Laryngeal Dysfunction in Chronic Cough

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Statement of Originality

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List of Abbreviations

(listed in order of appearance in document)

VCD=vocal cord dysfunction*

PVFM=paradoxical vocal fold movement*

CC=chronic cough

EAHR=extrathoracic airway hyperresponsiveness

ADP=anatomic diagnostic protocol

PNDS=post nasal drip syndrome

GORD=gastroesophageal reflux disease

NAEB=nonasthmatic eosinophilic bronchitis

ACE=angiotensin conversion enzyme

UACS=upper airways cough syndrome

ENT=ear nose throat

LOS=lower oesophageal sphincter

OSA=obstructive sleep apnoea

CPAP=continuous positive airway pressure

HAD=hospital anxiety and depression

STAI=state trait anxiety inventory
CCEI = crown crisp experimental index
RARs = rapidly adapting receptors
URTI = upper respiratory tract infection
RSV = respiratory syncytial virus
SARS = severe acute respiratory syndrome
CIC = chronic idiopathic cough
PCR = polymerase chain reaction
WTC = world trade centre
PCBs = polychlorinated biphenyls
SLN = superior laryngeal nerve
RLN = recurrent laryngeal nerve
PVVN = post viral vagal neuropathy
URI = upper respiratory infection
HSN1 = heredity sensory neuropathy-1
SPTLC1 = serine palmitoyltransferase-1
TRP = transient receptor potential
TRPV1 = transient receptor potential, vanilloid-1
TRPA1 = transient receptor potential, ankyriol-1
CGRP = calcitonin gene related peptide

ACCP = American college of chest physicians

LPR = laryngopharyngeal reflux

QOL = quality of life

CQLQ = cough-specific quality of life questionnaire

SHR = sensory hyperreactivity

MCS = multiple chemical sensitivity

PKC = protein kinase C

C2 = capsaicin dose inducing 2 coughs

C5 = capsaicin dose inducing 5 coughs

UTC = urge-to-cough

CICADA = cough in children and adults: diagnosis and assessment

PFT = pulmonary function testing

SPLI = speech language pathology intervention

BtxA = botulinum toxin type A

FVL = flow volume loop

FOL = fibre optic laryngoscopy

BHR = bronchial hyperresponsiveness
MIF=maximum inspiratory flow

* NB: VCD and PVFM are different terms for the same condition and both are used extensively throughout the literature therefore, they have been used interchangeably throughout this thesis document.
Abstract

Cough is one of the main reasons for seeking medical care in Australia with 11% to 16% of the general population reporting a persistent cough, and 7% describing a cough that is sufficient to interfere with activities of daily living on at least a weekly basis. Patients with chronic cough (CC) frequently report a range of physical symptoms such as musculoskeletal chest pains, sleep disturbance, a hoarse voice, syncope, stress incontinence, rib fractures and vomiting. The psychological impact of cough includes a high prevalence of depressive and anxiety symptoms, as well as worry about serious underlying diseases such as cancer and tuberculosis. Persistent cough can also have an adverse impact on social well being leading to difficulty in relationships, avoidance of public places, and disruption of employment.

Refractory cough refers to persistent cough that does not respond to usual medical treatment. Idiopathic chronic cough refers to cough that cannot be diagnosed even after a thorough systematic investigation has been conducted. Laryngeal dysfunction includes conditions such as vocal cord dysfunction (VCD) also known as paradoxical vocal fold movement (PVFM), and sensory laryngeal neuropathy. The relationship between laryngeal dysfunction and refractory and idiopathic cough is poorly characterised. This thesis addresses the significance of laryngeal dysfunction in CC by characterising the disorder, investigating potential mechanisms and assessing viable treatments. It also looks at the prevalence and mechanism of CC in adults and its association with upper airway hyperresponsiveness after respiratory infection.
The primary findings of this thesis are:

1. Laryngeal dysfunction presenting as PVFM and EAHR commonly occurs in CC.
   Fifty-six percent of participants have laryngeal dysfunction presenting as paradoxical vocal fold movement.

2. Individuals with CC and PVFM have increased extrathoracic airway hyperresponsiveness (EAHR) compared to individuals with CC alone and healthy controls.

3. Laryngeal dysfunction with CC is associated with quality of life impairment and sensory hyperreactivity of the cough reflex.

4. Laryngeal hypersensitivity may be a common mechanism in CC.

5. Successful treatment for CC with speech language pathology intervention leads to improvements in laryngeal dysfunction manifest as PVFM and EAHR.

6. Speech language pathology intervention for refractory and idiopathic CC leads to improvement in cough through reduced laryngeal irritation resulting in decreased cough sensitivity, decreased urge to cough and an increased cough threshold.

7. When compared to placebo, gabapentin effectively decreases cough frequency and increases quality of life in people with refractory or idiopathic CC. The likely mechanism for this is that gabapentin inhibits release of excitatory neurotransmitters at supraspinal sites.

8. EAHR is a feature of postinfectious cough.

9. Postinfectious cough due to H1N1 2009 influenza has similar characteristics to other postinfectious cough and is associated with cough reflex hypersensitivity.
Chapter 1  Chronic Cough: Background and Introduction

1.1 Definition

Cough is a protective mechanism that helps to clear excessive secretions and foreign matter from the airways. Cough is also an important factor in the droplet spread of respiratory infection within the community and is one of the most common symptoms for which individuals seek medical attention (1, 2). Cough involves a complex reflex beginning with the stimulation of sensory nerves in the airway epithelium that function as cough receptors. Afferent impulses from these receptors are conducted by the vagus nerve to a cough centre in the brainstem. Because cough can be voluntary, there can also be afferent input from the cerebral cortex that can modulate the cough reflex (3). The cough centre receives these impulses and produces a cough by activating efferent neural pathways to the diaphragm and laryngeal, thoracic, and abdominal muscles. The motor component of cough consists of 3 phases:

1. Inspiration-deep breath in.
2. Glottic closure-the opening between the vocal cords at the upper part of the larynx (glottis) shuts, trapping air in the lungs.
3. Forced expulsion-as the diaphragm and other muscles involved in breathing press against the lungs, the glottis suddenly opens, producing an explosive outflow of air.

Cough is classified for clinical purposes based upon its duration and whether aetiological factors are identified [Table 1:1].
### Table 1:1 Classification of cough

<table>
<thead>
<tr>
<th>Clinical Cough Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Cough that lasts for &lt;3 weeks.</td>
</tr>
<tr>
<td>Subacute</td>
<td>Cough that lasts 3 to 8 weeks.</td>
</tr>
<tr>
<td>Chronic</td>
<td>Cough that lasts &gt;8 weeks</td>
</tr>
<tr>
<td>Refractory</td>
<td>Cough that does not respond to usual medical treatment such as the ADP*.</td>
</tr>
<tr>
<td>Chronic Idiopathic</td>
<td>Cough with no underlying cause even after a thorough systematic review.</td>
</tr>
<tr>
<td>Specific</td>
<td>A known underlying disease causing the cough.</td>
</tr>
</tbody>
</table>

*ADP=Anatomical Diagnostic Protocol

Acute cough lasts less than 3 weeks and is considered beneficial to the respiratory system by removing noxious substances and excessive mucous. Chronic cough (CC) lasts for greater than 8 weeks \(^{(2, 4)}\). Coughing that lasts from 3 to 8 weeks is referred to as subacute cough \(^{(5)}\). CC has traditionally been seen as a symptom, the cause of which is often difficult to diagnose and treat. Consequently, CC is further classified according to whether a known cause has been identified: specific cough; or if no cause is apparent: idiopathic cough. CC can also be classified based on the response to treatment and a nonresponding CC is termed refractory cough.

While the majority of individuals do respond to medical treatment, refractory cough is reported to occur in between 12 to 42% of cases \(^{(6, 7)}\). McGarvey \(^{(8)}\) provided a comprehensive synopsis of refractory CC and proposed several reasons why cough may fail to respond to medical treatment. These reasons included an inappropriate approach to diagnosis, failure to treat both pulmonary and extra pulmonary causes for the cough and inadequate dose or duration of treatment trials.

Idiopathic CC refers to cough that cannot be diagnosed even after a thorough, systematic investigation has been conducted. Idiopathic CC has been shown to be one of the most common reasons for new patient visits to respirologists \(^{(9)}\) and it is the complications and concerns related to cough that leads the patient to seek medical
attention in the first place. The most common of these complications are exhaustion, embarrassment, a fear of throat cancer or other life-threatening condition, insomnia, hoarseness, musculoskeletal pain and stress urinary incontinence.

1.2 Aetiology and Associated Conditions

The medical management of CC aims to suppress or eliminate the cough by identifying and treating the underlying cause \(^1\). While acute cough is mostly due to the common cold, CC is often due to a wide variety of apparently unrelated diseases, or more than one condition. The aetiology of CC can be considered from knowledge of the afferent limb of the cough reflex, and by identification of diseases at various sites on this reflex that can stimulate cough. This approach is called the anatomic-diagnostic protocol (ADP) [Section 1.7.1].

Several studies have applied this protocol and their results are shown [Table 1:2]. A combination of three diseases, asthma, rhinitis/post nasal drip syndrome (PNDS) and gastroesophageal reflux disease (GORD) can account for most causes of CC. Even in areas where tuberculosis is endemic and is considered as a cause of CC, PNDS, asthma, non-asthmatic eosinophilic bronchitis (NAEB) [Section 1.2.2] and GORD are still the most common causes seen \(^1\) and each of these entities may present only as cough with no associated clinical findings (ie, silent PNDS, cough variant asthma (CVA) and silent GORD) \(^1,11-13\).
Table 1.2: Most common causes of chronic cough in subjects investigated in specialist clinics \(^{(14)}\)


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Excluding smoking and lung pathology, PNDS, asthma, and/or GORD and/or the use of some medications such as angiotensin conversion enzyme (ACE) \(^{(15)}\) inhibitors either alone or in combination, have been found to explain the aetiology of CC in between 60% and 95% of cases. CC may also be post viral and spontaneously resolve over time \(^{(2)}\).

1.2.1 Post nasal drip syndrome/Rhinosinusitis/Upper airway cough syndrome

Post nasal drip describes the drainage of secretions from the nose or paranasal sinuses into the pharynx. There has been some scepticism as to whether PNDS is a “true” cause of cough \(^{(16,17)}\). Consequently, in subjects with CC related to upper airway abnormalities, it has been recommended that the term upper airway cough syndrome (UACS) be used instead of PNDS. For simplicity of this thesis, I will use the term post nasal drip syndrome. PNDS, rhinitis and sinusitis (diseases of the upper airway) have a long association with CC. PNDS in association with cough varies largely between different countries and may be due to a societal difference in the appreciation of cough related symptoms. While cough associated with upper airways disease frequently occurs in European practice, the term post nasal drip is not usually applied to the cough/cold syndrome, whereas in American society the term is widely used \(^{(16)}\). PNDS solely or in combination with other conditions has been shown to be the most common
cause of cough (2) and as PNDS has also been shown to be a principal cause of cough associated with the common cold it follows that PNDS is the most common cause of acute cough as well (18).

Bucca et al (19) found cough to be significantly associated with PNDS as the sole symptom or in combination with wheeze and/or dyspnea. Cough was also found to be the symptom of strongest correlation with post nasal drip. The differential diagnosis of PNDS-induced cough includes allergic rhinitis, perennial nonallergic rhinitis, post infectious rhinitis, bacterial sinusitis, allergic fungal sinusitis, occupational rhinitis, and physical or chemical irritant rhinitis. It is not known whether these listed conditions actually produce cough through a final common pathway of post nasal drip or whether, in some circumstances they cause irritation or inflammation of upper airway structures that directly stimulate cough receptors and produce cough independently of, or in addition to, any associated PND (18). Rather than a specific diagnosis, PNDS is a symptom or description of a potential mechanism that may initiate cough via stimulation of pharyngeal cough receptors. It is usually a reflection of underlying rhinitis and/or sinusitis and there is evidence that subjects with sinusitis and rhinitis may have CC without the sensation of PNDS and without any abnormal physical findings such as mucosal cobblestoning or radiographic findings. PNDS is also typically present in patients with CC from other causes. This includes patients with asthma and allergic rhinitis, as well as patients with proximal GORD where rhinosinusitis is a well described supra-oesophageal complication. In patients with cough and GORD pepsin has been detected in the paranasal sinuses as well as the middle ear. Similarly, chronic parenchymal lung disease and CC may result from
aspiration of nasal secretions (20). While PNDS has been found to account for around 35% or more (multiple studies have shown prevalence estimates ranging from 8 to 87% (13, 21, 22) of CC cases, it has been difficult to explain why many individuals with rhinosinusitis have large amounts of mucus in the throat, sense post nasal drip and yet do not have a CC (23).

Common symptoms associated with PNDS are throat clearing, a tickling sensation within the throat area, nasal congestion, nasal discharge and hoarseness. Often medical examination is normal, but ENT/otolaryngology examination with nasendoscopy is indicated where oropharyngeal mucosal cobblestoning has been described and sometimes paranasal sinus imaging may be required (20). PNDS, like GORD may be clinically silent (13), suggesting that self-report of symptoms may not accurately elicit these problems sufficiently to be confident of any associations in population studies (24).

### 1.2.2 Eosinophilic Bronchitis

Gibson et al (25) described CC occurring in association with eosinophilic bronchitis but with no features of asthma. Brightling et al (26) showed that 13% of CC cases are due to NAEB. The prevalence of NAEB is higher in Asian populations, and Ayik et al (27), identified NAEB as a cause of CC in approximately 33% of cough patients presenting to their outpatient clinic in Turkey. In NAEB variable airflow obstruction and bronchial hyperresponsiveness do not occur but the condition does respond to inhaled and oral corticosteroids. Its presence can be reliably determined by staining induced sputum for eosinophils and should be considered early on in the diagnostic evaluation because of the good response to therapy.
1.2.3 Asthma

Asthma is described as a chronic inflammatory disease of the airways presenting with characteristic symptoms and associated characteristic physiologic abnormalities of variable airflow obstruction and airway hyperresponsiveness. Asthma is considered to be one of the top three causes of CC in the United States. Cough occurs in the majority of asthmatic patients and in descriptive studies of subjects with CC due to asthma, cough has been the only asthma symptom from 6.5 to 57% of the time (2). This condition is called ‘cough variant asthma’ (CVA).

CVA is a common cause of cough accounting for up to 30% of referrals to cough clinics (5,14). Symptoms of CVA include nocturnal cough, cough after exercise, and cough after allergen exposure. Diagnosis requires the demonstration of variable airflow obstruction and/or airway hyperresponsiveness. Patients with CVA have been shown to be less sensitive and less reactive to inhaled methacholine than those with classic asthma. Frequent coughing during bronchoconstriction may be a distinctive feature of CVA (28).

Many people with CVA develop wheezing within three years (29). A negative bronchial provocation test excludes asthma. Some patients with cough and asthma have non-eosinophilic airway inflammation (30). This airway inflammation has been associated with corticosteroid resistance (30,31); it is possible that it might be associated with a bronchodilator response with corticosteroid resistant cough (32).

1.2.4 Gastroesophageal Reflux Disease

GORD is a common cause of CC (33,34). Gastroesophageal reflux refers to the movement of acid and other noxious substances from the stomach into the oesophagus. In healthy
people, reflux is a normal asymptomatic event. When reflux leads to symptoms such as heartburn, epigastric discomfort, and chest pain or to physical complications such as oesophagitis, or oesophageal ulceration then the definition of GORD is applied.

GORD as a cause of cough is involved in its pathogenesis through a number of different mechanisms. These include a vagally mediated distal oesophageal-tracheobronchial reflex, gross aspiration, microaspiration, altered cough threshold and impaired oesophageal motility \(^{(35)}\).

Vagally mediated distal oesophageal-tracheobronchial reflex mechanisms have been described in subjects with asthma as well as CC without asthma \(^{(2)}\). Cough associated with GORD in patients with idiopathic chronic cough is likely to be a result of gastric contents stimulating a distal oesophageal-tracheobronchial reflex mechanism with no evidence of microaspiration or proximal oesophageal reflux \(^{(36, 37)}\). This phenomena was investigated in a study by Ing et al \(^{(36)}\) which showed that patients with chronic persistent cough and proven GORD by oesophageal pH testing experienced significantly greater number of coughs, increased cough amplitude and decreased cough latency compared to control subjects. The afferent pathway originating from acid-sensitive oesophageal receptors had been inhibited by the oesophageal instillation of local anaesthetic (4% topical lignocaine) while the efferent pathway had been inhibited by nebulised ipratropium bromide \(^{(36)}\).

Gross aspiration resulting in pulmonary aspiration syndromes is usually a result of free oesophageal reflux with large volume refluxate \(^{(2)}\). Frequently there is a reduced
basal lower oesophageal sphincter tone, impaired oesophageal motility \(^{(38)}\) and oesophageal clearance [Figure 1:1].

![Diagram showing the vital role of the lower oesophageal sphincter (LOS) in the movement of refluxate.](image)

**Figure 1:1** Diagram showing the vital role of the lower oesophageal sphincter (LOS) in the movement of refluxate.

There are often severe pathologic changes seen on endoscopy and up to 75\% of subjects with chronic bronchial disease and reflux symptoms may have some degree of lung contamination \(^{(39)}\).

Microaspiration from proximal oesophageal reflux results in less serious respiratory complications, but cough and hoarseness are major complaints. It results from a smaller amount of refluxate and produces laryngeal inflammation with or without bronchial inflammation.

Reflux of gastric contents to the larynx (laryngopharyngeal reflux) can cause reflux laryngitis with thickening, erythema, and oedema of the posterior larynx \(^{(40)}\). The patient may report few symptoms of heartburn and regurgitation, but may present with persistent cough, throat clearing, globus, and hoarseness \(^{(41)}\). Subjects with GORD
have an increased cough reflex sensitivity that improves with anti reflux treatment \(^{(42, 43)}\).

Idiopathic CC has been shown to be associated with increased episodes of asymptomatic gastroesophageal reflux \(^{(44)}\) however healthy subjects without cough also exhibit some reflux. Ing et al \(^{(45)}\) postulated that healthy subjects have prompt clearance of refluxed acid from the oesophagus which plays an important role in the prevention of CC and therefore subjects with CC may have impaired clearance. It was found that subjects with CC had significantly more episodes of reflux per 24 hours, median [range] (88.3 [5.0 to 338.0] vs 5.7 [0 to 13.0]; \(p<0.0001\)) and had impaired clearance of oesophageal acid as measured by the duration of individual reflux episodes, median [range] 3.0 [0.1 to 20.5] min per reflux vs 0.7 [0 to 2.5] min per reflux; \(p<0.01\)) than control subjects. The authors concluded that subjects with chronic persistent cough have impaired clearance of oesophageal acid, which allows increased exposure of the oesophageal mucosa to gastric acid thereby increasing the likelihood of mucosal injury.

Cough is triggered by the oesophageal tracheobronchial reflex due to the stimulation of oesophageal acid-sensitive receptors by mucosal injury. This would also explain why the control subjects did not cough despite having reflux episodes. The development of oesophagitis may be avoided by normal oesophageal clearance of acid \(^{(45)}\).

Recently, a number of studies have found that GORD may also be involved in the development of cough via altered laryngeal sensitivity \(^{(46)}\), heredity sensory neuropathy \(^{(47)}\), and non-acid reflux \(^{(48)}\). Most subjects with CC and GORD present with cough as their sole symptom of reflux disease. In a survey by Morice \(^{(49)}\), regurgitation was highly associated with CC (more than heartburn) inferring the importance of the
non-acid component of reflux. Often a positive feedback cycle exists between the cough and GORD, with GORD triggering cough via the above mechanisms and cough worsening GORD via increases in transdiaphragmatic pressure and transient LOS relaxation (20).

1.2.5 Angiotensin-converting enzyme Inhibitors

CC is a well known symptom of angiotensin-converting enzyme (ACE) inhibitor use (50). It was first reported in 1985 with the drug captopril. It is not dose related and time to onset is variable, ranging from hours after ingestion to more than a year after start of treatment (32). The cough is typically dry with a tickling or scratching sensation in the throat (51) and the reported prevalence ranges from 5 to 35% among subjects (50, 52). Prospective, descriptive studies that evaluated the aetiology of CC, ACE inhibitors were found responsible in 0 to 3% of presenting cases (33, 53). ACE inhibitor cough has been found to occur more often in women (54, 55), non-smokers (50, 55) (although a more recent large retrospective cohort study identified smoking as a risk factor for ACE inhibitor associated cough (56), and persons of Chinese origin (57, 58). ACE inhibitor cough does not appear to result in pulmonary dysfunction hence asthmatics are not at increased risk of ACE inhibitor induced cough (2). ACE inhibitors are associated with an increased sensitivity of the cough reflex thereby potentiating other causes of cough (59). The cough invariably resolves within 1 to 4 weeks (51) after cessation of the drug although it has been known to take up to 40 weeks (32) for some individuals.

1.2.6 Obstructive Sleep Apnoea

Obstructive Sleep Apnoea (OSA) syndrome is used to describe the constellation of recurrent apnoeas (absence of airflow for >10 seconds) or hypopnoea (reductions in
airflow >10 seconds, sufficient to cause a fall in oxygen saturation of arousal from sleep) occurring at least five times per hour and associated with snoring and symptoms of daytime sleepiness or fatigue (60).

Upper airway collapse due to sleep related loss of muscle tone associated with a small oropharyngeal area is considered the cause of most OSA cases (61). A diagnosis of OSA should be made from a combination of history, examination, one of the following four tests (laboratory attended polysomnography, home unattended polysomnography, cardiopulmonary monitoring, or single channel cardiopulmonary monitoring) and occasionally a trial of therapy (61). More than 60% of adults occasionally snore and more than 30% regularly snore. OSA (62) occurs in around 10% of females and 25% of males, of whom 2 and 4% respectively have OSA with sleepiness. In children, 12% snore regularly and 2% have OSA (61). The prevalence of sleep related symptoms, snoring and OSA is likely to have increased due to the rise in obesity and reduction in sleeping times (63).

Sleep disturbance is common in patients with cough. Sleep suppresses cough however, the biological mechanism for this is not fully understood. Although there is no direct evidence to support this, it is likely to be located in the cerebral cortex (64). The low frequency of cough during sleep suggests that all mechanisms of cough are suppressed. While it is uncommon for healthy people to cough at night, approximately 50% of CC subjects report sleep disruption due to cough. At night there is less voluntary cough than at daytime, there is reduced exposure to tussive stimuli and decreased cough reflex sensitivity which may contribute to a much lower cough frequency at night than during the day (65, 66).
Idiopathic CC has recently been reported as a presenting feature of OSA (67). Patients are primarily female and report GORD and rhinitis. Continuous positive airway pressure therapy (CPAP) is effective in alleviating cough. Patients with CC and OSA are likely to have upper airway injury and inflammation from snoring and recurrent episodes of airway obstruction. Birring et al (67) presented four subjects with CC and OSA and three of these had raised sputum neutrophil counts consistent with inflammation in the large airways. In a study by Chan et al (68) 33% of subjects with sleep-disordered breathing had a CC further supporting a causal link between OSA and cough.

Patients with OSA are seen to have raised levels of inflammatory mediators in the upper airways that may sensitise cough receptors leading to heightened cough reflex sensitivity like that seen in cough due to asthma and eosinophilic bronchitis (69, 70). Another possible mechanism is that cough may result from mechanical causes independent of airway inflammation since the effect of CPAP on subjects is rapid. Bonnet et al (71) described five subjects with nocturnal cough and increased airway collapsibility that responded to CPAP therapy. Another potentially important mechanism of cough with OSA is GORD associated cough, since OSA may exacerbate GORD. There is strong evidence that GORD and OSA exhibit a two-way, mutually reinforcing relationship. The physiological antireflux mechanisms-swallowing rate, salivation, the pressure of the upper and lower oesophageal sphincters, and gastric emptying are reduced and the heartburn signal is depressed during sleep (72, 73). During the obstructive apnoea period, significant changes in transdiaphragmatic pressure facilitate migration of gastric contents toward the oesophagus. In addition, these same
repetitive pressure changes destroy the phrenoesophageal ligament leading to lower oesophageal sphincter insufficiency-an ultimate reason for GORD development. It is also possible that GORD contributes to the development of arousal from sleep consequently adding to the changes in some cognitive functions. Further the presence of a high pressure gradient in the supine position may facilitate reflux up to the pharyngeal region which could result in microaspiration, triggering coughing attacks (74). While the coincidence of the reflux and apnoea events remains an issue to be resolved, the number of reflux events has been found to be reduced with nasal CPAP treatment for both OSA and GORD subjects, which would imply that OSA is a causal factor regarding GORD. Conversely, Senior et al treated patients with a confirmed OSA-GORD condition with 20mg omeprazole two times a day and observed a significant improvement concerning OSA in 30% of the subjects (75).

In a study by Birring et al (26) OSA was not apparent in the initial presentation of subjects hence cough investigations were determined using a standardised diagnostic algorithm. Daytime somnolence was not reported by subjects or recognised by the physician. This symptom may not have been apparent due to the severity of the cough, nor was it considered since OSA is not a recognised cause of CC. Lack of clinical suspicion of OSA at patient presentation with cough led to delays in diagnosis however, once CPAP therapy was initiated there was a rapid improvement of cough and symptoms of OSA within days (67). This result was consistent with a case report of a 3-year-old-boy with chronic nocturnal cough, snoring and upper airway obstruction on polysomnography. There was complete resolution of the cough after commencing CPAP therapy (76).
1.2.7 Psychogenic Cough

Psychogenic Cough is the term given to CC that has no obvious organic basis, is refractory to medical treatment and may be considered as having a psychological or psychiatric basis (2). It is described as presenting with a throat-clearing noise by a withdrawn and self-conscious patient who often believes that they have a serious chest problem. While psychogenic cough is reportedly uncommon in the adult population, it is relatively common in the paediatric population. The diagnosis is made in 3 to 10% of children with cough of unknown aetiology persisting for > 1 month (77). The typical presentation is a student with CC who is unconcerned about symptoms, submits willingly to examination and procedures, and is happy to remain away from school for the duration of the cough (78). Psychogenic cough is more common in girls and has been related to school phobia. Milgrom et al (79) mentioned that although psychogenic cough is rare, psychological factors may affect the progression of symptom in CC generally. This was expanded upon by Carney et al (80) who used a validated psychological profile questionnaire, the Symptom Checklist-90 item revised, to examine psychiatric symptomatology in CC subjects. The 90 items in the scale were clustered into 9 clinical axes of psychopathology, including somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychosis. Whilst there was no difference in scores between CC subjects and healthy controls for most of the psychological domains there was a significantly higher score in somatisation and hostility domains for the subjects compared to controls. Recently McGarvey et al (81) assessed the co-existence of psychomorbidity with cough among successfully treated cough subjects and other subjects with refractory to treatment
cough. Using the Hospital Anxiety and Depression (HAD) scale (82) it was found that 33% of all cough subjects were identified as anxious and 16% experienced depression. The State Trait Anxiety Inventory (STAI) (83) scores suggested moderate or high trait anxiety in 48% of all coughers and were significantly higher among both cough groups when compared to a healthy adult population. On the Crown Crisp Experimental Index (CCEI) (84), mean scores on phobic anxiety, somatisation, depression, and obsession subscales were significantly higher among both successfully treated and refractory cough subjects than published mean scores for healthy controls. They also found that only state anxiety was significantly higher in the idiopathic cough subjects compared to the successfully treated cough subjects. The authors concluded that while subjects with CC appear to have increased levels of emotional upset, psychological questionnaires did not readily distinguish between idiopathic cough and treated cough.

The strong association of CC and impaired mental health, particularly depression, indicates that CC is not a minor problem and therefore deserves thorough evaluation and treatment (24). This is particularly relevant as most subjects respond to treatment for CC (85) and in one study, successful treatment of cough correlated with improvements in depression scores in 70% of subjects (86). Dicpinigaitis et al demonstrated that depressive symptomatology is very common in subjects with CC (53% of women and 52% of men studied). Improvement in cough score correlated significantly with improvement in depression score after cough treatment and none of the subjects required antidepressant medication. The authors concluded from this study that as depressive symptoms are very common in subjects with CC, physicians and their care
givers should be conscious of the significant risk of clinical depression in this patient population (86). Evaluation and management of psychological morbidity is recommended in CC patients within the community and those seen in referral centres. This is especially necessary in people in whom coughing persists without an identifiable cause and/or extended trials of empirical therapy have been ineffective (87). Under-diagnosis of depression in subjects with somatisation, particularly depression has been identified as a significant problem in primary care (88).

1.2.8 Smoking

Cough is a frequent symptom of cigarette smokers and is often the first symptom of disease that precedes the development of airflow obstruction (15). Cough and sputum production for at least 3 months of the year in two consecutive years is used to define chronic bronchitis and are usually prominent features of early disease resulting from chronic cigarette smoking. Cigarette exposure enhances symptoms of asthma including cough, especially in children (89). The potential mechanisms of cough induced by cigarette smoking are numerous. Inflammatory mechanisms induced by constituents of cigarette smoke may lead to heightened cough reflex sensitivity, and excessive mucus production may directly induce cough (15). In a study by Bergren (90) cigarette smoke-exposed guineapigs were found to develop an enhanced cough reflex to citric acid or capsaicin. Acute tobacco smoke challenge activates both airway rapidly adapting receptors (RARs) (91) and C-fibre endings (92). Both RARs and C-fibres are thought to initiate cough (93, 94). It is possible that chronic tobacco smoke exposure or airway sensitisation alters the cough threshold by inducing hyperirritability of either or both category of sensory receptor in the airways.
Millqvist and Bende (95) examined the effect of smoking on capsaicin provocation. Healthy smokers and non-smokers were challenged with capsaicin in increasing doses. The coughs were counted and irritation of the lower airways was graded on a symptom score. Smokers reacted to provocation with significantly fewer coughs. This result astonished the authors as smoking often leads to chronic bronchitis, with coughing as a major symptom. It was thought that nicotine in high doses eliminates neuropeptides from the C-fibre endings in a similar way that capsaicin does (96). Such a theory may also explain the increasing symptoms from the upper and lower airways so often seen in subjects who have ceased to smoke (95).

1.2.9 Upper Respiratory Tract Infection

Upper respiratory tract infection (URTI) represents the most common acute illness evaluated in the outpatient setting. URTIs range from the common cold-typically a mild, self-limited, catarrhal syndrome of the nasopharynx to life-threatening illnesses such as epiglottitis. Viruses account for most URTIs. The upper respiratory tract includes the sinuses, nasal passages, pharynx, and larynx, which serve as gateways to the trachea, bronchi, and pulmonary alveolar spaces. The common cold is a conventional term for a mild URTI with common symptoms being nasal stuffiness and discharge, sneezing, sore throat, and cough (97). Rhinitis, pharyngitis, sinusitis, epiglottitis, laryngitis, and tracheitis are specific manifestations of URTIs that have also been implicated as causes of acute bronchitis (98). URTIs are the most common infectious illness in the general population. The incidence of the common cold varies by age. Children have about 3-8 viral respiratory illnesses per year. Adolescents and adults have approximately 2-4 colds a year, and people older than 60 years have less
than one cold per year. If one takes a rate of URTI of two episodes per person per year, then a conservative estimate of incidence in Australia is 45 million episodes of URTI per year. Only a proportion of cases of URTI are associated with cough as a symptom. In naturally acquired URTI, cough was found to be present in 40-50% of subjects (99, 100).

Acute bronchitis begins as a respiratory tract infection that is manifest predominantly by cough with or without sputum that lasts for up to 3 weeks (98). Cough associated with the common cold is an upper airway cough syndrome that is often associated with throat clearing and the sensation of post nasal drip. The presumed lower airway cough of acute bronchitis is also at times accompanied by PNDS, further compounding the difficulties in diagnosis (101). The viruses that have been identified in subjects with acute bronchitis are known to involve the lower respiratory tract, such as influenza B, influenza A, parainfluenza, and respiratory synctial virus (RSV). Severe acute respiratory syndrome (SARS) must be also considered in patients with influenza-like illness. The cause of cough in the diagnosis of uncomplicated acute bronchitis is likely multifactorial, and begins with mucosal injury, epithelial cell damage, and the release of proinflammatory mediators (102). Transient airflow obstruction (103-105) and transient bronchial hyperresponsiveness (103, 106-108) can be seen in around 40% of previously healthy individuals with an acute viral respiratory tract infection, and a reversibility of FEV\(_1\)>15% has been demonstrated in 17% of subjects (104). Subjects with documented M pneumoniae or C pneumoniae infections have significantly lower FEV\(_1\) values and a greater degree of reversibility that those with viral aetiologies (104).

A cough due to a URTI or acute bronchitis is considered to be a self-limited respiratory disorder, but when the cough persists for >3 weeks other diagnoses must be
considered, including postinfectious cough, PNDS, asthma, and GORD. Chronic idiopathic cough (CIC) is likely to consist of a variety of unidentified pathologies, but an identifiable pattern in the characteristics of these subjects has emerged (6). The classic story is one of a URTI that initially triggers the cough. The infection subsides, but the cough persists. In some of these subjects, the cough subsides within a few months and Haque et al has diagnosed this as post viral cough (6). In others, the cough persists for years and presents with an exquisitely sensitive cough reflex (CIC).

Taramarcaz et al (109) reported an association between viral URTI and vocal cord dysfunction (VCD). Viral URTI was found to induce transient VCD in two of the three cases reported and exacerbate pre-existing VCD in the other case. The respiratory tract viral infections were detected by validated polymerase chain reaction (PCR) techniques with either picornavirus, influenza A virus, or hMPV being isolated. The identification of hPMV (from the paramyxovirus family) is of importance as it presents with a spectrum of disease ranging from mild respiratory symptoms to severe cough, wheeze and pneumonia. The authors were also able to demonstrate in two of the cases that VCD was completely reversible after recovery from the acute viral infection highlighting the heterogeneity of VCD in that it can clinically present as a transitory response to a viral infection or as a recurrent illness. The role of viral infections preceding VCD/PVFM and associated CC will be investigated further and presented in this thesis.

Treatment of cough associated with acute URTI is primarily based on the treatment of cough as a symptom rather than treating the underlying viral infection. Many cough medications for the treatment of cough associated with URTI contain codeine or
dextromethorphan, which are believed to act by inhibiting the central control of cough \(^\text{(110)}\). However, studies on the antitussive effects of codeine and dextromethorphan in subjects with cough associated with URTI have failed to demonstrate that these medicines have any greater effect on cough than placebo treatment \(^\text{(111, 112)}\), [Figure 1.2].

![Figure 1.2: Median cough frequency for subjects with cough associated with upper respiratory tract infection.](image)

A single dose of 30 mg dextromethorphan powder in a hard gelatine capsule or matched placebo containing lactose powder was ingested by the patient with a small amount of water. Treatment groups: placebo (■), n=22; dextromethorphan (□), n=21 Figure adapted from Lee et al \(^\text{(113)}\).

1.2.9.1 Post Infectious Cough

Although cough associated with an acute URTI is usually transient, in a subgroup of patients a dry cough may persist for weeks to months after resolution of other symptoms \(^\text{(114)}\). Respiratory viral infections likely initiate most cases of postinfectious cough; however, *Chlamydia pneumoniae*, strain TWAR \(^\text{(115)}\), *Mycoplasma pneumoniae* and *Bordetella pertussis* \(^\text{(2, 116)}\) have also been implicated in children and adults. Past studies have reported a variable frequency of postinfectious cough of between 11% in retrospective studies \(^\text{(5, 117, 118)}\) to 50% during outbreaks of pertussis infections \(^\text{(116, 119)}\). In a
study by Hallander et al, 99 of 155 episodes of cough with less than 100 days duration were studied. The most common single agent identified as the cause of the cough was found to be Bordetella pertussis (56%, with a median cough duration of 51 days), followed by Mycoplasma pneumoniae (26%, 23 days), Chlamydophyla pneumoniae (17%, 26 days), and Bordetella parapertussis (2%) all confirmed by laboratory analysis. In children with cough for more than 100 days, B. Pertussis was responsible for 83% (65 out of 78 subjects studied), and in 21% as a co-infection. However, in adults there have been a number of studies in cough clinics that have failed to observe postinfectious cough even when many of the subjects had a history of preceding URTI. The explanation for this variable frequency is not clear.

The diagnosis of postinfectious cough is clinical and one of exclusion. It should be considered when patients complain of cough only after a respiratory tract infection and have normal chest radiographs. The pathogenesis of post infectious cough is believed to be related to inflammation and epithelial damage to the upper and lower airways. Several potential mechanisms for post infectious cough have been proposed. These include post infectious bronchial hyperresponsiveness; transient vocal cord dysfunction; cough reflex hypersensitivity; nasal and sinus inflammation; and GORD.

Postinfectious cough can be particularly difficult to treat and in a study by Freestone and Eccles, codeine was shown to be ineffective in the acute phase of an URTI. As infection-induced, persistent airway inflammation is the likely cause of enhanced cough sensitivity during an URTI, anti-inflammatory therapy with corticosteroids for severe, debilitating cough seems logical. Although oral corticosteroids have been
shown to be effective in this setting \(^{(21)}\), inhaled corticosteroids, which are commonly prescribed for postinfectious cough, have not been properly evaluated in clinical trials \(^{(114)}\). Although not specifically a study on postinfectious cough, Pizzichini et al \(^{(124)}\) demonstrated that a 2-4 week course of budesonide was ineffective in the treatment of nonasthmatic idiopathic CC. Inhaled ipratropium bromide has been shown to be effective in chronic postinfectious cough \(^{(125)}\), while a combination therapy of oral H\(_1\) antagonist, oxatomide, and dextromethorphan demonstrated antitussive activity \(^{(126)}\).

### 1.2.10 Occupational and Environmental Cough

Work place sensitisers can lead to CC as can dust and/or chemical exposure at home \(^{(32)}\). Persistent cough as a presenting feature of occupational sensitisation of the airways has been reported in a number of studies and case reports \(^{(127)}\). There has been a significantly higher prevalence for CC, chronic phlegm and chronic bronchitis in several occupational groups: farm workers compared to healthy controls \(^{(127)}\); workers exposed to hot acidic solutions in a bottle factory \(^{(128)}\); and workers exposed to hot chilli peppers \(^{(129)}\). Of interest, the main respiratory health consequence from the collapse of the World Trade Centre (WTC) on September 11, 2001 has been the “WTC Cough Syndrome”. Syndrome incidence and severity has been linked to WTC dust exposure intensity that spread throughout lower Manhattan and beyond after an aerial terrorist attack on the WTC \(^{(130)}\). An estimated 525,000 people were potentially exposed to the resulting pollutants of dust and smouldering ash during the collapse, rescue, recovery and clean up efforts \(^{(131, 132)}\). Contaminants such as asbestos, hydrochloric acid, PCBs (polychlorinated biphenyls), silica, and heavy metals were found in the dust and ash...
from the WTC collapse\(^{133-137}\). In a study of 39 fire fighters from the Fire Dept. of New York 10 months after exposure\(^{138}\), it was demonstrated that the WTC dust did make it down into the lower airways as particulate matter (>10 µm), with associated increases in inflammatory cells and cytokines in induced sputum. The WTC Cough Syndrome is a CC syndrome, thought to be a consequence of upper and lower respiratory diseases. Not many references describing the treatment of WTC or disaster-related CC or dyspnea have been published; however, recent consensus treatment guidelines have been published as a joint collaborative effort\(^{139}\).

1.2.11 Chronic Idiopathic Cough

Idiopathic chronic cough or chronic idiopathic cough (CIC) is the term given to a subgroup of patients with CC in whom a diagnosis cannot be made even after thorough, systematic investigation. An initial descriptive series of CC using an anatomic diagnostic protocol (ADP) to systematically evaluate pulmonary and extrapulmonary sites of afferent cough receptors reported that cough could be successfully diagnosed and treated in up to 98% of cases\(^{33}\) resulting in a stepwise diagnostic approach being recommended\(^{2}\). However, many studies since have shown that utilising a similar diagnostic approach results in no clear cause of cough being elucidated in up to 30% of subjects even after the protocol was meticulously adhered to\(^{140}\). The description of a typical phenotype gives credence to the genuine existence of an idiopathic cohort. This phenotype is typically women of middle age who report prolonged duration of cough\(^{20}\). One such study by Haque et al\(^{6}\) compared 42 subjects identified with CIC to 58 subjects in whom another diagnosis for cough had been made. This group was described as non-CIC and did not differ in age or female
predominance from the CIC group. The median duration of cough in the CIC group was significantly longer than that of the non-CIC group and 48% of the CIC group described the onset of their cough as being triggered by an URTI, compared with 24% in the non-CIC group. They also found that the CIC group demonstrated significantly increased cough sensitivity compared with the non-CIC group. The high prevalence of CIC within this study is in stark contrast to that of other reported cough studies. The authors feel that this is due to their CIC group consisting of a variety of as-yet unidentified pathologies, but that they have uncovered an identifiable pattern in the characteristics of these patients. This pattern is one of URTI cough aetiology, where the infection subsides, but the cough persists. Where the cough persists for years, the patient describes clear symptoms of heightened cough sensitivity. Foods, smells, laughing, increased breathing rate, temperature changes are enough to trigger coughing. This phenomenon is demonstrated by increased capsaicin sensitivity when compared to other diagnosed CC cases. Further, there appears to be an over-representation of females with some cough clinic centres reporting more than 80% female presentation rates.

Typically, the female subjects are in the peri- or post menopause period with a preceding URTI and have heightened cough reflex to tussive stimuli suggesting that there may be a distinct clinical phenotype. Further studies into this cohort have revealed bronchoalveolar lymphocytosis and a high prevalence of organ specific autoimmune antibodies and autoimmune disease. The percentage of subjects that fall into the idiopathic cough description has been reported to be as high as 31% and 42%.
1.2.12 Sensory Laryngeal Neuropathy

Sensory neuropathy presenting as CC, laryngospasm, and/or paradoxical vocal cord adduction is described as another cause of CC (147). It is not considered in the ADP, but rather is reported in the otolaryngology literature. Although most patients with these symptoms have rhinosinusitis, allergy, or reflux, patients who do not respond to empiric therapy for these conditions should be considered for sensory neuropathy of the superior laryngeal nerve (SLN) or recurrent laryngeal nerve (RLN) (5, 148, 149). On routine nasolaryngoscopy the larynx may appear normal, lacking obvious signs of RLN or SLN. Neurogenic cough is often misdiagnosed as laryngopharyngeal reflux, VCD, or psychogenic cough and the only signs of RLN or SLN may be found with videostroboscopy where a detailed examination of glottal function is gained (147). The report by Lee and Woo (147) presented a group of subjects with cough, globus and throat irritation who were subsequently diagnosed with sensory neuropathy. While sensory neuropathy is considered an uncommon condition, the authors observed that laryngospasm and CC due to laryngeal neuropathy may be an under recognised entity. This study presented a case series of 28 subjects in whom sensory neuropathy of the SLN or RLN was suspected. These subjects were then started on a course of gabapentin (Neurontin) treatment beginning at 100mg/d and increasing the dosage up to 900mg/d in divided doses over a 4-week period. The subjects titrated the dose of medication until the symptoms resolved or until side effects developed. For responders, the medication was continued for 3 months at which point attempts to taper the dosage were made. Overall improvement of cough and sensory neuropathy with gabapentin
was 68% and in those subjects with clear motor neuropathy the treatment response was as high as 80%.

