ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

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Introduction

Cough is a vital protective reflex preventing aspiration and enhancing airway clearance. Pathologically excessive and protracted cough is however a common and disabling complaint affecting perhaps 5 to 10 percent of the adult population[1]. When severe, it causes a major decrement in the quality of life with comorbidity such as incontinence, cough syncope and dysphonia leading to social isolation, depression, and difficulties in relationships[2].

Whilst a wide range of diseases may be associated with chronic cough it has become increasingly clear that the majority of adult patients presenting with chronic cough as the primary complaint have a common clinical presentation[3]. They often complain of exquisite sensitivity to inhalation of environmental irritants such as perfumes, bleaches, and cold air which result in sensations of tickling/irritation in the throat and an urge to cough; features suggestive of heightened sensitivity of the neuronal pathways mediating cough[4]. There is also a unique epidemiology with two thirds of patients being female and the peak prevalence in their fifties and sixties. These observations have led to the concept of cough hypersensitivity syndrome as a diagnosis[5]. In children chronic cough presents in a markedly different fashion with different aetiology. They are not miniature adults[6].

This guideline aims to improve diagnostic accuracy and promote evidence-based therapy for both paediatric and adult patients in both primary and secondary care. The guideline is intended for use by all health care professionals looking after patients with chronic cough. The guideline has been developed by a multidisciplinary international panel of clinicians and scientists with a published record of expertise in the field. Input on patient views and preferences was sought via the European Lung Foundation who provided an advisory group of patient representatives who expressed their preferences via teleconferences, attendance at the ERS Congress, and in writing. They contributed to formulating and prioritising the key questions.

Guideline scope and structure

This guideline follows the hybrid model of the ERS Guidelines Working Group and Science Council[7], which combines the scientific rigor of the GRADE framework for key questions of uncertainty with a narrative component to reflect the expert consensus of the guideline task force. The narrative covers clinically important aspects of chronic cough while the eight key questions systematically explore the evidence in areas of clinically important controversy.

Full details of the methodological process and the analysis of the individual questions can be found in the online supplement. Table 1 provides a summary of the eight questions (two diagnostic and six therapeutic questions), the level of evidence, and the recommendations arising from the systematic review. All other propositions should be regarded as narrative statements.

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Definition of chronic cough

To define a chronic cough on the basis of longevity is clearly an arbitrary paradigm. Early studies used three months based on the MRC definition of chronic bronchitis[8]. More recent guidelines have adopted eight weeks in adults[9] and four weeks in children[10]. Inclusion criteria for studies of novel antitussives require a cough refractory to treatment to be present for over a year. Whilst some patients cough on a daily basis over many years for others the disease has a relapsing and remitting course making a definition based purely on a temporal basis difficult to sustain. The diagnosis of chronic cough should be made on a global clinical assessment taking into account the other features of the phenotypes of cough detailed below. The failure to recognise that the patient is suffering from the syndrome of chronic cough may lead to misdiagnosis with the patient labelled as suffering from recurrent chest infections, treatment resistant asthma, or exacerbations of COPD.

The commonly used definition of chronic cough in children is 4 weeks, although cough in children lasting 3 to 8 weeks has been termed prolonged acute cough[10, 11]. Irrespective of the exact duration, chronic cough in children is different from that in adults due to differences in the airway morphology, a higher degree of vulnerability to noxious insults, reduced control of the cough reflex and differences in maturation of the neurological and immunological system in the different paediatric age groups[6]. Chronic cough in children is best seen as a symptom of an underlying disease.

Epidemiology

Cough is a common medical problem and the socioeconomic burden is substantial[12]. However, there is no precise data on the burden of chronic cough, probably because chronic cough was previously perceived not as a clinical entity but as the consequent symptom from other respiratory conditions. There is no agreed definition of chronic cough for use in epidemiological studies[8].

A meta-analysis estimated the global prevalence of chronic cough in the general adult population as about 10%[1]. It was more prevalent in Europe, America and Oceania than in Asia and Africa. Notably, the prevalence of chronic cough in adults is associated with a number of characteristics [13-16]. In a recent international survey of 10,032 adult patients attending specialist cough clinics, two-thirds were females and the most common age for presentation was in the sixth decade [3]. The distinct demographic pattern is thought to be related to sex differences in central processing of cough sensation. The most commonly associated conditions are irritable bowel syndrome, obesity and a variety of neuropathic syndromes. Iatrogenic chronic cough from drug treatments is frequently unrecognised.

About 35 % of preschool children report cough at any given time in a month[17]; however, so far, no studies have systematically compared the prevalence of chronic cough in children worldwide. Reports of chronic cough in populations vary between 1% in India[18], 9% in Eastern Europe[19] and 5-12 % in China with increases in areas with higher air pollution[20]. Subjective perception and

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parental reporting of symptoms further biases prevalence reports[21]. Studies comparing prevalence rates worldwide are warranted.

Impact on patients

Chronic cough is highly disruptive to the individual affected and those around them. The most common reasons why patients with cough seek medical attention include concern about a serious underlying illness, vomiting, exhaustion, sleep disruption, social embarrassment, difficulty speaking on the telephone, urinary incontinence and annoyance to family, friends and workmates[22].

The consequence of chronic cough is a wide range of complications of coughing[23]. Most impactful on Health-Related Quality of Life (HRQOL) are stress urinary incontinence, interference with speech and depression[24]. However, there are many others that can be equally bothersome, such as syncope. Individuals report, on average, eight adverse symptoms associated with cough[22].

Stress urinary incontinence is particularly impactful, as cough affects females disproportionately compared to males. Female patients with cough and urinary incontinence have worse HRQOL compared to those without incontinence[24]. In a quarter of patients, the incontinence is severe but rarely discussed. Thus incontinence should be enquired about during a consultation.

The impact of cough can be assessed and quantified formally with validated HRQOL tools, such as the Leicester Cough Questionnaire (LCQ) or the Cough-specific Quality of Life Questionnaire (CQLQ)[25, 26]. A strength of cough HRQOL tools is that they can be used to demonstrate the efficacy of anti-tussive therapy that is clinically meaningful. In the clinic simply asking “score your cough out of 10” is perhaps the easiest subjective measure of treatment success[27] and should be asked at each consultation.

In children, the caregiver’s worries about the underlying reason for the cough are a major driver to seek medical attention[28]. Paediatric cough is best considered as a symptom of an underlying disease. Therefore, the burden of disease is influenced by the quality of the health care system as well as health care independent factors such as age range[29-31], gender, and indoor and outdoor air pollution[32].

Aetiology and mechanisms

Cough is a vital protective reflex preventing aspiration into the lung. Patients with a poor cough reflex such as those who suffer from neurological conditions succumb to recurrent episodes of aspiration[33] frequently misdiagnosed as “chest infections”. Cough is a vagal reflex evoked by stimulation of afferents carried by the tenth cranial nerve, with their receptive fields primarily in the larynx and conducting airways, but also potentially in the alveolar septa and parenchyma of the lung (e.g. pulmonary embolism, heart failure, altitude sickness), the pharynx and oesophagus, and even the ear, with vagal afferents projecting to the auricular canal from the superior vagal (jugular) ganglia (Arnolds reflex)[34].

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Noxious stimuli (e.g. gastric fluid, protons, cigarette smoke, particulates, hyper or hypotonicity) are detected through receptors and ion channels (e.g. TRPV1, TRPA1, TRPV4, ASIC, P2X3) localized to vagal afferent nerve terminations in the airways mucosa[35]. The vagal afferent nerves regulating cough are polymodal i.e. responding to a variety of different chemical and mechanical stimuli. Cellular stress releasing ATP appears to be an important stimulus[36]. Afferent neuronal traffic is relayed via vagal axons to the brainstem via at are least two different biochemical pathways[37]. Cortical influences modulate the reflex, with women having a greater area of the somatosensory cortex devoted to cough. The system is characterised by marked redundancy, plasticity and adaption. The neurobiology of cough has recently been comprehensively reviewed[38].

Cough may be caused by excessive stimulation of a normal cough reflex such as occurs following inhalation of a foreign body or noxious vapours. However, most patients presenting with a chronic cough have features of cough reflex hypersensitivity, responding to exposure to low levels of thermal, chemical, or mechanical stimulation[5]. The cough hypersensitivity syndrome has been adopted as an overarching diagnosis with the different phenotypes dependent on the type and location of the inflammation seen. Both central and peripheral mechanisms have been postulated for cough reflex hypersensitivity[39].

The aetiological mechanisms for cough hypersensitivity remain controversial and are dealt with in greater depth below. In the airways, T2 inflammation occurs in approximately a quarter of patients although this may be through stimulation of the innate immune system rather than atopy[40]. This gives rise to the phenotypes of cough variant asthma and eosinophilic bronchitis[41]. Reflux, particularly nonacid gaseous airway reflux, and oesophageal dysmotility are common features[42]. Central mechanisms for cough hypersensitivity have also been postulated, with circumstantial supportive evidence generated using fMRI[43]. It is suggested that there is an underlying neuropathic process responsible for cough hypersensitivity[44], a view that is supported by the development of cough in certain forms of hereditary somatosensory neuropathy[45].

Phenotypes of chronic cough

Asthmatic Cough / Eosinophilic Bronchitis

Asthma is a clinical diagnosis. There is no agreed single diagnostic test to diagnose or exclude asthma and because of its heterogeneous presentation opinions differ on how to describe the syndrome in patients with chronic cough. Eosinophilic inflammation may be a useful biomarker of asthmatic cough and may have utility in directing therapeutics. All adults and children with chronic cough may be assessed for eosinophilic inflammation. Sputum eosinophilia is perhaps the most accurate indicator, but is not routinely available, time-consuming, and requires expert interpretation. Exhaled nitric oxide can be used as a surrogate marker of eosinophilic airway inflammation and steroid responsiveness in classic asthma, but its role in asthma and chronic cough is questioned below. A meta-analysis of observational studies showed exhaled nitric oxide to have a relatively high specificity of 0.85 in predicting asthma among adult patients with chronic cough[46]; however, there is still no consensus on the cut-off level for the diagnosis. Blood eosinophilia is a simple and readily available measure, but is characterised by diurnal and seasonal variability[47] so multiple

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assessments should be made[48]. An eosinophil count of greater than 0.3 cells/µL may be taken to indicate eosinophilic airway inflammation[49, 50].

Three subgroups of asthmatic cough have been recognised. Classic asthma is characterised by airflow variability and bronchial hyperresponsiveness. Spirometry is thus an obligatory investigation. Cough variant asthma (CVA)) was originally described as those patients with asthma and cough as the sole symptom and where treatment with bronchodilators improved coughing [51]. Opinions vary as to whether this should be sought by performing bronchial provocation test. Some centres see this as an important part of the workup, whereas others find it adds little to the patient pathway. The third form of asthmatic cough is eosinophilic bronchitis (EB) without bronchoconstriction or hyperresponsiveness. The lack of these latter two features has been suggested to indicate that EB is a separate condition – Non-Asthmatic Eosinophilic Bronchitis[52]. However, in chronic cough communication with patients and other health care professionals may be enhanced if it is considered as part of an asthmatic spectrum, particularly as all three subgroups can respond to anti-inflammatory asthma therapy. The vital importance of establishing or refuting the diagnosis of asthmatic cough lies in the therapeutics (discussed in questions below) as it may be considered as a treatable trait.

Reflux cough

The role of reflux, oesophageal dysmotility, and aspiration in chronic cough is controversial. Its prevalence has been estimated from 0 to almost 100%. Early studies using the criteria of acid reflux found a low incidence and poor temporal relationship[53]. A systematic review[54] found no significant benefits over placebo of PPIs in patients without acid reflux and only modest benefits even in patients with acid reflux. It was suggested that non-acid reflux, both liquid and gaseous, may be an aetiological factor[55]. However no technology reliably detects such reflux and the diagnosis relies on the clinical history supported by validated questionnaires such as the Hull Airway Reflux Questionnaire (HARQ)[56] (see issc.info for multi lingual versions) or Reflux Symptom Index[57]. The picture is complicated by the observation that there is a high prevalence of oesophageal dysmotility in patients with chronic cough[42] and thus oesophago-pharyngeal reflux rather than GORD/GERD may be the problem.

Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration. Voice change, nasal symptoms and dysgeusia are common[58]. Frequent “chest infections” bronchitis, and even frank bronchiectasis may be the consequence rather than the cause of cough through repeated aspiration. Unsurprisingly following aspiration of contents from the GI tract there is an inflammatory response. This might be neutrophilic or eosinophilic giving rise to asthmatic cough and mucus hypersecretion[59].

Postnasal drip syndrome/Upper airways cough syndrome

The 2006 American College of Chest Physicians (ACCP) cough management guidelines suggested the term upper airways cough syndrome (UACS) to describe the variety of signs and symptoms previously referred to by other synonyms including postnasal drip syndrome, rhinitis and

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rhinosinusitis[60]. The revised nomenclature however did not resolve ongoing controversy regarding the existence of this syndrome and the mechanism(s) by which it may induce chronic cough.

A first-generation antihistamine and decongestant were recommended as the treatment, in the absence of adequate randomised controlled trial (RCT) evidence. The first-generation antihistamines however are thought to be antitussive through their action as centrally penetrant anticholinergics[61].

However UACS could be accepted as an aetiology of chronic cough in some patients by acting as a trigger for cough hypersensitivity although the mechanism remains obscure. The absence of evidence for localised treatment might suggest that upper airway symptoms merely reflect generalised airway inflammation consequent to asthma or airway reflux.

Iatrogenic cough

Chronic cough occurs in approximately 15% of patients taking angiotensin-converting enzyme inhibitors (ACEI). ACEI increases the sensitivity of the cough reflex in most subjects[62] and it is probable that additional factors are required to produce clinical impact. Since the reflex is reset there may be no close temporal relation to drug administration or withdrawal and the cough[63]. No patient with a cough or who develops one should be given ACEI. Angiotensin II antagonists do not affect the cough reflex.

Drugs such as bisphosphonates or calcium channel antagonists may worsen pre-existing reflux disease causing increased cough. Prostanoid eye drops such as latanoprost may descend the lacrimal duct irritating the pharynx[64].

Chronic cough in children

Chronic cough in children differs from that in adults in terms of common aetiologies and management and is increasingly defined as cough that lasts more than 4 weeks. Regardless of setting and age, children with chronic cough should be evaluated carefully using children-specific protocols[65].

During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence the cough reflex. Additionally, immunological responses undergo developmental and memorial processes that make infection and congenital abnormalities the predominant causes of cough in children[66]. Thus, tracheomalacia, protracted bacterial bronchitis (PBB), and bronchiectasis occur, in addition to common aetiologies such as asthma and post-infectious cough[67]. PBB is not a new entity and PBB-like conditions were being reported in the 1980s[68]. An ERS task force has recently advanced a reliable definition of PBB for day-to-day clinical practice when all three of the following criteria are fulfilled: 1) Presence of continuous chronic (>4 weeks' duration) wet or productive cough; 2) absence of symptoms or signs (i.e. specific cough pointers) suggestive of other causes of wet or productive cough; and 3) cough

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resolved following a 2–4-week course of an appropriate oral antibiotic[69]. PBB may be a precursor of bronchiectasis[70].

Initial assessment for chronic cough in children includes a detailed history and thorough physical examination to identify possible specific causes due to an underlying disease. A sudden onset of cough in an otherwise healthy preschool child may suggest foreign body aspiration and requires bronchoscopy. A chest x-ray as well as spirometry in collaborative children is essential. If specific cause for the chronic cough is suspected, further investigations are necessary. In case no specific pointers are detected and chest x-ray and spirometry are normal then the guideline panel considered that another period of observation of up to four weeks was indicated. In case of persistence of cough differentiate between dry and wet cough[71]. Exposure to airborne irritants (e.g. tobacco exposure, combustions, traffic related exposure etc.), allergen exposure or postinfectious cough may be a reason for dry chronic cough. In case of wet cough, sputum cultures should be attempted.

Habit/tic cough is another aetiology found particularly in children, manifesting the core clinical features of tics including suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation whether the cough is single or one of many tic. The formerly called psychosomatic cough should now be labelled somatic cough disorder and this diagnosis should only be made after an extensive evaluation that includes ruling out tic disorders and uncommon causes of chronic cough[72].

Psycho-morbidity is present in all patients with chronic cough with a variety of aetiologies, and tends to decrease following successful treatment[73]. There are limited criteria for the diagnosis of psychogenic (or somatic) cough and features of psychogenic cough reported in the literature are not unique to psychogenic cough[72]. Somatic cough disorder has been commonly used to describe cough without obvious aetiology. However, recent research has revealed neurobiological phenomena are responsible for psychogenic cough[43]. The presence of depression and/or anxiety cannot be used to diagnose psychogenic cough because, as in adults, patients with a persistently troublesome chronic cough can develop these psychologic symptoms when their coughs remain untreatable. Non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counselling, or referral to a psychologist and/or psychiatrist have been suggested in management, but such strategies lack an evidence base.

Chronic refractory cough

A proportion of patients with chronic cough, particularly among adults, have persistent cough despite thorough investigation and treatment according to published practice guidelines. Terms such as idiopathic chronic cough, unexplained chronic cough and chronic refractory cough have been utilized to describe this clinical condition[74]. Successful trials of drugs with neuromodulatory effects such as opiates, gabapentin, and P2X3 antagonists suggest that aberrant neurophysiology is likely to underlying this condition. Here the term chronic refractory cough is used to indicate that the cough is refractory to conventional treatment of cough-associated conditions or traits.

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Chronic cough in other diseases

Most chronic respiratory disease is associated with cough. Physical distortion of the airway such as occurs in lung cancer or the bronchorrhea of cystic fibrosis and chronic bronchitis produces cough by mechanical effects. However cough hypersensitivity through cell damage and inflammation underlies much of the increased cough seen in other pathologies. The different pathological processes in individual conditions contribute to the disease specific, heterogeneous, aetiology of cough in other lung disease.

As an example, cough in interstitial lung diseases (ILDs) is common with a prevalence of 30 to 90%. Patients with ILD often respond poorly to general anti-tussive therapy. In an open label study of idiopathic pulmonary fibrosis (IPF) pirfenidone reduced 24-hr objective cough counts and improved cough-related QoL[75]. Reformulated sodium cromoglicate improved 24-hr objective cough by 31% in patient with IPF whereas there was no effect in chronic idiopathic cough[76]. It seems likely that each individual respiratory condition will have its own profile dependent on the tussigenic factors expressed in that disease.

Chronic cough, tobacco and nicotine

Smoking is the major remediable cause of chronic cough and is inextricably linked to chronic obstructive pulmonary disease (COPD). Epidemiological studies have demonstrated a relationship between cumulative smoking exposure and chronic cough[77]. Furthermore, smoking history and current cigarette consumption are predictors of objectively-measured cough frequency[78]. A natural inference therefore would be to ascribe a protussive effect to tobacco smoke and its components. Research in otherwise healthy smokers and nonsmokers, however, has provided additional insights, some of which contradict general assumption.

Multiple studies of otherwise healthy smokers have demonstrated suppressed cough reflex sensitivity to inhaled capsaicin[79, 80]. The development of electronic cigarettes (e-cigs) provided a mechanism of non-combustible delivery of nicotine to the lungs. One tobacco cigarette equivalent induced significant suppression of cough reflex sensitivity[81]. These data are consistent with previous clinical observations of transient increase in cough within the first month after smoking cessation[82]. All patients should quit smoking and they should be warned there may be a transient increase in coughing. For those unable to quit because of excessive coughing e-cigs may be a supportive therapy[83].

Assessing cough in the clinic

Initial assessment

The history, examination, and investigations for patients with chronic cough are performed to exclude treatable traits of the disease for which directed therapy can be offered. The guideline

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panel placed higher value on control of any on-going pathology such as reflux or airway eosinophilia before currently available neuro-modulatory treatments are considered. A detailed history and examination should be directed to exclude malignancy, infection, foreign body inhalation or the use of an angiotensin converting enzyme (ACE) inhibitor. The impact of cough should be assessed either by recording simple measures such a cough score out of 10 or VAS or by more detailed, validated measures of cough quality of life (LCQ or CQLQ). Validated questionnaires may help to detect features of airway reflux (HARQ and RSI) and airway hypersensitivity[84].

Initial evaluation should include spirometry and a recent chest x-ray (CXR) (Good Practice Statement).

Chest CT

Question 1: Should chest CT scan be routinely performed on chronic cough patients with normal chest X-ray and physical examination?

We suggest that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have normal chest x-ray and physical examination (conditional recommendation, very low quality evidence).

Some prospective and retrospective cohorts identified CT findings in a range of 6.5% to 58% of patients with cough and normal CXR; however the causal relationship was either not specified or considered as unlikely related to cough [85-87]. There is a concern about potential cancer risk from CT radiation exposure [88, 89]. Thus the potential radiation risk needs to be weighed against possible diagnostic yields, particularly in susceptible populations such as children and females.

Further investigations to identify treatable traits in chronic cough

Further investigations for asthma, EB, reflux and oesophageal dysmotility, and rhinosinusitis should be considered depending on the clinical history.

Asthma and eosinophilic inflammation

Objective evidence of classic asthmatic cough conventionally requires some evidence of variable airflow obstruction such as peak flow variability, or reversibility to salbutamol of more than 12-15%. However, these investigations have a very low negative predictive value particularly in patients with normal lung function[86]. Further investigation of bronchial hyper-responsiveness (BHR) using either methacholine or histamine inhalational challenge is advocated by some although its utility in diagnosis is questioned. Evidence for ongoing airway eosinophilic inflammation can be sought by performing differential cell counts on samples from sputum induction or bronchoalveolar lavage. In such cases, elevated eosinophils (>3%) in the airways in the absence of BHR would suggests EB, which has been reported in up to 13% of patients attending cough clinics[41]. However, most centres do not have such facilities available, hence a non-invasive alternative is the use of fractional exhaled nitric oxide (FeNO) in breath or blood eosinophilia as a surrogate marker to assess airway eosinophilia. The clinical usefulness of FeNO or blood eosinophils in aiding diagnosis or predicting treatment response in patients with chronic cough has not yet been systematically evaluated[90].

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

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There is a need for convenient and practical tests for predicting anti-inflammatory treatment responses in patients with chronic cough. However, there is a still lack of quality evidence. Placebo-controlled trials are warranted to assess their utility and also consensus is required on threshold levels in patients with chronic cough.

One RCT [91] in adult non-smoking patients with chronic cough shows that baseline FeNO levels (greater than 30ppb or lower than 20 ppb) did not predict response to anti-leukotrienes. Cough frequency and quality of life were similar between high and low FeNO groups at the end of treatment. Observational studies suggested that non-responders to ICS may have significant lower levels of FeNO at baseline [92, 93], but the findings were not consistent[94]. Randomised placebo-controlled trials are required to validate the utility or otherwise of FeNO as a predictor of treatment response in chronic cough patients. Currently, there is no study examining the predictive utility of blood eosinophils in patients with chronic cough.

