ECRONICON OPEN ACCESS

EC PAEDIATRICS
Review Article

Acute and Chronic Cough in Children and Antitussive Drugs in the Office and in Practice. Review of the Literature

Salavoura Katerina*

Children's' Hospital 'Agia Sophia', Pediatric Clinic University of Athens, Greece

***Corresponding Author**: Salavoura Katerina, Children's' Hospital 'Agia Sophia', Pediatric Clinic University of Athens, Greece.

Received: July 23, 2018; **Published:** August 28, 2018

Abstract

Acute cough is the most frequent complaint of parents in pediatric practice. However, according to our current knowledge, there is no acceptable treatment and parents' common practice is to ask advice from not professional staff and to use over the counter regimes. This is a common practice also in chronic cough, although the disease has more complex etiology. There are provided data according the etiology and treatment of acute and chronic cough as well as the common practice of patients.

Keywords: *Acute Cough; Chronic Cough; Antitussive Drugs*

Introduction

Cough is a protective reflex activity partly controlled voluntary and it is mainly activated from a foreign body or mucous within the respiratory tract. As the British society is defining "Cough is a forced expulsive maneuver, usually against a closed glottis and which is associated with a characteristic sound [1]".

Cough is the most common symptom in the pediatric population reaching 50% of new patient attendance in primary care and 10 - 20% of cases investigated in the pediatric departments. However, it is impressive the fact that in practice, the major source of consultation is the pharmacy and that 87% of cases could be treated by general practices [2]. Symptomatic treatment is the main stream. Unfortunately, much of the over-the-counter (OTC) therapy currently recommended throughout Europe is based on custom and practice and it is not supported by clinical studies of sufficient quality to meet the standards of modern evidence-based medicine as well that most of research concerns adults rather than young children [2].

Antitussive drugs are amongst the most widely used medications worldwide; however no new class of drugs have been introduced into the market the recent 30 years. Antitussive drugs have an impact of $4 billion per year [3].

Etiology of acute cough and treatment

In practice, clinically useful definitions are based mainly on the duration of cough. Acute cough is a cough arbitrarily defined as being of < 2 weeks duration or 3 weeks duration according to the British society [1].

The most common cause of acute cough in children is acute bronchitis. Actually, most of the cases are caused by a virus infection (90%) and the responsible virus is rhinovirus of the common cold in 50% [2]. Influenza is another frequent cause that shows a clear seasonality peaking at the turn of the year. The production of cough is relevant to the destruction of the epithelium by inflammatory mediators [1].

Epidemiological studies reveal that acute cough in otherwise healthy children is a benign and self-limited disease with an average duration of the symptoms around 14 days, although it can be prolonged as 25 days. It is estimated that children normally suffer from

symptoms of acute cough 7 - 8 times per year [1]. However, in addition to viral infections, acute cough is the presenting symptom of an acute exacerbation of asthma or another pulmonary disease and caution during clinical examination is obvious [1].

According to etiology, prescription of medications is regarded as unnecessary [1]. However, in practice in the primary care, acute bronchitis is frequently treated with antibiotics in 85% of cases, because symptoms are rather disturbing [1]. It is a fact also that it is a common to use palliative drugs such as antitussives. Actually, the treatment of acute cough is the higher percentage of the sales in the market [3]. The only accepted medications based on studies are dextromethorphan, menthol, sedative antihistamines and codeine or pholcodine [4].

Antitussives in the market or over the counter drugs are available without prescription and they are often in combinations with analgetics, adrenergics for rhinorrhea and congestion [4]. However, they are usually of not well documented quality and their use follows a geographical distribution [5]. In fact, in most cases it is not obvious if the drug or the spontaneous recovery is the reason for amelioration of the symptoms. Thus, in the US and Britain are used OTC oral decongestant/first-generation (sedating) H1 antihistamines, in Germany mainly mucolytics, in France helicidine and in Greece mainly codeine. The estimated adverse effects in children are reported to stand at 25% of emergency care visits [5].

