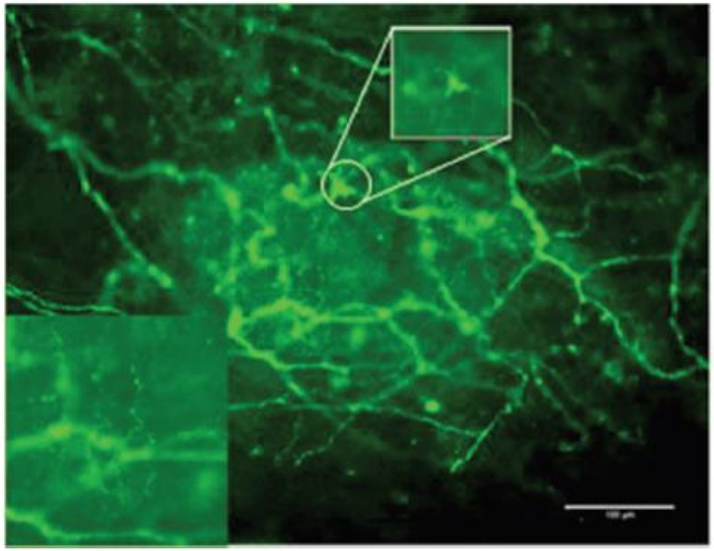
Morice survey 2014

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

Nicole M Ryan, Surinder S Birring, Peter G Gibson

- Improvement in cough-specific quality of life
- Improvement in cough severity
- Improvement in frequency
- Well tolerated
- Replication studies needed

www.thelancet.com Published online August 28, 2012 http://dx.doi.org/10.1016/S0140-6736(12)60776-4



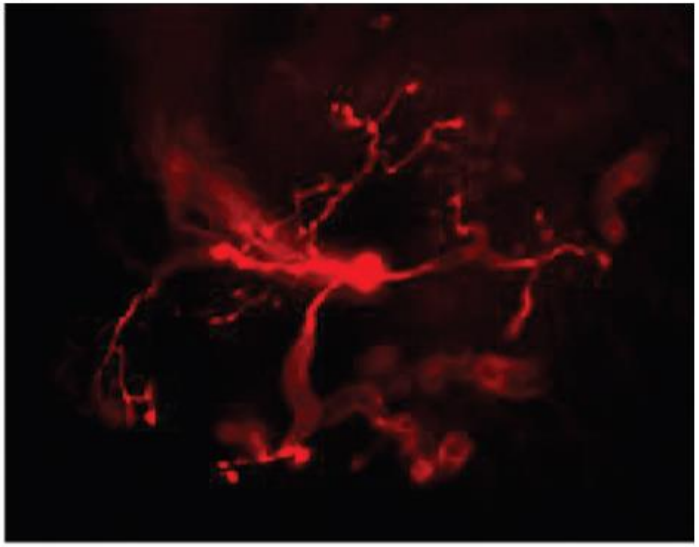


Fig 1. Structure of human airway nerves. A – thin unmyelinated c-fibres located near the epithelial membrane; B – sub-epithelial myelinated Aδ fibres. Reprinted with permission of the American Thoracic Society.[9] Copyright © 2016 American Thoracic Society.

