Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial

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Summary

Background Increased oxidative stress and inflammation has a role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Drugs with antioxidant and anti-inflammatory properties, such as N-acetylcysteine, might provide a useful therapeutic approach for COPD. We aimed to assess whether N-acetylcysteine could reduce the rate of exacerbations in patients with COPD.

Methods In our prospective, randomised, double-blind, placebo-controlled, parallel-group study, we enrolled patients aged 40–80 years with moderate-to-severe COPD (post-bronchodilator forced expiratory volume in 1 s [FEV_1]/forced vital capacity <0·7 and FEV_1 of 30–70% of predicted) at 34 hospitals in China. We stratified patients according to use of inhaled corticosteroids (regular use or not) at baseline and randomly allocated them to receive N-acetylcysteine (one 600 mg tablet, twice daily) or matched placebo for 1 year. The primary endpoint was the annual exacerbation rate in patients who received at least one dose of study drug and had at least one assessment visit after randomisation. This study is registered with the Chinese Clinical Trials Registry, ChiCTR-TRC-09000460.

Findings Between June 25, 2009, and Dec 29, 2010, we screened 1297 patients, of whom 1006 were eligible for randomisation (504 to N-acetylcysteine and 502 to placebo). After 1 year, we noted 497 acute exacerbations in 482 patients in the N-acetylcysteine group who received at least one dose and had at least one assessment visit (1·16 exacerbations per patient-year) and 641 acute exacerbations in 482 patients in the placebo group (1·49 exacerbations per patient-year; risk ratio 0·78, 95% CI 0·67–0·90; p=0·0011). N-acetylcysteine was well tolerated: 146 (29%) of 495 patients who received at least one dose of N-acetylcysteine had adverse events (48 serious), as did 130 (26%) of 495 patients who received at least one dose of placebo (46 serious). The most common serious adverse event was acute exacerbation of COPD, occurring in 32 (6%) of 495 patients in the N-acetylcysteine group and 36 (7%) of 495 patients in the placebo group.

Interpretation Our findings show that in Chinese patients with moderate-to-severe COPD, long-term use of N-acetylcysteine 600 mg twice daily can prevent exacerbations, especially in disease of moderate severity. Future studies are needed to explore efficacy in patients with mild COPD (GOLD I).

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Introduction

COPD is characterised by persistent airflow limitation and frequent recurrent acute exacerbations that contribute to disease severity in individual patients.[1] COPD with acute exacerbations results in a faster decline in lung function,[2] impairment of health status,[3] reduction in exercise tolerance, and high economic burden,[4] leading to substantial rates of hospital admission, readmission and mortality. Therefore, effective prevention and treatment of exacerbations has been strongly recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1]

Many factors are involved in the pathophysiology of COPD, such as mucus hypersecretion, oxidative stress, and inflammation of the airways and lungs.[1] Thus, drugs that have antioxidative and anti-inflammatory properties, and mucolytic activity, might be effective for treatment of COPD.

N-acetylcysteine is a well-known, effective mucolytic drug that reduces sputum viscosity and elasticity, improves mucociliary clearance and modulates the inflammatory response.[5,6] Furthermore, N-acetylcysteine has both direct and indirect antioxidant properties, which have been extensively assessed in in-vitro and in-vivo studies,[7–9] and might be important for the long-term management of patients with COPD.

Previous studies showed that treatment with N-acetylcysteine (400–1200 mg per day) reduced rates of acute COPD exacerbations[10] and hospital readmissions.[11] Nevertheless, these studies were not recognised as strong evidence because of limitations in their design, such as small sample sizes, absence of double-blinding and placebo controls, or a short study duration. Moreover, inconsistent results have been reported. In the BRONCUS study,[12] 523 patients with moderate-to-severe COPD were treated with N-acetylcysteine (600 mg

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per day) for 3 years; compared with placebo, active treatment did not significantly reduce the exacerbation rate, apart from in patients not concomitantly treated with inhaled corticosteroids.[12] Schermer and colleagues[13] reported that exacerbation rates did not reduce significantly in a trial of 286 patients with COPD or chronic bronchitis who were treated with twice daily inhaled fluticasone propionate 500 µg, once daily oral N-acetylcysteine 600 mg, or placebo for 3 years. For these reasons, N-acetylcysteine is not widely used in patients with COPD.

Because a dose-effect association of N-acetylcysteine has been shown,[11,14] we postulated that an increased dose of N-acetylcysteine might achieve improved outcomes. We aimed to assess whether long-term treatment with high-dose N-acetylcysteine could reduce COPD exacerbation rates, and whether the benefits of treatment would be apparent with and without concomitant treatment with inhaled corticosteroids.

