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Acute Cough in the Elderly

Aetiology, Diagnosis and Therapy

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Abstract

Although the frequency of physician consultations and the sale of over-the--counter remedies establish the high prevalence of acute cough in the elderly, epidemiological studies have tended to be imprecise. However, respiratory tract infections in nose, larynx and/or bronchi, either viral or bacterial or both, are by far the commonest cause of acute cough. These are especially frequent and hazardous in the elderly, and community living and institutionalisation may aggravate this problem. A variety of viruses and bacteria have been incriminated, with rhinovirus, influenza and respiratory syncytial viruses, and *Streptococcus pneumoniae, Haemophilus influenza* and *Bordetella pertussis* being especially important. Viral infections can readily lead to community-acquired pneumonia. Successful diagnosis should point to successful treatment, and in this respect clinical examination and patient history are paramount, supplemented by chest X-ray, viral and bacterial culture and serological testing. Depending on the results of these tests, specific antibacterial therapy may be called for, although there is dispute as to the merits of antibacterial therapy in cases of uncertain diagnosis. Prevention and prophylaxis for influenza and *S. pneumoniae* infections are now commendably routine in the elderly, especially those in communities. Treatment, as well as the use of antibacterials, may also be directed against the inflammatory and infective processes in the airways. Non-specific antitussive therapy is common and usually highly desirable to prevent the adverse effects of repeated coughing. There have been few advances in antitussive therapy in recent years, opioids and dextromethorphan being the most commonly used agents; they act centrally on the brainstem, but also have a large placebo effect. However they work, they are much appreciated by patients and their partners. Moreover, striking advances in our understanding of the peripheral sensory and central nervous pathways of the cough reflex in recent years should soon lead to a new and more specific choice of agents to inhibit cough.

1. Introduction

In spite of the very high incidence of cough in the population, there is little information about its exact prevalence, epidemiology and relation to age, other than in paediatric conditions. In all countries where figures are available, it is the most common symptom for which medical advice is sought, excluding conditions related to poverty, war and starvation.[1-4] However, probably the majority of patients with cough, certainly with acute cough, go to a pharmacist rather than a physician and therefore escape epidemiological surveys. This is partly because acute cough is, by definition, self-limiting and most patients know they will get better without medical advice. Even with chronic cough, the majority of patients probably do not go to either a pharmacist or physician; this is because the most common causes of chronic cough (cigarette smoking and atmospheric pollution) are not regarded as 'diseases' until conditions such as chronic obstructive pulmonary disease (COPD), chronic bronchitis or cancer develop. The extensive research on the pathological results of cigarette smoking and pollution has been largely limited to studies involving serious chronic pulmonary disease, ignoring the earlier years of repetitive coughing.

The size of the problem is reflected by the expenditure on OTC remedies for 'coughs-and-colds' (of course the two are not the same, but over 90% of colds induce coughing). In 1999 over $US2 billion

was spent in the US and over £300 million in the UK on OTC cough/cold medicines.[1,2] It is impossible to further analyse these figures, in terms of population subgroups or individual medications, because such data are not available.

In 1997 in the US, of the 30 million medical consultations for cough, a third were attributed to acute tracheobronchitis.[5-7] In 1972 in the UK, the presenting complaint in over half of the medical consultations was cough.[3,8] In 1991–92 in the UK, there was an average of two consultations every year per patient for acute respiratory tract infection in adults attending general practices.[3,8] Later data generally support these very high incidences. Most surveys have not analysed the data into young adult and elderly subgroups, but for influenza and pneumonia there were 20 000 deaths per year in the US, and 90% of them were 65 years of age or older.[9]

In discussing acute cough in the elderly, there are three general considerations.

1.1 Acute and Chronic Cough

Since this review deals with acute cough it must be defined and here there is no uniform agreement. Some authorities refer rather imprecisely to 'acute, self-limiting episodes' in contrast with 'chronic persistent cough'. Three weeks is often taken as the limit of the acute phase and 8 weeks is usually accepted as the time when acute cough becomes chronic. From 3 to 8 weeks is sometimes referred to as 'subacute'. A recent study showed that with an 'acute' upper respiratory tract infection (URTI) [infecting agent not defined], cough could last from 1 to 10 weeks.[10] The distinction may not be important provided the limit is defined.

