Chronic Cough
Ron Balkissoon MD M.Sc. FRCP(C)

Conflict of Interest

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Relationship</th>
<th>Topics</th>
<th>Payment</th>
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<tr>
<td>Astra Zeneca</td>
<td>Speaker’s Bureau Advisory Board</td>
<td>COPD/Asthma</td>
<td>Honoraria</td>
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<td>Glaxo Smith Kline</td>
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<td>CSL Behring</td>
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</table>

Outline

1. Burden of Chronic Cough
2. Causes of Chronic Cough
3. Guideline Recommendations
4. Cough Hypersensitivity Syndrome
   – The Cough Reflex
   – Upper Airway Cough Syndrome
   – Cough and Reflux Disease
   – Cough hypersensitivity Syndrome
5. Management of Cough Hypersensitivity Syndrome
**Cough Definitions**

1. Acute: < 3 weeks
2. Sub-Acute: 3-8 weeks
3. Chronic: > than 8 weeks

Irwin et al Chest 2006

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**Burden of Illness from Chronic Cough**

- 30 million clinical visits in US annually
- 40% of clinic OP pulmonary practice
- 93 million Pounds in UK spent on Anti-tussives
- Females > males
  - Higher cough reflex sensitivity
- Significant impact on Quality of life

1. Irwin et al. Chest 2006;129:1S

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**Cough Reflex**
Afferent Cough Receptors

“Laryngeal” Sensory Receptors

**Cough Receptors**:  
- Myelinated rapidly adapting irritant receptors (Nociceptors)  
- Non myelinated slowly adapting C fibers

**Afferent Nerves** - trigeminal, glossopharyngeal, superior laryngeal or vagus n.

Laryngeal Sensory Receptors

**Chemoreceptors**
- Isotonic sugars
- Water
- Ammonia
- CO2, SO2
- Cigarette smoke
- milk, gastric content

**Mechanoreceptors**
- Pressure (touch)
- Flow (flow, cooling)
- Proprioception
- Drive (laryngeal muscle contraction)
Laryngeal Sensory Receptors

- Irritant receptors
  - Nociceptive C fibers
  - G-Protein coupled receptors (GPCR)
  - Transient receptor potential vanilloid (TRPV-1)
  - Transient receptor potential ankyrin 1 (TRPA-1)

Activation of Nociceptors in Trachea

Undem B J, Carr M J. Chest 2010;137:177-184
Causes of Chronic Cough

MAJOR CAUSES OF CHRONIC COUGH
1. Upper Airway Cough Syndrome
2. Eosinophilic Airway Disease
3. Gastrointestinal Reflux Disease
### Major Causes of Cough

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th># Patients</th>
<th>PND/BA/GERD (%)</th>
<th>EB (%)</th>
<th>PI (%)</th>
<th>CB (%)</th>
<th>Misc or No Dx (%)</th>
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<tbody>
<tr>
<td>Irwin et al</td>
<td>1981</td>
<td>49</td>
<td>82</td>
<td>0</td>
<td>0</td>
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<td>102</td>
<td>86</td>
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<td>Pratter et al</td>
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<td>96</td>
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<td>0</td>
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<td>O’Connell et al</td>
<td>1994</td>
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<td>Melo et al et al</td>
<td>1996</td>
<td>88</td>
<td>92</td>
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<td>0</td>
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<td>McGarvey et al</td>
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<td>1999</td>
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<td>47</td>
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<td>Palombini et al</td>
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<td>94</td>
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<td>0</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Ayik et al</td>
<td>2003</td>
<td>39</td>
<td>44</td>
<td>31</td>
<td>5</td>
<td>0</td>
<td>20</td>
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### Other Common Etiologies of Chronic Cough

- Post-infectious
- Drugs (ACE inhib.)
- Chronic Bronchitis
- Bronchiolitis
- Bronchiectasis
- Lung Cancer
- Foreign body
- Habitual
- Psychogenic

### ACE inhibitor Induced Cough

- Subjects with ACE inhibitor induced cough typically report a tickle or scratching sensation in throat
- Mechanism unknown however:
  - Bradykinin, substance P normally broken down by ACE therefore accumulate in upper airway and or lung in patients on ACE inhibitors
  - Bradykinin causes increase prostaglandin production
  - Bradykinin may induce increased sensitivity of laryngeal airways
  - Studies show increased sensitivity to Capsaicin challenge