Post viral vagal neuropathy (PVVN) has also been identified as a potential cause of CC when all other possibilities have been eliminated. Vagal neuropathy is a condition that occurs following an upper respiratory illness, which represents injury to various branches of the vagus nerve. A carefully taken patient history often reveals that the coughing started after an URTI and persisted long after the other symptoms resolved. Patients with this condition may present with breathy dysphonia, vocal fatigue, effortful phonation, odynophonia, cough, globus, and/or dysphagia, lasting long after resolution of the acute viral illness. The patterns of symptoms and findings in this condition are consistent with the hypothesis that viral infection causes or triggers vagal dysfunction. These patients may also have airway hyperresponsiveness persisting beyond the acute URTI that manifests as a decrease in cough threshold in response to irritating chemical or mechanical stimuli. PVVN cough is not usually included as a standard cause of CC. There is no standard of care for PVVN cough. However, two recent studies by Bastian et al. and Jeyakumar et al. investigated the favourable treatment response of Amitriptyline use in the suppression of CC resulting from PVVN. Amitriptyline has been used for years in the treatment of neuropathic pain. PVVN appears to have similarities with other post viral neuropathic disorders, such as glossopharyngeal neuralgia and Bell’s palsy which represent isolated nerve injuries that result in motor or sensory dysfunction depending on the nerves affected. The first of these studies performed by Bastian et al. consisted of 12 subjects treated with amitriptyline 10mg two hours before bedtime for
21 days. All of the subjects except one had prompt significant reduction of their cough with this treatment. Jeyakumar et al (154) took this one step further with a prospective, randomised controlled trial comparing the effectiveness of amitriptyline versus codeine/guaifenesin for select cases of CC resulting from suspected PVVN. Again, a majority of subjects achieved a complete response on a 10mg/d dose at bedtime for 10 days.

Autosomal dominant hereditary sensory neuropathy (HSN I) is a clinically and genetically heterogeneous group of disorders, and in some families it is due to mutations in serine palmitoyltransferase (SPTLC1). Spring et al (47) characterised two families with HSN I associated with cough and GORD. Clinical information and blood for genetic analysis was collected from two Australian families. The affected individuals had an adult onset of paroxysmal cough, GORD and distal sensory loss. Their cough could be triggered by noxious odours or by pressure in the external auditory canal (Arnold’s ear–cough reflex). Other features included throat clearing, hoarse voice, cough syncope and sensorineural hearing loss. Neurophysiological and pathological studies demonstrated a sensory axonal neuropathy. Most affected individuals were shown on 24 h ambulatory oesophageal pH monitoring to have multiple episodes of GORD, closely temporally associated with coughing. The cough was likely to be due to a combination of denervation hypersensitivity of the upper airways and oesophagus, and prominent GORD. Hoarse voice may have been attributable to acid-induced laryngeal damage. No other cause for the cough could be found on respiratory or otorhinological studies conducted. Linkage to chromosome 3p22–p24 was found in both families, with no evidence of linkage to loci for known
HSN I, autosomal dominant hereditary motor and sensory neuropathy, hereditary GORD or triple A syndrome. It was concluded that these families represented a genetically novel variant of HSN I, with a distinctive cough owing to involvement of the upper aerodigestive tract.

1.2.13 Cough hypersensitivity syndrome

Just recently a single diagnosis for CC has emerged: cough hypersensitivity syndrome (155). This terminology arose due to the homogeneous nature of the clinical history and investigational results of subjects attending cough clinics. Objective testing with capsaicin and other protussive agents demonstrates the hypersensitivity facet of the syndrome. Although there are different phenotypes within the cough hypersensitivity syndrome the similarities between these far outweighs the differences unifying a diagnosis of cough hypersensitivity syndrome (155).

The clinical history of patients with CC contains many examples of upper airway hypersensitivity. Cough can be precipitated by temperature changes, minute amounts of sensory irritants such as cleaning fluids and perfumes as well as tobacco smoke exposure. The pathophysiological basis of this hypersensitivity may be upregulation of the transient receptor potential (TRP) nociceptors. Capsaicin hypersensitivity is mediated through transient receptor potential, vanilloid-1 (TRPV1) (156-158). It can be defined as a hot receptor, giving capsaicin its pungency. The fact that TRP temperature receptors have been utilised in nociception for cough explains the change-in-atmospheric temperature complaint made by many CC subjects. The very cold receptor transient receptor potential, ankyriol-1 (TRPA1) has recently been identified as being a more generalised nociceptor producing cough (155). TRPA1 is able to bind and be
activated by a range of noxious substances known to cause cough\textsuperscript{(159)}. If upregulation of TRPA1 in disease causing CC can be demonstrated then the mechanism behind this hypersensitivity could be established.

Cough hypersensitivity syndrome encompasses different phenotypes and obviates the need for the use of the term idiopathic cough since these patients could be classed as having cough hypersensitivity syndrome without an obvious phenotype.

Unfortunately, there is no agreed upon single stimulus that precipitates cough hypersensitivity. Morice\textsuperscript{(155)} however believes that this single precipitant for cough hypersensitivity could be reflux. Not the reflux that characterises GORD but the reflux that may be of neutral pH, most likely gaseous and may be of short length exposure, that is oesophagopharyngeal reflux. This reflux gives rise to not only coughing but causes the inflammation needed for cough hypersensitivity syndrome. However as there is no diagnostic test presently available to prove this, it must at the present time be designated as speculation.

1.3 Epidemiology

Cough is the commonest symptom leading patients to consult with their doctor in the United States of America\textsuperscript{(160)}, UK\textsuperscript{(16)} and Australia\textsuperscript{(161)}, and CC is one of the commonest reasons for new referrals to respiratory/pulmonary specialists\textsuperscript{(2, 5)}. Most reports of the prevalence of CC in adults originate from specialist cough clinics and therefore reflect the experience of CC in secondary or tertiary care. Data on the prevalence and characteristics of cough in the general population are scarce\textsuperscript{(24)}. Where population data does exist they are limited by methodological problems such as selected age groups\textsuperscript{(162-165)}, self selection of questionnaire respondents\textsuperscript{(166)}, failure to differentiate between...
acute cough due to infection and CC\textsuperscript{(167)}; and the lack of information on other respiratory conditions\textsuperscript{(164)} making it difficult to differentiate the impact of CC from airway diseases such as asthma.

1.3.1 Prevalence

Twenty-nine and a half million visits to primary care physicians in the USA during 1998 were for cough\textsuperscript{(161)}, with the greatest majority of these likely due to acute cough associated with the common cold\textsuperscript{(123)}. Referral of a patient with a persistent CC of unknown aetiology has also been shown to be one of the most common reasons for new patient visits to respirologists\textsuperscript{(2)}. However, the exact prevalence of chronic persistent cough has proved difficult to estimate. Recurrent cough measured by questionnaire surveys has a reported prevalence of 3-40\% of the population [Table 1:3].

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort</th>
<th>Prevalence</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA\textsuperscript{(168)}</td>
<td>1109</td>
<td>18%</td>
<td>Chronic cough related to smoking</td>
</tr>
<tr>
<td>USA (Caucasian only)\textsuperscript{(163)}</td>
<td>5743 (&gt;45 yrs)</td>
<td>9.3% in those without airflow obstruction (8.3% with sputum)</td>
<td>Increasing prevalence with increasing airflow obstruction; 49% of subjects with FEV1&lt;35% had a chronic cough</td>
</tr>
<tr>
<td>USA (Seattle)\textsuperscript{(169)}</td>
<td>2397 schoolchildren (11-15 yrs)</td>
<td>7.2%</td>
<td>Chronic productive cough for at least 3 months per year. Associations with current asthma and environmental tobacco smoke exposure</td>
</tr>
<tr>
<td>South-East England\textsuperscript{(170, 171)}</td>
<td>9077</td>
<td>16% (13.2% produced sputum)</td>
<td>Cough every day or half the days of the year. 68% of chronic sputum producers were associated with cigarette smoking</td>
</tr>
<tr>
<td>North England\textsuperscript{(164)}</td>
<td>4003</td>
<td>12% (severe in 7%)</td>
<td>Regurgitation and irritable bowel syndrome were strong predictors of coughing</td>
</tr>
<tr>
<td>Europe (ECHRS)\textsuperscript{(165)}</td>
<td>18277 (20-48 yrs)</td>
<td>33%; 20% productive or non-productive cough in winter</td>
<td>Woken by attack of cough in past 12 months?</td>
</tr>
<tr>
<td>Country</td>
<td>Sample Size</td>
<td>Age Range</td>
<td>Prevalence</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Italy</td>
<td>18000</td>
<td>(20-44 yrs)</td>
<td>11.9% (similar gender prevalence)</td>
</tr>
<tr>
<td>Sweden (part of ECHRS)</td>
<td>623</td>
<td>(Mean age: 31 yrs)</td>
<td>11% non-productive cough; 8% productive; 38% with nocturnal cough.</td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>6610</td>
<td>(Ages: 35-36, 50-51, 65-66 yrs)</td>
<td>11%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>9651</td>
<td>(3232 current smokers) 18-60 yrs</td>
<td>Current smokers: 9.2%; never smokers: 3.3%</td>
</tr>
<tr>
<td>South Australia</td>
<td>3355</td>
<td>(&gt;18 yrs)</td>
<td>9% non-productive cough, and 4% productive cough in people without known respiratory disease; 4% cough with or without sputum production in people with a known respiratory disease.</td>
</tr>
</tbody>
</table>

ECHRS=European Community Respiratory Health Survey. FEV1=forced expiratory volume in 1 second. *These studies are published in English on the epidemiology of cough as a respiratory symptom in the general population. Table adapted from Chung and Pavord (41) with the addition of Adams et al study (24).

The accuracy of results from questionnaire surveys are often influenced by the studied population and the question/s posed (14). For example, a question that asks the respondent about nocturnal cough will often yield a positive response for acute cough (124). Irrespective of the failings of individual surveys, CC is clearly a very common symptom associated with considerable morbidity (14).

In a recent report by Adams et al (24) a representative population sample taken from the South Australian community found that chronic, dry cough is common among people without known respiratory disease, with a prevalence of nearly 9% among adults.

Cough productive of sputum occurred in a further 4% of those without known lung disease. Consistent with data taken from specialist CC clinics, people within the
general community with CC report significant impairments in quality of life and psychological health compared to those without cough. Across the population, Adams et al also found CC to be significantly associated with obesity and severe depression, to be more common in men, and in people aged over 60 years. Although cough was more common in people who currently smoke, when only non-smokers were analysed, the significant associations seen with depression, obesity, male gender and age persisted. The prevalence of cough in the community for the three continents of the USA, Europe and Australia is presented below [Figure 1:3].

![Figure 1:3 Percentage prevalence of persistent cough in the community by continent](image)

Cigarette smoking has a dose related influence on the prevalence of productive cough \(^{(165)}\) however, smokers rarely seek medical advice for this as they readily ascribe their cough to tobacco use. Consequently the prevalence of smoking related cough presenting to secondary care is low \(^{(170)}\). Deterioration in quality of life and cough related morbidity such as sleep disturbance, urinary incontinence in females, and/or syncope appear to be the main reason for the CC patient to consult a doctor \(^{(175-177)}\). Men
report cough more frequently than women in population surveys (170, 178, 179); however most patients referred to specialist cough clinics are women.

1.3.2 Cost of Chronic Cough

The cost of treating cough on a global basis while not known can be estimated to exceed billions of dollars. Several billion dollars are spent on over the counter treatments that have been found to be essentially ineffective. These figures do not include prescription drugs for the common cold and other causes of acute or sub acute cough or for the treatment of CC. However, when such patients are referred to a specialist cough clinic then a cause for the cough is mostly identified. In Europe a high prevalence of idiopathic cough and other aetiologies such as post viral cough exists, while in America experience points to a high prevalence of PNDS and multiple aetiologies for cough in an individual patient (16).

The American College of Chest Physicians (ACCP) recommendation that treatment of CC should follow testing has recently been questioned. Later evidence (180-182) suggests that empirical treatment of GORD is more cost effective than testing followed by treatment in both noncardiac chest pain and CC groups. In a study by Lin et al (183) a decision model was used to evaluate the cost-effectiveness of a variety of management strategies which included combined testing, combined treatment, sequential treatment, sequential testing, and different combinations of testing and treatment. The calculation of the expected cost of each strategy was the sum of direct costs and indirect costs. Direct cost is the costs of consultation, treating and testing of PNDS, asthma and GORD. The indirect cost is the costs borne by the patient for the inconvenience of the cough, such as a wrong or inefficient treatment strategy and therefore prolonged
duration of the cough. From the model evaluation, the authors were able to conclude
that the preferred strategies were Treat All, Test All Then Treat and Treat Sequentially
Starting with PNDS. This deduction was further strengthened when the authors
examined expected duration and expected direct costs of each strategy. While the
strategy Test All Then Treat had the shortest treatment duration, it was also the most
expensive. Conversely, the strategy Treat Sequentially starting with PNDS was the
cheapest, but with the longest treatment duration [Table 1:4].

Table 1:4 Strategy duration vs direct cost (183)

Reference: Lin L, Poh KL, Lim TK. Empirical treatment of chronic cough: a cost-

Table removed from online repository version due to copyright laws.

1.3.3 Chronic Cough and Quality of Life

CC has been shown to be associated with impaired health-related quality of life (175, 176,
184). It is also associated with psychosocial problems that may be more pronounced than
physical effects (166, 175, 176, 185), however from the few studies that have evaluated
psychological health (81, 86) the sampled population was taken from specialist clinics
rather than from the general population. McGarvey et al (81) recently studied
psychomorbidity prevalence in CC patients presenting to a specialist clinic. Using the
hospital anxiety and depression (HAD) scale, 33% of all cough patients were identified
as anxious, while 16% experienced depression. The state trait anxiety inventory (STAI)
scores suggested moderate or high trait anxiety in 48% of all coughers and this is
greater than the expected lifetime prevalence for anxiety disorders in the community
which has been estimated at 15% (186). On the crown crisp experiential index (CCEI),
mean scores on the phobic anxiety, somatisation, depression, and obsession subscales were significantly higher among all cough patients than the published mean scores for healthy controls. Only state anxiety was significantly higher in idiopathic cough patients compared with successfully treated cough patients (p < 0.05). The authors concluded that patients with CC appear to have increased levels of emotional upset although psychological questionnaires do not readily distinguish between idiopathic coughers and those successfully treated.

Adams et al examined the prevalence of CC in a representative adult population residing in north west Adelaide, Australia (24). Further they investigated cough not associated with diagnosed respiratory conditions, and examined the impact of cough on health and psychological health status. The population cohort consisted of people aged 18 years or older, randomly selected from the electronic white pages telephone directory. Survey data was collected on 3574 people and clinic data was collected on 3206 people. Of the 3355 people without identified lung disease, 18.2% reported CC with a dry non-productive CC being significantly more common in males, current smokers, obese, ACE inhibitor use, severe mental health disturbance and older age (≥60 years). Among non-smokers only, all cough was significantly more common in men, those with severe mental health disturbance and obesity. Further, participants reporting cough at any time were significantly more likely to have psychological disturbance on a validated psychological health measure (GHQ-12) and reported significantly lower quality of life compared to those without cough at any time (24). In conclusion, this study presented data showing that the frequency of CC independent of other lung disease is strongly associated with impaired mental health, particularly
depression, and significantly, reduced quality of life indicating that cough is a major contributor to morbidity in the community. The reduction in quality of life for general physical health is similar to that reported in Australian populations for asthma (187), diabetes (188), arthritis (189) and depression alone (188). Adams et al concluded that as major impairments were seen in a general health instrument (the SF-36) indicates that CC is not a minor problem and deserves thorough evaluation and treatment particularly as most patients are able to respond to treatment for CC (85).

Interestingly the Adams et al study also found obesity to be significantly associated with dry cough and cough in never/ex smokers (24). Janson et al (165) also reported cough being significantly associated with obesity, however this study group included people with asthma and other respiratory diseases and as obesity has been shown to be significantly associated with asthma it is unclear from the study whether obesity was linked to CC independent of airway disease. A possible mechanism is that obesity increases the risk for GORD - a major cause of CC. GORD with aspiration has been shown to be the cause of CC in 21% - 41% of cases. The majority of cough associated with oesophageal disease is due to reflux (33), however the precise definition used for reflux may significantly influence these findings during investigation. Twenty-four hour pH monitoring arose from the diagnosis of heartburn associated with reflux (38, 190). It has not been validated for GORD associated with cough or with laryngopharyngeal reflux (LPR). LPR is a condition in which inflammation arises in the larynx and pharynx due to increased sensitivity of the mucous membranes to gastric contents such as pepsin, and is not necessarily related to pH. Even though our understanding of oesophageal disease is evolving and the numbers of patients
identified with oesophageal disease increases with this understanding (192) there is still a lot of work to be done to define the nature and extent of reflux disease in association with CC (16).

1.4 Clinical Description

The clinical description of cough relies on its sound, its timing and whether or not there is expectoration (192). Coughing is presented by a sudden air expulsion from the airways which is characterised by a typical sound. This sound is so characteristic that it allows identification of the cough and its distinction from other vocal manifestations. The cough sound is a very important symptom of well over 100 diseases and other conditions of medical significance. Changes in its character may have a considerable value in identifying the mechanisms of airway pathology present in respiratory diseases. The character of the cough sound gives information about the behaviour of the glottis and whether the glottis behaves differently in different pathological conditions. Analysis of the cough sound record has significant value in prognosis because its changes may indicate the effectiveness of therapy or the progress of disease (193). Certain aspects of the timing of the coughing may give useful diagnostic clues. A cough that awakens the patient in the small hours of the night suggests asthma; wheezing need not be relevant. Cough with expectoration on rising in the morning is characteristic of chronic bronchitis, although it may also be reported by asthmatics. A bout of coughing with food or when lying down after a meal points to oesophageal, pharyngeal, or neuromuscular disease, causing penetration into the laryngeal vestibule or through the vocal folds into the trachea. Changes of posture can also set off coughing in patients with bronchiectasis; and free expectoration of sputum
at any time of the day is common in these patients. A dry cough that persists over many weeks can signify a neoplasm, but a non-productive barking cough that has lasted for years has been reported to be a nervous habit perpetuated by psychogenic factors, however, evidence for these claims are limited to case studies without formal psychiatric evaluation.

The diagnostic value of different types of cough is commonly used by Paediatricians as whooping cough, croup, bronchiolitis and cough associated with tracheo-oesophageal fistula have well recognised specific features (194, 195). Certain cough characteristics such as “croupy or brassy cough” [Table 1:5] are classically taught to point to specific aetiologies in children.

Table 1:5 Paediatric cough characteristics (196)


Table removed from online repository version due to copyright laws.

Data on the sensitivity and specificity of each classic, recognisable cough type are limited; only that for brassy cough (for tracheomalacia diagnosed at bronchoscopy) is known. Although a “pertussis-like” cough in children is generally due to Bordetella pertussis infection, it may also be caused by adenovirus, parainfluenza virus, respiratory syncytial virus or mycoplasma (196). Cough productive of sputum can be described as ‘moist’ or ‘loose’ (192). However, a cough may fail to produce expectoration
because there is nothing to produce, because secretions are swallowed (as is almost universal in children), because there is severe airways obstruction, because of weakness, or because the secretions are too viscid. In the last four instances, the sound quality of the cough differs from that of a dry cough, in the sense that secretions can be heard moving in the major airways. The distinction of dry and wet/moist cough is both valid and reliable (196).

During clinical examination of adults the quality of cough sounds are largely ignored (197) and although it is not uncommon to ask an adult to describe their cough during clinical assessment, it has previously been suggested that the patient’s own description of character, quality and timing is of little help in determining the cause (53). Characteristic cough descriptions and their related diseases include:

1. A dry cough with an irritative barking quality, short and often repeated, is heard in pharyngitis, tracheobronchitis, and early pneumonia.
2. With laryngitis the sound is harsh and hoarse (‘croup’).
3. The long inspiratory sound that gives whooping cough its name is also produced by tracheal and laryngeal inflammation.
4. Abductor paralysis of the vocal folds creates a cough that is prolonged and lowing like the sound of cattle, and hence described as ‘bovine’.
5. If lesions press on the trachea in the thorax but spare the nerve, the cough has a hard metallic quality described as ‘brassy’.
6. Unilateral abductor palsy of the larynx does not affect the voice, and even with additional abductor palsy the voice often remains good.
7. Complete paralysis of both vocal folds gives aphonia and a weak ineffectual cough \(^{(192)}\).

Weakness of the thoracic muscles, as in polyneuritis or the muscular dystrophies, will lessen the expulsive force in coughing, as will the general weakness of prostration, toxaemia, or the deeper states of unconsciousness. Cough may be suppressed when there is severe thoracic or upper abdominal pain.

A study by Mello et al \(^{(53)}\) sought to determine if the character, timing, or complications of CC were helpful in determining its cause. Eighty eight subjects were subsequently evaluated by a validated systematic diagnostic protocol \(^{(37)}\), a self-administered questionnaire, and by observation of the character of involuntary and voluntary coughs. The final diagnosis of the cause of cough required fulfilment of pre-treatment criteria and having cough disappear or substantially improve as a complaint with specific therapy. Cough was found to be the result of a single cause in 39% and multiple causes in 59% of the studied population. GORD, PNDS, and asthma were the three most common causes of CC and accounted for over 90% of diagnoses irrespective of patient estimated quantity of daily sputum production. A carefully taken history with detailed questioning of the character, timing, and complications of CC was found to be not very useful in diagnosing the cause of cough and that instead the cause can be determined and successfully treated with specific therapy in the greatest majority of cases.

There is little known about how those who work in adult respiratory medicine use the many descriptions of cough available. Smith et al \(^{(197)}\) sought to answer this question by
using spontaneous cough sounds from overnight cough recordings in subjects with common respiratory conditions. Healthcare professionals were asked to describe the cough sounds and these descriptions were compared to specific sound qualities assessed by acoustic analysis and the suggested diagnosis made using these cough sounds was assessed. The results of this study showed that gender of the person coughing was correctly identified in 93% of cases and the presence or absence of mucus was correctly identified in 76.1% cases. However, wheeze was identified in just 39.3% of cases, and the correct identification of the clinical diagnosis from the cough sounds was also low at 34%. This finding suggests that while healthcare professionals can recognise some of the qualities of cough sounds they are poor at making a diagnosis from them. A wide range of cough descriptors were used by the subjects and cluster analysis suggested that they reflect the acoustic properties of the cough sounds rather than the diagnostic category (197). Poor diagnosis from cough sound alone is not surprising. Previous work looking at voluntary cough sounds has suggested that some differences occur between diagnostic groups (193). In keeping with this study’s finding a previous study investigated the quality of cough sounds in children undergoing bronchoscopy. This study examined the agreement between descriptions of the cough as wet or dry by clinicians and parents and the bronchoscopic appearances. Good agreement was found for both clinician and parent rating of coughs (198).

1.5 Complications of cough

Coughing is a very vigorous activity and as a result, CC can lead to a number of complications (199) [Table 1.6]. Coughing generates intrathoracic pressures of up to 300 mm Hg (200) and expiratory velocities of up to 28 000 cm/s (85% of the speed of
Coughing produces hemodynamic changes of a magnitude comparable to chest compressions; systolic pressures approach 140 mm Hg compared with 75 mm Hg during chest compressions and during the expiratory phase of vigorous coughing. Consequently, coughing can cause a multitude of problems and these complications can be considered as either acute or chronic. Acute complications include cough syncope, which occurs when coughs are extended and forceful and result in reduced blood flow to the brain. Other acute complications include insomnia, cough induced vomiting, chest pain due to muscular strain, and rupture of abulla causing pneumothorax. Prolonged coughing can also cause fatigue, fractures of lower ribs and costochondritis, and swelling of the connective tissue between the breastbone and the ribs. In certain cases, it can even lead to abdominal or pelvic hernias. In women, cough micturition (urination) is a common problem. Cough defecation can also happen, though this is less common. Physical and psychosocial complications such as in Table 1:6 indicate that the intensity of the cough is severe and these have the potential to lead to a significant decrease in health-related quality of life (QOL).

**Table 1:6 Potential complications from excessive cough**

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Central nervous system</th>
<th>Musculoskeletal</th>
<th>Gastrointestinal</th>
<th>Constitutional</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>Cardiac dysrhythmias</td>
<td>Syncope</td>
<td>Intercostal muscle pain</td>
<td>Oesophageal perforation</td>
<td>Excessive sweating</td>
<td>Social Embarrassment</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>Loss of consciousness</td>
<td>Headaches</td>
<td>Rupture of rectus abdominis muscle</td>
<td>Gastroesophageal reflux events</td>
<td>Anorexia</td>
<td>Depression</td>
</tr>
<tr>
<td>Pneumomediastinum</td>
<td>Subconjunctival, nasal, and anal haemorrhage</td>
<td>Cerebral air embolism</td>
<td>Increase in serum creatine phosphokinase</td>
<td>Hemiations</td>
<td>Exhaustion</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>Arterial hypotension</td>
<td>Dizziness</td>
<td>Cervical disc prolapse</td>
<td>Malfunction of gastronomy</td>
<td>Disruption of surgical</td>
<td></td>
</tr>
</tbody>
</table>
The quality of evidence for the majority of complications in [Table 1:6] consist primarily of case reports and small retrospective and prospective observational studies (199). Four studies (175, 176, 184, 203) have prospectively shown that cough can have an adverse affect on health-related QOL. The first of these studies (176) used the Sickness Impact Profile to assess the effects of cough in a before-and-after treatment intervention trial, and found that CC was associated with a significant deterioration in patient’s QOL that was most likely due to psychosocial factors.

The second study (203) utilised a cough-specific quality of life questionnaire (CQLQ) that assessed the 28 most common reasons why patients seek medical attention because of coughing. A comparison of total CQLQ scores for both chronic and acute coughers to control subjects found that the CC subjects complained significantly more of physical complaints such as headaches, dizziness, hoarseness, insomnia, aches and exhaustion. There was also a significant difference in psychosocial issues such as difficulty talking on the phone, embarrassment, self-consciousness and intolerance by others; social impairment such as lifestyle changes, no longer attending social activities, and not being able to sing; to emotional wellbeing, such as fear of AIDS, breaking a rib, incontinence, cancer or that there is something seriously wrong.
The last of these studies\(^{(203)}\) also utilised the CQLQ to assess gender differences in health-related QOL in subjects complaining of CC compared to a control group of smokers not complaining of cough. Women with CC were more likely to seek medical attention than men as their health-related QOL was more adversely affected and because they experienced more physical complaints such as stress urinary incontinence. Cornford\(^{(177)}\) studied illness behaviour (defined as the way a symptom is perceived, evaluated, and acted upon-or not acted upon\(^{(204)}\)) in subjects with a cough. It was found that consulting patients appeared to differ from non-consulting people in believing that their cough was abnormal (usually abnormally severe), would interfere with social roles, and was more worrying. For consulting patients, cough was not a trivial illness and they were concerned about the effects their cough may have on the heart.

Two large epidemiologic studies\(^{(205, 206)}\) have provided evidence that CC, as a clinical manifestation of pulmonary infection or chronic inflammation, is associated with an increased risk of coronary artery disease or myocardial infarction. Overall, these studies indicate that complications of CC are common, significant and contribute to clinic presentations for this illness.

1.5.1 Laryngeal complications

Since the larynx is the gateway to the lower airway, laryngeal disease may result in obstruction of the airway. Aspiration on swallowing, ineffective cough, and breathy voice are symptoms caused by the loss of sphincteric function, and can occur in addition to hoarseness in subjects with true vocal fold paralysis\(^{(207)}\). Dysphonia from URTI occurs from viral laryngitis, overuse during a viral illness that leads to oedema
and inflammation, paralysis from herpetic infection, and formation of granulomas secondary to severe coughing spells. Laryngopharyngeal reflux often leads to hoarseness and is associated with CC (48). PVFM, in which the vocal folds adduct during inspiration, is a cough related laryngeal condition (4). Milgrom et al (79) found 20% of their CC subjects also had abnormal vocal fold motion on fibroptic laryngoscopy. Morrison et al (208) hypothesised a mechanism linking CC and PVFM in the description of the irritable larynx syndrome (ILS). The ILS links features such as CC, dysphagia, globus, PVFM, and muscle tension dysphonia as a subset of hyperfunctional laryngeal symptoms. Common underlying aetiologies such as asthma, GORD, and PNDS may coexist with PVFM and are causal of CC (2). Dysphonia is an often mentioned coexisting symptom of CC and PVFM. The ILS (208) provided a plausible explanation for the relationship between CC, PVFM and voice symptoms, however many studies of CC and PVFM have not examined the nature of dysphonia or its relationship to these two conditions (4). People with traditional hyperfunctional voice disorders such as muscle tension dysphonia or vocal nodules may also exhibit a CC but will identify their problem as primarily a voice disorder rather than one of CC (4). This is in contrast to several articles (209-211) that suggest CC may cause or exacerbate dysphonia. Increased pharyngeal acid reflux events are more common in patients with vocal process granulomas compared to healthy controls (212). Laryngoscopy is helpful in determining whether anti-reflux treatment should be considered in managing a patient with hoarseness. Erythema in the vocal folds, arytenoid mucosa, and posterior commissure has been found to improve with
omeprazole treatment in subjects with sore throat, throat clearing, hoarseness, and/or cough \(^{(213)}\).

1.6 Cough Mechanisms

Cough involves a complex reflex beginning with the stimulation of sensory nerves in the airway epithelium that function as cough receptors. Afferent impulses from these receptors are conducted by the vagus nerve to a cough centre in the brainstem. Because cough can be voluntary, there can also be afferent input from the cerebral cortex. The cough centre receives these impulses and produces a cough by activating efferent nervous pathways to the diaphragm and laryngeal, thoracic, and abdominal muscles [Figure 1:4].

**Figure 1:4** Representative scheme of afferent and efferent pathways that regulate cough, and of the pathophysiology of the enhanced cough reflex \(^{(41)}\).


*Figure removed from online repository version due to copyright laws.*

Activation of one or more subtypes of vagal afferent nerves in the airways and lungs initiates coughing \(^{(214)}\). An urge to cough and/or perception of airway irritation produced by a chemical or mechanical sub threshold stimulus frequently precedes the act of coughing \(^{(215, 216)}\). When the stimulus reaches the cough threshold this produces a cough. This pattern implies that the number of afferent nerves activated and/or the intensity of their activation may both determine the cough threshold. Non-neuronal factors regulating responsiveness to stimuli include the concentration of the stimulus, the duration of the stimulus exposure, the rate of clearance of the stimulant, the
integrity of the epithelial barrier and the rate of inactivation of the stimulus (216). Rapidly adapting receptors (RARs) and slowly adapting stretch receptors (SARs) innervating the intrapulmonary airways and lung may enhance and facilitate coughing. Bronchopulmonary C-fibres can be sensitised directly and indirectly by a variety of stimuli and once sensitised are rendered hyperresponsive to subsequent challenges, which may also result in an increased cough response (214, 216). When cough is initiated voluntarily or by stimulation of tracheobronchial receptors, it typically begins with an inspiratory phase characterised by an enhanced contraction of the diaphragm and abductor muscles of the larynx. However, when stimuli act at the level of the vocal folds, the preparatory inspiration may be absent and this is considered a separate reflex termed the expiration reflex (217). Next follows the compressive phase, when laryngeal adductor muscles close the glottis, while the expiratory muscles contract. During the expulsive phase of cough, there is a sudden opening of the glottis and continued forceful contraction of the expiratory muscles. This can result in trauma to the vocal folds and airways (217). The larynx is the site of a large number of reflexes; however, the main respiratory responses initiated by laryngeal stimulation are apnoea, coughing, expiratory efforts, and laryngeal closure.

### 1.6.1.1 Cough Reflex Sensitivity (CRS)

The human cough reflex consists of an afferent arm comprising cough receptors, afferent pathways, central processing, and an efferent pathway (154). The cough reflex can be modified at any point along this reflex and one potential mechanism is by mediator-induced regulation of transducer sensitivity. Examples of transducers present in the airway afferent nerve endings whose function may be modulated following
inflammation includes the capsaicin receptor TRPV1 and transducers that detect mechanical stimuli \(^{(218)}\). The precise type of afferent sensory nerve responsible for human cough is unknown but suspected candidates include: rapidly adapting receptors (RARs) located on A\(\delta\)-type nerves (chemical and mechanical sensitivity), small non-myelinated C-fibres (chemosensitive) and a specific sodium ATPase receptor expressed from mechanically sensitive afferents innervating the larynx, trachea, and mainstem bronchi \(^{(214, 216)}\).

### 1.6.1.2 Cough Nerve Fibres

**Rapidly Adapting Receptors (RARs)**

RARs discharge during lung inflation and sometimes during the deflation phase of a respiratory cycle, becoming more active as the rate and volume of inflation and/or deflation increases \(^{(219)}\). RARs are relatively insensitive to direct chemical stimuli; however bronchospasm and obstruction resulting from mucus secretion or oedema evoked by substances such as capsaicin, substance P and bradykinin \(^{(214, 220)}\) initiates or copies the mechanical consequences of lung inhalation and deflation. The evidence that RARs cause cough is based on their localisation at the sites of the airway most sensitive for cough (larynx and carina), that mechanical and chemical stimuli causing cough also excites them, and that many of the observed epithelial nonmyelinated fibres are connected to myelinated vagal trunk fibres \(^{(221)}\).

**C-fibres**

Bronchopulmonary C-fibres are relatively insensitive to mechanical stimulation and lung inflation, but strongly responsive to bradykinin and capsaicin. Bradykinin and capsaicin-evoked activation of their nerve endings in the airways is enhanced by PGE2,
adrenaline and adenosine, bronchodilators that largely oppose the end organ effects
associated with these stimuli and the resulting C-fibre activation \(^{(214, 219, 222)}\). Airway
C fibres can be subdivided into bronchial and pulmonary C-fibres and it is more
plausible that the bronchial C-fibre receptors mediate cough. Apart from being site
appropriate, they respond to the same mediators and irritants as do RARs and
pulmonary C-fibre receptors \(^{(223)}\). Activation of C-fibre receptors in the airway releases
sensory neuropeptides which cause neurogenic inflammation \(^{(221)}\). Experiments with
capsaicin are the basis for the claim that C-fibre receptors may cause cough. When
capsaicin is given as an aerosol it is a powerful tussigenic agent in humans and other
animals. It is not specific for C-fibre receptors but systemically it stimulates RARs and
is the most plausible hypothesis that it is causing cough in this way \(^{(221)}\).

*Tachykinins and cough*

Capsaicin may act on both RARS and C-fibre receptors that release Tachykinins from
the latter further stimulating RARs, which enhances cough. The general view that
tachykinins are involved in cough is supported by the observation that tachykinin
antagonists block the cough caused by citric acid and cigarette smoke, and that
substance P-antagonists block the cough caused by bradykinin in patients during
infection with pertussis or chronic obstructive pulmonary disease \(^{(221)}\).

*RAR/C-fibre receptor interactions in cough*

The primary sensory pathways for cough are due to RARs in the larynx and the
tracheobronchial tree. C-fibre receptors cause neurogenic inflammation and inhibit
cough by a central gating mechanism through their own reflex action. Additionally
tachykinins released from the C-fibre receptors can activate the RARs resulting in a
complex mechanism of interaction. The degree of activation of C-fibre receptors and RARs by the tussive stimuli and the central inhibition of cough by C-fibre reflex action is the end result (221).

Capsaicin cough challenge data confirms the observation that subjects with dry cough show enhanced capsaicin sensitivity that normalises after successful treatment of the cough. This is true for all treatment groups and confirms that hypersensitivity of afferent cough nerves is an important pathogenic mechanism in patients with persistent non-productive cough regardless of the specific aetiology.

1.6.1.3 Cough Receptors

Vanilloid Receptor (TRPV1)

The capsaicin (or vanilloid) receptor, TRPV1, is a member of the transient receptor potential (TRP) gene family of ion channel subunits (224). Immunohistochemical studies confirm the presence of TRPV1 in airway sensory fibres lining the trachea, bronchi, and alveoli, as well as the larynx (157, 225, 226).

Capsaicin induces cough by stimulation of the TRPV1 (157). TRPV1 is considered to be the major pharmacological receptor of the cough reflex in both man and animals (156). TRPV1 is not expressed by RAR-type fibres in guinea-pig airways (227), and therefore the extent to which capsaicin can lead to RAR activation in vivo is likely through indirect means.

TRPV1 has the unique ability to be able to integrate disparate stimuli - i.e. the action of one TRPV1 agonist potentiates the action of the other (228). Stimulation of TRPV1 by agonists such as protons and heat leads to depolarisation of afferent sensory nerves
and the central appreciation of the stimulus (158). Integration is likely to be an important mechanism of increased sensitivity of nociceptive airway afferents involved in cough.

In the airways the physiological effect of TRPV1 activation is demonstrated by the response to inhalation of capsaicin and resiniferatoxin, the two most potent protussive agents known (229). There is a fivefold increase in the number of nerve profiles that express TRPV1 in airway biopsies from subjects with CC compared with normal controls (157). TRPV1 also has a role in the inflammatory cascade. Neurogenic inflammation triggered by activation of TRPV1 causes airway oedema, inflammatory cell infiltration, and bronchial hyperresponsiveness. Mitchell et al (158) compared the expression of TRPV1 in normal human airways with those from subjects with CC and found that there is up regulation in airways smooth muscle in disease. This increased expression appeared to be intracellular with TRPV1 being located in a thapsigargin insensitive compartment. The authors concluded that an increase in TRPV1 activity might have a role in the airway hypersensitivity seen in CC.

**TRPA Receptor**

Following the discovery of TRPV1, additional TRP channel subunits have been identified in sensory neurons. Transient receptor potential, ankyriol-1 (TRPA1) is the only member of the TRPA sub-branch of the TRP gene family in mammals, characterised by a large number of NH2-terminal ankyrin repeats.

In sensory neurons, TRPA1 was first identified as a cold-sensitive ion channel in a small subset (<4%) of peptidergic sensory neurons (230). However, later studies showed that TRPA1 expression is more widespread, encompassing 20–35% of sensory neurons (231, 232). Pharmacological experiments revealed that TRPA1 is the sensory
neuronal receptor for mustard oil (allyl isothiocyanate), the pungent ingredient in mustard and wasabi.

Similar to capsaicin, mustard oil activates peripheral C-fibres, causing acute pain, thermal and mechanical hyperalgesia, and neurogenic inflammation (233, 234). Functional imaging and electrophysiological studies have revealed that TRPA1 is expressed in a subpopulation of TRPV1-expressing C-fibre neurons and is permeable to calcium ions. A recent study identified hypochlorite (OCl–), the oxidative mediator of the potent airway irritant, chlorine gas, as a potent agonist of TRPA1. TRPA1 is essential for irritant induced airway responses in conscious animals in vivo (235). Calcium ions are essential co-activators of TRPA1 (231, 232, 236–239). Removal of extracellular and intracellular Ca2+ dramatically reduces the potency of mustard oil to activate TRPA1 and slows channel activation kinetics (231, 232).

Bradykinin is a potent tussive agent and bronchoconstrictor in people with asthma and is elevated in the serum and airway fluid of asthma and rhinitis subjects (240, 241). Blockade of ACE, an enzyme involved in degradation of bradykinin, results in heightened bradykinin levels, causing CC as a side effect in subjects treated with ACE inhibitors for hypertension (242). TRPV1 is crucial for bradykinin-induced excitation of vagal airway fibres. In TRPV1-deficient mice, bradykinin-induced fibre excitation is diminished but not completely abrogated (243, 244). Similar to TRPV1, TRPA1 is both activated and sensitised through inflammatory receptor pathways (231, 233, 245). Activation of bradykinin or histamine receptors induces TRPA1 activity, both in heterologous cells and native sensory neurons cultured from trigeminal ganglia (233, 245, 246). The role of TRPA1 in chemical hypersensitivity may extend to other less clearly defined
conditions, including sensory hyperreactivity (SHR) and multiple chemical sensitivity (MCS) \(^{(247, 248)}\). The studies summarised above provide strong support for a mechanism of activation of TRPA1 by covalent modification through reactive irritants. This mechanism implies that dose-response relationships and activation kinetics of TRPA1 do not conform to standard pharmacological paradigms and are highly dependent on the chemical status of the cellular and tissue environment.

By probing TRPA1 responsiveness with the irreversible cysteine-reactive agent, N-methylmaleimide, Hinman et al \(^{(249)}\) found that TRPA1 can be locked into a constitutively active state, indicating saturation of a reactive site. Through systematic mutation of candidate acceptor sites, these authors identified an essential cluster of cysteine and lysine residues in the cytosolic NH2-terminus of TRPA1. When non-reactive residues were introduced at these sites, TRPA1 became unresponsive to mustard oil \(^{(249)}\). The same sites were also found to be essential for activation of TRPA1 by chlorine, hydrogen peroxide and unsaturated aldehydes \(^{(235, 250, 251)}\). A separate study discovered that, although almost all cytosolic cysteine residues in TRPA1 were modified following chemical treatment with cysteine reactive agents, three cysteine residues were crucial for channel activation \(^{(159)}\).

TRPA1 is also activated by cinnamaldehyde, the active ingredient of cinnamon. In a recent study by Farugi and Morice \(^{(252)}\) inhalation of nebulised cinnamaldehyde was demonstrated to experimentally induce cough. The authors concluded that TRPA1 seemed to be a major site for chemesthetic sensation in the airways and important in the evaluation of the cough reflex.
An increased cough reflex usually represents enhanced cough sensitivity in the proximal upper airways, where cough receptors are usually located \(^{(253)}\). A chronic dry cough presents with an increased cough reflex which may be associated with viral URTI, PNDS or GORD, or without obvious cause \(^{(254, 255)}\). Acute and CC are both associated with airway inflammation responsible for the sensitisation of cough receptors \(^{(256)}\). Acute viral infection induces lower airway inflammation \(^{(257)}\) which may persist long after the infection has resolved \(^{(258)}\) [Figure 1:5].

