Eur Respir J 2000; 16: 253–262
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European Respiratory Journal
ISSN 0903-1936

The effect of oral *N*-acetylcysteine in chronic bronchitis: a quantitative systematic review

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The effect of oral N*-acetylcysteine in chronic bronchitis. A quantitative systematic review. C. Stey, J. Steurer, S. Bachmann, T.C. Medici, M.R. Tramer. ©ERS Journals Ltd 2000.*

ABSTRACT: The role of *N*-acetylcysteine (NAC) in the treatment of chronic bronchitis is unclear. Since a number of studies have been published on this topic, a systematic review of published studies seems justified.

A systematic search (Medline, Embase, Cochrane Library, bibliographies, no language restriction) for published randomized trials comparing oral NAC with placebo in patients with chronic bronchitis was performed. Dichotomous data on prevention of exacerbation, improvement of symptoms and adverse effects were extracted from original reports. The relative benefit and number-needed-to-treat were calculated for both individual trials and combined data.

Thirty-nine trials were retrieved; eleven (2,011 analysed patients), published 1976–1994, were regarded as relevant and valid according to preset criteria. 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)). With NAC, 68 of 666 (10.2%) patients reported gastrointestinal adverse effects compared with 73 of 671 (10.9%) taking placebo. With NAC, 79 of 1,207 (6.5%) patients withdrew from the study due to adverse effects, compared with 87 of 1,234 (7.1%) receiving placebo.

In conclusion, with treatment periods of ~12–24 weeks, oral *N*-acetylcysteine reduces the risk of exacerbations and improves symptoms in patients with chronic bronchitis compared with placebo, without increasing the risk of adverse effects. Whether this benefit is sufficient to justify the routine and long-term use of *N*-acetylcysteine in all patients with chronic bronchitis should be addressed in further studies and cost-effectiveness analyses.

Eur Respir J 2000; 16: 253–262.

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Keywords: Bronchitis
meta-analysis
N-acetylcysteine

Received: October 14 1999
Accepted after revision March 19 2000

This study was supported by a PROSPER grant (No. 3233-051939.97) from the Swiss National Research Foundation.

Chronic bronchitis is a frequent condition in smokers. It is defined as the presence of chronic productive cough for ≥3 months in each of 2 successive years [1, 2]. Chronic bronchitis may or may not be associated with airflow obstruction. Individuals with chronic bronchitis may suffer from recurrent exacerbations with an increase in cough, sputum volume and/or purulence, and dyspnoea. An important aim in the treatment of chronic bronchitis is, therefore, to reduce the frequency and duration of acute exacerbations, and to reduce symptoms in patients with exacerbations.

In some European countries, mucolytics, and especially *N*-acetylcysteine (NAC), which is mucolytic but may perhaps also act as an anti-inflammatory drug and an antioxidant [3–5], are widely prescribed in the belief that these agents reduce the frequency of exacerbations and improve symptoms in patients with chronic bronchitis [6, 7]. In other parts of the world, such as the UK, the USA or Australia, mucolytics are used infrequently because they are perceived to be ineffective [8–10]. The British Thoracic Society guidelines for the management of chronic obstructive pulmonary disease (COPD), for instance, claim that there is no role for mucolytics in COPD [8]. This society justifies this by the fact that these drugs are not mentioned in the *British National Formulary* for use in COPD because trials of their effectiveness have produced inconclusive results [8]. In the USA, only one controlled trial, a multicentre study of organic iodide, suggested some benefit with mucolytic agents in the management of chronic bronchitis [11]. Although this study demonstrated improvement of symptoms, the evidence of any beneficial effect was deemed insufficient by the Food and Drug Administration, and marketing of the drug was discontinued [9].

A recently updated systematic review of the efficacy of any oral mucolytic agents in patients with COPD came to the conclusion that with these drugs there was, on average, a reduction of 0.11 exacerbations, 0.65 days of disability and 0.68 days of antibiotic treatment per patient per month [12]. These results were statistically significant. This

systematic review included data from eight NAC trials; the clinical relevance of oral NAC treatment, however, remained unclear. The present study, therefore, set out to test the evidence that treatment with oral NAC, in patients with COPD, may be accompanied by a clinically relevant improvement. The number of patients without any exacerbation, the number of patients reporting improvement of their symptoms and the incidence of drug-related adverse effects were regarded as the most relevant outcomes for the purpose of this study.

Methods

Systematic search and critical appraisal

The literature was searched systematically for relevant clinical trials. Inclusion criteria were randomized comparisons between NAC and placebo or no treatment, and chronic bronchitis. Data from other mucolytic agents were not analysed.

Medline (from 1966), Embase (from 1982) and the Cochrane Library (1999, issue II) were searched using the free text terms "*N*-acetylcysteine", "NAC", "fluimucil" and "bronchitis" and combinations of these terms. The last electronic search was performed in July 1999. Bibliographies of retrieved reports and relevant systematic reviews [12] were checked. The search was not restricted to English language papers. Three manufacturers were contacted and asked for in-house databases on NAC and relevant unpublished data. Authors were not contacted.