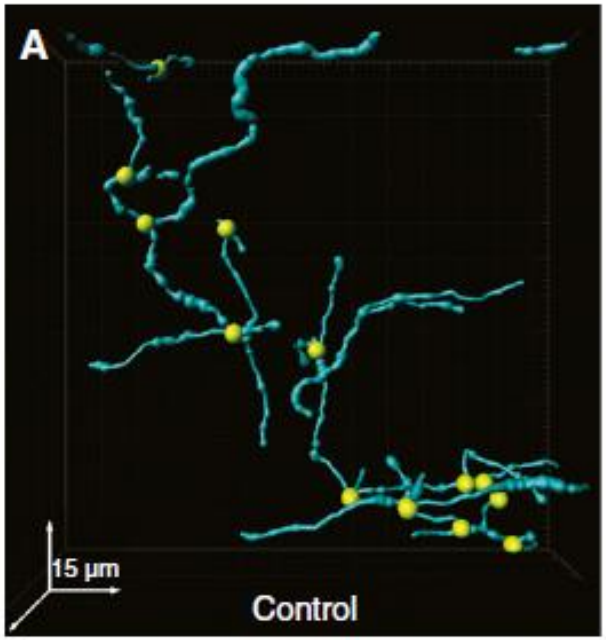
Satia, Clinical Medicine 2016

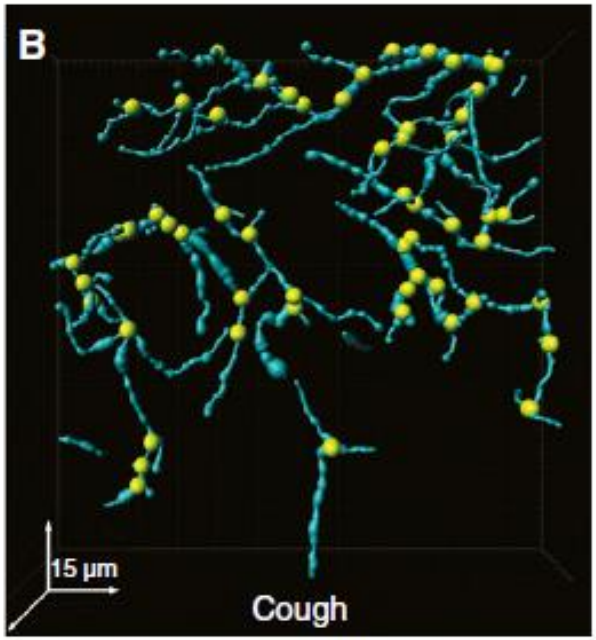
Airway Sensory Nerve Density Is Increased in Chronic Cough

Clare O. Shapiro[1], Becky J. Proskocil[1], Laura J. Oppegard[1], Emily D. Blum[1], Nicole L. Kappel[1], Christopher H. Chang[1], Allison D. Fryer[1], David B. Jacoby[1], Richard W. Costello[2], and Matthew G. Drake[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Oregon Health & Science University, Portland, Oregon; and [2]Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

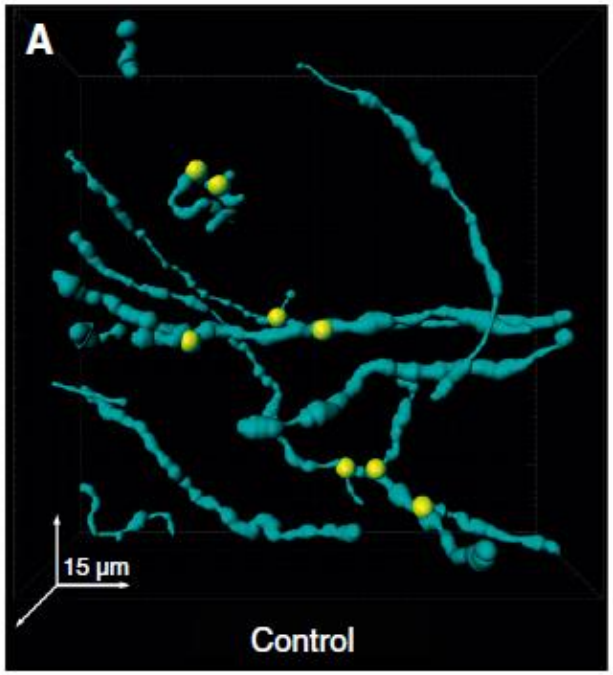
American Journal of Respiratory and Critical Care Medicine Volume 203 Number 3 | February 1 2021

