REVIEW

Mucoactive therapy in COPD

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ABSTRACT: **It has been shown that mucus hypersecretion is associated with greater susceptibility for chronic obstructive pulmonary disease (COPD), excess forced expiratory volume in 1 s decline, hospitalisations and excess mortality. The effects of mucoactive drugs on outcomes have been reviewed in several meta-analyses, the largest one including 26 studies. 21 studies were performed in patients with chronic bronchitis and five in patients with COPD. The majority of these trials were performed with N-acetylcysteine (n=13) and carbocysteine (n=3).**

Overall, there was a significant reduction in exacerbations (0.05 per patient per month) and the number of days with disability (0.56 days per patient per month). Mucolytics were well tolerated and the number of adverse events was lower than with placebo (odds ratio 0.78). In the largest and best designed study with N-acetylcysteine in 523 patients with COPD, the reduction in exacerbations was only observed in patients not taking inhaled corticosteroids. In addition, a 374 mL reduction in functional residual capacity was found. A recent large study (n=709) with high-dose carbocysteine (1,500 mg·day^{-1}) demonstrated a significant effect on exacerbations (25% reduction) and also reported an improvement in health-related quality of life (-4.06 units in St George's Respiratory Questionnaire).

It is unclear what the mechanisms underlying these effects may be and which phenotypes benefit from this treatment. On the basis of this evidence mucoactive drugs may deserve consideration in the long-term treatment of COPD.

KEYWORDS: ***N*-Acetylcysteine, antioxidants, carbocysteine, chronic bronchitis, chronic obstructive pulmonary disease, mucolytics**

Over the years evidence has accumulated that mucus hypersecretion is an important manifestation of chronic obstructive pulmonary disease (COPD). In the classical phenotype of chronic bronchitis, mucus hypersecretion is the key presenting symptom that appears independent of airflow obstruction [1]. More recent work has demonstrated that obstruction of the small airways by inflammatory exudates containing mucus is predictive of early death after volume reduction surgery in patients with advanced COPD [2]. It was hypothesised that such occlusion enhanced the probability of infection in the lower respiratory tract. BRUSASCO et al. [3] reviewed the mechanisms of how mucus may play a role in the pathogenesis of COPD. On the basis of their review, they concluded that the data called into question the unique role of inflammation in the pathogenesis of COPD.

In addition, several epidemiological studies showed an association between mucus hypersecretion and outcomes in patients with COPD. ANNESI et al. [4] concluded that respiratory mucus hypersecretion constituted more than a negligible public health problem. SPEIZER et al. [5] showed that respiratory symptoms, after adjusting for the level of function, remained a significant predictor of mortality in COPD. VESTBO et al. [6] demonstrated that chronic mucus hypersecretion was significantly and consistently associated with both an increase in forced expiratory volume in 1 s (FEV1) decline and an increase of subsequent hospitalisation because of COPD. Moreover, DE MARCO et al. [7] demonstrated that the incidence of COPD in subjects who confirmed the presence of chronic cough and phlegm at the end of follow-up in their study was four-fold higher than the incidence in subjects who had never reported these symptoms. Finally, in an analysis of the Framingham offspring cohort, the presence of respiratory symptoms (including phlegm) and/or a respiratory diagnosis during follow-up appeared to identify a group of smokers susceptible for the development of COPD [8]. All these data supported the concept that mucus hypersecretion is not an innocent disorder.

However, despite these observations, few studies to date have focussed on the effects of mucolytic

drugs in patients with COPD, even though some of these mucolytic drugs also appear to have antioxidant properties [9–11]. Indeed, there is clear evidence that COPD is also associated with increased oxidative stress [12–20]. The purpose of our study is to review the data available on the use of mucoactive (antioxidant) drugs in COPD. First, we will review the evidence available for the treatment of stable COPD and the prevention of exacerbations. Secondly, we will address the presumptive mechanisms by which potential effects of these drugs are obtained.

TREATMENT OF COPD WITH MUCOLYTIC DRUGS

A large number of studies have been performed on the use of mucolytic drugs in the treatment of chronic bronchitis and COPD. We will not distinguish between different actions of mucoactive drugs as this has already been covered in this issue of the *European Respiratory Review* by BALSAMO *et al.* [21]. The most comprehensive study, by POOLE and BLACK [22], identified 660 trials in their successive Cochrane reviews in 1997, 1999, 2006 [23] and 2010 [24]. The majority of these trials were not placebo-controlled trials in small groups of patients.