As an instrument of critical appraisal, the validated three-item five-point Oxford scale was used [13]. Thus each report was read independently by each author to assess adequacy of randomization and blinding, and description of withdrawals. According to this scale, the minimum score of an included randomized controlled trial is 1, and the maximum score 5. Authors met to achieve consensus.

Data extraction

Information about patients, dose of NAC treatments, study period, concomitant medication, study end points and drug-related adverse effects were taken from each included report.

The end point of primary clinical interest was prevention of any exacerbation with NAC or placebo. A further end point of interest was the number of patients who reported, in a self-assessment score or scale, unequivocal improvement of their bronchitic symptoms. For instance patients rating the effect of their treatment as "good" or "excellent" on a five-point scale ranging from "worsening" to "no change", "fair", "good" and "excellent" would be included in this category. These end points of primary interest were extracted from relevant trials only when they were reported in dichotomous form (*i.e.* number of patients with NAC and placebo with the end point). There was no intention to analyse quantitatively forced expiratory volume. Data on forced expiratory volume in one second (FEV_1), peak flow, and viscosity and volume of mucus were not analysed because these end points were reported inconsistently, and because they were regarded as surrogate end points. Data on adverse drug reactions, when reported in dichotomous form, were extracted and analysed quantitatively.

Risk stratification

There was an attempt to estimate the efficacy of NAC in patient populations with different underlying risks. It was, therefore, intended to classify trial populations into those at "low", "medium" and "high" risk. Relevant factors considered were number of exacerbations in the previous year, number of previous hospitalizations and lung function before the start of the trial.

Data analysis

Relative benefit or relative risk was calculated with 95% confidence interval (CI) [14]. A fixed effect model [15] was used when data were combined. A statistically significant difference between NAC and control was assumed when the 95% CI of the relative benefit or risk did not include 1. As an estimate of the clinical relevance of a treatment effect, the number-needed-to-treat [16] was calculated for both individual trials and combined data. For estimation of the frequency of drug-related adverse effects, the number needed to harm was calculated as for number-needed-to-treat [17]. Combined numbers-needed-to-treat/harm were calculated using the weighted mean of the control event rate (*i.e.* the incidence of an end point with placebo) and the experimental event rate (*i.e.* the incidence of the same end point with NAC). A positive number-needed-to-treat indicated how many patients had to be exposed to NAC in order to achieve a particular outcome (*e.g.* prevention of any exacerbation) in one of them, who would not have had this outcome had they all received placebo. A negative number-needed-to-treat point estimate indicated that the end point happened more often with placebo. The 95% CI around the number-needed-to-treat was obtained by taking the reciprocals of the values defining the 95% CI for absolute risk reduction [18]. A 95% CI ranging from one limit with a negative value to another with a positive value indicated absence of a statistically significant difference between NAC and placebo (*i.e.* the CI included infinity). Calculations were performed using Excel version 98 on a Power Macintosh G3.

Results

Retrieved trials

Thirty-nine potentially relevant trials on the effect of oral NAC in patients with chronic bronchitis were retrieved. Of these, 28 were subsequently excluded. Thirteen had no placebo or "no treatment" control group [19–31], three were uncontrolled series [32–34], three reported efficacy data but not in dichotomous form [35–37], two were duplicate reports [38, 39] (*i.e.* the same data had been published previously as a full report [37, 40]) and six did not contain relevant data on efficacy or harm with oral NAC [41–46]. One report was in children [47]; it was decided to exclude this report from further analyses

because all other reports were in adults. No unpublished data were retrieved. Two of three manufacturers (Inpharzam, Cadempino, Switzerland and Novartis, Berne, Switzerland) answered our enquiry; none could provide any additional relevant data.

Eleven randomized controlled NAC trials from five countries (UK four, Italy three, Sweden two, Germany one, Denmark one), published between 1976 and 1994, were analysed (table 1) [40, 48–57]. A recently updated Cochrane Review on the effect of different oral mucolytic agents in patients with chronic bronchitis included only eight NAC trials [12]. These reviewers excluded one paper [53] because "it did not report the standard deviation for the outcome measures of interest", and their search strategy failed to retrieve two further reports [40, 54], one of which was in German [54]. Thus the present analysis included three more trials [40, 53, 54], published between 1980 and 1986, with data from 331 patients.

In all eleven trials, a total of 2,540 patients were randomized to either NAC or placebo; efficacy data from 2,011 (79% of all randomized) patients were subsequently analysed by the original trialists. Dropout rates were highest (35.5%) in the largest trial [55]. The most frequently reported reasons for dropout were losts to follow-up and adverse effect-related withdrawal (see below). For efficacy data, an intention-to-treat analysis was not possible because the original trials reported such data inconsistently. Of the 2,011 analysed patients, 996 received NAC and 1,015 received placebo. The mean number of analysed patients who received NAC per trial was 91 (range 10–258). The median validity score was 4 (range 3–5). All but three trials [48, 54, 57] used placebo and NAC tablets of identical shape, form and taste.

All NAC treatments were given orally, two or three times daily, at doses of 400 or 600 $mg \cdot day^{-1}$. Treatment periods were 4 weeks in one small trial [40], 12 weeks in one [53], 20 weeks in one [50], 22 weeks in one [52], 24 weeks in six [49, 51, 54–57] and 23–32 weeks in one [48].

