

National Essential Medicine List Medication Review Process
Primary Healthcare Medication
Component: Respiratory medicines

Medication name: N-acetylcysteine/S-carboxycysteine/bromhexine

Date of review: June 2013

Indication: Prevention of acute exacerbations of COPD

Executive summary:

COPD is a common disease in South Africa. Mucolytic medicines are cheap, safe and effective for reducing COPD exacerbations and should be considered as additional therapy in certain patients.

Introduction and contextualisation:

Chronic obstructive pulmonary disease (COPD) is common in South Africa, with an estimated prevalence of 22% (GOLD stage II or higher).ⁱ Mucolytic medicines are a relatively inexpensive treatment for reducing acute exacerbations in COPD, and are associated with few adverse effects.ⁱⁱ Treatment guidelines vary widely in their recommendations regarding the use of mucolytics. Current South African guidelines don't recommend them for 'alleviation of breathlessness and improvement in effort tolerance', but don't mention them at all for prevention of exacerbations.ⁱⁱⁱ Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that their widespread use 'cannot be recommended at present'.^{iv} The current combined European and American guideline doesn't mention them at all.^v Australian guidelines state that mucolytics may reduce exacerbations.^{vi} United Kingdom (National Institute for Clinical Excellence) guidelines don't recommend their routine use, but state that they should be considered in patients with chronic productive cough and continued only if there is an improvement in symptoms.^{vii}

Search strategy:

Pubmed search terms:

Mucolytics in COPD: systematic reviews:

("expectorants"[MeSH Terms] OR "expectorants"[All Fields] OR "mucolytics"[All Fields] OR "expectorants"[Pharmacological Action]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields])

Selection of studies:

Inclusion criteria:

Types of studies: systematic reviews of randomized controlled trials
Participants: patients with COPD
Interventions: any mucolytic agent
Control: placebo/no treatment
Outcomes: prevention of acute exacerbations

Results:

The Pubmed search identified 127 studies. Two met the inclusion criteria.

Evidence synthesis:

Poole et al's 2012 Cochrane Review included 30 trials and 7436 participants with chronic bronchitis or COPD.ⁱⁱ The most commonly used mucolytics were N-acetylcysteine (15 studies) and carbocysteine (4 studies). Mucolytics significantly reduced the risk of acute exacerbations. The odds ratio (OR) for no exacerbations in the study period (mucolytic versus placebo) was 1.84 (95% CI 1.63 to 2.07), with a number needed to treat (NNT) of 7 (95% CI 6 to 9) to prevent 1 acute exacerbation over 10 months. In a sub-group analysis of patients who were not on an inhaled corticosteroid (ICS), there was no significant difference in exacerbation rates between patients on mucolytics versus placebo. There were fewer adverse effects in the treated group (versus the placebo group), OR 0.82 (95% CI 0.71 to 0.95); and no significant difference in mortality, OR 0.75 (95% CI 0.35 to 1.64).

Sutherland et al included 8 studies and 2214 participants with COPD.^{viii} They included trials that used N-acetylcysteine only. N-acetylcysteine reduced the odds of acute exacerbations, OR 0.49 (95% CI 0.32 to 0.74). In contrast to Poole et al, they found that the treatment effect was greater in patients who were not on an ICS, OR 0.42 (95% CI 0.32 to 0.54).

Evidence quality:

Both studies are systematic reviews and meta-analyses of randomized controlled trials.

Alternative agents:

Barr et al's meta-analysis showed that tiotropium (versus ipratropium or placebo) reduced exacerbations, OR 0.73 (95% CI 0.66 to 0.81), with a NNT of 13 (95% CI 10 to 21) to prevent 1 exacerbation per year.^{ix}

Black et al^x calculated a NNT for fluticasone plus salmeterol versus placebo based on Calverley et's RCT.^{xi} The NNT was 4 to prevent 1 exacerbation per year.

Black et al^x calculated a NNT for prophylactic antibiotics based on Staykova et al's meta-analysis.^{xii} The relative risk for acute exacerbations (prophylactic antibiotics versus placebo) was 0.91 (95% CI 0.84 to 0.99) and the NNT was 14 to prevent 1 exacerbation.

Summary:

Mucolytics appear to have a modest effect on reducing exacerbations in COPD and are not associated with an increased risk of adverse effects. Our search did not find any head-to-head

comparisons with other interventions, but their treatment effect compares favourably with more expensive (currently unaffordable) interventions.

Recommendation:

Mucolytics not be recommended as modest evidence of benefit and no available product on tender, currently.

References:

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- ⁱ Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007;370:741-750.
- ⁱⁱ Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub4.
- ⁱⁱⁱ Abdool-Gaffar MS, Ambaram A, Ainslie GM, Bolliger CT, Feldman C, Geffen L, Irusen EM, Joubert J, Laloo UG, Mabaso TT, Nyamande K, O'Brien J, Otto W, Raine R, Richards G, Smith C, Stickells D, Venter A, Visser S, Wong M. Guideline for the management of chronic obstructive pulmonary disease – 2011 update. *S Afr Med J* 2011; 101: 61-73.
- ^{iv} From the *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: <http://www.goldcopd.org/>.
- ^v Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner, G, van der Molen T, Marciniuk DD, Denberg T, Schu¨ nemann H, Wedzicha W, MacDonald, R, Shekelle P for the American College of Physicians, the American College of Chest Physicians, the American Thoracic Society, and the European Respiratory Society*Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med.* 2011;155:179-191.
- ^{vi} David K McKenzie, Michael Abramson, Alan J Crockett, Eli Dabscheck, Nicholas Glasgow, Sue Jenkins, Christine McDonald, Richard Wood-Baker, Ian Yang, Peter A Frith on behalf of Lung Foundation Australia and the Thoracic Society of Australia and New Zealand. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease V2.32, 2012.
- ^{vii} National Clinical Guideline Centre for Acute and Chronic Conditions. Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Jun. 61 p. (Clinical guideline; no. 101).
- ^{viii} Sutherland ER, Crapo JD, Bowler RP. N-acetylcysteine and exacerbations of chronic obstructive pulmonary disease. *COPD.* 2006 Dec;3(4):195-202.
- ^{ix} Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006;61:854–62.
- ^x Black PN, McDonald CF. Interventions to reduce the frequency of exacerbations of chronic obstructive pulmonary disease. *Postgrad Med J* 2009;85:141–147
- ^{xi} Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–89.
- ^{xii} Staykova T, Black PN, Chacko EE, Poole P. Prophylactic antibiotic therapy for chronic bronchitis. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD004105. DOI: 10.1002/14651858.CD004105.