Given the uncertainty of diagnostic testing, a therapeutic trial may be indicated for asthmatic cough. In adults oral prednisolone for one week may cause a dramatic decrease in cough[95]. Inhaled corticosteroids (ICS) may be used when oral is contraindicated and is preferable in children. However it may be less effective since inflammation in CVA and EB is located in different parts of the airway from that seen in classic asthma[96], and may be driven by other pathways such as the innate immune system[97]. This also may explain the greater efficacy of systemic leukotriene antagonists such as montelukast in asthmatic cough[98].

Reflux and dysmotility

In the absence of peptic symptoms 24-hour pH monitoring for the investigation of reflux disease is not helpful. However abnormal oesophageal physiology is very common in patients with chronic cough and may be detected with poor sensitivity by a barium swallow. More accurately, high resolution oesophageal manometry provides diagnostic information as to the site and mechanism of dysmotility in the majority of patients[42].

The upper airways

In patients who report upper airway symptoms fibre optic laryngoscopy may be performed. The larynx is commonly found to be red and inflamed. However, the test has poor sensitivity and specificity. In select patients, laryngoscopy may be useful in identifying inducible laryngeal obstruction (ILO) associated with cough, and this may help plan the need for future cough control therapy[99]. Rhinoscopy may be helpful in identifying polyps and clearing mucus from blocked sinuses in patients with recurrent sinus and nasal inflammation, but routine laryngoscopy, rhinoscopy or CT sinuses is not advised as nasal findings are not directly associated with cough[100, 101].

Chronic cough in children

Chronic cough in children should be approached using paediatric-specific cough management protocols or algorithms and basing the management on the aetiology of the cough. The most

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common recognized aetiologies for chronic cough in children are post-infectious or natural resolution, asthma and PBB. Refer to the flow diagram on page x.

Treatment of chronic cough

Even after a thorough clinical assessment it may be impossible to identify which of the treatable traits is most likely to underlie the patient's chronic cough. Individuals may vary in their response to the different modalities of treatment. The guideline panel considered that it was preferable to undertake sequential therapeutic trials of each agent in turn and if no responses were observed therapy should be stopped. The length of the trial depends on the pharmacology. Response to morphine occurs within one week. ICS may take a month. If successful, the guideline panel believes that treatment may be continued for several months to allow for resolution of neuronal hypersensitivity. Treatment may be then withdrawn to determine whether remission has occurred. The reader is referred to table 1 for commentary on the recommendations below.

Anti-asthmatic drugs

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

We suggest a short-term ICS trial (2-4 weeks) in adult patients with chronic cough (conditional recommendation, low quality evidence).

Ten RCTs were identified for chronic cough, but with considerable heterogeneity in patient characteristics, intervention, measured outcomes and treatments responses. Two studies of chronic cough patients (unselected by airway hyper-responsiveness or sputum eosinophilia) found significant benefits from a 2-week high dose ICS treatment over placebo in reducing cough severity[102] and subjective cough frequency. However, in a study of patients with chronic cough and at least one additional respiratory symptom but with normal lung function, an 8-week medium dose ICS treatment did not produce a significant improvement in cough severity score over placebo. In two studies of patients with non-asthmatic chronic cough (defined by negative methacholine airway-hyper-responsiveness), ICS treatment was not superior to placebo in improving cough outcomes[103, 104]. In studies of patients with chronic bronchitis or chronic obstructive pulmonary disease (COPD), ICS treatment did not significantly improve subjective cough scores compared to placebo[105-108].

Although the original definition of CVA demonstrated improvement of coughing in a small number of asthmatic subjects with bronchodilator therapy, we do not recommend the use of a lone bronchodilator therapy as maintenance treatment for cough in asthmatic patients. The current GINA 2019 guideline recommend the use of low dose ICS-formoterol or low dose ICS. Effectiveness of these treatment regimes in CVA and asthmatic cough still requires further evaluation.

We suggest a short-term ICS trial in children with chronic dry cough (2-4 weeks) (conditional recommendation, low quality evidence).

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Two RCTs were identified. A trial of 50 children aged 1-10 years with persistent nocturnal cough found that there is a modest but significant benefit in objective cough frequency from a 2-week course of high dose ICS over placebo[109]. Another study of 43 children aged 6-17 years with recurrent cough (two episodes of cough, each lasting two weeks in the past 12 months) found no significant effects of ICS in cough outcomes at 4-5 weeks; there was no association between ICS treatment response and airway hyper-responsiveness in hypertonic saline challenge[110].

We suggest a short-term anti-leukotriene trial (2-4 weeks) in adult patients with chronic cough, particularly in those with asthmatic cough (conditional recommendation, low quality evidence).

Three RCTs were identified. Two clinical trials[111, 112] of adults with cough variant asthma (defined by clinical history, absence of other common diseases, and presence of methacholine hyper-responsiveness) found significant benefits of oral anti-leukotriene (for 2-4 weeks) over placebo in subjective cough frequency or severity scores. However, a single trial of adults with atopic cough (defined as chronic cough with increased capsaicin cough sensitivity and atopic constitution but without bronchial hyper-responsiveness) did not find any significant benefits of 2-weeks montelukast over placebo in subjective cough score[113]. Adverse drug event was reported in one study, without any significant event related to the treatment[112]. There are no trials conducted in unselected chronic cough patients.

No RCTs are available for children. Mild, transient neuropsychiatric adverse events are common (>10%) in children[114].

We suggest a short-term trial (2-4 weeks) of ICS and long-acting bronchodilator combination in adults with chronic cough and fixed airflow obstruction (conditional recommendation, moderate quality evidence).

A single RCT[108] of COPD patients with chronic bronchitis, smoking history and at least one episode of COPD symptom exacerbation in the previous year found that the combination of 50 µg salmeterol and 500 µg fluticasone twice daily produced a significant improvement in cough severity score compared to placebo (scale: 0-4) (mean difference: −0.09; 95% CI: −0.17 to −0.01), whereas salmeterol or fluticasone monotherapy did not. The treatment was well-tolerated, except for an increased incidence of oropharyngeal candidiasis (8% in the combination treatment group vs. 2% in the placebo group).

Anti-acids

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

We suggest that clinicians do not routinely prescribe anti-acid drugs in adult patients with chronic cough (conditional recommendation, low quality evidence).

Anti-acid drugs are unlikely to be useful in improving cough outcomes, unless patients have peptic symptoms or evidence of acid reflux. Systematic reviews have found no significant benefits from PPI over placebo in adult patients without acid reflux and possible modest effect in those with acid

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reflux [54]. Faruqi et al. found no significant benefits of esomeprazole 20 mg twice daily therapy over placebo in subjective cough frequency, cough severity, or cough-specific quality of life scores at 8 weeks. There was a trend towards greater improvement in the PPI treatment arm in patients with dyspepsia[115]. In a study of chronic cough patients with rare or no heartburn, there were no benefits from a long-term high-dose PPI therapy (esomeprazole 40 mg twice daily for 12 weeks) in cough-specific quality of life or cough scores [116]. Whilst PPI is frequently considered safe observational studies reported potential risks of iron deficiency, vitamin B12 deficiency, hypomagnesemia, Clostridium difficile–associated diarrhoea, osteoporosis-related bone fracture, dementia, or pneumonia[117, 118]. However, direct evidence about the safety issues is lacking in chronic cough population. There is not enough evidence to draw a specific recommendation for PPI use in children.

Drugs with promotility activity

Question 5: Should drugs with promotility activity be used to treat patients with chronic cough?

There is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A one month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship. (conditional recommendation, low quality evidence).

No RCTs have been undertaken with pro-motility agents, such as baclofen, metoclopramide or domperidone, in patients with chronic cough. There are three RCTs with macrolides with pro-motility activity in adult patients with chronic cough. One study of patients with COPD GOLD stage ≥ 2 and chronic productive cough demonstrated a significant benefit of a 12-week low dose azithromycin (250 mg three times a week) over placebo for improving cough-specific quality of life (LCQ; MD 1.3; 95% CI 0.3 to 2.3; p=0.01)[119]. Adverse events were not significantly different. In two other trials of patients with unexplained cough or treatment-resistant cough, low-dose macrolide treatments (erythromycin 250 mg daily for 12 weeks or azithromycin 250 mg three times a week for 8 weeks) did not provide significant benefits over placebo for objective cough frequency, cough severity or cough-specific quality of life[120, 121].

Neuromodulators

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics and opiates) should be used to treat patients with chronic cough?

We recommend a trial of low dose slow release morphine (5-10 mg bd) in adult patients with chronic refractory cough (strong recommendation, moderate quality evidence).

A single RCT of low dose morphine (5 to 10 mg twice daily) in adults with chronic refractory cough found significant benefits over placebo in reducing cough severity (self-reported scale 0 to 9 points) (MD -1.96 points; 95%CI -1.09 to -2.11) and improving cough-specific quality of life (LCQ) (MD 2 points; 95%CI 0.93 to 3.07)[27]. Common adverse effects in this clinical trial were constipation and drowsiness in patients receiving morphine.

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We suggest a trial of gabapentin or pregabalin in adults with chronic refractory cough (conditional recommendation, low quality evidence).

A single RCT of gabapentin therapy (maximum tolerable daily dose of 1800 mg) in adults with chronic refractory cough found significant benefits over placebo in improving LCQ (MD 1.8 points; 95%CI 0.56 to 3.04) and reducing cough frequency (although only of a single hour of observation) (MD -27.31%; 95%CI -2.87 to -51.75) and severity (VAS 0 to 100 points) (MD -12.33 points; 95%CI -1.23 to -23.23)[122]. There is one RCT of pregabalin therapy (300 mg daily) in adult patients with chronic refractory cough alongside speech pathology therapy [123]. Pregabalin plus speech pathology therapy significantly improved cough-specific quality of life (LCQ) (MD 3.5 points; 95%CI 1.11 to 5.89: MID: 1.3 points) and cough severity (VAS 0 to 100 points) (MD -25.1 points; 95%CI -10.6 to -39.6) over placebo plus speech pathology therapy. There was no significant reduction in cough frequency. There is no comparison between pregabalin and placebo alone. An explanation for a lack of effect on cough frequency is that centrally acting therapies may be altering perception of cough rather than having truly anti-tussive effects. They could also be affecting the intensity of coughing without reducing the frequency. Dizziness, fatigue, cognitive changes, nausea, or blurred vision are common side effects of gabapentin and pregabalin. A systematic review revealed that the risk of withdrawal due to adverse events is 2.3 times higher than placebo[124].

Agents acting directly on cough hypersensitivity rather than the treatable traits causing hypersensitivity is a promising strategy for future developments. Current agents have been shown to be effective in adults, but the side effect profile is significant and may be mitigated by the use of lower doses than those used to treat pain.

Cough neuromodulators, such as opioids, gabapentin or pregabalin, are not used in children, due to reported adverse events, possible toxicity and lack of clinical trials[125].

Non-pharmacological cough control therapy

Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

We suggest a trial of cough control therapy in adult patients with chronic cough (conditional recommendation, moderate quality evidence).

Two RCTs of physiotherapy/speech and language therapy (cough control therapy) in adult patients with chronic refractory cough have been reported. Vertigan et al. demonstrated that the 2-month intervention significantly reduced subjective cough score compared to placebo treatment (self-reported scale 2 to 10 points) (MD 2.8 points; 95% CI 1.3 to 4.0)[126]. In a multi-centre study by Chamberlain et al., the weekly intervention for 4 weeks showed benefits over placebo for cough-specific quality of life (LCQ; 1.53 points; 95% CI 0.21 to 2.85) and objective cough frequency (fold change) (0.59; 95% CI 0.36 to 0.95), but not for VAS severity or other quality of life outcomes. The improvements in the intervention group were sustained up to 3 months, but not beyond. No adverse effects were found[127]. There are no RCTs in children. This is a complex intervention that requires further study to determine which components are of value. Experienced practitioners should undertake cough-directed physiotherapy and speech and language therapy interventions.

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Question 8: In children with chronic wet cough with normal chest x-ray, normal spirometry and no warning signs, should a trial of antibiotics be used?

A trial of antibiotics is suggested in children with chronic wet cough with normal chest x-rays, normal spirometry and no warning signs (conditional recommendation, low quality evidence).

A single RCT of antibiotics in young children (mean age 1.9 years; IQR 0.9 to 5.1) with chronic wet cough (>3 weeks)[128]. A 2-week regimen of twice daily oral amoxycillin clavulanate treatment (22.5 mg/kg/dose) was compared. Cough resolution rates (defined as >75% reduction) were significantly higher in children who received amoxycillin clavulanate compared with those who received placebo (48% vs. 16%; p=0.015). Side effects were not significantly different between two groups; however, mild diarrhoea was found slightly more in the in the amoxycillin clavulanate group than in the placebo group (5/25 vs. 2/25)[128].

Future directions and new drugs

As the population ages the worldwide prevalence of chronic cough increases. This is partially due to an increasing awareness of the problem, changing diagnostic labels, air pollution, and increased efforts in educating health professionals. Changes in society such as the rise in obesity will also predispose to a greater incidence of causal factors related to chronic cough. Our understanding of the pathophysiological basis of chronic cough has dramatically advanced over the past decade with the realisation that neuronal hypersensitivity underlies the syndrome. Desensitisation through the use of agonists such as capsaicin has recently shown promise as a therapeutic strategy[129]. However, we are still grossly ignorant of the complex interplay in the peripheral and central nervous system. fMRI has given us insights into the central pathways of cough and will continue to do so in the future. However it is the pharmacology of the peripheral afferent vagus which has given us the most hopeful future therapeutic developments.

Much effort was devoted in the development of blockers of the nociceptors, mainly TRP receptors, which are responsible for the irritant sensation leading to the tickle that precedes cough. Whilst effective in animal models these agents have failed in the clinic[130, 131]. The substance P antagonist orvepitant has shown modest efficacy in phase 2 studies. One class of drugs has however produced a dramatic improvement in chronic cough in phase 2 studies[132]. ATP is released during cell damage and acts on afferent sensory nerves through P2X3 purinergic receptors. The first antagonist, gefapixant, has been studied in several hundred patients with chronic cough with resolution in the majority. Other compounds in this class are in development and we may have the first effective drugs for chronic cough in over 40 years.

Research gaps and recommendations for future studies

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Because chronic cough has only recently been recognised as a separate entity a major challenge is the promulgation of the concept of cough hypersensitivity in adults and conditions such as protracted bacterial bronchitis in children. Whilst the aim of these guidelines is to further awareness we recognise the scale of the task and recommend the ERS should advocate chronic cough as a classification in the WHO ICD.

Very little is known of the natural history of chronic cough. We recommend observational cohort studies to identify: –

- The true prevalence of chronic cough in the population.
- The demographic characteristics of this patient population.
- The natural history of chronic cough over time.
- The clinical and psychosocial impact of chronic cough on patients.
- The economic burden of chronic cough both to the individual and society.

The assessment of chronic cough in both the clinical and research settings needs further development. Current instruments to assess quality of life need refinement to be useful in routine clinical practice. Patient reported outcomes need to be developed and validated. There is an urgent need for fully automated cough recording technology that continuously monitors patients in real-time. Such devices may help confirm the diagnosis in the clinic, allow for objective assessment of clinical response, and ensure the entry of the correct population into clinical studies. In addition, the current clinical approach is largely based on sequential therapeutic trials; thus, practical biomarkers need to be developed to target treatable traits and guide treatment decisions in the clinic.

There are very few studies of cough in other diseases and currently patients with the syndrome of chronic cough are frequently mislabelled as suffering from other conditions. Studies of the overlap between respiratory disease and chronic cough are urgently need, particularly in view of the differences in pathophysiology and treatable traits.

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Table 1. Table of recommendations, strength and level of evidence, and supporting remarks

Recommendation	Strength of recommendation	Level of evidence	Values and preferences	Remarks
Question 1: Should chest CT scan be routinely performed on chronic cough patient with normal chest X-ray and physician examination?				
Recommendation 1: We suggest that clinicians do not routinely perform *a chest CT scan in patients with chronic cough who have a normal chest X-ray and physical examination.*	Conditional	Very low	This recommendation places relatively higher value on the impact on patient management and outcomes including adverse events from radiation exposure. Lower value was given to diagnostic sensitivity and specificity.	• In chronic cough patients with normal chest X-rays and physical examination, rates of any positive findings on chest CT scan varied widely in the literature. However, the Task Force members found that these abnormalities were unlikely to explain cough and may not influence management of the patients. • For those patients without a clear diagnosis or a chronic cough that is refractory to treatment of associated conditions, a high-resolution CT scan of the chest may identify subtle interstitial lung disease not visible on chest X-rays, e.g. pulmonary fibrosis, hypersensitivity pneumonitis and bronchiectasis, or areas of mucus plugging, which

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				may prompt the need for bronchoscopy for clearance, lavage, and culture. However, whether these subtle changes are the cause of the cough or a consequence of an underlying condition, such as recurrent aspiration, is unknown. • There is a concern about potential cancer risk from CT radiation exposure[89]. According to an estimation study[88], a projected number of future cancers that could be related to chest CT scans performed in the US was 4100 (95% uncertainty limits, 1900–8100) cases from 7,100,000 scans, and the estimated rates were higher in children and women.
Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?				
Recommendation 2: - Research recommendation		Very low	This recommendation places relatively higher value on predictability for the treatment response and the impact on the treatment decision. Lower value	• There is a need for convenient, safe, and practical tests for detecting predicting anti-inflammatory treatment responses in chronic cough. In randomised controlled trials of patients with

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			was given to diagnostic sensitivity and specificity.	different respiratory conditions, FeNO or blood eosinophil levels were positively associated with anti-inflammatory treatment responses[133-135]. However, there is no high-quality evidence to guide the use of FeNO or blood eosinophil counts as treatment response predictors in patients with chronic cough. In addition, there are still no optimal cut-off levels determined for the use in chronic cough populations.
Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?				
Recommendation 3a: We suggest *a short-term ICS trial (2–4 weeks) in adult patients with chronic cough.*	Conditional	Low	This recommendation is based on the higher value of the clinical benefits from ICS in some patients with asthmatic cough (or airway eosinophilic inflammation) and lower value on adverse events.	• Asthmatic cough (cough variant asthma and eosinophilic bronchitis) is a frequent phenotype of chronic cough. Evidence for ongoing airway eosinophilic inflammation can be collected by performing differential cell counts on samples from sputum induction or bronchoalveolar lavage; however, these tests are not available at most clinics. Moreover, there is no high-quality evidence

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for the routine use of FeNO or blood eosinophil counts in patients with chronic cough (as recommendation 2). Therefore, empirical therapy for asthmatic cough may be considered.

- In the literature, there is a heterogeneity in the efficacy of ICS in adult patients with chronic cough. The variability in the treatment response is likely primarily related to patient characteristics, particularly eosinophilic inflammation.
- Available evidence suggests that a high dose of ICS might be more effective than a low to moderate dose regimen, as an empirical trial.
- A treatment response is usually seen within 2–4 weeks. Thus, the empirical trial should be stopped if there is no response within 2–4 weeks.
- The Task Force members were concerned about long-term overuse of ICS in the absence of evidence or treatment response. They were also

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				concerned about pneumonia in relation to fluticasone use in patients comorbid with COPD.
Recommendation 3b: We suggest *a short-term ICS trial (2-4 weeks) in children with chronic dry cough.*	Conditional	Low	This recommendation is based on a higher value of the clinical benefits from ICS in some patients with asthmatic cough (or eosinophilic inflammation) and a lower value on adverse events.	• Overall remarks are the same as those in adults. • The empirical trial should be stopped if there is no response within 2-4 weeks.
Recommendation 3c: We suggest *a short-term anti-leukotriene trial (2–4 weeks) in adults with chronic cough, particularly in those with asthmatic cough.*	Conditional	Low	This recommendation is based on higher value on the clinical benefits from anti-leukotriene in some patients with asthmatic cough (or airway eosinophilic inflammation) and lower value on adverse events.	• Overall remarks are similar to those for ICS. • Currently, clinical evidence is only available in specific subgroups of patients, such as cough variant asthma or atopic cough. Overall efficacy of leukotriene receptor antagonist in non-specific chronic cough patients is uncertain. • The empirical trial should be stopped if there is no response within 2–4 weeks.
Recommendation 3d: We suggest *a short-term trial*	Conditional	Moderate	This recommendation is based on higher value on the clinical benefits	• There is a concern about pneumonia in relation to fluticasone use in patients comorbid with COPD.

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(2–4 weeks) of ICS and long-acting bronchodilator combination in adults with chronic cough and fixed airflow obstruction.			from ICS and long-acting bronchodilator combination in some patients with chronic obstructive pulmonary disease and a lower value on adverse events.	• The empirical trial should be stopped if there is no response within 2–4 weeks.
Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?				
Recommendation 4: We suggest that clinicians do not routinely use anti-acid drugs in adult patients with chronic cough.	Conditional	Low	This recommendation is based on higher value of the clinical benefits from anti-acid drugs only in some patients with acid reflux and a lower value on adverse events.	• Anti-acid drugs are unlikely to be useful in improving cough outcomes, unless patients have peptic symptoms or evidence of acid reflux. • Clinical benefits from PPI over placebo on cough outcomes are not significant in patients without acid reflux and only modest in those with acid reflux. These agents effectively block gastric acid production and relieve acid-related symptoms but have little effect on the number and volume of reflux events. Gastric acid does not appear to play a major role in the aetiology of chronic cough.

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				• PPIs are mostly considered well tolerated. However, there is a potential concern about increased risks of complications, such as pneumonia, iron deficiency, vitamin B2 deficiency, small intestinal bacterial overgrowth, Clostridium difficile-associated diarrhoea, or bone fracture [118].
Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?				
Recommendation 5: *There is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A one month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into*	Conditional	Low	This recommendation is based on higher value on the clinical benefits from drugs with pro-motility activity only in some patients with chronic bronchitis and lower value on adverse events.	• Current evidence only supports the use of azithromycin in patients with chronic bronchitis phenotype. However, mechanisms of azithromycin in improving cough outcomes are suggested to include prokinetic effects[136]. • Since oesophageal dysmotility is a frequent finding in chronic cough patients, promotility agents such as metoclopramide, domperidone, and azithromycin might be considered, although the clinical trial evidence in cough is sparse.