Some conditions are clearly chronic and will not be discussed further in this review. They include: cough due to COPD/chronic bronchitis, bronchopulmonary cancer, cystic fibrosis (CF), bronchiectasis, ACE-inhibition, gastro-oesophageal reflux, asthma and habit-cough.[1,2] COPD, asthma and CF may include acute episodes of cough, e.g. acute bronchitic exacerbation of COPD, but the underlying cause of the cough is chronic.[5,11,12] Other conditions that may be either acute or chronic include cough because of post-nasal drip (PND),[13] which may be related to acute or chronic rhinosinusitis, or to URTI, where cough can continue for many weeks or even months after symptomatic resolution of the primary inflammatory condition.[1,2] Most acute coughs are owing to URTI, with or without acute bronchitis; acute bronchitis may occur without URTI.[5] As indicated earlier in this section, all these conditions may lead to chronic cough.

1.2 'Wet' and 'Dry' Cough

The terms 'wet' and 'dry' cough are frequently used. They have some limited diagnostic value. Dry cough may point to acute laryngitis and URTI, but it can also occur in the chronic coughs of gastro-oesophageal reflux, ACE-inhibition and asthma. Wet cough usually applies to acute or, especially, chronic bronchitis, and conditions such as CF and bronchiectasis. At first sight wet cough should be definitive of bronchopulmonary diseases with excessive production of mucus which reaches the larynx and causes cough and expectoration. However, wet cough also occurs in PND where the secretions arise in the upper airways.

It is important to note that the terms are mostly qualitative and depend solely on the subjective impression of the patient. Copious amounts of mucus can be collected in a sputum pot, but this is an inaccurate method that adds little in terms of diagnostic value for borderline conditions. However, it is important to assess 'wetness' and 'dryness', because this classification may eliminate some diagnoses and point to others, and therefore suggest certain therapeutic antitussive approaches.

1.3 Age and Cough

There have been extensive studies of acute cough in children, for example in relation to infections with *Bordetella pertussis* (when cough may be subacute or chronic, depending on definition), and in infants with bronchiolitis and infections with respiratory

syncytial virus (RSV). But in general, studies on adults have not been separated into young, middle aged and elderly. Yet we know that the spectrum of cough-inducing pathology changes with age in adults, as do the quantitative physiological mechanisms of the upper airways, including cough. Thus, elderly patients seem to have a weaker cough response to distilled water aerosol than younger patients.[14] It must also be remembered that women have a higher sensitivity to cough-inducing aerosols than men,[15,16] although it has not been shown if this difference changes with age. This gender-related effect may be relevant in the elderly, as there is a preponderance of female patients attending specialist cough clinics,[16] as there is in community practice.[1]

2. Epidemiology

Acute cough is nearly always due to respiratory tract infection (RTI), viral infections being the most common cause,[17-19] and typically the cough is nonproductive ('dry').[20] With or without cough, viruses account for over 90% of acute respiratory illnesses.[21-24] Bacterial infections, whether superimposed on a viral infection or not, and including conditions such as community-acquired pneumonia (CAP), are less common. Table I lists the main viral and bacterial causes of acute RTI.

Selective populations have been used to study the epidemiology of acute cough; in the case of the elderly they are often institutionalised or in home care facilities, while most children and young adults attend respiratory or general medical clinical units. It is difficult to ascertain the exact prevalence of acute cough in the general population, as there are many patients who do not seek professional medical advice, but consult a pharmacist instead. Therefore, these selective biases may overestimate the incidence of more serious causes of cough, such as acute PND and bronchitis, as patients with these conditions are more likely to go to units that publish papers on aetiology.

Table I. Viral and bacterial causes of acute respiratory tract infection

Virus	Bacteria
Rhinovirus	*Mycoplasma pneumoniae*
Influenza virus A	*Chlamydia pneumoniae*
Influenza virus B	*Bordetella pertussis*
Parainfluenza virus	*Haemophilus influenzae*
Respiratory syncytial virus	*Streptococcus pneumoniae*
Adenovirus	*Staphylococcus aureus*
Coronavirus	*Legionella pneumoniae*
Coxsackie virus A21	*Pseudomonas aeruginosa*

2.1 Acute Rhinitis and Rhinosinusitis

Cough can only be induced by inflammation or irritation of the larynx, trachea and bronchi.[25,26] Therefore, infections of the nose and pharynx cannot *per se* cause cough, which will only arise if the infection extends into the larynx and lower respiratory tract, or if nasopharyngeal secretions flow to the larynx and either stimulate it mechanically or chemically. PND is considered an important aetiological factor in chronic cough[1,13] and presumably is the cause of cough in acute rhinitis and rhinosinusitis.

