The evidence for the use of oral mucolytic agents in chronic obstructive pulmonary disease (COPD)

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Introduction: Oral mucolytics are now recommended in some treatment guidelines for the management of chronic obstructive pulmonary disease (COPD). This article reviews the evidence for their use and their possible benefits.

Sources of data: The review is based upon peer reviewed publications relating to the use of mucolytics in COPD cited in PubMed.

Areas of agreement: Much of the published evidence is of somewhat poor quality and many studies include patients with both chronic bronchitis and COPD. Mucolytics reduce exacerbations by up to 0.8 exacerbations per year, but have little additional benefit in those on standard maximum therapy.

Areas of controversy: Data that mucolytics improve symptoms, alter mucus or impact health-related quality of life in COPD patients receiving other standard therapy are unconvincing. In those on little or no other treatment, they may reduce exacerbation rate.

Growing points: The use of mucolytics to treat acute exacerbations is promising.

Areas timely for developing research: Head-to-head trials of mucolytics versus long-acting bronchodilators and/or inhaled corticosteroids are lacking. Even in patients with severe COPD who remain symptomatic despite maximal inhaled therapy the role of mucolytics remains unproven.

Keywords: oral mucolytics/COPD/exacerbations of COPD

Introduction

The use of orally active mucolytic drugs in respiratory disease in general and chronic obstructive pulmonary disease (COPD) in particular has fluctuated widely with time and place. Having once been commonly prescribed for patients with ‘bronchitic’ symptoms in the UK they were for many years blacklisted, i.e. not covered under the NHS tariff for medical reimbursement, before returning to favour more
recently as drugs to help control cough. This contrasts with the attitude in many parts of southern and central Europe where these agents are still widely prescribed as part of the multicomponent drug regime for COPD management. The reasons for these discrepancies within the same continent, and for the EU members, the same regulatory framework, are complex. In part this reflects local custom and practice which has varied in different countries and also the negative perception about COPD care, which argues that so little can be done everything possible should be offered. For those who do not currently prescribe these drugs, the arguments have until recently been more straightforward and the important ones are considered below.

Defining the drugs

Although the term mucolytic appears to be self-evident, it is difficult to define in practice. There is no universally agreed standard to indicate efficacy in terms of changing the physical properties of mucus. We do not know how these properties vary from day to day in stable disease that makes assessing the impact of a drug that may modify mucus somewhat hard. Making the mucus easier to expectorate would seem a sensible goal but changing its physical properties may affect the ability of the mucociliary escalator to clear mucus efficiently. Likewise the anti-tussive effects of these drugs are difficult to assess in the absence of properly validated cough measurement instruments. Thus there is genuine uncertainty about what these drugs should do and how to measure whether they do it.

Many mucolytic agents belong to the cysteine family of drugs and have potentially important antioxidant properties. There is a growing body of evidence that oxidative stress is one of the key pathological mechanisms leading to lung damage and potentially relevant systemic complications in COPD. Decreasing the impact of oxidative stress is an attractive, although possibly unduly simple, target for drug treatment. This might relate to more measurable outcomes in COPD, like changes in lung function over time and the occurrence of exacerbations, both of which have been linked to overall health status in this disease. Pharmacokinetically, N-acetylcysteine (NAC) is the best studied of these drugs. Data suggest that NAC given orally is rapidly deacetylated to cysteine, with resulting increases in plasma cysteine concentrations. Six hundred milligrams/day NAC given orally for 5 days prior to bronchoscopy reduces glutathione both in plasma and in the airways, which temporarily increases the antioxidant capacity of the lung. Although the antioxidant properties of mucolytic drugs have seldom been quantified in the relevant tissue in vivo (an issue when
choosing the dose of the drug), these agents offer promise of a more rational treatment for COPD patients.

Standards of evidence

A second related issue is the quality of the evidence available to evaluate these drugs. Many of these agents were used before the modern era of properly conducted randomized controlled trials and the methodological quality of much of the early evidence is poor. Initially little distinction was made between those drugs with antioxidant properties and those without, although more recent studies have focused on the former group. Likewise the diagnostic classification of patients was very variable. Most early studies reported patients with exacerbations of chronic bronchitis without any lung function data; a limitation when assessing the evidence.

Despite these problems a significant body of data exists about the use of mucolytic drugs in COPD patients, mostly conducted in stable disease. This forms the basis of this review.

Methods/sources of data

This review is based upon peer reviewed clinically orientated publications relating to the use of mucolytics in patients with COPD cited in PubMed. The majority of studies have examined the short- to medium-term efficacy of these drugs.