**Figure 1:5 Proposed changes in cough reflex sensitivity following viral upper respiratory tract infection**

Following a viral infection, the cough reflex becomes hyperreactive and remains in this activated state for a variable period of time (two-three weeks) during which cough may be provoked by innocuous stimuli such as exposure to scents, aerosols and changes in air temperature. In the majority of subjects, the hyperreactivity diminishes and the cough reflex responsiveness returns to its baseline state. However, in some circumstances this hypersensitized state persists long after the initial triggering event leading to a chronic cough state. Adapted from McGarvey et al (2009) \(^{(256)}\).

**Effect of Airway Inflammation**

Bronchial biopsies from patients with CC have demonstrated inflammatory changes including damaged bronchial epithelial, basement thickening and a chronic
inflammatory infiltrate which is mainly lymphocytic (259). Eosinophils, mast cells and their respective mediators have been detected in both airway lavage samples and induced sputum from chronic coughers (69, 260, 261). Evidence to support the notion that airway inflammation influences neural function and in so doing may sensitize the cough reflex has been demonstrated in guinea pigs exposed to sulphur dioxide (262).

Sulphur dioxide an environmental pollutant is known to induce airway inflammation, which can be blocked by the anti-inflammatory agent dexamethasone. Allergic inflammation has been shown to induce expression of neuropeptides in neurones that would not typically express these inflammatory proteins (227). While this underlies the powerful influence of inflammation on neural function the precise mechanism and specific inflammatory cells and mediators responsible are not completely understood. The expression of receptors for a number of mediators including histamine, tryptase, TNF-α, IL-1β, IL-6, IL-8, bradykinin and PGE2 from a variety of airway cells including neutrophils, macrophages, bronchial epithelium and mast cells suggests an important role for non-neuronal airway cells in cough reflex sensitisation (256).

Mast cells release histamine and tryptase, both of which have been detected in the airways of cough patients (69, 260). Neuropeptides such as substance P and neurokinin A are elevated in the airways of asthmatic patients with cough (263) and airway levels of calcitonin gene related peptide (CGRP) are positively correlated with capsaicin cough reflex sensitivity (264).
Eosinophils are also a potential source of inflammatory mediators that may modify cough. Eosinophils selectively localise to airway nerves of humans promoting the release of eosinophil granule proteins \(^{(265, 266)}\). Both bradykinin and PGE2 inhalation is known to sensitishe the cough reflex \(^{(267)}\) by acting on B1/B2 receptors on the nociceptor terminal and via the protein kinase C (PKC) pathway sensitisises TRPV1 channels \(^{(268)}\) [Table 1.6].

**Figure 1.6 Proposed schematic of the direct and indirect activation of nociceptors on neuronal and non-neuronal cells in the airway by chemical, thermal and mechanical stimuli \(^{(256)}\).**


*Figure removed from online repository version due to copyright laws.*

As the bronchial epithelium is the first point of contact for noxious stimuli to the airway cells storing and releasing inflammatory mediators such as NGF have been demonstrated to increase capsaicin cough sensitivity in the airway of patients with pulmonary fibrosis \(^{(269)}\). Subjects with airway sensory hyperreactivity to scents and chemicals have been found to have significantly greater increases in nasal lavage NGF levels than healthy controls \(^{(270)}\).

*Capsaicin sensitivity*

Capsaicin, which is present in red pepper, excites TRPV1 receptors on certain afferent C-fibre nerves of the respiratory mucosa at the level of the larynx and has been used to induce cough in provocation challenges \(^{(3)}\). On inhalation of capsaicin the glottis...
immediately closes to protect the lower airways and coughing rapidly follows closure
of the airway (271). Capsaicin has an immediate dose-dependent effect and the cough
ceases promptly after the stimulus has been removed (272). A possible explanation for
the rapid onset and short duration of the cough response to inhaled capsaicin is that
capsaicin triggers coughing as soon as it comes into contact with the larynx and that
cough removes capsaicin contaminating mucus from the larynx and expels any
suspended capsaicin as nebulised particles in the dead space air (271). In the non-
coughing population there is little variability in the cough reflex sensitivity, ie, very
few people do not cough or have very sensitive reflexes. Patients with stable disease
without cough, chiefly asthma, have a normal reflex (114); however, if the disease is
associated with dry cough then an increased sensitivity of the reflex has been
observed (254) [Figure 1:7].

![Figure 1:7](image)

**Figure 1:7** The log concentration (µmol/L) of capsaicin (C5, ■) that caused at least five
coughs in subjects with no cough, dry cough and productive cough
Data significantly different in the dry cough group compared to the other groups, *p<0.01) Figure adapted
from Choudry and Fuller (1992) (254)

In a study by Choudry and Fuller (254) the sensitivity of the cough reflex was measured
in 363 individuals with capsaicin as the stimulant. A questionnaire was used to divide
subjects into three groups: non-coughing controls; subjects with dry cough; and
subjects with productive cough. The subjects with dry cough were significantly more
sensitive to inhaled capsaicin than the other two groups while no significant difference
was observed between the control group and the productive cough group. Some
differences were found when subgroups were examined within the dry cough and
productive cough groups. Subjects with post-nasal drip were found to have a normal
sensitivity of the cough reflex and were, therefore, different from the remainder of
subjects with dry cough. Subjects in the productive cough group with bronchiectasis
and current infection showed an increase in the sensitivity of their cough reflex. It was
concluded that cough can occur in association with either excess mucus production
leading to productive cough or an increase in the sensitivity of the cough reflex,
possibly leading to non-productive cough. Twenty seven of thirty three subjects with
post nasal drip and CC studied by Cho et al (273) were also found to have normal cough
sensitivity to capsaicin.

Kastelik et al (274) tested the hypothesis that the sensitivity of the cough reflex is greater
in female compared with male subjects with CC. They investigated this by inhalation
cough challenges with capsaicin in a large group (101, 60 female) of subjects with CC.
The concentration of capsaicin causing two (C2) and five (C5) coughs were calculated.
Capsaicin cough reflex sensitivity was found to be significantly heightened for female
cough subjects compared with male cough subjects. It was concluded that there is a
gender difference in cough sensitivity in subjects with CC, as previously reported in
healthy volunteers (275, 276), and that this may explain the female preponderance in cough
clinics. The explanation for the increase in cough reflex sensitivity among females is
unknown. However, one possible explanation is an endocrine influence on the cough reflex \(^{(274)}\). There is also evidence of persistent airway inflammation, with increased numbers of neutrophils, eosinophils, and mast cells in subjects with CC \(^{(143, 259, 260)}\). Studies have described the expression of oestrogen and progesterone receptors on inflammatory cells, including neutrophils \(^{(277)}\), eosinophils \(^{(278)}\), and mast cells \(^{(279)}\). Sex hormones may therefore regulate airway inflammation and influence evoked cough. However, reports that postmenopausal women have greater cough reflex sensitivity than premenopausal women \(^{(276)}\), and more frequently suffer from ACE-I induced cough \(^{(54)}\) would argue against this hypothesis.

Nieto et al \(^{(280)}\) assessed the use of capsaicin testing in the differential diagnosis of non-productive causes of CC and the effects of treatment on this reflex. The 101 participants with CC consisted of 54 with asthma, 35 with GORD and 12 with PNDS and these were compared to 86 healthy volunteers. Spirometry, bronchoprovocation test with histamine and cough challenge with capsaicin were performed in all subjects. CC subjects were then treated for 3 months according to the cause of the cough and capsaicin testing was again performed to determine the effects of the treatment. Consistent with the Kastelik et al \(^{(274)}\) study women with CC were found to be more sensitive to cough challenge than men. Capsaicin sensitivity measured as C2 and C5 (capsaicin concentrations that elicited two (C2) and five or more coughs (C5)) was significantly heightened in subjects with asthma or GORD than in subjects with PNDS as the origin of their cough. Of interest is the finding that cough sensitivity did not improve significantly in most subjects with asthma or GORD despite adequate medical treatment for these conditions. The discriminative value of capsaicin testing to
differentiate healthy subjects from CC subjects with asthma or GORD was found to be poor and therefore the authors concluded that while capsaicin cough sensitivity testing is a safe and reproducible tool in the study of CC, its usefulness for the management and differential diagnosis is limited. Although there was a favourable clinical response to treatment in both the CC with asthma and CC with GORD subjects, the persistence of cough reflex sensitivity maybe a valuable objective parameter to continue with treatment until a normal sensitivity has been attained (280).

More recently a study by Birring et al (65) assessed cough frequency as measured by an automated ambulatory digital cough monitor called the Leicester Cough Monitor and related this to capsaicin cough sensitivity and cough specific health status measured by questionnaire. The cough frequency measured as cough counts/hour were found to be repeatable and correlated significantly with cough health status and capsaicin cough sensitivity in subjects with CC but not in healthy controls. A difference in cough frequency between different diagnostic groups or gender in subjects with CC was not found. However, as the patient numbers in this study were small and it was not the authors aim to study disease specific cough frequency it was possible that differences could have been missed due to lack of power. There was a positive relationship found between cough frequency and capsaicin cough sensitivity measured as C2 and C5 (65).

Haque et al (6) utilised the capsaicin cough sensitivity test to compare the clinical characteristics of patients with CIC to those of patients with cough in whom a diagnosis had been established. Of the 100 CC subjects, 71% were female with median cough duration of 48 months. The primary diagnoses were CIC (42%), PNDS (22%), GORD (16%), asthma (7%), and others (13%). The CIC subjects had a longer median
duration of cough (72 months vs 24 months) and were more likely to report an upper respiratory tract infection as the initial trigger of their cough. Capsaicin sensitivity testing was again measured as C5 (the lowest capsaicin concentration to elicit five or more coughs) and was found to be significantly heightened in the CIC group compared with the non-CIC group. These subjects clearly described symptoms of exquisitely sensitive cough reflexes. Crumbly foods such as bread and biscuits along with strong smells from perfume and cooking trigger their cough. Sometimes laughing or any increase in the rate of breathing was sufficient to cause coughing. This heightened cough sensitivity was objectively demonstrated by the increased capsaicin sensitivity when compared to other diagnosed coughers. While the mechanisms of CIC are unknown, this greatly sensitised cough reflex may be similar to other sensory hyperalgesias, where there is a long-standing reduction in sensory nerve threshold to stimulation \((156, 281)\). This may follow sensory nerve injury, and it is possible that sensory nerves may be damaged during some URTIs. CIC may therefore be a variation of “postviral cough” but with an extremely prolonged clinical course \((6)\). The mechanisms of idiopathic and refractory CC are largely uninvestigated and unknown. A greater understanding of this area is important for diagnosis and the development of effective treatment and its characterization and investigation form part of this thesis.

Patients with CC describe upper airway hypersensitivity on a regular basis. Examples of these are cough precipitated by a change in atmosphere, such as moving from a room of one temperature to another, and hypersensitivity to even minute amounts of irritants such as strong smells, cleaning fluids, perfumes and tobacco smoke \((155)\).
Millqvist (282) showed capsaicin provocation to be an objective method for demonstrating airway sensitivity to chemical irritants in subjects with asthma-like symptoms. Two syndromes that masquerade as asthma are paradoxical vocal fold movement with asthma-like symptoms often induced by exercise (283, 284) and reactive airways dysfunction with asthma-like symptoms after exposure to one or more high concentration chemical irritants (285, 286). Symptoms primarily include heavy breathing, difficulties in getting air into the lungs, pressure or load over the chest, coughing, phlegm, hoarseness, stuffy nose, and eye irritation. Other patients who suffer asthma-like symptoms induced by agents such as perfume, strong scents, and cigarette smoke also complain of these symptoms but without the stuffy nose and eye irritation.

Subjects with asthma-like symptoms coughed more after capsaicin provocation than did healthy subjects and subjects with asthma. Asthma-like symptoms and the increased cough sensitivity in these subjects are induced by a hyperreactive state of the sensory nerve system in the airways (282).

Although the subjects with asthma had cough they did not differ from healthy controls in the cough response, unlike those with asthma-like symptoms. This indicates that the hypersensitivity to methacholine of many asthmatics is not related to sensitivity to all chemical agents. This sensitivity may originate in the sensory nervous system and be due to an increase in sensory nerve cell endings or to a remodulation of the nerve receptor (247).

Cough can depend also upon CNS function, both voluntary and involuntary. Cough that is induced by a reflex from the respiratory tract is hard to control, but it is possible to do so. However, in view of the dose-response effect of the capsaicin provocation and
the blind randomization of the doses, it seems unlikely that subjects with asthma-like symptoms could have influenced the number of coughs voluntarily. The subjects do not have asthma, nor are the pathophysiologic mechanisms of asthma and asthma-like symptoms the same. The results also confirm a previous report in which capsaicin-induced cough in healthy subjects was dose-dependently inhibited by a preceding inhalation of lidocaine (272). The common chemical sense that induces pain and irritation in the eyes and airways by chemical agents is known to depend on trigeminal innervation, and not on stimulation of the olfactory sense (287, 288).

1.6.1.4 Cough Threshold
Cough reflex hyper-sensitivity is an important part of the pathophysiology of CC. Individuals with CC have a sensitised cough reflex (114) whereby cough is evoked by tussive stimuli that are normally sub threshold for initiating the cough reflex (289), or by non-tussive stimuli that do not normally trigger cough. Cough receptors in CC become more easily stimulated and thus respond more readily to lower levels of stimuli. Repeated coughing continues to irritate the airways and stimulate the cough receptors, lowering the threshold for continued coughing.

Cough threshold is defined as the lowest concentration of a chemical irritant such as capsaicin or citric acid that elicits one to several coughs (290, 291). Cough threshold to citric acid has been measured by Wang (291) who demonstrated a reduced cough threshold in subjects with spinal cord injuries. Wang postulated that people with chronic spinal cord injury may have morphological or osmolarity changes in the airway epithelium increasing the exposure of the receptor to chemical irritants thus increasing the vagal afferent or efferent activities.
Confusingly, cough threshold has also been expressed as the lowest dose of capsaicin to elicit two or more coughs (C2) or lowest capsaicin dose to elicit five or more coughs (C5) and appears to be interchangeable with cough reflex and/or cough sensitivity.

Ferrari et al (42) investigated the influence of GORD on cough threshold in subjects with digestive symptoms but free from respiratory involvement. The capsaicin threshold was evaluated by inhalation of increasing doses of capsaicin and expressed as the dose of capsaicin eliciting five coughs (PD5). PD5 was found to be significantly lower in refluxers than in nonrefluxers while there was no difference in airway responsiveness to methacholine between the two groups. Fujimura et al (276) studied the influence of gender on cough threshold to capsaicin. The cough threshold was defined as the lowest concentration of inhaled capsaicin causing five or more coughs. The cough threshold was 3–5 fold lower in females than in males both in young and middle-aged subjects. The results extended their previous findings that females have a lower cough threshold to inhaled tartaric acid than males (292).

1.6.1.5 Cough Suppression

I have already described that cough unlike other respiratory reflexes such as sneezing can be induced voluntarily and therefore can be voluntarily suppressed, at least for a short period (271). Hutchings et al (271) sought to answer several basic questions about voluntary control of cough such as

1. Can cough be totally suppressed by voluntary control or is the control limited to delaying the cough for a few seconds?
2. Is cough suppression possible after inhalation of an irritant such as capsaicin or is suppression restricted to natural cough associated with respiratory tract infection? and,

3. If cough can be suppressed voluntarily then this may be a complicating and uncontrolled variable in cough studies aimed at testing new antitussives.

The mechanism of voluntary suppression was also considered interesting, as it may be this control mechanism that is influenced by antitussives. Hence, the aim of this study was to determine if voluntary suppression of cough was possible after inhalation of capsaicin and to quantify the degree of voluntary suppression relative to a dose-response curve for capsaicin-induced cough. Two capsaicin challenges were given to the healthy volunteers five minutes apart. During one of these challenges the volunteer was allowed to cough when required, and during the other they were asked to suppress cough. In the non-suppressed challenge 23 of the 24 subjects coughed on inhalation of capsaicin while in the suppressed challenge only three of the 24 subjects coughed. It was concluded that based on these results cough induced by inhalation of capsaicin could be voluntarily suppressed. The mechanism of voluntary suppression was not realised from this study but it was suggested that suppression could occur at the level of the brainstem or at the spinal outflow to expiratory muscles (271). As voluntary cough suppression was quantified in a dose-response relationship it was recognised that the mechanism of voluntary control as a point of attack for antitussives (293) is a real possibility.
Eccles (294) proposed that the cerebral cortex plays an important role in the generation of cough and that two different pathways, the voluntary pathway and the reflex pathway, are involved in the control of cough.

It is proposed that the voluntary initiation of cough may be due to a sensation of irritation, caused by physical or chemical irritants. The irritation may also be caused by the presence of inflammatory mediators that cause cough receptor hypersensitivity during acute URTIs (295, 296). A model of the possible cough control mechanism (297), with the voluntary pathway illustrated by green lines is shown below [Figure 1:8].
Irritation of airway receptors may cause reflex cough via a brainstem cough control area. A sensation of irritation may cause cough via higher centres such as the cerebral cortex. Cough can be voluntarily initiated and inhibited via the cerebral cortex that influences cough by two pathways; via the brainstem; and via a descending pathway to the spinal cord. Adapted from Lee et al (2002).

The sensory afferents relay in the respiratory area of the brainstem, and then pass to the cerebral cortex where the sensation of irritation is mediated. By acting centrally on the respiratory area of the brainstem, or at the spinal level, the cerebral cortex may initiate the cough response. This cough may be reduced or abolished by inhibition within the cerebral cortex that suppresses the urge to cough. The degree of inhibition...
may be related to the psychological characteristics of individuals, as there is evidence to show that the ability to suppress cough is influenced by psychological factors such as obsessional mood and symptoms (299). It has been shown that placebo treatment causes a 50% reduction in cough frequency in subjects with common cold (300). This placebo effect may be explained by a mind-body interaction affecting the voluntary component of cough.

Cough may be generated via the reflex pathway (red lines) when the cough stimulus has reached a reflex threshold in the brainstem [Figure 1:8]. During respiratory infections or physical/chemical stimulations, cough can be a mixture of voluntary and reflex cough.

1.6.1.6 Urge to Cough

The urge to cough (UTC) is a component of the brain motivation system that mediates cognitive responses to cough stimuli (301). There are six stages to the cough motivation-to-action system [Figure 1:9, Table 1:7] and these are detailed below.
1. Cough stimulus: cough sensory receptors located throughout the upper respiratory and lower respiratory tract are activated by chemical or mechanical stimuli. These afferents project to central neural structures and trigger a sequence of intrinsic neural events that lead to activation of the “urge” neural system (215, 302).

2. Activation of the neural urge, converts the physical stimuli into a biological urge (the limbic system).
3. The urge to action projects to the cortex where the urge is translated into a targeted desire such as the desire to cough or suppress the cough. The strength of the urge is critical in this process as regardless of the desire, if the urge is of sufficient strength, the cough may be obligatory despite a desire to suppress cough.

4. This stage is the descending neural drive for motor action. Eventually the urge-desire achieves its goal and the individual makes the physical response to satisfy the urge-desire, which can be an attempt to suppress cough, motor production of a cough, or behaviourally modulate the cough (such as covering the mouth).

5. The cough action stimulates a feedback system that provides the CNS with evidence of the motor action. The brain receives evidence or feedback on the pattern of the action and if that action was completed.

6. The feedback projects via a limbic pathway that mediates the affective sense of reward for action. The brain rewards the urge by providing cognitive information to the individual that the right action occurred and rewards the continuance of the action. Alternatively, the reward system signals that the action is sufficient to stop further action, producing a feeling of fulfilment.

Urge to cough is related to three fundamental types of cough:

1. reflex cough,

2. voluntary cough, and

3. behavioural cough.

Urge to cough with reflex cough can be studied by measuring the sensations elicited by a cough stimulus such as inhaled capsaicin. Neural processes with voluntary cough
can be studied using magnitude production cognitive psychometric methods such as asking the patient to produce three individual coughs of varying magnitude or intensity. Cough as a behavioural signal unrelated to airway function is the least investigated type of cognitive cough. Behavioural cough is identified as a nervous cough, anxious cough, or a stress-related cough and is commonly used by people to draw on someone’s attention. Studies of this type of cough require unique experimental methods that include psychological state-trait assessment of the patient \(^{(301)}\).

### 1.7 Treatment

#### 1.7.1 The Anatomic Diagnostic Protocol for Chronic Cough

In 1977, a review by Irwin and colleagues proposed an approach to CC based on the anatomic locations of the receptors and afferent pathways involved in the cough reflex. Using such an approach, Irwin and colleagues reported in 1981 \(^{(120)}\) and again in 1990 \(^{(33)}\) that the cause of CC could be determined 100% of the time and that subsequent cause-specific treatment was almost always successful. From this descriptive series a stepwise diagnostic approach, termed the anatomic-diagnostic protocol (ADP), was recommended by the American College of Chest Physicians in 1998 \(^{(2)}\). Essentially the ADP involves a targeted patient history and physical examination to investigate the possible cause/s of their cough based on knowledge of the afferent cough reflex pathway, and using this information to initiate a stepwise treatment management program until there is resolution of the cough symptoms [Figure 1:10].

*Figure 1:10 Guidelines for evaluating chronic cough in immunocompetent adults \(^{(2)}\)*

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1.7.1.1 Investigation and treatment for common causes of CC according to the Anatomic Diagnostic Protocol

Post Nasal Drip Syndrome: As described in the ADP, either singly or in combination with other conditions, PNDS is the most common cause of CC for which patients seek medical attention. The symptoms and signs of PNDS are nonspecific; therefore, a definitive diagnosis of PNDS-induced cough cannot be made from history and physical examination alone. A favourable response to specific therapy for PNDS, with resolution of cough, is a crucial step in confirming that PNDS is present and is the cause of the cough. Therapy should be directed at the underlying diagnosis which may include Allergic Rhinitis, Perennial Nonallergic Rhinitis, Vasomotor Rhinitis, Post Infectious Rhinitis and Bacterial Sinusitis. However most guidelines recommend empirical therapy of PNDS with first generation sedating antihistamines in combination with sympathomimetic decongestants (2), although this is primarily based on descriptive, uncontrolled studies (20). If a specific diagnosis is made then a specific therapy is indicated. Cough secondary to allergic rhinitis responds to allergen avoidance, intranasal steroids, and oral leukotriene antagonists. Post infectious rhinitis cough responds to dextromethorphan and azatidine (303), Vasomotor rhinitis responds to antihistamines and inhaled ipatropium bromide, while antibiotics have been found effective in alleviating cough to bacterial sinusitis (18).
Asthma: Cough occurs in virtually all asthmatics as part of the symptom complex of asthma. In addition, cough can be the sole presenting symptom of asthma, a condition termed cough-variant asthma. In prospective descriptive studies of subjects with CC due to asthma cough has been the only asthma symptom from 6.5 to 57% of the time. Combined with the presence of variable airflow obstruction and airway hyperresponsiveness a diagnosis of cough variant asthma is likely but only confirmed when the cough resolves with asthma medications. The treatment of cough variant asthma is the same as the treatment for asthma presenting with other symptoms. Temporary relief from the cough can be obtained by using inhaled β₂-agonists. Nedocromil sodium also has been shown in a randomized, double-blind, placebo-controlled study to be effective in treating cough in asthmatics (304). However, the most benefit is likely to be obtained with corticosteroids, either oral corticosteroids initially followed by inhaled corticosteroids if the symptoms are severe, or with inhaled corticosteroids alone, together with inhaled β₂-agonists to relieve acute symptoms. The inhaled medications should be delivered from a dry powder device, or pressurized metered-dose inhaler (pMDI) together with a valved holding chamber (spacer). Inhalation from a pMDI alone can exacerbate cough, this side effect may disappear by changing to another corticosteroid formulation. The maximal symptomatic relief may take up to 8 weeks. Ongoing corticosteroid treatment is guided by assessments of asthma control.

Gastroesophageal Reflux Disease (GORD): has long been associated with pulmonary symptoms and diseases, many of which present with cough. GORD has been shown in many studies to be one of the most common causes of CC in all age groups (13, 21, 33, 53, 77).
Twenty-four hour oesophageal pH monitoring is the most sensitive and specific test for GORD. Subjects with normal standard parameters may still have reflux as a cause of cough if a temporal relationship exists. When 24-hour oesophageal pH monitoring cannot be done, an empiric trial of antireflux medication is appropriate when GORD is suspected as a cause of cough. Because consistently effective therapy for GORD-induced CC is not known, initial treatment should include diet and lifestyle changes in addition to medication.

Cough due to ACEIs is a side effect of this class of medication and not dose-related. There is no laboratory test to predict who has ACEI-induced cough, therefore the diagnosis is considered in any patient who has a cough while taking an ACEI. Definitive treatment of ACEI-induced cough is discontinuation of the drug.

Hargreaves and Benson (305) studied the effects of inhaled sodium cromoglycate in 10 subjects with ACE-inhibitor cough in a double-blind crossover study. After a 2-week run-in, subjects were randomised to either 2 weeks’ inhaled sodium cromoglycate or placebo followed by a further 2 weeks on the other treatment. Subjects kept a cough diary during each study period. Cough severity was recorded on a scale from 0 to 12. At the end of each study period the cough threshold to inhaled capsaicin was measured. Nine subjects reported a reduction in cough after sodium cromoglycate. Overall, there was a significant 50% reduction in cough score during the treatment period compared with placebo. Median cough scores improved immediately after the introduction of cromoglycate and continued to improve throughout the treatment period. There was a significant relation between initial cough severity and benefit from sodium cromoglycate; and cough-reflex sensitivity to inhaled capsaicin was
significantly reduced. The authors concluded that inhaled sodium cromoglycate is an effective treatment for ACE-inhibitor cough and that its effect may be due to suppression of afferent vagal activity.

Postinfectious cough is a diagnosis of exclusion; it should be considered when a patient complains only of cough after a respiratory tract infection and has a normal chest radiograph. Postinfectious cough ultimately resolves spontaneously over time. Oral or inhaled corticosteroids, or ipratropium bromide may attenuate the cough in postinfectious cough.

Cough is a primary feature of chronic bronchitis and its treatment should be directed to reduction of sputum production and airway inflammation (eg, smoking cessation and removal of environmental irritants). Ipratropium can decrease sputum production and cough.

Habit and psychogenic cough are diagnoses of exclusion. The character of the cough such as honking is not diagnostically helpful in adults. After exclusion of other causes, psychological counselling and short term antitussive therapy may be appropriate treatments.

1.7.1.2 Modifications to the Anatomic Diagnostic Protocol for Chronic Cough

Several modifications to the ADP have been proposed, largely seeking to simplify the assessment and management of CC. Pratter et al \(^{13}\) evaluated a sequential, stepped approach to CC, emphasising initial treatment of all patients with an antihistamine-decongestant for possible PNDS caused by rhinitis. They also determined the value of routine bronchoprovocation challenge for predicting whether asthma was a causative...
factor in cough. The outcome of this study was a marked improvement (mean 3.1 weeks) and resolution (7.1 weeks) in cough, with resolution resulting in 96% of subjects. The antihistamine-decongestant therapy was beneficial in 39 of 45 subjects. Bronchoprovocation challenge was found to be useful in evaluating subjects with CC but could be delayed until the initial response to the antihistamine-decongestant therapy had been assessed.

More recently, Kastelik et al\(^{(306)}\) developed a novel algorithm for the management of CC, in which an assessment of clinical probability of disease determined the need to proceed to investigation. Of the 131 referred subjects with the principal presenting symptom of cough (duration >8 weeks), a cause of cough was established in 93% of cases. The most frequent diagnoses were asthma (24%), GORD (22%), post-viral cough (8%), bronchiectasis (8%) and interstitial lung disease (8%). A small proportion (<8%) of subjects had multiple causes of cough. Treatment was commenced based upon the clinical probability of asthma, GORD or rhinosinusitis being present. This was a central feature differentiating this work from previous strategies. Thus, when there was a high probability of asthma, GORD or rhinosinusitis, subjects proceeded immediately to therapeutic trials. In contrast, when the clinical probability of these disorders were low, subjects underwent investigations to detect a cause of cough and treatment was commenced on the basis of abnormal results. Use of this algorithm resulted in identification of the cause of cough and successful treatment in the large majority of cases [Table 1:8].
Table 1: Causes of chronic cough in order of decreasing frequency


Table removed from online repository version due to copyright laws.

The pattern of diagnoses reached in this study differed from several previously published studies. Particularly it was found that asthma, GORD and rhinitis were present together in only about half of the subjects. It was also found that other forms of pulmonary disease (primarily bronchiectasis, interstitial lung disease and COPD) explained >20% of cases, and that post-viral cough and ACE inhibitor therapy were also relatively common causes of CC. What is consistent with other reports is that only a small proportion (8%) of subjects were found to have multiple causes of CC. Cough was categorised as idiopathic on only 9 occasions.

Yu et al evaluated sequential empiric therapy in the management of CC in a Chinese population. The therapies were administered in a sequential order based on the prevalence of CC due to PNDS, asthma and GORD. Consequently, first line therapy was administered as antihistamine and bronchodilator (to treat PNDS and asthma). Second-line therapy consisted of oral corticosteroids (prednisone), 25 mg once a day for 1 week, followed by inhaled budesonide, 200 mg twice a day, in those subjects whose cough showed a favourable response to the oral corticosteroid. If improvement, but not complete resolution of the cough occurred within 4 weeks of the first step of the treatment, then the third step was directly combined with the first step without using the second step. The third line of therapy was directed at GORD with a
proton pump inhibitor and prokinetic agent. The therapy was discontinued if the symptom failed to improve after 8 weeks with the third step of the treatment [Figure 1:11]. This approach had an overall success rate of 88%, and the cough was controlled in <4 weeks in 79% of subjects. No side effects were reported.

**Figure 1:11 Algorithm for sequential three-step empirical therapy and effectiveness by step in 102 subjects with chronic cough**


*Figure removed from online repository version due to copyright laws.*

These approaches to CC are based around the ADP, and while such an approach and its modifications have not been subjected to randomised trials to establish the efficacy, in case series the efficacy appears high. The modifications to the ADP can lead to successful control of cough in most patients, while offering efficiency in terms of both time and reduced use of investigations/laboratory testing.

**1.7.2 Chronic Cough Guidelines**

The management approaches to CC have been systematised in clinical practice guidelines published in several countries. These guidelines seek to present and evaluate the best evidence for cough management, as well as offering a standardised approach to investigation and management of CC.

**1.7.2.1 ACCP Evidence-Based Clinical Practice Guidelines**

The American College of Chest Physicians evaluated each component of the ADP and provided a set of user-friendly guides for clinical practice on the investigation and treatment of cough. Each of these guidelines was based on a comprehensive review of
the literature using specific medical subject headings. For example, for the guideline on postinfectious cough (117) the terms “cough”, “postinfectious cough”, “post viral cough” “Bordetella pertussis”, “pertussis infection” and “whooping cough” were used.

Generally, each guideline detailed prevalence, diagnosis and treatment recommendations for each of the major causes of cough. There are twenty eight individual guidelines in this series (1, 10, 18, 51, 101, 117, 191, 199, 303, 310-328) from the ACCP concerning cough. Each guideline included a recommendation grading, level of evidence, and benefit to the patient.

1.7.2.2 CICADA: Cough in Children and Adults: Diagnosis and Assessment: Australian Cough Guidelines Summary Statement.

The Australian Cough guidelines “CICADA” have recently been published (329). CICADA is a clinical guideline for the assessment and management of persistent cough in children and adults. It was developed by a multidisciplinary expert committee (Allied Health/Otolaryngology/Respiratory and Psychology) after a needs assessment by clinicians. CICADA’s recommendations utilise the principles of evidence-based medicine and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (330) to determine the strength of treatment recommendations made in guidelines as either strong, weak, or “no specific recommendation“. Based on an assessment of the strength of evidence, and possible adverse effects and costs of using the therapy, the CICADA expert panel used the GRADE system to determine the strength of cough treatment recommendations [Table 1:9]. The combination of adult and paediatric populations in the one guideline and the
addition of newer conditions such as obstructive sleep apnoea and vocal cord
dysfunction (PVFM) as causes of specific cough are unique.

<table>
<thead>
<tr>
<th>In CHILDREN</th>
<th>Recommended treatment/approach</th>
<th>Strength of recommendation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cough types</td>
<td>Cessation of parental smoking</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with allergic rhinitis</td>
<td>According to current rhinitis management guidelines, involving topical nasal corticosteroids, antihistamines and allergen management</td>
<td>Weak</td>
</tr>
<tr>
<td>Cough with obstructive sleep apnoea</td>
<td>Tonsillectomy and adenoidectomy</td>
<td>Weak</td>
</tr>
<tr>
<td>Cough with asthma</td>
<td>According to current asthma management guidelines, involving education, self-management, inhaled bronchodilators and inhaled corticosteroids</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with protracted bacterial bronchitis</td>
<td>Medium-term antibiotic therapy (2–6 weeks) for protracted bacterial bronchitis</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with GORD</td>
<td>Empirical trial of high-dose PPI therapy (eg, any standard-dose PPI twice daily for 8–12 weeks) if there is a reasonable suspicion that GORD may be contributing to chronic cough</td>
<td>NSR</td>
</tr>
<tr>
<td>Non-specific or refractory cough</td>
<td>Laparoscopic fundoplication for chronic cough</td>
<td>Strong recommendation against surgery</td>
</tr>
<tr>
<td></td>
<td>Address patient/parental stress and concerns</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Address exacerbating factors</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Minimise use of medications other than demulcents such as honey (if no contraindications to its use exist)</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Adopt counsel, watch, wait and review approach</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Empirical trial of inhaled corticosteroid therapy</td>
<td>NSR</td>
</tr>
<tr>
<td></td>
<td>Empirical trial of PPIs</td>
<td>NSR</td>
</tr>
<tr>
<td></td>
<td>Speech pathology techniques designed to relieve glottal constriction during inspiration and to recognise and alter the response to precipitants</td>
<td>NSR</td>
</tr>
<tr>
<td></td>
<td>Antitussive therapy with narcotics</td>
<td>Strong recommendation against use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In ADULTS</th>
<th>Recommended treatment/approach</th>
<th>Strength of recommendation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough with allergic rhinitis</td>
<td>According to current rhinitis management guidelines, involving topical nasal corticosteroids, antihistamines and allergen management</td>
<td>Weak</td>
</tr>
<tr>
<td>Cough with chronic rhinosinusitis</td>
<td>According to current rhinosinusitis management guidelines, involving topical nasal corticosteroids, antibiotics and non-specific therapy</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with vocal cord dysfunction</td>
<td>Medical management of comorbid conditions (eg, asthma, rhinosinusitis, GORD, use of ACE inhibitors)</td>
<td>Weak</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td>Recommendation</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Cough with obstructive sleep apnoea</td>
<td>Nasal continuous positive airway pressure</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with asthma</td>
<td>According to current asthma management guidelines, involving education, self-management, inhaled bronchodilators and inhaled corticosteroids</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with eosinophilic bronchitis</td>
<td>Inhaled corticosteroid therapy for 2–4 weeks</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with protracted bacterial bronchitis</td>
<td>Medium-term antibiotic therapy (2–6 weeks) for protracted bacterial bronchitis</td>
<td>Strong</td>
</tr>
<tr>
<td>Cough with GORD</td>
<td>Empirical trial of high-dose PPI therapy (eg, any standard-dose PPI twice daily for 8–12 weeks) if there is a reasonable suspicion that GORD may be contributing to chronic cough</td>
<td>Strong</td>
</tr>
<tr>
<td>Non-specific and refractory cough</td>
<td>Laparoscopic fundoplication for chronic cough</td>
<td>NSR</td>
</tr>
<tr>
<td></td>
<td>Address patient stress and concerns</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Address exacerbating factors</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Empirical trial of inhaled corticosteroid therapy</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Empirical trial of PPIs</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Speech pathology techniques designed to relieve glottal constriction during inspiration and to recognise and alter the response to precipitants</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Antitussive therapy with narcotics</td>
<td>NSR</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme. GORD = gastro-oesophageal reflux disease. NSR = no specific recommendation. PPI = proton-pump inhibitor. * The treatment recommendation refers to the efficacy of treatment for cough occurring in association with the conditions specified. † The strength of each recommendation was classified by the Cough in Children and Adults: Diagnosis and Assessment panel according to the GRADE system.

Table reproduced with permission from Gibson et al (2010) (329).

1.7.3 Psychological interventions for Chronic Cough

Psychological intervention studies for the treatment of CC have been primarily limited to case studies and are typically used when the cough is considered psychogenic. There has been no uniformity to the psychological approaches used to treat CC. Examples of psychological approaches include aversion therapy such as mild electric shock (331, 332), and suggestion therapy whereby the clinician informed the patient that the cough was a habit unrelated to any physical illness, and that it must cease (333, 334). Other techniques
have included biofeedback of air flow and desensitisation to airflow by breathing through a straw.

The outcomes of most psychological approaches to CC have been positive. The study by Creer et al reported total suppression of the cough after treatment. Conversely, the study by Alexander et al reported a significant increase in the cough and hostility from the patient requiring subsequent modification to the program.

There are however several limitations to studies reporting psychological approaches to CC. Firstly, the validity of the diagnosis of psychogenic cough has not been confirmed and many studies failed to demonstrate that psychological or psychiatric issues were implicated in the pathogenesis of cough. One case study diagnosed a patient with psychogenic cough because he coughed in response to saline, which was considered a physiological substance. Secondly, there is considerable controversy surrounding the use of aversive procedures when non-aversive procedures have been empirically validated as viable alternatives. Finally, these studies included confounding variables, did not use control groups, and provided limited data on pre- and post-treatment assessments.

1.7.4 Speech Language Pathology Treatment for Chronic Cough
Speech language pathology intervention for CC addresses symptoms rather than the underlying cause. The aim of speech language pathology management of CC is to teach individuals to voluntarily suppress the cough, to reduce laryngeal irritation that could exacerbate the cough and to optimise vocal behaviour. Speech language pathologists manage a small subset of the total population with CC as individuals with
CC are generally referred to speech language pathology once the cough is deemed refractory to medical treatment.

One of the first reports of speech language pathology management for CC was by Gay et al (339) who utilised a treatment program involving speech therapy, relaxation and psychotherapy in four subjects with psychogenic habit cough. A critical component of the treatment program was redefinition of the illness to encourage subjects to relinquish the notion of an organic cause. The subjects who accepted their diagnosis demonstrated reduced hospitalisations, reduced corticosteroid use and improvements in socialisation and happiness. One patient did not accept the CC diagnosis and required rehospitalisation for the cough and respiratory symptoms. The authors claimed that medical personnel should emphasise that behavioural approaches such as those used by speech language pathologists are specific treatments for CC; otherwise, subjects will feel unconvinced and will then repeatedly seek further medications.

Blager et al (340) reported a similar treatment program and applied techniques such as diaphragmatic breathing, laryngeal tension reduction and psychotherapy in four subjects with chronic habit cough. Two subjects were fully compliant with all aspects of the program while a further two completed the psychotherapy component without the full speech language pathology component. Following treatment, all subjects experienced a reduction in the severity of their coughing attacks and were able to cease taking steroid medication. However, the frequency of coughing remained unchanged in the two subjects who had not completed the full speech language pathology program.
Recently, two studies have expanded on this work. Murry et al. (341) described the outcome of subjects with chronic cough and PVFM treated with respiratory retraining therapy and management of laryngopharyngeal reflux (LPR). Twenty subjects given a diagnosis of PVFM and associated cough were treated with proton pump inhibitors for a minimum of 6 months followed by 3 to 5 sessions of respiratory retraining therapy consisting of a program, described by Christopher et al. (342) in 1983 as a type of speech therapy and elaborated upon by Martin et al. (343). The subjects in the Murry et al study were taught to relax the chest and shoulder muscles by swinging their arms as they walked at a slower than normal pace. At the same time, they were instructed to breathe rhythmically, for example “Exhale on every other left/right foot”. They were instructed to relax the abdominal muscles (extend them) after each breath. By not focusing on inhalation, they relaxed the upper torso and swinging the arms gently helped to keep the shoulders in a relaxed posture. Once the basic rhythm and posture of breathing were established, the subjects were asked to increase the speed of walking and to increase the expiratory force by controlling the exhalation phase with the abdominal muscles. Voice production as described by Blager (344) and rhythmic breathing trials with and without voice in the sitting position were also added once the basic control of breathing was abdominally focused. The subjects were encouraged to practice without distraction 3 to 4 times per day. Pulmonary function testing (PFT) and subjective rating of cough and reflux were performed. In addition, PFT and rating of cough were performed on 10 healthy volunteers with no complaint of cough. The baseline cough rating and ratio of forced inspiratory volume at 0.5 second to forced inspiratory vital capacity on PFT were significantly worse in the treatment group than in the control.
group. After therapy, 100% of subjects experienced improvement in cough, 95% experienced improvement on PFT, and 85% experienced improvement in the reflux score. The authors concluded that the respiratory retraining program combined with management of LPR is an effective treatment for subjects with cough and PVFM when a single-modality treatment is not sufficient (341).

Vertigan et al (345) also in 2006 investigated the efficacy of speech language therapy in the treatment of CC. This single blind, randomised, placebo controlled trial was conducted in 87 subjects with CC refractory to usual medical treatment. Subjects were randomised to receive either a specifically designed speech language intervention or a placebo intervention. Participants in the intervention group had a significant reduction in cough, breathing, upper airway and voice symptom scores and limitation ratings following intervention. In addition, clinical judgment of outcome indicated successful ratings in 88% of participants in the treatment group compared to 14% in the placebo group. Participants assigned to the treatment group undertook a four component treatment programme [Table 1:10].

<table>
<thead>
<tr>
<th>Component</th>
<th>Example of Treatment Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>No physiological benefit from cough, capacity for voluntary cough control.</td>
</tr>
<tr>
<td>Strategies to reduce cough</td>
<td>Identify warning signs for cough &amp; replace with modified swallowing technique, pursed lip breathing exercise, or relaxed throat breathing.</td>
</tr>
<tr>
<td>Reduce laryngeal irritation</td>
<td>Increase hydration, decrease exposure to irritating stimuli.</td>
</tr>
<tr>
<td>Psychoeducational counselling</td>
<td>Internalising locus of control; acceptance that treatment is hard work; setting realistic goals.</td>
</tr>
</tbody>
</table>

Speech language pathology intervention (SLPI) appears effective for refractory CC, but several key questions remain. These are whether this therapy is associated with any
changes in objective cough parameters, such as cough reflex sensitivity. It is also possible that SLPI may have a role in chronic persistent cough, or cough associated with PVFM. It is likely that the most effective treatment for CC with laryngeal dysfunction such as VCD may encompass a multi-faceted approach (148) including a cough diagnostic protocol combined with a SPLI for cough. As the primary diseases associated with CC, namely asthma, GORD, and PNDS, are also commonly associated with VCD/PVFM (4, 283, 346-351) such an approach is justified. This approach has not been evaluated, but forms part of the studies in this thesis.