The viruses that commonly infect the nose and upper respiratory tract (rhinovirus, adenovirus and coronavirus) may also spread to the lower airways.[19,24,27-29] Even rhinovirus, which may preferentially infect the nose, since it grows most readily in cultures at 33°C, can be found in bronchial biopsies from infected patients.[30] Since there are over 100 serotypes of rhinovirus, it is not surprising that it is not only the most common cause of acute rhinitis, but is also a major contributor to lower respiratory tract infection (LRTI) in the community, especially in elderly patients.[19,27-29]

In a prospective study of 533 patients aged 60–90 years with RTIs, LRTIs were defined by the presence of cough, wheezing and/or chest pain, and URTIs by their absence; 65% of patients had LRT symptoms and 98% URT symptoms. Thus, 66% of patients with 'rhinitis' also had LRTI including the symptoms of cough.[20] A pathogen was identified in 42% of patients; the commonest pathogens were rhinovirus (52%), coronavirus (26%) and influenza

virus (10%). A similar study with elderly patients (mean age 79 years) showed the importance of influenza A, coronavirus and RSV in RTI, and showed that the older group had significantly more LRT symptoms, including cough, than the younger (mean age 36 years) group.[29] Other studies support the importance of viruses associated with the common cold, rhinovirus and coronavirus, with LRTI and cough in the elderly.[27-29]

With regard to bacterial infections, 70% are due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, although *Moraxella catarrhalis* may also be found.[13]

2.2 Acute Laryngitis

Cough originates from an irritated or inflamed larynx. Theoretically, it seems unlikely that the descent of mucus into the pharynx would provide an adequate mechanical stimulus for cough, since the mucus would preferentially be swallowed, while mucus ascending up the trachea may contact the vocal folds and provide the stimulus to cough. However, this is conjectural due to the lack of research and insight on mucus flow as a stimulus to cough. What is certain is that URTI frequently, if not usually, leads to cough or expiratory efforts. If the cough is dry, i.e. no mucus is present, the 'urge to cough' may be related to the irritation of the laryngeal sensory receptors.

As noted in section 2.1, some authors would diagnose LRTI by the presence of cough. This may be dependent on whether the larynx is defined as part of the URT or of the LRT, but this distinction is also important in terms of mechanisms. Acute laryngitis can occur in the absence of tracheobronchial symptoms (wheeze, chest pain and mucus production). In the absence of laryngoscopy, acute laryngitis can be identified by the sensations of irritation, soreness and even pain in the laryngeal region.

2.3 Acute Viral Bronchitis (Viral Tracheobronchitis)

The viruses that usually cause acute rhinitis (rhinovirus, adenovirus and coronavirus) presumably always reach the LRT, but in many instances do not cause bronchitis. Moreover, rhinovirus can be detected in bronchial biopsies of patients with URTI,[30] and because of the high frequency of respiratory infections due to rhinovirus compared with other viruses, it probably contributes frequently to LRTI, especially in the elderly.[31,32] Furthermore, rhinovirus infection is the most common cause of acute exacerbation of asthma,[33] and a major cause of acute exacerbation in COPD and CF.[11,34-37] Infections with the other respiratory viruses, influenza A and B, parainfluenza and RSV, probably always involve the LRT and quite often the nose. The incidence of LRT viral infections was RSV > influenza A > coronavirus in one study,[27] rhinovirus > coronavirus > influenza in another,[20] and coronavirus > rhinovirus in a third.[29] In a group of elderly patients, RSV was isolated more frequently than rhinovirus;[32] these two topped the list of 41 types of virus isolated. In a group of 168 elderly patients hospitalised with acute respiratory disease, 18% had infection with influenza A virus.[38,39] While the selection criteria of the groups may differ, and not provide the best representation of the general population, the viruses listed earlier in this section are most likely responsible for most cases of acute bronchitis in the elderly, as well as in adults generally.

2.4 Bacterial Pneumonia

About 5–10% of adult patients with acute tracheobronchitis develop pneumonia with a bacterial infection deep in the lungs.[18] The most common agents in elderly patients are *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *B. pertussis*,[18,19] although *H. influenzae, M. catarrhalis* and *Staphylococcus aureus* have also been detected.[27] One study showed that in elderly patients with acute bronchitis, *S. pneumoniae* and *H. influenzae* were

the most frequent bacterial pathogens.[40] Some serological studies are consistent with these findings.[41] *B. pertussis* is being increasingly identified in patients with acute bronchitis, probably due to the now common use of the polymerase chain reaction.[42-44] This infection becomes more prevalent with increasing age, possibly because immunity may wane in previously vaccinated individuals, and thus the infection and cough may be more common in elderly patients.[45,46] Since bacterial infections may prolong the course of a viral tracheobronchitis, cough may last longer.