Results

Poole and Black’s Cochrane review ‘Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease’ looked at the evidence from 26 randomized, double-blind, placebo-controlled trials that had enrolled 7335 patients. For inclusion, minimum treatment duration was 2 months. Oral mucolytics included: NAC (13 studies), ambroxol, sobrerol, carbocysteine, carbocysteine sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine, myrtol and erdosteine. All studies were conducted in Europe, in particular in Italy, except for one which was undertaken in the USA.

The review is extensive and thorough but the limitation for this article is that it included patients with chronic bronchitis and/or COPD, as indeed do many mucolytic studies. The primary objective was to determine whether mucolytics had any effect on the frequency
of exacerbations or days of disability in participants. The secondary objectives were to determine whether mucolytics led to an improvement in lung function [as measured by forced expiratory volume in one second (FEV1), forced vital capacity and peak expiratory flow] and to look at the frequency of adverse effects. The authors originally intended to look at symptoms as a further secondary outcome, but symptoms were not reported consistently and it was not possible to standardize scores.

The great majority of patients had chronic bronchitis with or without COPD and only five studies had recruited solely COPD patients. The first of these\(^8\) has been published only in the abstract form. Three hundred and thirteen patients with COPD with a mean age of 57 years, 60% male and mean FEV1 of 60% predicted were entered into a double-blind, placebo-controlled parallel-group study of NAC 600 mg daily. The mean study duration was 8 months. There was a reduction in the number of exacerbations per patient per month (0.03 NAC versus 0.06 placebo) and more patients in the NAC group remained exacerbation free during the study. Pela et al.\(^9\) published a similar study of 169 Italian COPD patients randomly allocated in an open, controlled study to NAC 600 mg daily or placebo. At baseline, most patients were treated with inhaled bronchodilators, 40% with inhaled corticosteroids and half with oral theophyllines. They showed a 41% decrease in the number of exacerbations in the treated group and again an increase in those remaining exacerbation free. The number of sick days was less (82) in the NAC group compared with the standard therapy group (155). They also reported a small but numerically significant improvement in lung function in the actively treated group as measured by FEV1 (1.53 ± 0.65 to 1.58 ± 0.63 l; \(P < 0.05\)) but the clinical significance of this is doubtful.

In 2004, there was a further Italian publication by the EQUALIFE study group.\(^10\) This was a randomized, double-blind, placebo-controlled, parallel-group study of erdosteine (300 mg b.d.) in COPD patients over 8 months. One hundred and fifty-five patients were enrolled of whom 124 completed the study. There was no difference in drop-out rate in the two study arms. The actively treated group had significantly fewer exacerbations and spent fewer days in hospital than the placebo group. Those treated with erdosteine also showed a significant improvement in health-related quality of life as measured by the Short Form-36 (physical score improved by 4.9 units) and the St George’s Respiratory Questionnaire (SGRQ). The mean total COPD-related disease costs per patient were lower in the erdosteine group. In the same year, yet another Italian group published a well-conducted, though again small, 1-year study of ambroxol (75 mg b.d.) versus placebo in COPD patients.\(^11\) There was no difference in the
percentage of patients remaining exacerbation free, but in a post hoc analysis, a subset of 45 patients with more severe symptoms at enrolment had a greater likelihood of remaining exacerbation free when treated with ambroxol (63 versus 37%; \(P = 0.038\)).

The final, and by far the largest of these five publications, the BRONCUS study, looked at the effects of 600 mg o.d. NAC on lung function and exacerbation rate, was prospectively studied in the ref. (12) (Table 1). This multi-centre, randomized, placebo-controlled trial recruited 523 COPD patients who were followed for 3 years. The primary outcomes were yearly reduction in FEV\(_1\) and the number of exacerbations per year. The mean age of the study population was 62 (8) years, almost half were current smokers and the mean % predicted FEV\(_1\) was 57 (9). Yearly exacerbation rate prior to study entry was 2.4 and at enrolment 70% were treated with inhaled corticosteroids, despite the fact that patients mostly fell into GOLD stage II of disease for which this treatment is not currently recommended.\(^\text{13}\) The drop-out rate was greater in the placebo group than in the NAC group (\(P = 0.018\)). Overall, there was no difference in the rate of decline of lung function, annual exacerbation rate or deterioration in health status between the groups. However, in a subgroup analysis, patients who were not taking inhaled corticosteroids had a significantly decreased risk for exacerbation.