POOLE and BLACK [22] eventually identified 26 trials that were methodologically acceptable for further analysis (fig. 1). Thus, the analysis is based on slightly less than 4% of the published studies. The total number of participants was 7,335. All 26 studies were double-blind, randomised, placebo-controlled trials with a study duration ranging from 2 months to 3 yrs. 21 of the studies had a Jadad score of >3. The Jadad score ranges from 0 to 5 and expresses the quality of the design and the reporting of a randomised controlled trial [25]. The age of the participants ranged from 40–67 yrs and the percentage of smokers ranged from 55–100%. The large majority of these studies were performed with either *N*-acetylcysteine (n=13) or carbocysteine (n=3). 21 studies dealt with chronic bronchitis and five studies with COPD. The primary outcomes of the analysis were: 1) exacerbations; and 2) the number of days with disability. The secondary outcomes were: 1) pulmonary function; and 2) adverse events. As symptoms were not recorded in a consistent manner across the different studies, they were not used as an outcome. The number of drop-outs ranged from 0% to 38%. In the study of longest duration [26], drop-out was 37% over a 3-yr period in the placebo group. In most studies, except the former study, analysis was performed on the completer population rather than on the intention-to-treat population.

The results were as follows. A statistically significant reduction in the number of exacerbations was found (0.05 exacerbations per patient per month, 95% CI -0.05–0.04; p<0.01) (fig. 2). The reduction was greater (0.079 exacerbations per month) if the five COPD trials were excluded. In the largest study, no effect on exacerbations was found in the total study population [26]. There was, however, a significant reduction in the patients not taking inhaled corticosteroids (HR 0.79, 95% CI 0.63–0.99; p=0.04). A similar result was found in another study in COPD patients who were denied inhaled corticosteroids [47]. In addition, the odds ratio for not having an exacerbation was increased with mucolytics (OR 2.13, 95% CI 1.86–2.42; p<0.01) (fig. 3). If the analysis was only performed in the trials that were conducted for ≤8 months during the winter months, the effect was greater (OR 2.23, 95% CI 1.95–2.56; p<0.01). Finally,

there was a significant reduction in the number of days with disability (0.56 days per patient per month, 95% CI 0.77–0.35; p<0.01).

In addition, effects were also found on secondary outcomes. There appeared to be a small effect on FEV_1 or FEV_1 % predicted (p<0.01). In a large 3-yr study no effect on the rate of decline of FEV_1 was found, but a 374-mL reduction in functional residual capacity was observed (p<0.01) [26]. The results on quality of life were variable with one study showing an effect [48] and another showing none [26], whereas it had not been measured in the other studies. Finally, fewer adverse events were noted with mucolytic drugs compared with placebo, largely due to the reduction in exacerbations (OR 0.78, 95% CI 0.67–0.92; p=0.002).

The authors concluded that there was a significant reduction in the number of exacerbations with a mucolytic, the effect being 0.05 exacerbations per patient per month [22]. Taking into account a mean exacerbation rate of 2.6 exacerbations per year in the placebo group, this would correspond to a reduction with 0.5 exacerbations per year, or a 20% relative risk reduction. However, a significant heterogeneity was present for this effect, suggesting that caution should be taken in interpreting these data. Factors related to this heterogeneity were FEV_1 % pred, dose, duration of therapy, history of exacerbations and the use of inhaled corticosteroids. There was also a significant reduction in the number of sick days (0.56 days per patient per month). Some heterogeneity was also observed for this effect. These findings were largely in keeping with two previous reviews on the effects of *N*-acetylcysteine. A review by STEY *et al.* [49] included 11 randomised controlled trials and found a significant reduction in exacerbations (OR 1.56, 95% CI 1.37–1.77) and symptoms (OR 1.78, 95% CI 1.54–2.05). Another review, by GRANDJEAN *et al.* [50], confirmed the significant effect on exacerbations (OR -1.37, 95% CI -1.5– -1.25).