Peter V. Dzikangadzi, MD, FCCP
ACCP guidelines Chest 2006
Less Common Etiologies of Chronic Cough

- Interstitial lung disease
- Lung Abscess
- Environmental exposures
- CHF
- Mitral valve disease
- Irritation of tympanic membrane

Upper Airway Cough Syndrome

Eosinophil Airway Diseases

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Cough Variant Asthma</th>
<th>Eosinophilic Bronchitis</th>
<th>Atopic Cough</th>
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<td>Symptomatic</td>
<td>Cough</td>
<td>Cough</td>
<td>Cough and Sputum</td>
<td>Cough</td>
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<td>Atopy</td>
<td>Common</td>
<td>Common</td>
<td>normal</td>
<td>By definition</td>
</tr>
<tr>
<td>AHR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BDR</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sputum Eos (&gt;3%)</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Frequent</td>
<td>By definition</td>
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<tr>
<td>Basement Membrane</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Not known</td>
</tr>
<tr>
<td>ICS Response</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H1 Antagonist Response</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Magni et al. Multidisciplinary Respiratory Medicine 2010
Laryngopharyngeal Reflux

Laryngopharyngeal findings & reflux

- Posterior-predominant supraglottic edema/erythema
- Glottic abnormalities
- Epiglottic malformations
- Posterior pharyngeal wall effects
- Lingual tonsillar hypertrophy
Laryngo-Pharyngeal Reflux (LPR)

Aryepiglottic fold edema and erythema

Posterior Commissure Thickening (pachyderma)

Posterior Cobblestoning

Laryngoscopic Features of LPR

Laryngeal Biopsy (Patient)

Abnormal 48h pH study

Normal 48h pH study

Retrograde Bolus Movement

Combined Cough probe
and pH/impedance Monitor

Sifrim et al. Weakly Acidic
Reflex in Patients with Chronic
Unexplained Cough During 24
Hour Pressure, pH and
Impedance Monitoring; GUT;
2005; 54:449-454

Courtesy of J. Mabary
Sandhill Scientific
Temporal Relationships of Cough to Reflux
N=647 Cough Events

D. Sifrim et al; Weakly Acidic Reflux in Patients with Chronic Unexplained Cough During 24 Hour Pressure, pH and Impedance Monitoring; GUT; 2005; 54:449-454

Aspiration

- A 69-year-old female was admitted for the evaluation of chronic persistent cough. Upper gastrointestinal X-ray films revealed barium reflux up to the cervical esophagus.
- Gastrointestinal fiberoscopy showed reflux esophagitis.
- Bronchial biopsy specimens taken by fiberoptic bronchoscopy showed chronic inflammatory changes of bronchial mucosa with focal squamous metaplasia, mucosal basement membrane thickening, and lymphocytic infiltration in the submucosa.
- She made favorable progress following treatment with a histamine H2 blocker and risperidone for six weeks.
- She met Irwin's criteria and we concluded that her cough was caused by GER.
- We speculate that repeated tracheobronchial microaspirations of refluxed gastric acid may cause chronic inflammatory changes of the bronchial mucosa resulting in persistent cough.

METHODS:
Sixty-eight participants underwent 24-hour pH testing,
- chronic rhinosinusitis (CRS) patients symptomatic after endoscopic sinus surgery
- CRS patients successfully treated by endoscopic sinus surgery
- volunteers without a CRS history.

Assessment:
1. pH probes:
   • nasopharyngeal (NP)
   • laryngopharyngeal (LP)
   • distal esophageal sensors.
2. SNOT questionnaire
3. MRSI PND questionnaire

RESULTS:
Positive correlation of $r = 0.87$ between SNOT-20 and MRSI PND items.

NPR < pH 4
- no significant difference existed between participants with and without reflux on the SNOT-20 or MRSI ($p > 0.05$).
NPR < pH 5,
- reflux-positive participants exhibited significantly more PND symptoms on the SNOT-20 ($p = 0.030$) and the MRSI ($p = 0.018$) compared with participants without reflux.

Participants with LPR had significantly more PND symptomatology on the SNOT-20 ($p = 0.010$) versus those without LPR.