Methods

Study design and participants

Details of our study's rationale, design, and analysis plan have been published elsewhere.[15] In our multicentre, prospective, randomised, double-blind, placebo-controlled, parallel-group trial (the Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease [PANTHEON] study), all participants were stratified by previous use of inhaled corticosteroid at baseline, which was defined as regular use of 500–2000 µg per day of beclomethasone or equivalent in the previous 3 months. The proportion of users to non-users of inhaled corticosteroids was predetermined as around 4:6 from investigators' experience of clinical practice in China. At 34 academic hospital-based pulmonary clinics in China, we enrolled patients with a clinical diagnosis of moderate-to-severe COPD (defined by GOLD classification), post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) of less than 0·7, and FEV_1 30–70% of predicted. Eligible patients were aged 40–80 years, with a history of at least two exacerbations within the previous 2 years and clinically stable for at least 4 weeks before enrolment. Key exclusion criteria were a diagnosis of bronchial asthma, requirement for long-term oxygen therapy (≥12 h per day) or pulmonary rehabilitation, and poor reliability or compliance. The study was approved by local ethics committees. All patients provided written informed consent.

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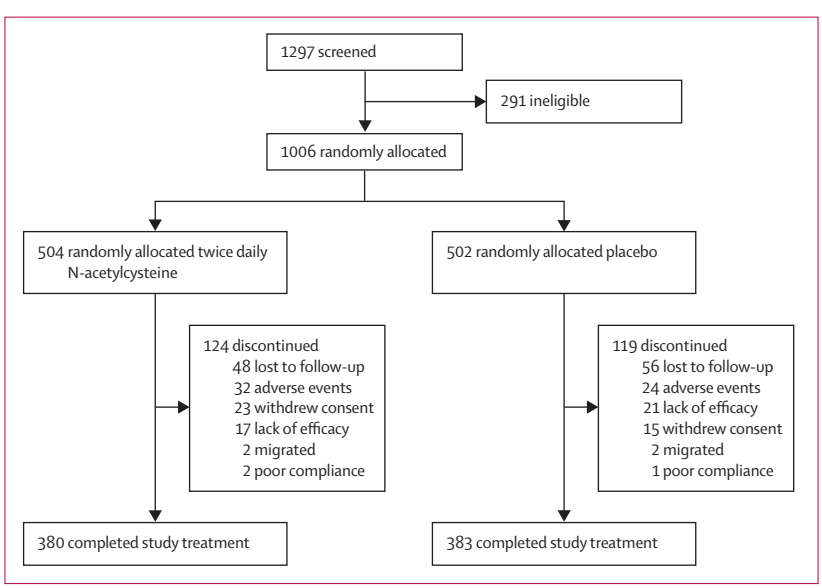

Figure 1: **Trial profile**
Details about ineligibility for randomisation are shown in the appendix.

Randomisation and masking

After a 2 week run-in period, eligible patients were allocated in a 1:1 ratio to either N-acetylcysteine (one 600 mg tablet twice daily) or placebo (one tablet twice daily) for 1 year in addition to existing individual therapy according to GOLD guidelines. After randomisation, clinical visits occurred at 1, 3, 6, 9, and 12 months. No follow-up study was planned.

An independent statistician (MedKey Med-Tec Development, Shanghai, China) randomly allocated patients to receive N-acetylcysteine or placebo according to a predetermined computer-generated sequence, with stratified block randomisation and block sizes of 8. At each centre, the enrolled participants were allocated to the N-acetylcysteine group or the placebo group in order of their assigned numbers.

N-acetylcysteine and placebo tablets were manufactured and provided by Hainan Zambon Pharmaceutical (Haikou, China). The placebo was identical in composition, shape, colour, and size, but did not contain any active ingredients. N-acetylcysteine or placebo tablets were packaged identically. Supplies of tablets for every patient were identified with a four-digit number. A sealed envelope that contained the randomisation code for any given patient was kept by the investigator but not opened during the study, apart from in cases of a serious life-threatening adverse event. Opening of any envelope, whether intentional or accidental, had to be recorded on the case report form, and the patient had to be withdrawn from the study. The patients, investigators, and statisticians in charge of the analysis were masked to the treatment-group allocations during the study.