Two recently published studies deserve special mention, particularly because of the size of their patient population
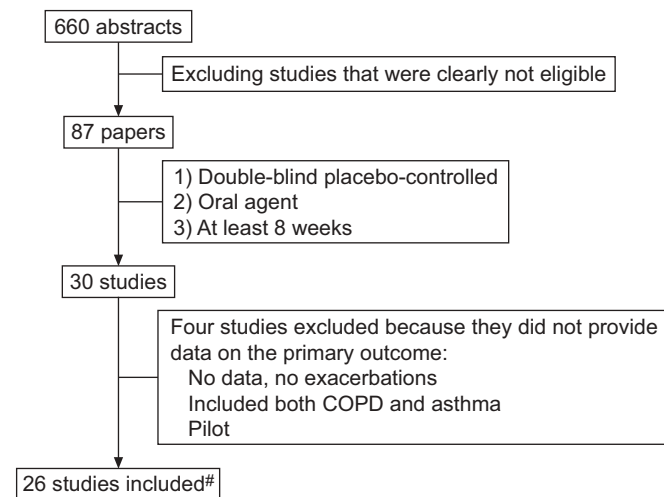

FIGURE 1. Flow chart showing of the number of studies incorporated in the Cochrane review. COPD: chronic obstructive pulmonary disease. #: <4% of the original number identified.
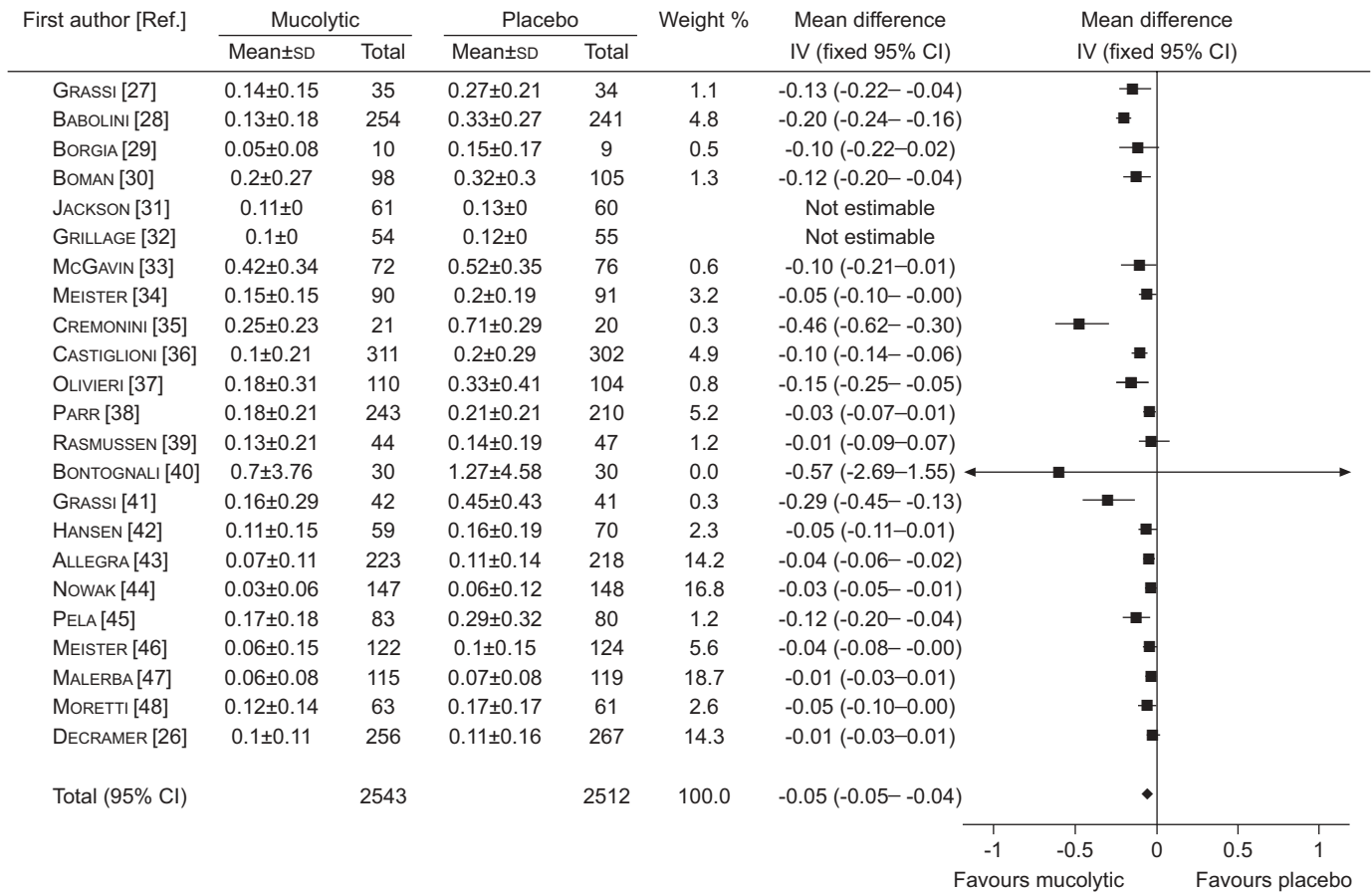
First author [Ref.]	Mucolytic		Placebo		Weight %	Mean difference	Mean difference
	Mean±SD	Total	Mean±SD	Total		IV (fixed 95% CI)	IV (fixed 95% CI)
GRASSI [27]	0.14±0.15	35	0.27±0.21	34	1.1	-0.13 (-0.22– -0.04)	
BABOLINI [28]	0.13±0.18	254	0.33±0.27	241	4.8	-0.20 (-0.24– -0.16)	
BORGIA [29]	0.05±0.08	10	0.15±0.17	9	0.5	-0.10 (-0.22–0.02)	
BOMAN [30]	0.2±0.27	98	0.32±0.3	105	1.3	-0.12 (-0.20– -0.04)	
JACKSON [31]	0.11±0	61	0.13±0	60		Not estimable	
GRILLAGE [32]	0.1±0	54	0.12±0	55		Not estimable	
McGAVIN [33]	0.42±0.34	72	0.52±0.35	76	0.6	-0.10 (-0.21–0.01)	
MEISTER [34]	0.15±0.15	90	0.2±0.19	91	3.2	-0.05 (-0.10– -0.00)	
CREMONINI [35]	0.25±0.23	21	0.71±0.29	20	0.3	-0.46 (-0.62– -0.30)	
CASTIGLIONI [36]	0.1±0.21	311	0.2±0.29	302	4.9	-0.10 (-0.14– -0.06)	
OLIVIERI [37]	0.18±0.31	110	0.33±0.41	104	0.8	-0.15 (-0.25– -0.05)	