Etiology of chronic cough and treatment

Chronic cough is defined the one lasting more than 4 weeks or 8 weeks in the UK [1]. Surveys in Japan and Great Britain estimated that the prevalence of chronic cough in the general population is 10.2% and 12%, respectively [6]. Persistent cough of unexplained origin is a significant health issue that occurs in up to 5% to 10% of patients seeking medical assistance for a chronic cough and from 0% to 46% of patients referred to specialty cough clinics [7].

The cause of chronic cough in adults are asthma, chronic obstructive pulmonary disease, gastro esophageal reflux disease (GERD) and allergic rhinitis, while in children asthma and protracted bronchitis are the main culprits of chronic cough [8]. Despite the high prevalence of cough in children, the topic has been poorly researched, especially in children [9].

Asthma is characterized by episodic, non-productive cough accompanied frequently by dyspnea or wheezing. In children conditions requiring further investigation are congenital airway abnormalities or obstructive sleep apnea due to enlarged tonsils or adenoids, foreign body inhalation, parenchymal lung disease such as cystic fibrosis, interstitial pulmonary disease or sarcoidosis, and infections such as tuberculosis and pertussis [10]. Gastrointestinal reflux is a diagnosis established by PH monitoring in patients with gastrointestinal or pulmonary symptoms. Cough in those cases is related to micro aspirations or vagal stimulation by the acid content of the reflex [1].

During childhood, the respiratory track and nervous system undergo maturation processes that influence cough. In addition the immune system undergoes significant changes and it is characterized by lack of memory and exposure to new infection agents [9]. Environmental factors such as indoors smoking or heating practices or outdoor air pollution should not underestimated [10]. The levels of particulate matter, especially PM_{10}, and the living distance from a high traffic road is considered the main environmental factor triggering cough [1].

In the 8th International Symposium for cough, it was proposed that chronic cough is not only a symptom but rather a distinct clinical entity termed cough hypersensitivity syndrome. It has also been proposed that the common pathophysiological mechanism underlying cough, regardless of the etiology, is an inflammation-induced injurious effect of the nervous system. The disease is characterized by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure. Patients frequently report that simple things such as changes in ambient temperature, taking a deep breath, sprays, scents, or eating crumbly dry food are common triggers for their cough. The pathophysiologic is linked to an enhancement of the afferent pathways of the cough reflex both at the peripheral and central levels. What leads to this enhancement is still unclear but inflammatory mechanisms through an interaction with cough reflex pathways may be important [11].

A laboratory evaluation including an X-ray and spirometry is mandatory in all cases. In cases with suspected asthma, a methacholine or histamine hyper responsiveness test should be offered. Routine challenge test with capsaicin or citric acid is not recommended [1]. Some specialists recommend an induced sputum analysis and measurement of eosinophils [1].

Other rare causes of chronic cough are sinusitis requiring a prolonged administration of antibiotics in combination with nasal corticosteroids. Post nasal drip is considered the main cause of chronic cough in the US, although this is not a universal finding [1]. The use of drugs such as converting enzyme inhibitor requires the cessation of the drug and chronic cough of unknown origin as well as psychogenic requires treatment with antitussives. Studies show that 20% of cases of chronic cough are undiagnosed and thus the cough considered as idiopathic [1]. Organ specific autoimmune disease emerges in 30% of cases, usually autoimmune thyroiditis [2].

Clinical and laboratory findings that raise the consciousness of the examiner should be prominent dyspnea especially at rest and during exercise, recurrent episodes of productive cough, cough accompanied by fever, failure to thrive or weight loss, feeding difficulties, recurrent pneumonia and abnormal sounds on examination and abnormal findings on the X-ray [10]. Persistent cough is reported in almost 20% of the general population in the US and UK, although geographical differences are significant [1]. The impact of cough on social well-being depends on individual circumstances and may result in difficulty in relationships, avoidance of public places, and disruption of employment [1].