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account local guidelines on antimicrobial stewardship.				
Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?				
Recommendation 6a: We recommend *a trial of low dose morphine (5–10 mg bd) in adult patients with chronic refractory cough.*	Strong	Moderate	This recommendation is based on a higher value of the clinical benefits and adverse events from opiates for chronic refractory cough.	• Agents acting directly on cough hypersensitivity rather than the treatable traits causing hypersensitivity is a promising strategy for future developments. Current agents have been shown to be effective, but the side effect profile is significant and may be mitigated by the use of lower doses than that used to treat pain. • Clinical experience suggests that only a proportion of patients (approximately half) respond to opiates. In responders, treatment response is very rapid and clear (usually seen in a week). Thus, discontinuation is recommended if there is no response in 1 or 2 weeks. • Codeine is generally not recommended (except where it is the only available opiate) due to inter-

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				individual genetic variability in drug metabolism (CYP2D6) and consequent less predictable treatment response and side effect profile particularly in children.
Recommendation 6b: We suggest *a trial of gabapentin or pregabalin in adult patients with chronic refractory cough.*	Conditional	Low	This recommendation is based on a higher value of the clinical benefits and adverse events from gabapentin in chronic refractory cough.	• Clinical experience suggests the response rates of gabapentin and pregabalin are lower than that of opiates, and adverse events are more common. Common adverse effects are blurred vision, disorientation, dizziness, dry mouth, fatigue, and nausea.
Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?				
Recommendation 7: We suggest a trial of *cough control therapy in adult patients with chronic cough.*	Conditional	Moderate	This recommendation is based on a higher value of the clinical benefits from cough control therapy in chronic refractory cough, but lower value on adverse events.	• Multi-component physiotherapy/speech and language therapy interventions may be considered for short-term improvement of health-related quality of life and cough frequency in patients with refractory chronic cough or who wish an alternative to drug treatment. However, this is a complex intervention that requires further study

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				to determine which components are of value. Thus, experienced practitioners should undertake cough-directed physiotherapy and speech and language therapy intervention. The pool of individuals qualified for cough control therapy is currently lacking in many countries and should be increased.
Question 8: Should a trial of antibiotics be used in children with chronic wet cough with normal chest x ray, normal spirometry and no warning signs?				
Recommendation 8: We suggest *a trial of antibiotics in children with chronic wet cough with normal chest X-rays, normal spirometry, and no warning signs.*	Conditional	Low	This recommendation is based on higher value of the clinical benefit from antibiotics in chronic wet cough, but lower value on adverse events.	• Protracted bacterial bronchitis is a common treatable trait in children. Preferred antibacterial, dose, and duration of therapy is unknown. • Signs and symptoms suggestive of specific disease should always be investigated.

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Abstract

These present European Respiratory Society guidelines incorporate the recent advances in chronic cough pathophysiology, diagnosis and treatment. Recent introduction of The the concept of cough hypersensitivity has allowed an umbrella term that explains the exquisite sensitivity of patients to external stimuli such a cold air, perfumes, smoke and bleach. Thus aAdults with chronic cough now have a firm physical explanation for their symptoms based on vagal afferent hypersensitivity. Different treatable traits may exist in patients with chronic cough, such as cough variant asthma /, eosinophilic bronchitis responding to anti inflammatory treatment and non acidgastroesophageal reflux being treated with promotility agents rather the anti acid drugs. Therefore, identification and treatment of these traits is the mainstay in the management of chronic cough. However, in patients with chronic refractory cough, aA usefuln alternative antitussive strategy is to reduce hypersensitivity by direct neuromodulation. Low dose morphine is highly effective in a subset of patients with cough resistant to other treatments. Gabapentin and pregabalin are also advocated but in clinical experience they are limited by adverse events. Perhaps the most promising future developments in pharmacotherapy are drugs which tackle neuronal hypersensitivity by blocking excitability of afferent nerves by inhibiting targets such as the ATP receptor (P2X3). Finally non-pharmacological cough suppression control therapy when performed by competent practitioners can be highly effective.

Children are not small adults and a pursuit of an underlying cause for cough is advocated. Thus in toddlers inhalation of a foreign body is common. Persistent bacterial bronchitis is a common and previously unrecognized cause of wet cough in children. Thus, a trial of Antibioticsantibiotics, (which, dose, and duration need to be determined) can be curativeis considered. Paediatric specific algorithm should be used.

In the present guidelines, eight important questions of clinical uncertainty were addressed using the GRADE framework, in addition to narrative components to reflect the expert consensus of the guideline task force.

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Online-Only Supplement Part 1.

1. Methods

Scope and purpose

The purpose of these guidelines is to provide guidance for the diagnosis and treatment of chronic cough in adults and children. The guidelines aim to improve diagnostic accuracy and promote evidence-based therapy for paediatric and adult patients in primary and secondary care. The guidelines are intended for use by all healthcare professionals treating patients with chronic cough.

Panel composition

The Task Force (TF) chairs (A.H. Morice and E. Millqvist) led all aspects of project management and selected the TF members. The TF consisted of a multidisciplinary international panel of clinicians and scientists with a published record of expertise in the field, a junior member, and methodologists. European Respiratory Society (ERS) methodologists (T. Tonia and D. Rigau) provided expertise in guideline development following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. The methodologists coordinated and guided TF members throughout the entire process of conducting systematic reviews, generating recommendations, and ensuring methodological robustness, according to the GRADE approach. Input on patient views and preferences was sought via the European Lung Foundation, which provided an advisory group of patient representatives who

expressed their preferences via teleconferences, attendance at the ERS Congress, and in writing. They contributed to formulating and prioritising the key questions.

Formulating clinical questions

The TF members compiled a list of issues that they considered important and relevant to the management of chronic cough. The questions were rephrased by the methodologists using the Population, Intervention, Comparator and Outcomes (PICO) format. Discussion and consensus among the chairs and TF members was used to decide the eight questions of clinical uncertainty that would be addressed in the guidelines.

Outcome importance rating

After choosing the eight PICO questions, the TF identified outcomes that they considered relevant to each question. The following outcomes were considered for the PICO questions on treatment: cough frequency, cough severity, cough-specific quality of life, cough-related complications, specific impact of cough (on self-esteem, sleep, fatigue, depression, social isolation), tussive response to cough challenge, and adverse events. Sensitivity/specificity, association to the treatment response, change in the treatment decision, and adverse events were considered for the PICO questions on diagnostics. Then, all TF members including the patient representatives rated the importance of each outcome using a scale from 1–9: a rating of 1–3 to outcomes of low importance; 4–6 to outcomes important; and 7–9 to outcomes critically important for decision-making. A teleconference was convened during which the ratings were discussed, and some additional outcomes were rated. At the conclusion of the teleconference, all outcomes were categorised as “not important,” “important,” or “critical” for decision-making during development of the guidelines.

Literature search

The methodology group performed a full systematic review of the literature for each PICO question to identify and summarise the current evidence about the effects of diagnostics or therapeutics on cough outcomes. A systematic search was also conducted to collect information about patients' values and preferences. Pubmed MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases were searched for relevant articles from inception until August 2017, and updated in June 2018. The search strategy was constructed with professional assistance from a methodologist (H.J. Kim, Institute for Evidence-based Medicine and Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea). Manual searches were performed for cross-referenced articles.

Selection criteria

Study eligibility was assessed using pre-defined criteria for each PICO question. Common eligibility criteria for inclusion were: 1) a population with chronic cough as the main complaint regardless of their underlying conditions (chronic cough defined as cough lasting > 8 weeks in adults and > 4 weeks in children), 2) intervention (or investigation) and/or comparison relevant to each PICO question, and 3) outcomes related to cough. The population criteria were based on the recent ERS Task Force report, which views chronic cough as a clinical syndrome presenting as cough hypersensitivity [1]. Thus, studies of specific chronic cough conditions, such as cough variant asthma, eosinophilic bronchitis, chronic bronchitis in chronic obstructive pulmonary disease, and chronic wet cough, were also considered. Only full-text publications were considered. Only randomised placebo-controlled trials were considered for the treatment efficacy for PICO questions, because placebo or period effects are substantial in cough. Cross-over trials

were considered for inclusion depending on the availability of parallel trials and the pharmacology of drugs. Randomised controlled trials (RCTs) and observational studies were considered for diagnostic questions. There was no language restriction in the selection criteria.

Study selection

The relevancy of the retrieved studies was determined by at least two independent reviewers per PICO questions, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Briefly, the titles and abstracts of initially retrieved studies were screened and the full texts were reviewed for potentially relevant studies. Reasons for full-text exclusion were specified. Disagreements between reviewers were resolved by discussion and consensus within the committee.

Evidence synthesis

Study characteristics, type of participants, interventions (or investigations), the outcomes measured, and results were extracted from each study. If the data were amenable to pooling, effects were estimated via meta-analysis using Review Manager (version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). The random effects model was primarily utilised for the meta-analyses, unless otherwise specified. Dichotomous outcomes are reported as odds ratios and continuous outcomes are reported as mean differences or standardised mean differences (SMD), unless otherwise specified. To facilitate understanding of the SMD, we used an interpretation of the effect size following Cohen's criteria [2]: small, SMD = 0.2; moderate, SMD = 0.5; and large, SMD = 0.8.

The methodologists appraised the quality of the evidence using the GRADE approach. The methodologists used the GRADEpro tool (McMaster University, Hamilton, ON, Canada) to

develop evidence profiles that summarised the findings for each outcome and the rationale for the quality of the evidence appraisal. Thresholds for clinically important changes were based on published literature when available, but also relied on the clinical experience of the TF members, as many of the previous outcomes were not validated.

Formulating and grading the recommendations

The evidence profiles were sent to the TF members for review. Using an iterative process conducted face to face, via teleconference, and via email, consensus recommendations were formulated based on the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention (or investigation), quality of the evidence, patient values and preferences, and feasibility.

The quality of the evidence was rated for outcomes of interest in each PICO question according to the GRADE approach. Briefly, the evidence supported by RCTs was considered high quality, while that of observational studies was considered low quality. Five factors were considered for possible down-rating of a study (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and three factors for possible up-rating (large effects, dose response, and all plausible residual confounders). Then, the committee members determined the direction and strength of the recommendations based on the following considerations: balance of benefits and undesirable consequences of intervention (or investigation), quality of evidence, patient values and preferences, and feasibility.

Briefly, one of two grades (strong or conditional) was assigned to describe the strength of the recommendations. The criterion for a strong recommendation was evidence that the desirable effects clearly outweighed the undesirable effects (or vice versa). The criterion for a conditional

recommendation was evidence that the desirable effects likely or slightly outweighed the undesirable effects (or vice versa). Two classifications were used to indicate the direction of the recommendations (for or against) of a specific treatment or test.

Reference

1 Morice AH, Millqvist E, Belvisi MG, *et al.* Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J* 2014; 44: 1132-1148.

2 Cohen J. Statistical power analysis for the behavioral sciences. Routledge, 2013.

ERS guidelines on the diagnosis and treatment of chronic cough in adults and children

Online-Only Supplement Part 2.

2. Research Protocols

Research Protocol, Question 1	
Question	Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?
Objective	To examine the diagnostic utility of chest CT in chronic cough patients with normal chest X-rays and physical examination
Criteria	Randomised trials or observational studies on the diagnostic utility of chest CT in in chronic cough patients with normal chest X-rays and physical examination
Population	Chronic cough patients with normal chest X-ray and physical examination
Investigation	Chest CT scan
Comparison	None
Outcomes	• Change in treatment decision (important) • Sensitivity and specificity (important) • Direct adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND chest CT Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised trial or observational study Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 2

Question	Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?
Objective	To examine the utility of FeNO and blood eosinophils to predict treatment response to corticosteroids and anti-leukotrienes in chronic cough patients
Criteria	Randomised trials or observational studies on the utility of FeNO and blood eosinophils to predict treatment response to corticosteroids and anti-leukotrienes in chronic cough patients
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Investigation	FeNO or blood eosinophils
Comparison	None
Outcomes	• Association with treatment response (important) • Change in treatment decision (important) • Sensitivity and specificity (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND FeNO/blood eosinophils AND corticosteroids/anti-leukotrienes Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised trial or observational study Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 3	
Question	Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?
Objective	To compare anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) to placebo for improving cough outcomes in chronic cough patients

Criteria	Randomised placebo-controlled trials comparing anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND anti-asthmatic drugs (inhaled or systemic corticosteroids, inhaled bronchodilators, or anti-leukotrienes) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 4

Question	Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?
Objective	To compare anti-acid drugs (PPIs and H2 antagonists) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing anti-acid drugs (PPIs and H2 antagonists) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	PPIs or H2 antagonists
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND anti-acid drugs (PPIs and H2 antagonists) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 5	
Question	Should drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) be used to treat patients with chronic cough?
Objective	To compare drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Reflux inhibitors, prokinetics, or macrolides with pro-motility activity
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important) • Treatment specific adverse events (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND drugs with pro-motility activity (reflux inhibitors, prokinetics, or macrolides with pro-motility activity) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL)

	Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 6	
Question	Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?
Objective	To compare cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) to placebo for improving cough outcomes in adults with chronic cough
Criteria	Randomised placebo-controlled trials comparing cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) with placebo in adults with chronic cough as the main complaint (regardless of underlying conditions)
Population	Adult with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Pregabalin, gabapentin, tricyclics, or opiates
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Treatment specific adverse events (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important)

Search strategy	Chronic cough populations (regardless of underlying conditions) AND cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 7	
Question	Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?
Objective	To compare non-pharmacological therapy (cough control therapy) to placebo for improving cough outcomes in chronic cough patients
Criteria	Randomised placebo-controlled trials comparing non-pharmacological therapy (cough control therapy) with placebo in adults or children with chronic cough as the main complaint (regardless of underlying conditions)
Population	Patients with chronic cough as the main complaint regardless of their underlying conditions
Intervention	Cough control therapy
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical) • Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important)

	• Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Tussive response to cough challenge (important)
Search strategy	Chronic cough populations (regardless of underlying conditions) AND non-pharmacological therapy (cough control therapy) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

Research Protocol, Question 8	
Question	Should a trial of antibiotics be used in children with chronic wet cough with~~out - warning signs,~~ normal chest x ray ~~and,~~ normal spirometry and no warning signs?
Objective	To compare a trial of antibiotics to placebo for improving cough outcomes in children with chronic cough
Criteria	Randomised placebo-controlled trials comparing a trial of antibiotics with placebo in children with chronic wet cough with normal chest X-rays, normal spirometry and no warning signs~~chronic cough as the main complaint (regardless of underlying conditions)~~
Population	Children with chronic wet cough with normal chest X-rays, normal spirometry and no warning signs
Intervention	Antibiotics (amoxicillin, clavulanate, erythromycin or clarithromycin)
Comparison	Placebo
Outcomes	• Cough frequency (critical) • Cough severity VAS (critical) • Cough-specific quality-of-life questionnaire (critical)

	• Cough severity symptom score (important) • Generic quality-of-life questionnaire (important) • Incontinence (important) • Impact of cough on self-esteem, sleep, fatigue, depression, social isolation etc. (important) • Treatment specific adverse events (important) • Tussive response to cough challenge (important)
Search strategy	Chronic wet cough or bronchitis populations ~~(regardless of underlying conditions)~~ AND a trial of antibiotics (amoxicillin, clavulanate, erythromycin or clarithromycin) Source: Pubmed/Medline, Embase and Cochrane Controlled Register of Trials (CENTRAL) Study type: Randomised placebo-controlled trial Year: From inception to 2018 June Language: Not restricted

3. Electronic search strategies

Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Last search: June 2018

Pubmed MEDLINE

#1. ("Cough"[Mesh] OR cough[TIAB] OR coughing[TIAB] OR coughs[TIAB] OR "Bronchitis"[Mesh:NoExp] OR "Bronchitis, Chronic"[Mesh] OR bronchitis[TIAB] OR bronchitic[TIAB])

#2. (chronic[TIAB] OR persistent[TIAB] OR longstanding[TIAB] OR long-standing[TIAB] OR longterm[TIAB] OR long-term[TIAB] OR uncontrolled[TIAB] OR “poorly controlled” [TIAB] OR lingering[TIAB] OR nagging[TIAB] OR resistant[TIAB] OR refractory[TIAB] OR unexplained[TIAB] OR idiopathic[TIAB] OR frequent[TIAB])

#3. #1 AND #2

#4. "Tomography, X-Ray Computed"[Mesh] OR ct[TIAB] OR "computed tomography"[TIAB] OR "computed tomogram"[TIAB] OR "computerized tomography"[TIAB] OR “computerised tomography”[TIAB] OR “computed X-ray tomography”[TIAB] OR "computer assisted tomography"[TIAB] OR "computerized axial tomography"[TIAB] OR “computerised axial tomography”[TIAB]

#5. #3 AND #4

#6. #5 NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term]))

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. chronic:ab,ti OR persistent:ab,ti OR longstanding:ab,ti OR 'long standing':ab,ti OR longterm:ab,ti OR 'long term':ab,ti OR uncontrolled:ab,ti OR 'poorly controlled':ab,ti OR lingering:ab,ti OR nagging:ab,ti OR resistant:ab,ti OR refractory:ab,ti OR unexplained:ab,ti OR idiopathic:ab,ti OR frequent:ab,ti = 3417568

#3. #1 AND #2

#4. 'computer assisted tomography'/exp OR ct:ab,ti OR "computed tomography":ab,ti OR "computed tomogram":ab,ti OR "computerized tomography":ab,ti OR “computerised tomography”:ab,ti OR “computed X-ray tomography”:ab,ti OR "computer assisted tomography":ab,ti OR "computerized axial tomography":ab,ti OR “computerised axial tomography”:ab,ti

#5. #3 AND #4

#6. #5 NOT ('animal experiment'/de OR 'animal model'/de OR 'in vitro study'/de OR 'nonhuman'/de)

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. chronic or persistent or longstanding or long-standing or longterm or long-term or uncontrolled or "poorly controlled" or lingering or nagging or resistant or refractory or unexplained or idiopathic or frequent:ti,ab,kw (Word variations have been searched)

#8. #6 AND #7

#9. MeSH descriptor: [Tomography, X-Ray Computed] explode all trees

#10. ct or "computed tomography" or "computed tomogram" or "computerized tomography" or "computerised tomography" or "computed X-ray tomography" or "computer assisted tomography" or "computerized axial tomography" or "computerised axial tomography":ti,ab,kw (Word variations have been searched)

#11. #9 OR #10

#12. #8 AND #11

#13. #12 in Trials

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Adrenal Cortex Hormones"[Mesh:NoExp] OR "Glucocorticoids"[Mesh] OR "Hydroxycorticosteroids"[Mesh:NoExp] OR "Steroids"[Mesh:NoExp] OR "Beclomethasone"[Mesh] OR "Betamethasone"[Mesh] OR "Budesonide"[Mesh] OR "Fluticasone"[Mesh] OR "Mometasone Furoate"[Mesh] OR "Triamcinolone"[Mesh] OR "ciclesonide" [Supplementary Concept] OR "flunisolide" [Supplementary Concept] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Dexamethasone"[Mesh] OR "Cortisone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Leukotriene Antagonists"[Mesh] OR "montelukast" [Supplementary Concept] OR "pranlukast" [Supplementary Concept] OR "zafirlukast" [Supplementary Concept]

#3. (glucocorticoid[TIAB] OR glucocorticoids[TIAB] OR corticosteroid[TIAB] OR corticosteroids[TIAB] OR steroid[TIAB] OR steroids[TIAB]) OR beclomethasone[TIAB] OR betamethasone[TIAB] OR budesonide[TIAB] OR fluticasone[TIAB] OR mometasone[TIAB] OR triamcinolone[TIAB] OR ciclesonide[TIAB] OR

flunisolide[TIAB] OR prednisolone[TIAB] OR prednisone[TIAB] OR methylprednisolone[TIAB] OR dexamethasone[TIAB] OR cortisone[TIAB] OR hydrocortisone[TIAB] OR montelukast[TIAB] OR pranlukast[TIAB] OR zafirlukast[TIAB] OR leukotriene[TIAB] OR leukotrienes[TIAB] OR leukotrien[TIAB] OR leucotriene[TIAB] OR leucotrienes[TIAB] OR leucotrien[TIAB] OR anti-leukotriene[TIAB] OR anti-leukotrienes[TIAB] OR anti-leukotrien[TIAB] OR anti-leucotriene[TIAB] OR anti-leucotrienes[TIAB] OR anti-leucotrien[TIAB]

#4. "Nitric Oxide"[Mesh] OR "Eosinophils"[Mesh] OR "Biomarkers"[Mesh] OR "Sensitivity and Specificity"[Mesh]

#5. "nitric oxide"[TIAB] OR eno[TIAB] OR feno[TIAB] OR eosinophil[TIAB] OR eosinophils[TIAB] OR eosinophilic[TIAB] OR biomarker[TIAB] OR biomarkers[TIAB] OR predict[TIAB] OR predictive[TIAB] OR predictable[TIAB] OR predictability[TIAB] OR predicted[TIAB] OR predicts[TIAB] OR predictor[TIAB] OR predictors[TIAB] OR sensitivity[TIAB] OR sensitive[TIAB] OR sensitivities[TIAB] specificity[TIAB] OR specific[TIAB] OR specificities[TIAB] OR accuracy[TIAB] OR accurate[TIAB] OR accuracies[TIAB] OR “diagnostic value”[TIAB] OR “diagnostic test value”[TIAB] OR “diagnostic utility”[TIAB] OR “diagnostic test utility”[TIAB]

#6. #2 OR #3

#7. #4 OR #5

#8. #1 AND #6 AND #7

#9. #8 NOT ("review"[Publication Type] OR "review literature as topic"[MeSH Terms])

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'corticosteroid'/de OR 'glucocorticoid'/de OR 'hydroxycorticosteroid'/exp OR 'steroid'/de OR 'beclometasone'/exp OR 'betamethasone'/exp OR 'budesonide'/exp OR 'fluticasone'/exp OR 'mometasone furoate'/exp OR 'triamcinolone'/exp OR 'ciclesonide'/exp OR 'flunisolide'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'methylprednisolone'/exp OR 'dexamethasone'/exp OR 'cortisone'/exp OR 'hydrocortisone'/exp OR 'leukotriene receptor blocking agent'/de OR 'montelukast'/exp OR 'pranlukast'/exp OR 'zafirlukast'/exp

#3. corticosteroid:ab,ti OR corticosteroids:ab,ti OR glucocorticoid:ab,ti OR glucocorticoids:ab,ti OR steroid:ab,ti OR steroids:ab,ti OR beclomethasone:ab,ti OR betamethasone:ab,ti OR budesonide:ab,ti OR fluticasone:ab,ti OR mometasone:ab,ti OR triamcinolone:ab,ti OR ciclesonide:ab,ti OR flunisolide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR cortisone:ab,ti OR hydrocortisone:ab,ti

OR montelukast:ab,ti OR pranlukast:ab,ti OR zafirlukast:ab,ti OR leukotriene:ab,ti OR leukotrienes:ab,ti OR leukotrien:ab,ti OR leucotriene:ab,ti OR leucotrienes:ab,ti OR leucotrien:ab,ti OR 'anti leukotriene':ab,ti OR 'anti leukotrienes':ab,ti OR 'anti leukotrien':ab,ti OR 'anti leucotriene':ab,ti OR 'anti leucotrienes':ab,ti OR 'anti leucotrien':ab,ti

#4. 'nitric oxide'/exp OR 'eosinophil'/exp OR 'biological marker'/exp OR 'pharmacological biomarker'/exp OR 'sensitivity and specificity'/exp OR 'predictive value'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'diagnostic value'/exp

#5. 'nitric oxide':ab,ti OR eno:ab,ti OR feno:ab,ti OR eosinophil:ab,ti OR eosinophils:ab,ti OR eosinophilic:ab,ti OR biomarker:ab,ti OR biomarkers:ab,ti OR predict:ab,ti OR predictive:ab,ti OR predictable:ab,ti OR predictability:ab,ti OR predicted:ab,ti OR predicts:ab,ti OR predictor:ab,ti OR predictors:ab,ti OR sensitivity:ab,ti OR sensitive:ab,ti OR sensitivities:ab,ti OR specificity:ab,ti OR specific:ab,ti OR specificities:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR accuracies:ab,ti OR 'diagnostic value':ab,ti OR 'diagnostic test value':ab,ti OR 'diagnostic utility':ab,ti OR 'diagnostic test utility':ab,ti

