

***N*-acetylcysteine reduces the risk of re-hospitalisation among patients with chronic obstructive pulmonary disease**

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ABSTRACT: The aim of this study was to evaluate the effect of oral *N*-acetylcysteine in the prevention of re-hospitalisation for chronic obstructive pulmonary disease (COPD) exacerbations.

Using the PHARmacoMOrbidity linkage (PHARMO) system the authors included all patients aged ≥ 55 yrs who had been dispensed medication, labelled for respiratory indications (anatomical therapeutic chemical (ATC) classification system: R03), between 1986–1998 and who had also been hospitalised for COPD (International Classification of Diseases (ICD)-9: 491, 492, 496) in this time frame. These subjects were subsequently divided into two groups, those who had received *N*-acetylcysteine following discharge from their first admission between 1986–1998 and those who had not. All the patients were studied starting from their initial discharge, until their first readmission, death or end of data collection period. The maximum follow-up period was 1 yr.

A total of 1,219 patients, who were hospitalised for COPD between 1986–1998, were included in this study. After adjustment for disease severity, it was observed that the use of *N*-acetylcysteine was significantly associated with a reduced risk of readmission. The readmission risk was significantly lower in patients with high average daily doses of *N*-acetylcysteine.

In conclusion it was observed that *N*-acetylcysteine reduces the risk of re-hospitalisation for chronic obstructive pulmonary disease by $\sim 30\%$ and that this risk reduction is dose-dependent.

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In the elderly, the most common respiratory illness is chronic obstructive pulmonary disease (COPD). COPD is a leading chronic disorder in Western society and is characterised by chronic airflow limitation that is not fully reversible, usually progressive and this airway obstruction is associated with inflammation of the airways [1]. In Europe and the USA COPD is ranked as the third and fourth most common cause of death, respectively [1, 2]. Many COPD patients suffer from acute episodes of an increase in severity of the disease with irreversible airway obstruction, known as exacerbations. The frequency of these exacerbations varies between 1.3–4.0·yr⁻¹, depending on the definition and grading of severity, and can often lead to hospitalisation [3–5]. Since exacerbations are a major cause of loss of quality of life, increased morbidity, hospitalisation or death, one of the major objectives of treatment of COPD (from both a medical and an economical perspective) is the prevention, identification and prompt treatment of exacerbations [1, 4].

Chronic mucus hypersecretion is significantly and consistently associated with an increased risk of hospitalisation for COPD patients [6]. *N*-acetylcysteine, a mucolytic agent with additional antioxidative properties, has an extensive and sometimes controversial history of use in the treatment of COPD [7, 8]. In some European countries *N*-acetylcysteine is used extensively for the treatment of COPD, where as prescribers in the USA, UK and Australia are less convinced that the drug is effective [9]. Mucolytics increase expectoration of sputum by reducing its viscosity and/or hypersecretion

[10]. Treatment with *N*-acetylcysteine has been shown to result in symptomatic improvement in patients with COPD [7]. Moreover, a recent systematic overview related treatment with *N*-acetylcysteine with a reduction in acute exacerbations and days of illness [9]. Several reports have shown that treating chronic bronchitis patients with *N*-acetylcysteine is both beneficial and cost-effective [11, 12].

To date little data are available on the role of *N*-acetylcysteine in the prevention of hospital admission for COPD sufferers [9]. The objective of the present study was to evaluate the effect of *N*-acetylcysteine on the prevention of re-hospitalisation for COPD exacerbations.

Methods

Data for the present study were obtained from the PHARmacoMOrbidity linkage (PHARMO) system. This system includes patient histories of hospital admissions and outpatient drug usage of the 450,000 residents of eight cities in the Netherlands. The data available was from 1985 onwards and is continuously updated. The hospital records consist of a discharge diagnosis, and up to nine secondary diagnoses (International Classification of Diseases (ICD)-9-CM) and related operations and procedures. Detailed information (type, prescriber, dose, costs, legend duration of use, *etc.*) of all prescribed and truly dispensed drugs are available for each individual patient with an average follow-up period of

7–8 yrs. Both hospital admissions and histories of drug use are virtually complete and linked on a patient level using probabilistic record linkage techniques that have been rigorously validated for up to 10,000 patients. Data from the PHARMO system have been used for >40 studies published in major peer-reviewed journals [13–14].