Patient characteristics

All patients were adults and had chronic bronchitis, in nine trials according to the definition of the Medical Research Council [2]. The percentages of patients per trial who were smokers or exsmokers ranged 72–100%. A clear risk stratification was not possible because studies reported patient characteristics, risk factors and lung function inconsistently. For instance one study only reported previous hospital admission as a risk factor [50]. Another indicator of the underlying risk, the mean number of exacerbations in the year preceding the trial, was not reported in four trials [40, 49, 51, 53]. In seven trials, this number was 1–3 [48, 50, 52, 54–57]. In two of these, this number was >3 in a subgroup of the study population [48, 55].

Yet another indicator of the underlying risk may be lung function. However, two studies reported neither lung function nor exacerbation rate before the start of the trial [51, 53]; a third study reported the mean exacerbation rate in the previous year but no lung function data [56]. In two studies, the mean FEV_1 was <50% of the predicted value [40, 50].

Prevention of exacerbations

Nine of the eleven valid trials reported prevention of any exacerbation as an outcome in 1,456 patients who were treated for 12–24 weeks (table 2) [48–55, 57]. In all studies that provided a definition of exacerbation, it was defined according to clinical symptoms (*i.e.* increase in cough, mucopurulent sputum and/or dyspnoea). The event rate scatter suggested superiority of NAC compared with placebo for prevention of exacerbation (fig. 1). For each trial, the percentage of patients without any exacerbation was higher with NAC than with placebo. The difference reached statistical significance in the two largest trials with 698 patients (48% of the patients of all nine trials) (table 2) [48, 55]. There was no evidence of a relationship between efficacy (*i.e.* prevention of any exacerbation) and duration of treatment with NAC or cumulative dose of NAC, respectively (fig. 2).

One trial with 72 treated patients produced an outlier [50]. In this trial, the FEV_1 before the start of treatment was reported and suggested severe airway obstruction (*i.e.* <50% pred). The treatment period was 20 weeks and the cumulative NAC dose 84 g. Only 10.5% of patients receiving placebo and 15.3% of those receiving NAC had no exacerbation (figs. 1 and 2); this difference was not statistically significant; the number-needed-to-treat point estimate was 21, compared with placebo (table 2).

In the other trials, 19–60% of patients receiving placebo and 40–70% of those receiving NAC had no exacerbation (figs. 1 and 2). In one trial, mean peak flow values suggested mild airflow obstruction in the study population; no beneficial effect of NAC on prevention of exacerbations was detectable (number-needed-to-treat point estimate 27, compared with placebo) [54]. The other trials either did not report any FEV_1 [51, 53] or, when reported, they suggested mild airway obstruction, and the numbers needed to treat to prevent any exacerbation with NAC compared with placebo ranged 3.5–8.0 (table 2).

When data from all trials which reported exacerbation were combined, the difference between NAC and placebo was statistically significant (table 2). With NAC, 351 of 723 (48.5%) patients were free of any exacerbation during the study period compared with 229 of 733 (31.2%) receiving placebo (fig. 1). The relative benefit with NAC was 1.56 (95% CI 1.37–1.77); the number-needed-to-treat for one patient having no exacerbation with NAC compared with placebo was 5.8 (95% CI 4.5–8.1). Exclusion of the trial which produced the outlier [50] from the combined analysis had no significant impact on this result.

Only one trial reported the number of patients having an exacerbation leading to hospitalization [56]. With NAC, four of 258 (1.6%) patients had to be hospitalized within the 24-week study period and with placebo nine of 268 (3.4%), a difference which was not statistically significant (relative benefit 0.47 (0.16–1.42), number-needed-to-treat 55 (95% CI -23–121).

Patient self-assessment

In five trials (928 patients), different three- to six-point scales of patient self-assessment of treatment efficacy were reported, and extraction of the number of patients who

Table 1. – *N*-acetylcysteine (NAC) and chronic bronchitis. Analysed randomized controlled trials