It is worthwhile mentioning that empirical treatment is the first line of treating chronic cough. When symptoms persist further evaluation is needed to identify the etiology of cough and an etiologic management should be established. However, even with a clear diagnosis, cough could be difficult to handle and could be associated with impaired quality of life [1]. Evaluation does not follow an established protocol and it should be individualized. Treatment success is evaluated to be between 68% - 100%, even if it is completed in a specialized center [1].

Therefore, empirical treatment in primary care suggests avoidance of irritating factors and a sequential step approach management of symptoms. First, oral first generation antihistamines could be beneficial by inhibiting irritation. First generation antihistamines are more effective, while the effectiveness of second line antihistamines is controversial. In patients whose cough persists a trial of inhaled corticosteroids or/and b adrenergic antagonists will eliminate the symptoms of patients with asthma or obstructive pulmonary disease. Moreover, patients who respond only partially to the treatment should receive anti-reflux treatment with PPIs or anti-kinetics for a three month period time. Anti-reflux therapy follows an improvement of 75 - 10% of cases in uncontrolled studies, whereas ranitidine offers relief in 54% of cases [1].

Protracted bacterial bronchitis

In 2006, the work by Marchant., *et al.* became a cornerstone to the approach of chronic cough in children. They established by performing early bronchoscopy and Broncho alveolar Lavage that the main cause of chronic chough in children was protracted bacterial bronchitis (PBB), while the main reasons causing chronic cough in adults represented only 9% of the diagnosis in children. The diagnoses on this paper of children under investigation were asthma (54.5%), chronic bronchitis (2%), and lack of diagnosis (62%). Diagnosis based on the clinical presentation was confirmed in 90.8% of cases whereas bronchoscopy was performed in 45.5% of the cases [12]. Another survey by Kantar., *et al.* found a wider distribution of this diagnosis [9].

As protracted bacterial bronchitis is denominated the disease that causes productive cough more than 3 weeks. The etiology is bacterial infection due to typical respiratory organisms, including *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus Pneumonia* or viral infections caused by rhinovirus. Moreover, the cytological profile revealed neutrophilic inflammation. If untreated, the condition would lead to bronchiectasis. Diagnosis is empirical for ethical reasons, but bronchoscopy is suggested to recurrent cases. Treatment

with a course of antibiotics, mainly amoxicillin/clavulanate in high doses (80 - 90 mg/kg/day divided q8 h) for a period of 2 - 4 weeks is recommended. The role of neutrophils in the place of inflammation was underestimated previously. Neutrophils are increased as a result of bacterial infection ant they do not appear transiently, but permanently causing irreversible lung damage [12].

The first guidelines for cough were published by the American College of Chest Physicians in 1998 and the last revision was in 2016 in London. Some of the recommendations for treatment given below should be cautiously applied to children [13].

1. Patients with acute cough (as well as post nasal drip and throat clearing) associated with the common cold can be treated with a first-generation antihistamine preparation. (Brompheniramine and sustained-release pseudoephedrine).
2. In patients with the common cold, newer generation no sedating antihistamines are ineffective for reducing cough and should not be used.
3. In patients with acute cough due to the common cold, over the counter combination.
4. Cold medications, with the exception of an older antihistamine-decongestant, are not recommended until randomized controlled trials prove they are effective cough suppressants. In children with cough, cough suppressants and other over-the-counter cough medicines should not be used as they may experience significant morbidity and mortality.
5. In a patient with chronic cough, asthma should always be considered as a potential etiology because asthma is a common condition with which cough is commonly associated.
6. In patients with chronic cough, while tests that link GERD with cough suggest a potential cause-effect relationship, a definitive diagnosis of cough due to GERD requires that cough nearly or completely disappear with anti-reflux treatment.
7. For stable patients with chronic bronchitis, there is no evidence that the currently available expectorants are effective and therefore they should not be used.
8. In patients with chronic bacterial bronchiolitis, prolonged antibiotic therapy improves cough and is recommended. In post infectious cough antibiotics is not recommended.
9. A short course of oral corticosteroids and central acting antitussive agents such as codeine and dextromethorphan should be considered when other measures fail in chronic bronchitis.
10. In patients with cough due to upper respiratory infection, peripheral cough suppressants have limited efficacy and are not recommended for this use. Central cough suppressants are recommended in patients with chronic bronchitis.
11. Agents that alter mucus production and deduction are not recommended for releasing chronic cough.
12. If there exists an upper respiratory infection or chronic bronchitis the appropriate anticholinergic agent is ipratropium bromide.
13. The use of albuterol is not recommended for other causes apart from asthma.