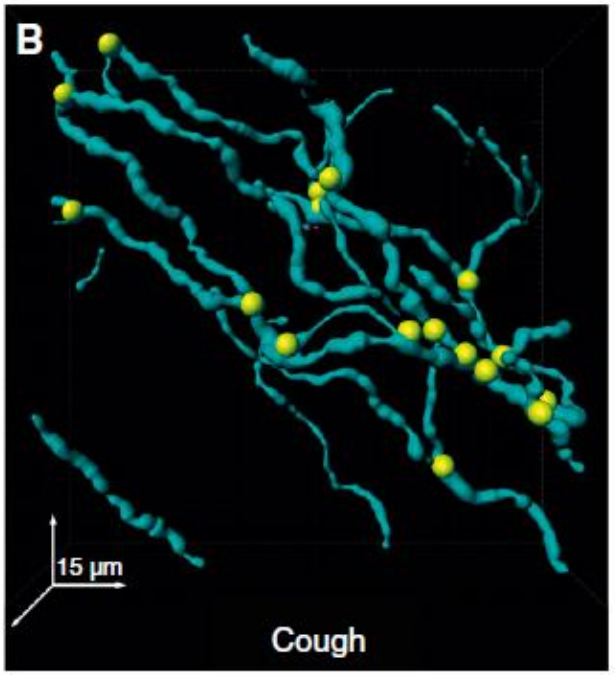




Shapiro et al

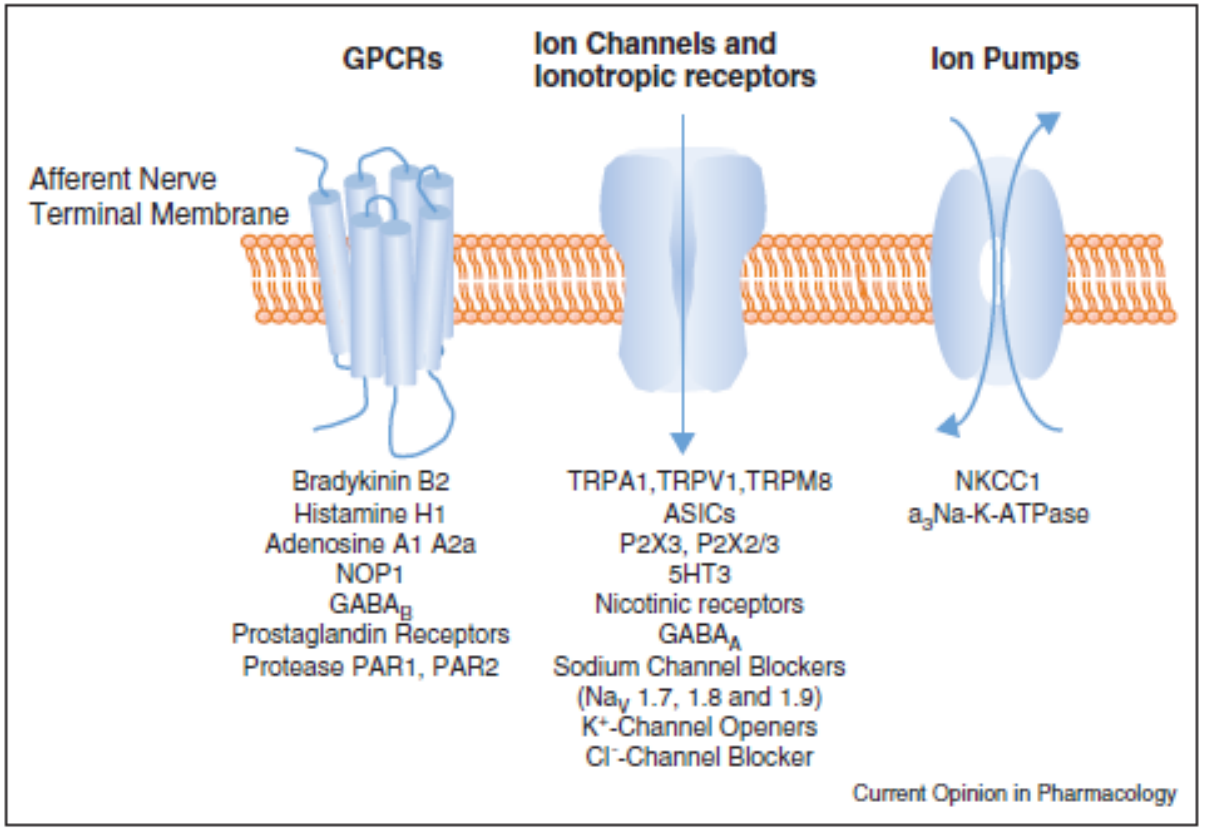
Epithelial sensory innervation is increased in chronic cough.