PARR [38]	0.18±0.21	243	0.21±0.21	210	5.2	-0.03 (-0.07–0.01)	
RASMUSSEN [39]	0.13±0.21	44	0.14±0.19	47	1.2	-0.01 (-0.09–0.07)	
BONTOGNALI [40]	0.7±3.76	30	1.27±4.58	30	0.0	-0.57 (-2.69–1.55)	
GRASSI [41]	0.16±0.29	42	0.45±0.43	41	0.3	-0.29 (-0.45– -0.13)	
HANSEN [42]	0.11±0.15	59	0.16±0.19	70	2.3	-0.05 (-0.11–0.01)	
ALLEGRA [43]	0.07±0.11	223	0.11±0.14	218	14.2	-0.04 (-0.06– -0.02)	
NOWAK [44]	0.03±0.06	147	0.06±0.12	148	16.8	-0.03 (-0.05– -0.01)	
PELA [45]	0.17±0.18	83	0.29±0.32	80	1.2	-0.12 (-0.20– -0.04)	
MEISTER [46]	0.06±0.15	122	0.1±0.15	124	5.6	-0.04 (-0.08– -0.00)	
MALERBA [47]	0.06±0.08	115	0.07±0.08	119	18.7	-0.01 (-0.03–0.01)	
MORETTI [48]	0.12±0.14	63	0.17±0.17	61	2.6	-0.05 (-0.10–0.00)	
DECRAMER [26]	0.1±0.11	256	0.11±0.16	267	14.3	-0.01 (-0.03–0.01)	
Total (95% CI)		2543		2512	100.0	-0.05 (-0.05– -0.04)	

-1   -0.5   0   0.5   1

Favours mucolytic   Favours placebo

FIGURE 2. Forest plot comparison of mucolytics *versus* placebo for the number of exacerbations per patient per month. Heterogenetity: Chi-squared 138.08; degrees of freedom 20 (p<0.00001); I^2 96%. Test for overall effect: z-score 10.06 (p<0.000001). IV: linear instrumental variable regression. Reproduced from [23] with permission from the publisher.