Antitussive medication

Pathogenic mechanisms for the release of cough reflex are currently well recognized. Tissue infection of the upper and lower respiratory track, but also secondary stimuli from other organs such as esophagus provoke mechanic and chemical stimuli such as cytokines on the peripheral tissue neuronal receptors shared frequently by the receptors for pain. The stimuli could be mechanical or chemical. The afferent nerves starting from the spinal cord transmit the signals to the nucleus tractus solitarius [14]. The brain has not a particular location for the sense of the stimuli emerging cough and the signal is diffused in many locations producing inhibitory or enhancer activation. It is suggested that midbrain areas recorded to introduce hypersensitivity to pain stimuli are also engaged in the cough circuit. There are very important commonalities in this respect between chronic cough and chronic pain, and in addition between chronic cough and other conditions such as chronic itch and chronic breathlessness [15]. The underlying mechanism should be neuroglia

activation. The reflux is closed by stimuli driving muscles into contraction. There is a lot of progress defining the mechanism of cough and new strategies of treatment mainly through blocking peripheral terminals of Broncho pulmonary vagal afferent nerves [15].

Thus medications for cough are divided to the central and peripheral ones acting in different parts of the reflux. However, their effectiveness is not confirmed by different studies despite by their overuse by the public. The lack of effectiveness is the yet unexplained stimuli to the peripheral receptors [11].

Few medications have been investigated in pediatric population (Table 1) [4]. Moreover, the increased placebo effect should be considered in children. Regarding the medications with central action the well-known is codeine.

Antitussive	Studies in adults	Studies in children
Antihistamines	No = 2 (350 patients) Berkowitz 1991; Terfenadine Gaffey 1988; Terfenadine No improvement	**No = 3 (363 patients)** Sakchainanont 1990; clemastine 0.05 mg/kg/H + chlorpheniramine 0.35 mg/kg/day Paul 2004; Diphenhydramine Bhattacharya 2012; Promethazine No improvement
+ Decongestant	No = 2 (356 patients) Berkowitz 1989; (loratadine/epinephrine 5/120 mg) Curley 1988; dexbrompheniramine/pseudo ephedrine 6 mg/120 mg twice No improvement	No = 2 (155 patients), Clemens 1997; Brompheniramine/fenyl propanolamine (2/12. mg) Hutton 1991; brompheniramine/phenylephrine/ propanolamine No improvement
Other combinations	No = 4 (836 patients) Kurth 1978; Mizoguchi 2007; Thackray 1978; Tukiainen 1986; No compatibility EM-Vier(Minetten) improvement (25%-11%) Vicks Medinite improvement (57.6%-32.2%) Tukiainen 1986; dextromethorphan/salbutamol No Improvement Mizoguchi 2007; dextromethorphan/salbutamol/ doxylamine, Improvement	No = 2 (94 patients) Reece 1966; Triaminicol syrup, Dorcol paediatric cough syrup. Improvement in 69%/57% placebo Korppi 1991b; dextro methorphan/salbutamol 1.5 mg/0.2 mg. No difference
Codeine	No = 903, 6+placebo (1526 patients) Eccles 1992 30 mg Freestone 1997 50 mg. No overbalance to placebo	No = 4+placebo (327 patients) Taylor 1993 No overbalance to placebo
Dextromethorphan	No = 3 (451 patients) Pavesi 2001, 30 mg Lee 2000 30 mg Parvez 1996 30 mg Overbalance to placebo (36%/19%)	Korpi 1991a: 1.5 mg**X**3, 3mgX3 Paul 2004 1.5 mg**X**3, 3 mgX3 dextromethorphan/ antihistamine, 5 mgX3-4 Bhattacharya 2012 No overbalance to placebo
Expectorants		
Guaifenesin	No = 3 (604 patients), Albrecht 2012; 12 years, no improvement Kuhn 1982; guaifenesin, improvement of frequency and severity Robinson 1977; guaifenesin, improvement 31% Improvement compared to control, decrase of moucus (96%)	No studies
Mucolytics	No = 1 (99 patients) Nesswetha 1967; bromhexine 5 mg Decreased frequency	No = 1 (40 patients) Nespoli 1989; Letosteine Improvement
Honey		No = 1 (300 patients) Avner Cohen 2012: Eucalyptus honey, citrus honey or labetiae honey) or silane date extract Improvement with honey