Patients with CAP usually present with symptoms (including cough) of acute bronchitis. Four million patients in the US develop CAP each year, with 50% of them being >65 years old.[47] There are 70 000 deaths per year in the US from CAP, with 90% of them being in the elderly group.[47,48] The most frequent agent detected is *S. pneumoniae*, followed by *H. influenza, Staphylococcus aureus, C. pneumoniae, M. pneumoniae, Legionella pneumoniae* and respiratory viruses.[49,50] The incidence of CAP increases in elderly patients and the bacterial spectrum may change from that in younger adults.

The possible existence of comorbidities is important, especially in the elderly.[47] This consideration applies to many neurological disorders, such as Parkinson's disease and cerebrovascular diseases such as stroke. Here, not only may the disease depress the cough mechanism, but aspiration may also lead to pneumonia superimposed on a defective cough reflex. Other conditions are alcoholism and mental deterioration, where cough may be weak and the chances of contracting bacterial pneumonia are enhanced.

In summary, epidemiological studies on acute cough and its underlying causes have identified many viral and bacterial pathogens. While the detailed patterns of effective causes vary, presumably because of different population groups and methods of study, the general pattern is clear; an identified range of pathogens can lead to the respiratory conditions associated with acute cough. Diagnosis and therapy will depend, among other factors, on the identification of these pathogens.

3. Diagnosis and Management of Patients with Acute Cough

In the great majority of patients, diagnosis of the cause of cough is by patient history and physical examination. In a small minority of patients, more sophisticated tests are necessary and this may be especially true in the elderly where symptoms may be more detrimental, or may be masked by aging processes. Signs and symptoms may be restricted to one or two parts of the respiratory tract, the nose, larynx and lungs, even though the infection probably affects all parts of the respiratory system. Diagnosis of the cause of the acute cough is important not only for the patient's treatment, but also to limit the spread of infection.

Whereas most cases of acute cough start with a viral infection, the development of bacterial infection is a potentially more hazardous state which may require specific therapy. Hospitalisation and ventilatory support may be urgently required, with or without chemotherapy.[47,49]

It should be noted that repeated and vigourous coughing may in itself have adverse effects on the elderly patient. These effects include incontinence (especially in females), rib fractures and vagally mediated cardiac instabilities.

3.1 Viral Infections

The diagnosis of viral influenza is important to distinguish it from the common cold, and to anticipate the possible development of bacterial pneumonia, leading to appropriate anti-infective treatment.[50]

With influenza, there is sudden onset of malaise and fever, followed by cough, headache, myalgia and nasal and chest symptoms. Cough is the commonest symptom, present in 95% of patients.[51] In the elderly, the signs and symptoms of influenza may be atypical and consist of low-grade fever,

lassitude, confusion and nasal obstruction; tachypnoea may be prominent especially if pneumonia develops.[18,48,49] The risk factors for developing complications include age >50 years, residence in a nursing home or chronic care facility, and various chronic diseases, including pulmonary diseases, that are frequent in the elderly.[50]

Initially influenza may be difficult to distinguish from the common cold, but the dominance of constitutional symptoms and the course of development rapidly make the distinction clear.[52] The Center for Disease Control and Prevention in the US has defined clinical criteria for influenza infection as having a fever of at least 100°F orally and at least one of the following: cough, sore throat or rhinorrhoea (the first criterion, fever, may not be applicable to the elderly).[53] Influenza can be diagnosed by viral culture from respiratory secretions obtained by pharyngeal swab, sputum or nasopharyngeal aspiration, although the older methods of culture may be too slow in relation to the time-course of the disease. More rapid diagnostic tests are available[48] and some can distinguish between influenza types A and B.

RSV infection is more serious in the elderly[38,54] and in some studies it has been found to be more prevalent than influenza infection.[27,32] Diagnostic tests, such as antigen detection and culture, tend to be slow and rather insensitive.[38,55] Clinical examination in the elderly may suggest RSV rather than influenza infection: fever is low grade, there may be more prominent nasal congestion and secretions in combination with wheezing and clinical deterioration.[55]

3.2 Nasal Infections

Here the diagnosis is clear from the patient history, symptoms and clinical examination, and the main question is whether a superimposed bacterial infection requires specific treatment. Simple radiographs may be unhelpful, since abnormalities in the sinuses may not be detectable.[13] Computerised axial tomography scans, when practical, allow for a more accurate delineation of sinus involvement.[13,56] Bacteriological and serological tests may identify the infective agent and suggest appropriate chemotherapy.