In 2000, Stey et al.\(^\text{14}\) conducted a quantitative systematic review of the effects of NAC in chronic bronchitis, rather than COPD per se. Thirty-nine trials were retrieved; 11 (2011 patients) of which were regarded as relevant and valid according to preset criteria. Seven of these trials were also included in the Cochrane review,\(^\text{6}\) but none recruited only COPD patients. In nine studies, 351 of 723 (48.5%) patients receiving NAC had no exacerbation compared with 229 of 733 (31.2%) patients receiving placebo [relative benefit 1.56 (95% confidence interval, CI: 1.37–1.77), number-needed-to-treat 5.8 (95% CI: 4.5–8.1)]. There was no evidence of any effect of study period (12–24 weeks) or cumulative dose of NAC on efficacy. In five trials, 286 of 466 (61.4%)
patients receiving NAC reported improvement of their symptoms compared with 160 of 462 (34.6%) patients receiving placebo [relative benefit 1.78 (95% CI: 1.54–2.05), number-needed-to-treat 3.7 (95% CI: 3.0–4.9)]. They concluded that, with treatment periods of approximately 12–24 weeks, oral NAC reduced the risk of exacerbations and improved symptoms in patients with chronic bronchitis compared with placebo.

A large, retrospective, study using a pharmacological database in the Netherlands examined the effect of oral NAC in the prevention of re-hospitalization for COPD exacerbations. The study included 1219 patients aged 55 years and over who had been dispensed medication labelled for respiratory indications between 1986 and 1998 and who had also been hospitalized for COPD in this time frame. These subjects were subsequently divided into two groups, those who had received NAC following discharge from their first admission and those who had not. Patients were studied from their initial discharge, until their first readmission, death or end of the data collection period for a maximum follow-up of 1 year. After adjustment for disease severity, it was observed that NAC reduced the risk of re-hospitalization for COPD by approximately 30% and that this risk reduction was dose dependent.

Since the last Cochrane review, the PEACE study has examined the effect of 3 years’ treatment with carbocisteine (2 × 250 mg t.d.s) on the rate of COPD exacerbation in 709 Chinese patients. The study population was well defined with more patients into GOLD stages III and IV than most other studies, including BRONCUS. Because of the differences in prescribing practice in China, less than 20% of this study population was receiving inhaled corticosteroids and indeed the great majority of patients were not prescribed any inhaled bronchodilators. The 1 year cumulative number of exacerbations was 325 in the carbocisteine group and 439 in the placebo group, corresponding to 1.01 (SE: 0.06) exacerbations per patient year in the active arm versus 1.35 (SE: 0.06) in the placebo arm (a 24.5% reduction). In this patient population, carbocisteine also reduced the decline in health-related quality of life, with a difference between the groups starting to be seen at 2 years. However, there was no difference in the SGRQ symptoms score domain between the active and placebo arms.

The Cochrane review concluded that mucolytics result in a small but statistically significant effect on exacerbation rates in patients with chronic bronchitis and/or COPD of about 0.05 exacerbations per month, or 0.5 exacerbations per year. This is almost a 20% reduction in the number of exacerbations when compared with the control group. There was the suggestion that exacerbations that did occur were less serious and shorter, with an effect of mucolytics on days of disability of −0.56 days per patient per month. Mucolytics are very safe with
no increase in reported adverse events when compared with placebo. The authors note that over the course of updating their review (which has now been undertaken three times, between 1998 and 2008), the effect size on exacerbations has reduced by almost 50% from their original report. They hypothesize that this is likely due to:

- improved study design, executing and reporting with the possible additional effect of early publication bias
- the now common use of concomitant inhaled corticosteroids in the management of patients with moderate to severe COPD.

Are mucolytics helpful in the treatment, rather than the prevention of exacerbations?

Erdosteine is the only mucolytic licensed in the UK for the symptomatic, short-term treatment of patients with acute exacerbations of chronic bronchitis and there is limited evidence that erdosteine 300 mg twice daily for 7–10 days may improve symptoms and reduce the time course of the exacerbation. However, the few trials published\(^1\) give little indication of the severity of patient’s COPD (if indeed they have COPD), participants were not always treated with standard proven exacerbation therapy and once again, researchers run into difficulty as the symptom scores used, which are usually the primary outcome measures here, are unvalidated.

### Limitations

There are many problems with the studies to date. With the exception of the BRONCUS and PEACE studies, most had a small sample size. In addition, many of the older studies are not double blinded or lack placebo control and most are of short duration.

Importantly, enrolled patients often have a mixture of underlying diagnoses (e.g. bronchitis, COPD, COPD and bronchiectasis). In smokers with chronic bronchitis but no airflow obstruction, it is sensible to encourage and provide support for smoking cessation rather than adding medication, as it is clear that quitting smoking leads to great improvements in the symptoms of chronic bronchitis, as well as having additional long-term health benefits.

The end points studied vary enormously and the tools available to measure symptoms of cough and sputum production are not well validated. Although cough questionnaires and cough counters are now becoming more reliable, this is a recent development and questionnaires used in these studies were not robust. There has been little headway in developing tools to accurately measure either quantity or viscosity of daily sputum production.
We now have a range of effective treatment options for COPD patients, many of which including long-acting bronchodilators and inhaled corticosteroids reduce exacerbation risk, improve exercise tolerance and impact health-related quality of life. Data suggest that mucolytics have few, if any, additional benefits over these well-proven therapies (Table 2).