Subepithelial sensory innervation is similar in chronic cough and in control.

Treating the Afferent Nerve in Cough

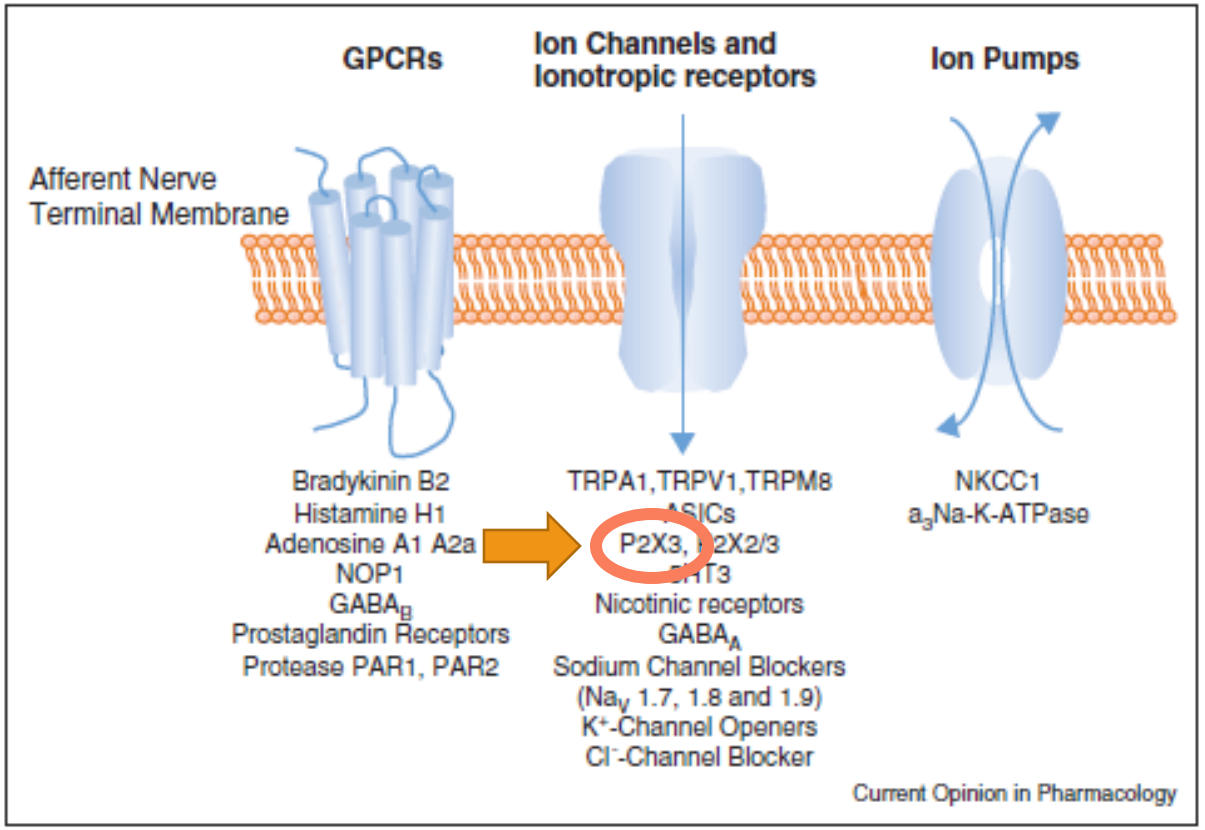


Schematic illustrating numerous potential targets for drugs aimed at limiting the activity of primary afferent nerves in the airways.