3.3 Acute Bronchitis

The distinction between viral and bacterial infection in bronchitis may be difficult by clinical examination alone, yet the identification of bacterial pneumonia, if present, is crucial in terms of treatment[5] (see section 3.4). A review concluded that chest x-ray (CXR) was no more helpful than clinical examination of the chest and patient history;[57] however, this may not apply to the elderly who may have chest infections but present with mainly non-respiratory symptoms, such as confusion or frequent falls.[58] CXR is strongly recommended if pneumonia is suspected,[5,18,47] although in a minority of patients the CXR signs are marginal and may not clearly distinguish between viral and bacterial pneumonias. As with nasal investigations, the use of sputum Gram stains and culture are not very precise, and their value is disputed.[59-62] Moreover, satisfactory samples are sometimes difficult to obtain in the elderly and, in one study, in only 42% of patients could an aetiological agent be identified.[63] Serological tests, particularly for influenza and *B. pertussis*, may be more informative[5,58-60] and help in choosing the appropriate therapy.

3.4 Bacterial Pneumonia

Bacterial infections account for the majority of cases of pneumonia.[18,47] The classical signs of pneumonia may be insignificant or absent in the elderly: only 40% may have fever,[47,64] and other symptoms may be insignificant due to mental confusion. Physical findings, such as lobar consolidation, may also be absent.[65] On the other hand, tachypnoea may be conspicuous.[66] With viral pneumonia, the typical symptoms of influenza deteriorate with the development of more severe cough and fever, and the appearance of dyspnoea and cyanosis; the CXR may show bilateral signs, but without

consolidation. The development of bacterial pneumonia may be signalled by a recurrence and exacerbation of symptoms, their prolongation beyond 7–10 days, and the appearance of areas of consolidation on the CXR. Based on a large study, patients with CAP were classified into five grades to predict the likelihood of survival. Patients with the lowest scores had a mortality rate of less then 1%, whereas those with the highest scores had a rate of 8–31%.[67] This approach could be an adjunct to assessment of the need for ventilatory support.

4. Specific Treatment of Cough-Causing Conditions

Because approved names for drugs, and also their availability, vary widely between countries and those of OTC remedies even more, drugs will only be referred to generically in this section and very selectively in section 5.

4.1 Prevention and Prophylaxis

Annual immunisation against influenza is standard practice for patients over the age of 60 or 65 years; inactivated viruses are used because of the increased risk in the elderly of incapacitation and further complications, including infection.[53,68] Vaccinations are administered in October or November, in anticipation of an increased risk of infection in January to March, in the northern hemisphere. The subtypes of virus anticipated vary from year to year, as therefore do the vaccines. Strains of both influenza A and B are targeted. The safety of the vaccine is established in asthmatics,[69] however, its efficacy is limited. In the old and the incapacitated, about 50% of those vaccinated still develop influenza as the immune response may be inadequate.[51-53,70] However, the morbidity and mortality of those contracting the disease are considerably reduced.[71] One study showed that mortality was reduced by 80% and hospitalisation and pneumonia by over 50%.[54] Nasal vaccines are effective especially in children.[72] Furthermore, population spread is reduced by 80%, a feature especially important in communities of the elderly.[52]

Chemoprophylaxis with antiviral agents is about 80% effective in preventing influenza infection; they are effective against influenza A and, perhaps to a lesser extent, influenza B.[48,70,73] Sialidase inhibitors may be 70–90% effective in preventing influenza,[48,74] including the elderly.[48]

In the case of pneumonia, especially CAP, vaccination against *S. pneumoniae* is recommended for patients aged ≥65 years.[47,75-77] Although it is often given only once in a lifetime, it probably does not provide immunity for all the known varieties of the organism, and there may be a case for revaccination.[75-77] As implied above, it is particularly valuable in communities of the elderly.