and rigorous design. The first is the so-called BRONCUS study (Bronchitis Randomized on NAC Cost-Utility Study), which was published in 2005 [26]. This double-blind, placebo-controlled, randomised study included 523 patients who were followed for 3 yrs to examine the effects of *N*-acetylcysteine 600 mg·day^{-1} compared to placebo. On average, patients had moderate COPD with an FEV1 of 57±9% pred with the inclusion criterion of presence of at least two exacerbations in the year preceding the study. The patients were followed for 3 yrs and were also stratified for the use of inhaled corticosteroids. The drop-out rate was 27% in the *N*-acetylcysteine group and 37% in the placebo group (p=0.018). The primary end-points were rate of decline of FEV1 and exacerbations. Rate of decline of FEV1 was unaffected by treatment (54 mL·yr^{-1} *versus* 47 mL·yr^{-1} in *N*-acetylcysteine and placebo, respectively). *N*-acetylcysteine also did not affect exacerbation rate (risk ratio 0.99, 95% CI 0.89–1.10), but it did reduce exacerbations in the subgroup of patients not taking inhaled corticosteroids (risk ratio 0.79, 95% CI 0.63–0.99).

Secondary end-points were health-related quality of life and cost-utility. Treatment did not affect health-related quality of life either measured with the St George's Respiratory Questionnaire or the Euro-QOL. Unexpectedly, a significant reduction in functional residual capacity (374 mL; p<0.001)

was observed in the *N*-acetylcysteine group, indicating that *N*-acetylcysteine might reduce hyperinflation in COPD patients. Such an effect was recently confirmed during exercise in a smaller study [51].

The negative results in this trial could be explained by a number of reasons. First, patients with moderate COPD were studied, whereas the effects might have been more pronounced in patients with severe COPD, as was observed with inhaled corticosteroids [52]. Secondly, although the dose studied was, at that time, the recommended dose, an effect might have been observed with a higher dose, *e.g.* 600 mg three times daily. Indeed, such doses were well tolerated and produced effects on pulmonary function and diffusing capacity in patients with idiopathic pulmonary fibrosis [53]. In addition, a clear effect was observed with a higher dose of carbocysteine. Thirdly, patients with FEV1 reversibility with salbutamol were excluded, which likely introduced a bias against an effect. Finally, since the use of inhaled corticosteroids appeared to modulate the effect, the fact that 70% of the patients were on inhaled steroids might have minimised potential effects.