Selection of study subjects

Due to the increased probability of COPD, relative to other respiratory conditions *e.g.* asthma, occurring in persons aged >55 yrs only patients aged ≥ 55 yrs were selected for this study. These subjects were required to have been dispensed a drug with a respiratory indication (anatomical therapeutic chemical (ATC) classification system: R03) during 1986–1998. These drugs were short- or long-acting beta-agonists, xanthine-derivatives, parasympatholytics, inhaled corticosteroids, cromones, and systemic beta-agonists. From this base cohort, patients who were hospitalised for COPD at any point during 1986–1998, as defined by a first primary discharge diagnosis of chronic bronchitis (ICD-9: 491), emphysema (ICD-9: 492) or chronic airway obstruction (ICD-9: 496), were followed after their initial known hospital discharge. These patients were divided into two categories, those who received *N*-acetylcysteine immediately after discharge and those who did not. The follow-up of patients admitted for COPD started the day of discharge until the first re-admission for chronic bronchitis (ICD-9: 491), emphysema (ICD-9: 492), or chronic airway obstruction (ICD-9: 496), death, or end of data collection, whichever of these events came first. The maximum follow-up period was 1 yr.

Potential risk factors

Since patients with more severe forms of the disease are at an increased risk of undergoing exacerbations that require readmission to hospital when compared to patients with less severe disease, the authors controlled for severity of disease. This was conducted by using an algorithm based on the patterns of use of respiratory drugs [15, 16]. In brief, as antibiotics are usually prescribed to patients who experience an exacerbation, these drugs were considered as a proxy for a severe episode. The same is true for oral corticosteroids and nebulised beta-agonists. The use of three or more classes of respiratory drugs, were also considered a proxy for disease severity. Previous reports have indicated that antihistamines, as well as antitussive medication and nasal compounds, are associated with exacerbations of obstructive lung diseases. Although these findings were mainly based on studies in asthma, the present authors considered the use of these drugs as signatures for increasing complexity of respiratory disease [17]. All these markers of disease severity were ascertained dichotomously (yes/no) every 2 months during the follow-up and were treated as time-dependent covariates in the statistical model.

Analyses

The relative risk of re-hospitalisation for COPD among patients using *N*-acetylcysteine, compared to non-users, was estimated from Cox proportional hazards survival analysis. The severity markers, as defined above, were included as time-dependent covariates, measured in periods of 2 months during an individual's follow-up period. The average daily dose of *N*-acetylcysteine was measured by dividing the total amount

of dispensed milligrams per person by the total follow-up period for that individual. All relative risks were expressed as point estimates with 95% confidence intervals (CI). A separate Kaplan-Meier analysis was performed to visualise the treatment effect of *N*-acetylcysteine over time during the year of follow-up.

Results

A total of 1,219 patients were identified as having been admitted to hospital for COPD between 1986–1998 (table 1). The total follow-up of these patients was 337,485 person days (average follow-up time was 276 days). In this cohort of hospitalised patients the ratio of males to females was ~2:3 (59.6%) and ratio of patients >75 yrs was >1:3 (36.7%). At the time of discharge, xanthine derivatives (45.9%) were the most frequently prescribed drugs, followed by inhaled short-acting beta-agonists (39.1%), inhaled steroids (35.9%) and parasympatholytics (35.2%). Moreover, the use of oral corticosteroids (51.4%) was highly prevalent immediately after discharge.

From the 1,219 patients identified, 311 (25.5%) were readmitted at least once within 1 yr after the last hospitalisation. The association between *N*-acetylcysteine and hospitalisation is shown in table 2. The numbers of *N*-acetylcysteine users represents patients that have been dispensed this drug at least once in the follow-up period. In general the use of *N*-acetylcysteine was significantly associated with a lower risk of re-hospitalisation, with relative risk=0.67 (95% CI: 0.53–0.85). Stratifying, by average daily dose of *N*-acetylcysteine, showed that the readmission risk was significantly lower in patients with high average daily doses (dose/response trend: $p < 0.0001$). The average time between the two consecutive admissions for the *N*-acetylcysteine users was 139 days and 87.6% of these patients had *N*-acetylcysteine at their disposal at the readmission date. Figure 1 shows the Kaplan-Meier curve for patients treated with and without *N*-acetylcysteine,