#6. #2 OR #3

#7. #4 OR #5

#8. #1 AND #6 AND #7

#9. #8 NOT ('conference review'/it OR 'review'/it)

Cochrane Library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Adrenal Cortex Hormones] this term only

#8. MeSH descriptor: [Glucocorticoids] explode all trees

#9. MeSH descriptor: [Hydroxycorticosteroids] this term only

#10. MeSH descriptor: [Beclomethasone] explode all trees

#11. MeSH descriptor: [Beclomethasone] explode all trees

#12. MeSH descriptor: [Betamethasone] explode all trees

#13. MeSH descriptor: [Budesonide] explode all trees

#14. MeSH descriptor: [Fluticasone] explode all trees

#15. MeSH descriptor: [Mometasone Furoate] explode all trees

#16. MeSH descriptor: [Triamcinolone] explode all trees

#17. MeSH descriptor: [Prednisolone] explode all trees

#18. MeSH descriptor: [Prednisone] explode all trees

#19. MeSH descriptor: [Dexamethasone] explode all trees

#20. MeSH descriptor: [Cortisone] explode all trees

#21. MeSH descriptor: [Hydrocortisone] explode all trees

#22. MeSH descriptor: [Leukotriene Antagonists] explode all trees

#23. glucocorticoid or glucocorticoids or corticosteroid or corticosteroids or steroid or steroids or beclomethasone or betamethasone or budesonide or fluticasone or mometasone or triamcinolone or ciclesonide or flunisolide or prednisolone or prednisone or methylprednisolone or dexamethasone or cortisone or hydrocortisone or montelukast or pranlukast or zafirlukast or leukotriene or leukotrienes or leukotrien or leucotriene or leucotrienes or leucotrien or anti-leukotriene or anti-leukotrienes or anti-leukotrien or anti-leucotriene or anti-leucotrienes or anti-leucotrien:ti,ab,kw (Word variations have been searched)

#24. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23

#25. MeSH descriptor: [Nitric Oxide] explode all trees

#26. MeSH descriptor: [Eosinophils] explode all trees

#27. MeSH descriptor: [Biomarkers] explode all trees

#28. MeSH descriptor: [Sensitivity and Specificity] explode all trees

#29. "nitric oxide" or eno or feno or eosinophil or eosinophils or eosinophilic or biomarker or biomarkers or predict or predictive or predictable or predictability or predicted or predicts or predictor or predictors or sensitivity or sensitive or sensitivities specificity or specific or specificities or accuracy or accurate or accuracies or "diagnostic value" or "diagnostic test value" or "diagnostic utility" or "diagnostic test utility":ti,ab,kw (Word variations have been searched)

#29. #25 or #26 or #27 or #28 or #29

#30. #6 and #24 and #29

#31. #30 in Trials

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Beclomethasone"[Mesh] OR "Betamethasone"[Mesh] OR "Budesonide"[Mesh] OR "Fluticasone"[Mesh] OR "Mometasone Furoate"[Mesh] OR "Triamcinolone"[Mesh] OR "ciclesonide" [Supplementary Concept] OR "flunisolide" [Supplementary Concept] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Dexamethasone"[Mesh] OR "Cortisone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Leukotriene Antagonists"[Mesh] OR "montelukast" [Supplementary Concept] OR "pranlukast" [Supplementary Concept] OR "zafirlukast" [Supplementary Concept]

#3. "Adrenergic beta-2 Receptor Agonists"[Mesh] OR "Formoterol Fumarate"[Mesh] OR "vilanterol"[Supplementary Concept] OR "Salmeterol Xinafoate"[Mesh] OR "indacaterol"[Supplementary Concept] OR "olodaterol"[Supplementary Concept] OR "Albuterol"[Mesh] OR "tulobuterol"[Supplementary Concept] OR "Terbutaline"[Mesh] OR “Cholinergic Antagonists"[Mesh:NoExp] OR "Muscarinic Antagonists"[Mesh] OR "Ipratropium"[Mesh] OR "Glycopyrrolate"[Mesh] OR "Tiotropium Bromide"[Mesh] OR "aclidinium bromide"[Supplementary Concept] OR "GSK573719"[Supplementary Concept]

#4. beclomethasone[TIAB] OR betamethasone[TIAB] OR budesonide[TIAB] OR fluticasone[TIAB] OR mometasone[TIAB] OR triamcinolone[TIAB] OR ciclesonide[TIAB] OR flunisolide[TIAB] OR prednisolone[TIAB] OR prednisone[TIAB] OR methylprednisolone[TIAB] OR dexamethasone[TIAB] OR cortisone[TIAB] OR hydrocortisone[TIAB] OR montelukast[TIAB] OR pranlukast[TIAB] OR zafirlukast[TIAB]

#5. formoterol[TIAB] OR vilanterol[TIAB] OR salmeterol[TIAB] OR indacaterol[TIAB] OR olodaterol[TIAB] OR albuterol[TIAB] OR salbutamol[TIAB] OR levalbuterol[TIAB] OR tulobuterol[TIAB] OR terbutaline[TIAB] OR ipratropium[TIAB] OR glycopyrrolate[TIAB] OR tiotropium[TIAB] OR aclidinium[TIAB] OR umeclidinium[TIAB]

#6. #2-5/OR

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'beclometasone'/exp OR 'betamethasone'/exp OR 'budesonide'/exp OR 'fluticasone'/exp OR 'mometasone furoate'/exp OR 'triamcinolone'/exp OR 'ciclesonide'/exp OR 'flunisolide'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR 'methylprednisolone'/exp OR 'dexamethasone'/exp OR 'cortisone'/exp OR 'hydrocortisone'/exp OR 'leukotriene receptor blocking agent'/de OR 'montelukast'/exp OR 'pranlukast'/exp OR 'zafirlukast'/exp

#3. 'beta 2 adrenergic receptor stimulating agent'/exp OR 'formoterol'/exp OR 'vilanterol'/exp OR 'salmeterol'/exp OR 'indacaterol'/exp OR 'olodaterol'/exp OR 'salbutamol'/exp OR 'tulobuterol'/exp OR 'terbutaline'/exp OR

'cholinergic receptor blocking agent'/de OR 'muscarinic receptor blocking agent'/de OR 'ipratropium bromide'/exp OR 'glycopyrronium'/exp OR 'tiotropium bromide'/exp OR 'aclidinium bromide'/exp OR 'umeclidinium'/exp

#4. beclomethasone:ab,ti OR betamethasone:ab,ti OR budesonide:ab,ti OR fluticasone:ab,ti OR mometasone:ab,ti OR triamcinolone:ab,ti OR ciclesonide:ab,ti OR flunisolide:ab,ti OR prednisolone:ab,ti OR prednisone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR cortisone:ab,ti OR hydrocortisone:ab,ti OR montelukast:ab,ti OR pranlukast:ab,ti OR zafirlukast:ab,ti

#5. formoterol:ab,ti OR vilanterol:ab,ti OR salmeterol:ab,ti OR indacaterol:ab,ti OR olodaterol:ab,ti OR albuterol:ab,ti OR salbutamol:ab,ti OR levalbuterol:ab,ti OR tulobuterol:ab,ti OR terbutaline:ab,ti OR ipratropium:ab,ti OR glycopyrrolate:ab,ti OR tiotropium:ab,ti OR aclidinium:ab,ti OR umeclidinium:ab,ti

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#9. #7 AND #8

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Beclomethasone] explode all trees

#8. MeSH descriptor: [Betamethasone] explode all trees

#9. MeSH descriptor: [Budesonide] explode all trees

#10. MeSH descriptor: [Fluticasone] explode all trees

#11. MeSH descriptor: [Mometasone Furoate] explode all trees

#12. MeSH descriptor: [Triamcinolone] explode all trees

#13. MeSH descriptor: [Prednisolone] explode all trees

#14. MeSH descriptor: [Prednisone] explode all trees

#15. MeSH descriptor: [Dexamethasone] explode all trees

#16. MeSH descriptor: [Cortisone] explode all trees

#17. MeSH descriptor: [Hydrocortisone] explode all trees

#18. MeSH descriptor: [Leukotriene Antagonists] explode all trees

#19. beclomethasone or betamethasone or budesonide or fluticasone or mometasone or triamcinolone or ciclesonide or flunisolide or prednisolone or prednisone or methylprednisolone or dexamethasone or cortisone or hydrocortisone or montelukast or pranlukast or zafirlukast:ti,ab,kw (Word variations have been searched)

#20. MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] explode all trees

#21. MeSH descriptor: [Formoterol Fumarate] explode all trees

#22. MeSH descriptor: [Salmeterol Xinafoate] explode all trees

#23. MeSH descriptor: [Albuterol] explode all trees

#24. MeSH descriptor: [Terbutaline] explode all trees

#25. MeSH descriptor: [Cholinergic Antagonists] this term only

#26. MeSH descriptor: [Muscarinic Antagonists] explode all trees

#27. MeSH descriptor: [Ipratropium] explode all trees

#28. MeSH descriptor: [Glycopyrrolate] explode all trees

#29. MeSH descriptor: [Tiotropium Bromide] explode all trees

#30. formoterol or vilanterol or salmeterol or indacaterol or olodaterol or albuterol or salbutamol or levalbuterol or tulobuterol or terbutaline or ipratropium or glycopyrrolate or tiotropium or aclidinium or umeclidinium:ti,ab,kw (Word variations have been searched)

#31. #7-30/OR

#32. #6 AND #31

#33. #32 in Trials

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. "Cough"[Mesh]

#2. cough[TIAB] OR coughing[TIAB] OR coughs[TIAB]

#3. ("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh]

#4. bronchitis[TIAB] OR bronchitic[TIAB]

#5. #1 OR #2 OR #3 OR #4

#6. "Proton Pump Inhibitors"[Mesh] OR "Proton Pump Inhibitors" [Pharmacological Action]

#7. "proton pump inhibitor"[TIAB] OR "proton pump inhibitors"[TIAB] OR ppi[TIAB] OR omeprazole[TIAB] OR esomeprazole[TIAB] OR lansoprazole[TIAB] OR dexlansoprazole[TIAB] OR pantoprazole[TIAB] OR rabeprazole[TIAB] OR timoprazole[TIAB]

#8. #6 OR #7

#9. "Histamine H2 Antagonists"[Mesh] OR "Histamine H2 Antagonists"[Pharmacological Action]

#10. “H2 receptor blockaders”[TIAB] OR “H2 receptor blockader”[TIAB] OR “H2 receptor blockade”[TIAB] OR “H2 receptor blockers”[TIAB] OR “H2 receptor blocking”[TIAB] OR “H2 receptor blockers”[TIAB] OR “H2 receptor blocker”[TIAB] OR “H2 receptor antagonists”[TIAB] OR “H2 receptor antagonist”[TIAB] OR “H2 blockaders”[TIAB] OR “H2 blockader”[TIAB] OR "h2 blockade"[TIAB] OR “H2 blocking”[TIAB] OR “H2 blockers”[TIAB] OR “H2 blocker”[TIAB] OR “H2 antagonists”[TIAB] OR “H2 antagonist”[TIAB] OR (H2[TIAB] AND antihistamin*[TIAB]) OR (H2[TIAB] AND anti-histamin*[TIAB]) OR h2ra[TIAB] OR cimetidine[TIAB] OR famotidine[TIAB] OR lafutidine[TIAB] OR nizatidine[TIAB] OR ranitidine[TIAB] OR roxatidine[TIAB]

#11. #9 OR #10

#12. #8 OR #11

#13. #5 AND #12

#14. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#15. #13 AND #14

Embase

#1. 'coughing'/exp

#2. cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti

#3. 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp

#4. bronchitis:ab,ti OR bronchitic:ab,ti

#5. #1 OR #2 OR #3 OR #4

#6. 'proton pump inhibitor'/exp

#7. 'proton pump inhibitor':ab,ti OR 'proton pump inhibitors':ab,ti OR ppi:ab,ti OR omeprazole:ab,ti OR esomeprazole:ab,ti OR lansoprazole:ab,ti OR dexlansoprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR timoprazole:ab,ti

#8. 'histamine h2 receptor antagonist'/exp

#9. 'h2 receptor blockaders':ab,ti OR 'h2 receptor blockader':ab,ti OR 'h2 receptor blockade':ab,ti OR 'h2 receptor blocking':ab,ti OR 'h2 receptor blockers':ab,ti OR 'h2 receptor blocker':ab,ti OR 'h2 receptor antagonists':ab,ti OR 'h2 receptor antagonist':ab,ti OR 'h2 blockaders':ab,ti OR 'h2 blockader':ab,ti OR 'h2 blockade':ab,ti OR 'h2 blocking':ab,ti OR 'h2 blockers':ab,ti OR 'h2 blocker':ab,ti OR 'h2 antagonists':ab,ti OR 'h2 antagonist':ab,ti OR (h2:ab,ti AND antihistamin*:ab,ti) OR (h2:ab,ti AND 'anti histamin*':ab,ti) OR h2ra:ab,ti OR cimetidine:ab,ti OR famotidine:ab,ti OR lafutidine:ab,ti OR nizatidine:ab,ti OR ranitidine:ab,ti OR roxatidine:ab,ti

#10. #6 OR #7

#11. #8 OR #9

#12. #10 OR #11

#13. #5 AND #12

#14. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#15. #13 AND #14

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Proton Pump Inhibitors] explode all trees

#8. 'proton pump inhibitor' or 'proton pump inhibitors' or ppi or omeprazole or esomeprazole or lansoprazole or dexlansoprazole or pantoprazole or rabeprazole or timoprazole:ti,ab,kw (Word variations have been searched)

#9. MeSH descriptor: [Histamine H2 Antagonists] explode all trees

#10. "H2 receptor blockaders" or "H2 receptor blockader" or "H2 receptor blockade" or "H2 receptor blockers" or "H2 receptor blocking" or "H2 receptor blockers" or "H2 receptor blocker" or "H2 receptor antagonists" or "H2 receptor antagonist" or "H2 blockaders" or "H2 blockader" or "h2 blockade" or "H2 blocking" or "H2 blockers" or "H2 blocker" or "H2 antagonists" or "H2 antagonist" or (H2 and antihistamin*) or (H2 and anti-histamin*) or h2ra or cimetidine or famotidine or lafutidine or nizatidine or ranitidine or roxatidine:ti,ab,kw (Word variations have been searched)

#11. #7 OR #8

#12. #9 OR #10

#13. #11 OR #12

#14. #13 in Trials

Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Metoclopramide"[Mesh] OR Metoclopramide[TIAB] OR Metaclopramide[TIAB] OR Metoclopromide[TIAB] OR Maxolon[TIAB] OR Primperan[TIAB] OR Reglan[TIAB] OR Cerucal[TIAB]

#3. "Domperidone"[Mesh] OR Domperidone[TIAB] OR Domperidon[TIAB] OR Motilium[TIAB]

#4. "Baclofen"[Mesh] OR Baclofen[TIAB] OR Baclophen[TIAB]

#5. "Macrolides"[Mesh:NoExp] OR Macrolides[TIAB] OR Macrolide[TIAB] OR "Erythromycin"[Mesh] OR Erythromycin[TIAB] OR Monomycin[TIAB] OR Mitemcinal[TIAB] OR Azithromycin[TIAB] OR Azythromycin[TIAB] OR Zithromax[TIAB] OR Sumamed[TIAB] OR Clarithromycin[TIAB] OR Biaxin[TIAB] OR Ketolides[TIAB] OR Roxithromycin[TIAB] OR Rulide[TIAB] OR Rulid[TIAB] OR "Troleandomycin"[Mesh] OR Troleandomycin[TIAB] OR Triacetyloleandomycin[TIAB] OR Telithromycin[TIAB] OR Ketek[TIAB]

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'metoclopramide'/exp OR metoclopramide:ab,ti OR metaclopramide:ab,ti OR metoclopromide:ab,ti OR maxolon:ab,ti OR primperan:ab,ti OR reglan:ab,ti OR cerucal:ab,ti

#3. 'domperidone'/exp OR domperidone:ab,ti OR domperidon:ab,ti OR motilium:ab,ti

#4. 'macrolide'/de OR 'erythromycin'/exp OR 'mitemcinal'/exp OR 'erythromycin derivative'/exp OR 'azithromycin'/exp OR 'clarithromycin'/exp OR 'telithromycin'/exp OR 'roxithromycin'/exp OR 'troleandomycin'/exp OR macrolides:ab,ti OR macrolide:ab,ti OR erythromycin:ab,ti OR monomycin:ab,ti OR mitemcinal:ab,ti OR azithromycin:ab,ti OR azythromycin:ab,ti OR zithromax:ab,ti OR sumamed:ab,ti OR clarithromycin:ab,ti OR biaxin:ab,ti OR ketolides:ab,ti OR roxithromycin:ab,ti OR rulide:ab,ti OR rulid:ab,ti OR troleandomycin:ab,ti OR triacetyloleandomycin:ab,ti OR telithromycin:ab,ti OR ketek:ab,ti

#5. #2 OR #3 OR #4

#6. #1 AND #5

#7. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#8. #6 AND #7

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Metoclopramide] explode all trees

#8. Metoclopramide or Metaclopramide or Metoclopromide or Maxolon or Primperan or Reglan or Cerucal:ti,ab,kw (Word variations have been searched)

#9. MeSH descriptor: [Domperidone] explode all trees

#10. Domperidone or Domperidon or Motilium:ti,ab,kw (Word variations have been searched)

#11. MeSH descriptor: [Baclofen] explode all trees

#12. Baclofen or Baclophen:ti,ab,kw (Word variations have been searched)

#13. MeSH descriptor: [Macrolides] this term only

#14. MeSH descriptor: [Erythromycin] explode all trees

#15. MeSH descriptor: [Troleandomycin] explode all trees

#16. Macrolides or Macrolide or Erythromycin or Monomycin or Mitemcinal or Azithromycin or Azythromycin or Zithromax or Sumamed or Clarithromycin or Biaxin or Ketolides or Roxithromycin or Rulide or Rulid or Troleandomycin or Triacetyloleandomycin or Telithromycin or Ketek:ti,ab,kw (Word variations have been searched)

#17. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18. #6 and #17

#19. #18 in Trials

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Pregabalin"[Mesh] OR Pregabalin[TIAB] OR Lyrica[TIAB]

#3. "gabapentin" [Supplementary Concept] OR Gabapentin[TIAB] OR Neurontin[TIAB]

#4. "Antidepressive Agents, Tricyclic"[Mesh] OR (tricyclic[TIAB] AND (antidepressant[TIAB] OR antidepressants[TIAB] OR antidepressive[TIAB])) OR "Amitriptyline"[Mesh] OR Amitriptyline[TIAB] OR Amitriptylin[TIAB] OR Amitriptiline[TIAB] OR Amitriptilin[TIAB] OR Elavil[TIAB] OR "Clomipramine"[Mesh] OR Clomipramine[TIAB] OR Chlomipramine[TIAB] OR Chlorimipramine[TIAB] OR Anafranil[TIAB] OR Cyclobenzaprine[TIAB] OR Flexeril[TIAB] OR "Desipramine"[Mesh] OR Desipramine[TIAB] OR Desmethylimipramine[TIAB] OR Demethylimipramine[TIAB] OR Norpramin[TIAB] OR Pertofrane[TIAB] OR Desmethyldoxepin[TIAB] OR Dibenzepin[TIAB] OR Noveril[TIAB] OR "Dothiepin"[Mesh] OR Dothiepin[TIAB] OR Dosulepin[TIAB] OR Prothiaden[TIAB] OR "Doxepin"[Mesh] OR Doxepin[TIAB] OR Sinequan[TIAB] OR "Imipramine"[Mesh] OR Imipramine[TIAB] OR Melipramine[TIAB] OR Tofranil[TIAB] OR "Iprindole"[Mesh] OR Iprindole[TIAB] OR "Lofepramine"[Mesh] OR Lofepramine[TIAB] OR Melitracene[TIAB] OR Metapramine[TIAB] OR Mirtazapine[TIAB] OR Remeron[TIAB] OR "Nortriptyline"[Mesh] OR Nortriptyline[TIAB] OR Nortriptylin[TIAB] OR Nortriptiline[TIAB] OR Nortriptilin[TIAB] OR Aventyl[TIAB] OR Sensival[TIAB] OR Noxiptilin[TIAB] OR "Opipramol"[Mesh] OR Opipramol[TIAB] OR insidon[TIAB] OR "Protriptyline"[Mesh] OR Protriptyline[TIAB] OR Tianeptine[TIAB] OR "Trimipramine"[Mesh] OR Trimipramine[TIAB] OR Surmontil[TIAB]

#5. "Analgesics, Opioid"[Mesh] OR "Opium"[Mesh] OR "Opiate Alkaloids"[Mesh:NoExp] OR opioid[TIAB] OR opioids[TIAB] OR opium[TIAB] OR opiate[TIAB] OR opiates[TIAB] OR "Morphine"[Mesh] OR Morphine[TIAB] OR morphia[TIAB] OR "Codeine"[Mesh] OR codeine[TIAB] OR "pholcodine" [Supplementary Concept] OR pholcodine[TIAB]

#6. #2 OR #3 OR #4 OR #5

#7. #1 AND #6

#8. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#9. #7 AND #8

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'pregabalin'/exp OR pregabalin:ab,ti OR lyrica:ab,ti

#3. 'gabapentin'/exp OR gabapentin:ab,ti OR neurontin:ab,ti

#4. 'tricyclic antidepressant agent'/exp OR (tricyclic:ab,ti AND (antidepressant:ab,ti OR antidepressants:ab,ti OR antidepressive:ab,ti)) OR amitriptyline:ab,ti OR amitriptylin:ab,ti OR amitriptiline:ab,ti OR amitriptilin:ab,ti OR elavil:ab,ti OR clomipramine:ab,ti OR chlomipramine:ab,ti OR chlorimipramine:ab,ti OR anafranil:ab,ti OR cyclobenzaprine:ab,ti OR flexeril:ab,ti OR desipramine:ab,ti OR desmethylimipramine:ab,ti OR demethylimipramine:ab,ti OR norpramin:ab,ti OR pertofrane:ab,ti OR desmethyldoxepin:ab,ti OR dibenzepin:ab,ti

OR noveril:ab,ti OR dothiepin:ab,ti OR dosulepin:ab,ti OR prothiaden:ab,ti OR doxepin:ab,ti OR sinequan:ab,ti OR imipramine:ab,ti OR melipramine:ab,ti OR tofranil:ab,ti OR iprindole:ab,ti OR lofepramine:ab,ti OR melitracene:ab,ti OR metapramine:ab,ti OR mirtazapine:ab,ti OR remeron:ab,ti OR nortriptyline:ab,ti OR nortriptylin:ab,ti OR nortriptiline:ab,ti OR nortriptilin:ab,ti OR aventyl:ab,ti OR sensival:ab,ti OR noxiptilin:ab,ti OR opipramol:ab,ti OR insidon:ab,ti OR protriptyline:ab,ti OR tianeptine:ab,ti OR trimipramine:ab,ti OR surmontil:ab,ti