Outcomes

The primary endpoint was exacerbation rate in 1 year. We defined exacerbation and types according to Anthonisen and colleagues;[16] briefly, exacerbation was defined as at least a 2 day persistence of two (type II moderate) or all three (type III, severe) major symptoms (worsening dyspnoea, increase in sputum purulence or volume), or

of any onemajor symptom plus at least one minor symptom (type I, mild) (upper airway infection, unexplained fever, and increased wheezing). The exacerbation was assessed from patients' diary card report[17] or documented hospital visits due to respiratory disorders, and confirmed by investigators based on Anthonisen's criteria.[16] Secondary endpoints included time-to-first exacerbation and time-to-recurrent exacerbation, number of patients with exacerbations requiring systemic corticosteroids or antibiotics, or use of short-acting β_2-agonist as rescue drug. We measured quality of life (QoL) at each study visit with a validated Chinese version of the St George's Respiratory Questionnaire (SGRQ), and did post-bronchodilator spirometry at baseline, 6 months, and 12 months. We measured FEV_1, FVC, and forced expiratory volume in 6 s (FEV_6). We also recorded incidence of adverse events (including laboratory abnormalities).

Statistical analysis

We determined sample size on the basis of the primary outcome. Referring to the PEACE study,[18] we assumed that to detect a reduction of at least 20% in the yearly exacerbation rate, with a standard deviation of about 85% in the placebo yearly rate, a Wilcoxon-Mann-Whitney rank-sum test at a 5% two-sided significance level would provide 95% power. We estimated that 1250 patients would need to be enrolled.

The primary efficacy analysis population included patients who received at least one dose of study drug and had at least one visit assessment after randomisation. We used negative binomial regression to analyse the annual exacerbation rate. Apart from inhaled corticosteroid status, additional covariate candidates included GOLD severity, smoking status, age, sex, body-mass index, and concomitant drug use. We calculated risk ratio (RR) and 95% CIs for N-acetylcysteine versus placebo. We analysed time to first exacerbation and time to recurrent exacerbation with the Cox proportional hazard model. We constructed Kaplan-Meier curves of the probability of exacerbation-free status.

We did predefined exploratory analyses on exacerbations requiring treatment of systemic corticosteroids or antibiotics. We did post-hoc analysis on exacerbation rates stratified by months on treatment (3 months, 6 months, and 9 months). We analysed SGRQ total score and domain changes from baseline by a mixed model for repeated measures, whereas we analysed spirometric changes from baseline with ANCOVA. We applied Fisher's exact tests to the analysis of number and frequency of patients with systemic corticosteroids or

	N-acetylcysteine 1200 mg group (n=504)	Placebo group (n=502)
Sex		
Male	415 (82%)	409 (81%)
Female	89 (18%)	93 (19%)
Age, years	66·15 (8·72)	66·38 (8·80)
BMI, kg/m²	23·10 (3·74)	22·82 (3·54)
BMI status		
Underweight (<18·5 kg/m²)	51 (10%)	54 (11%)
Normal weight (18·5–<24 kg/m²)	251 (50%)	265 (53%)
Overweight (≥24 kg/m²)	202 (40%)	183 (36%)
Smoking status		
Current smoker	95 (19%)	84 (17%)
Ex-smoker	285 (57%)	303 (60%)
Non-smoker	124 (25%)	115 (23%)
Smoking history, packs per year		
Current smoker	35·75 (24·67)	34·20 (25·86)
Ex-smoker	38·05 (23·14)	36·88 (25·26)
GOLD stage		
II	230 (46%)	230 (46%)
III	268 (53%)	263 (52%)
IV	6 (1%)	9 (2%)
Use of inhaled corticosteroids		
No	282 (56%)	280 (56%)
Yes	222 (44%)	222 (44%)
Exacerbations in previous 2 years	3·47 (2·01)	3·53 (1·95)

Data are n (%) or mean (SD). BMI=body-mass index. GOLD=Global Initiative for Chronic Obstructive Lung Disease.

Table 1: **Baseline characteristics**

	N-acetylcysteine 1200 mg group (n=504)	Placebo group (n=502)
Baseline spirometry		
Post-bronchodilator FEV_1, L	1·22 (0·37)	1·20 (0·38)
Predicted post-bronchodilator FEV_1, %	49·08% (11·88)	48·81% (11·72)
Post-bronchodilator FVC, L	2·47 (0·62)	2·47 (0·67)
Post-bronchodilator FEV_1/FVC, %	50·03% (9·98)	49·01% (9·84)
SGRQ score		
Total	39·98 (19·01)	41·53 (19·55)
Symptom	43·31 (21·33)	44·45 (22·60)
Activity	50·72 (20·85)	52·11 (21·39)
Impact	32·73 (22·24)	34·45 (22·36)
COPD drug use before enrolment		
ICS alone	22 (4%)	21 (4%)
LABA	11 (2%)	13 (3%)
ICS and LABA	236 (47%)	243 (48%)
SABA	54 (11%)	60 (12%)
SAMA	77 (15%)	81 (16%)
LAMA	48 (10%)	50 (10%)
Theophylline	135 (27%)	134 (27%)

Data are mean (SD) or n (%). Concomitant ICS included both regular use and irregular use of ICS. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. SGRQ=St George's Respiratory Questionnaire. COPD=chronic obstructive pulmonary disease. ICS=inhaled corticosteroids. LABA=long-acting β-agonist. SABA=short-acting β-agonist. SAMA=short acting muscarinic antagonist. LAMA=long acting muscarinic antagonist.