The second study that deserves a separate mention is the recent publication by ZHENG *et al.* [54], which is the PEACE Study. This double-blind, placebo-controlled trial included 709
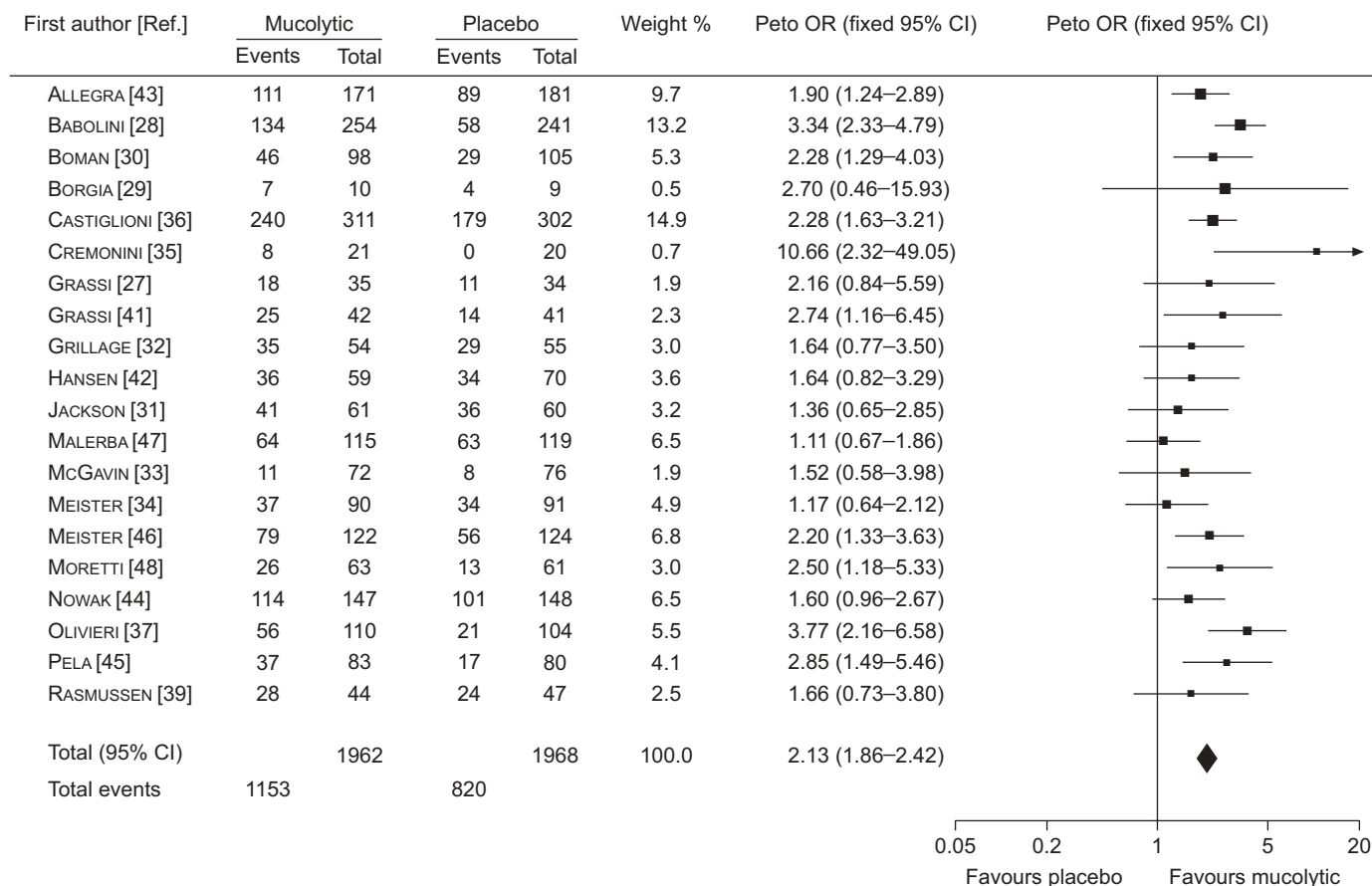
First author [Ref.]	Mucolytic		Placebo		Weight %	Peto OR (fixed 95% CI)	Peto OR (fixed 95% CI)
	Events	Total	Events	Total			
ALLEGRA [43]	111	171	89	181	9.7	1.90 (1.24–2.89)	
BABOLINI [28]	134	254	58	241	13.2	3.34 (2.33–4.79)	
BOMAN [30]	46	98	29	105	5.3	2.28 (1.29–4.03)	
BORGIA [29]	7	10	4	9	0.5	2.70 (0.46–15.93)	
CASTIGLIONI [36]	240	311	179	302	14.9	2.28 (1.63–3.21)	
CREMONINI [35]	8	21	0	20	0.7	10.66 (2.32–49.05)	
GRASSI [27]	18	35	11	34	1.9	2.16 (0.84–5.59)	
GRASSI [41]	25	42	14	41	2.3	2.74 (1.16–6.45)	
GRILLAGE [32]	35	54	29	55	3.0	1.64 (0.77–3.50)	
HANSEN [42]	36	59	34	70	3.6	1.64 (0.82–3.29)	
JACKSON [31]	41	61	36	60	3.2	1.36 (0.65–2.85)	
MALERBA [47]	64	115	63	119	6.5	1.11 (0.67–1.86)	
McGAVIN [33]	11	72	8	76	1.9	1.52 (0.58–3.98)	
MEISTER [34]	37	90	34	91	4.9	1.17 (0.64–2.12)	
MEISTER [46]	79	122	56	124	6.8	2.20 (1.33–3.63)	
MORETTI [48]	26	63	13	61	3.0	2.50 (1.18–5.33)	
NOWAK [44]	114	147	101	148	6.5	1.60 (0.96–2.67)	
OLIVIERI [37]	56	110	21	104	5.5	3.77 (2.16–6.58)	
PELA [45]	37	83	17	80	4.1	2.85 (1.49–5.46)	
RASMUSSEN [39]	28	44	24	47	2.5	1.66 (0.73–3.80)	
Total (95% CI)		1962		1968	100.0	2.13 (1.86–2.42)	
Total events	1153		820				

FIGURE 3. Forest plot comparison of mucolytics *versus* placebo for the number of patients with no exacerbations during the study period. Heterogenetity: Chi-squared 30.56; degrees of freedom 19 (p<0.05); I^2 38%. Test for overall effect: z-score 11.28 (p<0.00001). Reproduced from [23] with permission from the publisher.