Table 1: *Review of the literature regarding over the counter medications [4].*

Codeine is an alkaloid opioid used from ancient times for the inhibition of pain and cough. It acts on the opioid receptors of the central nervous system or through its sedative results [15]. It comes from the plant *Papaver somniferum* and its extract was distillated by the chemist Jean Robiquet in 1930. Its commercial use is combined with antihistamines, antipyretics, decongestants and expectorants and it is frequently given without prescription. However, a Cochrane library meta-analysis failed to conclude about its overall efficacy in acute and chronic cough [15]. Codeine has serious side effects such as respiratory depression, itching, rashes, angioedema, vomiting and ataxia. Its effectiveness regarding the amelioration of cough has not been confirmed in some patients. The drug is metabolized in the liver in morphine and the rate of metabolism is related to individualized factors. Thus, its effectiveness limits to one third of people using it. Although there have been published considerable side effects, codeine is available commercially without prescription. European conferences and FDA are seriously concerned with this practice and they suggest banning of its use in children under 18 years old [15]. Morphine has only been proposed for amelioration of chronic cough symptoms [16].

Other antitussives with central action are pentoxyverine, butamirate and gabapentin which is an old anticonvulsive drug possessing an effect to neuropathic pain [11]. All those medications although frequently used, their effectiveness is not established compared to placebo. However, gabapentin use is suggested as the best option for use in chronic idiopathic cough [7]. Perhaps dextromethorphan, an antitussive with central action, has a similar mechanism of action [7].

Dextromethorphan is considered the only medication effective for coughing using objective methods [2]. Although a derivative of morphine, it has less analgesic and sedative properties [3]. Similarly to codeine, it is not effective in the management of acute cough.

Some other antitussives with peripheral action are levodropropizine used in south Europe especially in Italy, dextromethorphan and expectorants used in Germany by 23% of patients, such as ambroxol (metabolite of bromoxine) and N-acetylcysteine. Regarding antihistamines, 1st generation drugs are frequently used in the USA and in the UK as antitussives for common cold as diphenhydramine combined with decongests. Other antihistamines in use are oxomemazine and hydroxyzine [2].

As antitussive drugs have been used many extracts from plants or animals such as hexidine from *Helix pomatia* in France, which combines an antibacterial function especially against pertussis or menthol from the plant *Mentha arvensis* [2].

A recent Cochrane meta-analysis review concluded that there was ‘‘no good evidence for or against over the counter (OTC) medicines in acute cough’’. A national telephone survey of medication use in the US indicated that in a given week, 10% of children are given an OTC cough preparation by their caregivers. Some studies of cough preparations have been shown to reduce cough symptoms, whereas others found no effect compared with placebo [16].

Our understanding of the underlying mechanism of the cough reflex leads to the production of a new generation of antitussives currently under clinical trials. Such medication work binding central or peripheral receptors of the neuronal circuits and will be the future against cough (Figure 1) [11,15].