#5. 'opiate'/exp OR 'opiate agonist'/de OR 'codeine'/exp OR 'morphine'/exp OR 'pholcodine'/exp OR opioid:ab,ti OR opioids:ab,ti OR opium:ab,ti OR opiate:ab,ti OR opiates:ab,ti OR morphine:ab,ti OR morphia:ab,ti OR codeine:ab,ti OR pholcodine:ab,ti

#6. #2 or #3 or #4 or #5

#7. #1 AND #6

#8. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#9. #7 AND #8

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Pregabalin] explode all trees

#8. MeSH descriptor: [Antidepressive Agents, Tricyclic] explode all trees

#9. MeSH descriptor: [Amitriptyline] explode all trees

#10. MeSH descriptor: [Clomipramine] explode all trees

#11. MeSH descriptor: [Desipramine] explode all trees

#12. MeSH descriptor: [Dothiepin] explode all trees

#13. MeSH descriptor: [Doxepin] explode all trees

#14. MeSH descriptor: [Imipramine] explode all trees

#15. MeSH descriptor: [Iprindole] explode all trees

#16. MeSH descriptor: [Lofepramine] explode all trees

#17. MeSH descriptor: [Nortriptyline] explode all trees

#18. MeSH descriptor: [Opipramol] explode all trees

#19. MeSH descriptor: [Protriptyline] explode all trees

#20. MeSH descriptor: [Trimipramine] explode all trees

#21. MeSH descriptor: [Analgesics, Opioid] explode all trees

#22. MeSH descriptor: [Opium] explode all trees

#23. MeSH descriptor: [Opiate Alkaloids] this term only

#24. MeSH descriptor: [Morphine] explode all trees

#25. MeSH descriptor: [Codeine] explode all trees

#26. pregabalin or lyrica:ti,ab,kw (Word variations have been searched)

#27. gabapentin or neurontin:ti,ab,kw (Word variations have been searched)

#28. (tricyclic and (antidepressant or antidepressants or antidepressive)) or Amitriptyline or Amitriptylin or Amitriptiline or Amitriptilin or Elavil or Clomipramine or Chlomipramine or Chlorimipramine or Anafranil or Cyclobenzaprine or Flexeril or Desipramine or Desmethylimipramine or Demethylimipramine or Norpramin or Pertofrane or Desmethyldoxepin or Dibenzepin or Noveril or Dothiepin or Dosulepin or Prothiaden or Doxepin or Sinequan or Imipramine or Melipramine or Tofranil or Iprindole or Lofepramine or Melitracene or Metapramine or Mirtazapine or Remeron or Nortriptyline or Nortriptylin or Nortriptiline or Nortriptilin or Aventyl or Sensival or Noxiptilin or Opipramol or insidon or Protriptyline or Tianeptine or Trimipramine or Surmontil:ti,ab,kw (Word variations have been searched)

#29. opioid or opioids or opium or opiate or opiates or Morphine or morphia or codeine or pholcodine:ti,ab,kw (Word variations have been searched)

#30. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

#32. #6 and #30

#33. #32 in Trials

Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Rehabilitation of Speech and Language Disorders"[Mesh] OR "Speech-Language Pathology"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR (“speech pathology”[TIAB] OR “speech therapy”[TIAB] OR “speech therapist”[TIAB] OR “speech pathologist”[TIAB] OR “speech rehabilitation”[TIAB] OR “speech disorder”[TIAB] OR “language pathology”[TIAB] OR “language therapy”[TIAB] OR “language therapist”[TIAB] OR “language pathologist”[TIAB] OR “language rehabilitation”[TIAB] OR physiotherapy[TIAB] OR physiotherapist[TIAB] OR “physical therapy”[TIAB] OR “physical therapist”[TIAB] OR neurophysiotherapy[TIAB] OR neurophysiotherapist[TIAB])

#3. #1 AND #2

#4. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#5. #3 AND #4

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'speech and language rehabilitation'/exp OR 'speech language pathologist'/exp OR 'speech disorder'/exp OR 'physiotherapy'/exp OR ‘speech pathology’:ab,ti OR ‘speech therapy’:ab,ti OR ‘speech therapist’:ab,ti OR ‘speech pathologist’:ab,ti OR ‘speech rehabilitation’:ab,ti OR ‘speech disorder’:ab,ti OR ‘language pathology’:ab,ti OR ‘language therapy’:ab,ti OR ‘language therapist’:ab,ti OR ‘language pathologist’:ab,ti OR ‘language rehabilitation’:ab,ti OR physiotherapy:ab,ti OR physiotherapist:ab,ti OR ‘physical therapy’:ab,ti OR ‘physical therapist’:ab,ti OR neurophysiotherapy:ab,ti OR neurophysiotherapist:ab,ti

#3. #1 AND #2

#4. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#5. #3 AND #4

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Rehabilitation of Speech and Language Disorders] explode all trees

#8. MeSH descriptor: [Speech-Language Pathology] explode all trees

#9. MeSH descriptor: [Physical Therapy Modalities] explode all trees

#10. "speech pathology" or "speech therapy" or "speech therapist" or "speech pathologist" or "speech rehabilitation" or "speech disorder" or "language pathology" or "language therapy" or "language therapist" or "language pathologist" or "language rehabilitation" or physiotherapy or physiotherapist or "physical therapy" or "physical therapist" or neurophysiotherapy or neurophysiotherapist:ti,ab,kw (Word variations have been searched)

#11. #7 OR #8 OR #9 OR #10

#12. #6 AND #11

#13. #12 in Trials

Question 8: Should a trial of antibiotics be used in children with chronic wet cough with~~out~~ ~~warning signs,~~ normal chest x ray ~~and~~, normal spirometry and no warning signs?

Last search: June 2018

Pubmed MEDLINE

#1. ((("Cough"[Mesh]) OR (cough[TIAB] OR coughing[TIAB] OR coughs[TIAB])) OR (("Bronchitis"[Mesh:NoExp]) OR "Bronchitis, Chronic"[Mesh])) OR (bronchitis[TIAB] OR bronchitic[TIAB])

#2. "Amoxicillin"[Mesh] OR "Clavulanic Acids"[Mesh] OR "Erythromycin"[Mesh:NoExp] OR "Clarithromycin"[Mesh]

#3. amoxicillin[TIAb] OR amoxycillin[TIAB] OR clavulanate[TIAB] OR “clavulanic acids”[TIAB] OR “clavulanic acid”[TIAB] OR augmentin[TIAB] OR co-amoxiclav[TIAB] OR coamoxiclav[TIAB] OR erythromycin[TIAB] OR clarithromycin[TIAB]

#4. #2 OR #3

#5. #1 AND #4

#6. (groups[tiab] OR trial[TIAB] OR randomly[TIAB] OR "drug therapy"[SH] OR placebo[TIAB] OR randomized[TIAB] OR "controlled clinical trial"[PT] OR "randomized controlled trial"[PT]) NOT (animals[MH] NOT (humans[MH] AND animals[MH]))

#7. #5 AND #6

Embase

#1. 'coughing'/exp OR cough:ab,ti OR coughing:ab,ti OR coughs:ab,ti OR 'bronchitis'/de OR 'chronic bronchitis'/exp OR 'laryngotracheobronchitis'/exp OR 'tracheobronchitis'/exp OR bronchitis:ab,ti OR bronchitic:ab,ti

#2. 'amoxicillin'/exp OR 'clavulanic acid'/exp OR 'amoxicillin plus clavulanic acid'/exp OR 'erythromycin'/exp OR 'clarithromycin'/exp

#3. amoxicillin:ab,ti OR amoxycillin:ab,ti OR clavulanate:ab,ti OR 'clavulanic acids':ab,ti OR 'clavulanic acid':ab,ti OR augmentin:ab,ti OR 'co amoxiclav':ab,ti OR coamoxiclav:ab,ti OR erythromycin:ab,ti OR clarithromycin:ab,ti

#4. #2 OR #3

#5. #1 AND #4

#6. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*

#7. #5 AND #6

Cochrane library

#1. MeSH descriptor: [Cough] explode all trees

#2. cough:ti,ab,kw (Word variations have been searched)

#3. MeSH descriptor: [Bronchitis] this term only

#4. MeSH descriptor: [Bronchitis, Chronic] explode all trees

#5. bronchitis:ti,ab,kw (Word variations have been searched)

#6. #1 OR #2 OR #3 OR #4 OR #5

#7. MeSH descriptor: [Amoxicillin] explode all trees

#8. MeSH descriptor: [Clavulanic Acids] explode all trees

#15. MeSH descriptor: [Erythromycin] this term only

#16. MeSH descriptor: [Clarithromycin] explode all trees

#22. amoxicillin or amoxycillin or clavulanate or "clavulanic acids" or "clavulanic acid" or augmentin or co-amoxiclav or coamoxiclav or erythromycin or clarithromycin:ti,ab,kw (Word variations have been searched)

#23. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

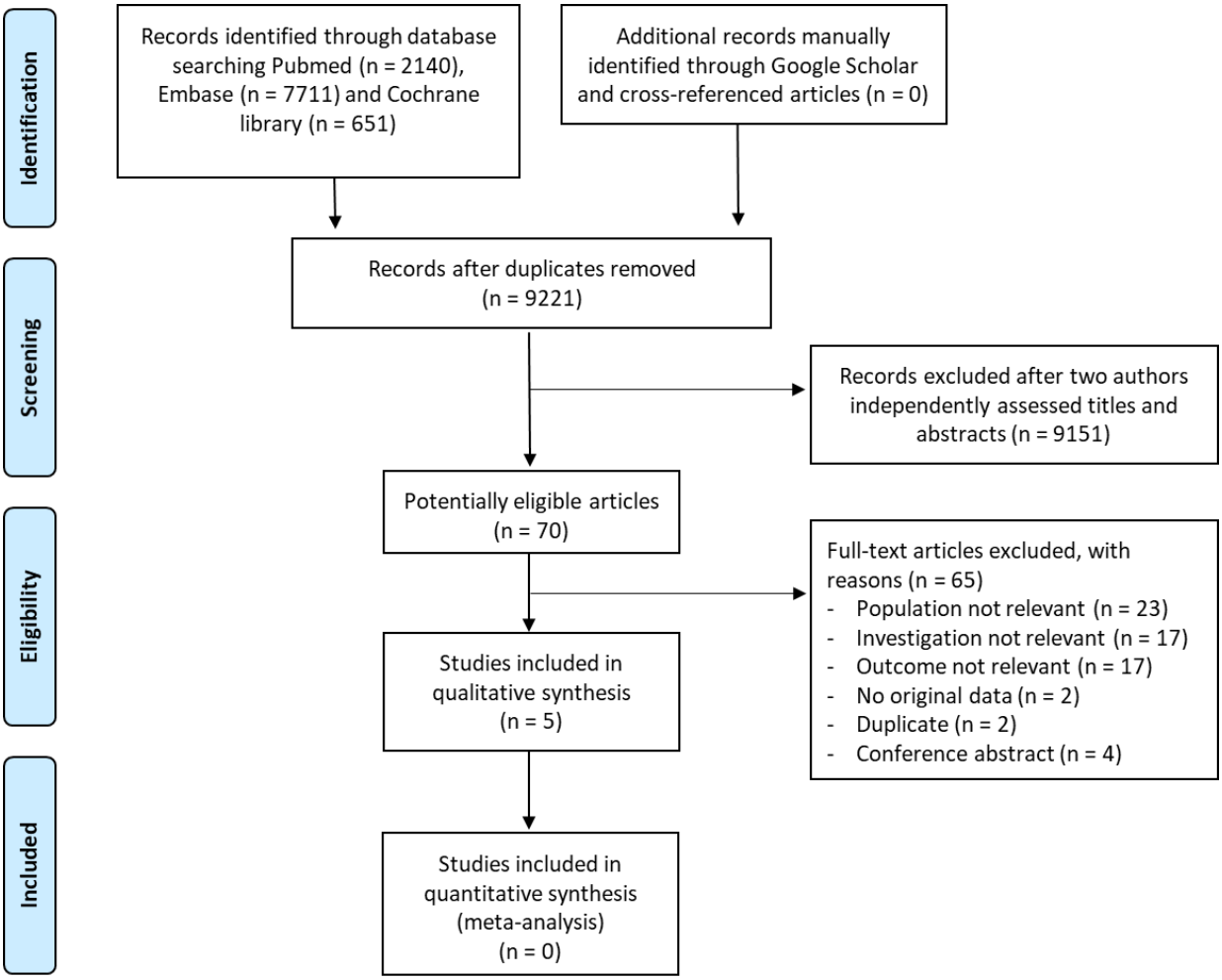
#24. #6 AND #23

#25. #24 in Trials

4. PRIMSA flow diagrams

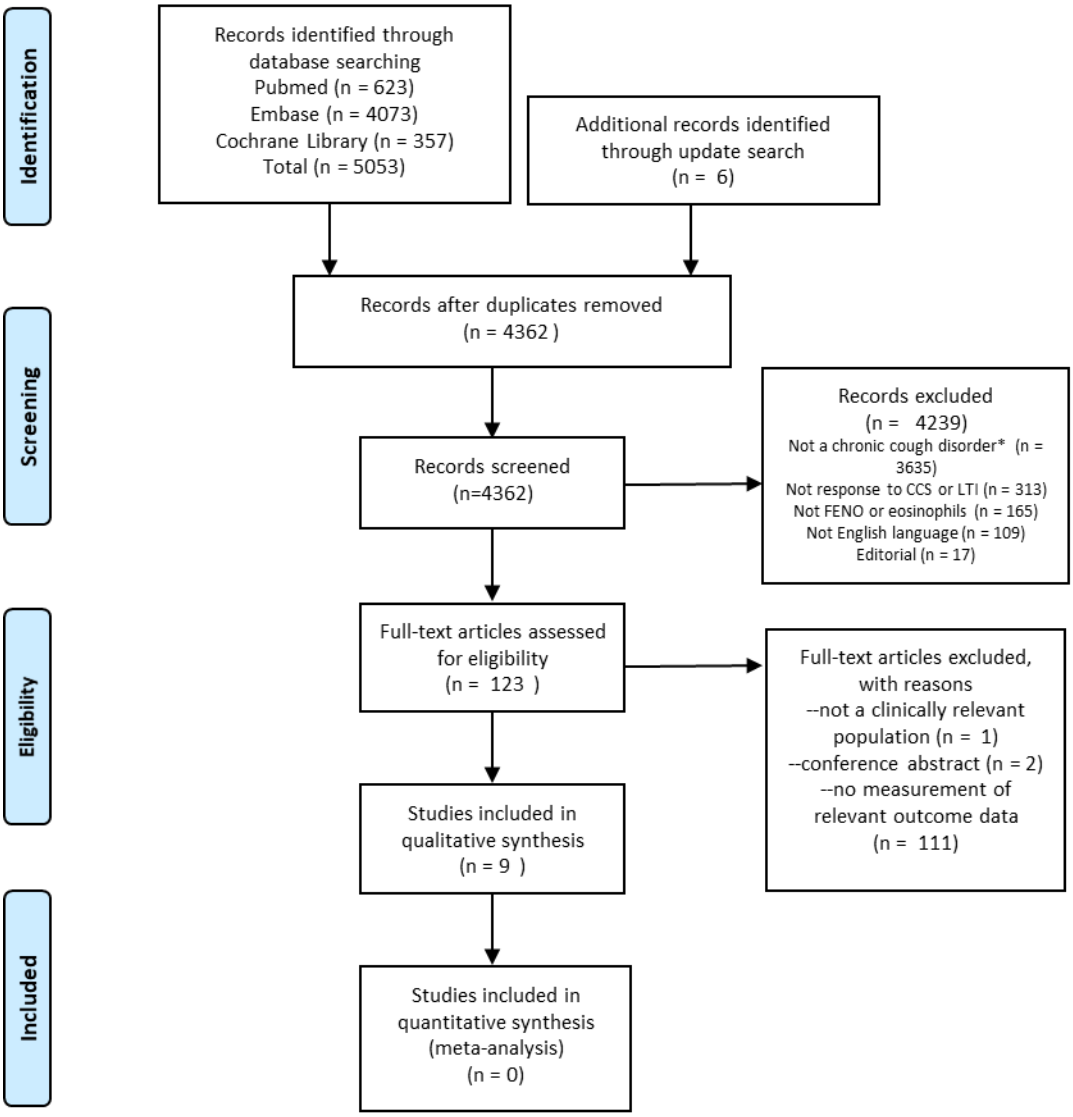
Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Last search: June 2018



Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

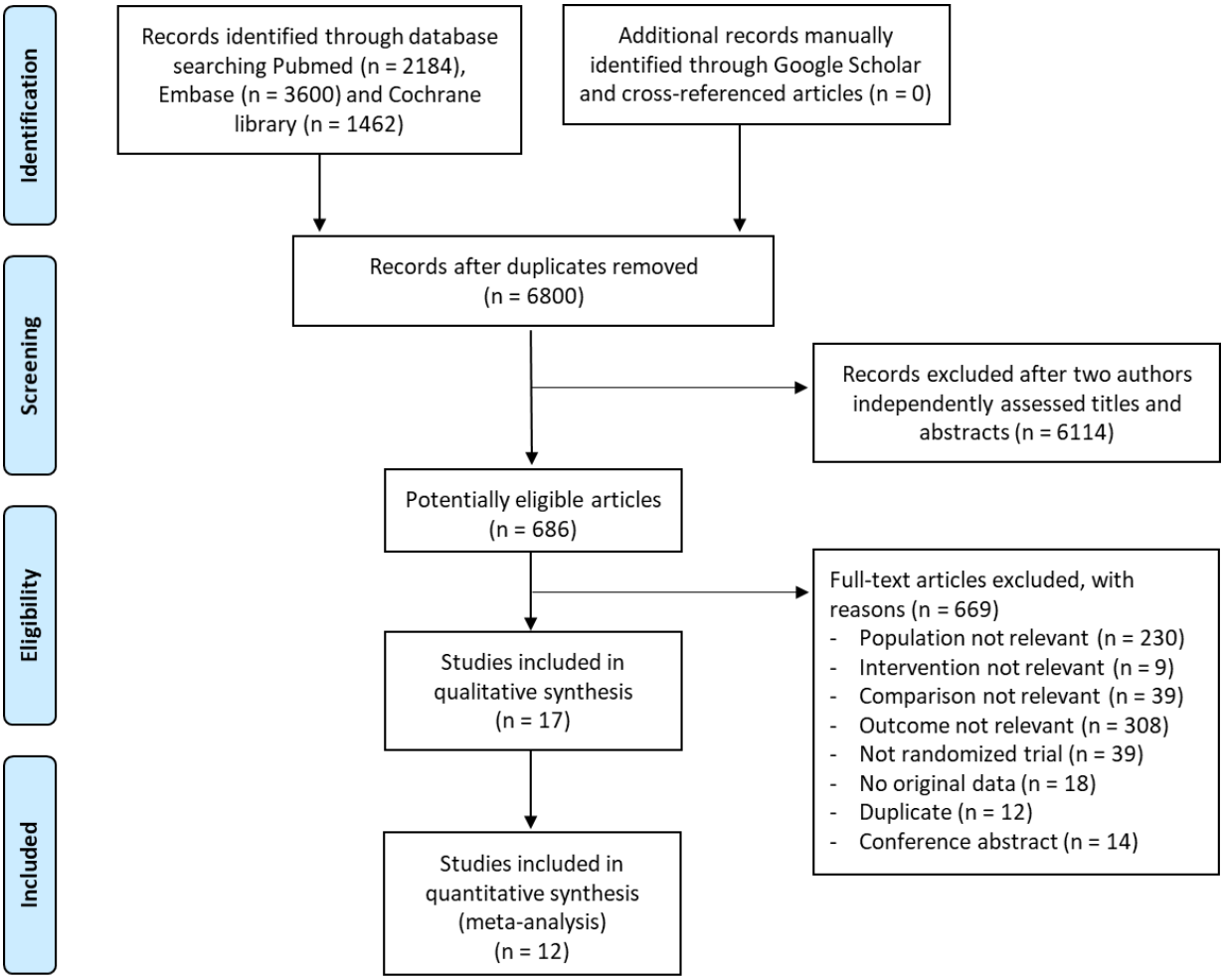
Last search: June 2018



* Included conditions: chronic cough, cough variant asthma, eosinophilic bronchitis, chronic bronchitis, atopic cough, psychogenic cough, cough hypersensitivity syndrome. Asthma and COPD were included if: cough was mentioned as a key feature AND diagnostic criteria/terminology were non-specific AND interventions/outcomes were relevant.