Table 2: **Baseline lung function, health status, and concomitant COPD drug use**

antibiotics, and use of short-acting β_2-agonists as rescue drug, between treatment groups.

We assessed incidence of adverse events in a safety analysis set of all patients who received at least one dose of study drug. We coded adverse events with the Medical Dictionary for Regulatory Activities (MedDRA). All hypothesis tests were two-sided, and p<0·05 was defined as significant. No interim analysis was planned.

MedKey (Shanghai) Med-Tec Development (Shanghai, China) an independent contract research organisation took responsibility for data collection, quality assurance, and statistical analysis. SAS (version 9.2) was used for all statistical analyses.

This trial was registered in the Chinese Clinical Trials Registry, ChiCTR-TRC-09000460.

Role of the funding source

This study was sponsored by Hainan Zambon Pharmaceutical. The funding source had no role in the study design, data collection, analysis, or interpretation. Preparation of the report was done in collaboration with the sponsor. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the findings for publication.

Results

Between June 25, 2009, and Dec 29, 2010, we screened 1297 patients, of whom 1006 were eligible for randomisation (figure 1). Reasons for screening failure were much the same between groups (appendix). Baseline characteristics and lung function parameters did not differ between completers and patients who did not complete treatment, apart from baseline FVC, which was slightly higher in completers (appendix).

Mean treatment duration was 319·0 days (SD 102·3) in the N-acetylcysteine group and 319·1 days (105·2) in the placebo groups. Baseline characteristics did not differ in the two treatment groups (tables 1, 2). Mean predicted post-bronchodilator FEV_1 was about 49% of predicted at baseline. Disease severity was classified as GOLD II (moderate) in about half the patients and mainly GOLD III (severe) in the rest of the patients. 756 (75%) of 1006 patients had previously received treatment for COPD.

After 1 year of treatment, we noted 497 acute exacerbations in 482 patients in the N-acetylcysteine group and 641 acute exacerbations in 482 patients in the placebo group, corresponding to 1·16 exacerbations per patient-year with N-acetylcysteine versus 1·49 with placebo (RR 0·78, 95% CI 0·67–0·90; p=0·0011). Mean duration of exacerbation was 14·8 days (SD 13·9) in the N-acetylcysteine group compared with 19·2 days (21·1) in the placebo group (p=0·003). Previous inhaled corticosteroid use was the only covariate that significantly affected the rate of COPD exacerbations (p<0·0001), but we noted no significant interaction between treatment effect and inhaled corticosteroid use (p=0·27) or smoking status (p=0·35), or between GOLD severity and inhaled corticosteroid concomitant use (p=0·34).

N-acetylcysteine treatment was more effective in patients with GOLD II (moderate) disease than in patients with GOLD III (severe) disease (p=0·0077; figure 2).

The yearly exacerbation rate in patients with Anthonisen type II acute COPD exacerbations was lower in the N-acetylcysteine group than it was in the placebo group (RR 0·73, 95% CI 0·55–0·96, p=0·0231; appendix). However, this difference was not noted in patients with mild exacerbations (Anthonisen type I; RR 0·70, 95% CI 0·48–1·01, p=0·0550), or severe exacerbations (Anthonisen type III; 0·83, 0·68–1·01, p=0·0650).

Time to first exacerbation did not differ between treatment groups, but time to second exacerbation and time to third exacerbation was shorter in the control group than the N-acetylcysteine group (figure 3). N-acetylcysteine treatment prolonged the time to first exacerbation in patients with GOLD II (moderate) COPD (p=0·0126), but not in patients with GOLD III (severe) COPD (p=0·76). With regard to the duration of treatment, differences in exacerbation rates between the two groups were significant as early as 6 months (RR 0·83, 95% CI 0·70–0·99, p=0·0375 at 6 months and 0·81, 0·69–0·95, p=0·0105 at 9 months).