[Ref.]	Patients n					Patient characteristics			Active drug*	Score
	Entering trial	Rand.	Total analysed	Analysed NAC	Analysed placebo	Risk factors	Lung function at baseline	Concomitant medication		
[40]	34	34	29	15	14	Chronic bronchitis in all^{+}; 21 (72%) of analysed patients smokers; previous exacerbation rate not reported	FEV1 20–70% pred	Corticosteroid (route NA)	NAC 200 mg *t.i.d. p.o.* 4 weeks	4
[48]	285	259	203	98	105	Chronic bronchitis in all^{+}; 203 (100%) of analysed patients smokers/ exsmokers; ≥1 exacerbation·yr^{-1}	FEV1 >50% pred (mean 80% pred)	β_2-Agonists, theophylline, corticosteroids (route NA)	NAC 200 mg *b.i.d. p.o.* 23–32 weeks	4
[49]	21	21	19	10	9	Chronic bronchitis in all^{+}; previous exacerbation rate not reported	FEV1 >40% pred	NA	NAC 200 mg *b.i.d. p.o.* 24 weeks	4
[50]	244	200	148	72	76	Chronic bronchitis in all^{+}; 179 (99%) of evaluable patients smokers/ exsmokers; ≥1 exacerbation·yr^{-1} in 3 preceeding yrs	FEV1 <50% pred	NA	NAC 200 mg *b.i.d. p.o.* 20 weeks	5
[51]	80	80	69	35	34	Chronic bronchitis in all^{+}; previous exacerbation rate not reported	NA	Tetracyclines, broncho-dilators, orciprenaline	NAC 300 mg *b.i.d. p.o.* 3× weekly 24 weeks	4
[52]	165	153	129	59	70	Chronic bronchitis in all^{+}; 153 (100%) of patients who entered the trial smokers/exsmokers	Mean FEV1 >50% pred; NAC 2.34±0.10 L, P 2.34±0.09 L	Yes, not specified	NAC 300 mg *b.i.d. p.o.* 22 weeks	3
[53]	155	155	121	61	60	Chronic bronchitis in all; 107 (88%) of analysed patients smokers/ exsmokers; previous exacerbation rate not reported	NA	Bronchodilators	NAC 200 mg *t.i.d. p.o.* 12 weeks	4
[54]	252	252	181	90	91	Chronic bronchitis in all; 223 (88%) of patients who entered the trial smokers/exsmokers; ≥1 exacerbation·yr^{-1}	PEF:NAC 300±115 L·min^{-1}, P 306±136 L·min^{-1}	Bronchospasmolytics, corticosteroids, antiallergics	NAC 300 mg *b.i.d. p.o.* 24 weeks	3
[55]	744	744	495	254	241	Chronic bronchitis in all^{+}; 121 (24%) of analysed patients with noxious work environment, 328 (66%) smokers/exsmokers; exacerbation rate 0, 1–3, 4–6 exacerbations·yr^{-1}	FEV1 >40% pred	Cardiovascular drugs, diuretics, bronchodilators, corticosteroids	NAC 200 mg *b.i.d. p.o.* 24 weeks	4
[56]	526	526	526	258	268	All chronic bronchitis^{+}; 451 (86%) of randomized patients smokers/ exsmokers; ≥1 exacerbation·yr^{-1} (mean 3)	NA	Cardiovascular drugs, xanthines, steroids (inhaled and *p.o.*), thiazide and loop diuretics	NAC 200 mg *t.i.d. p.o.* 24 weeks	4
[57]	116	116	91	44	47	All chronic bronchitis^{+}; 116 (100%) smokers/exsmokers; ≥1 exacerbation·yr^{-1}	Mean peak flow 305 L·min^{-1}	β-Agonists, theophylline, steroids	NAC 300 mg *b.i.d. p.o.* 24 weeks	3

*: in all cases, the comparator was placebo (P) (same route, frequency and duration); $^{+}$: as defined in [2]. FEV1: forced expiratory volume in one second; NA: not available; PEF: peak expiratory flow; % pred: percentage of the predicted value.

Table 2. – *N*-acetylcysteine *versus* placebo in chronic bronchitis. Efficacy data

[Ref.]	Event rates %		Patients with end point/total patients n		Relative benefit	Number-needed-to-treat
	With NAC	With placebo	With NAC	With placebo	Mean (95% CI)	Mean (95% CI)
Prevention of any exacerbation						
[48]	39.8	19.0	39/98	20/105	2.09 (1.31–3.32)	4.8 (3–12)
[49]	70.0	44.4	7/10	4/9	1.58 (0.68–3.63)	3.9 (1.5–-5.7)
[50]	15.3	10.5	11/72	8/76	1.45 (0.62–3.40)	21 (6.4–-17)
[51]	51.4	32.4	18/35	11/34	1.59 (0.89–2.85)	5.2 (2.4–-27)
[52]	61.0	48.6	36/59	34/70	1.26 (0.92–1.72)	8.0 (3.4–-22)
[53]	67.2	60.0	41/61	36/60	1.12 (0.85–1.47)	14 (4.1–-10)
[54]	41.1	37.4	37/90	34/91	1.10 (0.77–1.58)	27 (5.6–-9.6)
[55]	52.8	24.1	134/254	58/241	2.19 (1.70–2.82)	3.5 (2.7–4.9)
[57]	63.6	51.1	28/44	24/47	1.25 (0.87–1.78)	8.0 (3.1–-13)
Combined	48.5	31.2	351/723	229/733	1.56 (1.37–1.77)	5.8 (4.5–8.1)
Improvement rated by patients						
[40]	53.3	21.4	8/15	3/14	2.49 (0.82–7.55)	3.1 (1.5–-80)
[49]	70.0	33.3	7/10	3/9	2.10 (0.77–5.76)	2.7 (1.3–-19)
[50]	61.1	55.3	44/72	42/76	1.11 (0.84–1.45)	17 (4.6–-10)
[53]	34.4	25.0	21/61	15/60	1.38 (0.79–2.41)	11 (3.9–-15)
[55]	66.9	32.0	206/308	97/303	2.09 (1.74–2.51)	2.9 (2.4–3.6)
Combined	61.4	34.6	286/466	160/462	1.78 (1.54–2.05)	3.7 (3.0–4.9)

CI: confidence interval.