4.2 Antiviral Agents

As indicated in section 4.1, antiviral agents are only effective against influenza A and B viruses, and when given within 48 hours of the onset of illness, reduce the severity and duration of the disease. Because of renal impairment in the elderly, the drug dosage may have to be limited since the agents and their metabolites are excreted in the kidneys.[70,74]

Sialidase inhibitors given within 48 hours of the first symptoms are also effective in reducing the duration and severity of symptoms.[47,48,70,78,79]

4.3 Antibacterials

There has been considerable controversy with regards to the use or overuse of antibacterials in respiratory infections. It is generally agreed that, if a bacterial infection is unlikely, antibacterial therapy is not required and should not be used, but if a bacterial infection is established antibacterial therapy remains valuable.[18,49,50] There is a notable area of uncertainty, at least in the elderly, with regard to the presence or absence of bacterial infection, and generally it may be wise to err on the side of caution and to use antibacterials. The degree of morbidity may be the decisive factor. In practice, antibacterials are usually given in the US if there is purulent nasal

discharge, green phlegm, use of tobacco or tonsillar exudates.[80] Whether or not a bacterial infection had been established, the use of antibacterials led to a small improvement in cough and sputum production, and better general improvement at follow-up.[81,82] The duration of the illness does not seem to be affected.[83-85] Another extensive study showed no such improvement.[85] Guidelines for the determination of treatment with antibacterials have been published.[86,87]

If bacterial infection is definitely established, the use of antibacterials is highly desirable, especially in the elderly,[88-90] as recommended by the American Thoracic Society for CAP.[90] A large number of studies support this view.[18,91,92]

Antibacterials are recommended for rhinosinusitis with bacterial infection of the upper respiratory tract.[13,57,93,94] The most frequent bacterial invaders that require appropriate antibacterial therapy are *S. pneumoniae* and *H. influenza*.[13]

4.4 Other Treatments

Bronchodilators, such as β-adrenoceptor agonists, shorten the duration of cough in patients with bronchial hyperresponsiveness or wheezing, but are not effective in the absence of airflow limitation.[5,95] Corticosteroids have been tested to shorten the duration of cough, but apparently without effect.[5] Protussive therapies, such as humidified air and drugs such as guaifenesin, are widely included in OTC remedies; there is little evidence that they are effective against cough.[96]

Other agents used to treat cough because of nasal infections include antihistamines, oral or topical vasoconstrictors, atropinic agents and corticosteroids.[13,93,94] The first-generation antihistamines may have a stronger antitussive action than the second-generation drugs, since they have central nervous sedative effects that could depress cough. In general, if any of these agents inhibit the nasal pathology that is producing cough, one would expect them also to inhibit cough.

5. Symptomatic (Non-Specific) Treatment of Acute Cough

In general, physicians are hesitant to treat cough in acute respiratory conditions. This is partly because the cough normally lasts a few days, is probably at its peak when consultation takes place and is believed to improve, especially if there is effective specific treatment. There may also be some doubt surrounding the effectiveness of antitussive agents administered at usual dosages and fears about their adverse effects. This is especially relevant in elderly patients. Most studies on antitussive drugs have been on children or non-elderly adults, but there is no reason to believe that the results in general do not also apply to the elderly.

Obviously, specific treatment is better because it aims to cure the condition, hence alleviate the symptoms. Symptomatic treatment may be required, in addition or in place of specific treatment, if the cough is sufficiently severe or if the cough is idiopathic.

The main indications for antitussive therapy are if the cough prevents sleep or if the inflammation causing cough (or the cough itself) is painful, as in acute laryngitis or in the chest pain of acute bronchitis. These are the reasons most patients consult their physician or go to the pharmacy for a cough/cold remedy. An additional reason is social, for example, if the cough annoys or distresses members of the family at home, or fellow workers.

Cough in itself is seldom harmful, unless it is prolonged and excessive, as with whooping cough in the young, or it is debilitating because of the poor general condition of the patient. The latter applies in the elderly; it is in these patients that the adverse effects of the antitussive agents may cause most harm. The main adverse effects of antitussive agents are mental confusion, nausea and constipation, especially for the opioids, and effects that are especially undesirable in the elderly. Respiratory depression is also claimed to be an adverse effect of the opioids, although there seems to be little evidence to support this view in humans; this may have arisen from the

sedation, drowsiness and ease of sleep in patients. In animals, very large doses of opioids are needed to cause respiratory depression.[97]

It is believed that antitussive medication should not be used if the cough is 'wet', because this will lead to the accumulation of mucus in the chest. This is an axiom taught to all medical students. There is little evidence to support it. Cough, airway mucociliary transport and possibly mucus secretion are depressed during sleep without adverse effect.[98] If a patient with a 'wet' cough sleeps through the night there is usually no adverse effect when they wake, although more mucus may be coughed up, as in smokers. Patients with cough, including the elderly, spend a fortune at the pharmacy for OTC antitussives, probably without paying any attention to the wet or dry nature of their cough.

