

DRUG UPDATE

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ORAL MUCOLYPTICS IN COPD

Compared with placebo, regular mucolytic use is associated with a modest reduction in the frequency of acute exacerbations of chronic bronchitis and possibly COPD. Adverse effects appear minimal. Mucolytics are likely to be most useful in those patients with frequent, prolonged and/or severe exacerbations or in those requiring repeated admissions to hospital. A four-week trial should be carried out to ascertain if there is symptomatic improvement. Treatment should be withdrawn if benefit is not achieved.

What are they?

Mucolytics are used to increase expectoration by reducing sputum viscosity or hypersecretion.^{1,2} Two oral mucolytics are licensed in the UK and available on FP10, carbocisteine (Mucodyne®) initiated at 750mg TDS reducing to 1.5g daily in divided doses and mecysteine (Visclair®) initiated at 200mg QDS for 2 days, then 200mg TDS for 6 weeks, and then 200mg BD for maintenance.³ Oral N-acetylcysteine (NAC), although unlicensed in the UK, is the most widely studied mucolytic.

What is the evidence for their benefit in COPD?

Two six-month, double blind, placebo-controlled trials studied carbocisteine in patients with chronic bronchitis (CB) over the winter.^{4,5} One (n=662) compared continuous carbocisteine 2.7g OD, intermittent carbocisteine 2.7g OD on alternate weeks and placebo in patients with an FEV₁ of 40-70% of predicted and at least 2 acute exacerbations in the preceding year.⁴ 70.4%, 57% and 54.1%, respectively, experienced no exacerbations (continuous carbocisteine vs. placebo, p=0.001). 23% of patients withdrew from the study. Significant improvements were also seen between continuous carbocisteine and placebo in time to first exacerbation (p=0.029), average days with respiratory illness (p<0.01) and average days of antibiotic use (p<0.02).⁴

The other trial, published in 1985 (n=109), comparing carbocisteine 750mg TDS with placebo found no significant differences in frequency of acute exacerbations.⁵

Two trials compared mecysteine with placebo in patients with CB.^{6,7} One trial (n=169), published in 1962, evaluating mecysteine 2 tablets TDS or placebo over 4 weeks showed significant reduction in cough (p<0.01) and sputum production (p<0.05) with active treatment.⁶ The second trial (n=30), published in 1978, compared mecysteine, 1200mg OD in week 1, 800mg OD in week 2 and then 600mg OD in weeks 3 to 6 with placebo in patients with an FEV₁ of 20-70% of predicted.⁷ Cough severity and frequency (p<0.001), and ease of expectoration (p<0.01) improved compared to placebo and sputum consistency decreased (p<0.01) at study end, but these were not maintained after

discontinuation of therapy.⁷

A Cochrane review (n=6,415, 23 RCTs, duration 2 to 24 months) of patients with CB or mild chronic obstructive pulmonary disease (COPD) treated with 10 different oral mucolytics found that patients taking oral mucolytics had 0.07 fewer exacerbations and 0.56 fewer days of disability (e.g. days in bed/off work) per month than those taking placebo (p<0.0001 and p<0.001 respectively, compared to placebo).^{2,8} This equates to 6 patients requiring mucolytic treatment for one patient to be free from exacerbation during the study period. However, 21 trials used unlicensed mucolytics and only 2 were in patients with COPD. Most benefit occurred early as indicated by greater reductions in exacerbation rate in trials lasting ≤12 weeks.²

A systematic review (n=2,011, 11 RCTs) of oral NAC (400-600mg daily) in CB over 12-24 weeks aimed to establish whether treatment with NAC was accompanied by clinically relevant improvement.⁹ NAC reduced the number of exacerbations and showed an improvement in symptoms compared to placebo.⁹ However, a separate meta-analysis, which also showed a reduced incidence of acute exacerbations, demonstrated non-homogeneity among eight of the above trials (p<0.001).¹⁰

Most of the above studies were short-term and performed in winter, and so may overestimate the annual reduced exacerbation rates. Whether there are differences in effectiveness between the different mucolytics used is unknown and the varying mucolytic dosages were not consistently accounted for. The consequences of high drop out rates in some trials are also unknown.¹

A retrospective study (n=1,219) investigating risk of re-hospitalisation for an exacerbation of COPD within 1 year of previous hospitalisation showed the risk was significantly lower in those taking oral NAC vs. non-users, (relative risk 0.67 [95%CI:0.53-0.85], absolute risk reduction 8%).¹¹

Overall, mucolytic treatment was associated with a modest reduction in acute exacerbations compared with placebo and a reduction in total number of days of disability. Compared with non-use, mucolytics reduced the need for re-

hospitalisation and showed no significant adverse effects.