CONCLUSION: Objective evidence of NPR and LPR exists in patients reporting PND. Reflux treatment may reduce PND complaints.

- 38 patients with previous endoscopic sinus surgery
- 76 vs 24% of CRS group had NPR (p=.00003)
- pH < 5 greater number of events than pH<4


METHODS:
- Middle ear effusions (MEEs) and adenoidal tissue biopsies from:
  1. Patients undergoing tympanostomy tube placement and adenoidectomy
  2. Adenoid specimens were taken during adenoidectomy (+/- tonsillectomy) from children with no history of OME.

- Adenoid tissues were analyzed immunohistochemically to confirm the presence of pepsinogen.
- MEE total pepsinogen levels were measured with enzyme-linked immunosorbent assay.

RESULTS:
- Adenoid tissue of the OME group (n = 25) demonstrated significantly higher pepsinogen immunoreactivity when compared with the adenoid tissue of the control group (n = 29),
- Pepsinogen was detected in 84% of MEEs from the OME group,
- Concentrations 1.86 to 12.5 times higher than that of serum

CONCLUSION: LPR plays an important role in the pathogenesis of OME as gastric reflux reaches the middle ear through the nasopharyngeal and eustachian tube to cause OME.

Cough Hypersensitivity Syndrome
Cough Hypersensitivity Syndrome

Upregulated cough reflex sensitivity:
- Change in local environment of afferents
  - Inflammation, edema
- Inflammatory mediators sensitize C-fibres
- Increased sensitivity persists
- Change in gene expression profile of afferents
  - Phenotype change of neurons
  - Mechanoreceptors to chemoreceptors or nociceptors

REFERENCES

- Mutoh et al. Hypersensitivity of Laryngeal C-Fibers Induced by Volatile Anesthetics in Young Guinea Pigs. AJRCCM 2003

Hypersensitive Larynx Syndrome:
Neural Plastic Response to Repetitive Nocistimulation

Hypothesized “Vicious Cycle”
Upper Respiratory Tract Infection/
(Non)/Allergic rhinitis
↓
Cough
↓
GERD
↓
Laryngopharyngeal Reflux
↓
Nasopharyngeal Reflux

Aspiration

Chronic Cough

Cough

Hypersensitivity Syndrome

Diagnosis and Management of Cough
Executive Summary: AACCPEvidence‐Based Clinical Practice Guidelines
(Irwin et al. Chest 2006)

ChesT 2006;129;15-235
Supplement 1S

Chronic Cough

Hypersensitivity Syndrome

Cough Suppressants
Speech Therapy

Adapted from ACCP Guidelines: Chest 2006;129:15-235
Summary

- Cough is a protective reflex
- Neurologic Pathways for upper airway cough syndrome are complex
- Common causes of chronic cough all lead to laryngeal irritation
- Unified airway suggests lower airway disease may cause reflex sensations in throat that induce cough
- Neural plasticity may lead to lower threshold for cough reflex with chronic nociceptive input

Management Issues:

Upper Airway Cough Syndrome

- Nasal Rinses
- Antihistamines
- Inhaled Nasal Steroids
- Nasal rinse steroids? (approved for polyps)
- Nasal rinse antibiotics?

Department of Surgery-Otolaryngology, University of Adelaide, Woodville, Australia.

Abstract

OBJECTIVES/HYPOTHESIS: To examine the efficacy and tolerability of topical mupirocin for the management of surgically recalcitrant chronic rhinosinusitis (CRS) associated with Staphylococcus aureus infection.

STUDY DESIGN: Prospective open-label pilot study.

METHODS: Patients with surgically recalcitrant CRS who had positive nasendoscopically guided cultures for Staphylococcus aureus were treated with twice daily nasal lavages containing 0.05% Mupirocin and lactated ringers salts. The duration of treatment was 3 weeks. Patients were assessed before and after treatment in terms of nasendoscopic findings, microbiology results, and Sinonasal Outcome Test (SNOT-20) and visual analogue scale questionnaires.

RESULTS: Fifteen of 16 patients had improved nasendoscopic findings after treatment. Twelve of 16 patients noted overall symptom improvement. Fifteen of 16 patients had negative swab results for Staphylococcus aureus after treatment. Only minimal adverse effects were experienced.