GPCR = G protein coupled receptor

Muroi, 2011

Treating the Afferent Nerve in Cough



Schematic illustrating numerous potential targets for drugs aimed at limiting the activity of primary afferent nerves in the airways.

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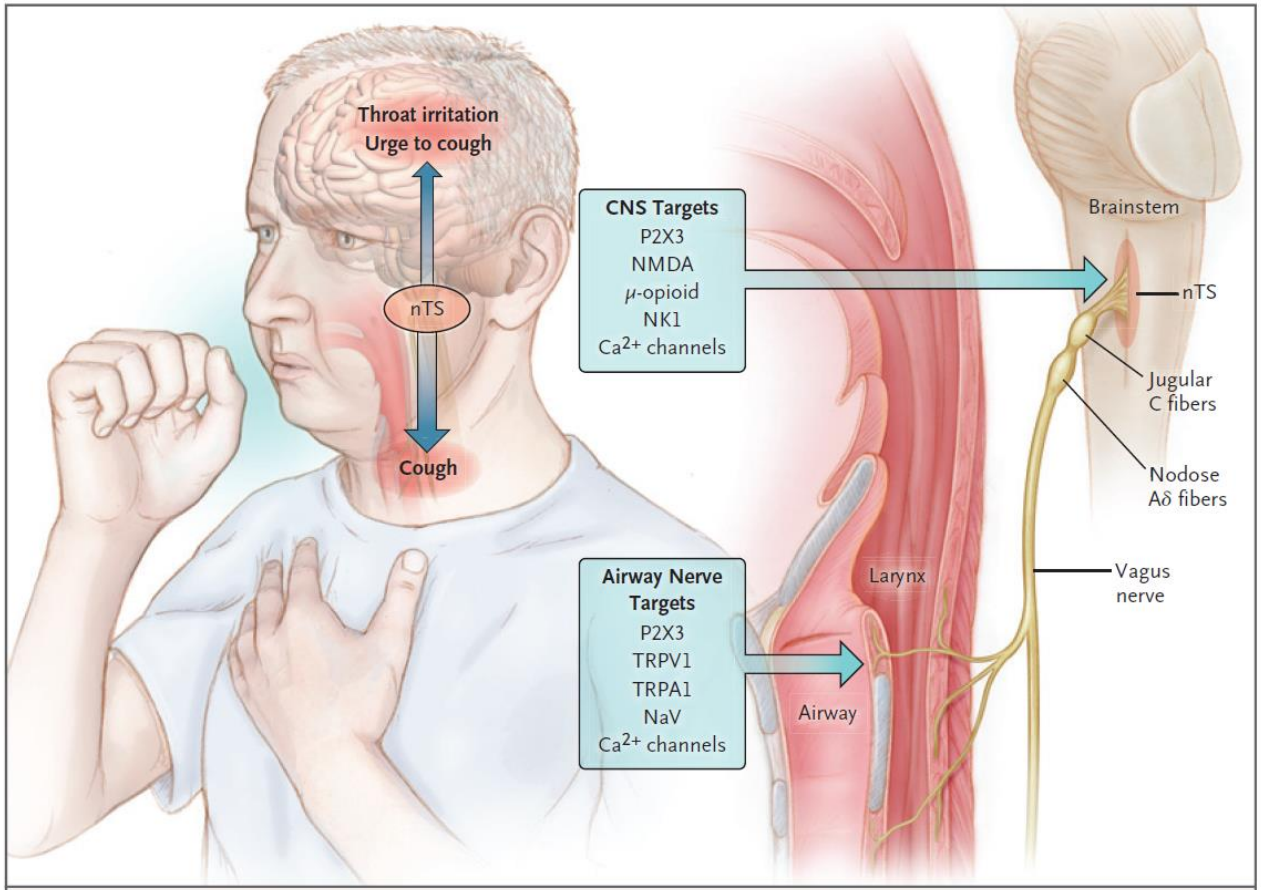


Figure 2. Neuronal Pathways Controlling Cough, and Targets of Available Antitussive Agents and of Those in Development.