### Discussion/areas of agreement and controversy

There is now little doubt that mucolytic drugs with antioxidant properties reduce the likelihood of COPD patients experiencing a health-care defined exacerbation. Mucolytics reduce exacerbations by up to 0.8 exacerbations per year, with a greater effect in those with more severe COPD. This effect size is of a similar magnitude to that seen with inhaled corticosteroids and long-acting anticholinergics, but there have been no head-to-head trials. Similarly there are no health status data which allow us to evaluate the impact of this reduction in events. In many of the smaller studies exacerbation rates were reported using statistical methods that were not ideal, a topic that has recently been reviewed in depth. However, data from the PEACE study used the correct techniques and exacerbations were its primary outcome. Interpreting the clinical relevance of these data in the developed medical economy is difficult since participants in the PEACE study use relatively little background therapy. There is good evidence that the use

| Table 2: Are mucolytics useful in the management of patients with COPD? |
|---------------------------------|-------------------------------------------------------------|
| **Chronic disease**            | **Possible beneficial effect. Possible benefits for patients not treated with inhaled corticosteroids (NAC and carbocisteine)** |
| Exacerbation rate              | Some studies show benefit                                   |
| Days of disability             | No reliable data                                            |
| Length of hospitalization      | No effect                                                   |
| Lung function decline          | Some benefit in patients not treated with standard COPD therapy |
| Health-related quality of life | No reliable tools or data                                   |
| Symptoms                        | **Possible beneficial effect**. Possible benefits for patients not treated with inhaled corticosteroids (NAC and carboxisteine)** |
| Cough                           | Possibly improved by erdosteine                             |
| Sputum production              | Possibly improved by erdosteine                             |
| Ease of expectoration          | Very safe and well tolerated. No difference in total numbers of adverse events between placebo and active drug |
| Utility during exacerbations   | Cheaper than long-acting inhaled bronchodilators and inhaled corticosteroids |
| Symptom reduction              |                                                            |
| Length of exacerbation         |                                                            |
| Safety                         |                                                            |
| Cost                           |                                                            |
of long-acting inhaled bronchodilators with or without inhaled corticosteroids reduces COPD exacerbation rates. These drugs also affect health status, exercise performance and potentially both mortality and disease progression. In contrast the mucolytic agents are relatively specific in their clinical effects with no impact on lung function and the only clear benefits being seen in exacerbation prevention. Whether there is a ceiling in terms of the number /type of episodes which can be prevented by all of these treatments is unclear but participants in the BRONCUS study only experienced benefit when they were not using an inhaled corticosteroid.

Further studies are clearly needed. Mucolytic agents are well tolerated and higher doses, e.g. 1200– 1800 mg per day NAC would provide a better proof of principle than those used so far. Appropriately powered comparative studies with outcomes such as hospitalization or mortality in those with severe disease or the need for additional courses of antibiotics in those with mild COPD would help our understanding of where these drugs might fit into the treatment paradigm. In the UK they are likely to be an ‘add-on’ therapy and so we need to know whether they do provide additional benefit. Unfortunately the costs of conducting such studies are substantial and it seems unlikely given the modest profit margins available that trials of this kind will be funded, leaving us with the unsatisfactory situation of suspecting a clinical benefit without being able to make an evidence-based recommendation to that effect. Additional mucolytics, such as the lysine salt of NAC, are under development and it remains to be seen what their role will be in the management of patients with COPD.

**Conclusion**

There are no convincing data that mucolytics improve cough, aid expectoration, alter the properties of mucus or impact health-related quality of life in COPD patients receiving other standard therapy. In those on little or no other treatment, they are likely to be beneficial in reducing the risk of exacerbation. The trials that need to be done, to determine whether the drugs have additional benefit when combined with long-acting bronchodilators and inhaled corticosteroids, are unlikely to be carried out.

The evidence suggests that mucolytics may be useful in patients who are unable to take long-acting bronchodilators and/or inhaled corticosteroids, either because of side effects or in health economies where these drugs are prohibitively expensive. However, currently in the UK, mucolytic therapy is most often considered in patients with severe COPD who remain symptomatic despite maximal inhaled therapy,
those with frequent or prolonged exacerbations and those who have frequent hospital admissions. Using these drugs in this way is not evidence-based practice.

Conflict of interest: PMAC has advised Arnold Pharma, makers of erdosteine a mucolytic drug, on the design of a planned clinical trial of this agent. LD will be the principal UK investigator when this study begins. No other conflicts for PMAC or LD.

Funding

PMAC has led clinical trails, spoken at sponsored meetings and received research funding from GSK, AstraZeneca, Boehringer Ingelheim and Nycomed all of whom make drugs used to treat COPD patients and prevent exacerbations of COPD.

References