Table 1. – General characteristics of the 1219 study population hospitalised for chronic obstructive pulmonary disease

Variable	n	%
Female	492	40.4
Male	727	59.6
Age yrs		
55–64	257	21.1
65–74	515	42.2
≥ 75	447	36.7
Year of hospitalisation		
1986–1989	97	8.0
1990–1994	649	53.2
1995–1998	473	38.8
Drug usage at time of discharge		
Respiratory drugs		
Xanthine-derivates	560	45.9
Short-acting beta-agonists	477	39.1
Inhaled steroids	438	35.9
Parasympatholytics	429	35.2
Long-acting beta-agonists	110	9.0
Systemic beta-agonists	37	3.0
Cromones/nedocromil	18	1.5
Markers for severity		
Oral corticosteroids	627	51.4
≥ 3 respiratory drugs	214	17.6
Oral antibiotics	179	14.7
Antihistamines	58	4.8

Table 2. – Association of *N*-acetylcysteine use in patients and risk of readmission to hospital for chronic obstructive pulmonary disease

	Re-hospitalised			Not re-hospitalised			Relative risk [#] (95% CI)
	n	%	Person-days	n	%	Person-days	
Subjects n	311			908			
Overall use of <i>N</i> -acetylcysteine	97	31.2	13525	368	40.5	122503	0.67 (0.53–0.85)
Average daily dose mg							
0	214	68.8	28183	540	59.5	173274	1.00 (reference)
0–200	78	25.1	10457	217	23.9	70192	0.89 (0.68–1.15)
200–400	14	4.5	1938	62	6.8	20283	0.55 (0.32–0.95)
400–600	3	1.0	557	49	5.4	17637	0.16 (0.05–0.49)
>600	2	0.6	573	40	4.4	14391	0.13 (0.03–0.51)

CI: confidence interval. [#]: Adjusted by Cox regression for age, sex, year of first hospitalisation and disease severity (time-dependent).

demonstrating a protective effect of *N*-acetylcysteine for re-hospitalisation for COPD (log-rank test $p < 0.05$).

Discussion

The present study shows that the use of a mucolytic agent *N*-acetylcysteine, in patients ≥ 55 yrs, reduces the risk of re-hospitalisation for COPD exacerbations within 1 yr after previous hospitalisation, by $\sim 30\%$. This study also indicates that the relative risk of hospital readmission gradually and significantly decreases with increasing average daily dose of *N*-acetylcysteine.

In a recent review of the literature, POOLE and BLACK [9] found that regular use of mucolytics resulted in the significant reduction of exacerbations by 0.07 exacerbations·month⁻¹, they also showed a significant reduction in exposure days to antibiotics by 0.53·month⁻¹ and a reduction in the number of illness days per subject of 0.56 days·month⁻¹. The latter corresponds to >6.5 days on a yearly basis. The significant decline in days of sick leave was corroborated by the results of GRANDJEAN *et al.* [11]. This latter study further deduced from univariate sensitivity analysis that cost neutrality is reached with 0.6 (<0.25 –1.94, 95% CI) acute exacerbations per 6 months. Another meta-analysis revealed that in order to prevent one exacerbation per 12–24 weeks, six patients have to be treated with 400–600 mg·day⁻¹ of *N*-acetylcysteine [12]. It was also shown that four patients had to be treated during

this time frame in order for one patient to report an improvement in symptoms [12].

In chronic obstructive bronchitis, the airway component of COPD, mucus hypersecretion is by definition prominent, whereas the tracheobronchial clearance in these patients is often impaired [1]. A study by VESTBO *et al.* [6] showed that chronic mucus hypersecretion is significantly associated with an increased risk of hospitalisation for COPD patients [6]. Due to the loss of mucociliary clearance in combination with hypersecretion, mucus is pooled and this stimulates the colonisation of bacteria, although the precise role of bacteria in COPD exacerbations remains an issue of debate [18]. Subjects with COPD and chronic mucus hypersecretion are more prone to death from pulmonary infections than subjects without chronic mucus hypersecretion [19]. *N*-acetylcysteine modifies rheologic properties as the sulphhydryl groups it contains, directly split disulphide linkages of mucoproteins, enhancing airway clearance and consequently adversely affecting the conditions of bacterial colonisation. A study by RIISE *et al.* [20] showed that *N*-acetylcysteine is associated with low bacterial counts. Moreover, *N*-acetylcysteine may also directly prevent bacterial adherence to epithelial cells [21].