1.7.5 Other Treatments

1.7.5.1 Pharmaceutical treatments: Amitriptyline, Gabapentin and Pregabalin
Sensory neuropathic cough, postviral vagal neuropathy (PVVN), or laryngeal sensory neuropathy appear to respond well to amitriptyline, a tricyclic antidepressant also used in low doses in the management of chronic pain syndromes and neuralgias. Amitriptyline promotes neuronal activity by blocking the membrane pump mechanism, which is responsible for the absorption of serotonin and norepinephrine in serotonergic and adrenergic neurons. Although amitriptyline is approved for the treatment of depression, it has been used off-label for many years for the treatment of headache, irritable bowel syndrome, pain syndromes and postherpetic neuralgia. Amitriptyline is hepatically metabolised via P450 CYP2D6 and is renally excreted almost entirely in metabolite form (352).

Bastian et al (150) treated 12 subjects with amitriptyline 10mg two hours before bedtime for 21 days. All of the subjects except one had prompt significant reduction of their cough with this treatment. Bastian postulated that amitriptyline lowers the sensory
threshold of the afferent nerve endings thereby inhibiting the cough reflex. A prospective, randomised controlled trial comparing the effectiveness of amitriptyline versus codeine/guaifenesin for select cases of CC resulting from suspected PVVN supports this finding. Jeyakumar et al (154) studied 28 subjects randomised to either 20mg amitriptyline at bedtime or 10 to 100 mg/5mL, 10mL codeine/guaifenesin every 6 hours standing dose while awake. The majority of the subjects in the amitriptyline arm achieved a complete response while none of the codeine/guaifenesin group achieved a complete response.

Laryngeal irritability has much in common with trigeminal neuralgia and other neuropathic pain where a recognised “trigger” may be identified. Cranial neuralgia refers to pain syndromes in the head and neck as a result of sudden or excessive discharge from the involved nerve. It is a pain that results from lowered threshold and/or exaggerated response to stimuli. Bastian et al (150) suggested that vagal neuralgia could manifest as a sudden and exaggerated, but non painful sensation that the vagus nerve normally mediates-a bogus tickle leading to uncontrolled coughing. The cough reflex has become hypersensitive and therefore minimal stimulation to no stimulation could initiate a strong and irresistible urge to cough.

Gabapentin is widely used for the treatment of neuropathic pain of different origins. It has also been evaluated in CC in several case series. In a study by Lee and Woo (147) twenty eight subjects with CC or throat clearing as a manifestation of sensory neuropathy involving the laryngeal nerve were treated with Gabapentin 100 to 900 mg/d. Symptomatic relief was achieved in 68% of their subjects and as high as 80% relief for the subjects positively identified with motor neuropathy. Treatment duration
varied from three months to four years depending on symptom control. Mintz and Lee (353) described six cases of gabapentin treatment for idiopathic CC. Five of the six subjects responded to treatment with either complete resolution or substantial improvement in cough. The duration of improvement ranged from 6 months to ongoing. In both these studies, responders generally improved within the first few weeks of therapy, and treatment length varied depending on symptom control.

Currently, there is no explanation for gabapentin’s effect on CC; however since it is a centrally acting neurotransmitter it is likely that it is exerting its effect through this mechanism. Gabapentin is approved in the treatment of seizure and postherpetic neuralgia. Gabapentin is not metabolised and is entirely excreted renally unchanged. The advantages of Gabapentin are that it is normally well tolerated and has relatively few drug interactions. It is cleared by the kidney, so it does not interact at the level of the liver (352).

The usefulness of gabapentin and amitriptyline for neuropathic sensory cough can be limited by their sedating side effects (354). Pregabalin is FDA approved for neuropathic pain conditions such as postherpetic neuralgia and diabetic peripheral neuropathy (355-358). Pregabalin is closely related in structure to gabapentin and shares many of its favourable qualities, including rapid titration and onset of activity, minimal drug-drug interactions, and negligible hepatic metabolism. Advantages of pregabalin over gabapentin include greater absorption, increased bioavailability, and less frequent (twice-daily) dosing (359, 360).
In a retrospective study of 12 subjects prescribed pregabalin for symptoms of laryngeal sensory neuropathy, Halum et al \(^{(354)}\) reviewed pre and post-treatment questionnaires asking subjects to rate symptoms on a scale from 0 to 5. Adverse effects and evidence of drug tolerance were also recorded. The results of this study implied that pregabalin therapy for laryngeal sensory neuropathy was effective (pre-treatment severity rating mean of 3.9 to post-treatment symptom rating mean of 1.2) after one month of treatment. None of the subjects developed drug tolerance effects over time and somnolence was the most common side effect. Similarly, to the amitriptyline and gabapentin studies, two of the subjects in this study were able to discontinue pregabalin one to two months after therapy with little to no recurrence in symptoms.

Pregabalin is a \(\gamma\)-aminobutyric acid (GABA) analog that strongly binds to the alpha (2)-delta site in the central nervous system tissues. Binding to the alpha(2)-delta subunit may be involved in pregabalin’s effects on neuropathic pain. Pregabalin reduces the calcium-dependent release of several neurotransmitters, including glutamate, noradrenaline, and substance P, possibly by modulation of calcium channel function; however, the exact mechanism of action is unknown \(^{(352)}\).

**1.7.5.2 Narcotics: Codeine, Morphine and Tramadol**

The goal of non-specific antitussive therapy is to suppress bothersome cough by inhibiting the cough reflex regardless of the cause of cough and therefore its use is only appropriate under particular circumstances. These include:

1. when the specific aetiology of the cough cannot be determined (idiopathic) ;
2. when severe cough needs to be suppressed while awaiting the effect of specific antitussive therapy or the resolution of postinfectious cough; and

3. when the aetiology of cough is known but the cause is irreversible, such as inoperable lung cancer (114).

Non-specific antitussive agents are broadly classified as central or peripheral, based on their site of action. Opioids, especially codeine and morphine are classified as centrally acting agents that have been shown to suppress cough in a number of animal models (361-363) and in humans (364, 365) to a range of different stimuli including capsaicin and citric acid. Of the five-receptor subtypes known, it is thought that the antitussive actions of these drugs is via stimulation of \( \mu \)-opioid receptors. \( \mu \)-Opioid receptors are found within the cough centres of the brain and it is believed that opioids exert their antitussive effects via a central action (364, 366). There is a possibility that opioids suppress cough also by a peripheral mechanism of action and as such, this led to the development of BW443C, a peripherally acting \( \mu \)-opioid receptor agonist for the treatment of cough. Follenfant et al (367) showed that BW443C was unable to cross the blood-brain barrier in chemically induced writhing models. BW443C inhibits activity in airway sensory neurones originating from RARS and C-fibre receptors (368, 369). It has not been tested as an antitussive in humans however.

The use of morphine or diamorphine for the intractable cough in terminal disease is advantageous in that these drugs also possess analgesic properties. However, at their effective doses, these antitussives cause drowsiness, nausea and vomiting, and constipation, and often cause physical dependence. Codeine is therefore the preferred narcotic antitussive because of its more favourable side-effect profile and lower
potential for abuse. Nevertheless, codeine in antitussive doses can cause sedation, nausea, vomiting and constipation.

Morice et al (370) tested the hypothesis that morphine sulphate in the dose of 5 mg twice daily would bring about a reduction in cough frequency and severity in subjects failing to respond to specific measures. Subjects were recruited from a cough clinic and enrolled into a randomised double-blind placebo-controlled study using 4 weeks of slow-release morphine sulphate and a corresponding period of matched placebo. An open-labelled extension of the core study allowed dose escalation to 10 mg twice daily. Cough was assessed using the Leicester Cough Questionnaire, daily symptom diary, and citric acid cough challenge. Of the 27 subjects that completed the core study on slow-release morphine sulphate treatment there was a significant improvement in cough-related quality of life measured by the Leicester Cough Questionnaire, and a rapid and highly significant reduction of 40% in daily cough scores. However, objective testing of the cough reflex using citric acid cough challenge tests did not show any significant changes. The authors believed that this result questioned the validity of citric acid cough challenge testing in the monitoring of clinically important cough as disparity between cough reflex sensitivity and subjective cough scores has been previously observed (184, 371, 372). Twelve subjects opted to increase the morphine to 10 mg twice daily and at the end of 3 months, there was a similar improvement in cough between the 5- and 10-mg groups. Subject tolerance of the drug in this study was good with the most common side effects being constipation (40%) and drowsiness (25%). Morice et al concluded that morphine sulphate is an effective antitussive in intractable chronic cough at the doses of 5 to 10 mg twice daily (370).
Tramadol is a weak opiate, which appears to have enhanced antitussive effects compared with codeine. In a study by Szekely and Vickers (373) the effect of tramadol on laryngeal reflex activity was assessed in a double-blind cross-over study in six volunteers receiving single oral doses of either codeine 50 mg, tramadol 50 mg or tramadol 100 mg. Laryngeal reactivity was measured by the response to the inhalation of dilute ammonia vapour. The minimum ammonia concentration required to induce a glottic stop was recorded prior to drug administration, and at 15, 30, 45, 60, 90, 120, 150 and 180 min thereafter. Psychometric tests were performed at 0, 45 and 105 min to detect any relationship between central sedation and changes in laryngeal reflex activity. The concentration of ammonia required to induce a glottic stop increased in all treatment groups, but more so in the tramadol groups. The time course suggested that the codeine effect peaked early, and had returned to normal within two hours. For tramadol 100 mg, laryngeal depression appeared to be still increasing at the end of the three hour study period. No correlation was found between laryngeal and sedative effects. Tramadol is produced as a racemic mixture, in which one isomer acts through an opioid receptor pathway whilst the other affects noradrenergic and serotonergic mechanisms. Both of these routes of action may be involved in the suppression of the response to experimentally induced cough. Altman et al (148) have also found tramadol to be highly effective in the treatment of subjects with vagal neuropathy induced cough that has persisted after allergen avoidance and or GORD treatment.

1.7.5.3 Botulinum Toxin Type A

Chu et al (374) investigated the effectiveness of Botulinum Toxin Type A (BtxA) in the treatment of CC in adults. All of the four subjects studied had significant relief of
cough after BtxA injection, with complete resolution after a median of seven injections over a mean duration of 25.7 months. A neuropathic model for CC caused by neuroplastic changes and laryngeal hyperactivity as an explanation for the effectiveness of BtxA treatment is presented below [Figure 1:12].

Figure 1:12 Neurophysiology of cough reflex

BtxA appears to be effective in directly decreasing laryngeal hypertonicity and possibly reducing neurogenic inflammation and neuropeptides-mediated cough and could be considered for CC refractory to other medical therapies (374).
1.8 Laryngeal Function and Dysfunction

1.8.1 Paradoxical vocal fold movement and vocal cord dysfunction

Paradoxical Vocal Fold Movement (PVFM), also called vocal cord dysfunction, is a laryngeal disorder that affects respiratory function. It has gained significant recognition over the past two decades and there have been a number of case studies reporting PVFM as a masquerader of asthma, allergies, and severe upper airways obstruction with consequent misdiagnosis and mismanagement (375). Although the literature is full of descriptions of PVFM, variation in the reporting of its presentation, patient profiles, and proposed aetiologies has lead to a non-unified understanding of the disorder. Hicks et al (375) recently sought to address these issues in a single all encompassing paper dedicated to interpreting the current literature and clinical practice up until 2008. The clinical presentation of PVFM is described as ranging from mild dyspnea to acute, severe respiratory distress (376). Patients complain of sudden onset of breathing difficulty, usually on inhalation, air deprivation, tightness in the throat or neck, cough, and often stridor or laryngeal wheeze (283, 377-379). Other symptoms and signs include dry cough; chest tightness; neck or chest retractions; difficulty swallowing; sensation of a lump in the throat (globus pharyngeus); choking; suffocating; intermittent loss of voice (aphonia); deviant voice quality (dysphonia); fatigue; and throat clearing (4, 283, 284, 377-382) [Table 1:11].

<table>
<thead>
<tr>
<th>PVFM Characteristics</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Stridor, Dyspnea, Cough Wheeze, Shortness of Breath, Inspiratory Hunger</td>
</tr>
<tr>
<td>Voice</td>
<td>Dysphonia, Aphonia</td>
</tr>
<tr>
<td>Upper Airway Dysfunction</td>
<td>Tightness in neck muscles, irritation/tickling sensation in throat, choking, dry throat</td>
</tr>
</tbody>
</table>

Table 1:11 Characteristics of paradoxical vocal fold movement
PVFM episodes frequently begin and end abruptly and may or may not have an identified trigger. Self-reported triggers include URTI; occupational exposures; eating; talking; laughing; singing; coughing; acid reflux; physical exertion; intense exercise; postnasal drip; weather changes; emotional stressors; perfumes and strong scents; fumes; solvents; air pollution; and smoke \(^{(208, 377)}\). The acute presentation of PVFM is usually a frightening and emotional one and may elicit panic and anxiety in some sufferers \(^{(375)}\). PVFM patients are typically misdiagnosed as having asthma and therefore are refractory to asthma medications. These patients frequently have severe side effects from unnecessary high-dose corticosteroid medications and other interventions such as intubation and tracheostomy \(^{(283, 383-385)}\). Some of the distinguishing features of PVFM from asthma have been tabled by Ibrahim et al \(^{(347)}\) and are reproduced below [Table 1:12].

**Table 1:12** Features distinguishing paradoxical vocal fold movement disorder from asthma \(^{(347)}\)


*Table removed from online repository version due to copyright laws.*

Other stimuli such as acid reflux can initiate or contribute to laryngeal hyperresponsiveness. Nineteen out of 22 subjects had laryngoscopic changes suggestive of reflux disease in a study by Powell et al \(^{(386)}\). Twenty eight of 127 PVFM subjects had symptomatic GORD in the Perkner et al \(^{(350)}\) study and a further nine of these subjects had symptoms relating to irritant exposure to ammonia and cleaning fluids.
1.8.1.1 Diagnosis of PVFM

A diagnosis of PVFM becomes more difficult if it co-exists with asthma. In PVFM the vocal folds adduct involuntarily during inspiration while a normal respiration pattern results in the vocal folds abducting slightly during inspiration and adducting slightly during expiration. PVFM was described by Christopher et al in 1983 (342) as upper airway stridor characterised by involuntary, paradoxical adduction of the vocal folds and ventricular folds during inspiration, with closure of the vocal folds being present during the entire respiratory cycle in some cases. Pulmonary function assessment and the use of either a flexible fiberoptic rhinolaryngoscope or a Hopkins-rod right-angle telescopic laryngoscope were also importantly introduced as a means of diagnosing PVFM (342). Using these tools of diagnosis a comprehensive description of five cases of refractory asthma was presented by Christopher et al (342). These subjects were found to have normal pulmonary function tests and no bronchial hyperresponsiveness. During symptomatic episodes however, there was visualisation of inspiratory flow restriction and almost complete adduction of the true vocal folds with glottis narrowing to a small posterior diamond-shaped chink [Figure 1:13].

![Figure 1:13 Visual of A) normal vocal cords (folds) during inspiration and, B) vocal cords during a symptomatic episode showing paradoxical adduction and posterior chinking (347)](figure)


*Figure removed from online repository version due to copyright laws.*

In PVFM, there is extrathoracic airway obstruction primarily due to glottal constriction. This obstruction is usually demonstrated by a reduced inspiratory curve on the flow
volume loop (FVL) during pulmonary function testing. FVL measures the speed and volume of expiration and inspiration. Airway challenge tests use noxious substances that act on the airways. The FVL in people with PVFM has been shown to have a normal expiratory phase but attenuation in the inspiratory phase whereas asthma has a normal inspiratory phase but attenuation in the expiratory phase.\(^{(148, 350, 380, 387-389)}\)

**Fibre Optic Laryngoscopy (FOL) or Rhinolaryngoscopy**

FOL enables direct visualisation of the vocal folds [Figure 1:14] while the patient is having symptoms [Figure 1:15] and is considered the gold standard for diagnosing PVFM.

**Figure 1:14** Fiberoptic laryngoscopy or rhinolaryngoscopy (used to visualise the voicebox and surrounding anatomic structures)

Expected image in this position shown to the right.


**Figure 1:15** Laryngoscopic image during inspiration of a symptomatic patient with PVFM \(^{(390)}\)


*Figure removed from online repository version due to copyright laws.*
The classic findings described by Christopher et al (342) are the hallmarks for diagnosis. However, these findings may also be present during expiration (expiratory PVFM).

Newman et al (283) diagnosed PVFM in 100% of their symptomatic subjects by laryngoscopy and 60% diagnosis of PVFM in their asymptomatic subjects. It is important to realise that the absence of a posterior glottic chink does not rule out a diagnosis of PVFM and if the paradoxical vocal fold adduction is not seen on initial examination, there are several manoeuvres that may be utilised to elicit the behaviour. These manoeuvres include coughing, throat clearing, repetitive deep inspiration (377), exercising (391) and introduction of a noxious substance such as hypertonic saline (100, 392) or histamine (387) on the airway tissues during an airway challenge test.

Pulmonary function tests with flow volume loops are often used to complement a diagnosis of PVFM by laryngoscopy. When patients are asymptomatic, the flow volume loop is usually normal. In symptomatic patients the FVL may show flattening or attenuation of the inspiratory arm suggesting variable extrathoracic obstruction [Figure 1:16].
Patients with expiratory PVFM may occasionally exhibit reduction in the expiratory curve (394). Patients with asthma will show a normal inspiratory curve but reduced expiratory curve hence the FVL can be used to suggest if a patient has asthma, PVFM or a combination of the two.

If methacholine or hypertonic saline challenge fails to elicit PVFM in patients with a compelling history, a specific irritant challenge may be indicated (148, 395). For example, where exercise is the primary trigger, a graded exercise challenge on a bicycle ergometer or treadmill is helpful (284, 378, 383).

Patients with pure PVFM have normal chest radiographs with no indication of hyperinflation (148, 395). Most patients with PVFM have normal oxygenation, as measured by pulse oximetry or arterial blood gas (342, 396) sampling unlike other causes of respiratory distress such as asthma where the alveolar-arterial oxygen difference is elevated (396). The absence of an increase in the alveolar-arterial oxygen difference (P\text{A\textsubscript{O}2}-P\text{a\textsubscript{O}2}) during an acute attack is a useful indicator of PVFM as this finding occurs in over 90% of severe asthmatic attacks (397).

The cause of PVFM is not completely clear, however, it is thought to occur by autonomic imbalance between sensory information transmitted via the vagus nerve to the medulla and motor outflow also via the vagus. Ayres and Gabbott (398) have proposed that this can become imbalanced by laryngeal hyperresponsiveness by some sort of inflammatory insult or from a central stimulus (psychological factors). Morrison et al (208) also proposed a similar mechanism where chronic irritation of the larynx by
gastroesophageal reflux enhances glottic spasm sensitivity. More than one of these factors may exist in any one patient \(^{(399)}\). A result of this persistence of factors is abnormal adduction of the vocal folds during the respiratory cycle leading to upper airway obstruction and symptoms.

In patients with prolonged cough after an URTI, the presumptive injury occurs at the muscarinic receptors of the vagus nerve, especially the M2 receptors. These receptors, when stimulated, normally inhibit airway reactivity. Damage to these receptors results in airway hyperresponsiveness that persists beyond the resolution of the acute URTI \(^{(152)}\).

1.8.2 PVFM and Cough

Cough is a common symptom in PVFM, being present in approximately 50% of cases \(^{(79,283,350,377)}\). The potential relevance of cough in PVFM is multifactorial. Cough may be a manifestation of laryngeal hypersensitivity, or an exaggerated response to an irritant exposure. Cough in PVFM may also be a protective manoeuvre, such that cough is induced to promote opening of the vocal folds and minimise paradoxical adduction \(^{(400)}\).

Perkner et al \(^{(350)}\) described a series of subjects with occupational irritant-induced PVFM. Typically, these subjects reported initiation of symptoms after high-level exposures to workplace irritant fumes, vapours, or odours (smoke inhalation, ammonia or chlorine, dust). What distinguished this group from non-occupationally associated PVFM cases was central chest pain. Lower airway injury with biopsy-proven chronic lymphocytic inflammation has been found in other irritant-induced
PVFM subjects (401-403). The histologic pattern is distinct from the typical asthma pattern and it has been proposed that the airway injury renders these individuals with a “hypersensitive” glottic closure reflex (148). The exact mechanism is unknown but it is hypothesised that the glottic closure reflex is accentuated in patients with PVFM whereby various intrinsic and extrinsic stimuli can trigger reflex closure of the vocal fold as an adaptive protective response. This may augment a normal physiologic response by lowering the threshold levels for initiation compared with normal individuals. Further, chronic irritation of the larynx from GORD, allergies and rhinosinusitis, or inhaled irritant exposures, with the consequent frequent throat clearing and cough, predisposes the larynx to being more sensitive to various external stimuli triggering PVFM attacks (208, 346, 350).

While chronic persistent cough is recognised as a common symptom in VCD/PVFM by clinicians that recognise and treat VCD/PVFM, this condition (VCD/PVFM) is not recognised by clinicians who treat CC, and consequently, VCD/PVFM does not appear as a cause of CC in current cough guidelines (10, 303). This is a somewhat paradoxical situation and suggests the need to investigate the laryngeal function in CC and to look for features of PVFM in CC, as proposed in this thesis. Although CC is common in PVFM, this cause of CC, which is effectively treated by speech language therapy, is not described in the ACCP or European cough guidelines.

1.8.3 Extrathoracic Airway Hyperresponsiveness

Extrathoracic airway hyperresponsiveness (EAHR) is an objective measure of laryngeal hypersensitivity that overlaps with PVFM. Airway challenge tests are designed to assess the response of the airway to various stimuli. They were developed to assess
asthma, since in asthma the intrathoracic airways respond both excessively and with increased sensitivity to a range of stimuli. These tests involve measurement of lung function at baseline followed by administration of a challenge agent and further measurement of flow volume loops to assess the response to the stimuli. Airway challenge tests can be direct or indirect, depending on the agent used. Direct challenge tests for asthma utilise pharmacological agents such as histamine and methacholine that act directly on airway smooth muscle to cause bronchoconstriction (404). Indirect tests use agents such as exercise, hypertonic saline, mannitol, and eucapnic hyperventilation that indirectly cause bronchoconstriction by release of mediators from inflammatory cells and airway nerves. Indirect stimuli tend to be less potent than direct stimuli. Bronchial hyperresponsiveness (BHR) is measured as a greater than 20% fall in FEV1 to a direct stimulus, or >15% fall to an indirect stimulus.

These tests can also be used to assess hypersensitivity of the upper airway and confirm the presence of EAHR. In order to do this, the tests measure the response to the provocation stimulus by using inspiratory and expiratory flow-volume loops. Bucca et al (387, 405) correlated the fall in inspiratory flow during histamine provocation testing with observed constriction of the glottis under direct visualisation. They demonstrated that a greater than 25% drop in maximum inspiratory flow (MIF) during histamine provocation testing best reflected changes in mid inspiratory glottic area, and this response is termed EAHR. The test was evaluated in subjects with episodic respiratory symptoms, and in 25 of 40 subjects presenting with episodic breathlessness with wheeze and/or cough, EAHR was observed to be present, either with or without BHR. It is significant that all seven of the 25 subjects in the study that underwent
laryngoscopy all displayed vocal cord adduction during forced inspiration. In confirmation of this finding five out of the 15 subjects who did not display EAHR and underwent laryngoscopy displayed normal findings (387). This demonstrates that EAHR can be detected by inhalation challenge, and corresponds to PVFM seen at laryngoscopy.

In a larger study, EAHR was shown to be responsible for asthma-like symptoms in 117 out of 441 subjects (19). The combination of EAHR and BHR occurred in a further 179 subjects within the study [Figure 1:17].

![Figure 1:17 Combination EAHR (attenuated inspiratory limb) and BHR (reduction in the expiratory limb).](image)

This study included 151 subjects with cough as their only symptom. The CC subjects were more likely to have EAHR and less likely to have bronchial hyperreactivity than were subjects in the other symptom groups. When cough was associated with wheeze and/or dyspnoea, subjects were more likely to have both upper and lower airway hyperresponsiveness. Bucca et al and Rolla et al have extended these findings to show
that EAHR is a common mechanism underlying symptoms in subjects with sinusitis, GORD, and ACEI use\(^{(346, 405, 406)}\). The possibility that a reflex can be triggered by stimulation of pharyngo-laryngeal receptors independent of the lower airways is further supported by the finding of EAHR in 72% of subjects with sinusitis\(^{(346)}\).

Reactivity measurements were related by the researchers to four extrathoracic diseases diagnosed from a symptom questionnaire (pharyngitis, PNDS, laryngitis, and sinusitis). Extrathoracic hyperreactivity alone or combined with bronchial hyperreactivity was associated with all four disorders, by comparison with subjects without hyperreactivity and in contrast to subjects with bronchial hyperreactivity alone. Therefore, CC and upper airways disorders such as PNDS, pharyngitis, and sinusitis seem to be associated with upper airway hyperreactivity to histamine in subjects without asthma. However, the nature of the relationship is uncertain. Does pharyngitis or PNDS cause extrathoracic hyperreactivity, which in turn causes cough, or does the underlying disease process cause symptoms and upper airway hyperresponsiveness?\(^{(407)}\)

Histamine and methacholine provocation are commonly used in cough clinics to assess the presence of asthma\(^{(408)}\) however there are several limitations to the use of these substances for provocation testing in CC and PVFM. Methacholine is a direct airway smooth muscle agonist, but is relatively poor at activating upper airway responses. Histamine can also induce airway oedema, and the fall in inspiratory flow may therefore occur from oedema or upper airway constriction. McGarvey\(^{(408)}\) claimed that the interpretation of results, particularly when normal, is variable and that results can be affected by the presence of recent URTI or GORD. Chevalier and Schwartzstein\(^{(409)}\)
found that over 82% of subjects with shortness of breath or cough and a questionable response to inhaled bronchodilators did not demonstrate airway hyperresponsiveness on the methacholine inhalation challenge.

Indirect challenge tests include the use of hypertonic saline and exercise, which change the osmolarity of airway fluid, trigger mediator release from inflammatory or mast cells and activate airway sensory nerves (404). Hypertonic saline has a low false-positive response in healthy individuals and the stimulus can be more easily quantified than exercise. The use of hypertonic saline to detect EAHR has been described by Gibson et al (410) where a reduction in inspiratory flow of 20% or more during hypertonic saline challenge has been correlated with glottal constriction and may be an associated feature in PVFM [Figure 1:18].

![Flow Volume Loop]

Figure 1:18 Flow Volume Loop
Pre hypertonic saline challenge (red), normal expiratory flow with reduced inspiratory flow during hypertonic saline challenge (green)
Capsaicin is used to study cough because it activates sensory nerves. In a study by Cho et al (273) 77 subjects with dry cough persisting for three or more weeks, normal spirometry and chest radiography, and 15 controls, underwent capsaicin cough provocation test to determine the relationship between EAHR and cough sensitivity. Elicited cough number and flow volume curve were examined after inhalation of capsaicin. With regard to EAHR, the capsaicin concentration causing a 20% fall in peak inspiratory flow from baseline was used as a threshold of extrathoracic airway constriction. Additionally, the flow volume curve was carefully observed to detect a pattern of variable extrathoracic airway obstruction that showed a flattened configuration of the mid-point inspiratory flow-volume curve. Cough sensitivity was found to be enhanced in 14 subjects with CVA who showed BHR, and EAHR to inhaled capsaicin was present in 12 of those. The remaining 30 subjects were tentatively diagnosed as idiopathic CC and 11 of these showed enhanced cough sensitivity and EAHR to inhaled capsaicin while 19 subjects showed normal values. Control subjects showed no extrathoracic airway narrowing up to the highest dose of capsaicin used, nor did they display cough sensitivity. From these results, the authors concluded that cough sensitivity is closely related with EAHR during capsaicin provocation in some CC subjects. It is suggested that EAHR may be one of the mechanisms developing some subtypes of CC (273).

1.8.4 Laryngeal function and hypersensitivity in chronic cough

1.8.4.1 Normal laryngeal physiology

The three basic functions of the larynx, protection, respiration, and phonation, are controlled by a complex interrelationship of neurosensory reflexes and the brainstem.
Sphincteric protection by the larynx on the lower airway is efficiently achieved by simultaneous adduction of both vocal folds. Such action serves to close the glottis by involving the activation of both thyroarytenoid muscles, among other groups of adductors. The protective function of the larynx is entirely reflexive and involuntary, whereas the respiratory and phonatory functions are initiated voluntarily but regulated involuntarily (411). Speech results from the production of a fundamental tone produced at the larynx and is modified by resonating chambers of the upper aerodigestive tract. Intelligible speech, therefore, represents the combined effect of the larynx, tongue, palate, and related structures of the oral vestibule. The production of the fundamental tone is due to the vibration of the vocal folds against each other, generated by the passage of air between them (411). Sensory nerves to the larynx are derived from the internal branch of the superior laryngeal nerve (iSLN) and the recurrent laryngeal nerves (RLNs). Both are branches of the vagus nerve. The iSLN and RLN innervate the mucosa above and below the level of the true vocal fold respectively. The RLN innervates all intrinsic laryngeal muscles except the cricothyroid muscle, which is innervated by the external division of the SLN (eSLN). Abduction of the vocal folds during respiration is brought about by the posterior cricoarytenoid muscle, whereas their adduction involves all the intrinsic muscles, particularly the thyroarytenoid and cricoarytenoid muscles. Reflexive glottic closure is achieved by simultaneous adduction of both vocal folds. Anaesthesia and sedation impair reflexive vocal fold closure and predispose to aspiration. Laryngeal denervation leads to vocal dysfunction and aspiration during swallowing (411).
Another critical component of airway protection is the cough reflex (148). The cough reflex and laryngeal closure reflex are not only important for protecting the airway during swallowing but also in response to potentially noxious inhaled stimuli. This reflex is triggered by stimulation of aerodigestive tract sensory receptors found in the larynx, trachea, and larger airways, which send afferent information to the brainstem mediated through sensory neuropeptides (148). These may respond to not only pressure but also irritant stimuli, thermal changes and chemicals.

1.8.4.2 Laryngeal hypersensitivity and chronic cough

Several studies have looked at the association of EAHR and inflammatory or infectious conditions. Bucca et al (346) studied EAHR and BHR in 106 nonasthmatic adults with acute exacerbations of their chronic sinusitis. A substantial 86% of them had EAHR, and two thirds of these also had BHR. Following treatment with two weeks of antibiotics and intranasal steroids, 76% of those with EAHR were resolved and another 21% were improved. There was also significant improvement and resolution of corresponding BHR in these same subjects. The authors proposed that both EAHR and BHR might be sustained by reflexes originating in the pharyngeal receptors made hypersensitive by local seeding of the inflammatory process. In a larger study by Bucca et al (19) 67% of the 441 subjects studied had EAHR. Concurrent upper respiratory tract diseases were also assessed and found to be substantial. These diseases included PNDS (55%), pharyngitis (55%), laryngitis (40%), and sinusitis (32%). These studies provide strong support for the theory that laryngeal and pharyngeal bombardment by inflammatory cells and mediators from the upper airway causes mucosal damage,
irritant sensory stimulation, and the glottic closure and similar reflexes that result in EAHR and PVFM \(^{(375)}\).

Campbell et al \(^{(412)}\) described upper airway (laryngeal) dysfunction in a series of six cases. All were men who had recurrent episodes occurring over months or years, of sudden, brief complete obstruction to respiration followed by dyspnoea with loud inspiratory stridor lasting two to five minutes. Attacks occurred during wakefulness and/or sleep. In one of these subjects, an episode was observed endoscopically: the initial obstruction was seen to be caused by complete laryngeal closure. The false vocal folds then opened, but the true vocal folds remained adducted and caused inspiratory stridor. The similarity of the attacks described by the other subjects suggested that they were all caused by laryngeal closure. These subjects were also able to simulate these episodes by voluntarily adducting their vocal folds. The symptoms were usually preceded by a sensation of throat irritation and in four of the cases symptoms of URTI were present. Associated features present in some of the subjects were PNDS, snoring, sleep apnoea and GORD. All of the subjects had cough and three of these displayed the characteristic flattened inspiratory flow volume curve of PVFM on spirometry. Treatment was aimed at reducing upper airway irritation such as with a nasal steroid spray for rhinitis, and voluntary inhibition of coughing such as when the throat felt irritable the patient was instructed to voluntarily suppress the subsequent cough and enforce quiet breathing until the irritation subsides. The authors concluded that persistent irritation of receptors within the larynx by associated factors of URTI, PNDS, cough, and possibly snoring and OSA induced laryngeal closure in their subjects.
Although CC and PVFM are considered separate and distinct disorders, they exhibit overlap in symptomatology and disease associations, namely asthma, GORD, and rhinosinusitis. GORD is also an important cause of EAHR. Canine models of GORD have indicated that a pH of 2.5 or less provokes laryngospasm through vagally mediated mechanisms and the sensitisation of mucosal chemoreceptors (413) and if CC is accepted as another manifestation of EAHR, then several studies have confirmed the association of GORD and EAHR. Polombini et al (414) proposed a pathogenic triad of asthma, PNDS, and GORD as the most common causes of CC. Altman et al (148) found allergic rhinitis, CVA, and GORD as the cause of CC in 86% of adult subjects. Vertigan et al (4) reported on GORD and PNDS as underlying factors in PVFM. Furthermore, a randomised controlled trial by this group has shown that speech pathology treatment based on the approach used in PVFM is effective in CC (345). This overlap in symptoms, associated diseases, and effective therapy raises the possibility that there may be an overlap in the mechanisms of CC and PVFM.

The role of laryngeal dysfunction in CC and its associated mechanisms will be investigated and characterised in this thesis. Treatments of this dysfunction will also be investigated and the results of these will be presented.

1.9 Hypothesis

The studies in this thesis assess the presence, characteristics and treatment of laryngeal dysfunction in CC. Several subject groups are studied, comprising: chronic persistent cough [Chapters 2, 3]; refractory and/or idiopathic cough [Chapters 4, 5]; and post infectious cough [chapters 6, 7].
The overlap in symptoms, associated diseases, and effective therapy raises the possibility that there may be an overlap in the mechanisms of CC and VCD/PVFM. I hypothesised that PVFM and EAHR may be present in chronic persistent cough and represent the motor consequences of sensory hyperreactivity. We sought to test this hypothesis by investigating EAHR and PVFM in unselected subjects with CC, and relating these motor consequences to cough reflex hypersensitivity [Chapter 2].

My next study evaluated the treatment of PVFM in the setting of persistent cough. Speech language pathology intervention is effective for PVFM and improves refractory CC. This therapy was combined with diagnosis based treatment in chronic persistent cough. I hypothesised that treatment of subjects with CC and laryngeal dysfunction would result in improvement of afferent cough reflex sensitivity and the laryngeal abnormalities of PVFM and EAHR. The aim of this study was to investigate effects of therapy for CC and PVFM in participants with chronic persistent cough [Chapter 3].

Refractory cough is a distressing problem. Subjective improvement occurs with speech language pathology treatment. Objective evaluation of this treatment is needed to provide supportive evidence of benefit and indicate the likely mechanism of effect. It was hypothesised that speech language pathology intervention for CC would result in decreased cough reflex sensitivity, reduced cough frequency, improvement in clinical outcome and improvement in cough and laryngeal subjective measures. I also sought to determine how many treatment sessions a patient required to show an improvement and if these benefits were maintained post intervention. My aim was to objectively measure changes in cough reflex sensitivity and cough frequency prior to, during and
after a speech language pathology treatment programme for refractory cough [Chapter 4].

Sensory hyperresponsiveness (SHR) is a common mechanism underlying the possible causes of idiopathic CC. SHR is also a feature of chronic pain syndromes and it is therefore possible that approaches found to be successful in chronic pain such as gabapentin will also be successful in CC. It was hypothesised that participants with chronic idiopathic cough would show an improvement in cough quality of life and reduced cough frequency after gabapentin treatment compared to placebo [Chapter 5].

Extrathoracic airway hyperresponsiveness (EAHR) represents variable extrathoracic airflow obstruction following inhalation provocation testing. It manifests as a fall in inspiratory airflow during challenge with histamine, exercise, or hypertonic saline. EAHR is a feature of cough due to ACE inhibitor use, rhinosinusitis and GORD, and possibly asthma. The mechanism of post-infectious cough is not known; however, upper airway sensory hyperresponsiveness might be one important mechanism in driving cough in some entities of CC and this current case suggests that EAHR may be a useful objective marker and relevant mechanism in post infectious cough [Chapter 6].

To date, prolonged symptoms such as CC remaining after the infection has cleared have not been examined. This study sought to investigate the characteristics and mechanisms of chronic persistent cough following acute respiratory illness from laboratory-confirmed H1N1 2009 influenza in comparison to ARI that was H1N1 2009 influenza negative and historical controls. I hypothesised that approximately 10% of
the population studied would have persistent cough with associated EAHR and cough reflex sensitivity as likely mechanisms [Chapter 7].

**STATEMENT I**

This statement explains the contribution of all authors in the article listed below:


**Table: Author contribution percentage and description of contribution to published article listed above**

<table>
<thead>
<tr>
<th>Author</th>
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<td>Nicole M Ryan</td>
<td>70</td>
<td>Co-designed and executed the study; Collected, analysed and interpreted the data; Wrote the manuscript.</td>
</tr>
<tr>
<td>Peter G Gibson</td>
<td>30</td>
<td>Co-designed the study; Performed laryngoscopy on subjects, Helped in the interpretation of data and edited manuscript.</td>
</tr>
</tbody>
</table>
Chapter 2  Characterisation of Laryngeal Dysfunction in Chronic Persistent Cough


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Running Title: Laryngeal Dysfunction in Chronic Cough

Competing Interests: none declared.

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2.2 Abstract

2.2.1 Rationale

Laryngeal symptoms are increasingly recognised to occur in chronic persistent cough and may result from the sensory hyperresponsiveness that characterizes this condition. Apart from cough, the motor consequences of sensory activation have not been well described in chronic persistent cough. The efficacy of speech pathology treatment for
chronic cough suggests that laryngeal dysfunction may be relevant in chronic persistent cough.

2.2.2 Objective
This study investigated the relationship between cough reflex sensitivity and laryngeal dysfunction, which was assessed as paradoxical vocal cord movement (PVCM) and extrathoracic airway hyperresponsiveness, in patients with chronic cough.

2.2.3 Methods
Adults with chronic persistent cough (n=25) and healthy controls (n=11) were assessed by cough-specific quality of life questionnaire, extrathoracic airway hyperresponsiveness to hypertonic saline provocation, capsaicin cough reflex hypersensitivity and fibreoptic laryngoscopy to assess PVCM.

2.2.4 Results
Laryngeal dysfunction was present in many patients with chronic persistent cough. PVCM was present in 56% of subjects with chronic cough and accompanied by cough reflex hypersensitivity and impaired quality of life. Inspiratory airflows were reduced in Cough with PVCM, and there was significant extrathoracic airway hyperresponsiveness.

2.2.5 Conclusions
Laryngeal dysfunction is common in chronic cough, where it is manifest as paradoxical vocal cord movement and extrathoracic airway hyperresponsiveness. Laryngeal dysfunction in chronic cough is associated with reduced quality of life. Laryngeal hypersensitivity may be a common mechanism that can be effectively treated by speech language therapy.
2.3 Introduction

Chronic persistent cough is a significant problem that has primarily been associated with rhinosinusitis, gastroesophageal reflux disease, asthma and ACE-inhibitor use. Hypersensitivity of the cough reflex to agents such as capsaicin is a unifying sensory mechanism and cough is recognised as the main motor consequence of this sensory activation. Laryngeal problems such as dysphonia have only recently been associated with chronic persistent cough. Vocal Cord Dysfunction (VCD) is another upper airway disorder where persistent cough is common. The underlying mechanism of vocal cord dysfunction is paradoxical vocal cord closure during inspiration (PVCM) that leads to reduced inspiratory airflow.

Although chronic cough and vocal cord dysfunction are considered separate and distinct disorders, they exhibit overlap in symptomatology such as cough and dysphonia, and overlap in disease associations, namely asthma, gastroesophageal reflux (GORD), and rhinosinusitis. Furthermore, a randomized controlled trial has shown that speech pathology treatment based on the approach used in vocal cord dysfunction is effective in chronic cough. The overlap in symptoms, associated diseases, and effective therapy raises the possibility that there may be an overlap in the mechanisms of chronic cough and vocal cord dysfunction. We hypothesized that PVCM and extrathoracic airway hyperresponsiveness may be present in chronic persistent cough and represent the motor consequences of sensory hyper-reactivity. We sought to test this hypothesis by investigating extrathoracic airway hyperresponsiveness and PVCM in unselected patients with chronic cough, and relating these motor consequences to cough reflex hypersensitivity.
2.4 Methods

2.4.1 Subjects

Subjects with persistent cough (n=25) were recruited from the Respiratory Ambulatory Care Service at John Hunter Hospital in Newcastle, New South Wales, Australia. Chronic cough subjects were aged between 18 and 80 years with a persistent cough of more than eight weeks. They were non-smokers or ex-smokers with less than ten pack years and had no other active respiratory or cardiac disease. Healthy controls (n=11) were volunteers from the Hunter Medical Research Institute register, allied health students, and contacts of staff and patients attending the respiratory department. Controls were aged between 18 and 80 years, non-smokers or ex-smokers with less than 10 pack years, and had no history of chronic cough, rhinitis, asthma, vocal cord dysfunction or gastroesophageal reflux disease. All subjects provided written informed consent for this study, which was approved by the University of Newcastle’s Human Research Ethics Committee.

2.4.2 Study Design

Subjects attended three visits. At visit 1, fractional expired nitric oxide (FENO) was measured followed by clinical history, current respiratory symptoms, a cough specific quality of life questionnaire (Leicester Cough Questionnaire, (LCQ)) smoking history, and an environmental exposures questionnaire.

