Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials

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Authors' objectives
To determine the effect of prolonged treatment with oral N-acetylcysteine (NAC) in chronic bronchitis (CB).

Searching
MEDLINE was searched from 1980 through 1995 for articles published in English, French, German or Italian, using the following keywords: 'acetylcysteine', N-acetylcysteine', 'double-blind method' and 'placebo-controlled'. References of identified studies were examined, and an updated electronic search of BioMedLink, MEDLINE, and the Current Drugs' databases was conducted in November 1999. Additional relevant published or unpublished trials were identified by reviewing textbooks and monographs, and by contacting clinical experts.

Study selection
Study designs of evaluations included in the review
Double-blind, placebo-controlled trials of at least 2 months' duration were eligible if they also reported sufficient data to calculate an outcome variable, which enabled direct comparison of the NAC and placebo groups. Uncontrolled trials and studies of less than 2 months' duration were excluded. One controlled trial that met the inclusion criteria but reported a disproportionately high effect size, was subsequently excluded from the meta-analysis.

Specific interventions included in the review
Studies comparing prolonged (at least 2 months) prophylactic oral NAC with placebo were eligible. Doses of NAC varied among trials from 600 mg three times weekly to 1200 mg/day. The most frequently used dose was 400 mg/day, and both slow- and controlled-release formulations were used. The duration of therapy ranged from 3 to 6 months.

Participants included in the review
Patients with CB disease were eligible. Patients with acute clinical conditions were excluded, as were studies of nonhomogeneous populations. Two studies considered smokers only. The definitions of CB varied among primary studies, although in all but one study, it was based on the definition of CB in the Medical Research Council criteria (see Other Publications of Related Interest no.1). The inclusion criterion in one study was severe airways obstruction, i.e. the forced expiratory volume in 1 second (FEV1), less than or equal to 50% of the predicted value. For the other three studies, the exclusion criteria were an FEV1 equal or less than 40%, 50%, and 50%, respectively.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of outcomes. The primary outcome was taken as the study-specific primary efficacy variable, which included the number of episodes (monthly, over 6 months, and the total number), clinical assessment, and the number of exacerbations. Secondary outcomes included the number of acute exacerbations and adverse reactions.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Only double-blind controlled studies were included. No formal validity assessment was undertaken.

Data extraction
Two reviewers independently extracted the following data: author, title and year of publication; NAC dose; duration of administration; number of patients per treatment arm; major end points; and adverse events.

Methods of synthesis
How were the studies combined?
The effect size was estimated for each study using the standardised difference between the average values of the primary efficacy variable of each treatment group. A summary effect size was then calculated, where the weighting factor for each study was equal to the inverse of the estimated variance (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
The Q statistic was used to assess statistical homogeneity. When significant heterogeneity was detected, a mathematical sensitivity analysis was used to obtain a more homogeneous sample. The analysis was repeated using only those studies with the number of acute exacerbations as the primary efficacy variable. A separate meta-analysis was also conducted using only those studies published in peer-reviewed journals.

Results of the review
Eight controlled trials with 1,408 patients were included in the meta-analysis.

NAC was more efficacious than placebo. The summary effect size was -1.37 (95% confidence interval, CI: -1.5, -1.25), and statistical heterogeneity was present (Q=165, d.f.=7, p<0.001).

The sensitivity analysis resulted in the selection of 4 homogeneous studies (500 patients) with no specific clinical features (Q=2.07, d.f.=3, 0.5<p< 0.7). The subsequent meta-analysis of these trials yielded an effect size of -1.84 (95% CI: -2.05, -1.63).

Number of acute exacerbations (6 controlled trials with 821 patients): compared with placebo, NAC reduced the number of exacerbations. The summary mean difference in the number of exacerbations was -0.32 (95% CI: -0.50, -0.18), and statistical heterogeneity was not detected (Q=0.02, d.f.=5, p>0.05).

Trials published in peer-reviewed journals (5 controlled studies with 640 patients): the results were unchanged with a mean difference of -0.36 (95% CI: -0.55, -0.18), and statistical heterogeneity was not detected (Q=0.025, p>0.05).

Adverse effects: adverse effects were usually mild, mostly gastrointestinal, and there were no significant differences between treatment groups (data were not shown).

Authors’ conclusions
A prolonged course of oral NAC prevents acute exacerbations of chronic bronchitis, thus possibly decreasing morbidity and health care costs.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design, participants and intervention. Two relevant databases were searched, attempts were made to locate unpublished material, and articles in any one of four languages were eligible. The primary studies were restricted to double-blind, placebo-controlled studies, but no formal validity assessment was undertaken and the discussion did not include any comment on the quality of the included studies. Some relevant information was presented in tables, and methods used to extract data were described.

One study with a disproportionately high effect size was excluded from the meta-analysis, and no attempt was made to explore the reasons for this extreme result. Studies were pooled in a meta-analysis despite unexplained statistical heterogeneity, and a sensitivity analysis was used to select a subset of statistically homogeneous studies. Potential causes of this statistical heterogeneity were mentioned in the discussion; these included disparity in NAC doses and study selection criteria. Sensitivity analyses were conducted but other more appropriate analysis could have been undertaken.
Caution must be advised when considering the results of this review, given the lack of formal assessment of the validity of the studies, the lack of complete information on the primary studies on which the conclusions were based, and the unexplained statistical heterogeneity.

**Implications of the review for practice and research**

**Practice:** The authors state that 3 to 6 months' therapy with oral NAC results in a definite, although not extreme, reduction in the expected number of acute exacerbations of CB.

**Research:** The authors did not state any implications for further research.

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