How to treat a cough

Sean Parker
Consultant Respiratory Physician
North Tyneside General Hospital
@drsmparker
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!).

- Individual vulnerability
  - Psychological (worry)
  - Fear
  - Resynchronising factors: stress, sleep disturbance, illness.

- More than just a cough
  - Symptoms of the cough: accompanying, through cough – some very severe (breathing, pain, incontinence).
  - Emotional impact (embarrassment, sadness, disappointment, guilt).

- The social sphere
  - Overt nature: others notice.
  - The contagious nature of a cough: social effort of dealing with others' reactions.

- Cough & identity
  - Cough becomes ingrained in their identity, vs it's own persona.
  - Known by their cough.
  - Clash of person's identity and the cough image (seen in 'bad light'.)

Vicious circles
- Coughing to relieve the irritation (feeling of mucus or tickle).
- Thinking about the cough made it worse (stress, anticipatory anxiety).

- 'At the end of the line': the healthcare journey
  - Some felt dismissed.
  - Reassured nothing serious.
  - Physical and psychological very separate entities.
  - Search for answers.
  - Doc done everything… would try anything.

Cough & identity
- Cough becomes ingrained in their identity, vs its own persona.
- Clash of person's identity and the cough image (seen in 'bad light').

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

IPF
- 80% IPF patients cough. ↓QOL
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.
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”.
• 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.

What is a cough? ‘Cough’ and ‘expiratory reflex’

![Diagram showing cough reflex phases]

Normal protective reflex

Enhanced protective reflex

Impaired protective reflex

- Aspiration
- Pneumonia
- Elderly
- EOL

Normal cough

Enhanced cough

Impaired cough

- Unpleasant symptoms
- ↓QOL
**Afferent input**

**AIRWAY**
- Pharynx (IX)
- Larynx
- Large airways (lung)

**Vagus nerve (X)**

**Brainstem**
- NTS
- Pa5

**X**

**Trigeminal nerve (V)**

**UPPER AIRWAY**
- Oesophagus
- Ear (Arnolds reflex)

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

**Aδ Fibres** (fast, mechanically sensitive)
- "cough receptors"
- Punctate mechanical stimuli
- ASIC
- Stretch

---

**Fig. 2. Schematic diagram representing the cough reflex.** Afferent afferent fibres travel from the airways to the medulla to the NTS and posterior nucleus tractus solitarius (PONS) in the brainstem. Neural signals are then transmitted to the sensory nucleus via the thalamus, causing brain stimulation and urge to cough. These sensations, if great enough, lead to cough via activation of spinal motor neurons.
Higher cerebral control – not just a brainstem reflex

Thalamus
Somatosensory cortex
Motor cortex
Prefrontal cortex/DLPFC
Limbic brain

AIRWAY
Pharynx (IX)
Larynx
Large airways
(lung)

Vagus nerve (X)
NTS
Pa5

Brainstem

'Cough'

Capsaicin cough challenge

TRPV1 (Vagal C fibres)

Cough

Number of coughs

Concentration of capsaicin (μM)

Volitional control of cough

TRPV1 (Vagal C fibres)

Cough

No suppression

'Try not to cough' → voluntary cough suppression


Dicpinigiaitis
Hand exp pharm 2009

Capsaicin cough challenge
Urge to cough (UTC)- a key respiratory sensation

TRPV1 (Vagal C fibres) → Placebo
Smoking/nicotine

Urge to Cough (UTC)
Irritation/tickle/something stuck/hair in throat.
Neck-Chest

Anxiety
Nicotine withdrawal

---

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

- Affective component (perceived as unpleasant) → action that causes sensation of relief ‘homeostatic emotion’.
  - If coughing behaviour satisfies the urge then the UTC will be relieved, if not then the urge continues.

- Survival, social function?

- Often described by patients with cough

---

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

---

1. Davenport et al Pulm Pharm Ther 2007
2. Ditpinigiaitis et al Respirology 2012
3. Widdicombe Resp Physiol Neurobiol 2009
5. Eccles Hand Exp Pharm 2009
6. Mazzone et al cough 2013
7. Van den Bergh Lung 2012
8. Davenport Hand Exp Pharm 2009
9. La Crette et al Thorax 2012
Higher brain control of cough-fMRI studies

- Cough not simply a brainstem reflex.
- Neural activation is seen\(^1\) with capsaicin cough challenge:
  - **Sensory**
    - Somatosensory cortex (primary somatosensory cortex, anterior insula)
    - Spatial discrimination (posterior parietal cortex, DLPFC)
    - Separate areas decode stimulus intensity (anterior insula) and perception (primary SSCTX)
  - **Cognitive**
    - Orbitofrontal cortex, cingulate cortex, limbic system
  - **Motor**
    - Voluntary cough (sensorimotor cortex, supplementary motor area, cerebellum)
    - Reflex cough (posterior insula, post cingulate ctx, medulla)
  - **Suppression** (anterior insula, supplementary motor area, motor cingulate ctx, right inferior frontal gyrus)

1. Mazzone et al. Cough 2013

Higher cerebral control of cough

Airway: Pharynx (IX), Larynx, Large airways (lung)

Braintem: NTS, Pa5

Vagus nerve (X)

Voluntary cough (Distinct pathway)

Inhibitory pathways

Thalamus

Somatosensory cortex

Motor cortex

Prefrontal cortex/DLPFC

Limbic brain

Descending inhibitory control-similar to pain.