At Visit 2 capsaicin cough reflex sensitivity testing (CRS) followed by sputum induction using 4.5% saline were performed. Visit 3 included a fibreoptic laryngoscopy, followed by hypertonic saline provocation challenge with inspiratory flow volume curve measurement and then post-challenge laryngoscopy.
2.4.3 Measurements

2.4.3.1 Forced Expired Nitric Oxide

Forced Expired Nitric Oxide (FENO) was measured using an on-line chemiluminescence analyser (NiOx, Aerocrine AB, Smidesvägen 12, SE-171 41 Solna, Sweden) according to published European Respiratory Society/American Thoracic Society guidelines (417). The mean of the three replicate FENO values was used with collection at an expiratory flow rate of 50mL/sec.

2.4.3.2 Capsaicin Cough Reflex Sensitivity testing (CRS)

Each day fresh solutions of capsaicin (Sigma-Aldrich Co., Castle Hill, Australia) were prepared by dissolving 30.5mg capsaicin in 1ml of 99% ethanol and 1 ml polyoxyethylenesorbitan (Tween 80) and then 8 ml physiologic saline. This stock solution (0.01M) was further diluted to make serial doubling concentrations ranging from 0.98 to 500 µM that were inhaled by subjects every minute from a dosimeter (KoKo Digidoser 323200, Technipro, Sydney) as described (65, 418). Cough counting was done for 30s after each dose, and the test ended when the subject coughed five or more times in response to one dose, or received a dose of the highest concentration. Inspiratory flow volume curves were also recorded after each dose of capsaicin to assess the effect of capsaicin on glottic closure.

2.4.3.3 Hypertonic Saline Challenge (HSC)

Subjects withheld bronchodilators and antihistamine for their duration of action and were instructed in the correct performance of inspiratory and expiratory Flow Volume Loops (FVL). At least 2 reproducible inspiratory and expiratory FVLs were obtained before proceeding to the HSC (392). Saline (4.5%) was inhaled for doubling time periods (30 seconds, 1 minute, 2 minutes, 4 minutes, 2x4 minutes) from a DeVilbiss ultrasonic
nebuliser (Sunrise Medical Limited, Stourbridge, United Kingdom) and aerosol delivered via a two-way non-breathing Hans Rudolph valve box (Hans Rudolph, Kansas City, MO) An inspiratory-expiratory FVL was measured, in duplicate, 60 seconds after each saline dose using a KoKo K323200 Spirometer (Technipro, North Parramatta, Australia). Forced expiratory time was held constant at subsequent manoeuvres in order to ensure consistency. The test was stopped when the FEV₁ had fallen by more than 15%, if 15.5mL of the aerosol had been delivered or at the subject’s request if severe symptoms developed. If the FEV₁ fell by more than 15%, 200µg of salbutamol was administered via a valved holding chamber (Volumatic, Allen and Hanburys, GlaxoSmithKline Australia Pty Ltd, Boronia, Australia). The dose of 4.5% saline delivered to the mouth was assessed by weighing the nebuliser cup and tubing before and after each challenge.

2.4.3.4 Fibre Optic Laryngoscopy (FOL)

Flexible fibreoptic rhinopharyngolaryngoscopy (Pentax VNL-1330, Asahi Optical Co, Tokyo, Japan) was performed at baseline and immediately after a saline challenge (392, 410). Prior to the procedure, the nasal cavity was anesthetised with 100µL lignocaine hydrochloride 5.0% and phenylephrine 0.5% (ENT Technologies, Malvern, Victoria, Australia). The Nasendoscope was then passed into the nares and positioned above the larynx. The movements of the true vocal cords were observed during tidal respiration over a period ≥ 2 minutes. If a scope-induced gag reflex was present, the duration of the vocal cord visualisation was extended until we could observe 2 minutes of quiet respiration. Both the baseline and post challenge laryngoscopy were recorded onto video media.
Adduction of the vocal cords throughout the inspiratory phase and/or the beginning of expiration was considered as PVCM. These findings encompassed paradoxical glottic closure during several respiratory cycles ranging from a partial (> 50%) adduction of the true vocal cords without cordal contact to a total closure of the anterior two-third of the vocal cords. The presence of an open posterior glottic chink was noted if present. Adduction that occurred only during the second part of exhalation was considered a normal variant \(^{(35)}\). The gold standard used for the diagnosis of PVCM during the study was a positive laryngoscopy demonstrating paradoxical vocal cord motion at baseline and/or post-HSC while symptomatic.

2.4.3.5 Analysis

All analyses were performed using statistical and data analysis software STATA (Statacorp, Texas, USA). Non-parametric quantitative data were reported as Median (IQR) (where IQR = the interquartile range between the 25\(^{th}\) and 75\(^{th}\) percentile), and compared using the Kruskal-Wallis Test with Bonferroni correction for multiple comparisons with the significance level set at p<0.0083 for a 3 group comparison. Parametric quantitative data were reported as Mean±Standard Error of the Mean \(^{(42)}\), and compared using ANOVA.

2.5 Results

Twenty-five subjects with a chronic persistent cough and 11 healthy controls participated in the study. One cough subject failed to complete laryngoscopy and was excluded from further analysis. The cough subjects had a median (IQR) cough duration of 24 (13-84) months and were predominantly female. Symptomatic rhinitis was
present in 21 cough subjects, and 20 had significant symptoms of GORD. Twelve subjects had asthma and 4 had eosinophilic bronchitis.

PVCM was observed in 14 cough subjects (56%) and 1 healthy control (9.1%, p<0.0001). The PVCM was asymptomatic in the control subject. For further analysis the cough subjects were grouped into those with (Cough+PVCM, n=14) or without PVCM (Cough alone, n=10) and compared to healthy controls (n=11). The subjects with Cough+PVCM were predominantly female (n=12) Table 2:1. The Cough+PVCM subjects had decreased disease-specific quality of life scores, similar to Cough alone, and with significantly greater impairment than healthy controls.

<table>
<thead>
<tr>
<th>Table 2:1: Subject characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Data</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Sex, M/F</td>
</tr>
<tr>
<td>Age years</td>
</tr>
<tr>
<td>Age Range</td>
</tr>
<tr>
<td>Cough Duration, months</td>
</tr>
<tr>
<td>Associated Disorders, n</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>GORD</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
<tr>
<td>Eosinophilic bronchitis</td>
</tr>
<tr>
<td>ACE-I use, n</td>
</tr>
<tr>
<td>Sleep Apnoea</td>
</tr>
<tr>
<td>LCQ</td>
</tr>
</tbody>
</table>

* p<0.0001 versus HC

PVCM was present at the baseline FOL in 8 of the Cough+PVCM group, and present after challenge in 12(85.7%). PVCM was present at both baseline and after challenge in 6(42.9%) subjects. PVCM was not observed in any of the subjects in the cough alone group.
Cough reflex hypersensitivity was increased in Cough+PVCM and Cough alone groups, compared to the healthy control group [Table 2:2, Figure 2:1].

<table>
<thead>
<tr>
<th>Measurement</th>
<th>CC+PVCM</th>
<th>CC</th>
<th>HC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough Reflex Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2, μM</td>
<td>2.94 (2.94)*</td>
<td>1.96 (5.88)*</td>
<td>15.7 (54.9)</td>
<td>0.0009</td>
</tr>
<tr>
<td>C5, μM</td>
<td>5.88 (11.78)*</td>
<td>2.94 (5.88)*</td>
<td>500 (437.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Extrathoracic Airway Hyperresponsiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIF50 Max %Fall</td>
<td>21.6 (12.2)*</td>
<td>12.3 (12.2)</td>
<td>12.8 (12.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Exhaled Nitric Oxide, ppb</td>
<td>13.7 (8.8)</td>
<td>26.0 (18.9)</td>
<td>17.7 (13.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1(%pred)~</td>
<td>90.8±19.3</td>
<td>90.8±26.5</td>
<td>108.4±17</td>
<td>0.085</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>99.6(29.1)††</td>
<td>100.9(15.9)</td>
<td>109.9 (15.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>82 (8)</td>
<td>74 (11)</td>
<td>80 (7)</td>
<td>0.046</td>
</tr>
<tr>
<td>FIF50% (L/s)</td>
<td>2.97 (1.72) ††</td>
<td>4.07 (1.47)</td>
<td>4.61 (3.87)</td>
<td>0.010</td>
</tr>
<tr>
<td>FIF50% (%pred) ~</td>
<td>78.3±30.0 ††</td>
<td>96.2±36.5</td>
<td>119.1±40.9</td>
<td>0.039</td>
</tr>
</tbody>
</table>

* p≤0.001 versus CC, HC
††p<0.008 versus HC

Abbreviations: CC+PVCM = Chronic Cough + Paradoxical Vocal Cord Movement; CC=chronic cough; HC=Healthy Control; EAHR-DRS: Extrathoracic airway hyperresponsiveness as FIF50 Dose response slope; (%fallFIF50/mL) = greatest %fall in FIF50% divided by cumulative mL of nebulised saline; C2=capsaicin dose to elicit 2 or more coughs 30sec after dose administered; C5= capsaicin dose to elicit 5 or more coughs 30sec after dose administered, Median (IQR) unless otherwise stated, ~Mean±SEM

Figure 2:1 Cough Reflex Sensitivity at Baseline
Median (IQR), *p<0.0005 vs. HC. C5= capsaicin dose to elicit 5 or more coughs 30sec after dose administered, PVCM: CC+paradoxical vocal cord movement, CC: chronic cough, HC: healthy controls
The maximum fall in FIF$_{50\%}$ during capsaicin challenge was similar across the 3 groups (p=0.52), with a median (IQR) fall in CC+PVCM of 19.5% (43.8), Cough alone 14.0% (12.9), and healthy controls 8.9% (21.2). Examination of the FIF$_{50\%}$-capsaicin dose response curves identified an initial, non sustained fall in FIF$_{50\%}$ after capsaicin inhalation. There was no correlation seen between the maximum fall in capsaicin and maximum fall in hypertonic saline suggesting that different mechanisms are occurring.

In contrast, the maximum fall in FIF$_{50\%}$ after hypertonic saline inhalation (Extrathoracic airway hyperresponsiveness) was significantly increased and sustained in the Cough+PVCM group. The maximum fall in FIF$_{50\%}$ for CC+PVCM was median (IQR) 21.6% (12.2) compared to that of Cough alone median (IQR) 12.3% (12.2) and the healthy controls, median (IQR) 12.8% (12.5) (p<0.001); [Table 2:2,Figure 2:2]. EAHR in the Cough alone group was not significantly different to healthy controls (p>0.05).

![Figure 2:2 Extrathoracic Airway Hyperresponsiveness as Maximum Fall in FIF$_{50\%}$](image)

* Median (IQR), * p<0.001 vs. HC, CC. PVCM: CC+Paradoxical vocal cord movement, CC: chronic cough, HC: healthy controls
FIF50% was significantly reduced at baseline in the Cough + PVCM group, compared to the healthy control group and reduced compared to the cough alone groups (p<0.05). FIF50% in the Cough alone group was not different to the healthy control group. The other spirometry parameters were not different across the groups.

Lower airway inflammation was assessed by FENO and induced sputum. FENO was noticeably higher in the Cough alone group when compared to the CC+PVCM and healthy control groups although this was not statistically significant [Table 2:2]. Induced sputum results for Cough+PVCM were within the normal range, indicating no evidence of lower airway inflammation in Cough +PVCM [Table 2:3]. Sputum eosinophils for the Cough alone group, median (IQR) were 6.75% (39.8), were significantly higher than that of Cough+PVCM, 0.25% (0.5), and Controls 0.25% (0.25) (p=0.003). Other sputum parameters were similar across groups [Table 2:3].

<table>
<thead>
<tr>
<th>Table 2:3 Induced Sputum Cell Counts</th>
</tr>
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<tbody>
<tr>
<td><strong>Induced Sputum Cell Counts</strong></td>
</tr>
<tr>
<td><strong>CC+PVCM</strong></td>
</tr>
<tr>
<td><strong>CC</strong></td>
</tr>
<tr>
<td><strong>HC</strong></td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>TCCx10^6/mL</td>
</tr>
<tr>
<td>2.79 (3.8)</td>
</tr>
<tr>
<td>3.87 (4.3)</td>
</tr>
<tr>
<td>2.88 (3.2)</td>
</tr>
<tr>
<td>0.92</td>
</tr>
<tr>
<td>Squamous (%)</td>
</tr>
<tr>
<td>3.85 (3.5)</td>
</tr>
<tr>
<td>2.9 (5.7)</td>
</tr>
<tr>
<td>3.85 (7.6)</td>
</tr>
<tr>
<td>0.71</td>
</tr>
<tr>
<td>Neutrophils(%)</td>
</tr>
<tr>
<td>24.8 (43.2)</td>
</tr>
<tr>
<td>17.1 (29.5)</td>
</tr>
<tr>
<td>22.0 (34.0)</td>
</tr>
<tr>
<td>0.60</td>
</tr>
<tr>
<td>Eosinophils(%)</td>
</tr>
<tr>
<td>0.25 (0.5)</td>
</tr>
<tr>
<td>6.75 (39.8)*</td>
</tr>
<tr>
<td>0.25 (0.25)</td>
</tr>
<tr>
<td>0.008</td>
</tr>
<tr>
<td>Macrophages(%)</td>
</tr>
<tr>
<td>51.5 (43.5)</td>
</tr>
<tr>
<td>56.5 (45.0)</td>
</tr>
<tr>
<td>74 (44.5)</td>
</tr>
<tr>
<td>0.16</td>
</tr>
<tr>
<td>Lymphocytes(%)</td>
</tr>
<tr>
<td>1.25 (2.75)</td>
</tr>
<tr>
<td>0 (0.25)</td>
</tr>
<tr>
<td>0.83 (1.5)</td>
</tr>
<tr>
<td>0.10</td>
</tr>
<tr>
<td>Col. Epithelial(%)</td>
</tr>
<tr>
<td>5.5 (4.7)</td>
</tr>
<tr>
<td>8.3 (12.8)</td>
</tr>
<tr>
<td>1.6 (2.7)</td>
</tr>
<tr>
<td>0.15</td>
</tr>
</tbody>
</table>

*p<0.005 versus HC and CC+PVCM. Abbreviations: CC+PVCM = Chronic Cough + Paradoxical Vocal Cord Movement; CC=chronic cough; HC=Healthy Control, Median (IQR)

**2.6 Discussion**

This study has identified that paradoxical vocal cord movement is commonly present in chronic persistent cough, being observed in 56% of subjects studied. Extrathoracic airway hyperresponsiveness was also significantly increased in the Cough+PVCM group compared to that of the Cough alone and healthy control groups. PVCM and
EAHR are both manifestations of laryngeal dysfunction, and these data provide objective evidence of laryngeal dysfunction in chronic cough and demonstrates that it is associated with quality of life impairment and sensory hyperreactivity of the cough reflex.

PVCM has typically been associated with Vocal Cord Dysfunction, however there is now reason to suspect an overlap between VCD and chronic persistent cough (4). Vertigan et al. reported an overlap in the symptomatology of the 2 conditions (415). Milgrom et al (79) claimed that 20% of their patients with chronic cough also had abnormal vocal fold motion on laryngoscopy. Andrianopoulos et al (377) found that 59% of their subjects with ‘symptomatic episodic paroxysmal laryngospasm’, another term for vocal cord dysfunction, presented with cough as their primary symptom. Murry et al. has reported several cases of refractory cough and PVCM, where respiratory retraining together with proton pump inhibitors for laryngopharyngeal reflux successfully resolved the symptoms (349, 416).

The effect of PVCM is to cause glottic closure and upper airway narrowing. This narrowing of the upper airway causes symptoms such as cough, shortness of breath and wheeze and is commonly mistaken for asthma. Paradoxical vocal cord closure during inspiration results in reduced inspiratory airflows and when assessed after a provocation stimulus, the laryngeal response is termed extrathoracic airway hyperresponsiveness (19, 387). Asthma, gastroesophageal reflux, and rhinosinusitis are associated with extrathoracic airway hyperresponsiveness and also PVCM.
Prudon et al have reported an enhanced glottic stop reflex in chronic cough patients (419) in response to inhaled ammonia. Accentuation of the glottic closure reflex has been proposed as a mechanism of PVCM in response to irritant exposures, or chronic inflammation of the larynx from GORD or rhinosinusitis that predisposes the larynx to become more sensitive to inhaled irritant exposures that trigger PVCM (148). Vertigan et al (4) also proposed extrathoracic airway hyperresponsiveness as a common mechanism that may explain the overlap between refractory chronic cough and Vocal Cord Dysfunction and suggested that treatment approaches for Vocal cord dysfunction, such as speech language therapy, could be applicable to people with chronic cough. A subsequent randomised trial found that speech language therapy was effective in refractory chronic cough (345). The results of the present study provide a mechanistic explanation for these responses by demonstrating that laryngeal dysfunction is common in chronic cough.

Other possible explanations for our findings include PVCM being secondary to cough, PVCM causing cough, and that cough and PVCM are unrelated. Our data favours a common sensory hypersensitivity to explain both cough and PVCM; however, a randomised treatment trial would be required to confirm this. There is little prior work to support PVCM as a secondary effect of coughing, however some have suggested that cough may occur in response to PVCM. In vocal cord dysfunction, PVCM is the defining characteristic seen in all patients, and cough is also common, occurring in over 50% of vocal cord dysfunction subjects. One explanation for this is that cough occurs in response to paradoxical vocal cord movement as a protective reflex response to open the vocal cords. If this were the case, then treatment that reduced cough
frequency would potentially increase PVCM. So far there are no direct observations to support this hypothesis, however data are limited and the cough response to successful vocal cord dysfunction treatment has not been reported.

It has also been postulated that there is a common sensory hyperreactivity that underlies VCD and cough, that has previously been described as the ‘irritable larynx syndrome’ (377). Cough, PVCM, and extrathoracic airway hyperresponsiveness can be seen to represent the efferent/motor consequences of this hypersensitivity.

The subjects with cough in this study were recruited from a clinic setting and consisted of primarily middle-aged females (79%) with cough duration of median 24 months. These characteristics are consistent with those previously reported chronic cough patients (33, 65, 280, 420). Like other cough series, the medical conditions that were associated with persistent cough included asthma, gastroesophageal reflux, rhinitis/post nasal drip, eosinophilic bronchitis and angiotensin converting enzyme inhibitor use. Cough reflex sensitivity was assessed using a validated technique (65, 418) and we found similar levels of cough reflex hypersensitivity in chronic cough to those reported elsewhere (65, 418, 420) and similar CRS values for our control population to that previously reported (65, 280). Together, these observations suggest that we have studied a group of patients with chronic cough that are representative of those previously reported in the literature, and similarly, we have used an appropriate control group for comparison. Induced sputum cell counts were normal in the Cough+PVCM subjects. This suggests that there is no lower airway inflammation (bronchitis) in these subjects, and supports the localisation of their problem to the larynx and upper airway.
In conclusion, this study identifies that laryngeal dysfunction commonly occurs in chronic persistent cough where it causes laryngeal symptoms, quality of life impairment and paradoxical vocal cord movement. It is accompanied by hyperresponsiveness of the extrathoracic airway to inhaled stimuli that lead to reduced inspiratory airflow. This is a clinically significant problem that provides an explanation for the proven success of speech pathology treatment as part of the treatment programme for chronic persistent cough.
STATEMENT II

This statement explains the contribution of all authors in the article listed below:


Table: Author contribution percentage and description of contribution to published article listed above

<table>
<thead>
<tr>
<th>Author</th>
<th>Contribution %</th>
<th>Description of Contribution to Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicole Ryan</td>
<td>70</td>
<td>Co-designed and executed the study. Collected, analysed and interpreted the data. Wrote the manuscript.</td>
</tr>
<tr>
<td>Anne Vertigan</td>
<td>10</td>
<td>Performed speech language pathology treatment on subjects. Reviewed and contributed to manuscript.</td>
</tr>
<tr>
<td>Peter Gibson</td>
<td>20</td>
<td>Co-designed the study. Performed physical examinations and laryngoscopy on subjects. Prescribed medication. Helped in the interpretation of data and edited manuscript.</td>
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</table>
Chapter 3 Chronic cough and laryngeal dysfunction improve with specific treatment of cough and paradoxical vocal fold movement


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3.1 Abstract

3.1.1 Rationale

Chronic persistent cough can be associated with laryngeal dysfunction that leads to symptoms such as dysphonia, sensory hyperresponsiveness to capsaicin, and motor dysfunction with paradoxical vocal fold movement and variable extrathoracic airflow obstruction (reduced inspiratory airflow). Successful therapy of chronic persistent
cough improves symptoms and sensory hyperresponsiveness. The effects of treatment for chronic cough on laryngeal dysfunction are not known.

### 3.1.2 Objective
The aim of this study was to investigate effects of therapy for chronic cough and paradoxical vocal fold movement.

### 3.1.3 Methods
Adults with chronic cough (n=24) were assessed before and after treatment for chronic persistent cough by measuring quality of life, extrathoracic airway hyperresponsiveness to hypertonic saline provocation, capsaicin cough reflex hypersensitivity and fibreoptic laryngoscopy to observe paradoxical vocal fold movement. Subjects with chronic cough were classified into those with (n=14) or without (n=10) paradoxical vocal fold movement based on direct observation at laryngoscopy.

### 3.1.4 Results
Following treatment there was a significant improvement in cough related quality of life and cough reflex sensitivity in both groups. Subjects with chronic cough and paradoxical vocal fold movement also had additional improvements in extrathoracic airway hyperresponsiveness and paradoxical vocal fold movement. The degree of improvement in cough reflex sensitivity correlated with the improvement in extrathoracic airway hyperresponsiveness.

### 3.1.5 Conclusions
Laryngeal dysfunction is common in chronic persistent cough, where it is manifest as paradoxical vocal fold movement and extrathoracic airway hyperresponsiveness.
Successful treatment for chronic persistent cough leads to improvements in these features of laryngeal dysfunction.

3.2 Background

Chronic persistent cough is responsible for a significant illness burden in the community \(^{(166)}\). Laryngeal problems are increasingly recognised as being part of the chronic cough syndrome, and include voice symptoms such as dysphonia \(^{(415)}\), hyperresponsiveness of the extrathoracic airway with enhanced glottic stop reflex \(^{(419)}\), reduced inspiratory airflow following a provocation stimulus \(^{(345, 346, 387)}\), and paradoxical vocal fold movement (PVFM) where the vocal folds paradoxically adduct during inspiration \(^{(4, 349)}\). Speech language therapy is effective for laryngeal dysfunction, and a randomised controlled trial has shown that speech language therapy treatment based on the approaches used in vocal cord dysfunction and hyperfunctional voice disorders is also effective in chronic cough \(^{(345)}\). Speech language therapy has been shown to improve symptoms \(^{(345)}\) and voice abnormalities \(^{(421)}\) in refractory chronic cough, however the effect on other laryngeal problems in chronic persistent cough is not known. We hypothesised that treatment of patients with chronic cough and laryngeal dysfunction would result in improvement of afferent cough reflex sensitivity and the laryngeal abnormalities of paradoxical vocal fold movement and extrathoracic airway hyperresponsiveness. The aim of this study was to investigate effects of therapy for chronic cough and paradoxical vocal fold movement.
3.3 Methods

3.3.1 Subjects

Subjects with chronic persistent cough (n=24) were recruited from the Respiratory Ambulatory Care Service at John Hunter Hospital in Newcastle, New South Wales, Australia. Subjects were aged between 18 and 80 years with a persistent cough of more than eight weeks. They were non-smokers or ex-smokers with less than ten pack years, had no other active respiratory or cardiac disease, and were required to have a normal chest radiograph. They were classified into 2 groups based on the presence (n=14; Cough+PVFM) or absence (n=10; Cough alone) of PVFM observed at fiberoptic laryngoscopy. All subjects provided written informed consent for this study, which was approved by the University of Newcastle’s Human Research Ethics Committee and the Hunter New England Human Research Ethics Committee.

3.3.2 Study Design

Subjects attended a total of 5 visits over a period of 18 weeks. At visit 1, clinical history, current respiratory symptoms, medication use, passive smoking history and an in-house rhinitis symptoms score were recorded. A number of questionnaires were also administered and these included a cough specific quality of life questionnaire (Leicester Cough Questionnaire, (LCQ))\(^{(184)}\), a gastroesophageal reflux symptoms questionnaire \(^{(422)}\), a generic quality of life questionnaire (SF36) \(^{(423)}\) and a laryngeal dysfunction questionnaire (LDQ) \(^{(424)}\).

All subjects were non-smokers or ex-smokers with less than 10 pack years and not exposed to current passive smoking and this was confirmed by exhaled carbon monoxide measurement \(^{(425, 426)}\). Fractional expired nitric oxide (FENO) was also
measured (417). At visit 2 each subject underwent capsaicin cough reflex sensitivity testing (CRS) (65, 418) followed by sputum induction using 4.5% saline (427). Visit 3 included a fibreoptic laryngoscopy, followed by hypertonic saline provocation challenge (HSC) with inspiratory flow volume curve measurement (392, 410) and then post-challenge laryngoscopy. The chronic cough subjects were then treated for their cough-related diagnoses (see below). Subjects returned 8 weeks after treatment to complete post treatment visits. Visit 4 repeated symptom questionnaires, FENO, CRS and sputum induction. Laryngoscopy was repeated before and after hypertonic saline provocation challenge at visit 5. Inspiratory/ expiratory flow volume curves were performed before and during saline challenge, after each dose.

### 3.3.3 Treatment Programme

A probability based diagnostic assessment approach was used (306) with the addition of induced sputum analysis to identify eosinophilic bronchitis (428), fibreoptic laryngoscopy to identify PVFM (109), and history and polysomnography to identify obstructive sleep apnoea (67). Asthma was established by doctor’s diagnosis and current bronchial hyperresponsiveness and subjects were treated with inhaled corticosteroid/long-acting beta agonist combination (budesonide/eformoterol 200/6mcg bd via Turbuhaler, AstraZeneca Sweden). Gastroesophageal reflux was suggested by a history of heartburn, dysphagia, or acid regurgitation, or an association between cough and posture or eating. Antireflux therapy included proton pump inhibitor (omeprazole 20mg bid) and antireflux measures including advice about diet and sleeping posture. Rhinosinusitis was suggested by symptoms of nasal obstruction or sneezing, postnasal drip, nasal discharge, and when clinical or fibreoptic nasendoscopic examination of the
nasopharynx and oropharynx revealed mucosal inflammation or mucopurulent secretions. In the absence of these criteria, a sinus computed tomography (CT) scan was performed if there was strong clinical suspicion of rhinosinusitis. Subjects with rhinitis received oral antihistamine (cetirizine, 10 mg od) and nasal corticosteroid spray (budesonide 128 mcg bid). Angiotensin Converting Enzyme inhibitors (ACE-I) were ceased and replaced with alternate antihypertensive medication. Subjects with eosinophilic bronchitis (induced sputum eosinophils > 3%) received inhaled corticosteroid (budesonide 200mcg bd via turbuhaler, AstraZeneca, Sweden). Subjects with PVFM were treated with speech language therapy that was administered by a speech pathologist that involved 4 weekly sessions addressing education, vocal hygiene, cough suppression strategies, relaxed throat breathing techniques and psychoeducational counseling. Obstructive sleep apnea was suggested by a history of snoring, sleep disturbance or excessive daytime somnolence, confirmed by overnight polysomnography, and treated by nasal continuous airways pressure (nCPAP).

3.3.4 Clinical Methods

3.3.4.1 Forced Expired Nitric Oxide

Forced Expired Nitric Oxide (FENO) was measured using an on-line chemiluminescence analyser (NiOx, Aerocrine AB, Smidesvägen 12, SE-171 41 Solna, Sweden) according to published European Respiratory Society/American Thoracic Society guidelines. Subjects inhaled medical-grade compressed air that contained < 2 ppb NO and then exhaled via a high expiratory resistance while targeting a mouth pressure of 20 mm Hg. This produces an expiratory flow rate of 50 mL/s (including
analyser sampling rate). Exhalations were repeated until three plateau FENO values vary by < 5%. The mean of the three replicate FENO values was used.

3.3.4.2 Hypertonic Saline Challenge (HSC)

Prior to HSC (429), subjects withheld bronchodilators for their duration of action and antihistamines for 48 hours. Subjects were instructed in the correct performance of inspiratory and expiratory Flow Volume Loops (FVL). The manoeuvre consisted of tidal breathing, deep inspiration to total lung capacity, forced expiration to residual volume followed by deep inspiration to total lung capacity. Hypertonic saline (4.5%) was inhaled for doubling time periods and a inspiratory-expiratory FVL was measured, in duplicate, 60 seconds after each saline dose using a KoKo K323200 Spirometer (Technipro, North Parramatta, Australia). Forced expiratory time was held constant at subsequent manoeuvres in order to ensure consistency. If the FEV₁ fell by more than 15%, 200µg of salbutamol was administered via a valved holding chamber (Volumatic, Allen and Hanburys, GlaxoSmithKline Australia Pty Ltd, Boronia, Australia).

3.3.4.3 Capsaicin Cough Reflex Sensitivity testing (CRS)

Solutions of capsaicin (Sigma-Aldrich Co., Castle Hill, Australia) concentrations ranging from 0.98 to 500 µM were prepared daily. Subjects inhaled single breaths (from Functional Residual Capacity (FRC) to total lung capacity (TLC)) of capsaicin aerosol from a compressed air-driven nebulizer (model 646, Technipro, North Parramatta, Australia) controlled by a dosimeter (KoKo Digidoser 323200; Technipro Marketing Pty Ltd., Sydney, New South Wales, Australia). The inspiratory flow was standardised at 0.5L/s with an inspiratory flow regulator valve. Cough counting was done for 30s after
exposure to each dose, and the investigation ended when the subject coughed five or more times in response to one dose, or received a dose of the highest concentration.

3.3.4.4 Fibre Optic Laryngoscopy (FOL)
Flexible fibreoptic laryngoscopy (Pentax VNL-1330, Asahi Optical Co, Tokyo, Japan) was performed at baseline and immediately after a hypertonic saline challenge (392, 410). Prior to the procedure, the nasal cavity was anesthetised with lignocaine hydrochloride 5.0% and phenylephrine 0.5% (ENT Technologies, Malvern, Victoria, Australia). The nasendoscope was then passed into the nares and positioned above the larynx. The movements of the true vocal folds were observed during tidal respiration over a period ≥ 2 minutes. Adduction of the vocal folds throughout the inspiratory phase and/or the beginning of expiration was considered as PVFM. These findings encompassed paradoxical glottic closure during several respiratory cycles ranging from a partial (> 50%) adduction of the true vocal folds without cordal contact to a total closure of the anterior two-third of the vocal folds. The presence of an open posterior glottic chink was noted if present. Adduction that occurred only during the second part of exhalation is a normal variant and was not recorded as PVFM.

The gold standard used for the diagnosis of PVFM during the study was a positive laryngoscopy demonstrating paradoxical vocal fold motion at baseline and/or post-HSC while symptomatic.

3.3.5 Analysis
All analyses were performed using statistical and data analysis software STATA (Statacorp, Texas, USA). Non parametric quantitative data were compared using the
Wilcoxon rank sum test and for parametric data, t test for matched pair data was used. Significance for two group comparison was set at p<0.05.

3.4 Results

Twenty-four subjects with a chronic persistent cough participated in the study. The subjects had a median (IQR) cough duration of 24 (13-84) months and were predominantly female [Table 3:1]. There were 14 subjects with Cough+PVFM and 10 with Cough alone (CC).

<table>
<thead>
<tr>
<th>Table 3:1 Subject Characteristics</th>
<th>CC+PVFM</th>
<th>CC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>2/12</td>
<td>3/7</td>
<td>0.62</td>
</tr>
<tr>
<td>Age, years</td>
<td>56 (40)</td>
<td>58 (15)</td>
<td>0.88</td>
</tr>
<tr>
<td>Age Range, years</td>
<td>22-78</td>
<td>47-69</td>
<td></td>
</tr>
<tr>
<td>Exhaled CO, ppm, Mean±SEM</td>
<td>1.69±0.35</td>
<td>1.0±0.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Cough Duration, months</td>
<td>18 (48)</td>
<td>36 (168)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

CC+PVFM = Chronic Cough + Paradoxical vocal fold movement
CC= Chronic Cough alone, Median (IQR) unless otherwise stated

Subjects were treated [Table 3:2] and both groups responded with a significant improvement in cough-related quality of life (LCQ, p=0.001 for Cough+PVFM Group, p=0.01 for CC Group), [Table 3:3] and cough reflex sensitivity (C5, p=0.008 for Cough+PVFM Group and C5, p=0.04 for CC Group), [Figure 3:1Figure 3:2].

<table>
<thead>
<tr>
<th>Table 3:2 Subject Diagnosis and Treatment</th>
<th>CC+PVFM</th>
<th>CC</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>7</td>
<td>5</td>
<td>Inhaled Corticosteroid</td>
</tr>
<tr>
<td>GORD</td>
<td>11</td>
<td>10</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>11</td>
<td>7</td>
<td>Nasal Steroid</td>
</tr>
<tr>
<td>Eosinophilic Bronchitis</td>
<td>9</td>
<td>4</td>
<td>Antihistamine</td>
</tr>
<tr>
<td>Sleep Apnoea</td>
<td>1</td>
<td>3</td>
<td>Inhaled Corticosteroid</td>
</tr>
<tr>
<td>PVFM†</td>
<td>14*</td>
<td>0</td>
<td>nCPAP</td>
</tr>
</tbody>
</table>

*4 Subjects did not attend speech language therapy, PVFM=paradoxical vocal fold movement, CC=chronic cough alone, CC+PVFM = Chronic Cough + Paradoxical vocal fold movement , nCPAP=nasal continuous airways pressure
Table 3: Change in symptom questionnaires before and after treatment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>CC+PVFM</th>
<th>CC</th>
<th>p</th>
<th>CC+PVFM</th>
<th>CC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCQ Score</td>
<td>10.5 (3.1)</td>
<td>16.2 (1.5)</td>
<td>0.001*</td>
<td>10.4 (6.2)</td>
<td>17.5 (7.1)</td>
<td>0.01*</td>
</tr>
<tr>
<td>GORD Score</td>
<td>15 (7)</td>
<td>9 (6)</td>
<td>0.005*</td>
<td>15.5 (7)</td>
<td>11 (6)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Rhinitis Score</td>
<td>9 (5.5)</td>
<td>4.5 (9)</td>
<td>0.04*</td>
<td>10.5 (3.5)</td>
<td>5 (6.5)</td>
<td>0.03*</td>
</tr>
<tr>
<td>LDQ Score</td>
<td>5 (4)</td>
<td>3.5 (4)</td>
<td>0.008*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A value of p<0.05 considered to be significant, LCQ=Leicester cough questionnaire, GORD=Gastroesophageal reflux disease questionnaire, LDQ=Laryngeal dysfunction questionnaire, Median (IQR) unless otherwise stated.

Figure 3:1 Cough reflex sensitivity (CRS) to capsaicin before (pre) and after (post) treatment in the chronic cough with paradoxical vocal fold movement (CC+PVFM) group
Solid bars are median values, p=0.005, C5= capsaicin dose to elicit 5 or more coughs 30sec after dose administered

Figure 3:2 Cough reflex sensitivity (CRS) to capsaicin before (pre) and after (post) treatment in the chronic cough alone (CC) group
Solid bars are median values, p=0.04, C5= capsaicin dose to elicit 5 or more coughs 30sec after dose administered

For the Cough+PVFM subjects, we found that PVFM and extrathoracic airway hyperresponsiveness responded positively to treatment and was significantly reduced for the Cough+PVFM group, [Figure 3:3].

![Figure 3:3 Extrathoracic Airway Hyperresponsiveness (EAHR) represented as FIF<sub>50</sub> Dose Response Slope to hypertonic saline provocation before (pre) and after (post) treatment in the chronic cough with paradoxical vocal fold movement (CC+PVFM) group. Solid bars are median values, p=0.02](image)

Ten of the 14 subjects with PVFM attended speech language therapy. After treatment, PVFM had resolved in 8 of these 10 subjects (p=0.039 by McNemar’s chi square test).

Four of the Cough+PVFM subjects did not attend speech language therapy before returning for their post-treatment visits. PVFM did not resolve in 3 of these 4 subjects but did resolve in 1 subject. Interestingly this subject was the only male in this group of four and had the shortest cough duration (12 months) and youngest age (22 years).

In the Cough alone (CC) group, extrathoracic airway responsiveness was not increased and with therapy remained unchanged from baseline [Figure 3:4].
Baseline spirometry and FENO were not altered by treatment for both cough groups

[Table 3:4].

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CC+PVFM</th>
<th>p value</th>
<th>Baseline</th>
<th>CC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENO, ppb</td>
<td>13.7 (8.8)</td>
<td>12.9 (7.6)</td>
<td>0.83</td>
<td>26.0 (18.9)</td>
<td>21.7 (13.2)</td>
<td>0.33</td>
</tr>
<tr>
<td>FEV1 (%pred) Mean ± SEM</td>
<td>90.8 (±19.3)</td>
<td>90.7 (±18.3)</td>
<td>0.48</td>
<td>90.8 (±26.5)</td>
<td>91.9 (±24.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>99.6 (29.1)</td>
<td>93.1 (15.0)</td>
<td>0.55</td>
<td>100.9 (15.9)</td>
<td>102.2 (17.4)</td>
<td>0.88</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>82 (8)</td>
<td>82 (11)</td>
<td>0.90</td>
<td>74 (9)</td>
<td>74 (10)</td>
<td>0.54</td>
</tr>
<tr>
<td>FIF50% (L/s)</td>
<td>2.97 (1.72)</td>
<td>2.85 (1.10)</td>
<td>0.38</td>
<td>4.07 (1.47)</td>
<td>4.08 (1.52)</td>
<td>0.11</td>
</tr>
<tr>
<td>FIF50% (%pred)</td>
<td>78.3 (±30.0)</td>
<td>70.6 (±24.4)</td>
<td>0.24</td>
<td>96.2 (±36.5)</td>
<td>106.6 (±31.3)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Median (IQR) unless otherwise stated.

### 3.5 Discussion

This study has identified that paradoxical vocal fold movement and extrathoracic airway hyperresponsiveness are improved by treatment for chronic persistent cough, and that this improvement occurs alongside improvements in cough specific quality of life and cough reflex sensitivity. The data provides objective evidence of laryngeal dysfunction in some patients with chronic cough, and shows that it responds to therapy for chronic persistent cough. These results are consistent with Vertigan et al.\(^{(345)}\)
who found that a substantial proportion of their refractory chronic cough participants had extrathoracic airway hyperresponsiveness, similar to subjects who had vocal cord dysfunction (VCD) however they extend these results by showing that PVFM and EAHR can improve after treatment for chronic persistent cough.

Laryngeal dysfunction is increasingly recognised in chronic persistent cough. Symptoms such as voice hoarseness, dyspnoea, wheeze and cough may all occur as a result of laryngeal dysfunction (415). Prudon et al have also reported laryngeal dysfunction in chronic cough where they described an enhanced glottic stop reflex in chronic cough patients (419). These patients exhibited enhanced glottic closure in response to inhaled ammonia. Extrathoracic airway hyperresponsiveness is another manifestation of laryngeal dysfunction and has been reported in several conditions where cough is prominent, such as rhinosinusitis, ACE inhibitor cough, gastroesophageal reflux, and patients with asthma-like symptoms (19, 346, 387). Speech language therapy is effective for laryngeal dysfunction, and it has previously been shown to be effective for refractory cough (345). The results of the current study provide a mechanistic explanation for these responses by demonstrating that laryngeal dysfunction is responsive to treatment for chronic persistent cough, and correlates with an improvement in cough reflex sensitivity.

In this study we used an open design with objective measures to assess outcome. Although a nonrandomized design is a limitation, our primary purpose was to determine if the measures of laryngeal dysfunction that occur in chronic persistent cough are responsive to effective therapy. The study achieved these aims by using objective measures and has provided novel data on how PVFM and EAHR improve
with therapy of chronic persistent cough. The results extend what is known about how successful therapy works in chronic persistent cough, and provide data that supports the favourable responses reported for symptoms, cough frequency, and measures of cough reflex sensitivity. We now show that laryngeal dysfunction also improves with treatment of chronic persistent cough in those patients with cough and PVFM. Future studies could provide further evidence of efficacy by using a randomised design, and potentially assessing any incremental benefits of speech language treatment.

We studied subjects who were representative of those with chronic persistent cough. They were primarily middle-aged females (80%) with a significant cough duration and similar prevalence of the medical conditions that have been associated with persistent cough (65, 280, 420). We assessed cough reflex sensitivity to capsaicin using a validated technique and we found similar levels of cough reflex hypersensitivity to those reported elsewhere (65, 280). This suggests that the results can be generalised to patients with chronic persistent cough.

There was a moderately significant \( r= -0.65, p=0.02 \) correlation in the Cough+PVFM Group for treatment related changes in extrathoracic airway hyperresponsiveness dose response slope and CRS-C5 [Figure 3:5]. This decrease in cough sensitivity corresponding with a fall in extrathoracic airway hyperresponsiveness dose response slope further supports validity of PVFM treatment with speech language therapy compared to no correlation between these two measures for the CC Group who did not undertake speech language therapy.
In conclusion, this study identifies that the laryngeal dysfunction that occurs in some patients with chronic persistent cough is responsive to therapy.

Competing Interests: the authors declare that they have no competing interests.

Author's contributions: NR and PG planned the study. NR recruited the subjects and performed the objective cough and EAHHR methods, questionnaires, assisted with fibreoptic laryngoscopy, collected and reviewed data, participated in the design and drafted the manuscript. PG performed patient assessment, physical examinations and fibreoptic laryngoscopy and prescribed medication. AV performed speech pathology treatment and reviewed the manuscript. PG also participated in the manuscript drafting and coordination of the manuscript. All authors read and approved the final manuscript.

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STATEMENT III

This statement explains the contribution of all authors in the article listed below:

Ryan NM, Vertigan AE, Bone SB, Gibson PG. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough Cough. 2010;6:5.

Table: Author contribution percentage and description of contribution to published article listed above

<table>
<thead>
<tr>
<th>Author</th>
<th>Contribution %</th>
<th>Description of Contribution to Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicole Ryan</td>
<td>65</td>
<td>Co-designed and executed the study. Collected, analysed and interpreted the data. Wrote the manuscript.</td>
</tr>
<tr>
<td>Anne Vertigan</td>
<td>15</td>
<td>Co-designed study. Performed speech language pathology intervention. Interpreted speech/voice data. Reviewed and contributed to manuscript.</td>
</tr>
<tr>
<td>Sarah Bone</td>
<td>10</td>
<td>Performed speech language intervention. Entered and interpreted speech/voice data. Reviewed manuscript.</td>
</tr>
<tr>
<td>Peter Gibson</td>
<td>10</td>
<td>Co-designed the study. Helped in the interpretation of data and edited manuscript.</td>
</tr>
</tbody>
</table>
Chapter 4  Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough

Ryan NM, Vertigan AE, Bone SL, Gibson PG. Cough reflex sensitivity improves with speech language pathology management of refractory chronic cough Cough. 2010;6:5.