C fibers, with bodies in the superior vagal (jugular) ganglion, and Aδ fibers, with cell bodies in the inferior vagal (nodose) ganglion, are the main vagal fibers mediating cough.[46] The key receptors and ion channels located on the terminals of airway sensory afferent vagal nerves that are capable of modulating cough are shown. P2X3 purinergic receptors are found mainly on peripheral sensory nerves, with some expression in the nucleus tractus solitarius (nTS) of the brainstem. Transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) are found on nerve terminals and are capable of initiating action potentials, and voltage-gated sodium channels (NaV) are responsible for action potential transmission. Antagonists for these targets are in development or early-phase clinical trials. In the central nervous system (CNS), the *N*-methyl-D-aspartate (NMDA) receptor is the main target for the over-the-counter therapy dextromethorphan. Morphine is thought to exert antitussive effects through the μ-opioid receptor, whereas gabapentin and pregabalin modulate calcium channels in central and peripheral pathways. The neurokinin-1 (NK1) receptor has been implicated in the sensitization of synapses in the nTS, and its antagonist (aprepitant) was recently found to reduce cough in patients with lung cancer.[47]

Smith, NEJM 2016

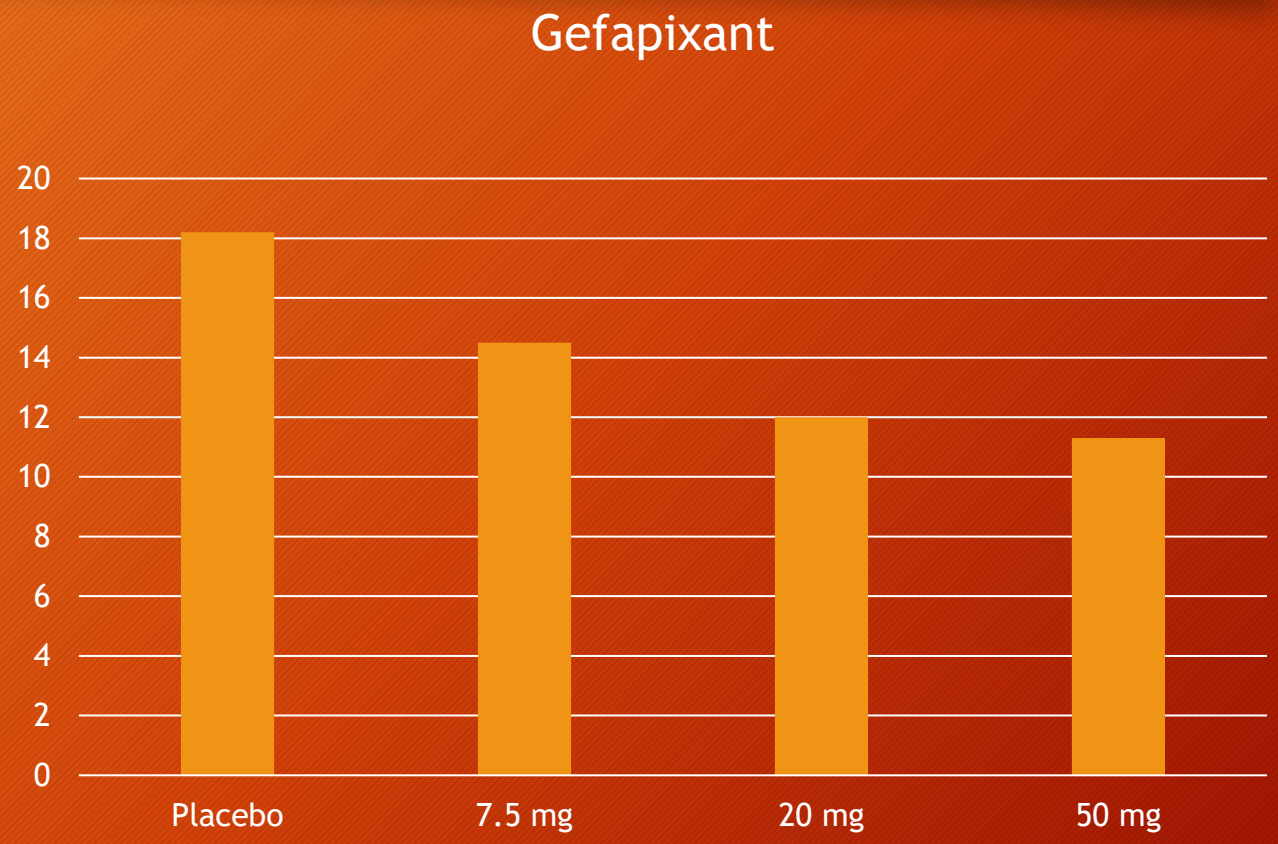
Gefapixant, a P2X3 Receptor Antagonist, for the Treatment of Refractory or Unexplained Chronic Cough: A Randomised, Double-Blind, Controlled, Parallel-Group, Phase 2b Trial