reported improvement of their symptoms was possible (table 2) [40, 49, 50, 53, 55]. Data from patients reporting "good" or "excellent" improvement in two studies [53, 55], "much better" or "better" in one [50], "improvement" in one [40], and "discreto", "buono" or "ottimo" in one [49] were pooled for analysis. In four of these trials, the study period was 12–24 weeks and in one it was 4 weeks [40]. The event rate scatter suggested superiority of NAC (fig. 3). For each trial, the event rate (*i.e.* percentage of patients reporting improvement) was higher with NAC than with placebo. The difference in favour of NAC reached statistical significance in the largest trial with 611 patients (66% of the patients of all trials) (table 2) [55]. When the data from all five trials were combined, the difference between NAC and placebo was statistically significant. With NAC, 286 of 466 (61.4%) patients reported improvement, compared with 160 of 462 (34.6%) receiving placebo. The relative benefit with NAC was 1.78 (95% CI 1.54–2.05); the number-needed-to-treat for one patient reporting improvement of their bronchitis-related symptoms compared with placebo was 3.7 (95% CI 3.0–4.9). Exclusion of the trial with the shortest study period [40] had no impact on this result (relative benefit in favour of NAC 1.76 (95% CI 1.53–2.04); number-needed-to-treat 3.8 (95% CI 3.0–4.9).

Sensitivity analysis: impact of trial size

The end point "no exacerbation" was chosen to test the impact of trial size on outcome. For each trial which reported the number of patients without any exacerbation (table 2), the size of the NAC group was plotted against control event rate (*i.e.* the incidence of the end point with placebo), relative benefit and number-needed-to-treat, respectively (fig. 4). In eight of the nine trials, group sizes ranged 10–98 patients. In the ninth trial, the group size was 254 patients [55]. Control event rates ranged ~11–60% [50, 53], relative benefit point estimates 1.10–2.09 [48, 54] and numbers-needed-to-treat 3.5–27 [54, 55]. The largest trial [55] had a control event rate of 24%, the highest relative benefit (2.19) and the lowest number-needed-to-treat (3.5). There was no evidence of any relationship between group size and control event rate, relative benefit or number-needed-to-treat, respectively.

Adverse effects

Six trials with 1,336 treated patients reported gastrointestinal adverse reactions [40, 48–50, 55, 57]. With NAC, 68 of 665 (10.2%) patients had dyspepsia, diarrhoea or heartburn during the study period, compared with 73 of 671 (10.9%) control patients (table 3). The relative risk with NAC was 0.96 (95% CI 0.70–1.30); the number-needed-to-harm for one patient having a gastrointestinal

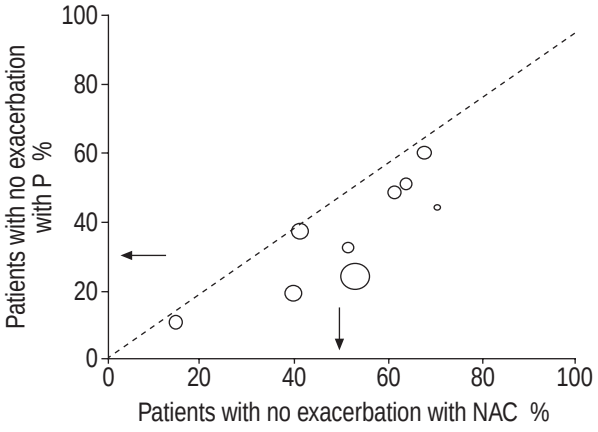

Fig. 1. – Absence of any exacerbation with oral *N*-acetylcysteine (NAC) or placebo (P) in chronic bronchitis. Each symbol represents one trial. Symbol sizes are proportional to trial sizes. Arrows are weighted means. - - - - : equality.

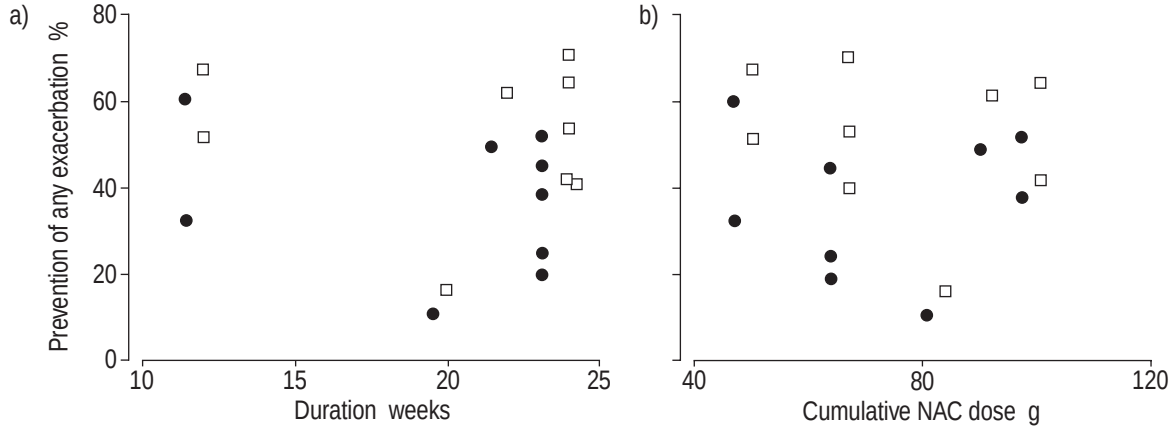

Fig. 2. – Lack of effect of: a) study period (12–24 weeks); and b) cumulative dose of oral *N*-acetylcysteine (50.4–100.8 g) on the prevention of exacerbations. Each trial is represented by two symbols (*i.e.* NAC (□) and placebo (●), respectively). Data from nine trials are shown.

adverse drug reaction with NAC compared with placebo was -153 (-25–38).