1,2Nicole M Ryan, 1,3Anne E Vertigan, 3 Sarah Bone, 1,2Peter G Gibson

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4.1 Abstract

4.1.1 Rationale

Speech language pathology is an effective management intervention for chronic cough that persists despite medical treatment. The mechanism behind the improvement has not been determined but may include active cough suppression, reduced cough sensitivity or increased cough threshold from reduced laryngeal irritation. Objective
measures such as cough reflex sensitivity and cough frequency could be used to
determine whether the treatment response was due to reduced underlying cough
sensitivity or to more deliberate control exerted by individual patients. The number of
treatments required to effect a response was also assessed.

4.1.2 Objective
The aim of this study was to investigate subjective and objective measures of cough
before, during and after speech language pathology treatment for refractory chronic
cough and the mechanism underlying the improvement.

4.1.3 Methods
Adults with chronic cough (n=17) were assessed before, during and after speech
language pathology intervention for refractory chronic cough. The primary outcome
measures were capsaicin cough reflex sensitivity, automated cough frequency
detection and cough-related quality of life.

4.1.4 Results
Following treatment there was a significant improvement in cough related quality of
life (Median (IQR) at baseline: 13.5 (6.3) vs. post treatment: 16.9 (4.9), p=0.002), objective
cough frequency (Mean±SD at baseline: 72.5±55.8 vs. post treatment: 25±27.9 coughs/hr,
p=0.009), and cough reflex sensitivity (Mean±SD log C5 at baseline: 0.88±0.48 vs. post
treatment: 1.65±0.88, p<0.0001).

4.1.5 Conclusions
This is the first study to show that speech language pathology management is an
effective intervention for refractory chronic cough and that the mechanism behind the
improvement is due to reduced laryngeal irritation which results in decreased cough
sensitivity, decreased urge to cough and an increased cough threshold. Speech language pathology may be a useful and sustained treatment for refractory chronic cough.

4.2 Introduction

Chronic cough that persists despite medical treatment (termed refractory cough) is a difficult problem frequently associated with increased cough reflex sensitivity \((6, 8, 321)\). Management using speech language pathology is effective for both refractory cough and its associated voice disorder \((345, 430)\) but the mechanism behind the symptom improvement has yet to be determined. Cough reflex hypersensitivity plays an important role in chronic cough \((254, 431)\) and it was hypothesised that speech language pathology would either increase the threshold for cough or reduce cough sensitivity \((345)\). These effects could be achieved by either a behavioural approach to cough suppression or improved vocal hygiene leading to reduced laryngeal irritation.

This study sought to investigate capsaicin cough reflex sensitivity and automated cough frequency monitoring in patients with refractory chronic cough undergoing speech language pathology intervention. Cough reflex sensitivity testing and cough frequency monitoring are two objective measures allowing standardised assessment as well as providing an understanding of possible mechanisms of effect. Capsaicin is an extract of hot peppers and is commonly used as a tussive agent in clinical research because it induces cough in a safe, dose-dependent and reproducible manner \((272, 418, 432)\). Our aim was to objectively measure changes in cough reflex sensitivity and cough frequency prior to, during and after a speech language pathology treatment programme for refractory cough.
It was hypothesised that speech language pathology intervention for chronic cough would result in decreased cough reflex sensitivity, reduced cough frequency, improvement in clinical outcome and improvement in cough and laryngeal subjective measures. We also sought to determine how many treatment sessions a patient required to show an improvement and if these benefits were maintained post intervention.

4.3 Methods
A previous pilot study compared two behavioural approaches (isolated cough suppression techniques and supportive counselling) for refractory chronic cough (CC) to a CC control group and showed that there was no change in cough reflex sensitivity (CRS) measured as C5 after 1 hour of intervention. These were used to establish the current study in the following ways;

1. C5 does not respond to isolated behavioural approaches,
2. C5 does not change after 1x1 hour session of an isolated behavioural approach, and,
3. CRS testing measured as C5 is a highly reproducible test.

4.3.1 Participants
Adult non-smokers (n=17) with chronic persistent cough that was refractory to medical assessment and treatment \(^{(5, 306)}\) and who were referred for speech language pathology management for cough \(^{\text{(345)}}\) were eligible for the study. All participants provided written informed consent for this study, which was approved by the University of Newcastle’s Human Research Ethics Committee and the Hunter New England Human
Research Ethics Committee. “For detailed description of the participants, procedures, and analysis, see additional file 1: Participant details and results.”

4.3.2 Study Design

Participants attended for a maximum of 6 visits (a baseline visit, up to 4 treatment visits and a post treatment visit) over a period of 14 to 18 weeks. At visit 1, there was a voice assessment by a qualified speech language pathologist. This involved a clinical case history, symptom frequency and severity rating\(^\text{(415)}\), auditory perceptual voice analysis and instrumental voice analysis utilizing acoustic and electroglottographic assessment. The auditory perceptual analysis was conducted utilizing the Perceptual Voice Profile by Oates and Russell\(^\text{(423)}\) whereby 15 perceptual parameters of voice pitch, loudness and quality are rated on a severity scale from normal to severe. A clinical research officer then administered several questionnaires,\(^\text{(82, 184, 422, 424, 434, 435)}\) and conducted cough reflex sensitivity with capsaicin testing\(^\text{(65, 418)}\) and cough frequency by Leicester Cough Monitor\(^\text{(436)}\) during the visit period. Visits 2-5 consisted of a 30 minute published speech language pathology programme for chronic persistent cough\(^\text{(345)}\) followed by cough reflex testing and cough frequency. A post treatment visit was conducted 2 to 3 weeks after the final speech language pathology programme session (Visit 6) for objective cough monitoring.

4.3.3 Speech Pathology treatment programme for chronic persistent cough

The speech pathology programme for chronic cough has been described previously\(^\text{(345)}\) and consisted of four components;

1. education,
2. specific cough suppression strategies such as the Cough Suppression Swallow, Cough Control Breathing or paradoxical vocal fold movement release breathing techniques,

3. vocal hygiene training, and

4. psychoeducational counselling.

All participants received each of the four components of the program.

4.3.4 Capsaicin Cough Reflex Sensitivity (CRS) testing

Capsaicin CRS (65, 418) was performed as previously reported with the addition of a participant urge-to-cough score (215) where the participant was asked to rate their urge to cough after each dose inhalation of capsaicin according to a modified Borg scale where 0 = “No urge to cough” up to 10 = “Maximum urge to cough”.

4.3.5 Leicester Cough Monitor (LCM)

The LCM (436) is a digital ambulatory cough monitor and external free-field microphone. This was attached to the participant at the beginning of each objective cough measurement visit and removed at the end of the visit. The cough frequency collection period therefore encompassed a recording time of about one hour in which questionnaires and cough reflex testing were performed. This measurement was used to complement the cough reflex sensitivity test by measuring any change in the patient’s frequency of coughing after speech pathology intervention. Data stored on the recorder was downloaded onto a computer where it was analysed by an automated cough detection algorithm (the Leicester Cough Algorithm, (437, 438). Cough was defined as a characteristic explosive sound (throat clears were classified by operator input as a “non-cough” to be consistent with CRS cough counting) and reported as coughs/hour.
4.3.6 Analysis

All analyses were performed using statistical and data analysis software STATA (Statacorp, Texas, USA). Comparisons of log cough sensitivity (measured as C5 and cough threshold) between baseline and each visit was undertaken using a generalised linear mixed model (GLMM) with a random intercept term which takes into account the repeated observations on individuals. Standard errors were estimated using bootstrapping \(^{[439]}\) and results were expressed as Mean±SD. Parametric bootstrap is a practical tool for addressing problems associated with inference from GLMMs by producing sensible estimates for standard errors. Similar models were used to examine the change in cough frequency although data was assumed to have a Poisson distribution. P values <0.05 were considered significant.

Figures were produced using GraphPad Prism 4 (GraphPad Software, Inc, California, USA).

4.4 Results

Seventeen participants (8 male and 9 female) with a chronic persistent cough participated in the study. The participants had a median (IQR) cough duration of 60 (147) months and age of 61 (20) years with normal spirometry [Table 4:1]. Co-morbidities included gastroesophageal reflux disease (n=10), asthma (n=2), eosinophilic bronchitis (n=1) and rhinitis (n=8). Treatment trials were implemented for these conditions including proton pump inhibitors for gastroesophageal reflux disease, inhaled corticosteroids for asthma and eosinophilic bronchitis, and nasal corticosteroid and/or antihistamine for rhinitis. When cough proved refractory to these treatments, speech language pathology was implemented. An initial participant cough assessment
performed by a speech language pathologist found that 63% of participants had abnormal auditory perceptual voice analysis. There was also a high incidence of abnormal acoustic and electrographic instrumental voice analysis [Table 4:1].

### Table 4:1 Subject Characteristics

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, (M/F)</td>
<td>17 (8/9)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61 (20)</td>
</tr>
<tr>
<td>Age Range, years</td>
<td>34-83</td>
</tr>
<tr>
<td>Cough Duration, months</td>
<td>60 (147)</td>
</tr>
<tr>
<td>FEV1, %predicted</td>
<td>88.2 (16.7)</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>88.5 (20.3)</td>
</tr>
<tr>
<td><strong>Auditory perceptual voice analysis</strong></td>
<td></td>
</tr>
<tr>
<td>% abnormal</td>
<td>63</td>
</tr>
<tr>
<td>Maximum phonation time, seconds</td>
<td>12.8 (8.9)</td>
</tr>
<tr>
<td>Range, seconds</td>
<td>1 – 26</td>
</tr>
<tr>
<td>Jitter, percent</td>
<td>1.7 (1.6)</td>
</tr>
<tr>
<td>Range, percent</td>
<td>0.4 – 6.5</td>
</tr>
<tr>
<td>Harmonic to noise ratio, dB SPL</td>
<td>15.9 (3.8)</td>
</tr>
<tr>
<td>Range, dB SPL</td>
<td>10 – 24.7</td>
</tr>
<tr>
<td>Speaking fundamental frequency, Hertz</td>
<td></td>
</tr>
<tr>
<td>Female:</td>
<td>178 (20)</td>
</tr>
<tr>
<td>Range, Hertz</td>
<td>154 – 198</td>
</tr>
<tr>
<td>Male:</td>
<td>110 (14)</td>
</tr>
<tr>
<td>Range, Hertz</td>
<td>97 - 133</td>
</tr>
<tr>
<td>Closed phase, percent</td>
<td>43.5 (6.4)</td>
</tr>
<tr>
<td>Range, percent</td>
<td>32 - 53</td>
</tr>
</tbody>
</table>

Median (IQR) unless otherwise stated.

The number of treatment sessions for each participant was determined by their response to the therapy; specifically this included the effectiveness of the technique, the participant’s ability to perform and implement the technique appropriately, their understanding of the rationale for the treatment, and availability to attend treatment sessions. Generally, participants attended 3 (n=4) or 4 (n=9) speech treatment sessions while 3 participants responded rapidly and only required 2 treatment sessions. One participant only received 1 treatment session due to personal reasons. Participant compliance was evaluated through informal interview between the participant and speech pathologist at the beginning of each session. Participant compliance with the
speech language pathology programme was determined to be “good” in 53% of the participants; “partial” in 35% and 12% were classified as non-adherent.

Participants responded to the treatment with a significant improvement in cough-related quality of life (LCQ, p=0.002), laryngeal dysfunction symptom questionnaire score (LDQ, p=0.003), cough score, p= 0.04 and total symptoms score, p=0.002 [Table 4:2, Figure 4:1].

<table>
<thead>
<tr>
<th>Table 4:2 Questionnaire Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement</td>
</tr>
<tr>
<td>Cough Symptom Score (Mean±SD)</td>
</tr>
<tr>
<td>Total Symptom Score</td>
</tr>
<tr>
<td>LCQ Score</td>
</tr>
<tr>
<td>GORD Score</td>
</tr>
<tr>
<td>Snot-20 Score</td>
</tr>
<tr>
<td>LDQ Score</td>
</tr>
<tr>
<td>HADS Anxiety Score</td>
</tr>
<tr>
<td>HADS Depression Score</td>
</tr>
</tbody>
</table>

LCQ= Leicester Cough Questionnaire, GORD = Gastroesophageal reflux disease, Snot-20 = 20-item Sino-Nasal Outcome Test, LDQ= Laryngeal Dysfunction Questionnaire, HADS = Hospital Anxiety and Depression Scale, Median (IQR) unless otherwise stated.

Figure 4:1 Effect of speech-language pathology treatment on refractory chronic cough outcomes

a) Cough symptoms scores, Mean±SD
b) Leicester cough questionnaire, Median (IQR)

There was a significant improvement in cough reflex sensitivity measured as C5 with speech language pathology treatment for chronic persistent cough. Cough reflex sensitivity was heightened at baseline, Mean±SD log C5 0.88±0.48 and significantly improved with treatment to log C5 1.65±0.88, p<0.0001[Individual log C5 data (baseline
Improvements in cough reflex sensitivity were apparent after each visit: treatment visit 1, Mean±SD log C5 (T1) 1.18±0.62, p=0.023, treatment visit 2 log C5 (T2) 1.46±0.78, p<0.0001, treatment visit 3 (T3) log C5 1.45±0.68 p<0.0001, and treatment visit 4 (T4) log C5 1.53±0.93, p<0.0001 [Table 4:1]. These results indicate that the improvement in cough reflex sensitivity occurred after the first treatment visit, increased at subsequent treatment visits (significant treatment response attained after 2 treatments and maximum treatment response after 4 treatments) and that the effect was sustained at the post treatment visit.

There was also a significant decrease in cough frequency with the speech language pathology treatment for chronic persistent cough.
Figure 4:3 Cough Frequency at baseline, and post treatment

The cough count at baseline was reduced after treatment: Mean±SD cough frequency, 72.5±55.8 vs. 25±27.9 coughs/hr, p=0.009 [Individual cough frequency data (baseline v post treatment) represented in Figure 4:3] and the cough count tended to reduce each treatment visit and reached significance after treatment visit 3: cough frequency Mean±SD treatment visit 1 (T1) 42.5±60.5 coughs/hr, p=0.23, treatment visit 2 (T2) 63.0±78.8 coughs/hr, p=0.34, treatment visit 3 (T3) 48.7±36.8 coughs/hr, p=0.005 and treatment visit 4 (T4) 29.4±18.4 coughs /hr, p<0.0001 [Table 4:3]. The effect of the treatment programme on cough frequency was not as immediate as the effect on C5 with a significant result occurring after treatment visit 3 rather than at visit 1. The effect of treatment on cough frequency continued for treatment visit 4 (maximum treatment response) and was sustained at the post treatment visit.
Table 4:3 Capsaicin cough reflex sensitivity test, urge-to-cough and Leicester cough monitor testing.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>Post Treatment</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log CRS, C5 µMol/L</td>
<td>0.88±0.48</td>
<td>1.18±0.62</td>
<td>1.46±0.78</td>
<td>1.45±0.68</td>
<td>1.53±0.93</td>
<td>1.65±0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cough Frequency (coughs/hr)</td>
<td>72.5±55.8</td>
<td>42.5±60.5</td>
<td>63.0±78.9</td>
<td>48.7±36.8</td>
<td>29.4±18.4</td>
<td>25.0±27.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Log Cough Threshold µMol/L</td>
<td>0.47±0.38</td>
<td>0.72±0.60</td>
<td>0.80±0.60</td>
<td>0.69±0.23</td>
<td>0.66±0.65</td>
<td>1.14±0.76</td>
<td>0.001</td>
</tr>
<tr>
<td>Urge to Cough Score, Median (IQR)</td>
<td>5 (1)</td>
<td>3.5 (4.0)</td>
<td>3 (5)</td>
<td>1.5 (3.0)</td>
<td>0.5 (1.0)</td>
<td>1 (4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Baseline vs Post Treatment , T=Treatment, Post=Post Treatment, Mean±SD unless otherwise indicated

Cough threshold at baseline was Mean±SD log CT 0.47±0.38 and was significantly altered during treatment: treatment visit 1, cough threshold (T1) log CT 0.72±0.60, p=0.024, treatment visit 2 (T2) log CT 0.80±0.60, p=0.025, treatment visit 3 (T3) log CT 0.69±0.23, p=0.002, until maximum effect had been achieved with no significant change at treatment visit 4 (T4) log CT 0.66±0.65, p=0.122. After completion of therapy, cough threshold improved significantly: log CT 1.14±0.76, p=0.001[Individual cough threshold data (baseline v post treatment) represented in [Figure 4:4].

![Figure 4:4 Effect of speech-language pathology treatment on refractory chronic cough outcomes](image_url)

a) Log Cough Threshold at baseline, and post treatment (Post Rx)
There was a significant decrease in urge-to-cough with the speech language pathology treatment for chronic persistent cough. The urge-to-cough at baseline was reduced after treatment: Median (IQR), 5 (1) vs. 1 (4), \( p=0.01 \) [Individual urge to cough data (baseline v post treatment) represented in Figure 4:5] and the urge-to-cough tended to reduce after each treatment visit and reached significance after treatment visit 3: urge to cough Median (IQR) treatment visit 1 (T1) 3.5 (4), \( p=0.38 \), treatment visit 2 (T2) 3 (5), \( p=0.61 \), treatment visit 3 (T3) 1.5 (3), \( p=0.005 \) and treatment visit 4 (T4) 0.5 (1), \( p=0.24 \).

Figure 4:5 Urge to Cough score at baseline (Base), and post treatment (Post Rx)

4.5 Discussion

This is the first study to objectively assess response to a speech language pathology programme for refractory chronic cough using measures of cough sensitivity and cough frequency. We have shown that patients with refractory chronic cough have significantly decreased cough sensitivity and cough frequency together with an improvement in clinical outcome and cough and laryngeal symptoms following the speech language pathology intervention. Participants had an early symptom response
to the speech language pathology program that was further improved upon throughout subsequent treatment sessions. Generally, a patient needed 3 to 4 treatment sessions and the response was maintained after the intervention ceased.

The speech language pathology program for refractory CC includes several components, and from a previously conducted pilot study (presented in the additional data file 1: Participant details and results) it was found that isolated components such as specific cough suppression techniques or counselling were not enough for a patient to achieve a clinical response. In a previous study, we showed the benefit of the speech language pathology program combined with a cough diagnostic and treatment algorithm on cough reflex sensitivity in chronic persistent cough patients with paradoxical vocal fold movement (PVFM). This study expands on those results by treating patients with cough that is refractory to usual medical care with or without the presence of PVFM and investigating the mechanism of action. Our aim was to objectively measure changes in cough reflex sensitivity and cough frequency prior to speech language pathology program, during the speech pathology language program and at a post-treatment visit. We found that both cough frequency and cough sensitivity improved progressively with the speech language pathology program. Statistically significant improvements in cough reflex sensitivity were apparent after 1 treatment session, and this resulted in significant reduction in cough frequency after 3 sessions.

Within the large population of patients with CC, there is a small subgroup that does not respond to usual medical treatment. In the past this group has been referred to as chronic idiopathic cough. This group has been shown to have increased
sensitivity to capsaicin challenge indicating a heightened cough reflex. The typical refractory cough patient will have coughing bouts triggered by normal daily activities such as exposure to aerosols, perfumes, cold air or when talking or laughing. Patients also describe a ‘tickle, irritation, lump or blockage’ in the throat preceding the urge to cough. While the mechanism/s of chronic idiopathic cough are currently unknown it has been proposed that chronic idiopathic cough maybe similar to other sensory hyperalgesias, where there is a long-standing reduction in sensory nerve threshold to stimulation (156, 281). We previously showed that up to 60% of refractory or idiopathic cough can be associated with paradoxical vocal fold movement - a sensory laryngeal hypersensitivity with heightened cough reflex sensitivity and extrathoracic airway hyperresponsiveness (431). Both extrathoracic airway hyperresponsiveness and cough reflex sensitivity respond to diagnostic medical treatment with the addition of speech language pathology in chronic cough, and in the current study, we now extend that data to show that refractory cough with or without PVFM responds to speech language pathology program for cough that persists after usual treatments have been exhausted. This study investigated the mechanism of the improvement in sensory hyperresponsiveness in chronic idiopathic cough following a speech language pathology programme. The mechanism of the effect is due to a reduction in cough reflex sensitivity. The speech language pathology program has several components that include cough suppression behaviour and vocal hygiene training. Voluntary cough suppression does not appear to be the primary mechanism of effect since we saw the effect of the speech language pathology program on cough threshold during the treatment programme. This is also supported by a pilot study where we examined
the individual speech language pathology program components and found no effect of the cough suppression component on cough reflex sensitivity.

The study does suggest that the effective speech language pathology programme components reduce cough reflex sensitivity. This effect could occur by improvement in vocal hygiene leading to reduce sensory nerve stimulation, and is supported by the improvements in C5 and urge to cough during the programme. It is also possible that the reduction in cough frequency subsequently reduces cough-related airway trauma, and this explains the delayed improvement in cough threshold.

In this study we used an open design with objective measures to assess outcome. Although a nonrandomized design is a limitation, our primary purpose was to treat refractory cough patients and determine their response to a therapy outside normal chronic cough treatment. We achieved this aim by using objective measures and presenting novel data showing that cough frequency and cough reflex hypersensitivity significantly improve after speech language pathology treatment. It is possible that a placebo effect such as cough suppression (271, 299, 301) may have influenced some of the measures used in this study. We believe however that this is unlikely as the majority of the subjects studied had a cough for more than 5 years duration and underwent numerous cough treatments prior to speech language pathology intervention. Also, if there was a placebo effect at work then an improvement in C5 and cough threshold may be seen but there would be no change in the subjects urge to cough (215, 302) as seen here.
We did not find a heightened cough reflex sensitivity in CC females compared to CC males (power 90%) and this was consistent with our previous research (431, 440) (for further results on this refer to additional file 1: Participant details and results). A gender difference in cough reflex sensitivity has been reported in some healthy subjects without cough (275, 276) but not all (280) studies. We studied subjects representative of those with refractory chronic persistent cough. They were primarily middle-aged with a significant cough duration, had been treated for the usual causes of cough (306) and had not responded to those treatments. We assessed cough reflex sensitivity to capsaicin and cough frequency using validated techniques (65, 275, 436) and present novel data on how this group respond to speech language pathology treatment for chronic cough.

4.5.1 Conclusion
In conclusion, this is the first study to show that speech language pathology management is an effective intervention for refractory chronic cough and that the mechanism behind the improvement is due to reduced laryngeal irritation which results in decreased cough sensitivity, decreased urge to cough and an increased cough threshold. This is accompanied with an improvement in cough symptoms, associated laryngeal symptoms, and cough quality of life. Speech language pathology may be a useful therapy for refractory chronic cough.

4.5.2 Additional data file 1: Participant details, supplemental methods and results
4.5.2.1 Participants
Adults (n=17) with chronic persistent cough that was refractory to medical assessment and treatment (5, 306) and who were referred for speech language pathology management for cough (345) were eligible for the study. They were aged between 18 and 80 years,
non-smokers or ex-smokers with less than ten pack years, had no other active respiratory or cardiac disease, and had a normal chest radiograph.

4.5.2.2 Study Design
Participants attended for a maximum of 6 visits over a period of 14 to 18 weeks. At visit 1, the participant underwent cough assessment by a qualified speech language pathologist. This involved a clinical case history, symptom frequency and severity rating (415), auditory perceptual voice analysis and instrumental voice analysis utilizing acoustic and electroglottographic assessment. A qualified clinical research officer then collected participant clinical history, current cough symptoms and medication use. A cough specific quality of life questionnaire (Leicester Cough Questionnaire, (LCQ)) (184), a gastroesophageal reflux disease (GORD) questionnaire (422), a rhinosinusitis questionnaire (Snot-20) (429), Asthma Control questionnaire (ACQ) (434), the Hospital Anxiety and Depression Scale (82) and a laryngeal dysfunction questionnaire (LDQ) (424) were then administered.

A baseline cough reflex sensitivity to capsaicin (CRS) (65, 418) and Urge-to-Cough score (301) were administered while the participant wore an automated cough monitor and microphone to record cough frequency (436) during the visit.

Visits 2-5 consisted of a published speech pathology programme for chronic persistent cough (345). Each treatment session lasted for approximately 30 minutes and was followed by cough reflex sensitivity testing with urge-to-cough score and objective cough monitoring of cough frequency.
A post treatment visit (visit 6) was conducted 2 to 3 weeks after the final treatment session with the speech language pathologist to ascertain whether the result was sustained once the one-on-one intervention had stopped. At this visit the participant repeated the same questionnaires as that for visit 1 followed by the capsaicin cough reflex sensitivity test, Urge-to-Cough score, and objective monitoring of cough frequency.

The education component was designed to explain that in contrast to acute cough, there is no physiological benefit from cough and that there are negative side effects to cough. The cough suppression strategies trained participants to identify precipitating warning signs for cough and then to substitute competing responses. These responses included the cough suppression swallow, relaxed throat breathing with abdominal support, paradoxical vocal fold movement release breathing or cough control breathing. Vocal hygiene training was designed to reduce laryngeal irritation and maintain adequate hydration. These strategies involved systemic and surface hydration and minimization of irritants such as alcohol, caffeine and laryngopharyngeal reflux. The final component was psycho-educational counselling which aimed to help participants to internalize control over the cough and view it as a behaviour occurring in response to laryngeal irritation rather than an external or chance event. It also involved setting realistic treatment goals, reframing their response to laryngeal irritation, and accepting the need to adhere to treatment and the requirement for daily practice.
4.5.2.3 Speech Pathology treatment programme for chronic persistent cough

The speech pathology programme for chronic cough has been described previously^{345} and consisted of four components: (a) education, (b) specific cough suppression strategies, (c) vocal hygiene training, and (d) psychoeducational counselling. All participants received each of the four components of the program however the duration and frequency of each component was tailored to the individual patient. The education component was designed to explain that in contrast to acute cough, there is no physiological benefit from cough and that there are negative side effects to cough. The cough suppression strategies trained participants to identify precipitating warning signs for cough and then to substitute competing responses. These responses included the cough suppression swallow, relaxed throat breathing with abdominal support, paradoxical vocal fold movement release breathing or cough control breathing. Vocal hygiene training was designed to reduce laryngeal irritation and maintain adequate hydration. These strategies involved systemic and surface hydration and minimization of irritants such as alcohol, caffeine and laryngopharyngeal reflux. The final component was vocal hygiene training which aimed to help participants to internalize control over the cough and view it as a behaviour occurring in response to laryngeal irritation rather than an external or chance event. It also involved setting realistic treatment goals, reframing their response to laryngeal irritation, and accepting the need to adhere to treatment and the requirement for daily practice.

4.5.2.4 Clinical Methods

Capsaicin Cough Reflex Sensitivity (CRS) testing

Solutions of capsaicin (Sigma-Aldrich Co., Castle Hill, Australia) concentrations ranging from 0.98 to 500 µM were prepared daily. Subjects inhaled single breaths (from
Functional Residual Capacity (FRC) to total lung capacity (TLC) of capsaicin aerosol from a compressed air-driven nebulizer (model 646, Technipro, North Parramatta, Australia) controlled by a dosimeter (KoKo Digidoser 323200; Technipro Marketing Pty Ltd., Sydney, New South Wales, Australia). The inspiratory flow was standardized at 0.5L/s with an inspiratory flow regulator valve. Cough counting was done for 30s after exposure to each dose, and the investigation ended when the subject coughed five or more times in response to one dose, or received a dose of the highest concentration.

Urge to cough score \(^{(501)}\) was recorded at baseline, (after spirometry just before the first administration of the capsaicin solution challenge), again after the administration of each capsaicin solution and at the conclusion of the CRS test \(^{(65,418)}\). The participant was asked to rate their urge to cough from a modified Borg scale with zero being “no need to cough” upto 10 being “maximum urge to cough”.

*Leicester Cough Monitor (LCM)*

The LCM\(^{(436)}\) is a digital ambulatory cough monitor that records sound from an external free-field microphone (Sennheiser MKE 2-ew Gold; Germany) positioned against the participant’s chest wall onto a digital sound recorder (dimensions 26.7x87x32 mm; iRiver iFP-799; iRiver America) at a sampling frequency of 16 kHz and with an encoding bit rate of 64 kbit.s\(^{-1}\) \(^{(436)}\). This was attached to the participant at the beginning of each visit and removed at the end of the visit. Data stored on the recorder was downloaded onto a computer where it was analysed by an automated cough detection algorithm (the Leicester Cough Algorithm, \(^{(437,438)}\)). Cough was defined as a characteristic explosive sound (throat clears were classified by operator input as a “non-cough” to be consistent with CRS cough counting) and reported as coughs/hour.
The algorithm identifies coughs as single events whether they occur as isolated events or in a cluster and reports the cough frequency as cough events and coughs/hour. This study reports cough frequency as coughs/hr.

**Analysis**
All analyses were performed using statistical and data analysis software STATA (Statacorp, Texas, USA). Comparisons of cough sensitivity (C5) between baseline and each visit was undertaken using a generalised linear mixed model with a random intercept term which takes into account the repeated observations on individuals. Standard errors were estimated using bootstrapping and results were expressed as Mean±SD. Similar models were used to examine the change in cough frequency although data was assumed to have a Poisson distribution. Correlations between parametric data were analysed using Pearson’s correlation coefficient or for non-parametric data using Spearman’s correlation coefficient. P values <0.05 were considered statistically significant.

Figures were produced using GraphPad Prism 4 (GraphPad Software, Inc, California, USA).

**4.5.2.5 Results**
In a previously conducted pilot study where 2 behavioural approaches (isolated cough suppression techniques and supportive counselling) for refractory chronic cough compared to a CC control group showed that after 1 hour of intervention or no intervention there was no change in CRS. Results from this pilot study were used to establish the current study in the following ways;

1. CRS does not respond to isolated behavioural approaches,
2. CRS does not change after 1x1 hour session of an isolated behavioural approach, and,

3. CRS testing measured as C5 is a highly reproducible test.

We did not find a heightened CRS in CC females compared to CC males (power 90%, Figure 4:6)

![Figure 4:6 Pilot Study Results](image)

**Figure 4:6 Pilot Study Results**
CS = isolated cough suppression technique, C = supportive Counselling, NI = no intervention, C5 = capsaicin dose to elicit 5 or more coughs 30sec after dose administered

There was no significant effect of gender on cough reflex sensitivity before and after treatment [Table 4:4].

<table>
<thead>
<tr>
<th>CRS, C5 (uMol/L)</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Visit</td>
<td>14.6±20.2</td>
<td>12.0±11.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Treatment Visit 1</td>
<td>33.4±25.6</td>
<td>24.3±24.6</td>
<td>0.46</td>
</tr>
<tr>
<td>Treatment Visit 2</td>
<td>118.5±189.9</td>
<td>107.8±168.9</td>
<td>0.91</td>
</tr>
<tr>
<td>Treatment Visit 3</td>
<td>36.1±25.7</td>
<td>116.4±177.9</td>
<td>0.34</td>
</tr>
<tr>
<td>Treatment Visit 4</td>
<td>99.3±131.5</td>
<td>175.3±251.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Post Treatment Visit</td>
<td>222.7±259.5</td>
<td>137.8±206.8</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Mean ± SEM represented
Chapter 5 Gabapentin for Idiopathic Chronic Cough: A Randomised Controlled Trial

5.1 Abstract

5.1.1 Background

Cough is one of the main reasons for seeking medical care in Australia. Many patients with chronic cough can be successfully treated with a systematic clinical guideline for cough, however, about 20-30% of chronic cough does not respond and is often classified as “idiopathic” or refractory cough. Numerous therapeutic interventions have been tried in patients with refractory chronic cough, and while one intervention may be effective for an individual another may not be, therefore, there is a need to identify additional treatments. The neuroleptic medication gabapentin has shown promise as an effective alternate treatment for idiopathic chronic cough however, these trials were uncontrolled case series with no objective testing. This study sought to address these issues.

5.1.2 Objective

The aim of this study was to investigate subjective and objective measures of cough before, during and after randomised treatment of gabapentin or matching placebo treatment for idiopathic chronic cough and assess the mechanism underlying any improvement.

5.1.3 Methods

Adults with chronic cough (n=56) were randomised to gabapentin or matching placebo for a twelve week period and assessed on an intent-to-treat basis. The outcomes assessed were capsaicin cough reflex sensitivity, automated cough frequency detection,
cough visual analogue scale (VAS), cough-related quality of life (LCQ), laryngeal symptoms, and extrathoracic airway hyperresponsiveness (EAHR). Cough related quality of life was assessed as a primary outcome.

5.1.4 Results

Gabapentin is more effective than placebo in some patients with idiopathic chronic cough for the subjective measures of Cough VAS and cough quality of life (LCQ) and this is supported by a reduction in cough frequency. Seventy-one percent of gabapentin treated participants had a clinically significant improvement in total LCQ score during the treatment period, compared to 48% in the placebo group [p=0.031]. Extrathoracic airway hyperresponsiveness was present in a number of participants and 50% of these responded to the gabapentin treatment while only 22% responded to the placebo intervention [p=0.052]. There was no significant difference in cough reflex sensitivity for gabapentin compared to placebo during the study. After cessation of active treatment the response was not sustained.

5.1.5 Conclusions

Idiopathic chronic cough continues to be an enigma to the medical community and there are a significant number of patients presenting with this problem. Neuropathic cough with sensory hyperresponsiveness should be considered in the workup of idiopathic cough. In this study gabapentin improved patients’ symptoms and quality of life, and therefore may be considered as a potential treatment option.

5.2 Introduction

Cough is one of the main reasons for seeking medical care in Australia. Epidemiological surveys estimate that between 11% and 16% of the general population
report a persistent cough, and 7% describe cough that is sufficient to interfere with activities of daily living on at least a weekly basis \(^{164}\). The illness burden from chronic cough arises from its high prevalence and its impact upon the physical, psychological, and social domains of health \(^{184}\). Many patients with chronic cough can be successfully treated by following one of several clinical practice guidelines that are generally based on the anatomic diagnostic protocol for cough \(^{120}\). Although this approach was initially reported to be successful in 98% of patients with chronic cough, many clinicians believe that this is an overestimate of the success of therapy. It is now acknowledged that there remains about 20-42\% \(^{6, 140, 144, 321}\) of chronic cough that persists after extensive investigation and treatment, a condition that is termed idiopathic cough \(^{6, 140}\).

Therapeutic interventions that have been tried in patients with idiopathic chronic cough include opioids \(^{370}\), nebulised topical anaesthetics, antireflux regimens, and behavioural cough control techniques \(^{254, 430, 441}\). Additional treatments are needed because the recommended therapies are either only partially effective, have a potentially unacceptable side-effect profile (eg opiates), are difficult to access, or have not been assessed using objective assessments.

There are a number of explanations \(^{142, 145, 147, 150, 442-444}\) for idiopathic chronic cough and the mechanisms underlying those are not mutually exclusive. Sensory hyperresponsiveness (SHR) is a common element. Similarities have been identified between idiopathic cough and chronic neuropathic pain syndromes. SHR is also a feature of chronic pain syndromes. It is therefore possible that approaches found to be successful in chronic pain such as gabapentin will also be successful in chronic cough. Two small case series have previously reported success with gabapentin in chronic
idiopathic cough\textsuperscript{(147, 353)}. However as these studies were uncontrolled case series and did not use objective measurement techniques to assess improvement our aim was to conduct a randomised double-blind placebo-controlled treatment trial of participants with idiopathic chronic cough and investigate the effect of gabapentin treatment on cough reflex sensitivity (CRS), cough frequency, cough severity (cough VAS) and cough quality of life (LCQ).

It was hypothesised that participants with chronic idiopathic cough will show a decrease in cough reflex sensitivity (CRS) and cough frequency and an increase in cough quality of life (LCQ) and cough severity after receiving treatment with gabapentin compared to placebo.

\textbf{5.3 Methods}

\textbf{5.3.1 Participants}

Adult non-smokers (n=56) with chronic persistent cough that was refractory to medical treatment\textsuperscript{(5, 306)} and who were referred to the trial by a respiratory specialist or responded to a media release about the study and were then reviewed and treated by a respiratory specialist were eligible for the study.

All participants provided written informed consent for this study that had been approved by the University of Newcastle’s Human Research Ethics Committee and the Hunter New England Human Research Ethics Committee.

\textbf{5.3.2 Study Design}

The study was a randomised, double blind, parallel group, controlled trial.
To determine study eligibility, potential participants underwent initial screening and were excluded based on the following criteria:

- cough productive of purulent sputum,
- current smoker,
- smoking related respiratory disease,
- pregnant or breast feeding,
- other active respiratory disease,
- inability to attend regular study visits,
- respiratory tract infection during month prior to randomisation,
- impaired liver function at Visit 1 as shown by AST, ALT, alkaline phosphatase or total bilirubin greater than the 2 times upper limit of normal,
- currently using ACE-I,
- untreated asthma (doctor’s diagnosis and positive test for airways hyperresponsiveness, AHR or bronchodilator reversibility, BDR)
- untreated symptomatic GORD,
- untreated symptomatic rhinosinusitis.

Participants then attended the cough research clinic for 5 visits (a baseline visit, 3 treatment review visits and a post treatment visit) over a period of 16 weeks according to the diagram below [Figure 5:1].

![Flow diagram](image)

**Figure 5:1 Flow diagram detailing telephone screening and five treatment visits to clinic for gabapentin v placebo trial**
Visit 1 was the randomisation and treatment initiation visit. At this visit a cough assessment and clinical history, and participant medication use was collected; a self assessed visual analogue scale (VAS) for cough severity \(^{(145, 146)}\) during the past 24 hours, and a 36 item quality of life \(^{(447)}\), cough symptom health status (LCQ) \(^{(184)}\) and laryngeal symptom \(^{(424)}\) (LDQ) questionnaire were also completed. This was followed by measurement of exhaled nitric oxide (FENO), and a hypertonic saline challenge \(^{(392)}\) to test for bronchial hyperresponsiveness (≥15% fall in FEV\(_1\)) and extrathoracic airway hyperresponsiveness (≥20% fall in FIF\(_{50\%}\)) \(^{(410)}\). To measure the frequency of coughs elicited by the participant during the remainder of the visit and during the capsaicin cough sensitivity test an automated cough monitor and external microphone \(^{(436)}\) were attached to the participant’s chest. Participants were then randomised to a treatment group ie; Gabapentin 300 or matching placebo and safety bloods for LFT were collected. Capsaicin cough reflex sensitivity with the outcomes of C5, and cough threshold were then completed. The participant was finally instructed by the research officer on where to collect their medication from, how to take their medication (dose schedule can be found under the Dose protocol section below), and completion of their cough diary card during the next 4 weeks.

At visit 2, the participant returned their medication bottle and reviewed their cough diary card with the research officer. Any adverse events were discussed and recorded in the participant’s medical record and clinical research folder. FENO, cough VAS, the LCQ, and the LDQ questionnaires were repeated. The capsaicin cough reflex sensitivity test was also repeated at this visit to ascertain any change in the participant’s cough sensitivity. Cough frequency was also recorded during the visit.
The participant was instructed to continue filling out their cough diary recording symptoms, cough severity and dose taken each day. At the end of the visit a new bottle of medication was dispensed from the pharmacy to the participant ensuring that the same randomly assigned medication was given to each participant and that the correct dose was being taken.

Visits 3 and 4 were also treatment review visits and included the same testing schedule as visit 2. The only difference was that at visit 3 the participant was given a withdrawal schedule for coming off the medication ready for the end of treatment visit (visit 4).

Visit 5 was the post treatment visit and was conducted 4 weeks after visit 4. It also had the same testing schedule but with the addition of the cough diary being retained by the research officer at the conclusion of the visit and therefore the study.

5.3.2.1 Dose Schedule and Randomisation

Known side effects of Gabapentin had been explained to the participants in the study information and consent form as well as at visit 1. Randomisation allocation was generated by the respiratory research unit data manager using Randomisation Generator Software with permuted blocks of six. This list was provided to the manufacturer (Stenlake Pharmaceuticals, Bondi Junction, Australia) who prepared the blinded active or placebo medication accordingly. The investigator and research team working with the participants did not have access to the randomisation schedule during the study.

The computer generated randomly assigned medication (Gabapentin 300mg or matching placebo) were then dispensed by the hospital pharmacy to ensure the
research staff and participant remained blinded to the intervention. The participant was instructed to begin at a dose of 300mg/d for the first day and then titrate up by one 300 mg capsule per day (divided dose) until either improvement was manifest, side effects were intolerable or a maximum 1800 mg daily dose was reached [Figure 5:2].

![Gabapentin (Placebo) Dose Schedule](image)

**Figure 5:2 Gabapentin (Placebo) Dose Schedule**

The participant remained on this dose until their next visit at the clinic. Response was assessed subjectively and objectively at each visit (as detailed below) by the research officer. The medication bottle with any remaining capsules were returned by the participant at each treatment visit. This ensured that the participant was taking their medication as prescribed (dose adherence) and so that the pharmacy could consolidate their dispensing and return account. At visit 2 the participant collected their new bottle of medication and continued on their currently prescribed dose. The dose taken each day was recorded by the participant on their cough diary and this was the same
procedure for visit 3. At the end of visit 3 the participant was given a dose reduction schedule whereby they were to reduce their current dose by 50% each 3 days until totally withdrawn from the medication. This medication withdrawal plan was calculated so the participant returned to the clinic for visit 4 (end of treatment visit) on the first day of taking no medication [Figure 5.2].

5.3.3 Clinical Methods

5.3.3.1 Fraction Expired Nitric Oxide

Fraction of Expired Nitric Oxide (FENO) was measured using an on-line chemiluminescence analyser (NiOx, Aerocrine AB, Smidesvägen 12, SE-171 41 Solna, Sweden) according to published European Respiratory Society/American Thoracic Society guidelines (417). The mean of the three replicate FENO values were used with collection at an expiratory flow rate of 50mL/sec.

5.3.3.2 Pulmonary function test with inspiratory flow (FIF50%)

Inspiratory-expiratory Flow Volume Loops were measured using a KoKo K323200 Spirometer (Technipro, North Parramatta, Australia). Forced expiratory and inspiratory times were held constant to ensure consistency and accuracy.