Smith et al, Lancet Respir Med. 2020 Feb 25;S2213-2600(19)30471-0. doi: 10.1016/S2213-2600(19)30471-0. Online ahead of print.

Methods (Gefapixant, Smith et al)

- 12-week, phase 2b, randomised, double-blind, placebo-controlled
- Patients with refractory chronic cough or unexplained chronic cough lasting 1 year or longer, no radiographic chest abnormality, and 40 mm or more on a 100-mm cough severity visual analogue scale at enrolment.
- Aged 18-80 years (mean age 60.2, 76% women)
- Recruited from 44 primarily outpatient pulmonologist or allergist sites in the UK and the USA.
- Funded by the manufacturer

Cough frequency at 12 weeks (Gefapixant, Smith et al)



Geometric SD 2.8-4.2

Dysgeusia

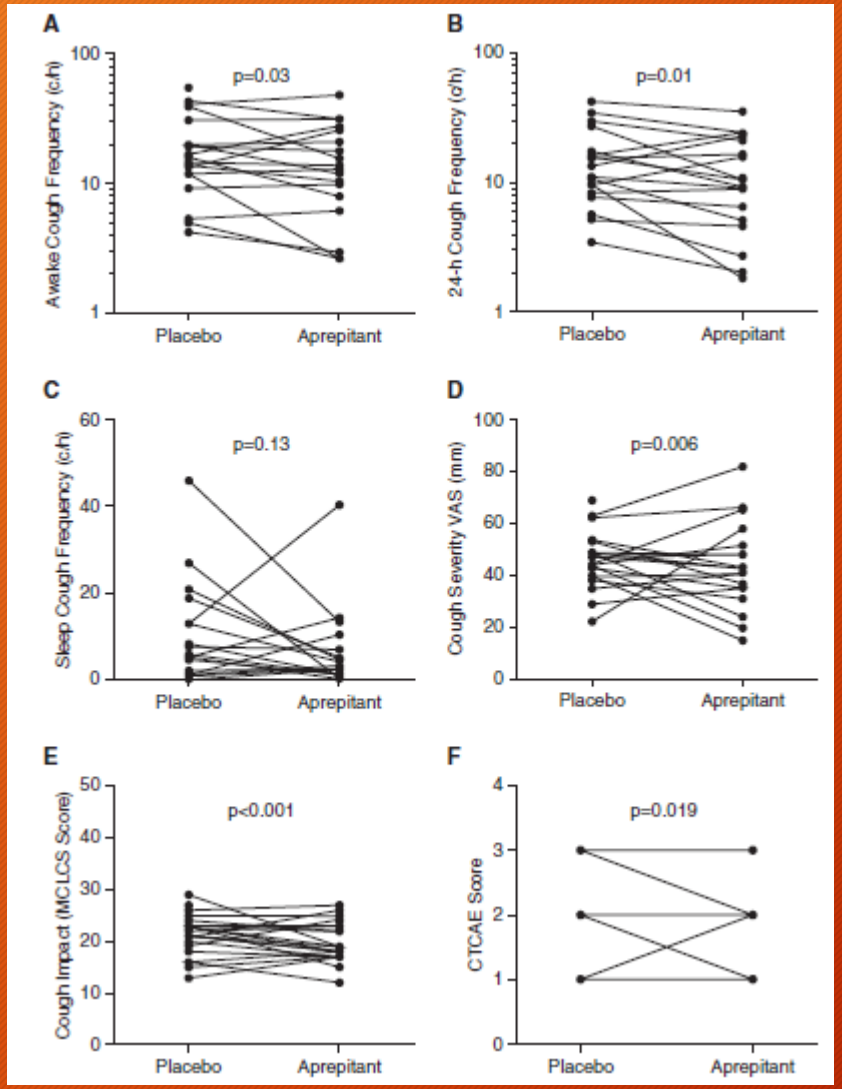
- Most common adverse event
- 3 (5%) patients given placebo
- 6 (10%) given 7·5 mg gefapixant
- 21 (33%) given 20 mg gefapixant
- 30 (48%) given 50 mg gefapixant