patients (table 1) and evaluated treatment with carbocysteine (500 mg three times daily) over a 1-yr follow-up period. On average, patients had severe COPD with an FEV_1 of 45% pred. The primary end-point was exacerbation rate and secondary end-points were quality of life, lung function and oxygen saturation. Exacerbations were significantly reduced in the carbocysteine group (1.01 *versus* 1.35 excerbations per patient per year, 25% reduction) (fig. 4). As shown in figure 4, this is primarily due to a reduction in exacerbations after the first exacerbation, as there was the same probability of being exacerbation free but a lower probability of exacerbation after the first one was observed. The risk ratio was 0.75 (95% CI 0.62–0.92). No treatment interaction was observed with Global Initiative for Chronic Obstructive Lung Disease stage or use of inhaled corticosteroids. It should be noted that the percentage of study patients taking inhaled corticosteroids (17%) was relatively low in contrast to the BRONCUS trial [26]. Quality of life was significantly improved with carbocysteine (-4.06 units in the St George's Respiratory Questionnaire; p=0.046). Clear effects on quality of life were also seen in the domain scores of symptoms and activity. No significant changes in lung function or oxygen saturation were observed. No adverse events were associated with the use of carbocysteine. Thus, this study clearly showed an effect of treatment with carbocysteine on exacerbations and quality of life in patients with, on average, severe COPD. However, in terms of magnitude of the

effect, it should be stressed that the study evaluated a population in which the majority of patients did not take any maintenance treatment for COPD. In addition, 25% of the patients were lifelong nonsmokers unlike in the other studies which were strictly confined to smokers. Finally, two other studies confirmed the reduction in exacerbations in COPD patients with carbocysteine 1,500 mg·day^{-1}. In the first study of 156 patients a risk ratio of 0.3 (95% CI 0.2–0.7) was reported and in the second study of 142 patients a risk ratio of 0.37 (95% CI 0.22–0.62) was observed [55, 56].

PRESUMPTIVE MECHANISMS OF ACTION
The studies documented above clearly demonstrate that treatment with mucoactive drugs reduces exacerbations in patients with COPD with virtually no side-effects, though the mechanisms by which these effects might be observed are still unclear. Originally, effects on mucous viscosity [57] and mucociliary clearance were declared [58, 59]. Although the compounds were originally marketed as mucolytic agents, an effect on mucociliary clearance or mucus impaction in the small airways has never been fully demonstrated. This may be related to the difficulty of measuring mucociliary transport in a reliable way [60].

A number of observations on both *N*-acetylcysteine and carbocysteine suggest that these drugs not only exert muco-ciliary properties but also act as antioxidant agents [61–63].

TABLE 1	Patient demographics and baseline characteristics	
	Carbocysteine	Placebo
Subjects	353	354
Males	273 (77)	282 (80)
Age yrs	65±9	65±9
Duration of COPD yrs	9±9	10±9
Baseline spirometry		
FEV1 L	1.07±0.41	1.12±0.43
FEV1 % pred	44±15	45±15
FVC L	2.20±0.74	2.28±0.75
FEV1/FVC %	50±13	50±13
GOLD stages		
II	167 (47)	177 (50)
III	139 (39)	140 (40)
IV	47 (13)	37 (11)
SGRQ total score	42±19	43±19
Medications for COPD prior to study		
β2-agonist	76 (22)	61 (17)
Anticholinergic agents	40 (11)	36 (10)
Inhaled corticosteroids	64 (18)	54 (15)
Xanthines	113 (30)	95 (27)

Data are presented as n, n (%) or mean± SD. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; SGRQ: St George's Respiratory Questionnaire. Reproduced from [54] with permission from the publisher.

There is accumulating evidence that oxidative stress may play an important role in the pathogenesis of COPD. This is supported by enhanced exhalation of hydrogen peroxide [13], nitric oxide [16], ethane [17], carbon monoxide [16] and isoprostane [12, 15], increased concentrations of 4-hydroxyl-2-nonenal in the lungs [19] or by increased urinary excretion of isoprostane [18]. Oxidative stress causes a number of secondary

effects, such as inactivation of anti-proteases, activation of proteases, and expression of interleukin-8 and tumour necrosis factor-α, through expression of nuclear factor-κB, further enhancing recruitment of neutrophils and formation of iso-prostane from the oxidation of arachidonic acid [12, 15].