A final consideration, that will be developed further, is with regard to the dosage of antitussive drugs. The doses of antitussive agents, either prescribed or bought OTC, are so low that their effectiveness is little better than placebo;[98-100] yet patients and their partners believe that they work, based mainly on relief of unpleasant soreness and the enhancement of sleep.

The list of available antitussive drugs, both prescribed and OTC, acting either centrally or peripherally, has changed little over the last decade or two. However, over the last few years there has been an explosion of research into the peripheral (sensory) and central nervous mechanisms of antitussive drugs, which should have a profound influence on the pharmacotherapy of cough. The pharmaceutical industry is investing heavily in antitussive research, which is not surprising in view of the potential market.

Most clinical tests with antitussives have been with animal models, on patients with chronic cough or on healthy patients with cough induced by tussigenic aerosols. While qualitative application of these results to patients with acute cough is largely accepted, more direct studies would be preferable. One might expect an aerosol-induced cough to mimic acute cough accurately in relation to therapy, but the former is conducted under closely defined laboratory conditions, while the latter is notoriously variable between patients and during the course of illness. In addition, there is growing evidence that the cough reflex is quantitatively different in health compared to airways' disease.[101,102] There have been few studies in the elderly.

While it is convenient and conventional to divide antitussive agents into centrally- and peripherally-acting, many drugs, including those in current use, can be shown to act at both sites, at least in animal models. This is not surprising since the nerve fibres responsible for cough stretch from the airway wall to the 'cough centre' in the brainstem, and they contain the same mediators and pharmacological membrane receptors along its entire course. The antitussive agents ability to cross the blood-brain barrier remains unclear. Most of the studies on localisation of the actions of antitussive drugs have been done on experimental animals and its application to humans is questionable.

The names of the antitussive agents available on prescription and those sold OTC, vary greatly from country-to-country, and the following account cannot make allowance for this.

5.1 Centrally-Acting Antitussive Agents

The central nervous generation of cough takes place in the medulla of the brainstem, in what used to be called the 'cough centre'. Detailed neuronal circuitry of this complex has been elucidated recently.[103,104] Two aspects are important in relation to cough therapy. Some agents that are powerful cough suppressants, such as dextromethorphan, do not influence breathing and therefore may not act as respiratory depressants in effective antitussive doses. Secondly, central nervous pathways for cough from the larynx have distinct brainstem neuronal connections from those innervating the tracheobronchial tree.[105] This opens up the prospect of drugs being developed with specific actions on different types of acute cough.

5.1.1 Opioid Antitussive Agents

Codeine and pholcodine are among the most popular prescribed and OTC antitussive drugs, at least in the UK, surpassed only by dextromethorphan. Both (especially codeine) have potential adverse effects, including addiction. Opioid analgesics, such as hydrocodone, hydromorphone, dihydrocodeine, methadone and even morphine, have been used as antitussives, but are usually restricted to the severely distressed and terminally ill patient.

The central action of opioid antitussive drugs has been extensively studied in experimental animals. At least four different types and subtypes of opioid receptor have been distinguished in the neuronal circuitry for cough[106,107] and the detailed pattern of action of several opioids has been studied.

Although the effectiveness of codeine in the treatment of chronic cough, and its suppression of aerosol-induced cough, have been shown to be statistically significant,[108-110] one study of patients with acute cough showed that it was no more effective than placebo[96]

5.1.2 Dextromethorphan

This is a non-narcotic opioid derivative that lacks many of the adverse effects of opioids, such as constipation, nausea, sedation and addiction; however, it may cause some confusion. It is effective against chronic and acute cough,[108,109,111] and in aerosol-induced cough under experimental conditions. It is believed to act on NMDA receptors, rather than opioid receptors in the brainstem, which may explain its failure to depress respiration.[107]

5.1.3 Baclofen

Although most often used to treat spasticity rather than cough, baclofen also has antitussive properties.[112-115] In this respect it works by activating γ-aminobutyric acid receptors in the brainstem that facilitate cough. It is effective against aerosol-induced cough under experimental conditions and experimental animals, and against idiopathic and ACE inhibitor-induced cough in patients, although there are few clinical trials.[114,115]

Other potential centrally-acting antitussive agents include antagonists to serotonin, substance P (neurokinin), opioid receptor-like (ORL1) receptors, glycine and glutamate. The involvement of these receptors in cough and the effectiveness of appropriate antitussive drugs against them, have been studied extensively in experimental animals.[105,106,116]

5.2 Peripherally-Acting Antitussive Agents

Although some of these drugs have been in use for a long time and are the constituents of many OTC preparations, they are seldom prescribed. Theoretically, they should act locally in the airways and therefore lack the adverse effects of centrally-acting antitussive drugs.