Aprepitant for Cough in Lung Cancer

A Randomized Placebo-controlled Trial and Mechanistic Insights

Jaclyn A. Smith[1,2*], Amélie Harle[3,4*], Rachel Dockry[1,2], Kimberley Holt[1,2], Philip Russell[3], Alex Molassiotis[5], Janelle Yorke[3,6], Ryan Robinson[7], Mark A. Birrell[7,8], Maria G. Belvisi[7,8], and Fiona Blackhall[3,4]

American Journal of Respiratory and Critical Care Medicine Volume 203 Number 6 | March 15 2021



Some investigational NK1 (neurokinin 1) receptor antagonists

- Aprepitant
- Orvepitant
- Serlopitant

Chronic cough

- Definition
- Differential diagnosis
- History
- Physical Exam
- Laboratory evaluation
- Treatment
- Speech pathology
- Cough hypersensitivity
  - Pathophysiology
  - New drugs for cough hypersensitivity
- Take home points

Future directions in unexplained chronic cough

TABLE 9] Future Research Directions in UCC

Diagnosis	Study Design
What are the diagnostic criteria for UCC?	What does an ideal study look like [PICOD]?
Is there evidence of a specific phenotype of UCC? [eg, based on sex, BMI, post viral history]	P: population: how should the population be selected and assessed prior to entry
What is the place of cough sensitivity testing in UCC?	I: description of the intervention
Is UCC a diagnosis of exclusion?	C: placebo effect in cough studies
What is the place of cough sensitivity tests such as capsaicin in UCC?	O: outcomes measures: objective, subjective; response characteristics,
What is the prevalence of UCC when intervention fidelity to cough diagnosis is adequately assessed?	D: design: discuss relative merits of different designs, eg randomized vs. before-after; parallel vs cross-over; single vs. multiple interventions
What is the place of assessment and treatment for nonacid gastroesophageal reflux in the assessment of UCC?	
What is the comparative efficacy of diagnostic testing vs. empiric corticosteroid trials for assessment of eosinophilia airway diseases associated with chronic cough?	

PICO = population, intervention, comparison, outcome. See Table 7 legend for expansion of other abbreviation.

Gibson, Chest 2016

Take home points

- Unexplained, rather than idiopathic, cough.
- Chronicity of symptoms can lead to acceptance of symptoms as normal.
- Ask open-ended questions.
- Take the time to listen carefully to the answers.
- Ask followup questions.
- Leave no relevant question unasked.
- Ask in more than one way.

Take home points

- Do not assume that someone has done what you asked them to do (ensure intervention fidelity).
- There’s always something you can do. That doesn’t mean you have to do it.

Take home points

- Clarify.
- Question the diagnosis.
- Look at the whole patient.
- Beware misdirection.
- Revisit the algorithm as needed.
- Think outside the box (or algorithm).
- New drugs to treat cough hypersensitivity are on the horizon.


Thank you!