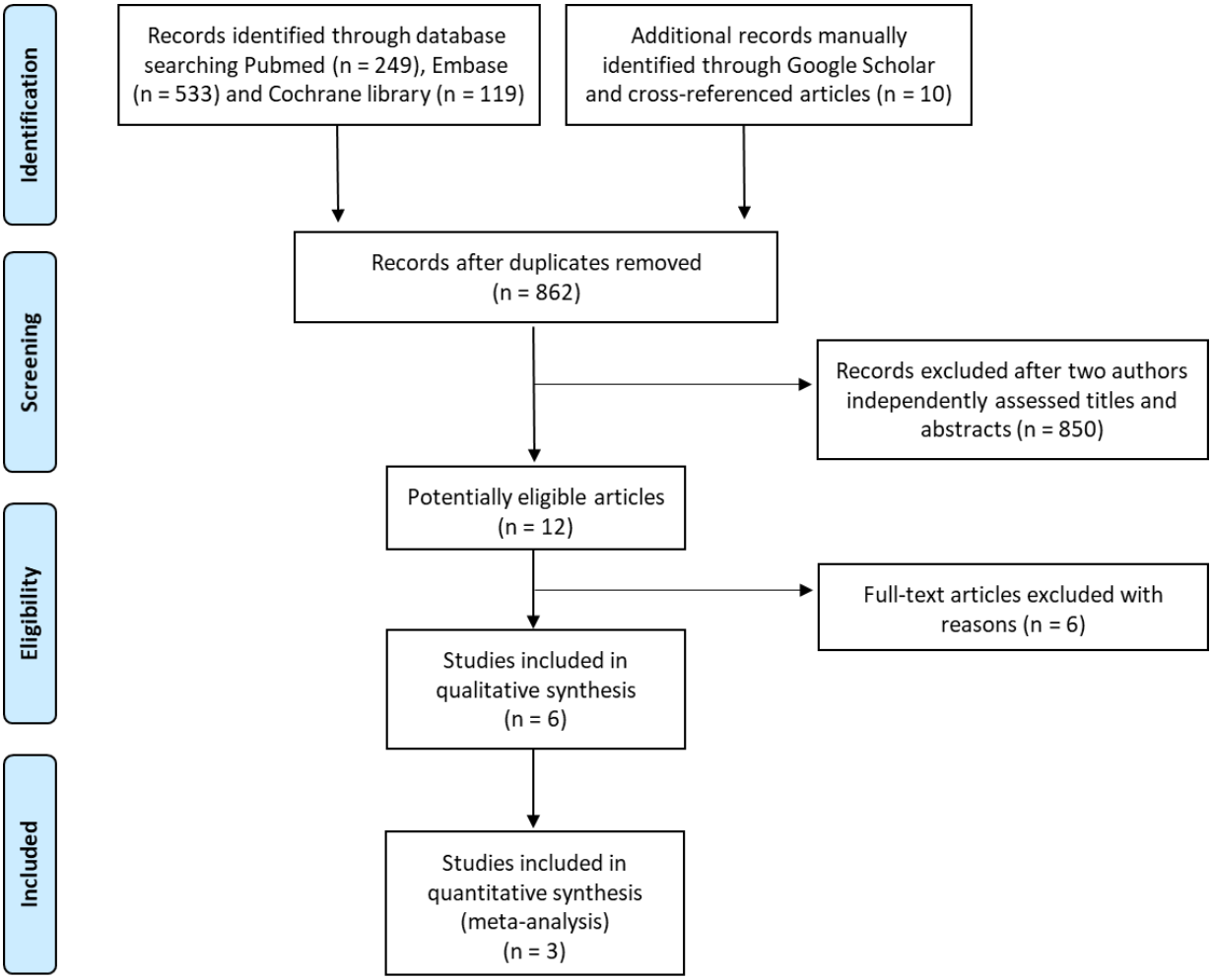
Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Last search: June 2018



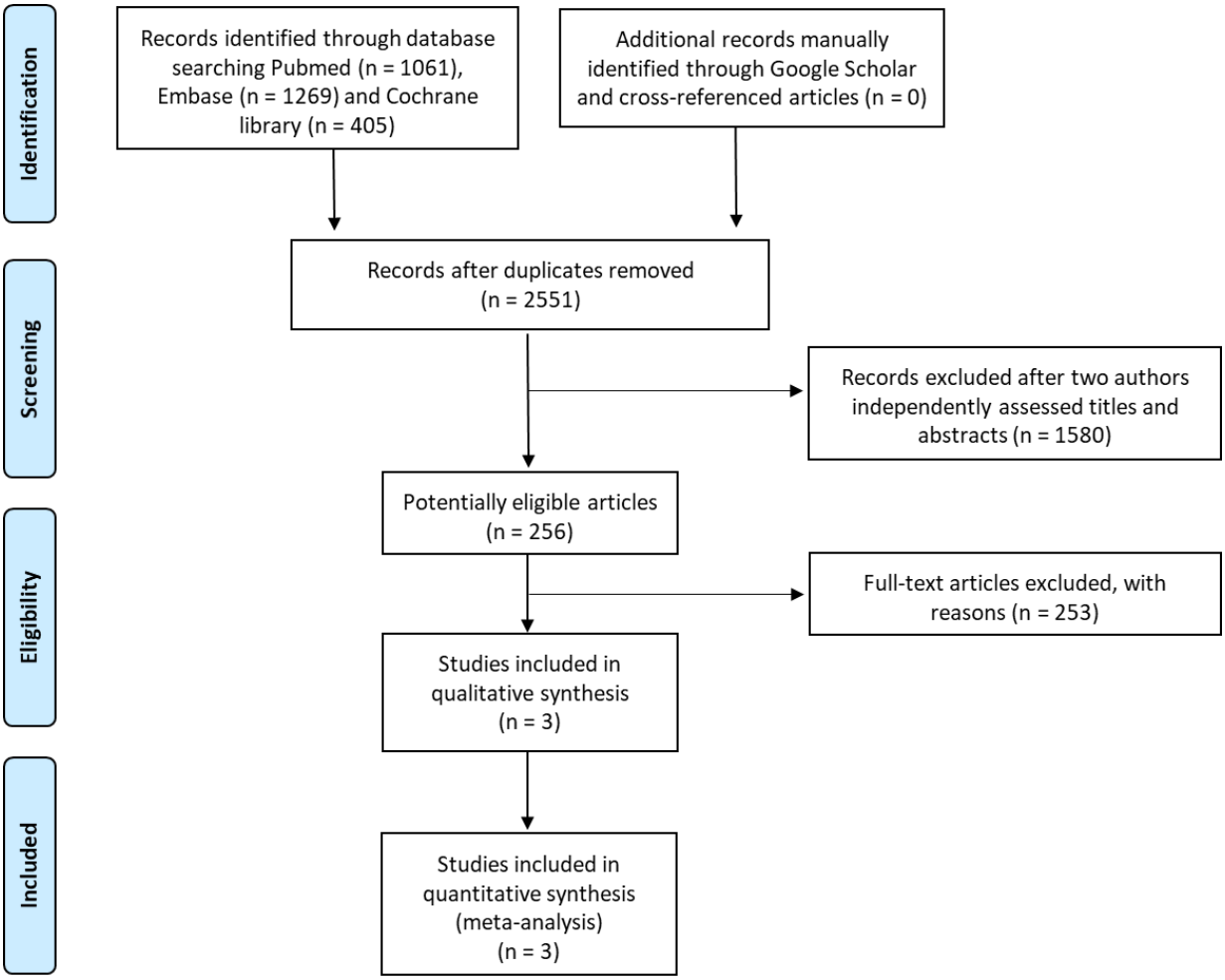
Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Last search: June 2018



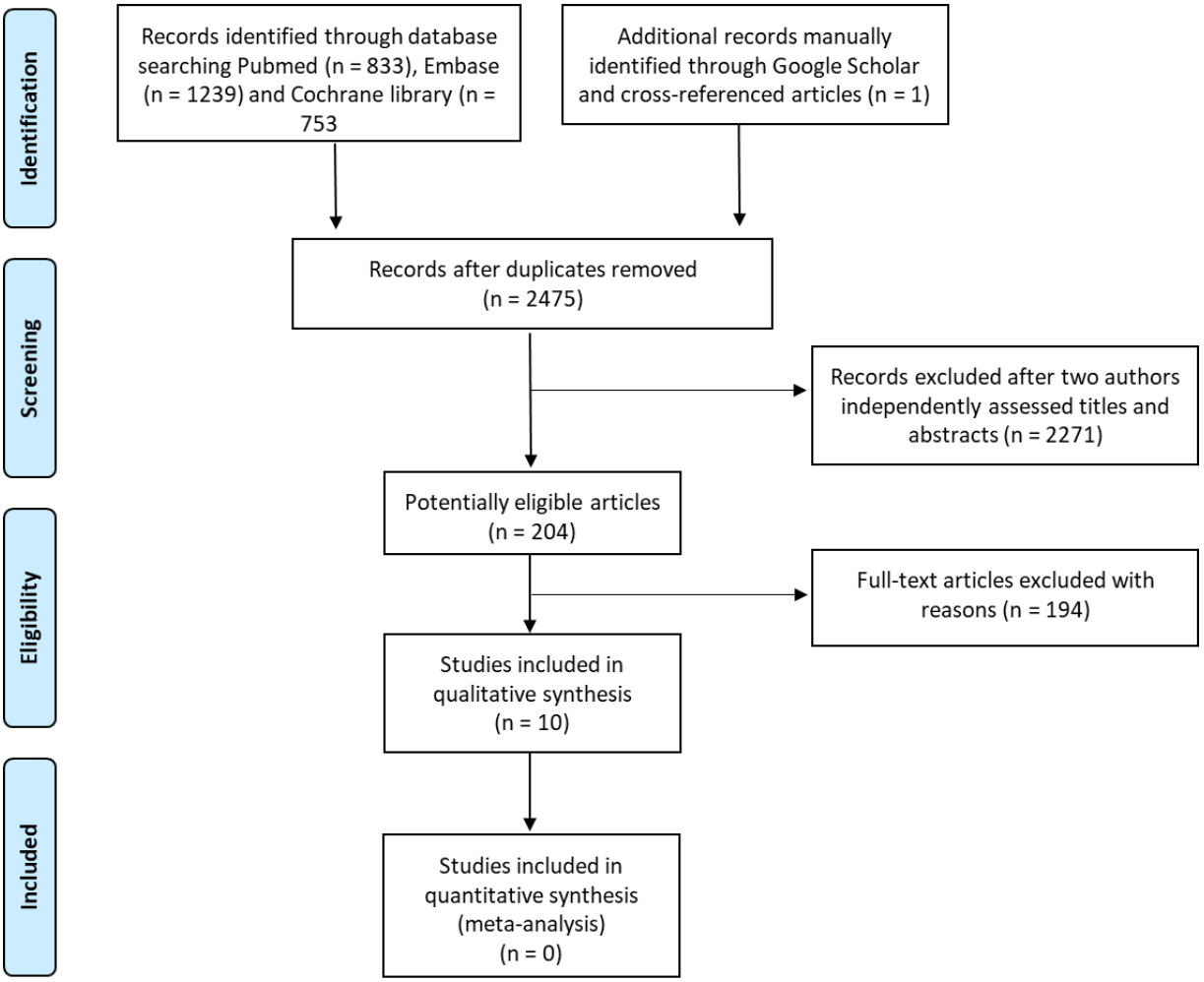
Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Last search: June 2018



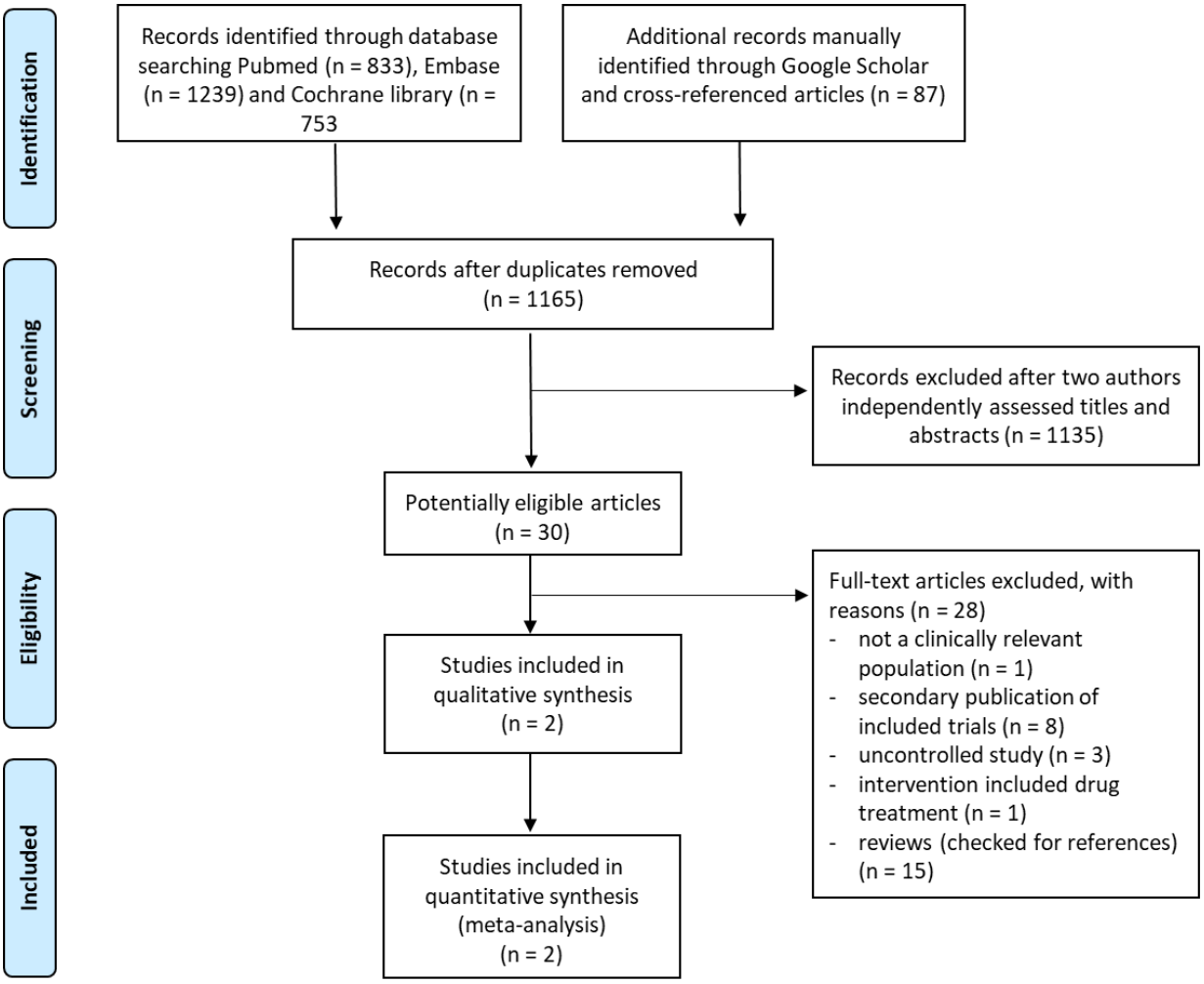
Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Last search: June 2018



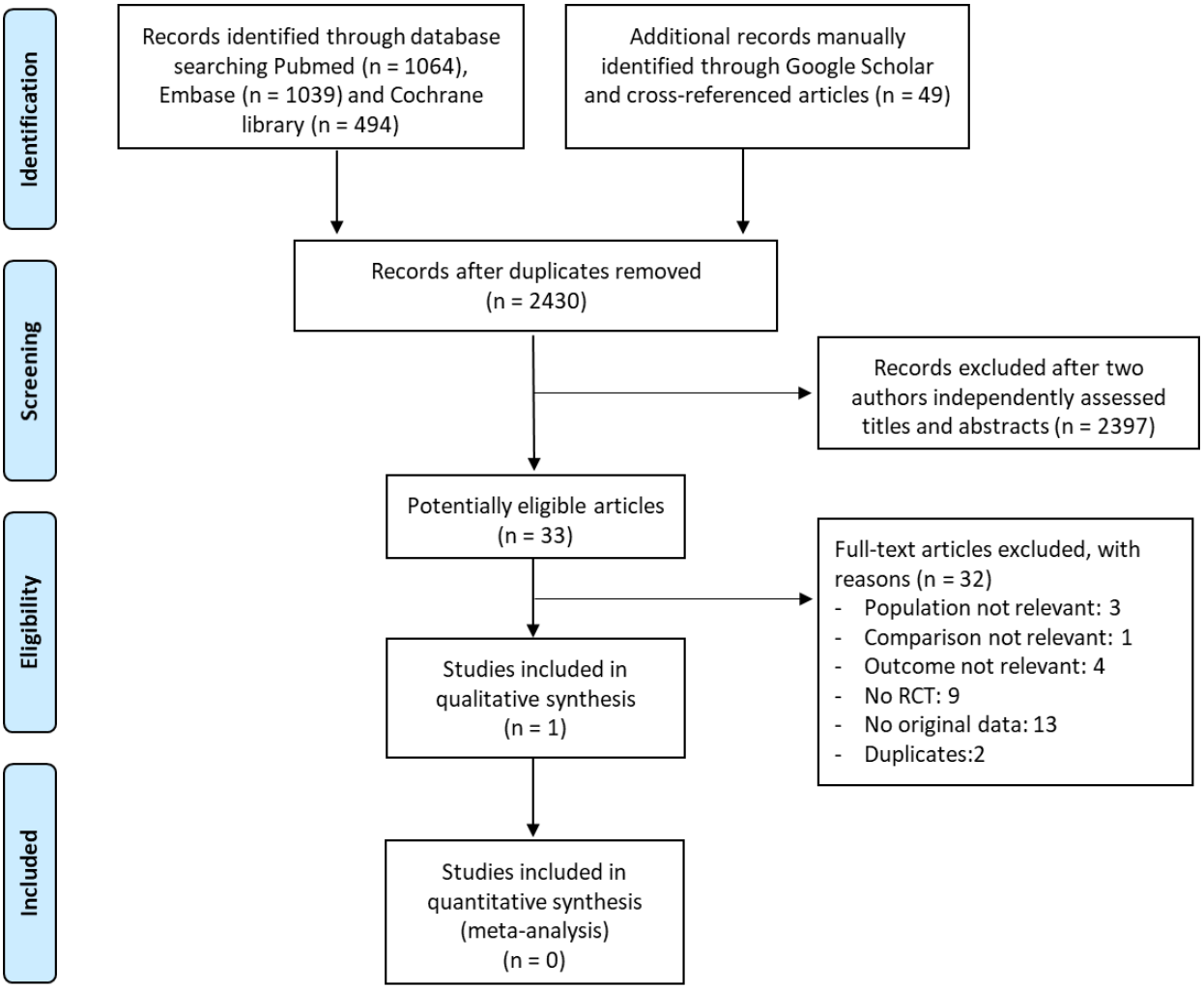
Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Last search: June 2018



Question 8: Should a trial of antibiotics be used in children with chronic wet cough with~~out warning signs,~~ normal chest x ray ~~and,~~ normal spirometry and no warning signs?

Last search: June 2018



5. Evidence GRADE profiles

Question 1: Should chest CT be routinely performed on chronic cough patient with normal chest X-ray and physical examination?

Summary of finding table including GRADE assessment (GRADE Evidence Profile).

Quality assessment							Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic yield									
4 [1,2,3,4]	Observational	serious [a]	serious [b]	serious [c]	serious [d]	none	Prospective study: - Kastelik 2005: 3 out of 46 (6.5%) CT findings despite normal chest X-rays (specific findings were not described; causal relationship of each finding was not specified) Retrospective studies: - McGarvey 1998: 20 out of 34 (58%) CT findings despite normal chest X-rays (specific findings were not described; causal relationship of each finding was not specified) - Barnes 2004: 9 out of 21 (43%) CT findings despite normal chest X-rays (none were likely to explain cough) - Truba 2018: 21 out of 59 (36%) CT findings despite normal chest X-rays. (Causal relationship of each finding was not specified)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

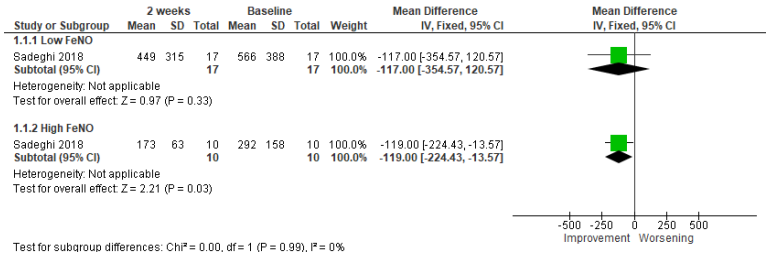
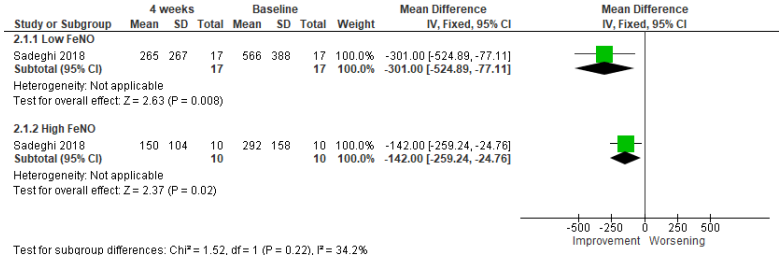
a. In most of studies CT scan was only performed in a subgroup of patients (about half of them)
b. Rate of positive findings varied broadly (from 6.5% to 58%)
c. Diagnostic yield / diagnostic accuracy are indirect findings of the effectiveness of CT scan on patients' important outcomes
d. Specific findings o causal relationship not described or not likely to explain the cough, the impact on final patient management and outcomes in comparison to not performing CT is not known.

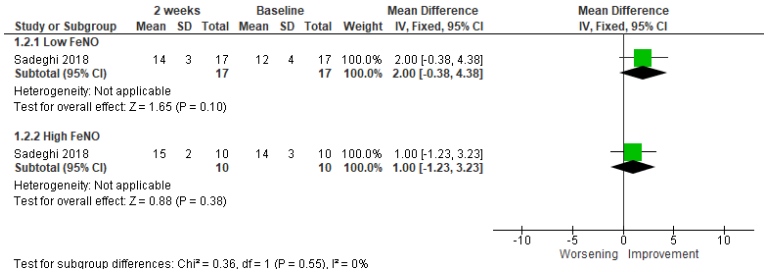
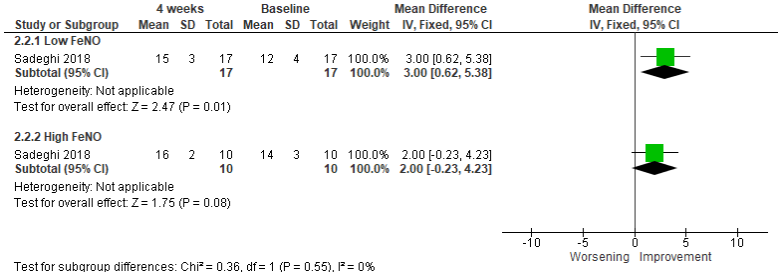
References

1. Kastelik JA, Aziz I, Ojoo JC, Thompson RH, Redington AE, Morice AH. Investigation and management of chronic cough using a probability-based algorithm. Eur Respir J. 2005 Feb;25(2):235-43.
2. Barnes TW, Afessa B, Swanson KL, Lim KG. The clinical utility of flexible bronchoscopy in the evaluation of chronic cough. Chest. 2004 Jul;126(1):268-72.
3. Truba O, Rybka A, Klimowicz K, Grabczak EM, Żukowska M, Dąbrowska M, Krenke R. Is a normal chest radiograph sufficient to exclude pulmonary abnormalities potentially associated with chronic cough? Adv Respir Med. 2018;86(3).
4. McGarvey LP, Heaney LG, Lawson JT, Johnston BT, Scally CM, Ennis M, Shepherd DR, MacMahon J. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. Thorax. 1998 Sep;53(9):738-43.

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - ANTI-LEUKOTRIENES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO measurement	no FeNO measurement	Relative (95% CI)	Absolute (95% CI)		
Cough frequency: 24-hours cough count at 2 weeks												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24-hours cough count at 2 weeks decreased in both groups (low and high FeNO at baseline) without differences between them: -117.00 [95%CI -354.57 to 120.57] and -119.00 [95%CI -224.43, -13.57] respectively 			⊕⊕◯◯ LOW	CRITICAL
Cough frequency: 24-hours cough count at 4 weeks												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24-hours cough count at 4 weeks decreased in both groups (low and high FeNO at baseline) without differences between them: -301.00 [95%CI -524.89 to -77.11] and -142.00 [95%CI -259.24 to -24.76] respectively 			⊕⊕◯◯ LOW	CRITICAL

Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points; Follow up: 2 weeks									
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	LCQ score at 2 weeks improved in both groups (low and high FeNO at baseline) without differences between them: 2.00 [95%CI -0.38 to 4.38] and 1.00 [95%CI -1.23 to 3.23] respectively  	⊕⊕◯◯ LOW	CRITICAL
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points; Follow up: 4 weeks									
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	LCQ score at 4 weeks improved in both groups (low and high FeNO at baseline) without differences between them: 3.00 [95%CI 0.62 to 5.38] and 2.00 [95%CI -0.23 to 4.23] respectively  	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. Patients with low FeNO levels (<20ppb) received montelukast 10 mg (28 days); patients with high FeNO levels (>30ppb) were randomised to receive prednisolone+montelukast or montelukast 10 mg (28 days). Only patients receiving montelukast were considered in the analysis, thus one arm was not randomised. Baseline characteristics were not similar between groups (higher percentage of females in low FeNO levels)

b. Very limited sample size, wide 95%CI making difficult to detect subgroup differences.