- Elevated activity in peri-acqueductal grey matter (PAG), n. cuneiformis, raphé 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 prefrontal 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\(^3\).

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

DMPC
Anterior mid-cingulate cortex
Right inferior frontal gyrus
Right anterior insula

Possible psychological factors

- Perception and attention
- Affect and emotion
- Beliefs and cognition
- Learning
- Habit formation
- Social factors and self regulation
Afferent/peripheral factors

- Infection
- ACE inhibitors
- pHreflux
- Upper airway disease
- Airway inflammation
- Underlying disease e.g. Cancer Fibrosis

Central factors

- Anxiety
- Psychological factors
- Predisposition or acquired hypersensitivity

Pathological cough / Hypertussia / Hypersensitivity

Placebo Voluntary control

Cough hypersensitivity

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

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 → mucus/lytics/nebulized saline/clearance techniques
Weak cough → physio/clearance/oral care

Bonneau: Can Fam Phys 2008

Birring et al: Chest 2018
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>
<thead>
<tr>
<th>Causes of Cough Among Patients With Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma, lung adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, lung metastases from other malignancies, lung abscesses, pulmonary embolism, bronchiectasis, pulmonary fibrosis, pleural effusion, chronic obstructive pulmonary disease, related to underlying problem</td>
</tr>
</tbody>
</table>

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

ACE Inhibitors
Enhance cough reflex sensitivity.
Afferent sensitisation
Onset hours–months
Resolves slowly (80% in 1/12, may take up to 6/12), improvement variable.

Stop in all patients with cough.
A2 receptor blockers replace and well tolerated.

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

Cough reflex sensitivity
Voluntary inhibition of cough
Nicotine inhibits the cough reflex
Cough worsens with stopping.

$\alpha_7$ nicotine receptor (drug target)

Dicpinigia et al. 2018
Cough suppressants/antitussives

Honey - Ancient Egyptians (and NICE!)

Opiates

Huge OTC market $9.5 billion/year in the USA.

Common physical properties

Very weak evidence base, many no better than placebo

![Image of cough suppressants]

1. Smith et al. Cochrane 2014

Cough treatments often no better than placebo..

![Graph showing cough frequency before and after treatment]

Fig. 1 Mean cough frequency before and after treatment with a single dose of codeine syrup R.P. (50 mg) in subjects with cough associated with acute upper respiratory tract infection. Square symbols indicate codeine syrup (n = 45) and round symbols indicate placebo syrup (n = 45) (redrawn from [1]).

![Graph showing cough frequency for no treatment and placebo]

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 [10]).

Patients do benefit however..

![Graph showing cough frequency improvement with placebo]

Eccles Lung 2010
Lee et al. Psychosom Med 2005
How does cough medicine work

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\(^2\)

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.
Sweet taste suppresses cough reflex

How does cough medicine work

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
   - Mucolysics
   - 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."\(^2\)

Dextromethorphan

- Dextromethorphan.
- Mechanism
  - Central action
  - Active metabolite dextrorphan
  - NMDA, \(\sigma\)-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.
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 (?)

Mucolytics

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

Antihistamines/decongestants

• H1 blockers. First generation antihistamines.
  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\(^1\).

\(^1\) Shingiogics et al Pharm rev 2014
Menthol

- Peppermint plant Mentha avensia.
- 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.

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.

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 (rebulised)

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.

---

**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
  - Central mechanism of action (descending pathways from cortex/thalamus to PAG/nucleus cuneiformis).
- Placebo pathways
- Lung opioid receptor? PNEC/s/c fibres.

---

**Neuromodulators: Gabapentin/Pregabalin**

- Mechanism unclear.
- Central. Not GABA!
- Blocks nociception, α2δ subunit presynaptic calcium channels?
- NMDA?\(^1\)
- 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. Morice et al AJRCCM 2007
2. Vertigan et al Chest 2016
3. Gibson and Vertigan Pulm Pharm Ther 2015

---

*18/06/2019*
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\textsubscript{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.

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
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).
- Not all patients respond.
- Side effects - taste disturbance in 100% of patients at study dose (600mg).