5.3.3.3 Hypertonic Saline Challenge for Bronchial Hyperresponsiveness and Extrathoracic Airway Hyperresponsiveness

Hypertonic saline challenge for BHR and EAHR was performed as described previously (440). The greatest fall in FEV1 and FIF50% during the provocation was calculated and presented as FEV1 %fall and FIF50% %fall respectively.

5.3.3.4 Capsaicin Cough Reflex Sensitivity (CRS) testing

Capsaicin CRS was performed as previously reported (65, 418).
5.3.3.5 Leicester Cough Monitor (LCM)

The LCM is a digital ambulatory cough monitor and external free-field microphone (436). This was attached to the participant at the beginning of each measurement visit and removed at the end of the visit. The cough frequency collection period therefore encompassed a recording time of about one hour in which questionnaires and cough reflex testing were performed. This measurement was used to complement the cough reflex sensitivity test by measuring any change in the patient’s frequency of coughing during the treatment trial. Data stored on the recorder was downloaded onto a computer where it was analysed by an automated cough detection algorithm (the Leicester Cough Algorithm, (437, 438)). Cough was defined as a characteristic explosive sound (throat clears were classified by operator input as a “non-cough” to be consistent with CRS cough counting) and reported as coughs/hour.

5.3.3.6 Statistical Analysis

Cough reflex sensitivity as measured by C5 and cough threshold, and cough frequency were log transformed for analysis and comparison of placebo and gabapentin for each of the visits using a repeat-measures ANCOVA (STATA by Statacorp, Texas, USA) which adjusts for the covariate of baseline measurements. Cough questionnaire (LCQ) was square root transformed, while cough VAS and laryngeal dysfunction questionnaire remained untransformed and also compared using ANCOVA.

Parametric participant characteristics at baseline were presented as mean (sd) and analysed using student’s t test, while non-parametric data was calculated as Median (IQR) and analysed using Wilcoxon ranksum test.
5.4 Results

Fifty-six participants (35 female) with a mean (SD) age of 61.9 (12.6) years were studied [Figure 5:3]. Twenty-seven participants with cough duration of 48 months were randomly assigned to the placebo group and 29 participants with cough duration of 36 months were randomly assigned to the treatment group [Table 5:1]. All participants presented with persistent chronic cough refractory to usual medical (cough) treatment. Both cough groups had tried a number of treatments with a higher proportion in the treatment group having trialled oral corticosteroids (p=0.038) and experiencing more nocturnal cough (p=0.015) than the placebo group [Table 5:1]. Participants from each group presented with a number of associated symptoms such as heartburn (52%), postnasal drip (68%) and voice change (75%). Current medications included short acting β2 agonist (23%), nasal steroids (20%), antihistamines (11%), combination corticosteroid/LABA (14%), and reflux medication (48%). These were continued unchanged throughout the study. Spirometry was unremarkable and there was no significant difference between the 2 groups for FEV1 %fall or FIF%50 %fall at baseline.

Table 5:1 Participant characterisation by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Gabapentin</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age #</td>
<td>61.4 (11.9)</td>
<td>62.4 (13.2)</td>
<td>0.766</td>
</tr>
<tr>
<td>Male/Female</td>
<td>10/17</td>
<td>11/18</td>
<td>0.945</td>
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<tr>
<td>Non/ex smoker</td>
<td>14/13</td>
<td>17/12</td>
<td>0.611</td>
</tr>
<tr>
<td>Pack years *</td>
<td>5.5 (3, 15)</td>
<td>4.0 (0, 5)</td>
<td>0.071</td>
</tr>
<tr>
<td>Cough duration, months *</td>
<td>48 (24, 156)</td>
<td>36 (18, 120)</td>
<td>0.455</td>
</tr>
<tr>
<td>Prior URTI §</td>
<td>5 (18.5%)</td>
<td>10 (34.5%)</td>
<td>0.178</td>
</tr>
<tr>
<td>BMI *</td>
<td>27.65 (25.2, 30.45)</td>
<td>29.0 (25.4, 31.2)</td>
<td>0.632</td>
</tr>
<tr>
<td>Ex NO, ppb *</td>
<td>13.1 (8.0, 21.0)</td>
<td>13.2 (8.9, 19.6)</td>
<td>0.859</td>
</tr>
<tr>
<td>Cough §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal</td>
<td>13 (48.2%)</td>
<td>23 (79.3%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Wakes from sleep</td>
<td>9 (33.3%)</td>
<td>17 (58.6%)</td>
<td>0.058</td>
</tr>
<tr>
<td>Difficulty going to sleep</td>
<td>5 (18.5%)</td>
<td>8 (27.6%)</td>
<td>0.422</td>
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<tr>
<td>Triggers §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>8 (29.6%)</td>
<td>13 (44.8%)</td>
<td>0.240</td>
</tr>
<tr>
<td>Cold air</td>
<td>13 (48.2%)</td>
<td>16 (55.2%)</td>
<td>0.599</td>
</tr>
<tr>
<td>Aerosols</td>
<td>12 (44.4%)</td>
<td>12 (41.4%)</td>
<td>0.817</td>
</tr>
<tr>
<td>Symptom</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Cough on rising</td>
<td>9 (33.3%)</td>
<td>11 (37.9%)</td>
<td>0.720</td>
</tr>
<tr>
<td>Talking/laughing/singing</td>
<td>20 (74.1%)</td>
<td>24 (82.3%)</td>
<td>0.429</td>
</tr>
<tr>
<td>Eating</td>
<td>11 (40.7%)</td>
<td>18 (62.1%)</td>
<td>0.110</td>
</tr>
<tr>
<td>Positional</td>
<td>14 (51.9%)</td>
<td>13 (44.8%)</td>
<td>0.599</td>
</tr>
<tr>
<td>After eating</td>
<td>9 (33.3%)</td>
<td>11 (37.9%)</td>
<td>0.720</td>
</tr>
<tr>
<td>Reliever medications §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over the counter</td>
<td>18 (66.7%)</td>
<td>22 (75.9%)</td>
<td>0.447</td>
</tr>
<tr>
<td>OCS courses</td>
<td>3 (11.1%)</td>
<td>10 (34.5%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>12 (44.4%)</td>
<td>17 (58.6%)</td>
<td>0.289</td>
</tr>
<tr>
<td>Codeine/opiates</td>
<td>6 (22.2%)</td>
<td>4 (13.8%)</td>
<td>0.411</td>
</tr>
<tr>
<td>Inhaled meds</td>
<td>19 (70.4%)</td>
<td>22 (75.9%)</td>
<td>0.643</td>
</tr>
<tr>
<td>Anti reflux meds</td>
<td>17 (63%)</td>
<td>21 (72.4%)</td>
<td>0.449</td>
</tr>
<tr>
<td>Nasal sprays</td>
<td>19 (66.7%)</td>
<td>19 (65.5%)</td>
<td>0.928</td>
</tr>
<tr>
<td>Homeopathic</td>
<td>3 (11.1%)</td>
<td>5 (17.2%)</td>
<td>0.512</td>
</tr>
<tr>
<td>Associated Symptoms §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn</td>
<td>13 (48.2%)</td>
<td>16 (55.17%)</td>
<td>0.599</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>16 (59.3%)</td>
<td>22 (75.9%)</td>
<td>0.184</td>
</tr>
<tr>
<td>Voice change</td>
<td>19 (70.4%)</td>
<td>23 (79.3%)</td>
<td>0.440</td>
</tr>
<tr>
<td>Past Respiratory Medical History §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood wheeze</td>
<td>2 (7.4%)</td>
<td>3 (10.3%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Atopy</td>
<td>7 (25.9%)</td>
<td>8 (27.6%)</td>
<td>0.889</td>
</tr>
<tr>
<td>Current Medications §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting β2 agonist</td>
<td>9 (33%)</td>
<td>4 (13.8%)</td>
<td>0.084</td>
</tr>
<tr>
<td>Long acting β2 agonist</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifier</td>
<td>0</td>
<td>1 (3.5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Short acting anti cholinergic</td>
<td>0</td>
<td>1 (3.5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Long acting anti cholinergic</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasal steroids</td>
<td>7 (25.9%)</td>
<td>4 (13.8%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Non steroidal anti inflammatory</td>
<td>2 (7.4%)</td>
<td>0</td>
<td>0.220</td>
</tr>
<tr>
<td>Theophylline</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Oral steroids</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>1 (3.7%)</td>
<td>2 (6.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICS/LABA</td>
<td>4 (14.8%)</td>
<td>4 (13.8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cough medications</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anti histamines</td>
<td>2 (7.4%)</td>
<td>4 (13.8%)</td>
<td>0.671</td>
</tr>
<tr>
<td>Reflux medications</td>
<td>13 (48.2%)</td>
<td>14 (48.3%)</td>
<td>0.992</td>
</tr>
<tr>
<td>Spirometry #</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment FEV1</td>
<td>2.74 (0.99)</td>
<td>2.57 (0.62)</td>
<td>0.442</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>96.9 (17.7)</td>
<td>90.95 (18.1)</td>
<td>0.216</td>
</tr>
<tr>
<td>Pre treatment FVC</td>
<td>3.43 (1.20)</td>
<td>3.22 (0.74)</td>
<td>0.445</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>94.9 (13.6)</td>
<td>89.8 (18.7)</td>
<td>0.255</td>
</tr>
<tr>
<td>FEV1 %fall *</td>
<td>4.8 (2.7, 10.5)</td>
<td>5.5 (3.1, 8.0)</td>
<td>0.483</td>
</tr>
<tr>
<td>Pre treatment FIF50% *</td>
<td>4.66 (3.24, 6.26)</td>
<td>4.30 (3.34, 6.05)</td>
<td>0.770</td>
</tr>
<tr>
<td>FIF50% predicted</td>
<td>100.29 (30.77)</td>
<td>94.79 (29.46)</td>
<td>0.498</td>
</tr>
<tr>
<td>FIF50% % fall *</td>
<td>21.7 (12, 34.6)</td>
<td>18.23 (15.7, 29.4)</td>
<td>0.664</td>
</tr>
<tr>
<td>SF36 #</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical summary</td>
<td>45.4 (11.9)</td>
<td>44.8 (8.9)</td>
<td>0.840</td>
</tr>
<tr>
<td>Mental summary</td>
<td>45.1 (11.2)</td>
<td>48.7 (10.5)</td>
<td>0.236</td>
</tr>
<tr>
<td>Efficacy variables *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough Vas #</td>
<td>40.9 (19.7)</td>
<td>44.7 (28.1)</td>
<td>0.587</td>
</tr>
<tr>
<td>LCQ #</td>
<td>12.3 (3.9)</td>
<td>13.3 (3.1)</td>
<td>0.289</td>
</tr>
<tr>
<td>LDQ #</td>
<td>4.5 (2.3)</td>
<td>4.6 (2.3)</td>
<td>0.958</td>
</tr>
<tr>
<td>Cough threshold</td>
<td>1.96 (0.98, 3.92)</td>
<td>1.96 (0.98, 3.92)</td>
<td>0.233</td>
</tr>
<tr>
<td>C5</td>
<td>3.92 (1.96, 7.84)</td>
<td>3.92 (3.92, 17.84)</td>
<td>0.207</td>
</tr>
<tr>
<td>Urge to cough</td>
<td>3 (3.5)</td>
<td>4 (3.5)</td>
<td>0.249</td>
</tr>
<tr>
<td>Cough frequency</td>
<td>73.5 (44.5, 90)</td>
<td>41 (17, 82)</td>
<td>0.036</td>
</tr>
</tbody>
</table>
At baseline there was no significant difference in subjective cough measures between the 2 groups and this was also true for the objective measures except cough frequency where the placebo group were found to have a higher cough frequency during the baseline visit than that of the treatment group (p=0.036) [Table 5:1].

There were 3 withdrawals from the placebo group and 5 withdrawals from the treatment group during the study. However, for the purposes of the study all participants were included in the intention-to-treat analysis [Figure 5:3].
Assessed for eligibility (n = 57)

Excluded (n = 1)
Not meeting inclusion criteria (n = 0)
Refused to participate (n = 0)
Other reasons (n = 1)

Randomised (n = 56)

Allocated to intervention (Gabapentin) (n = 29)
Received allocated intervention (n = 29)
Did not receive allocated intervention (n = 0)

Allocated to intervention (Placebo) (n = 27)
Received allocated intervention (n = 26)
Did not receive allocated intervention (n = 1)
(pharmacy error: received 2 months Placebo/1 month Gabapentin)

Follow up

Lost to follow up (n = 1) (DNA)
Discontinued intervention (n = 4)
1 x concern for possible side effects
1 x withdrawn by CI due to AE(rash)
1 x side effects
1 x pursuing other treatment for comorbidity

Lost to follow up (n = 0)
Discontinued intervention (n = 3)
1 x perceived lack of efficacy
1 x no change in cough symptoms
1 x AE unrelated to study med (probable gastroenteritis)

Analysis

Analysed (n = 29)
Excluded from analysis (n = 0)

Analysed (n = 27)
Excluded from analysis (n = 0)
Figure 5.3 Consort diagram showing flow of participants throughout RCT of gabapentin vs. placebo in the treatment of idiopathic chronic cough.

There were a few expected side effects reported for the gabapentin intervention [Table 5:2] but most of these settled down after the first week of treatment. For the participants who continued to find these intolerable their dosage was tapered back to a level of tolerance (generally, 900 to 1200 mg/d dose). Three of the placebo intervention participants also reported side effects [Table 5:2]

Table 5:2 Reported participant side effects

<table>
<thead>
<tr>
<th>Gabapentin Participant</th>
<th>Side Effect symptom</th>
<th>Placebo Participant</th>
<th>Side Effect symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Disorientation, nausea</td>
<td>19</td>
<td>Depression*</td>
</tr>
<tr>
<td>10</td>
<td>Disorientation, confusion</td>
<td>27</td>
<td>Nausea, stomach upset such as pain and bloating#</td>
</tr>
<tr>
<td>17</td>
<td>Somnolence, very dry mouth</td>
<td>42</td>
<td>Fatigue, stomach pain</td>
</tr>
<tr>
<td>24</td>
<td>Disorientation, confusion, dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Lack of concentration, memory loss, dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Dizziness, somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Somnolence, nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Memory loss, very dry mouth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*comorbidity? # possibly related to known lactose intolerance

There was an initial statistically significant (p=0.038) improvement in cough VAS for the participants on gabapentin compared to participants on placebo and this improvement remained clinically significant until the medication was tapered off for treatment visit 4, p=0.159 [Table 5:3, Figure 5:4].

Table 5:3 Subjective outcome measures for treatment (Gabapentin) vs. Placebo#

<table>
<thead>
<tr>
<th></th>
<th>Visit</th>
<th>N</th>
<th>Coefficient (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cough VAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA vs placebo</td>
<td>2</td>
<td>45</td>
<td>-14.68 (-28.54, -0.81)</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>43</td>
<td>-14.65 (-30.96, 1.67)</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>41</td>
<td>-10.19 (-24.55, 4.18)</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>42</td>
<td>11.9 (-2.99, 26.83)</td>
<td>0.114</td>
</tr>
<tr>
<td><strong>Leicester Cough Questionnaire (square root transformed)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA vs placebo</td>
<td>2</td>
<td>53</td>
<td>35.7 (-13.76, 85.22)</td>
<td>0.153</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>49</td>
<td>54.41 (2.73, 106.10)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>47</td>
<td>53.25 (-4.37, 110.87)</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>47</td>
<td>3.14 (-56.49, 62.76)</td>
<td>0.916</td>
</tr>
</tbody>
</table>

# adjusted for baseline measurements. GABA=Gabapentin
There was also a statistically significant improvement in cough quality of life for the gabapentin participants (p=0.039) during the treatment schedule compared to the participants receiving placebo. This improvement remained clinically significant until withdrawal from the medication (post treatment visit 5, p=0.916) [Table 5:3, Figure 5:5].

Fifty-nine percent of gabapentin treated participants had a clinically significant improvement in cough VAS during treatment [Visit 2 through to 4], compared to 29% in the placebo group (a clinically significant change in VAS for chronic pain is greater than 17 mm (449), this calculation was used here) and this was statistically significant, p=0.041.

Seventy-seven percent of gabapentin treated participants had a clinically significant improvement in total LCQ score during treatment [Visit 2 through to 4], compared to 48% in the placebo group, which was also statistically significant, p=0.031.

Extrathoracic airway hyperresponsiveness was present in a number of participants (23/43) and 50% of these responded to the gabapentin treatment while only 22% responded to the placebo intervention (as determined by a clinically significant change in LCQ of greater than 2.56 units, p=0.052).
Figure 5:4 Cough VAS recorded at each visit
Visit 1=baseline, v2-v3=full dose treatment, v4=tapering off medication, v5=post treatment

Figure 5:5 Leicester Cough Questionnaire recorded at each visit
visit 1=baseline, v2-v3=full dose treatment, v4=tapering off medication, v5=post treatment

There was no significant difference in cough reflex sensitivity measured as C5 and reported as logC5 between the participants on treatment (GABA) when compared to
the participants on placebo [Table 5:4]. This scenario was also true for cough threshold [Table 5:4].

There was no clinically significant change in C5 (ie, >1.2 doubling concentrations) for the gabapentin treated participants or the placebo treated participants during the treatment trial, p=0.589.

| Table 5:4 Objective outcome measures for treatment (Gabapentin) vs. Placebo* |
|-----------------|--------------|----------------|--------|
|                  | Visit | N   | Coefficient (95%CI) | P value |
| C5 (log transformed) GABA vs placebo | 2     | 50  | 0.04 (-0.59, 0.67) | 0.890   |
|                  | 3     | 49  | 0.11 (-0.47, 0.69) | 0.713   |
|                  | 4     | 46  | 0.50 (-0.29, 1.29) | 0.208   |
|                  | 5     | 48  | -0.50 (-1.11, 0.12) | 0.109   |
| Cough Frequency (log transformed) GABA vs placebo | 2     | 34  | 0.16 (-0.43, 0.74) | 0.588   |
|                  | 3     | 33  | -0.66 (-1.36, 0.03) | 0.059   |
|                  | 4     | 32  | -0.66 (-1.34, 0.03) | 0.060   |
|                  | 5     | 36  | -0.53 (-1.06, 0.01) | 0.052   |
| Cough Threshold (log transformed) GABA vs placebo | 2     | 50  | 0.54 (-0.08, 1.15) | 0.088   |
|                  | 3     | 49  | -0.17 (-0.60, 0.26) | 0.427   |
|                  | 4     | 46  | -0.07 (-0.66, 0.53) | 0.824   |
|                  | 5     | 48  | -0.61 (-1.21, -0.02) | 0.044   |

*adjusted for baseline measurements, GABA=Gabapentin.

Cough frequency decreased for the treatment (GABA) group, approached statistical significance during the treatment schedule and was maintained at the post treatment visit. In contrast, there was no change in cough frequency for the placebo group [Table 5:4,Figure 5:6].
Figure 5:6 Cough Frequency recorded at each visit
Visit 1=baseline, v2-v3=full dose treatment, v4=tapering off medication, v5=post treatment

Throughout the study, there was no change in laryngeal symptoms for the gabapentin treatment group compared with the placebo group [Table 5:5].

Table 5:5 Subjective outcome measure: Laryngeal Dysfunction for treatment (GABA) vs. Placebo

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Coefficient (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>52</td>
<td>0.20 (-0.93, 1.33)</td>
<td>0.720</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>-0.27 (-1.54, 1.0)</td>
<td>0.675</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>0.26 (-0.83, 1.35)</td>
<td>0.629</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>0.47 (-0.77, 1.70)</td>
<td>0.449</td>
</tr>
</tbody>
</table>

# adjusted for baseline measurements. GABA=Gabapentin.

5.5 Discussion
This is the first double-blind, randomised, placebo-controlled study to assess the efficacy of gabapentin, a neuroleptic medication, in the treatment of idiopathic chronic cough. The study design used a range of both subjective measures such as cough quality of life, and cough VAS, and objective measures such as cough reflex sensitivity testing and cough frequency monitoring to evaluate the treatment response. The study
results show that gabapentin is more effective than placebo in some patients with idiopathic chronic cough for the subjective measures of Cough VAS and cough quality of life (LCQ) and this is supported by a reduction in cough frequency monitored during the clinic visits.

For the participants that responded to gabapentin the effect was primarily seen within the first month of treatment (coughVAS) sometimes with startling results such as one incident of cough resolution on day three that required half dose gabapentin (900mg/d) for the remainder of the treatment program. For the majority of responders, improvement in cough quality of life (LCQ) was not sustained after treatment withdrawal (17.2% sustained effect for Gabapentin and 14.8% sustained effect for Placebo, LCQ).

It is of interest that there was no significant difference in the log mean of the capsaicin cough challenge for gabapentin compared to placebo. Disparity between cough reflex sensitivity and subjective cough scores has been previously observed (184, 370-372). This could occur if the mechanism of effect was not on peripheral chemoreceptors, but was centrally acting, and this is a plausible explanation for gabapentin’s mode of action. In this study, we used cough frequency monitoring as a backup objective test during each of the visits and as such found a decrease in cough frequency for gabapentin treated participants (p=0.059) over placebo treated participants and this result was sustained (p=0.052).

Gabapentin is a lipophilic structural analogue of the neurotransmitter, gamma-aminobutyric acid (GABA) (450). The mechanism by which gabapentin exerts its actions
in humans has not been clearly established and appears to be a complex synergy between increased GABA synthesis, non-NMDA receptor antagonism and binding to the alpha2delta subunit of voltage dependent L-type of calcium channels. The latter action inhibits the release of excitatory neurotransmitters. The site of action can include effects at peripheral primary afferent neurons, spinal neurons and supraspinal sites (451). Our data support an effect at supraspinal sites, as there was no accompanying change in cough reflex sensitivity or laryngeal symptoms. Patients with idiopathic chronic cough are predominantly middle-aged women who typically present with a long-standing chronic dry cough that often follows a respiratory tract infection. There is heightened cough sensitivity, with the cough triggered by strong smells and fumes (144). There are a number of potential explanations for idiopathic chronic cough including organ-specific autoimmune disease of the airways (142, 145), neurogenic airway inflammation (442), non-acid gastro-oesophageal reflux (443), cough secondary to irritation or injury of the airway from prolonged coughing (444), and, a laryngeal sensory neuropathy (147, 150). These mechanisms are not mutually exclusive, and sensory hyperresponsiveness is a common element, that may have different initiating mechanisms (eg, inflammation, or injury from chemical and/or mechanical causes).

The concept of idiopathic cough as a sensory neuropathy has been supported by studies in the ENT literature that report both sensory and motor abnormalities on direct testing. Similarities have been identified between idiopathic cough and chronic neuropathic pain syndromes. Features of neuralgic pain are a lowered threshold for response, and an exaggerated response to minimal stimuli. In chronic idiopathic cough there is a lowered cough threshold with cough reflex hypersensitivity and patients
frequently report an exaggerated response to non-specific triggers \( (4, 6, 415) \). Our study population was characteristically idiopathic in nature; primarily female, average age of 62 years, with median cough duration of 3.5 years, (range 1.5 to 13 years). All had been investigated and treated by primary care followed by specialist care and a significant number reported having been treated with inhaled (asthma) medication (73%), antibiotics (51%), nasal steroids (66%) and anti reflux medication (67%) with no response. This population is consistent with those studied previously by Lee and Woo \( (147) \), and Mintz and Lee \( (353) \). A number of our participants also presented with laryngeal neuroirritability with the common triggers being talking (especially on the telephone), laughing, singing, cold air and aerosols and these were associated with symptoms such as heartburn, post nasal drip and voice changes. Fifty percent of the gabapentin participants and 56% of the placebo participants had EAHR as measured by a greater than 20% fall in \( \text{FIF}_{50\%} \) during hypertonic saline provocation. Fifty percent of participants with EAHR responded to the gabapentin treatment and 22% responded to the placebo intervention.

A few small case series have previously reported success with gabapentin in chronic idiopathic cough. Mintz and Lee \( (353) \) treated six patients with idiopathic chronic cough and found that five of the six patients responded to the gabapentin treatment with either complete resolution or substantial improvement in cough symptoms. In a second study by Lee and Woo \( (147) \) similarities between idiopathic chronic cough and sensory neuropathy were recognised and as such twenty-eight patients with chronic cough or throat clearing as a manifestation of sensory neuropathy involving the superior or recurrent laryngeal nerve were treated with gabapentin 100 to 900 mg/d. Seventy-one
percent of the patients had concomitant superior laryngeal nerve or recurrent laryngeal nerve motor neuropathy. Treatment duration varied from three months to four years depending on symptom control and 68% of patients reported symptomatic cough improvement.

In another case series of chronic idiopathic cough with sensory neuropathy, gabapentin was successfully added when amitriptyline failed (150). A major limitation of these case studies was that they were uncontrolled and did not use objective measurement techniques to assess improvement, nor did they assess quality of life effects.

This current study is a placebo-controlled, double blind, randomly assigned intervention that used both subjective and objective measures. Subjective measures of cough VAS and cough quality of life (LCQ) showed a statistically significant improvement during a period of the gabapentin intervention but this effect was not sustained. Participants with laryngeal neuroirritability (EAHR) had an increased response to gabapentin that was not seen for placebo. The objective measure of cough reflex sensitivity showed no improvement for gabapentin treatment however, although not statistically significant (p=0.059) cough frequency did show a trending and sustained improvement for gabapentin treatment that was not seen for placebo.

It is not surprising that there is variability in the response to gabapentin, because it is probable that there are many different causes for “idiopathic” chronic cough (353). The efficacy of gabapentin in this current study appears to be less than that found in the case series by Mintz and Lee (353), and Lee and Woo (147) and this could be due to a number of reasons. We treated participants for a maximum of 12 weeks where as some
participants in the Lee and Woo trial required treatment for up to 4 years, and in the Mintz and Lee trial a dose duration of 3 to 12 months was required. This current study uses a more powerful study design (RCT), has a larger sample population and incorporates subjective and objective outcome measures of efficacy. Comparison of treatment to placebo is extremely important as a significant number of placebo participants in this study had a positive albeit lesser response to intervention. Typically, the effect size in controlled trials is less than in open-design studies, and our results concur with this. It is therefore recommended that further placebo-controlled randomised trials on the use of gabapentin in chronic cough be conducted.

5.5.1 Conclusion

In the workup for patients presenting with idiopathic chronic cough, neuropathic cough should be suspected and testing for sensory hyperresponsiveness conducted. Gabapentin provides an alternate treatment strategy for the management of this difficult group.
STATEMENT IV

This statement explains the contribution of all authors in the article listed below:


Table: Author contribution percentage and description of contribution to published article listed above

<table>
<thead>
<tr>
<th>Author</th>
<th>Contribution %</th>
<th>Description of Contribution to Article</th>
</tr>
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<tr>
<td>Nicole Ryan</td>
<td>80</td>
<td>NR carried out the flow volume loop and hyperonic saline challenge testing; assisted with laryngoscopy, collected and reviewed data, participated in the design and drafted the manuscript.</td>
</tr>
<tr>
<td>Peter Gibson</td>
<td>40</td>
<td>PG performed patient physical examination and laryngoscopy, initiated inpatient tests and prescribed medication. PG also participated in the case report design and coordination of the manuscript.</td>
</tr>
</tbody>
</table>
Chapter 6 Extrathoracic airway hyperresponsiveness as a mechanism of post infectious cough: case report


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Email address: NR – nicole.ryan@newcastle.edu.au; PG – peter.gibson@hnehealth.nsw.gov.au

Corresponding Author: Professor Peter Gibson, Room 3598, Level 3, John Hunter Hospital Lookout Road, New Lambton Heights, 2305 Australia. Phone: 61 (0)2 4985 5766 Fax: 61 (0)2 49855850.

6.1 Abstract

Post-infectious cough is a common diagnosis in people with chronic cough. However, the specific infectious aetiology and cough mechanisms are seldom identified.

We report a case of chronic cough after Mycoplasma pneumoniae lower respiratory tract infection with extrathoracic airway hyperresponsiveness as the cough mechanism. Extrathoracic airway hyperresponsiveness may be a common mechanism in post-infectious cough which may be useful both diagnostically and therapeutically since chronic cough with extrathoracic airway hyperresponsiveness responds to speech pathology treatment.
6.2 Background

Post-infectious cough is a common diagnosis, especially in primary care settings, although a specific infectious aetiology is rarely confirmed. Aside from pertussis, the role of other infectious agents in chronic cough is poorly understood. In specialist clinics chronic cough occurs in association with asthma, rhinitis, gastro-oesophageal reflux (GORD), and ACE inhibitor use (452). However, even in these settings, a respiratory infection is often reported at the onset of chronic cough. Extrathoracic airway hyperresponsiveness (EAHR) represents variable extrathoracic airflow obstruction following inhalation provocation testing (19, 405, 453-455). It manifests as a fall in inspiratory airflow during challenge with histamine, exercise, or hypertonic saline. EAHR is a feature of cough due to ACE inhibitor use (405), rhinosinusitis (453, 454) and GORD (455), and possibly asthma (19). The mechanism of post-infectious cough is not known, however, upper airway sensory hyperresponsiveness might be one important mechanism in driving cough in some entities of CC (456) and this current case suggests that EAHR may be a useful objective marker and relevant mechanism in post infectious cough.

6.3 Case Presentation

A 60 year old non-smoking male presented to the Emergency Department with a non-productive cough and cold symptoms. For the past week he had been confined to bed and reported severe bodily pain, a troublesome cough and shortness of breath when showering and toileting. His temperature was 38.6°C. Physical examination of the chest was unremarkable and chest radiograph showed increased bronchial markings centrally. Arterial Blood Gas results breathing room air were: pH 7.46, pCO2 4.6 kPa,
pO₂ 6.9 kPa. He was commenced on oral roxithromycin 150mg bd, inhaled salbutamol 100ug 2 puffs qid, and analgesia, and continued pre-existing carbamazepine 300mg bd for controlled epilepsy (a recent onset condition) and thyroxine 50/100mcg on alternative days for hypothyroidism which had developed five years prior. He was subsequently changed to oral azithromycin 500mg, improved and was discharged on day 5. Acute and convalescent serology confirmed recent infection with Mycoplasma pneumoniae (antibody titre 1:1280 (ref range <1:40).

At a seven week follow-up visit he described persistent cough, inspiratory dyspnoea, voice changes (characteristics common to paradoxical vocal cord movement (PVCM) and EAHR disorders) and fatigue. Hypertonic saline provocation test was requested and conducted 2 months later.

Spirometry was FEV₁ 84% predicted, FVC 86% predicted, FEV₁/FVC 78%; and FIF₅₀ 5.22 L/sec. Hypertonic (4.5%) saline provocation challenge identified EAHR with attenuation of the inspiratory flow curve. The FIF₅₀ decreased by 39% to 3.20L/s at a cumulative saline dose of 10.59mL [Figure 6:1, solid line]. The fall in FEV₁ (12%) was within normal limits. A trial of fluticasone/salmeterol and nedocromil sodium was commenced.

The patient’s cough and dyspnoea had greatly improved by three months. One year later the cough had resolved completely and an inspiratory/expiratory flow volume curve was normal. There was no EAHR or bronchial hyperresponsiveness after repeat hypertonic saline challenge [Figure 6:1, dotted line], fall in FEV₁ remained within
normal limits (8%) and laryngoscopy showed no posterior chinking during inspiration and no paradoxical vocal cord movement (PVCM).

![Dose Response Curve](image)

**Figure 6.1** Hypertonic saline provocation dose response curve for FIF₉₀% prior to treatment (demonstrating extrathoracic airway hyperresponsiveness) and after treatment. Solid line=pre treatment, dotted line=post treatment.

### 6.4 Discussion

This case report describes Mycoplasma pneumoniae respiratory tract infection as a cause of persistent cough, occurring in association with EAHR. EAHR was demonstrated by a 39% fall in inspiratory flow during hypertonic saline challenge. The cough resolved as the EAHR resolved. Extrathoracic airway sensory hyperresponsiveness might be an important mechanism in driving cough in some entities of chronic cough (CC) \(^{(456)}\). This case report extends these data to show that transient EAHR can occur with post infectious cough.

It has previously been proposed \(^{(457)}\) that some patients with CC sustain vagal injury from respiratory infection and that airway hyperresponsiveness may persist beyond
resolution of the acute upper respiratory tract infection (URTI). This hyperresponsiveness could decrease the cough threshold to irritating stimuli resulting in higher susceptibility to chemical or mechanical stimulation of the cough reflex.

Transient post-infectious bronchial (intrathoracic) hyperresponsiveness is well recognised. This case report identifies transient EAHR as an additional relevant mechanism associated with post infectious cough.

These observations have implications for the treatment of post infectious cough. There may be a role for inhibition of neuropeptide release, by cromoglycate, nedocromil, or specific neuropeptide antagonists in post infectious cough. Fontana et al. evaluated the effects of nedocromil sodium administration on cough threshold in a placebo-controlled study of healthy subjects. They found a significant increase in cough threshold values after nedocromil and an unaffected result after placebo suggesting that nedocromil sodium administration may be useful for treating cough, especially when the use of centrally acting antitussive drugs should be avoided. These agents are also of benefit in ACE Inhibitor cough, which is associated with EAHR. Also, given the similarity between PVCM and EAHR, adapting techniques used by speech language therapists that were developed for PVCM may be of benefit for post infectious cough with EAHR. In PVCM the vocal cords adduct episodically and involuntarily during inspiration. This phenomenon leads to reduced inspiratory airflow associated with signs of stridor and a perception of dyspnoea characterised by the inability to inspire sufficient air. EAHR is thought to be the primary underlying pathophysiology of PVCM. Speech language therapy has been shown to be a successful treatment in chronic persistent cough. Vertigan et al. conducted a randomised placebo-controlled
trial in 87 patients with CC persisting despite medical treatment. Half of these patients had EAHR and symptoms of PVCM. Patients were randomly assigned to receive either a specifically designed speech pathology intervention or placebo intervention. Participants in the treatment group were found to have a significant reduction in cough with 88% having a successful outcome compared to 14% in the placebo group. In a comprehensive literature review, Gallivan et al (388) presented cases of episodic paroxysmal laryngospasm with definitive diagnosis by videolaryngoscopy of paradoxical vocal cord adduction during inspiration and extrathoracic airway obstruction by attenuation of the inspiratory portion of the flow volume curve. Prior to this, Christopher et al (342) identified 5 patients with a functional disorder of the vocal cords that mimicked attacks of bronchial asthma, that is paroxysms of wheezing and dyspnoea refractory to standard asthma therapy. During episodes of wheezing, the maximal expiratory and inspiratory flow-volume relationship was consistent with variable extrathoracic obstruction. Laryngoscopy confirmed adduction of the true vocal and false vocal cords. While during asymptomatic periods the maximal flow-volume relationship and laryngoscopic examination were normal. Patients were not aware of the vocal-cord dysfunction, which uniformly and dramatically responded to speech language therapy where they were taught to focus attention away from the larynx and the inspiratory phase of breathing during episodes of wheeze and dyspnoea (342). EAHR may be a useful objective assessment measure to characterise laryngeal dysfunction in chronic cough.

EAHR can be assessed during inhalational provocation challenge. We prefer the use of hypertonic saline to assess EAHR as it is known to provoke neuropeptide release from
nonadrenergic-noncholinergic nerves, which are prevalent in the larynx. Inhaled
histamine to assess EAHR has been successfully used before \(^{(19)}\) where the histamine
concentration causing a 25% fall in mid-inspiratory flow was used as the respective
threshold of EAHR. It was found that patients presenting with cough as the sole
symptom had significantly greater probability of having EAHR. Histamine can
however cause oedema of the vocal cords furthering our preference for hypertonic
saline stimulus. Methacholine challenge appears to be a less sensitive stimulus for
EAHR. This is likely because of its specific action on cholinergic receptors in airway
smooth muscle, and unproven action on laryngeal responses. Exercise can also be used
to assess EAHR, although quantification of the stimulus may be more difficult.

Our male patient had pre-existing hypothyroidism which has been associated with
idiopathic chronic cough and airway inflammation \(^{(145)}\). This is unlikely to be the
primary cause of cough in the patient as the cough developed after a well-documented
*Mycoplasma pneumoniae* lower respiratory tract infection that occurred some 5 years
after the onset of hypothyroidism. Further there is a *female* predominance in cases of
idiopathic CC and its association with mild chronic lymphocytic airway inflammation
\(^{(142)}\). It is however possible that a pre-existing autoimmune lymphocytic bronchitis had
a permissive effect on the occurrence of post-Mycoplasma chronic cough. Prospective
studies would be helpful in evaluating this possibility.

### 6.4.1 Conclusion

Post infectious cough can occur with EAHR. There are opportunities to further
investigate the frequency and treatment of EAHR as a mechanism of post-infectious
cough with speech pathology.
Consent: written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interests: the authors declare that they have no competing interests.

Authors’ contributions: NR carried out the flow volume loop and hypertonic saline challenge testing, assisted with laryngoscopy, collected and reviewed data, participated in the design and drafted the manuscript. PG performed patient physical examination and laryngoscopy, initiated inpatient tests and prescribed medication. PG also participated in the case report design and coordination of the manuscript.

All authors read and approved the final manuscript.

Sources of Funding: Nicole M Ryan holds a PhD scholarship from the NHMRC CCRE in Respiratory and Sleep Medicine, Australia. Peter Gibson is an NHMRC Practitioner Fellow
STATEMENT V

This statement explains the contribution of all authors in the article listed below:

Ryan NM, Vertigan AE, Ferguson J, Wark P, Gibson PG. Chronic persistent cough following 2009 H1N1 influenza infection. (Submitted)

Table: Author contribution percentage and description of contribution to published article listed above

<table>
<thead>
<tr>
<th>Author</th>
<th>Contribution %</th>
<th>Description of Contribution to Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicole Ryan</td>
<td>60</td>
<td>Planned the study, recruited the participants, performed the objective cough and respiratory tests and questionnaires, collected and collated data, interpreted outcomes, drafted and edited manuscript.</td>
</tr>
<tr>
<td>Anne E Vertigan</td>
<td>8</td>
<td>Performed some voice analysis, calculated voice scores and interpreted voice data. Reviewed manuscript.</td>
</tr>
<tr>
<td>John Ferguson</td>
<td>12</td>
<td>Planned study, collated and co-ordinated MT-PCR data and authored MT-PCR Method. Reviewed manuscript.</td>
</tr>
<tr>
<td>Peter Wark</td>
<td>5</td>
<td>Help plan study. Reviewed final manuscript.</td>
</tr>
<tr>
<td>Peter Gibson</td>
<td>15</td>
<td>Planned study, interpreted data, co-drafted and edited manuscript.</td>
</tr>
</tbody>
</table>
Chapter 7  Chronic persistent cough following 2009 H1N1 influenza infection

Ryan NM, Vertigan AE, Ferguson J, Wark P, Gibson PG. Chronic persistent cough following 2009 H1N1 influenza infection. (Submitted)

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* Corresponding author

Conflict of Interests: All authors declare that they have no conflict of interests

7.1 Abstract

7.1.1 Background

Post infectious chronic cough is a disabling illness. In 2009 an influenza pandemic occurred due to a novel strain of H1N1 influenza causing mainly acute and self-limited illnesses, with a higher prevalence amongst children and young adults. Prolonged symptoms such as chronic cough remaining after the infection has cleared have not
been examined. This study sought to investigate the characteristics and mechanisms of chronic persistent cough following acute respiratory illness from laboratory-confirmed H1N1 2009 influenza.

7.1.2 Methods

One hundred and thirty six subjects who had current symptoms and had been tested for H1N1 2009 influenza by PCR assay participated in this study. Twenty-one of those continued onto clinical testing. Investigations to assess cough, airway and vocal functions included symptom questionnaires, hypertonic saline challenge, cough monitoring and voice analysis and assessment.

7.1.3 Results

Of the 136 participants 43% tested positive for H1N1 and 57% tested negative for H1N1. H1N1 infected participants were younger and predominantly female. The prevalence of post H1N1 persistent cough was 9.4%, and for non-H1N1 infection, 4.9%. Objectively measured cough frequency was 3 times greater; there was a 5-fold increase in cough reflex sensitivity, and greater quality of life impairment in the participants with chronic postinfectious cough than the non-cough participants.

7.1.4 Conclusions

This study reports the first evaluation of chronic persistent cough following the pandemic H1N1 influenza outbreak in 2009. We found that chronic cough was relatively common, mild in severity and tending to resolution with time. The characteristics of postH1N1 chronic cough were similar to other postinfectious cough and were associated with cough reflex hypersensitivity.
Introduction

Post infectious chronic cough is a disabling illness that can occur following respiratory tract infection (5) due to laryngeal dysfunction (109, 461) or bronchial hyperresponsiveness (122). An influenza pandemic occurred in 2009 due to a novel strain of H1N1 influenza (462-464). The influence of pandemic 2009H1N1 on chronic cough is not described. Pandemic 2009 H1N1 virus derives six genes from triple-reassortant North American swine virus lineages and two genes (encoding neuraminidase and matrix proteins) from Eurasian swine virus lineages (465). In experimentally infected animals, the level of pulmonary replication of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses (466-468) but the virus generally lacks mutations that are associated with increased pathogenicity in other influenza viruses. Initial cases of H1N1 infection were identified in March 2009, and by March 2010 almost all countries had reported H1N1 cases. An estimated 59 million illnesses, 265 000 hospitalizations, and 12 000 deaths had been caused by the 2009 H1N1 virus as of mid-February 2010. In
contrast, in a normal influenza season with an ordinary strain of influenza, there are 200 000 cases and 36 000 deaths in only a few months in the United States alone each year (463).

Most illnesses caused by H1N1 infection during the pandemic have been reported as acute and self-limited, with a higher prevalence amongst children and young adults. The typical presentation is with fever and acute cough that may be accompanied by sore throat and rhinorrhea. Gastrointestinal symptoms including nausea, vomiting, and diarrhoea have been reported to be more common than in seasonal influenza (462, 464). To date, prolonged symptoms such as chronic cough remaining after the infection has cleared have not been examined. This study sought to investigate the characteristics and mechanisms of chronic persistent cough following acute respiratory illness (ARI) from laboratory-confirmed H1N1 2009 influenza in comparison to ARI that was H1N1 2009 influenza negative and historical controls. We hypothesised that approximately 10% of the population studied would have persistent cough with associated extrathoracic airway hyperresponsiveness and cough reflex sensitivity as likely mechanisms.

7.3 Methods

7.3.1 Subjects

Eligible participants were those who had received H1N1 influenza testing by the Hunter Area Pathology Service at least 8 weeks previously, were aged above 8 years, and gave their/or their parent’s/guardian’s written and free consent to participate in the study. Ineligible participants were pregnant or breast feeding women, those who
had a current active respiratory disease such as COPD or bronchiectasis and/or were unable to attend study visits.