References

1. Sadeghi MH, Wright CE,Hart S,Crooks M,Morice A.. Phenotyping patients with chronic cough: evaluating the ability to predict the response to anti-inflammatory therapy.. Ann Allergy Asthma Immunol; 2018.

Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - CORTICOSTEROIDS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Responders	Non-responders	Relative (95% CI)	Absolute (95% CI)		
FeNO levels (follow up: range 4 weeks to 24 weeks; assessed with: difference between responders and non responders)												
3 [1,2,3]	observational studies	not serious	not serious [a]	very serious [b,c]	serious [d]	none	113	86	-	MD 23.31 ppb fewer (39.35 fewer to 7.27 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Although the analysis shows significant variability among effect estimates one study (Prieto 2009) contributes to most of the heterogeneity. This study assessed treatment response using he most objective score (>50% reduction in daily cough symptom score)
b. Studies show considerable heterogeneity in definition of 'high' versus 'low' FeNO (thresholds range from 16.3 to 38.0 ppb); ICS prescribing criteria, dose, and duration; and definition of treatment response
c. Indirect measure for predictive value of FeNO
d. Lower 95%CI (-7.27 ppb) probably does not allow discriminate populations and is not clinically meaningful.

References

1. Watanabe K, Shinkai M,Shinoda M,Hara Y,Yamaguchi N,Rubin BK. Measurement of eNO with portable analyser might improve the management of persistent cough at primary care practice in Japan. Clin Respir J; 2016.

2. Prieto L, Ferrer A,Ponce S,Palop J,Marin J.. Exhaled nitric oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest; 2009.

3. Hahn PY, Morgenthaler TI,Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clin Proc; 2007.

Question 3: Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - LTRA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	LTRA	Relative (95% CI)	Absolute (95% CI)		
Cough severity and frequency 'combined': mean change at 2 weeks in cough score from baseline (patient completed score: 0 [no cough] - 10 [cough as bad as it has ever been1 or as bad as at the first visit2])												
2 [1,2]	randomised trials	very serious [a]	serious [b]	serious [c]	very serious [d]	none	16	27	-	MD 3.10 lower (6.20 lower to 0.01 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Cough frequency (number of coughs/day): mean change at 1 week of daily cough frequency from baseline; assessed with: recorded objectively with an audio cough meter.												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	6	8	-	MD 29.63 lower (93.73 lower to 34.47 higher)	⊕⊕◯◯ LOW	CRITICAL
Cough frequency (number of coughs/day): mean change at 4 week of daily cough frequency from baseline; assessed with: recorded objectively with an audio cough meter.												
1 [3]	randomised trials	not serious	not serious	not serious	serious [e]	none	6	8	-	MD 144.06 lower (219.39 to 68.73 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Improvement in quality of life (not further specified)												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/6 (33%)	8/8 (100%)	OR 2.64 (0.97 to 7.23)	547 more per 1.000 (10 fewer to 2.077 more)	⊕⊕◯◯ LOW	IMPORTANT
Any adverse events: (any adverse or unusual experiences) documented by patients on a diary card at each visit												
1 [3]	randomised trials	not serious	not serious	not serious	very serious [d]	none	0/6 (0%)	0/8 (0%)	-	-	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **CVA**: cough-variant asthma; **LTRA**: leukotriene receptor antagonist; **MD**: mean difference; **RD**: risk difference; **RR**: risk ratio.

Explanations

a. Very high risk of selection bias and probably lack of blinding in one study.
b. Confidence intervals show only minimal overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).
c. Regarding the population of interest, the study population also includes patients with CVA and chronic atopic cough.
d. Low number of patients and 95% CI consistent with the possibility for benefit and the possibility of harm (dichotomous outcome)
e. Very low number of patients
f. Low number of patients and no events in both groups.

References

1. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2002;39(4):291-297.
2. Kita T, Fujimura M, Ogawa H, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. *Allergology international : official journal of the Japanese Society of Allergology.* 2010;59(2):185-192.
3. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2004;93(3):232-236.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS, ADULT POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Bronchodilator	Relative (95% CI)	Absolute (95% CI)		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD 0.08 lower (0.16 lower to 0.00 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Day-time cough severity: at 3 weeks; assessed with different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	43	43	-	SMD 1.63 lower (3.84 lower to 0.59 higher)	⊕⊕◯◯ LOW	IMPORTANT
Night-time cough severity: at 3 weeks; assessed with different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	43	43	-	SMD 0.98 lower (1.78 lower to 0.18 lower)	⊕⊕◯◯ LOW	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD 2.70 lower (5.08 lower to 0.32 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	372	-	MD 0.07 less (0.93 less to 0.79 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	20/372 (5.4%)	RR 0.88 (0.49 to 1.59)	7 Fewer per 1.000 (31 fewer to 36 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Any adverse events: (treatment related adverse events)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	49/361 (13.6%)	46/372 (12.4%)	RR 0.91 (0.63 to 1.33)	12 Fewer per 1.000 (50 fewer to 45 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: confidence interval; **MD**: mean difference; **SMD**: standardized mean difference; **RR**: risk ratio.

Explanations

a. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).
b. Confidence intervals show no overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).

References

4. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.
5. Ellul-Micallef R. Effect of terbutaline sulphate in chronic "allergic" cough. British medical journal (Clinical research ed). 1983;287(6397):940-943.
6. Holmes PW, Barter CE, Pierce RJ. Chronic persistent cough: use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respiratory medicine. 1992;86(5):425-29

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS, CHILDREN POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Bronchodilator	Relative (95% CI)	Absolute (95% CI)		
Cough severity – parent assessment: at 5-7days of treatment; assessed with VAS; Range 0 to 10 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	22	21	-	MD 0.4 lower (1.93 lower to 1.13 higher)	⊕⊕◯◯ LOW	IMPORTANT
Cough severity – parent assessment: at 5-7days of treatment; assessed with VAS; Range 0 to 10 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	22	21	-	MD 0.3 higher (1.19 lower to 1.79 higher)	⊕⊕◯◯ LOW	IMPORTANT
Response to treatment ("treatment success") defined as a ≥70% reduction in cough frequency at 5-7-days.												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [a]	none	5/22 (22.7%)	4/21 (19.0%)	RR 0.84 (0.26 to 2.70)	36 Fewer per 1.000 (168 fewer to 386 more)	⊕⊕◯◯ LOW	CRITICAL

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio.

Explanations

a. Confidence intervals show no overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large).

References

1. Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Archives of disease in childhood. 1998;79(1):6-11.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, Adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	ICS	Relative (95% CI)	Absolute (95% CI)		
Cough severity at 2 weeks– patient with chronic cough; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
2 [5,6]	randomised trials	not serious	not serious	not serious	serious [d]	none	111	109	-	MD 8.42 lower (15.5 lower to 1.34 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough frequency at 2 weeks– patient with chronic cough; assessed with patient completed score: 0 [no cough] - 4 [constant cough].												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [f]	none	20	44	-	MD 1 lower (1.6 lower to 0.4 lower)	⊕⊕◯◯ LOW	CRITICAL
Cough severity – patient with chronic cough: mean cough symptom score up to 8 weeks. Assessed with: different scales. Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.												
3 [1,2,3]	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	none	104	128	-	SMD 0.28 lower (0.79 lower to 0.23 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Cough severity – patient with chronic bronchitis: mean change in daily cough score (patient completed) from baseline (at 12 weeks): 0 (none), 1 (few coughs every day), 2 (repeated cough attacks, but only in the morning or during the day), 3 (persistent cough attacks during the night and day)												
1 [4]	randomised trials	not serious	not serious	serious [e]	very serious [f]	none	18	18	-	MD 0.03 lower (0.68 lower to 0.63 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Night interruptions– patient with chronic cough: mean change from baseline												
1 [2]	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	20	44	-	MD 0.31 less (0.81 less to 0.19 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Any adverse events– patient with chronic cough												
3 [2,3,6]	randomised trials	serious [a]	not serious	serious [c]	serious [d]	none	44/113 (38.9%)	50/135 (37.0%)	RR 1.07 (0.83 to 1.38)	27 more per 1.000 (66 fewer to 148 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Any adverse events– patient with chronic bronchitis												
2 [7,8]	randomised trials	very serious [g]	not serious	not serious	very serious [h]	none	0/44 (0%)	1/43 (2.3%)	RR 3.40 (0.15 to 77.34)	-	⊕◯◯◯ VERY LOW	IMPORTANT
Major adverse events– patient with chronic cough												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	ICS	Relative (95% CI)	Absolute (95% CI)		
2 [2,3]	randomised trials	serious [a]	not serious	serious [c]	very serious [h]	none	6/90 (6.7%)	5/114 (4.4%)	RR 0.83 (0.27 to 2.60)	11 fewer per 1.000 (49 fewer to 107 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; ICS: inhaled corticosteroids; SMD: standardized mean difference; MD: mean difference; RD: risk difference; RR: risk ratio.

Explanations

a. High risk of selective reporting.
b. High I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large, I^2 >50%).
c. Patients with airway symptoms suggestive of asthma, without fulfilling the functional criteria of asthma included.
d. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect.
e. All patients in the study were smokers with bronchitis.
f. Small number of patients; 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect.
g. Very high risk of selection bias.
h. Small number of patients and events; 95% CI was consistent with the possibility of large benefit or large harm.

References

1. Boulet LP, Milot J, Boutet M, St Georges F, Laviolette M. Airway inflammation in nonasthmatic subjects with chronic cough. *American journal of respiratory and critical care medicine.* 1994;149(2 Pt 1):482-489.
2. Ribeiro M, Pereira CA, Nery LE, Beppu OS, Silva CO. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2007;99(1):61-68.
3. Rytila P, Ghaly L, Varghese S, Chung W, Selroos O, Haahtela T. Treatment with inhaled steroids in patients with symptoms suggestive of asthma but with normal lung function. *The European respiratory journal.* 2008;32(4):989-996.
4. Engel T, Heinig JH, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. *The European respiratory journal.*1989;2(10):935-939.
5. Chaudhuri R, McMahon AD, Thomson LJ, et al. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *The Journal of allergy and clinical immunology.* 2004;113(6):1063-1070.
6. Pizzichini MM, Pizzichini E, Parameswaran K, et al. Nonasthmatic chronic cough: No effect of treatment with an inhaled corticosteroid in patients without sputum eosinophilia. *Canadian respiratory journal.* 1999;6(4):323-330.
7. Kozak-Szkopek EU, W. T. Inhalative Budesonid-Therapie bei chronischer Bronchitis. *Atemwegs- und Lunkenkrankheiten.* 1997;23(9):542-546.
8. Wesseling GJ, Quaedvlieg M, Wouters EF. Inhaled budesonide in chronic bronchitis. Effects on respiratory impedance. *The European respiratory journal.* 1991;4(9):1101-1105.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, COPD POPULATION

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	ICS	Relative (95% CI)	Absolute (95% CI)		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD 0.06 lower (0.14 lower to 0.02 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD 3.50 lower (5.80 lower to 1.20 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	374	-	MD 0.56 less (1.35 less to 0.23 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	26/374 (7.0%)	RR 1.14 (0.66 to 1.98)	9 more per 1.000 (21 fewer to 60 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Response to treatment ('treatment success'): at 24 weeks; defined as: no cough symptoms												
1 [2]	randomised trials	not serious	not serious	not serious	serious [a]	none	11/139 (7.9%)	26/142 (18.3%)	RR 2.31 (1.19 to 4.50)	104 more per 1.000 (15 to 277 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Exacerbations: number of patients with exacerbations up to 52 weeks.												
2 [1,2]	randomised trials	not serious	not serious	not serious	serious [a]	none	70/500 (14.0%)	55/516 (10.7%)	RR 0.74 (0.46 to 1.20)	36 fewer per 1.000 (76 fewer to 28 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Any adverse events: up to 52 weeks												
2 [1,2]	randomised trials	not serious	serious [b]	not serious	serious [a]	none	144/500 (28.8%)	161/516 (31.2%)	RR 1.11 (0.73 to 1.68)	32 more per 1.000 (78 fewer to 196 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio.

Explanations

c. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).
d. confidence intervals show only minimal overlap and high I^2 (i.e., the proportion of the variation in point estimates due to 'among-study differences' is large,

I^2 >50%).

References

7. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.
8. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo- controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet (London, England). 1998;351(9105):773-780.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – BRONCHODILATORS +ICS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Placebo	Bronchodilators +ICS	Relative (95% CI)	Absolute (95% CI)		
Cough severity: mean cough score at 52 weeks (patient completed daily score: 0 [no cough] - 3 [severe cough], recording of the previous 24 h before visit at week 52)												
1 [1]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	361	358	-	MD 0.09 lower (0.17 lower to 0.01 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). At 52 weeks. Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	358	-	MD 2.20 lower (4.55 lower to 0.15 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Night interruptions: mean change from baseline												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	361	358	-	MD 0.00 less (0.8 less to 0.8 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin bruises: number of bruises on the volar side of the forearm with a diameter >5 cm												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	22/361 (6.1%)	29/358 (8.1%)	RR 1.33 (0.78 to 2.27)	20 more per 1.000 (13 fewer to 77 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Any adverse events: (treatment related adverse events)												
1 [1]	randomised trials	not serious	not serious	not serious	serious [a]	none	49/361 (13.6%)	58/358 (16.2%)	RR 0.48 (0.22 to 1.04)	27 Fewer per 1.000 (41 fewer to 2 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: confidence interval; **MD**: mean difference; **SMD**: standardized mean difference; **RR**: risk ratio.

Explanations

a. Duration of intervention was
b. 95% CI was consistent with the possibility of improving and the possibility of worsening symptoms or no effect (continuous outcome).

References

9. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet (London, England). 2003;361(9356):449-456.

Summary of finding table including GRADE assessment (GRADE Evidence Profile) – ICS, Children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ICS	Placebo	Relative (95% CI)	Absolute (95% CI)		
Nocturnal cough frequency: mean change from baseline (objectively recorded) - At nights 15/16												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26	24	-	MD 60 lower (85.45 lower to 34.55 lower)	⊕⊕◯◯ LOW	
Cough severity: mean change from baseline (VAS score averaged over 1 week, at 4-5 weeks) - Parent completed												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	22	21	-	MD 0.6 higher (0.6 lower to 1.8 higher)	⊕⊕◯◯ LOW	
Cough severity: mean change from baseline (VAS score averaged over 1 week, at 4-5 weeks) - Child completed												
1 [2]	randomised trials	serious [a]	not serious	not serious	serious [c]	none	22	21	-	MD 0.6 higher (0.53 lower to 1.73 higher)	⊕⊕◯◯ LOW	
Response to treatment ('treatment succes') - **Defined as a ≥75% reduction in nocturnal cough** frequencys (at nights 15/16)												
1 [1]	randomised trials	serious [a]	not serious	not serious	serious [d]	none	17/26 (65.4%)	8/24 (33.3%)	RR 1.96 (1.04 to 3.69)	320 more per 1,000 (from 13 more to 897 more)	⊕⊕◯◯ LOW	
Response to treatment ('treatment succes') - **Defined as a ≥70% reduction in 24 h cough frequency (at 4/5 weeks)**												
1 [2]	randomised trials	serious [a]	not serious	not serious	very serious [d,e]	none	12/22 (54.5%)	14/21 (66.7%)	RR 0.82 (0.50 to 1.33)	120 fewer per 1,000 (from 333 fewer to 220 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Potential risk of carry-over effect, uncertainties in missinbg data and randomisation.

b. 95% CI was consistent with the possibility of improving and the possibility of no effect.

c. 95% CI was consistent with the possibility of worsening symptoms or no effect.

d. Low number of events and patients included

e. 95%CI was consistent with appreciable benefit or harm

References

1. Davies MJ, Fuller P, Picciotto A, McKenzie SA. Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. Arch Dis Child. 1999 Jul;81(1):38-44.
2. Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child. 1998 Jul;79(1):6-11.

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - Adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acid suppression therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cough severity (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
4 [1,2,3,4]	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	74	63	-	SMD 0.63 lower (1.37 lower to 0.1 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Cough frequency (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [2,3]	randomised trials	serious [d]	not serious	not serious	serious [c]	none	46	43	-	SMD 0.18 lower (0.6 lower to 0.23 higher)	⊕⊕◯◯ LOW	IMPORTANT
Quality of life specific questionnaires (different scales). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
3 [2,3,4]	randomised trials	serious [e]	not serious	not serious	serious [c]	none	65	51	-	SMD 0.72 SD lower (1.3 lower to 0.13 lower)	⊕⊕◯◯ LOW	CRITICAL
Tussive response to cough challenge. Assessed with: Citric acid cough challenge												
1 [2]	randomised trials	not serious	not serious	Serious [f]	serious [g]	none	There were no differences between treatment and placebo groups in the change from baseline concentration on inhaled citric acid (to trigger cough). Log C2; between-group p value 0.66 Log C5; between-group p value 0.57.				⊕⊕◯◯ LOW	IMPORTANT
Adverse events												
3 [2,3,4]	randomised trials	serious [e]	not serious	not serious	serious [h]	none	3 RCTs reported few adverse events with a similar incidence between intervention and placebo group. Faruqi: treatment 4/24 (17%) versus placebo 2/25 (8%) respiratory tract infection; Shaheen: no serious events/withdrawns in both groups; Park: treatment 2/19 (11%, both from high-dose group) urticaria versus placebo 2/8 (25%) 1 urticaria and 1 palpitation				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. 3 studies: non-validated subjective outcome measures; 1 study (Kiljander) no description on the number of dropouts according to treatment group or period; 1 study (Park): high drop-out rate (30%); 1 study (Park): significant different baseline characteristics and different dropout rates between groups

b. Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 11.70$, df = 3 (P = 0.008); $I^2 = 74\%$

c. SMD >0.5 and <0.8 representing a moderate difference

d. All studies: non-validated subjective outcome measures

e. 1 study (Park): high drop-out rate (30%); 1 study (Park): significant different baseline characteristics and different dropout rates between groups

f. Indirect (surrogate) measure of efficacy

g. single study with small sample size

h. Low number of patients and events

References

1. Kiljander TO1, Salomaa ER, Hietanen EK, Terho EO. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. Eur Respir J. 2000 Oct;16(4):633-8.
2. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology. 2011 Oct;16(7):1150-6.
3. Shaheen NJ, Crockett SD, Bright SD, Madanick RD, Buckmire R, Couch M, Dellon ES, Galanko JA, Sharpless G, Morgan DR, Spacek MB, Heidt-Davis P, Henke D. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011 Jan;33(2):225-34.
4. Park HJ, Park YM, Kim JH, Lee HS, Kim HJ, Ahn CM, Byun MK. Effectiveness of proton pump inhibitor in unexplained chronic cough. PLoS One. 2017 Oct 10;12(10):e0185397

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - Children

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acid suppression therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Daytime cough frequency. Assessed with : episodes/day												
1 [1]	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	4	4	-	MD 2.70 fewer (3.85 fewer to 1.55 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Night-time cough frequency. Assessed with : episodes/night												
1 [1]	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	4	4	-	MD 0.20 fewer (0.56 fewer to 0.16 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse event												
1	randomised trials	serious [a]	not serious	not serious	Very serious [b]	none	No adverse events reported by parents in both treatment and placebo group				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. non-validated subjective outcome measures; observer bias; unknown number of dropouts in treatment group

b. small groups (n=4)

References

1. Adamko DJ, Majaesic CM, Skappak C, Jones AB. A pilot trial on the treatment of gastroesophageal reflux-related cough in infants. Transl Pediatr. 2012 Jul;1(1):23-34.

Question 5: Should drugs with pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
3 [1,2,3]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	74	77	-	MD 1.27 higher (2.09 higher to 0.45 higher)	⊕⊕◯◯ LOW	CRITICAL
Cough severity (VAS or severity score). Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [1,3]	randomised trials	not serious	not serious	not serious	serious [b]	none	36	36	-	SMD 0.42 lower (0.89 lower to 0.05 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough frequency at 12 weeks (number of coughs/24h)												
1 [1]	randomised trials	not serious	not serious [c]	not serious	serious [d]	none	Mean difference in fold change 1.1 (95% CI 0.7 to 1.5)				⊕⊕⊕◯ MODERATE	CRITICAL
Capsaicin C2 at 12 weeks												
1	randomised trials	not serious	not serious [d]	serious [e]	serious [d]	none	Mean difference in fold change 0.7 (95% CI 0.4 to 1.3)				⊕⊕◯◯ LOW	IMPORTANT
Capsaicin C5 at 12 weeks												
1	randomised trials	not serious	not serious [d]	serious [e]	serious [d]	none	Mean difference in fold change 1.3 (95% CI 0.9 to 2.0)				⊕⊕◯◯ LOW	IMPORTANT
Generic Quality of life questionnaires - St. George's Respiratory Questionnaire (SGRQ). Scores range from 0 to 100, with higher scores indicating more limitations. MID: Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment												
1	randomised trials	not serious	not serious [d]	serious [a]	serious [b]	none	Mean difference in fold change -7.5 (95% CI -12.5 to -2.5)				⊕⊕◯◯ LOW	IMPORTANT
Adverse events - Gastrointestinal												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides	Placebo	Relative (95% CI)	Absolute (95% CI)		
2 [2,3]	randomised trials	not serious	serious [f]	not serious	serious [g]	none	13/58 (22.4%)	11/58 (19.0%)	OR 1.24 (0.50 to 3.09)	35 more per 1,000 (from 85 fewer to 230 more)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events - Respiratory												
2 [2,3]	randomised trials	not serious	not serious	not serious	serious [g]	none	8/58 (13.8%)	13/58 (22.4%)	OR 0.56 (0.21 to 1.46)	85 fewer per 1,000 (from 73 more to 167 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events - CNS												
1 [3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	1/21 (4.8%)	0/21 (0.0%)	OR 3.15 (0.12 to 81.74)	-	⊕⊕◯◯ LOW	IMPORTANT
Adverse events - Musculoskeletal												
1 [3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	0/21 (0.0%)	3/21 (14.3%)	OR 0.12 (0.01 to 2.54)	123 fewer per 1,000 (from 141 fewer to 155 more)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events - Cardiovascular												
1 [2,3]	randomised trials	not serious	not serious [c]	not serious	very serious [d]	none	2/37 (5.4%)	1/37 (2.7%)	OR 2.06 (0.18 to 23.72)	27 more per 1,000 (from 22 fewer to 370 more)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **OR:** Odds ratio

Explanations

a. Largest study includes patients with COPD and chronic cough
b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference.
c. Single study
d. Small study, probably not powered to detect differences.
e. Indirect measure of efficacy
f. Variability (heterogeneity) among effects estimates
g. Very low number of events, 95%CI indicates large benefit or harm.