In patients with acute COPD exacerbations requiring treatment with systemic corticosteroids or antibiotics, the yearly exacerbation rate was lower in the N-acetylcysteine group than it was in the placebo group (RR 0·83, 95% CI 0·69–0·99, p=0·0427). 33 patients in the N-acetylcysteine group and 36 patients in the control group were admitted to hospital (RR 0·92, 95% CI 0·58–1·45; p=0·80).

114 (24%) of 482 patients in the N-acetylcysteine group and 137 (28%) of 482 patients in the control group were treated with rescue medication (RR 0·83, 95% CI 0·67–1·03; p=0·11); however, we noted a difference for patients with GOLD II (moderate) disease severity: 57 (26%) of 221 patients allocated placebo required rescue treatment compared with 37 (17%) of 218 patients allocated N-acetylcysteine (RR 0·66, 95% CI 0·46–0·95; p=0·0272).

Patients treated with N-acetylcysteine had greater changes from baseline in SGRQ symptom domains after 1 year than did controls (–8·87 units *vs* –4·79 units; mixed model difference –3·37 units, 95% CI –6·64 to

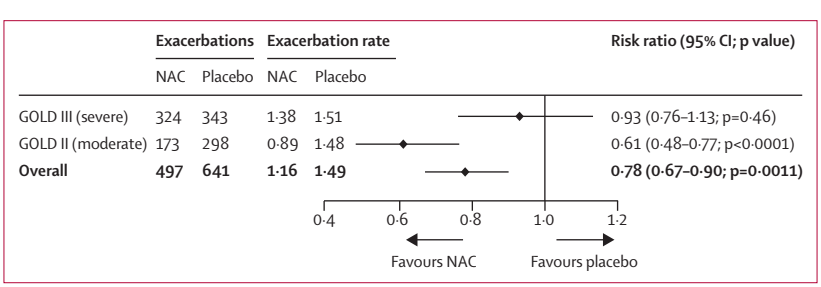

Figure 2: **Forest plot of exacerbations in all patients, and stratified by GOLD moderate and GOLD severe disease**
NAC=N-acetylcysteine 600 mg twice daily. GOLD=Global Initiative for Chronic Obstructive Lung Disease.

–0·11, p=0·0430). SGRQ total scores or other domains did not differ between groups (appendix).

Change from baseline in pre-bronchodilator and post-bronchodilator FEV_1, FVC, and FEV_6 did not differ between the groups (appendix).

146 (29%) of 495 patients who received at least one dose of N-acetylcysteine had adverse events, as did 130 (26%) of 495 patients who received at least one dose of placebo (table 3). 44 patients (9%) had adverse events regarded by the investigators as possibly related to study products, as did 34 (7%) patients who received placebo (p=0·29). 48 (10%) patients who received N-acetylcysteine and 46 (9%) patients who received placebo had serious adverse events. Five patients died during the study, including four patients in the N-acetylcysteine group (two from acute exacerbations of COPD, one from coronary artery disease, and one from pneumonia) and one patient in the placebo group (sudden death, reason unknown); no deaths were regarded by investigators as related to the study products. No notable laboratory abnormalities were reported.

Discussion

In our study, treatment of Chinese patients with twice daily N-acetylcysteine 600 mg was associated with a reduction in acute exacerbations of COPD compared with placebo. This finding was in line with the long-term PEACE study (of carbocisteine 1500 mg per day)[18] and the large TORCH[19] and UPLIFT[20] trials, which studied populations with much the same baseline characteristics as in our study (appendix). The exacerbation rate in the placebo group of this study was 1·49 per patient-year, which was consistent with previous 1 year COPD trials (eg, 1·35 per patient-year in the PEACE study[18] and 1·70 per patient-year in a study[21] of theophylline use). Our primary finding differed from that of BRONCUS,[12] in which no difference was noted between N-acetylcysteine 600 mg per day and placebo for the prevention of COPD with acute exacerbations, with the exception of in the group of patients without concomitant inhaled corticosteroid treatment (panel).

To allow assessment of the effect of inhaled corticosteroid use, we stratified enrolled patients before randomisation on the basis of concomitant regular use of these drugs. The proportion of previously treated patients to previously untreated patients was thus about 1:1 in the present study, which is a more equal distribution than that of the BRONCUS study (7:3), and provided a more accurate analysis of the effectiveness of N-acetylcysteine in patients already on a treatment that decreases exacerbations. By contrast with the BRONCUS study, we noted no interaction between treatment effect and inhaled corticosteroid use, suggesting the treatment effect was independent of inhaled corticosteroid use. Consequently, we did not do subgroup analyses of treated and untreated groups.