Efficacy Maintained at Lower Doses with Improved Tolerability

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>7.5 mg (N=63)</th>
<th>20 mg (N=63)</th>
<th>50 mg (N=63)</th>
<th>Total (N=189)</th>
<th>Placebo (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>6 (9.5%)</td>
<td>21 (33.3%)</td>
<td>30 (47.6%)</td>
<td>57 (30.2%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Hypogeusia</td>
<td>0</td>
<td>11 (17.5%)</td>
<td>15 (23.8%)</td>
<td>26 (13.8%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (6.3%)</td>
<td>12 (19.0%)</td>
<td>4 (6.3%)</td>
<td>20 (10.6%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5 (7.9%)</td>
<td>9 (14.3%)</td>
<td>6 (9.5%)</td>
<td>20 (10.6%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Apnea</td>
<td>0</td>
<td>3 (4.8%)</td>
<td>13 (20.6%)</td>
<td>16 (8.5%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Parasthesia Oral</td>
<td>4 (6.3%)</td>
<td>5 (7.9%)</td>
<td>4 (6.3%)</td>
<td>13 (6.9%)</td>
<td>5 (7.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (3.2%)</td>
<td>5 (7.9%)</td>
<td>5 (7.9%)</td>
<td>12 (6.3%)</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Hypoesthesia Oral</td>
<td>2 (3.2%)</td>
<td>4 (6.3%)</td>
<td>5 (7.9%)</td>
<td>11 (5.8%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4 (6.3%)</td>
<td>6 (9.5%)</td>
<td>10 (5.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3 (4.8%)</td>
<td>5 (7.9%)</td>
<td>2 (3.2%)</td>
<td>10 (5.3%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2 (3.2%)</td>
<td>3 (4.8%)</td>
<td>3 (4.8%)</td>
<td>8 (4.2%)</td>
<td>6 (9.5%)</td>
</tr>
</tbody>
</table>
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 azipropt (NK1 antagonist) in lung cancer, reduction in cough frequency.
- Volcano 1 RCT orvepitant (NK1 antagonist) in chronic refractory cough frequency (50% at week 4, improvement 2 DDS and QOL).
- 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.
- RCT TRPV4 antagonist (GSK2798745) negative trial.

1. Khalid et al JACI 2014
2. Ludbrok et al 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.

<table>
<thead>
<tr>
<th>Treatment component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Training to cough suppression, self-management of vocal folds, and breathing</td>
</tr>
<tr>
<td>Laryngeal hygiene &amp; hydration</td>
<td>Hydration, humidification, and laryngeal hygiene practices</td>
</tr>
<tr>
<td>Psycho-educational counselling</td>
<td>Psychological support, education on cough management, and coping strategies</td>
</tr>
</tbody>
</table>

Chamberlain et al. Thorax 2017

Original Article

Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial

Chamberlain Mitchell et al. Thorax 2017
Subjective Outcomes following CST

- Did Not Attend: 22.7%
- Treatment Unsuccessful: 7.6%
- Other: 4%
- Improved: 65.7%


Improvement in Mean LCQ post CST

- Mean change in LCQ = 4.7 (SD 3.3)
- MCID = 1.3

CST compares favourably to other treatments

- Mean change in LCQ score:
  - MST: 3.2
  - Gabapentin: 2.5
  - PSALTI: 3.4
  - Northumbria CST: 4.7

Morice et al. Am J Respir Crit Care Med 2007; 175: 312-315
Ryan et al. Lancet 2012; 380: 1583-1589
Mohammed et al. Thorax 2018
CST compares favourably to gabapentin (Mean Change in LCQ Score & Cost)

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin</th>
<th>PSALT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change in LCQ Score</td>
<td>2.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Cost</td>
<td>£471.42 for 3 month trial</td>
<td>£323.28 per patient</td>
</tr>
</tbody>
</table>

Biring et al., Pulmonary Pharmacology & Therapeutics 2017

CST is useful in non CRC

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>All patients</th>
<th>Asthma</th>
<th>COPD</th>
<th>Bronchodilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Inhaling cough reflex time (s)</td>
<td>Δ=3.76</td>
<td>Δ=4.27</td>
<td>Δ=4.50</td>
<td>Δ=3.41</td>
</tr>
</tbody>
</table>

Mohammed S, Steer J, Leitch I, Kajt, Smith I, Ryder IAB. Thorax 2018 BTS members

Summary 1: The cough reflex is complex...

Inhibitory pathways
Cough suppression network
?Naloxone (+pain)
Placebo
Voluntary suppression
?Psychological factors

Higher brain
Awareness of urge to cough

Voluntary cough
Impaired cough suppression network
?Psychological factors
Anxiety
Nicotine withdrawal

AIRWAY
Irritants
Stimuli

Brainstem
NTS
Pa5

Brainstem output to AIRWAY: 

Airway response to irritants and stimuli
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?

Sean Parker
Consultant Respiratory Physician
North Tyneside General Hospital
@drsmparker