Other effects that were demonstrated include: 1) inhibition of epithelial thickening and secretory cell hyperplasia induced by cigarette smoke in rats [64]; 2) reduction of neutrophil and monocyte chemotaxis and oxidative burst responses *in vitro* [65, 66]; 3) reductions of lysozyme and lactoferrin concentrations in smokers [67]; 4) reduction in the activation and number of neutrophils and macrophages in bronchoalveolar lavage fluid in smokers [68, 69]; and 5) inhibition of the adherence of bacteria to ciliated epithelial cells *in vitro* [70–72].

In view of these properties, *N*-acetylcysteine has not only been the subject of several controlled trials in stable COPD but has also been evaluated during acute exacerbations of COPD, which are typically accompanied by bursts of oxidative stress and inflammation [61, 73]. To date, patients receiving *N*-acetylcysteine in conjunction with standard therapy for acute exacerbations had more reduced inflammatory markers, improved bacterial eradication and better subjective outcomes when compared with placebo. However, no statistically significant difference in length of hospitalisation or change of FEV1 could be observed, a finding which might be explained by the low patient number and the lack of statistical power in these studies. Overall, although antioxidants such as *N*-acetylcysteine may reduce oxidative stress in patients with COPD and during exacerbations [9–11], this is presently not demonstrated nor is the consequence of such an effect in terms of outcomes in COPD clearly established.

CONCLUSIONS

Accumulating evidence suggests that mucolytic drugs reduce exacerbations, reduce the number of sick days, reduce hyperinflation and, perhaps, improve quality of life in patients with COPD. A number of unknowns remain, particularly concerning the dose at which these effects may appear, the
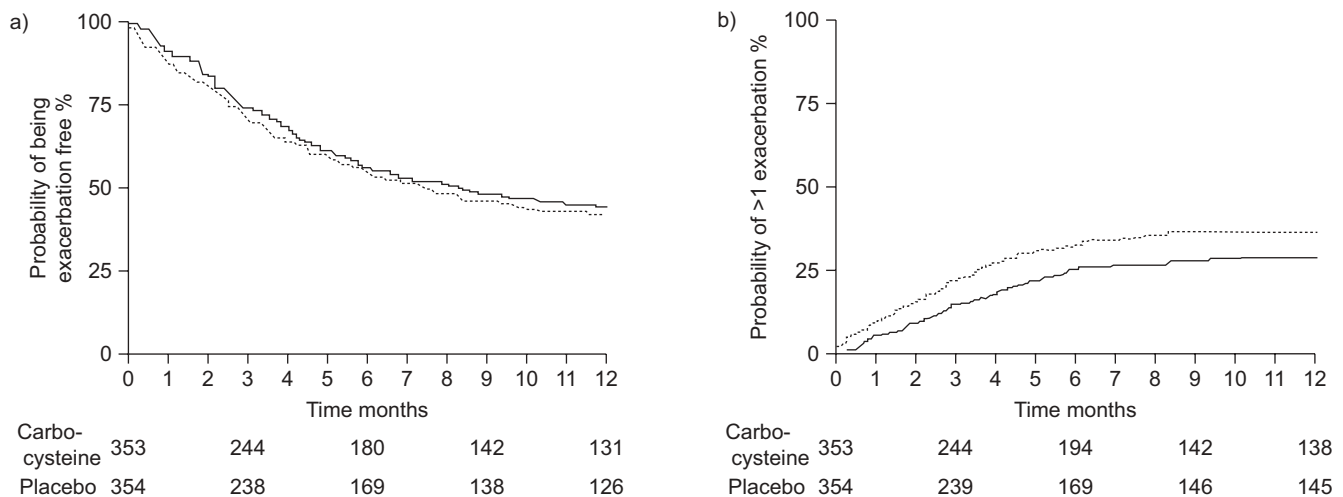
FIGURE 4. Kaplan–Meier plot of the probability of a) being exacerbation free or b) having more than one exacerbation at each time-point during the study. ——: carbocysteine; - - - -: placebo. Reproduced from [53] with permission from the publisher.

required duration of treatment, the interaction with Global Initiative for Chronic Obstructive Lung Disease stages and the potential effects on other outcomes in COPD. More studies are needed to determine which COPD patients respond to this treatment and how this treatment interacts with other treatments before these drugs can be incorporated into the standard treatment regimens for these patients.

STATEMENT OF INTEREST

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