Several explanations might explain our different results from the BRONCUS study. First, the dose of

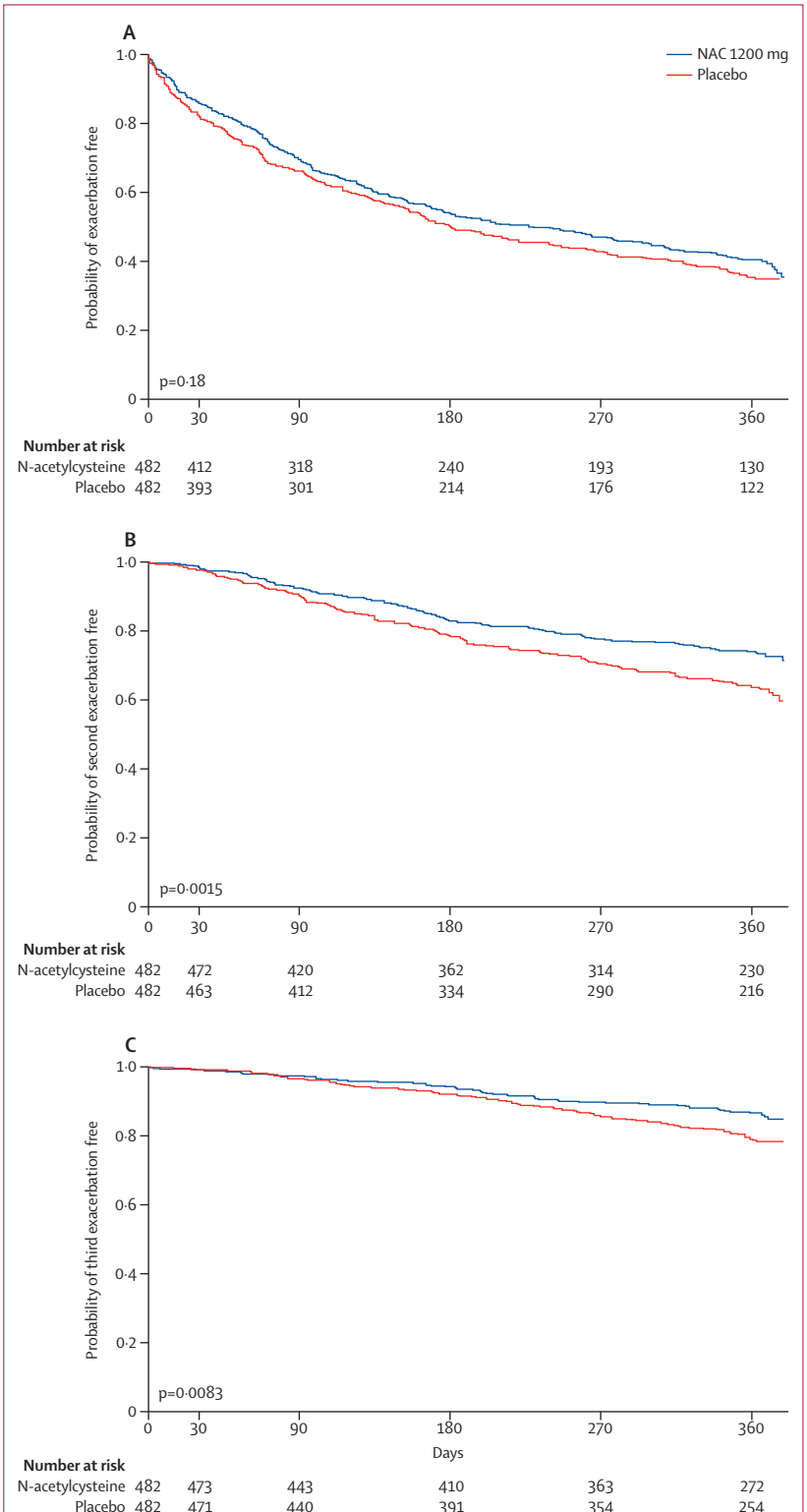

Figure 3: **Time to exacerbation events in patients receiving N-acetylcysteine or placebo**
Numbers show remaining patients at randomisation and during treatment of 30 days, 90 days, 180 days, 270 days, and 360 days. (A) Time to first exacerbation. (B) Time to second exacerbation. (C) Time to third exacerbation.