In ten trials with 2,441 randomized patients, study withdrawal due to adverse reactions was reported [40, 48, 50, 52–57]. With NAC, 79 of 1,207 (6.5%) patients were withdrawn. With placebo, 87 of 1,234 (7.1%) patients were withdrawn (table 3). The relative risk with NAC was 0.92 (95% CI 0.69–1.23); the number-needed-to-harm for one withdrawal due to adverse drug reactions with NAC compared with placebo was -198 (-40–67).

Other end points

Five studies reported FEV1 at both the beginning and the end of the study period [40, 48, 49, 52, 55]. In one study with severe COPD [40], FEV1 improved statistically significantly with NAC treatment from 25 to 30% pred, whereas they did not with placebo. The study period was short (4 weeks). The authors concluded that these changes were not "dramatic". In another trial with mild COPD and a longer study period (24 weeks) [55], patients receiving NAC treatment showed a statistically significant improvement in the FEV1 from 2.16 to 2.25 L; this was not the case with placebo. These authors concluded that the size of the mean effect was too small to be clinically meaningful. In the other three trials, NAC treatment had no effect on FEV1.

In two trials, peak expiratory flow was measured [54, 57]. However, only values before but not after the study period were reported.

Authors of two reports came to the conclusion that NAC had no beneficial effect in patients with chronic bronchitis [50, 56]. In all other reports, the conclusions of the original authors were in favour of NAC treatment.

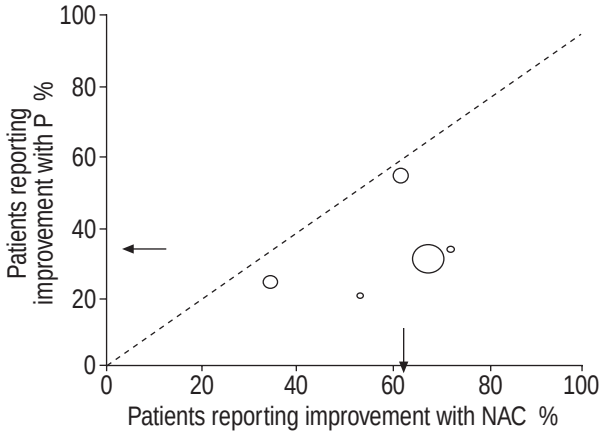

Fig. 3. – Improvement of symptoms (patient self-assessment) with oral *N*-acetylcysteine (NAC) compared with placebo (P) in chronic bronchitis. Each symbol represents one trial. Symbol sizes are proportional to trial sizes. Arrows are weighted means. - - - - : equality.

Discussion

The main conclusion of this meta-analysis is that oral NAC is more efficacious but not more harmful than placebo in the treatment of chronic bronchitis. Of 100 patients with chronic bronchitis taking oral NAC, 400–600 mg·day^{-1} for 12–24 weeks, 17 (number-needed-to-treat, 5.8), who would have had any exacerbation had they all received placebo, will not have one. Also, of 100 treated patients, 26 (number-needed-to-treat, 3.8) will report that the NAC treatment has led to improvement of their bronchitis-related symptoms, who would not have done so had they all received placebo. No difference could be found in the incidence of gastrointestinal adverse effects between patients receiving NAC and those receiving placebo. Nor was there any difference in the number of patients who had to be withdrawn from the studies because of adverse drug reactions. Thus, based on these systematically searched, relevant and valid data, oral NAC for 3–6 months seems to be of benefit in patients with chronic bronchitis.

How the benefit is achieved remains unclear. There is growing evidence that COPD may be related to increased oxidative and inflammatory stress [5]. NAC, as a thiol-containing compound, may act as an antioxidant, enhancing the intracellular production of glutathione, an important element in pulmonary antioxidant defence [5]. It has also been suggested that NAC may have an effect on bacterial adhesive capacity [58]. Whether or not these mechanisms are responsible for the favourable effect of NAC on exacerbations and symptoms in chronic bronchitis cannot be addressed in this review.