References

1. Yousaf, N., et al. (2010). "Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial." Thorax65(12): 1107-1110
2. Berkhof, F., et al. (2013) Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. Respir Res14, 125 DOI: 10.1186/1465-9921-14-125
3. Hodgson, D., et al. (2016). "The Effects of Azithromycin in Treatment-Resistant Cough: A Randomized, Double-Blind, Placebo-Controlled Trial." Chest149(4): 1052-1060

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - OPIATES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 4 weeks. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	27	27	-	MD 2 higher (3.07 higher to 0.93 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough severity score. Follow-up: 4 weeks. Range 0 to 9 points; higher scores indicate more severity; assessed with: Diary												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	27	27	-	MD 1.6 lower (2.11 lower to 1.09 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Tussive response to cough challenge. Follow up: 4 weeks; assessed with: Citric acid cough challenge.												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	not serious	none	27	27	-	MD 93 higher (27.88 lower to 213.88 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Adverse event - constipation												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [e]	none	40% in treatment group (11 patients)				⊕⊕◯◯ LOW	CRITICAL
Adverse event – drowsiness												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [e]	none	25% in treatment group (7 patients)				⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Single study

b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

c. Low number of patients included. Lower 95%CI does not exclude a meaningless difference

d. Indirect (surrogate) measure of efficacy

e. No information on control group. Frequency based on very limited number of patients and events. The expected frequency of this adverse events in no-treatment is zero ho wever it is not clear that these figures reflect an accurate measure.

References

1. Morice AH1, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, Thompson R. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007 Feb 15;175(4):312-5.

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - GABAPENTIN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 8 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	32	30	-	MD 1.8 higher (3.04 higher to 0.56 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough frequency at 8 weeks of treatment (number of coughs/h)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	32	30	-	MD 27.31 lower (51.75 lower to 2.87 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough severity at 8 weeks of treatment; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
1 [1]	randomised trials	not serious	not serious [a]	not serious	serious [c]	none	32	30	-	MD 12.23 lower (23.23 lower to 1.23 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Capsaicin C5 at 8 weeks of treatment												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	serious [e]	none	32	30	-	MD 3.12 lower (19.84 lower to 13.6 higher)	⊕⊕◯◯ LOW	IMPORTANT
Any adverse reactions												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [f]	none	17/32 (53.1%)	6/30 (20.0%)	OR 4.53 (1.46 to 14.07)	331 more per 1,000 (from 67 more to 579 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Blurred vision												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	OR 2.90 (0.11 to 74.10)	-	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Depression												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/32 (0.0%)	1/30 (3.3%)	OR 0.30 (0.01 to 7.72)	23 fewer per 1,000 (from 33 fewer to 177 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Disorientation												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/32 (6.3%)	0/30 (0.0%)	OR 5.00 (0.23 to 108.53)	-	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Dizziness												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/32 (9.4%)	1/30 (3.3%)	OR 3.00 (0.29 to 30.56)	60 more per 1,000 (from 23 fewer to 480 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Dry mouth												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/32 (6.3%)	1/30 (3.3%)	OR 1.93 (0.17 to 22.50)	29 more per 1,000 (from 28 fewer to 404 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Fatigue												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/32 (9.4%)	1/30 (3.3%)	OR 3.00 (0.29 to 30.56)	60 more per 1,000 (from 23 fewer to 480 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Headache												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	OR 2.90 (0.11 to 74.10)	-	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Memory loss												
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/32 (3.1%)	0/30 (0.0%)	OR 2.90 (0.11 to 74.10)	-	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Nausea, stomach pain												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomised trials	not serious	not serious	not serious	very serious [f]	none	4/32 (12.5%)	2/30 (6.7%)	OR 2.00 (0.34 to 11.82)	58 more per 1,000 (from 43 fewer to 391 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. Single study

b. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

c. Low number of patients included. Lower 95%CI does not exclude a meaningless difference

d. Indirect (surrogate) measure of efficacy

e. Low number of patients included. Lower 95%CI includes both benefit or harm

f. Very low number of events.

References

1. Ryan NM1, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012 Nov 3;380(9853):1583-9.

Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics, and opiates) should be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile) - PREGABALIN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 14 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [c]	none	20	20	-	MD 3.5 higher (5.89 higher to 1.11 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough frequency at 14 weeks of treatment (number of coughs/h)												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [d]	none	20	20	-	MD 2.3 lower (13.58 lower to 8.98 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough severity at 14 weeks of treatment; assessed with VAS; Range 0 to 100 points; higher scores indicate better higher severity.												
1	randomised trials	not serious [a]	not serious [b]	not serious	serious [c]	none	20	20	-	MD 25.1 lower (39.6 lower to 10.6 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Capsaicin C5 at 14 weeks of treatment												
1	randomised trials	not serious [a]	not serious [b]	serious [e]	serious [d]	none	20	20	-	MD 47 lower (174.35 lower to 80.35 higher)	⊕⊕◯◯ LOW	IMPORTANT
Adverse event - Blurred vision												
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	4/20 (20.0%)	1/20 (5.0%)	OR 4.75 (0.48 to 46.91)	150 more per 1,000 (from 25 fewer to 662 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Cognitive changes												
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	6/20 (30.0%)	1/20 (5.0%)	OR 8.14 (0.88 to 75.48)	250 more per 1,000 (from 6 fewer to 749 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Dizziness												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious [b]	not serious	very serious [f]	none	9/20 (45.0%)	1/20 (5.0%)	OR 15.55 (1.73 to 139.65)	400 more per 1,000 (from 33 more to 830 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Dry mouth												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	OR 2.11 (0.18 to 25.35)	50 more per 1,000 (from 41 fewer to 522 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Fatigue												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	7/20 (35.0%)	6/20 (30.0%)	OR 1.26 (0.33 to 4.73)	51 more per 1,000 (from 176 fewer to 370 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Headache												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/20 (0.0%)	2/20 (10.0%)	OR 0.18 (0.01 to 4.01)	80 fewer per 1,000 (from 99 fewer to 208 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Weight gain												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	5/20 (25.0%)	1/20 (5.0%)	OR 6.33 (0.67 to 60.16)	200 more per 1,000 (from 16 fewer to 710 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Sleep disturbance												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	0/20 (0.0%)	2/20 (10.0%)	OR 0.18 (0.01 to 4.01)	80 fewer per 1,000 (from 99 fewer to 208 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Gastrointestinal												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	5/20 (25.0%)	7/20 (35.0%)	OR 0.62 (0.16 to 2.43)	100 fewer per 1,000 (from 217 more to 271 fewer)	⨁⨁◯◯ LOW	CRITICAL
Adverse event - Respiratory												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	3/20 (15.0%)	3/20 (15.0%)	OR 1.00 (0.18 to 5.67)	0 fewer per 1,000 (from 119 fewer to 350 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Dermatological												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	1/20 (5.0%)	2/20 (10.0%)	OR 0.47 (0.04 to 5.69)	50 fewer per 1,000 (from 96 fewer to 287 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Fluid build-up												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	OR 2.11 (0.18 to 25.35)	50 more per 1,000 (from 41 fewer to 522 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse event - Tight leg and muscle cramp												
1	randomised trials	not serious	not serious	not serious	very serious [f]	none	2/20 (10.0%)	1/20 (5.0%)	OR 2.11 (0.18 to 25.35)	50 more per 1,000 (from 41 fewer to 522 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

a. No comparison to pregabalin or placebo alone. Mean cough duration is longer in the placebo group (151 months) than in the pregabalin group (94 months). Mean baseline LCQ score is higher in the placebo group (12.3) than in the pregabalin group (10.8).
b. Single study
c. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference
d. Low number of patients included. Lower 95%CI includes both benefit or harm
e. Indirect (surrogate) measure of efficacy
f. Very low number of events

Refetrences

1. Vertigan AE, Kapela SL, Ryan NM, Birring SS, McElduff P, Gibson PG. Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough: A Randomiz ed Controlled Trial. Chest. 2016 Mar;149(3):639-48.

Question 7: Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

Summary of finding table including GRADE assessment (GRADE Evidence Profile)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	speech pathology interventions	placebo	Relative (95% CI)	Absolute (95% CI)		
Cough frequency at 4 weeks of treatment (number of coughs/h)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious [b]	none	31	40	-	MD 7 less (8.34 less to 5.66 less)	⊕⊕⊕◯ MODERATE	CRITICAL
Cough severity at 4 weeks of treatment (assessed with different scales) Rules of thumb exist for interpreting SMDs: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect												
2 [1,2]	randomised trials	serious [c]	not serious	not serious	not serious	none	74	84	-	SMD 0,61 less (1.02 less to 0.20 less)	⊕⊕⊕◯ MODERATE	IMPORTANT
Cough severity at 4 weeks of treatment												
2 [1,2]	randomised trials	serious [c]	not serious	not serious	not serious	none	Chamberlain (2017): Mean difference between groups at 4 weeks −9.72 (−20.80 to 1.36) P=0.084 (VAS severity). Vertigan (2006): Mean difference between groups at 4 weeks 8.5 (95% CI 4.7 to 14.9) P<0.001 (23-item symptom score).				⊕⊕⊕◯ MODERATE	CRITICAL
Capsaicin C2 at 4 weeks of treatment												
1 [1]	randomised trials	not serious	not serious [a]	serious [d]	not serious	none	31	40	-	MD 1.11 C2 higher (0.76 higher to 1.61 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of life specific questionnaires – LCQ (Leicester Cough Questionnaire). Follow-up: 4 weeks on treatment. Range 3 to 21 points; higher scores indicate better quality of life. MID is estimated to be 1.3 points												
1 [1]	randomised trials	serious [c]	not serious [a]	not serious	serious [e]	none	31	40	-	MD 1.53 LCQ points higher (0.21 higher to 2.85 higher)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	speech pathology interventions	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
1 [1]	randomised trials	not serious	not serious [a]	not serious	not serious	none	None observed				⊕⊕⊕⊕ HIGH	IMPORTANT
Incontinence – not measured												
											-	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Single study

b. Low number of patients included, most probably underpowered to detect differences.

c. Single blinded study (patients were not aware of the intervention assignment), bias cannot be excluded for subjective outcomes

d. Indirect (surrogate) measure of efficacy

e. Low number of patients included. 95%CI includes a clinically important / large benefit and meaningless difference

References:

1. Chamberlain Mitchell, S. A., et al. (2017). "Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomise d control trial." Thorax 72(2): 129-136.
2. Vertigan, A., et al. (2006) Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax 61, 1065-1069

Question 8: Should a trial of antibiotics be used in children with chronic wet cough with~~out warning signs,~~ normal chest x ray ~~and,~~ normal spirometry and no warning signs?

Certainty assessment							N of patients		Effect			Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With no treatment	With antibiotics	Relative (95% CI)	Absolute (95% CI)			
Cough resolution rate: >75% reduction in cough score after 14 days or cessation of coughing for >3 days within the trial (=treatment) period (assessed with VCD score)													
1 [1]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	4/25 (16.0%)	12/25 (48.0%)	RR 3.00 (1.12 to 8.05)	320 more per 1.000 (19 more to 1.000 more)		⨁⨁◯◯ LOW	CRITICAL
Change in cough score (VCD score) after 14 days (VCD cough score from 0 to 5: 0=no cough, 1=cough for one or two short periods only, 2=cough for more than two short periods, 3=frequent coughing but does not interfere with school and other activities, 4=frequent coughing which interferes with school and other activities, 5=cannot perform most activities due to severe coughing)													
1 [1]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	24[c]	23[c]	-	MD 0.96 lower[e] (1.88 lower to 0.04 lower)		⨁⨁◯◯ LOW	CRITICAL
Adverse event: mild diarrhoea													
1 [1]	randomized trials	not serious	not serious	serious[a]	very serious[f]	none	2/25 (8.0%)	5/25 (20.0%)	RR 2.50 (0.53 to 11.70)	120 more per 1.000 (38 fewer to 856 more)		⨁◯◯◯ VERY LOW	IMPORTANT
Adverse event: vomiting													
1 [1]	randomized trials	not serious	not serious	serious[a]	very serious[f]	none	0/25 (0.0%)	1/25 (4.0%)	RR 3.00 (0.13 to 70.30)	Study population 0 per 1.000	0 fewer per 1.000 (from 0 fewer to 0 fewer)[g]	⨁◯◯◯ VERY LOW	IMPORTANT
										Low risk population[h] 10 per 1.000	20 more per 1.000 (from 9 fewer to 693 more)		

CI: Confidence interval; **RR**: Risk Ratio; **MD**: mean difference; **VCD**: verbal category descriptive cough score.

Explanations

a. Children in both groups were very young (median 1.9 years), therefore, the study findings don't apply to the age group which should be addressed according to the ERS; additionally, chest x ray was abnormal in 15 out of 42 children; 8 children did not receive a chest x ray; an abnormal chest x ray also raises concerns about indirectness considering the PICO provided by the ERS; spirometry was not conducted (according to authors, measurement is not valid in children <6 years).

b. Low number of included patients and few events.

c. Outcome addresses change in cough score, which is not a binary outcome; therefore, no event rates can be provided.

d. Change in cough score: in the primary study data were expressed as median and interquartile range (IQR); we calculated the mean change and standard deviation according to the methods described in Wan 2014.[5]

e. Change is in favour of the antibiotic treatment.

f. 95% CI was consistent with the possibility for benefit and the possibility of harm; additionally, (very) few events in both groups and a low number of included patients.

g. Due to zero events in the control group, it was not possible to calculate the risk difference with antibiotics.

h. Assumed baseline risk for a low risk population.

References

1. Marchant J, Masters I, Champion A, Petsky H, Chang A. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 2012:689-93.

Cough assessment in adults

History taking and physical examination on presentation

- Cough duration
- Cough impact and triggers
- Family history
- Cough score (using VAS or verbal out of 10)
- HARQ
- Associated symptoms: throat, chest, GI
- Risk factors: ACE inhibitor, smoking, sleep apnoea
- Physical examination: throat, chest, ear

Routine evaluation

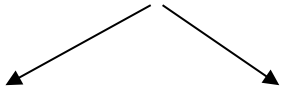
- Chest X-ray
- Pulmonary function test
- ?FeNO
- ?Blood count for eosinophils

Initial management

- Stop risk factors
- Initiate corticosteroids (oral or inhaled) or LTRA, particularly when FeNO or blood eosinophils high
- Initiate PPI only when peptic symptoms or evidence of acid reflux are present

Follow up assessment for cough

- Cough score (using VAS or 0 – 10)
- Associated symptoms



Improvement

- Continue for 3/12 and attempt withdrawal

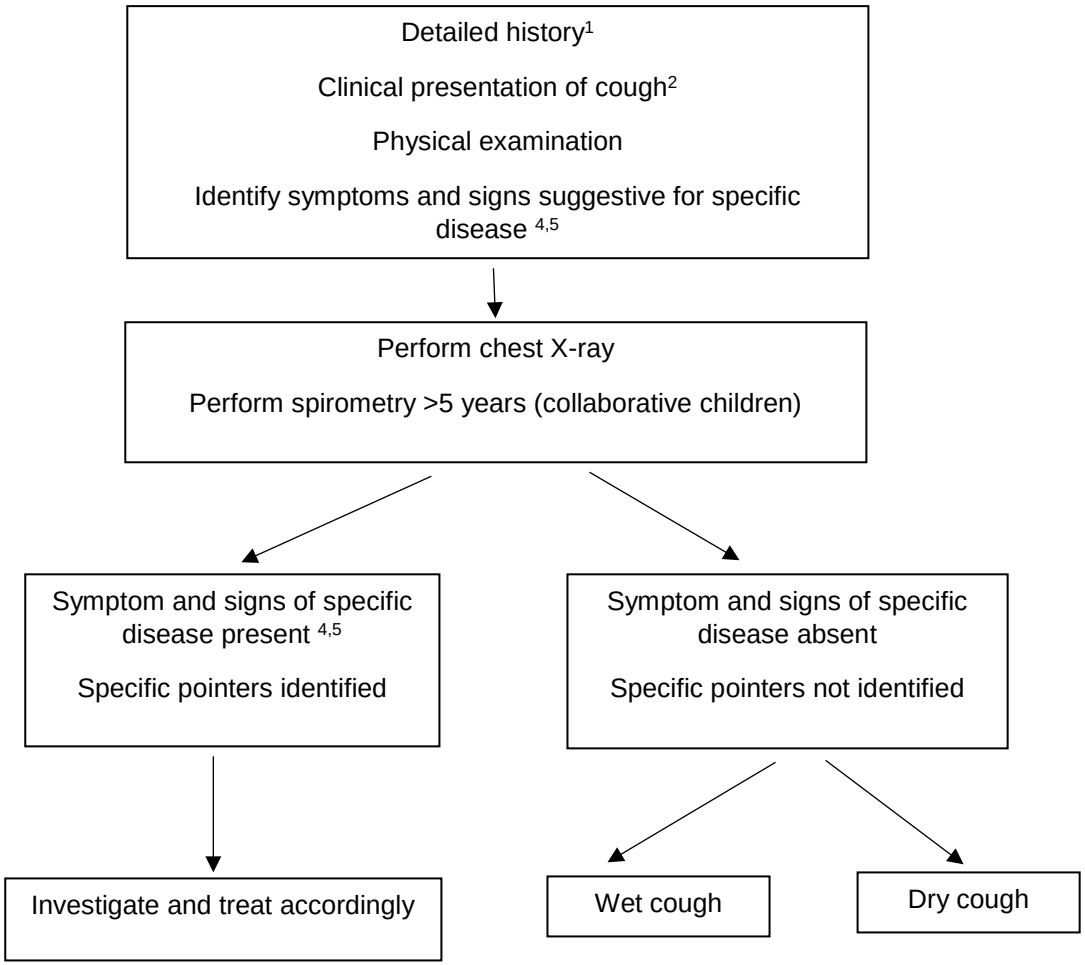
No improvement

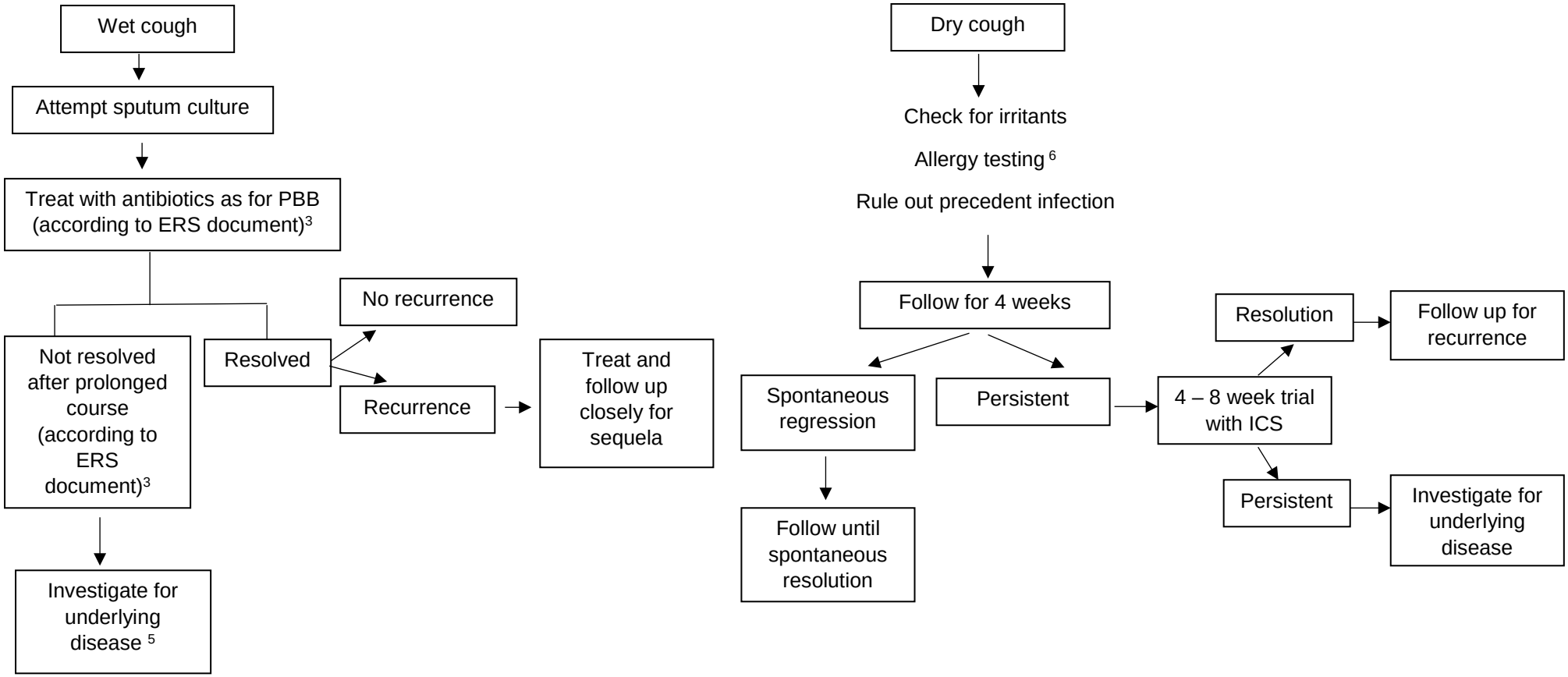
- consider low dose opiate
- consider promotility agent
- consider gabapentin
- consider pregabalin
- consider cough control therapy

Additional evaluation where indicated

- High resolution oesophageal manometry
- Induced sputum for eosinophils
- Sputum AAFB
- Laryngoscope
- Methacholine challenge
- Chest CT
- Bronchoscopy

Cough assessment flow chart in children




Wet cough
Attempt sputum culture
Treat with antibiotics as for PBB (according to ERS document)[3]
Not resolved after prolonged course (according to ERS document)[3]
Investigate for underlying disease [5]
Resolved
No recurrence
Recurrence
Treat and follow up closely for sequela
Dry cough
Check for irritants
Allergy testing [6]
Rule out precedent infection
Follow for 4 weeks
Spontaneous regression
Follow until spontaneous resolution
Persistent
4 – 8 week trial with ICS
Resolution
Follow up for recurrence
Persistent
Investigate for underlying disease

1. See - Reference 11
2. Clinical presentation of cough: How and when the cough started, time-course of cough, nature and quality of cough, symptoms associated with cough, triggers of cough, diurnal and nocturnal variations, cough associated with indoor and outdoor irritants.
3. See – Reference 69
4. Symptoms and signs of specific diseases: chest pain, history suggestive of inhaled foreign body, dyspnoea, exertional dyspnoea, haemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sinopulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis, signs of respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles, chest radiographic changes (other than perihilar changes).
5. Specific conditions and diseases: cystic fibrosis, primary ciliary dyskinesia, immune deficiency, tuberculosis, aspiration syndromes, tracheobronchomalacia, somatic and tic cough, bronchiectasis, children's interstitial lung disease**,** upper airway syndrome, asthma, ACE-inhibitor induced cough.
6. Testing for allergy not to be routinely performed, should be undertaken in presence of features and signs of allergy