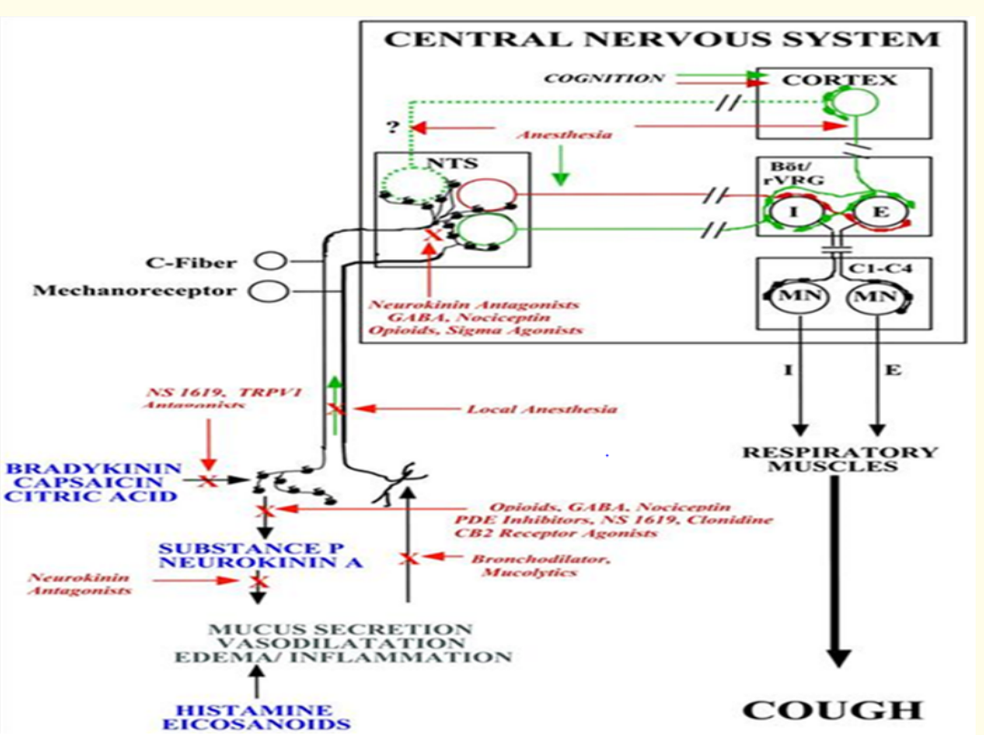

Figure 1: *Where and how central and peripheral new antitussive medications act.*

1. **Antagonists of TRPV receptors:** This medication inhibits the ion pump of valiloids and it is introduced when oxidative stress exists. TRPV1 is increased in cases of chronic cough mainly due to inflammation and the receptors are arbitrarily distributed to the airways. The scientific name is SB-705498, GRC 17536, but its effect does not seem adequate. The cold and menthol sensitive receptor (CMR1) has recently been characterized and cloned. TRPV1 is activated by capsaicin, a compound found in hot chili peppers, and an increase in epithelial nerve expression of its receptor has been identified in patients with non-asthmatic cough.

2. **TRPA1 antagonists:** This receptor works when neuropeptides are realized and coexists in the pathway of pain. Problems related to the use of those drugs are caused by the wide distribution of these receptors.

3. **Sodium channel blockers:** These drugs block the transmission of stimuli through the vagal nerve and they have been used only in experimental models.

4. **ATP receptor P2X3 antagonists:** These drugs also inhibit the transmission of stimuli through the vagal nerve. The AF-219 (600 mgX2/**H**) has contributed to the remission of cough in 75% of patients and it becomes a promising antitussive drug.

5. **Central neuromodulators ASID:** These receptors detect PH changes in the central nervous system. N-methyl-d-aspartate (NMDA) antagonists show effective cough inhibition and a well-known drug with the same function is nicotine.