Another possible mechanism, by which *N*-acetylcysteine may be beneficial in the prevention of COPD exacerbations, is by its antioxidant properties. There is increasingly persuasive evidence to suggest that increased oxidative stress, the imbalance between protective antioxidants and free radical activity, may be involved in the pathophysiology of COPD [7, 22]. Sources for these oxidants are for example, cigarette smoke, and activated inflammatory cells. Within the lung, powerful antioxidant enzymes are present both intra- and extracellularly, *e.g.* glutathione peroxidase and superoxide dismutase. Levels of both these antioxidant enzymes are lowered in patients with COPD [7]. *N*-acetylcysteine contains thiol which may act as an antioxidant by providing cysteine extracellularly for the enhanced production of glutathione and thus increasing the resistance against oxidative stress.

Some methodological strengths and limitations of this study have to be mentioned. In the present study the authors looked at rehospital admission rates. POOLE *et al.* [9] concluded in their review, on the role of *N*-acetylcysteine in preventing exacerbation in COPD, that none of the studies so far reported on the effects of treatment with mucolytics on hospital admission for COPD [9]. Evaluating intended drug effects in a nonrandomised fashion, as with the present study, always carry the risk of confounding by indication, *i.e.* subjects with the highest risk of disease exacerbation (measured as re-hospitalisation) are more likely to be prescribed *N*-acetylcysteine [23, 24]. Another source of this type of exposure misclassification in the direction of usage by more

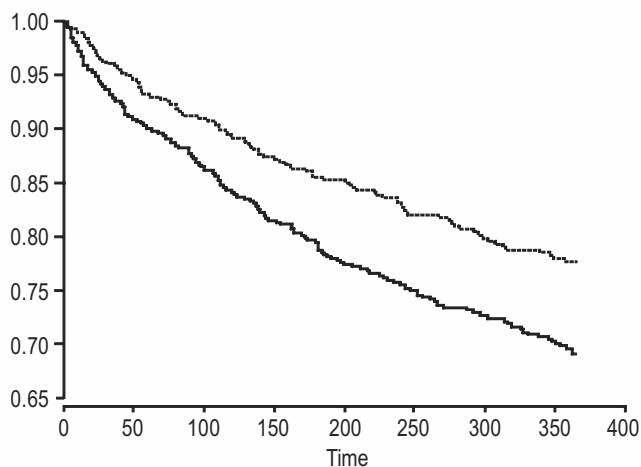


Fig. 1. – Kaplan-Meier curve showing risk of readmission to hospital for chronic obstructive pulmonary disease in patients with and without *N*-acetylcysteine (NAC). —: without NAC;: with NAC.

severely ill patients, could be the heavy debate on the efficacy of *N*-acetylcysteine in the mid and late 1990s in Dutch medical practices. This reflected the restricted reimbursement procedures for this drug in order to control prescribing [25]. By all means, confounding by indication would have resulted in an underestimation of the effect, *i.e.* bias towards the null. However, the present authors applied strategies to cope with this potential bias. All subjects, with or without *N*-acetylcysteine, were followed after hospitalisation for COPD, giving these patients a comparable baseline. Moreover, in order to reduce any residual risk of confounding by indication the authors adjusted, in the analysis, for the severity of the disease by means of time-dependent medication markers. Moreover, because of the changing prescription policies, the authors controlled for "year of hospitalisation" in the analysis. In addition, the percentage of *N*-acetylcysteine users was the same (36–40%) during the observed time period.

Since *N*-acetylcysteine can also be purchased without prescription, in which case the majority were not recorded into the PHARMO system, the authors might have missed some *N*-acetylcysteine usage in the observed patients. However, it was assumed that if this had occurred, it would be equally distributed among the rehospitalised and the non-rehospitalised patients. This nondifferential misclassification would also result in a bias towards the null.