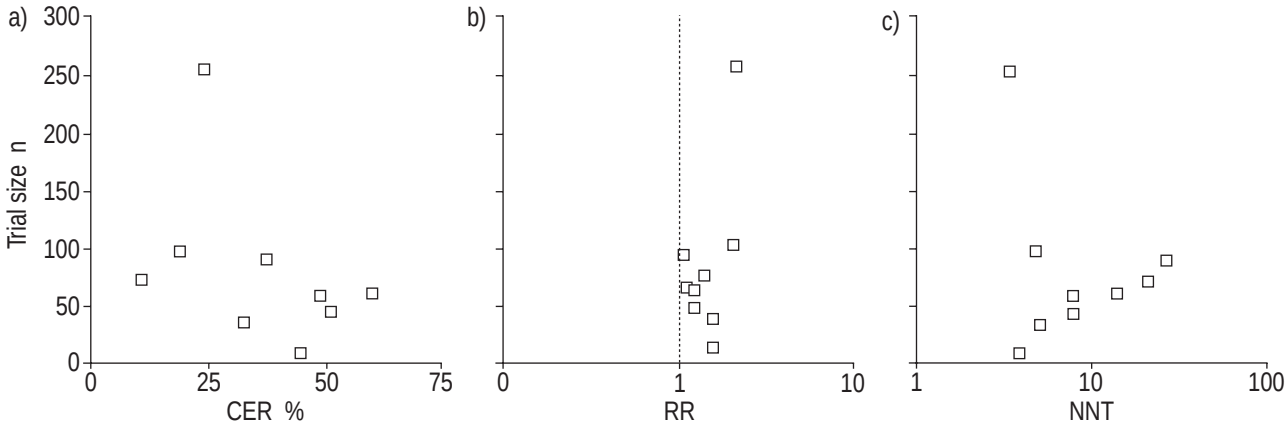

Fig. 4. – Efficacy of *N*-acetylcysteine (NAC) compared with placebo in prevention of exacerbations in nine randomized controlled trials. Relationship between trial size (number of patients treated with NAC) and: a) control event rate (CER); b) relative risk (RR); and c) number-needed-to-treat (NNT).

Two questions, however, need to be answered. First, what is the likelihood of this meta-analysis giving wrong results? Secondly, what is the clinical relevance of the results? A threat to meta-analysis is bias. It is obvious that including flawed data into a meta-analysis leads to flawed conclusions from that meta-analysis. The risk is that the effect of a treatment will be overestimated. Thus, it must be ensured that only valid data are analysed. Different sources of bias in clinical trials have been unearthed during the last few years, namely unconcealed treatment allocation and inadequate blinding [59], language selection [60], duplicate publication [61], small trial size [62] and poor trial quality [63]. In this meta-analysis, relevant reports were searched systematically and without language restriction, and data from randomized controlled trials only were considered. There was not much room, therefore, for selection bias. Minimizing observer bias by using indistinguishable placebo and NAC tablets was very common in the original reports. Also, the incidence of adverse effects was not increased with NAC compared with placebo; thus it may be assumed that unblinding of the study treatments due to adverse drug reactions did not happen. Duplicate publications were excluded from analyses [38, 39]. Sensitivity analysis suggested that smaller trials did not overestimate treatment effect compared with larger trials (fig. 4). Indeed, the largest trial [55] exaggerated treatment effect compared with the smaller trials (figs. 1 and 2). The observed variability in control event rates (*i.e.* the percentage of placebo patients without exacerbation), as seen in the smaller trials, may be explained by random variation in trials of these sizes [62]. Manufacturers but not authors were contacted, leaving the current authors open to the criticism of publication bias. However, there was no evidence of selective publication

Table 3. – *N*-acetylcysteine (NAC) *versus* placebo in chronic bronchitis. Adverse drug reactions

[Ref.]	Event rates %		Patients with end point/total patients n		Relative risk	Number-needed-to-harm
	With NAC	With placebo	With NAC	With placebo	Mean (95% CI)	Mean (95% CI)
Gastrointestinal symptoms (GI-ADR)						
[40]	16.7	6.3	3/18	1/16	2.67 (0.31–23.1)	9.6 (3.2–-9.5)
[48]	17.3	18.2	22/127	24/132	0.95 (0.56–1.61)	-116 (-9.8–12)
[49]	0.0	10.0	0/11	1/10	NA	-10 (-3.5–12)
[50]	18.8	15.6	16/85	15/96	1.20 (0.63–2.29)	31 (7–-13)
[55]	4.7	7.2	17/365	26/360	0.64 (0.36–1.17)	-39 (-17–114)
[57]	16.9	10.5	10/59	6/57	1.61 (0.63–4.14)	16 (5.3–17)
Combined	10.2	10.9	68/665	73/671	0.96 (0.70–1.30)	-153 (-25–38)
ADR leading to study withdrawal						
[40]	16.7	12.5	3/18	2/16	1.33 (0.25–7.0)	24 (3.6–-5.1)
[48]	3.9	2.3	5/127	3/132	1.73 (0.42–7.1)	60 (17–-39)
[49]	0.0	10.0	0/11	1/10	NA	-10 (-3.5–12)
[50]	1.2	2.1	1/85	2/96	0.56 (0.05–6.12)	-110 (-22–36)
[52]	1.3	0.0	1/75	0/78	NA	75 (26–-79)
[53]	5.3	6.3	4/75	5/80	0.85 (0.24–3.06)	-109 (-12–16)
[54]	6.3	6.5	8/128	8/124	0.97 (0.38–2.50)	-496 (-16–17)
[55]	1.6	3.5	6/371	13/373	0.46 (0.18–1.21)	-54 (-24–255)
[56]	15.9	17.2	41/258	46/268	0.93 (0.63–1.36)	-79 (-13–20)
[57]	16.9	12.3	10/59	7/57	1.38 (0.56–3.38)	21 (5.7–12)
Combined	6.5	7.1	79/1207	87/1234	0.92 (0.69–1.23)	-198 (-40–67)