Targeting peripheral and central neurons of the circuit of cough is the basis of those new treatments. In periphery, the nerve afferent signals, the duration of activation and the number of units activated determine the intensity of signals. Centrally acting agents, diminish the input from afferent nerves. The signalling can be also enhanced or inhibited by parallel neuronal circuits [11].

Regarding the opinion of the public, a survey using mobile telephones in 2012 showed that 84.6% of the responders had experienced at least 1 cold. Cough was the more disrupting symptom (73.1%). Cough was often persistent, lasting for 3 - 5 days in 45.3%, 6 - 12 days in 28.0%, and longer than 12 days in 7.2%. Almost half of the responders waited until the symptoms deteriorated (42.6%), while a significant proportion (36.1%) bought a medication from the beginning. Most of them bought a medication that had worked well previously. Interestingly, most of the responders though that an antibiotic should be provided (1/3) [17].

Conclusion

Cough is defined as acute or chronic which have a different etiology and they are combated by different medications. Regarding medications used for cough, data are conflicting. However, public frequently uses over the counter medications with controversial effectiveness due to the disturbing nature of the symptom. New treatments relative to our knowledge about the mechanism of cough are under investigation.

Bibliography

1. A H Morice., *et al*. "Recommendations for the management of cough in adults". *Thorax* 61.1 (2006): i1-i24.

2. A Morice and P Kardos. "Comprehensive evidence-based review on European antitussives". *BMJ Open Respiratory Research* 3.1 (2016): e000137.

3. S Birring. "Developing antitussives: The ideal clinical trials". *Pulmonary Pharmacology and Therapeutics* 22.2 (2009): 155-158.

4. Smith SM., *et al*. "Over-the-counter (OTC) medications for acute cough in children and adults in community settings (Review)". *The Cochrane Database of Systematic Reviews* 11 (2014): CD001831.

5. R Eccles., *et al*. "Treatment of Acute Cough Due to the Common Cold: Multi-component, Multi-symptom Therapy is Preferable to Single-Component, Single-Symptom Therapy-A Pro/Con Debate". Lung 194.1 (2016): 15-20.

6. R Irwin. "Overview of the Management of Cough. CHEST Guideline and Expert Panel Report". *Chest* 146.4 (2014): 885-889.

7. P Gibson., *et al*. "Treatment of Unexplained Chronic Cough CHEST Guideline and Expert Panel Report". *Chest* 149.1 (2016): 27-44.

8. J Smith and Ashley Woodcock. "Chronic Cough". *New England Journal of Medicine* 376.2 (2017): 183-184.

9. Ahmad Kantar. "Update on Pediatric Cough". *Lung* 194.1 (2016): 9-14.

10. P Gibson., *et al*. "CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian Cough Guidelines summary statement". *Medical Journal of Australia* 192.5 (2010): 265-271.

11. K F Chung., *et al*. "Eight International London Cough Symposium 2014: Cough Hypersensitivity Syndrome as the basis for chronic cough". *Pulmonary Pharmacology and Therapeutics* 35 (2015): 76-80.

12. Marchant JM and Chang AB. "Re: Evaluation and outcome of young children with chronic cough". *Chest* 130.4 (2006): 1279-1280.

13. RS Irwin and MH Baumann. "Diagnosis and Management of Cough Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines". *Chest* 129.1 (2006): 1S-23S.

14. BJ Canning. "Encoding of the cough reflex". *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 300.2 (2011): R369-R377.

15. Kian Fan Chung. "Advances in mechanisms and management of chronic cough: The Ninth London International Cough Symposium 2016". *Pulmonary Pharmacology and Therapeutics* 47 (2017): 2-8.

16. S J Gardiner., *et al*. "Codeine versus placebo for chronic cough in children". *Cochrane Database of Systematic Reviews* 7 (2016): CD011914.

17. MS Blaiss., *et al*. "Consumer Attitudes on Cough and Cold: US (ACHOO) Survey Results". *Current Medical Research and Opinion* 31.8 (2015): 1527-1538.

Volume 7 Issue 9 September 2018