	N-acetylcysteine 1200 mg group (n=495)	Placebo group (n=495)
Adverse events (reported by >1% of patients)		
Upper respiratory tract infection	42 (8%)	40 (8%)
Lower respiratory tract infection	10 (2%)	6 (1%)
Gastrointestinal pain	9 (2%)	7 (1%)
Epigastric discomfort	6 (1%)	10 (2%)
Pruritus	6 (1%)	1 (<1%)
Dizziness	4 (1%)	9 (2%)
Diarrhoea	5 (1%)	3 (1%)
Respiratory tract infection	5 (1%)	0
Serious adverse events (≥2 events overall)*		
Chronic obstructive pulmonary disease	32 (6%)	36 (7%)
Coronary artery disease	3 (1%)	0
Cerebral infarction	2 (<1%)	0
Lower respiratory tract infection	1 (<1%)	2 (<1%)
Upper respiratory tract infection	2 (<1%)	1 (<1%)
Osteoarthropathy	2 (<1%)	0

*All serious adverse events are listed in the appendix.

Table 3: **Adverse events**

N-acetylcysteine we chose (1200 mg per day) was double that used in BRONCUS (600 mg per day). A notable dose-effect association with N-acetylcysteine has been reported,[11,14] and therefore a dose increase might be expected to provide amplified treatment effects. Second, we enrolled more patients in our study than were enrolled in BRONCUS, which might have provided greater statistical power to detect differences between the study groups. In BRONCUS, the sample size of 523 patients was estimated on the basis of the primary endpoint (decline in FEV_1), whereas in PANTHEON study it was calculated by the reduction of yearly exacerbation rate, as in the PEACE study. Our finding of a reduced rate of exacerbations is in agreement with the long-term HIACE study,[22] which was done with the same dose of N-acetylcysteine in 120 Chinese patients (93% male, mean age 71 years) with stable moderate-to-severe COPD. In that study,[22] use of N-acetylcysteine was associated with a reduction in exacerbation frequency compared with placebo (0·96 per patient-year for N-acetylcysteine *vs* 1·71 per patient-year for placebo; p=0·019).

Another key finding from our study is that we noted a greater preventive effect of exacerbations in patients with moderate disease (GOLD II) than in severe disease (GOLD III), suggesting that N-acetylcysteine might have a more important role in the early stages of COPD. Our prespecified analysis of treatment effects by GOLD severity suggested a different result from the findings of the PEACE study,[18] in which no treatment interaction was noted between GOLD stage and treatment. However, our finding is in agreement with the TORCH[23] and UPLIFT[24] studies, which although assessed different drugs, noted greater reductions in the rates of exacerbations with early treatment in less advanced GOLD severities. Early intervention in COPD might help to provide better control of symptoms, reduce disease progression, and improve outcomes.

For the secondary endpoints of our study, time to first exacerbation did not differ between groups, but time to recurrent exacerbations was longer with N-acetylcysteine than placebo, which is consistent with the PEACE study.[25] Reduction of exacerbations without affecting time to first event is an interesting issue to be addressed. We postulate that because recurrent exacerbations occurred mostly in those with a history of exacerbations, the prevention of exacerbations by antioxidants is mainly focused on these recurrent exacerbations. This benefit is probably due to the antioxidant characteristics, which act slowly and progressively. As shown in the ECLIPSE study, the risk of exacerbation increased 5·72 times in individuals having previous exacerbations more than twice a year.[26] This finding suggests that the focus should not be solely on the overall exacerbation rate, but also the recurrent exacerbation rate, which might be more clinically relevant.

In the PANTHEON and PEACE studies, prevention of exacerbations was effective from 6 months onwards, suggesting that the preventive effects of N-acetylcysteine treatment are slow but progressive, and that long-term, regular treatment is necessary.

In the PANTHEON, PEACE,[18] and SFC[27] studies, both smokers and non-smokers with COPD were eligible for enrolment. These populations represent the reality of COPD in China and probably the rest of the world. In a nationwide Chinese survey,[28] COPD in non-smokers accounted for 38·6% of the total COPD population. Despite smoking being the most important risk factor to induce COPD, other risk factors such as exposure to biomass smoke and recurrent respiratory infections in childhood cannot be ignored. Therefore, patients with COPD unrelated to smoking were enrolled in these studies, which is different from some other large COPD trials such as TRISTAN,[29] TORCH, and UPLIFT. Responses to treatment between smoking and non-smoking COPD might differ. Our previous SFC study (salmeterol 50 μg and fluticasone propionate 500 μg) showed that the change of pre-dose FEV_1 from baseline was larger in non-smokers than in ex-smokers and current smokers.[27] Thomsen and colleagues[30] also noted that never smokers with COPD had different characteristics and milder disease than did current and former smokers. In the present study, we did not note an interaction between treatment effects and smoking status.

Mean SGRQ symptom scores were reduced in the N-acetylcysteine group compared with placebo, but did not differ in total score and other domains, which might be attributable to the lower SGRQ total score in the present study than was noted in some clinical trials of

Chinese patients with COPD, such as BUD/FORM[31] and SFC,[27] but was consistent with PEACE study[18] (appendix). The low SGRQ was probably attributable to the low severity of COPD spirometric impairment.