CONCLUSIONS: Nasal Lavage with 0.05% Mupirocin may represent an effective and well tolerated alternative treatment for postsurgical recalcitrant CRS.

GERD/LPR

- Lifestyle Measures
  - Diet changes
  - Weight loss
  - Eating habits
  - Raising the head of the bed
- Acid suppression (according to impedance)
- Lower esophageal sphincter modulation
- Prokinetics (select patients)
Non-Acid Reflux Medical Treatment

Increase LESP:  
bethanecol
  • Cholinergic
  • Stimulates receptors in smooth muscle to increase peristalsis

Decrease TLESRs:  
baclofen
  • GABA agonist
  • Reduces transient LES relaxation events

Increasing Gastric Emptying:  
domperidone
  cisapride

• Courtesy of Dr. Phil Hanna Chief Gastroenterology NJH

Fundoplication

Efficacy of Fundoplication at Treating Cough/Atypical Symptoms

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Cough or Atypical</th>
<th>N w silent GERD</th>
<th>Dx</th>
<th>Duration FU</th>
<th>Resolve /Improve</th>
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<tr>
<td>Brouwer 2002</td>
<td>C</td>
<td>19</td>
<td>0</td>
<td>pret</td>
<td>53% / 84%</td>
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<tr>
<td>Iqbal 2009</td>
<td>C</td>
<td>40</td>
<td>7</td>
<td>pret</td>
<td>41 mo 53% / 84%</td>
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<td>Allen 1998</td>
<td>C</td>
<td>42</td>
<td>5%</td>
<td>pret</td>
<td>6 mo 51% / 83%</td>
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<tr>
<td>Hamdy 2009</td>
<td>At</td>
<td>18</td>
<td>0</td>
<td>12mo</td>
<td>56% / 83%</td>
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<tr>
<td>Farrell 2001</td>
<td>At/At</td>
<td>95/5</td>
<td>56 67</td>
<td>pret</td>
<td>12 mo 43% / 94%</td>
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Courtesy Reginald Bell MD, Surg 1 Denver Colo
5 YEAR FOLLOW-UP OF FUNDOPICATION FOR COUGH


79 Patients followed for 5 years regarding outcome of fundoplication for cough.

<table>
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<th></th>
<th>6 mo</th>
<th>24 mo</th>
<th>60 mo</th>
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<tbody>
<tr>
<td>Cured</td>
<td>52%</td>
<td>43%</td>
<td>36%</td>
</tr>
<tr>
<td>Better</td>
<td>31%</td>
<td>31%</td>
<td>35%</td>
</tr>
<tr>
<td>Cured/Better</td>
<td>83%</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>No Change</td>
<td>11%</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Worse</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
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</tbody>
</table>

Recurrent cough does not necessarily mean recurrent reflux / surgical failure.

Courtesy Reginald Bell MD, Surg 1 Denver Colorado

RESPIRATORY SYMPTOMS AND DUAL CHANNEL pH TESTING


• 39 patients with respiratory symptoms including cough.
• All had abnormal acid exposure on pH testing.
• Cough symptom correlation evaluated by 2 channel pH testing.
• % Resolved Cough after Laparoscopic Fundoplication.

Proximal acid reflux treated by fundoplication predicts a good outcome for chronic cough attributable to gastro-oesophageal reflux disease.


Design:
81 patients with refractory chronic cough underwent manometry and dual-probe pH studies. In 59 patients, pathological reflux was confirmed, and 21 of these underwent laparoscopic fundoplication by a single surgeon. Proximal reflux was defined as an upper channel time pH <4 of >1.4%.

Conclusion:
• Patients with refractory chronic cough are significantly more likely to benefit from surgery if their pH study shows an upper channel pH time >1%. 