Nearly all forms of cough are due to the excitation of sensory receptors in the walls of airways by inhaled irritants or by inflammatory mediators released due to local tissue damage within the airways.[116,117] When stimulated they cause cough, among other reflexes, and also lead to the release of mediators, such as tachykinins, which further induce inflammatory changes in the airways. In airways' disease (including infections) these receptors are sensitised, so that cough and local effects are enhanced.[101,102,118,119] There has been extensive study of these sensory cough receptors, especially in recent years; unfortunately this research has been almost entirely on animal models, but its results are beginning to influence antitussive treatments in humans.[117-120]

5.2.1 Local Anaesthetics

Local anaesthetics include lidocaine (lignocaine),[121,122] bupivacaine,[123] benzonatate,[124] ambroxol[125] and mexiletine.[126] Given locally, either as aerosol or lozenge, they anaesthetise the sensory cough receptors in the airway mucosa; they may therefore be effective for acute cough owing to PND or laryngitis. They should also relieve any pain and soreness. Given orally, they probably act both peripherally and centrally. Benzonatate is the only oral local anaesthetic commonly used, especially in OTC preparations. For acute bronchitis, the use of aer-

osolised local anaesthetics may be risky in view of the possibility of inducing bronchoconstriction.

While there have been few studies on the antitussive actions of local anaesthetics in natural or induced cough, they do support its effectiveness.[119,120,123]

5.2.2 Other Peripherally-Acting Antitussive Drugs

These include levodropropizine,[127,128] levoclopererastine,[129] cloperastine[130] and moguisteine.[131-133] These are non-narcotic, non-opioids that act peripherally and can inhibit induced and natural cough. In most trials with cough in patients they were as effective as dextromethorphan or codeine, and better than placebo.

5.2.3 Future Peripherally-Acting Antitussive Agents

Extensive work with experimental animals, has identified several different types of cough sensory receptors in the airway mucosa, and analysed their membrane properties.[101,117,118,134] This research has led to development of a number of novel drugs which are active in suppressing induced cough in experimental animals, but which have not been adequately assessed in human patients as yet. Their action involves neurokinin, opioid, nociceptin/orphanin, vanilloid, Na^+-channel, dopamine and purine pharmacological receptors on the sensory neurone membranes. Some of the drugs may also act on the central nervous system.

5.3 Placebo Effects

A placebo response to antitussive drugs for acute and chronic cough is well established.[99] Indeed, some well-conducted studies show that the recommended doses of agents, including those found in many OTC therapies such as codeine and dextromethorphan, are statistically insignificant or no more effective than placebos.[99,100] This has led to the recommendation that use of these treatments should not be encouraged,[96] although this conclusion has been disputed.[135]

However, nearly all these studies have been with rather small cohorts of patients, with a high variance of mean results, which makes statistical significance less likely. This is not surprising as acute cough is very variable between patients and with time; differences in bodyweight (for a standard dose of drug) will cause more variation; and gender difference in cough sensitivity has seldom been allowed for.[15,16] Similar studies with induced cough in healthy participants, with the same doses of antitussive agent have shown that the drugs are statistically more effective than placebo; in these laboratory studies variance of results would be far smaller. A meta-analysis of 710 patients with acute cough because of URTI showed that the standard dose of dextromethorphan was statistically 17% more effective than placebo.[111]

Even if cough suppressants act mainly by a placebo effect, this is a poor reason not to use them. Patients believe they work, judged by their enormous popularity and by their facilitation of sleep. And if their effectiveness is small and close to that of a placebo, this lessens the likelihood of adverse effects including addiction.

6. Conclusion

Acute cough can be caused by viral or bacterial (or both) infections of any part of the respiratory tract. Its diagnosis is usually based on patient history and clinical examination. The causative agent may be one or more of a number of viruses and bacteria, the identification of which is seldom essential. If bacterial infection is established, antibacterial therapy may be called for, especially in the elderly. Viral or bacterial vaccination is highly desirable. Symptomatic therapy for the cough may be required and recent advances in our understanding of the physiology and pharmacology of cough mechanisms make it likely that a variety of novel antitussive drugs will be available in the future.

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