In analogy to BLAIS *et al.* [15] and GARRETT *et al.* [16], short courses of corticosteroids and antibiotics, and the use of three or more drugs with a labelled respiratory indication, were used as markers of disease severity. This is also in agreement with an "add-on-step-down" approach as recommended in different obstructive lung disease guidelines [1]. However, the authors realise not every physician will diminish the number of different drugs once a patient's COPD is under control. A better marker for severity would be clinical measurement. However, the authors had no data on lung function tests at their disposal.

In conclusion, this study has shown that the use of *N*-acetylcysteine can decrease the risk of re-hospitalisation for chronic obstructive pulmonary disease by ~30%. The risk reduction however, needs a minimum average dose of 400 mg·day⁻¹ in order to reach a protective effect. With respect to this conclusion it will be interesting to see what data the Bronchitis Randomised on NAC Cost-Utility Study (BRONCUS) trial will generate in the near future [26].

References

- Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
- Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1998; 53: 129–136.
- Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
- Fabbri L, Beghe B, Caramori G, Papi A, Saetta M. Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998; 53: 803–808.
- Dewan NA, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest* 2000; 117: 662–671.
- Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.
- Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. *Am J Respir Crit Care Med* 1997; 156: 341–357.
- Gallon AM. Evaluation of nebulised acetylcysteine and normal saline in the treatment of sputum retention following thoracotomy. *Thorax* 1996; 51: 429–432.
- Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001; 322: 1–6.
- Del Donno M, Olivieri D. Mucoactive drugs in the management of chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis* 1998; 53: 714–719.
- Grandjean EM, Berthet PH, Ruffmann R, Leuenberger P. Cost-effectiveness analysis of oral *N*-acetylcysteine as a preventive treatment in chronic bronchitis. *Pharmacol Res* 2000; 42: 39–50.
- Stey C, Steurer J, Bachmann S, Medici TC, Tramèr MR. The effect of oral *N*-acetylcysteine in chronic bronchitis: a quantitative systematic review. *Eur Respir J* 2000; 16: 253–262.
- Herings RM, de Boer A, Stricker BH, Leufkens HG, Porsius A. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; 345: 1195–1198.
- Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Intern Med* 1998; 158: 1108–1112.
- Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. *Am J Epidemiol* 1996 15; 144: 1161–1169.
- Garrett JE, Lanes SF, Kolbe J, Rea HH. Risk of severe life threatening asthma and beta agonist type: an example of confounding by severity. *Thorax* 1996; 51: 1093–1099.
- Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997; 10: 2216–2224.
- Hirshman JV. Do bacteria cause exacerbations of COPD? *Chest* 2000; 118: 193–193.
- Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995; 8: 1333–1338.
- Riise GC, Larsson S, Larsson P, Jeansson S, Andersson BA. The intrabronchial microbial flora in chronic bronchitis patients: a target for *N*-acetylcysteine therapy? *Eur Respir J* 1994; 7: 94–101.
- Riise GC, Qvarfordt I, Larsson S, Eliasson V, Andersson BA. Inhibitory effect of *N*-acetylcysteine on adherence of *Streptococcus pneumoniae* and *Haemophilus influenzae* to human oropharyngeal epithelial cells *in vitro*. *Respiration* 2000; 67: 552–558.
- Tsukagoshi H, Shimizu Y, Iwamae S, *et al.* Evidence of oxidative stress in asthma and COPD: potential inhibitory effect of theophylline. *Respir Med* 2000; 94: 584–588.
- Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *BMJ* 1997; 315: 1151–1154.
- Johnston SC. Identifying confounding by indication through blinded prospective review. *Am J Epidemiol* 2001; 154: 276–284.
- Geijer RM, Thomas S. Drug treatment of chronic obstructive lung disease. *Ned Tijdschr Geneesk* 1996; 140: 761–765.
- Decramer M, Dekhuijzen PNR, Troosters T, *et al.* The BRONCUS-trial Committee. The Bronchitis Randomized On NAC Cost-Utility Study (BRONCUS): hypothesis and design. *Eur Respir J* 2001; 17: 329–336.