Courtesy Reginald Bell MD, Surg 1 Denver Colorado
Pharmacological and Non-Pharmacological Management for Cough Hypersensitivity Syndrome

Management of Laryngeal Abuse

- Vocal Hygiene
  - Hydration
  - Minimize caffeine and alcohol intake
  - Quit smoking
- Chronic Cough
  - Cough control breathing techniques
- Vocal Abuse/Misuse and Behavior Modification
  - Chronic throat clearing
  - Muscle tension → Vocal strain/Dysphonia
  - Overuse
  - Inappropriate pitch/loudness

Breathing Techniques

- Respiratory Retraining
  - Easy flow breathing
  - Employment of diaphragmatic involvement with breathing
  - Reduce upper body/clavicular involvement
  - Reduce tension
  - Increased tension can increase cough!
- Cough Control Breathing Technique
  - Quick but relaxed inhale to abduct vocal folds, < 1 second
  - Pursed lip exhale to maintain abduction of vocal folds with back pressure, 2-3 seconds.
- Relaxed Throat Breathing
  - Increased focus on relaxation/ decreased UB tension
  - Slower inhale through the nose
  - Slow, controlled exhale through slightly pursed lips

Courtesy J Berquist SLT NJH
Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough
Ryan NM, Vertigan AE, Bone S, Gibson PG - Cough (2010)

Role of Antitussives and Other Medications for Chronic Refractory Cough

- Anticholinergics/ Tiotropium
- Codeine and dextromethorphan limited efficacy in subjects with chronic cough
- Morphine 5 mg/d effective
- Nicotine may suppress cough
- Mucolytics
- Anti-oxidants: N-acetylcysteine
- Erdosteine
- Amitryptiline
- Baclofen

Influence of selected agents on cough

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Codeine</td>
<td>Opioids No effect on cough due to COPD</td>
</tr>
<tr>
<td>Morphine</td>
<td>40% decrease in cough in patients with chronic cough refractory to specific therapy; well tolerated but long-term use potentially limited by side effects</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Non-opioid Slight but significant decrease in cough due to upper airway disorders; no effect on smoker’s cough</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Antioxidants Significant cough alleviation in antioxidant patients with chemical injury to lungs</td>
</tr>
<tr>
<td>Erdosteine</td>
<td>Potentiates cough suppressant effect of antibiotics during airway infection</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Anticholinergic Decreased capsaicin sensitivity/no effect on cough due to COPD</td>
</tr>
</tbody>
</table>


**METHOD:**
4 patients studied with history of Chronic cough deemed neuropathic

**INTERVENTION:**
- Electromyography-guided BtxA injections of the thyroarytenoid muscles.

**RESULTS:**
- 4 patients had significant relief of cough after BtxA injection
  - complete resolution after a median of 7 injections (range, 4-16),
  - mean dose of 4.0 U (range, 1.0-10.0 U) per treatment session
  - mean duration of 25.7 months (range, 7.2-42.9 months).

Role of Other Medications for Chronic Refractory Cough

- Nicotine may suppress cough
- Mucolytics: mixed results
- Amitryptilin: Beneficial in select patients with Neuropathic cough
- Baclofen: Beneficial in select patients with Neuropathic cough


Next Generation Medications for Chronic Refractory Cough

- TRP channel Blockers (Chronic Pain)
- Voltage gated Sodium channel blockers
- Central Nervous System Targets:
  - N-methyl-D-Aspartate (too many CNS effects)
  - Glial cell, astrocyte modulation
  - Non-blood brain barrier penetrating agents
    - Brainstem may have less tight BBB
- Reduce Mucus Adhesion
  - P2Y2 agonists
ACE Inhibitor Related Cough

- Do not appear to be any signs or symptoms suggestive of more common causes of cough
- If 4 weeks of an empiric treatment trial for the common causes of cough fails
- Discontinuation of ACE inhibitors and appropriate replacement therapy should be attempted right away.
- Cough will generally subside within 2-4 weeks.
- Any patient with cough on ACE inhibitor should have it stopped and if the cough persists despite being off the ACE inhibitor for 4 weeks it is unlikely the cause.
- If the cough does stop then after a period of 2-3 months of cessation it can be tried again but if the cough returns it should be discontinued.
- When substitution of an ACE inhibitor is not an option then medications commonly used to suppress cough can be tried including sodium cromoglycate, theophylline, sulindac, indomethacin, amlodipine, ferrous sulfate and picotamide may be tried.

Irwin et al. Chest 2006

Summary

- Most cases of chronic cough mix of difficult to manage common problem(s)
- Neuropathic cough rare may co-exist with common problems and part of habituation component
  - Cough suppression techniques, hypnosis
  - newer cough receptor antagonists (need more study, proper patient selection)