**CRD summary**
The authors concluded that oral N-acetylcysteine may be of benefit to a subset of patients with chronic obstructive pulmonary disease; the effects may be less in patients taking inhaled corticosteroids. There were limitations to this review but, overall, the authors’ cautious conclusions appear appropriate.

**Authors' objectives**
To evaluate the effect of N-acetylcysteine on exacerbations of chronic obstructive pulmonary disease (COPD).

**Searching**
MEDLINE, CINAHL, International Pharmaceutical Abstracts and the Cochrane CENTRAL Register were searched from inception to November 2005 using the reported search terms. In addition, the reference lists in identified studies were screened and experts in the field were contacted for additional studies. No language restrictions were applied to the search. Studies published only as abstracts were excluded.

**Study selection**
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a follow-up of at least 3 months were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared oral N-acetylcysteine plus standard care with placebo plus standard care were eligible for inclusion. The included studies evaluated between 400 and 1,200 mg/day oral N-acetylcysteine. Treatment duration was 5 to 6 months for all but one study, in which it was 3 years. Most of the included studies were conducted before inhaled corticosteroids were widely available.

Participants included in the review
Studies of patients with COPD were eligible for inclusion. Most of the patients in the included studies were between 51 and 70 years old. Where reported, the baseline forced expiratory volume in one second (FEV1) ranged from 29 to 81% of that predicted, and current smoking prevalence ranged from 23 to 95%.

Outcomes assessed in the review
Studies that reported the number of exacerbations in each treatment arm were eligible for inclusion. The primary review outcome was the odds of having one or more exacerbations over the study duration. Most of the included studies defined an exacerbation as a new or worsening cough and increased or purulent sputum.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened retrieved studies and all three reviewers selected studies for the review. Any disagreements were resolved by consensus.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
Where possible, two reviewers independently extracted the number of patients in each treatment group with zero and one or more exacerbations. For one study the relevant 6-month data were estimated from reported frequencies of exacerbations. Data were extracted for patients who completed individual studies.

**Methods of synthesis**
How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using an inverse variance-weighted
random-effects model. The number-needed-to-treat (NNT) with N-acetylcysteine to avoid one or more exacerbations was calculated. Publication bias was assessed using a funnel plot and Begg's test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. The influence of baseline lung function, current smoking prevalence and the use of inhaled corticosteroids were examined through subgroup analysis. Simple linear regression was used to examine the correlation between baseline FEV1% predicted and the effect of N-acetylcysteine.

Results of the review
Eight RCTs were included (2,214 randomised; 1,819 included in the meta-analysis).

N-acetylcysteine was associated with a significant reduction in the odds of experiencing one or more exacerbations over 6 months compared to placebo (OR 0.49, 95% CI: 0.32, 0.74, p=0.001); the NNT was 7. Statistically significant heterogeneity was detected (p=0.001). After excluding patients in one study who were taking concurrent inhaled corticosteroids, there was no evidence of statistical heterogeneity (p=0.41).

No significant correlation was found between baseline FEV1% predicted and the effect of N-acetylcysteine (p=0.6).

In studies in which more than 50% of patients were current smokers, N-acetylcysteine was associated with a significant reduction in the odds of experiencing one or more exacerbations compared with placebo (OR 0.36, 95% CI: 0.24, 0.55, p<0.001; 3 studies).

Among patients not using inhaled corticosteroids, N-acetylcysteine was associated with a significant reduction in the odds of experiencing one or more exacerbations compared with placebo (OR 0.42, 95% CI: 0.32, 0.54, p<0.0001).

There was no evidence of publication bias: the funnel plot was symmetrical and Begg's test was not statistically significant (p=0.62).

Authors’ conclusions
N-acetylcysteine reduces the risk of exacerbation in patients with COPD; the effects may be less in patients taking inhaled corticosteroids, but smoking status did not affect the efficacy of treatment.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and no language restrictions were applied, but studies published only as abstracts were excluded and it was unclear if unpublished studies were sought. The potential for publication bias was assessed and no evidence of it was found. Methods were used to minimise reviewer error and bias in the selection of studies and extraction of data. Study validity was not assessed, thus the results from these studies and any synthesis might not be reliable. Statistical heterogeneity was assessed and the studies were combined using meta-analysis. Potential reasons for significant heterogeneity were examined. There were limitations to this review but, overall, the authors’ cautious conclusions appear appropriate.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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