How safe are they?

Adverse effects seen in clinical trials were usually mild and mostly gastrointestinal in nature with one trial reporting adverse events in 1.8% of patients on carbocysteine and 4.1% on placebo.⁴

What other options are there?

Short acting inhaled β_2 agonists or anticholinergics are first line therapies for COPD. Second line therapy includes either adding in a long acting bronchodilator or combining the two short acting agents. If appropriate, modified release theophylline can also be tried. Inhaled corticosteroids should be prescribed in patients with an FEV₁ \leq 50% of predicted and \geq 2 exacerbations treated with antibiotics or oral corticosteroids per year (unlicensed for COPD monotherapy). If patients remain symptomatic, then further effective combinations include a long acting β_2 agonist with an inhaled corticosteroid or theophylline with either of the short acting bronchodilators. Acute exacerbations of COPD are

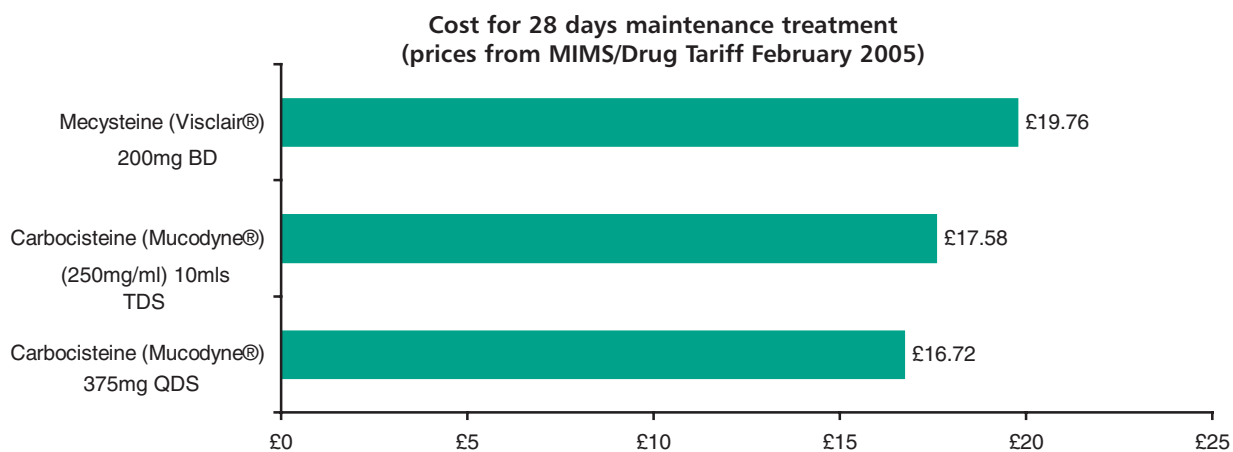
How much does it cost?

mainly treated with inhaled or nebulised bronchodilators and oxygen can be given if appropriate. Short courses of oral corticosteroids with or without antibiotics may also be required.¹² Steam inhalation and nebulised saline have also been used to help reduce sputum viscosity.

When should they be used?

The NICE guideline for COPD recommends that mucolytic therapy should be considered in patients with chronic cough productive of sputum and continued if there is symptomatic improvement e.g. reduction in frequency of cough and sputum production.¹² The Cochrane review suggests that benefit may be greatest in COPD patients with frequent, prolonged or severe exacerbations, or those repeatedly admitted to hospital.^{2,8}

If a 4-week trial of mucolytics is not successful (measured by symptomatic improvement and no unacceptable side effects) then treatment should be withdrawn.¹³ However, if therapy is successful, daily maintenance treatment for at least 3-6 months over winter would be required.⁸



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - Randomised Controlled Trial, CT - Controlled Trial, G - Guideline, MA - Meta-Analysis, R - Review, Abs - Abstract

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ERRATUM - Re: Drug Update No. 33, Domiciliary Oxygen Therapy.

The second sentence of the first paragraph should read "Improved survival has been demonstrated with long-term oxygen therapy (LTOT) for a minimum of 15 hours per day in normo- & hypercapnic COPD patients." The corrected version in pdf format is available on the website at www.nyrdtc.nhs.uk