7.3.2 Study Design

H1N1 2009 influenza testing by multiplexed tandem polymerase chain reaction (MT-PCR) was available to residents of the Hunter region of NSW, Australia with symptoms of an acute respiratory tract infection suspected as influenza, from 20th June 2009 onwards. Over this period test requests came from both outpatients and inpatients with influenza-like illness. The testing was performed by the Hunter Area Pathology Service (HAPS) located at John Hunter Hospital in Newcastle, New South Wales (NSW) Australia. During October 2009, the HAPS database was used to identify people who had been tested for H1N1 2009 influenza by MT-PCR assay at least 8 weeks previously. These people were then sent a letter of invitation and a study information and consent sheet requesting that they identify current symptoms including cough, and cough severity which was scored on a visual analogue scale (VAS) 100 mm in length with 0 representing “no cough” to 100 representing “worst cough”. Eight hundred and thirty six letters were sent and 136 responded by completing the current symptoms form and had been tested for H1N1 2009 influenza. Twenty one of these progressed to clinical testing at the hospital. A historical control group of healthy individuals without cough or recent ARI (431) of 11 provided control comparison data.

7.3.3 Clinical Investigations

Participants completed a range of investigations to assess cough, airway function and vocal function. Participants completed the Cough VAS (445, 446), the Leicester cough
questionnaire (LCQ) (184), Cough Reflex Sensitivity (CRS) using 4.5% hypertonic saline challenge (469, 470) and cough frequency by a cough recording monitor (65, 436). Upper airway dysfunction was assessed by the Laryngeal dysfunction questionnaire (LDQ) (424, 431) and hypertonic saline challenge for extrathoracic airway hyperresponsiveness (EAHR) (392, 410). Bronchial hyperresponsiveness (BHR) was assessed using spirometry and hypertonic saline challenge. Vocal function was assessed using auditory perceptual voice evaluation, acoustic voice analysis, and electroglottographic assessment with a qualified speech language pathologist. To investigate prevalence of risk factors associated with persistent cough and upper airway dysfunction, the following questionnaires were also completed: asthma control questionnaire (ACQ) (434), Rhinosinusitis (SNOT-20) (435), Gastroesophageal reflux disease (GORD) (422), ACE-I use, and Obstructive Sleep Apnoea (Berlin Questionnaire) (471).

All subjects provided written informed consent for this study, which was approved by the University of Newcastle's Human Research Ethics Committee and the Hunter New England Human Research Ethics Committee.

7.3.4 Clinical Methods

7.3.4.1 Multiplexed Tandem Polymerase Chain Reaction Method

Influenza MT-PCR testing on pooled nose and throat swabs was performed by the MT-PCR method targeting influenza A and B nucleoprotein and influenza A hemagglutinin gene sequences. The assay has a synthetic internal control sequence to act as an amplification control (472). Control influenza RNA for influenza A strains,
including pandemic strain 2009 H1N1 was run in parallel. The results distinguished influenza A (seasonal strains), influenza 2009 H1N1 and influenza B.

7.3.4.2 Pulmonary function test with inspiratory flow (FIF50%)

Inspiratory-expiratory Flow Volume Loops were measured using a KoKo K323200 Spirometer (Technipro, North Parramatta, Australia). Forced expiratory and inspiratory times were held constant to ensure consistency and accuracy.

7.3.4.3 Hypertonic Saline Challenge for Bronchial Hyperresponsiveness, Extrathoracic Airway Hyperresponsiveness and Cough Reflex Sensitivity

Hypertonic saline challenge for BHR and EAHR has been described previously (440). Bronchial hyperresponsiveness, was calculated as the dose response slope (DRS), according to the percent fall in FEV₁, divided by the cumulative dose of hypertonic saline (mL) delivered. Extrathoracic Airway Hyperresponsiveness DRS was calculated by dividing the percent fall in FIF50%, by the cumulative dose of hypertonic saline (mL) delivered. Cough Reflex Sensitivity was also calculated as DRS: cumulative number of coughs divided by the cumulative dose of hypertonic saline (mL) delivered. The participant’s perceived urge to cough (301) at cumulative 15 coughs was also recorded. Cough frequency was defined as the number of coughs recorded during the visit on the cough monitor and expressed as coughs/hr.

7.3.4.4 Voice measurement methodology

Formal voice analysis was conducted using auditory perceptual voice analysis, acoustic voice assessment and electroglottographic analysis. For acoustic and perceptual analysis, voice samples were recorded by a Studio Condenser Microphone NT3 (RODE into a personal computer using the PRAAT software program. Intensity measurements were obtained using a sound level meter during production of
sustained vowels and connected speech. Perceptual measures were made on connected speech samples by a qualified speech pathologist using the overall severity score on the Consensus Auditory Perceptual Evaluation – Voice. Acoustic measures included (a) maximum phonation time recorded in seconds, (b) mean fundamental frequency (Hz), (c) standard deviation of fundamental frequency, (d) jitter (%), (e) harmonic to noise ratio, (f) speaking fundamental frequency, and (g) phonation frequency range. Electroglottographic analysis was conducted using the Laryngograph Speech Studio. Specific measures from electroglottographic analysis included the second order distribution of fundamental frequency during connected speech, duration of closed phase of vocal fold vibration and irregularity of fundamental frequency.

7.3.5 Statistical Analysis
Data analysis was conducted using STATA statistical software (Statacorp, Texas, USA). Dichotomous categorical variables were tested by Pearson’s chi2 with Fishers’ exact test. Continuous non-parametric data for 2 group analysis were tested using Wilcoxon rank sum test, and for more than 2 groups with Kruskal-Wallis Test. Continuous parametric data were tested using students t-test for 2 groups and for more than 2 groups by ANOVA. All reported P values are 2 sided and a result of less than 0.05 was considered statistically significant.

7.4 Results
7.4.1 Participant Characteristics
From the 136 participants who returned the completed symptoms form, 58 (43%) tested positive for H1N1 and 78 (57%) tested negative for H1N1. H1N1 infected participants
were on average 15 years younger than the H1N1 negative group (p=0.0001, Table 7:1) and included a greater proportion of females (p=0.013, Table 7:1).

Table 7:1 H1N1 Tested Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pos H1N1</th>
<th>Neg H1N1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>58</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>16/42</td>
<td>38/40</td>
<td>0.013</td>
</tr>
<tr>
<td>Age, yr Mean±SD</td>
<td>38.4±18.1</td>
<td>53.7±23.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time, days (swab to letter) (^a)</td>
<td>103.5 (34.0)</td>
<td>100.5 (24.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cough (%)</td>
<td>43.1</td>
<td>35.9</td>
<td>0.39</td>
</tr>
<tr>
<td>Breath (%)</td>
<td>25.9</td>
<td>30.8</td>
<td>0.53</td>
</tr>
<tr>
<td>Voice (%)</td>
<td>27.6</td>
<td>16.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Cough Severity, Mean±SD</td>
<td>43.0±23.1</td>
<td>49.0±25.0</td>
<td>0.38</td>
</tr>
</tbody>
</table>

\(^a\) Median (IQR

There was a high prevalence of ongoing symptoms present at a median of 3 months after the acute respiratory illness. 43% of H1N1 participants reported chronic cough, 26% reported ongoing dyspnoea and 28% reported ongoing voice symptoms. Cough severity was moderate (mean=43 mm). There was no significant difference in the prevalence of persisting symptoms between the H1N1 positive group and the negative H1N1 group. The overall prevalence of post infectious cough was 6.9% (95% CI: 6.1, 8.2%). The prevalence of post H1N1 persistent cough was 9.4% (95% CI: 6.2, 13.6%), and for non-H1N1 infection, the prevalence of chronic persistent cough was 4.9% (95% CI: 3.3, 7.0%).

The youngest age group (participants less than 40 years of age, median age 22 years) had the highest H1N1 prevalence of 60%, [Figure 7:1], and 50% of those had persisting cough compared to 23% without a confirmed H1N1 respiratory infection, p=0.12. The oldest age group (age >60 years, median age of 72 years) had the lowest prevalence of H1N1 at 17.8%.
7.4.2 Clinical Testing

Twenty-one participants attended for clinical testing, of whom 12 (57%) were positive for H1N1, and 9 (43%) were negative for H1N1. These participants were tested a median (IQR) 221(40) days after confirmed H1N1 infection, and 113(46) days after their questionnaire responses. Cough severity was improving at the time of testing 34.5(34.0) mm to 20.0 (13.0) mm (p=0.03) There was no difference in cough parameters between H1N1 positive and H1N1 negative groups [data not shown].

The mechanisms and characteristics of chronic persistent post-infectious cough were examined in the 7(33%) participants with this problem (2 post H1N1, 5 after other infections, Table 7:2) and compared to those post Acute Respiratory illness without cough (n=14), and controls (n=11). Objectively measured cough frequency was 3 times greater in the participants with chronic postinfectious cough than the non-cough
subjects (p=0.02, Table 7:2, Figure 7:2), and they had greater quality of life impairment (p=0.001, Table 7:2).

Table 7:2 Characteristics of chronic persistent post-infectious cough compared with cough negative participants after acute respiratory illness and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Pos CC</th>
<th>Neg CC</th>
<th>Healthy Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age, Mean±SD</td>
<td>33.9±12.5</td>
<td>52.1±17.8</td>
<td>43.4±17.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>2/5</td>
<td>6/8</td>
<td>5/6</td>
<td>0.76</td>
</tr>
<tr>
<td>Smoking status, n, never/current/ex</td>
<td>4/1/2</td>
<td>11/1/2</td>
<td>8/0/3</td>
<td>0.67</td>
</tr>
<tr>
<td>FEV1 %pred, Mean±SD</td>
<td>90.5±21.6</td>
<td>99.8±12.9</td>
<td>108.4±17.0</td>
<td>0.09</td>
</tr>
<tr>
<td>FVC %pred, Mean±SD</td>
<td>88.9±17.8*</td>
<td>100±14</td>
<td>113.1±13.4</td>
<td>0.006</td>
</tr>
<tr>
<td>FEV1/FVC%, Mean±SD</td>
<td>85±7.3*</td>
<td>82.3±3.9*</td>
<td>99.1±7.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FIF50 %pred, Mean±SD</td>
<td>111±38.6</td>
<td>125.2±20.8</td>
<td>119.1±40.9</td>
<td>0.65</td>
</tr>
<tr>
<td>Cough Frequency, (coughs/hr) Mean±SD</td>
<td>157.9±154.4</td>
<td>47.5±45.8</td>
<td>N/A</td>
<td>0.02</td>
</tr>
<tr>
<td>Leicester Cough Questionnaire</td>
<td>18.6 (1.8)*</td>
<td>20.6 (1.9)*</td>
<td>20.9 (0.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Laryngeal Dysfunction Questionnaire</td>
<td>6 (5)*</td>
<td>2 (4)*</td>
<td>1 (1)</td>
<td>0.002</td>
</tr>
<tr>
<td>BHR-DRS</td>
<td>1.1 (3.5)*</td>
<td>0.7 (2.8)*</td>
<td>0.22 (0.26)</td>
<td>0.03</td>
</tr>
<tr>
<td>EAHR-DRS</td>
<td>3.8 (13.0)*</td>
<td>1.6 (3.2)*</td>
<td>0.41 (1.31)</td>
<td>0.01</td>
</tr>
<tr>
<td>CRS-DRS</td>
<td>13.9 (18.2)</td>
<td>2.29 (2.91)</td>
<td>N/A</td>
<td>0.009</td>
</tr>
<tr>
<td>Urge to Cough at PDCLM15Coughs</td>
<td>5 (1)</td>
<td>3 (2)</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

* vs Healthy Control, # vs Neg CC, Pos CC=positive for cough, Neg CC=negative for cough, Median (IQR) unless otherwise stated

Figure 7:2 Objective Cough Frequency
For persistent cough (Pos CC) and subjects without cough (Neg CC), Mean±SD

There was a 5-fold increase in cough reflex sensitivity in the post-infectious cough group (p=0.009, Table 7:2, Figure 7:3), and they had an increased urge to cough (p=0.01, Table 7:2, Figure 7:4).
The frequency and severity of both bronchial and extrathoracic airway hyperresponsiveness were not increased in the post infectious persistent cough group when compared to participants without post infectious cough but were increased.
compared to healthy controls [Table 7.2]. Voice assessment was similar between cough positive and negative groups [Table 7.3].

Table 7:3 Voice characteristics in postinfectious cough

<table>
<thead>
<tr>
<th></th>
<th>Pos CC</th>
<th>Neg CC</th>
<th>Normal Value/Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum phonation time (sec)</td>
<td>9.2 (5)</td>
<td>11.2 (6.9)</td>
<td>&gt;15 sec</td>
<td>0.42</td>
</tr>
<tr>
<td>Jitter (%)</td>
<td>0.9 (0.6)</td>
<td>0.8 (0.7)</td>
<td>&lt;1%</td>
<td>0.48</td>
</tr>
<tr>
<td>Harmonic to noise ratio (dB SPL)</td>
<td>20 (7.4)</td>
<td>18 (7.2)</td>
<td>20 db SPL</td>
<td>0.23</td>
</tr>
<tr>
<td>Phonation frequency range (semitones)</td>
<td>14 (9)</td>
<td>11 (5)</td>
<td>22 semitones</td>
<td>0.72</td>
</tr>
<tr>
<td>Standard deviation of fundamental frequency (Hz)</td>
<td>17.9 (23.6)</td>
<td>6.9 (5.9)</td>
<td>&lt; 10Hz (sustained vowels)</td>
<td>0.20</td>
</tr>
<tr>
<td>Intensity: vowel (dB SPL)</td>
<td>86 (6.2)</td>
<td>85.2 (6.2)</td>
<td>75-85 dB SPL</td>
<td>0.46</td>
</tr>
<tr>
<td>Intensity: connected speech (dB SPL)</td>
<td>67 (2)</td>
<td>68 (9)</td>
<td>70-80 dB SPL</td>
<td>0.57</td>
</tr>
<tr>
<td>CFx (%)</td>
<td>21.5 (22.5)</td>
<td>16 (36.3)</td>
<td>&lt;10%</td>
<td>0.35</td>
</tr>
<tr>
<td>Qx</td>
<td>54.5 (2)</td>
<td>49.5 (5)</td>
<td>45%</td>
<td>0.07</td>
</tr>
<tr>
<td>CAPE-V</td>
<td>5 (28)</td>
<td>3.5 (10)</td>
<td>0 = normal</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Median (IQR) unless otherwise stated

In chronic postinfectious cough, there was a tendency to more sinonasal symptoms 1.45 (1.0). None of the cough participants were taking ACE-I and sleep symptoms were similar between groups [Table 7:4].

Table 7:4 Chronic persistent post-infectious cough: associated risk factors

<table>
<thead>
<tr>
<th>Associated risk factor</th>
<th>Pos CC</th>
<th>Neg CC</th>
<th>Healthy Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORD</td>
<td>9 (12)</td>
<td>12.5 (5)*</td>
<td>7 (2)</td>
<td>0.03</td>
</tr>
<tr>
<td>ACQ</td>
<td>0.86 (0.43)</td>
<td>(0.28)</td>
<td>N/A</td>
<td>1.0</td>
</tr>
<tr>
<td>ACE-I use, %</td>
<td>0</td>
<td>21.4</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>Berlin risk for sleep apnea, %</td>
<td>42.9</td>
<td>42.9</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Sinusitis/Rhinitis Snot-20</td>
<td>1.45 (1.0)</td>
<td>0.35 (1.2)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

7.5 Discussion

This study reports the first evaluation of chronic persistent cough following the pandemic H1N1 influenza outbreak in 2009. We found that chronic cough was relatively common, mild in severity and tending to resolution with time. The characteristics of postH1N1 chronic cough were similar to other postinfectious cough and associated with cough reflex hypersensitivity.
The minimum prevalence of post H1N1 chronic cough was 9.4%. A limitation of the study was the response rate, however, since we had a complete dataset of those tested for H1N1 infection before the onset of chronic cough, we were able to estimate the minimum prevalence of post infectious cough. This study also allowed prospective assessment of this prevalence and used a sensitive and objective molecular assay to confirm H1N1 infection. We found that the prevalence of post infectious cough was at least 6.9%, and that post-infectious cough tended to be more common after H1N1 infection. Given that members of the general population can experience an average of 2.2 viral respiratory infections per year (473), a minimum prevalence of between 6.9 and 9.4% for post infectious cough indicates there is a high burden of illness from this problem in the community. Prior studies have reported a variable frequency of postinfectious cough of between 11% in retrospective studies (5,117,118) to 50% during outbreaks of pertussis infections (116,119). Studies in cough clinics have failed to observe postinfectious cough after acute respiratory infection (33). In our study, the prevalence was intermediate between the retrospective and prospective studies. The tendency to spontaneous improvement with time that we observed may explain the difference between the retrospective study results and those of cough clinics, since patients attending cough clinics typically have a long symptom duration before presentation.

The overall severity of postinfectious cough was similar between H1N1 confirmed cases and non-H1N1 cases. The objectively measured cough frequency in this current study was similar to what we have observed in chronic cough patients recruited from a cough clinic (474). Although the quality of life impairment in post infectious cough was significant, it was not as severe as seen in people with chronic cough presenting to
specialist cough centres (65, 420, 431). Similarly, the prevalence of cough – related
comorbidity such as asthma, reflux, rhinitis, and vocal disturbance was also lower than
in cough referral clinics. This indicates that although postinfectious cough is common,
it usually causes less distress than cough from other causes. Our data support the
hypothesis that seeking medical attention for persistent cough requires additional
factors such as a related co-morbidity, for example GORD, rhinitis, asthma or a voice
disorder. This would also explain why therapy targeting these conditions, as in the
anatomic-diagnostic protocol, is so successful in treating persistent cough in the cough
clinic setting (5).

The pathogenesis of post infectious cough is believed to be related to inflammation and
epithelial damage to the upper and lower airways. Several potential mechanisms for
post infectious cough have been proposed. These include post infectious bronchial
hyperresponsiveness (122); transient vocal cord dysfunction (109); cough reflex
hypersensitivity (43); nasal and sinus inflammation (123); and GORD (117). We examined
several of these mechanisms in this study and our results support increased cough
reflex sensitivity as the dominant mechanism for postinfectious chronic persistent
cough since there was a 5-fold increase in cough reflex sensitivity and no significant
increase in bronchial or extrathoracic hyperresponsiveness between cough and
noncough groups. The other mechanisms may be relevant in individual patients, but
do not emerge as a general mechanism for postinfectious cough.

Relevant treatment strategies for post (H1N1) infectious chronic persistent cough
include components of a diagnostic assessment approach (306). Vaccination appears to
be effective at reducing post pertussis chronic cough (116). An inactivated, split-virus
2009 H1N1 vaccine is available and is both immunogenic and safe in healthy adults (475). The efficacy of this vaccine in reducing cough prevalence needs further study.

In conclusion, this is the first study to evaluate chronic persistent cough following the pandemic H1N1 influenza outbreak of 2009. H1N1 infected participants were younger, primarily female and tended to have more persisting cough than those without H1N1. The minimum prevalence of post H1N1 chronic cough was 9.4%, mild in severity and tending to resolution with time. The characteristics of postH1N1 chronic cough were similar to other postinfectious cough and it was associated with cough reflex hypersensitivity.

Author’s contributions: NR, JF, PW and PG planned the study. JF collated and co-ordinated MT-PCR data and authored MT-PCR Method. NR recruited the participants, performed the objective cough and respiratory tests and questionnaires, collected and collated data, interpreted outcomes, drafted and edited manuscript. AV performed the voice analysis, calculated voice scores and interpreted voice data. PG interpreted data, co-drafted and edited manuscript. All authors read and approved the final manuscript.

Acknowledgements: Sarah Bone for voice testing and voice data collection. Colleen Shields for letter preparation and co-ordination of mail out.
Chapter 8  General Discussion

8.1 Primary findings of this thesis

8.1.1 Laryngeal dysfunction commonly occurs in chronic cough

The primary causes of CC have been well established and consist of GORD, asthma, rhinosinusitis, ACE-I use \((23, 33)\) and to a lesser extent NAEB \((25, 312)\). Cough is also common in the laryngeal disorder of vocal cord dysfunction. In a study by Andrianopoulos et al \((377)\) 59% of studied subjects with vocal cord dysfunction presented with cough as their primary symptom while in another study by Milgrom et al \((79)\) 20% of their patients with CC also had abnormal vocal fold motion on laryngoscopy. The role of laryngeal dysfunction in CC was assessed in this thesis. In the first study for this thesis, fifty-six percent of studied CC participants were found to have laryngeal dysfunction presenting as paradoxical vocal fold movement. PVFM has typically been associated with vocal cord dysfunction. There is now further reason to suspect an overlap between PVFM and CC. PVFM as a cause of chronic cough should therefore be considered in the workup for persistent cough.

8.1.2 Subjects with CC and PVFM have increased EAHR compared to subjects with CC alone

Although CC and PVFM are considered separate and distinct disorders, they exhibit overlap in symptomatology such as cough and dysphonia \((4, 415)\), and in disease associations, namely asthma, GORD, and rhinosinusitis \((346, 387, 406)\). PVFM is an upper airway disorder where persistent cough is common \((4, 283, 347)\) and results in reduced inspiratory airflow \((4, 283, 416)\) due to paradoxical vocal fold adduction. When assessed after a provocation stimulus such as with hypertonic saline the laryngeal response is
termed EAHR \(^{(19, 346, 387)}\). In the absence of bronchial hyperresponsiveness EAHR has been identified as an indicator of upper airway disease as a cause for cough \(^{(80)}\) and has been reported in several conditions where cough is prominent, such as rhinosinusitis, ACE inhibitor cough, gastroesophageal reflux, and patients with asthma-like symptoms \(^{(19, 346, 387)}\). Speech language therapy treatment based on the approaches used in vocal cord dysfunction and hyperfunctional voice disorders has been found to be effective in chronic cough \(^{(345)}\). CC with PVFM presents with reduced airway flow and cough and my objective testing of EAHR within this population group confirms this hypothesis. For the Cough with PVFM subjects, EAHR was elevated at baseline compared to the cough alone subjects. Cough with PVFM also responded positively to the cough with speech language pathology treatment resulting in reduced EAHR. Provocation testing to assess inspiratory airflow can be easily incorporated into bronchial challenge testing and should be routinely performed in patients presenting with CC to identify EAHR and determine an appropriate treatment strategy, such as speech language pathology intervention.

### 8.1.3 PVFM and EAHR manifest as laryngeal dysfunction in CC

PVFM where the vocal folds paradoxically adduct during inspiration \(^{(4, 349)}\) was first reported by Christopher \(^{(342)}\). Subjects with refractory asthma were found to have normal pulmonary function tests with visualisation of inspiratory flow restriction when symptomatic. Prudon et al reported laryngeal dysfunction in CC patients that exhibited an enhanced glottic closure in response to inhaled ammonia \(^{(419)}\). In PVFM there is extrathoracic airway obstruction primarily due to glottal constriction, and extrathoracic airway hyperresponsiveness (EAHR) is reduced inspiratory airflow.
following a provocation stimulus such as hypertonic saline that has been reported in several conditions where cough is prominent including rhinosinusitis, ACE inhibitor cough, gastroesophageal reflux, and patients with asthma-like symptoms (19, 346, 387).

In this thesis PVFM was detected by direct visualisation by Fibre Optic Laryngoscopy (FOL) the gold standard of diagnosis. EAHR was determined by hypertonic saline provocation and a fall of greater than 20% in mid inspiratory airflow is positive. There were a significant number of participants within this study diagnosed with PVFM and EAHR by these objective measures and when treatment was initiated there was a positive response. This outcome shows that PVFM and EAHR are under recognised conditions associated with CC and that objective testing for these should be included in the standard investigation and treatment protocol for chronic cough. PVFM and EAHR are both manifestations of laryngeal dysfunction resulting in reduced inspiratory airflow and objective evidence for this has been shown in this thesis.

8.1.4 Quality of life impairment and cough reflex hypersensitivity are associated with laryngeal dysfunction and CC

I am unaware of any literature reporting quality of life impairment and sensory hyperreactivity of the cough reflex in CC patients with laryngeal dysfunction. As reported in Chapter 1, CC alone has been shown to be associated with impaired health-related quality of life (175, 176, 184), specifically Adams et al examined the prevalence of CC in adults residing in north west Adelaide, Australia (24). Participants reporting cough at any time had significantly lower quality of life compared to those without cough at any time. Sandage and Schroth (476) reported treatment data for patients with chronic habit
cough. A generic quality of life questionnaire (SF36) demonstrated a trend towards improvement despite the presence of co-morbid conditions.

Idiopathic CC presents with symptoms of a hypersensitive cough reflex triggered by strong smells and fumes (6). This has been confirmed by objective evidence of cough reflex hypersensitivity whereby chronic idiopathic cough patients having a 4-fold increase in CRS over the responses seen in CC (120). Smith et al (477) reported a significant reduction in cough sensitivity for a psychological exercise group and a cough suppression group when compared to a no intervention control group.

This thesis reports evidence of impaired quality of life and objective evidence of sensory hyperreactivity of the cough reflex in participants with refractory CC and associated laryngeal dysfunction. CC with laryngeal dysfunction presents with significantly impaired quality of life and enhanced cough reflex sensitivity as found in CC of other causes.

8.1.5 Laryngeal hypersensitivity may be a common mechanism in chronic cough

Cho et al (456) showed that extrathoracic airway sensory hyperresponsiveness might be an important mechanism in driving cough in some entities of CC. Cough sensitivity and EAHR to inhaled capsaicin was found to be enhanced in subjects with cough variant asthma, and in subjects diagnosed with idiopathic chronic cough while control subjects showed no extrathoracic airway narrowing, nor did they display cough sensitivity. From these results, Cho et al concluded that cough sensitivity is closely related with EAHR during capsaicin provocation in some CC subjects. Within this thesis PVFM - a sensory laryngeal hypersensitivity with heightened EAHR was
identified by the objective measures of fibre optic laryngoscopy and hypertonic saline provoked cough in 56% of idiopathic chronic cough participants studied. Vertigan et al (4) has previously suggested that EAHR may be a common mechanism explaining the overlap between refractory CC and VCD and that treatment approaches for VCD, such as speech language therapy, could be applicable to people with chronic cough. The results of this thesis provide a mechanistic explanation for why this treatment approach is effective by demonstrating that laryngeal dysfunction is common in chronic cough.

8.1.6 Successful treatment for CC with speech language therapy leads to improvements in laryngeal dysfunction

Speech language therapy has been shown to be effective for laryngeal dysfunction and improve symptoms (345) and voice abnormalities (421) in refractory chronic cough, however its effect on laryngeal problems in CC has not been investigated. This thesis provided objective evidence of laryngeal dysfunction presenting as PVFM and EAHR in some patients with CC, and that it responds to therapy for chronic persistent cough with the addition of speech language therapy. These results are consistent with Vertigan et al (345) who found that a substantial proportion of their refractory CC participants had EAHR, however they extend these results by showing that PVFM and EAHR improve after successful treatment. This result provides strong objective evidence for standard cough guidelines to incorporate identification of CC associated with laryngeal dysfunction and its effective treatment with speech language therapy. This has been achieved in the recent Australian cough guidelines (329).
8.1.7 Speech language therapy for refractory and idiopathic CC leads to improvement in cough

Speech language therapy has been shown to be effective for refractory and idiopathic chronic cough \(^{(345, 430)}\); however, the mechanism behind the improvement is not known. Through the objective evidence of reduced cough sensitivity and cough frequency after a speech language pathology program for cough the mechanism behind the improvement was determined to be due to reduced laryngeal irritation. This resulted in decreased cough sensitivity, decreased urge to cough and an increased cough threshold accompanied with an improvement in cough symptoms, associated laryngeal symptoms, and cough quality of life. This result provides a mechanistic explanation for the improvement in refractory chronic cough after successful therapy with speech language pathology.

8.1.8 Gabapentin effectively decreases cough frequency and increases quality of life

Two small case series have previously reported success with gabapentin in chronic idiopathic cough \(^{(147, 353)}\). Mintz and Lee \(^{(353)}\) successfully treated 5 of 6 patients with gabapentin determined by a substantial improvement in cough symptoms. In a larger case series by Lee and Woo \(^{(147)}\) 68% of patients reported symptomatic cough improvement. In Chapter 5 of this thesis, gabapentin was compared to placebo treatment for idiopathic CC in a randomised double blind, placebo-controlled trial. Subjective measures of cough VAS and cough quality of life (LCQ) showed a statistically significant improvement in around 50% of participants during a period of the gabapentin intervention but this effect was not sustained post intervention. The efficacy of gabapentin in the treatment of idiopathic CC is less for this current study.
than that reported in the case series by Mintz and Lee\textsuperscript{(333)}, and Lee and Woo\textsuperscript{(147)}. This difference could be due to a number of reasons. In this current trial participants were treated for a maximum of 12 weeks whereas some participants in the Lee and Woo trial required treatment for up to 4 years. My study used a more powerful study design (RCT), and larger sample size. Typically, the effect size in controlled trials is less than in open-design studies and these results are consistent with this. Finally, subjective and objective measures of efficacy were employed unlike the previous case studies.

Therapeutic interventions that have been tried in patients with idiopathic CC are either partially effective, have a potentially unacceptable side-effect profile (e.g., opiates), are difficult to access, or have not been assessed using objective assessments. This thesis provides objective assessment of a potentially new treatment for idiopathic CC.

8.1.9 Gabapentin exerts its effect by inhibiting release of excitatory neurotransmitters at supraspinal sites

The mechanism by which gabapentin exerts its analgesic actions in humans has not been clearly established but appears to be a complex synergy between increased GABA synthesis, non-NMDA receptor antagonism and binding to the alpha2delta subunit of voltage dependent L-type of calcium channels\textsuperscript{(451)}. The latter action inhibits the release of excitatory neurotransmitters. The site of action can include effects at peripheral primary afferent neurons, spinal neurons and supraspinal sites\textsuperscript{(451)}. Data presented in this thesis supports an effect at supraspinal sites as there was no change in cough reflex sensitivity or laryngeal symptoms accompanying change in subjective cough quality of life and cough VAS. This result provides a mechanistic explanation for the analgesic
effect of gabapentin on nerve damage associated with chronic pain syndromes and neuropathic chronic cough.

### 8.1.10 EAH is a feature of postinfectious cough

EAHR is a feature of cough due to ACE inhibitor use (405), rhinosinusitis (453, 454) and GORD (455), and possibly asthma (19). The mechanism of post-infectious cough is not known, however, upper airway sensory hyperresponsiveness might be one important mechanism in driving cough in some entities of CC (456). Within this thesis, I reported a case of mycoplasma pneumoniae respiratory tract infection as a cause of persistent cough, occurring in association with EAHR. EAHR was demonstrated by a 39% fall in inspiratory flow during hypertonic saline challenge. The cough resolved as the EAHR resolved demonstrating that transient EAHR can occur with post infectious cough. Altman et al (457) proposed that some patients with CC sustain vagal injury from respiratory infection and that airway hyperresponsiveness may persist beyond resolution of the acute upper respiratory tract infection.

These observations have implications for the treatment of post infectious cough. Given the similarity between PVCM and EAHR (4), adapting techniques used by speech language therapists that were developed for PVCM may be of benefit for post infectious cough with EAHR. EAHR is thought to be the primary underlying pathophysiology of PVCM (396), and therefore a useful objective assessment measure to characterise laryngeal dysfunction in CC. Further investigation of the frequency and treatment of EAHR as a mechanism of post-infectious cough with speech language pathology is advised.
8.1.11 Post infectious cough due to H1N1 2009 influenza has similar characteristics to other postinfectious cough

Typical symptoms of postinfectious cough include a dry, non-productive persistent cough and may include tightness in the chest, and a tickle in the lungs. Postinfectious cough resolves with time and is usually the result of a preceding respiratory tract infection. The postinfectious cough due to H1N1 2009 influenza presented in this thesis was found to be self-limiting and mild in severity with similar characteristics to other postinfectious cough. The quality of life impairment was significant, but not as severe as that seen in people with CC presenting to specialist cough centres. Similarly, the prevalence of cough – related comorbidity such as asthma, reflux, rhinitis, and vocal disturbance was also lower than in cough referral clinics. Several potential mechanisms for postinfectious cough have been proposed including post infectious bronchial hyperresponsiveness; transient vocal cord dysfunction; cough reflex hypersensitivity; nasal and sinus inflammation; and GORD. Several of these were studied in this thesis with the results supporting an increased cough reflex sensitivity as the dominant mechanism since there was a 5-fold increase in cough reflex sensitivity and no significant increase in bronchial or extrathoracic hyperresponsiveness between the cough and noncough groups.

This study was the first to evaluate chronic persistent cough following the pandemic H1N1 influenza outbreak of 2009. Due to its similarity with other postinfectious cough relevant treatment strategies would include components of a diagnostic assessment approach for cough. As vaccination appears to be effective at reducing post pertussis chronic cough the efficacy of the 2009 H1N1 vaccine in reducing cough prevalence may be effective but requires further study.
8.2 Limitations of this thesis

8.2.1 Population

8.2.1.1 Cough clinic participants

The study participants were primarily middle-aged females with a chronic persistent cough recruited from a clinic setting. These characteristics are consistent with those reported elsewhere \((33, 65, 280, 420)\), and, like other cough series, the medical conditions that were associated with persistent cough included asthma, GORD, rhinitis/post nasal drip, eosinophilic bronchitis and ACE inhibitor use. Similar levels of cough reflex hypersensitivity for CC \((65, 418, 420)\) and for my control population \((65, 280)\) were also consistent to those found elsewhere. Together, these observations suggest that the currently studied CC population and control group (when included) was representative of those previously reported in the literature.

8.2.1.2 Refractory cough participants

Within the large population of patients with CC, a small subgroup does not respond to usual medical treatment \((87, 321)\) and is termed refractory cough. Refractory CC participants studied here were predominantly middle-aged women with a long-standing chronic dry cough that often followed a respiratory tract infection. There was heightened cough sensitivity, with the cough triggered by strong smells and fumes \((144)\) and this is consistent with reports published elsewhere \((4, 6, 415)\).

8.2.1.3 Primary care population

So far, my research has not studied participants solely from primary care and this is due to the following. The research conducted in this thesis concentrated on refractory and/or idiopathic chronic cough participants. These patients primarily progress to specialist care due to a troublesome, persistent cough refractory to usual medical care.
and standard treatment. As previously stated this is an under recognised group that requires significant measurement and assessment with the aim of identifying the causes, the mechanisms and effective treatments for a condition that presents with significant quality of life impairment. To achieve a more comprehensive understanding of cough the study of primary care patients would be well advised and this population subgroup will be addressed in future research.

8.2.2 Psychological health and placebo effect on chronic cough

While not a primary focus of this thesis, psychological health such as anxiety and depression can exert an influence on the presentation and clinical course of cough, including the response to treatment, and is an important area requiring further investigation. Adams et al. (24) showed that people with chronic cough report significant impairments in quality of life and psychological health compared to those without cough. Anxiety about underlying serious illness has been identified as a concern for most patients with chronic cough (478) and successful treatment of cough has been shown to improve depression (86). It is possible, but not yet proven, that reassurance and explanation, as occurs in a clinical trial setting, could improve anxiety about cough and then improve cough frequency. This may be one factor that led to improvements in cough in the observational trial we reported. A blinded, controlled and randomised intervention would be needed to determine the magnitude of this effect.

A placebo response is another possible explanation for the observed improvements in cough. Placebo responses have been reported to contribute between 65% to 80% of the response to antidepressant medications (479) and as previously discussed depression has been shown to accompany cough. The placebo effect has also been shown to be a major
component of any cough treatment. Lee et al (480) reported a 50% reduction in cough frequency (CF) with placebo treatment compared to no treatment. This large placebo effect had been previously demonstrated in similar studies on the effects of antitussive medication on cough associated with URTI. Eccles et al (112) reported a 44% reduction in CF associated with placebo treatment compared to codeine syrup (30 mg/mL) and Freestone et al (111) reported a 50% reduction in CF associated with placebo treatment compared to a single dose 50 mg codeine phosphate. The effects of placebo treatments have been most studied in relation to analgesia. Studies on pain with analgesics have shown that placebo treatment activates the endogenous opioid system (481, 482). It is reported that the opioid antagonist naloxene blocks the placebo analgesic response (483).

The placebo effect on respiration has also been proposed to be mediated by endogenous opioids (484). Interestingly, in the gabapentin placebo-controlled trial for idiopathic chronic cough [Chapter 5], the placebo effect was found to be less significant.

Further investigation into the psychological morbidity in chronic cough and association with the placebo effect on cough treatments is an area of important future research.

8.2.3 Study Design
8.2.3.1 Control group comparison
Within this thesis, two of my studies have not used a control group for comparison and this is a recognised limitation. An open design with no control group is inferior to a placebo-controlled randomised design however, the primary purpose of the study presented in Chapter 4 was to treat refractory cough patients and determine their
response to a therapy outside normal CC treatment and this was achieved by using objective measures to assess outcome. It is possible that a placebo effect such as cough suppression \(^{(271, 299, 301)}\) may have influenced some of the objective measures but I believe that this is unlikely as the majority of the participants studied had a cough for more than 5 years duration and underwent numerous cough treatments prior to speech language pathology intervention.

Chapter 7 compared patients with post infectious cough following acute respiratory infection to patients without cough following acute respiratory infection to determine the prevalence of CC attributable to the H1N1 2009 influenza. It could be argued that participants in the negative for H1N1 influenza group acted as the control group for this investigation however, a preferable design would have been to include a third healthy control group with no infection. As studies in cough clinics have failed to observe postinfectious cough after acute respiratory infection \(^{(33)}\) the primary aim of this study was to assess the prevalence of post infectious cough following H1N1 2009 influenza and again this was achieved by using subjective and objective cough measurements. A second limitation for this study was the response rate (sample size) however, as there was a complete dataset of those tested for H1N1 infection before the onset of CC, the minimum prevalence of post infectious cough was able to be calculated.

### 8.2.3.2 Outcome measures

A consistent strength of the studies presented in this thesis was the use of validated subjective and objective measures. This could be further enhanced by the validation of in-house questionnaires such as the laryngeal dysfunction questionnaire and laryngeal
sensation questionnaire. The objective measure of cough frequency by ambulatory cough monitor would be also enhanced by 24-hour cough monitoring in the participant’s environment.

8.2.3.3 Cough interventions

The discovery and associated investigation of new cough interventions has gained momentum during the last two decades but there is still a lot of work to be done in this area as well as further investigation and the use of objective measures in the assessment of current standard cough guidelines such as the ADP (2, 120). As discussed in Chapter 1 the ADP involves a targeted patient history and physical examination to investigate the possible cause/s of a patient's cough based on knowledge of the afferent cough reflex pathway. Using this information a stepwise treatment management program is initiated until there is resolution of the cough symptoms. Major limitations of this protocol are that the effectiveness of these interventions were not objectively assessed nor investigated in a placebo-controlled randomised design. The placebo effect in cough treatment is substantial in studies of antitussives (485, 486). Eccles (487) proposed that the perceived placebo effect could be due to a combination of the physiological effects of the placebo intervention, the true placebo effect, and non-specific aspects. The true placebo effect depends upon belief in effectiveness of treatment, the attitude of the patient towards the medical care giver and might influence cough via a psychoneuropharmacological response that releases endogenous active materials (485). Non-specific aspects of intervention include spontaneous recovery over time or rest. These issues could be addressed by utilising double-blind randomly
assigned placebo/intervention trials when investigating principles of the ADP and its associated guidelines.

In addition, the ADP and subsequent ACCP guidelines do not approach the assessment and specific treatment of CC from a multidisciplinary view and I believe this to be a downfall. The recent release of the Australian cough guidelines for adults and children (329) does address this issue and is a comprehensive clinical guideline developed by an expert committee of Allied Health, ENT, and Respiratory and Psychology experts after a needs assessment by clinicians. The combination of adult and paediatric populations in the one guideline and the addition and recognition of newer conditions such as obstructive sleep apnoea and vocal cord dysfunction as causes of specific cough are unique. Characterisation and treatment with speech language therapy of CC with PVFM/VCD has also been included in this guideline of which this thesis and work done by Vertigan et al (4, 345, 421, 430) plays a pivotal role.

8.3 Future Research
Replication studies of the work presented in this thesis would achieve a higher level of evidence for characterisation of chronic idiopathic cough and neuropathic cough as well as the efficacy of alternate treatments such as speech language pathology and neuroleptic drugs. Long-term follow up of this patient population assessing the effectiveness of treatment would be of interest. I would also like to conduct an RCT of speech language therapy in CC with objective 24-hour cough monitoring. Further research into gabapentin as a viable treatment for neuropathic sensory cough as well as other neuroleptic medications such as pregabalin is of immediate interest for me. There is also more work to be done on validating the laryngeal dysfunction questionnaire.
Finally, the study of primary care cough patients would significantly contribute to our understanding of cough aetiology, cough mechanisms and patient quality of life impairment and its associated effects such as anxiety and depression of which very few studies have looked at.

### 8.4 Conclusions

This thesis has shown that laryngeal dysfunction is common in patients with chronic persistent cough, postinfectious cough, and also refractory or idiopathic chronic cough. Laryngeal dysfunction associated with CC presents with impaired quality of life and cough reflex hypersensitivity consistent with other causes of CC. Paradoxical vocal fold movement and extrathoracic airway hyperresponsiveness are both manifestations of laryngeal dysfunction that have been identified and characterised by objective measures. Transient EAHR was found to be a mechanism of postinfectious cough following mycoplasma pneumoniae and postinfectious cough following H1N1 2009 influenza is associated with cough reflex hypersensitivity. Laryngeal hypersensitivity therefore appears to be a common mechanism in CC and this responds favourably to speech language pathology resulting in decreased cough reflex sensitivity. Laryngeal irritability has much in common with trigeminal neuralgia and other neuropathic pain. Gabapentin has been shown to be effective in the treatment of neuropathic pain \(^{488-490}\) and neuropathic/idiopathic cough \(^{147, 353}\) and this thesis provides confirmation of this through a placebo-controlled double-blind randomised trial. It appears that gabapentin exerts its effect by inhibiting release of excitatory neurotransmitters at supraspinal sites and this was confirmed through subjective and objective cough measures. Based on the findings of this thesis and in combination with work by others \(^{4, 147, 148, 208, 345, 349, 415}\) it is
recommended that international cough guidelines be updated to include investigation and treatment of laryngeal dysfunction in CC.
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