ADR: adverse drug reaction; GI-ADR: gastrointestinal ADR; CI: confidence interval.

of positive data (fig. 4). Finally, these trials were of acceptable methodological quality according to the instrument of critical appraisal used in the present study [13]. The large number of withdrawals in some trials, however, remains a matter of concern. The high mean dropout rate of patients who did not finish the trials may reflect the difficulty of running long-term studies in this setting. Most withdrawals (*i.e.* 166 of 539 patients) were related to adverse drug reactions, and these were not different between NAC and placebo. An intention-to-treat analysis for efficacy data was not possible. Thus the possibility that there was a link between an increased likelihood of drug-related adverse effects and a lack of efficacy with NAC cannot be excluded. Future trials should include intention-to-treat analyses.

Some further issues remain unresolved. These may help to define a research agenda. For instance, although stratification of the data into lower- and higher-risk populations was attempted, it was not possible to draw sensible conclusions regarding the efficacy of NAC in different patients with different underlying risks for exacerbations. The main reason for this was that the original reports were not consistent in reporting patient characteristics and baseline values. Thus it is still not known whether efficacy is different in a patient who suffers from frequent exacerbations, or in a patient with severe obstruction compared to one with mild obstruction. Individual patient data analyses are clearly needed.

Secondly, the clinical relevance of the beneficial effect on the prevention of exacerbations may be questioned. The role of exacerbations in causing permanent alteration or in accelerating long-term decline in pulmonary function is unclear [64]. Three prospective studies showed no correlation between exacerbation and long-term loss of pulmonary function [65–67], whereas another one did [68]. It may be argued that exacerbations may lead to frequent hospitalizations, and these are likely to have a major impact on healthcare for two reasons. First, in patients with chronic airways obstruction, hospitalization due to exacerbation is an indicator of poor outcome [69]. Secondly, hospitalization increases healthcare costs. Only one trial reported the number of patients needing hospitalization due to exacerbation [56]. In this trial, the rate of hospitalization with placebo was low (3.4%), and the number-needed-to-treat suggested that ~55 patients with NAC would have to be treated for one not to be hospitalized who would have been hospitalized had they all received placebo. This result, although not statistically significant, may be regarded as potentially relevant. The problem is that the event rate is low and large numbers are needed to show any statistically significant benefit with NAC. Indeed, if the rates of hospitalization with both placebo (3.4%) and NAC (1.6%) that were reported in this trial were approximately correct, >2,500 patients would have to be randomized to NAC or placebo in order to detect a statistically significant difference in the rate of hospitalization in favour of NAC. Thus, unless a very large trial is initiated, or relevant data from several smaller trials can be pooled in a meta-analysis, the economic impact of prevention of hospitalization due to exacerbations in patients with chronic obstructive bronchitis will remain unknown. Further end points in a future cost-effective analysis could be duration of disease-free intervals, saved days of absence of work and costs of concomitant medications (antibiotics and corticosteroids, for instance).

Thirdly, with respect to clinical relevance, it is important to remember that the duration of the longest study in this meta-analysis was only 6 months. Within this limit, there was no evidence of any impact of either study duration or cumulative NAC dose on treatment efficacy (fig. 3), and there was no increased risk of adverse drug reactions. However, if patients are to take NAC on a preventive basis, they are going to take it presumably all the time or at least every winter. There is clearly a need for studies that look at both the beneficial and adverse effects of regular treatment over a longer period of time.

Finally, the variability in end points reported in these trials suggests uncertainty of trialists about which end point is the most relevant in this clinical setting. Prevention of exacerbation, for instance, was not reported in all trials. Also, there was no evidence that the benefit from NAC was related to major changes in lung function. Thus parameters of lung function may be surrogate end points for estimation of the efficacy of mucolytic agents in COPD. The authors believe, however, that, in this clinical context, improvement of symptoms, as judged by the patients themselves, may be an important end point. One in four patients reported improvement of their symptoms while taking NAC compared with those receiving placebo (61.4 *versus* 34.6%). It is not known exactly what the end point "improvement of symptoms" means to the daily life of a patient with COPD. Quality of life, for instance, was not reported in any trial. It might be speculated that, in these patients, improvement of symptoms indicates an increased level of satisfaction or a better quality of life.

In conclusion, based on data from systematically searched randomized controlled trials, treatment for 3–6 months with oral *N*-acetylcysteine in patients with chronic bronchitis is associated with a statistically significant decrease in the risk of exacerbations, and an even greater effect on bronchitic symptoms. This treatment is well tolerated. Cost-effectiveness analyses in different populations with different underlying risks should address the questions as to whether the benefits of oral *N*-acetylcysteine are sufficient to justify its routine and long-term use in all patients with chronic bronchitis, or whether there are specific subgroups that would benefit most.

Acknowledgements. The authors thank D. Haake from the Documentation Service of the Swiss Academy of Medical Sciences for help in searching electronic databases.

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