We showed no change in spirometry results between N-acetylcysteine and placebo treatment in the present study, which was consistent with other antioxidant therapy in COPD such as PEACE[18] and HIACE[22] studies. We postulate that because antioxidants are not bronchodilators, it is not appropriated to assess their treatment effect in terms of FEV_1.

Although symptoms, breathlessness in particular, were the main reason that patients sought medical help, they were not developed to the point that they substantially affected daily life in most patients with moderately severe COPD. As a result, the percentages of rescue medication used in the present study were low. Nevertheless, a greater benefit in terms of less requirement for rescue therapy was noted in GOLD II (moderate) patients in the N-acetylcysteine group than in the placebo group. Improved symptom relief in patients with stable, moderate-to-severe COPD receiving N-acetylcysteine 600 mg twice daily might be attributed to reduced air trapping[32] and increased small airway function.[22]

The overall safety profile in our study was consistent with the established safety profile of N-acetylcysteine 600 mg per day.

Our study and the PEACE study support the strategy of long-term antioxidant therapy with N-acetylcysteine for the prevention of COPD exacerbations in Chinese patients. We postulate that this finding is an anti-oxidant class effect because of their antioxidant and anti-inflammatory effects.[7–9] Both N-acetylcysteine and carbocisteine are antioxidant drugs. However, carbocisteine is characterised by the presence of a bound sulfhydrylic group that is blocked in a different way from N-acetylcysteine. N-acetylcysteine contains a free thiol group that acts as a direct scavenger of reactive oxygen species and an indirect antioxidant by provision of cysteine (a direct precursor in the synthesis of intracellular glutathione). Other factors, such as reduction of bacterial adherence to ciliated epithelial cells and inhibition of respiratory syncytial virus infection[33] might also be used to explain the better than placebo treatment effects. Most COPD medications are administered by inhalation, whereas oral agents such as N-acetylcysteine might be more convenient and acceptable for patients.

To our knowledge, PANTHEON is the largest, evidence-based study done with N-acetylcysteine to date, and is the first study to compare the treatment difference between patients with moderate and severe COPD treated with N-acetylcysteine. However, our study had some limitations. The sample size was intended to be 1250, but enrolment was stopped when 1006 patients were randomised because of slower than expected enrolment. After discussion by the study steering committee, the revised sample size was regarded as acceptable to detect a difference in the primary endpoint. Another potential limitation was that assessment of exacerbations was partly based on recall of events by patients. Exacerbation might have been defined more precisely as treatment of patients with systemic corticosteroids or antibiotics. However, this definition could increase the risk of underdiagnosis because some patients did not receive antibiotics or systemic corticosteroids because of economic, transportation, or other reasons. This study was done in Chinese patients only. Patients with mild COPD (GOLD I), might also benefit from treatment with N-acetylcysteine and this group is worth investigating in future trials. A pharmacoeconomics analysis could also have been incorporated in this study.

***Panel:* Research in context**

Systematic review

We searched Medline for articles published in any language with the search terms "N-acetylcysteine", "chronic obstructive pulmonary disease", "chronic bronchitis", and "randomised trial" to identify publications reporting the treatment effects of N-acetylcysteine on patients with chronic obstructive pulmonary disease (COPD) or chronic bronchitis. Our last search was done on Nov 26, 2013. We identified 25 articles reporting randomised control trials. However, only four trials were studied for 1 year or more and only three trials enrolled more than 100 participants. In the BRONCUS study,[12] 523 patients with COPD were treated with N-acetylcysteine or placebo for 3 years; the exacerbation rate with treatment did not reduce significantly compared with placebo, apart from in patients without concomitant inhaled corticosteroid treatment. In Schermer and colleagues' study,[13] 286 patients with COPD or chronic bronchitis were treated with inhaled fluticasone propionate, oral N-acetylcysteine, or placebo for 3 years. No benefits were noted for any treatment in terms of exacerbation reduction, quality of life, and yearly decline in forced expiratory volume in 1 s. The doses of N-acetylcysteine shown in these two studies were 600 mg per day. Nevertheless, in the HIACE study[22] in which 120 patients with COPD were treated with N-acetylcysteine 600 mg twice daily or placebo, small airways function improved significantly and exacerbation frequency decreased significantly in the N-acetylcysteine group compared with placebo.

Interpretation

Our findings suggest that the strategy of antioxidant therapy, such as high dose N-acetylcysteine, is important for the reduction of COPD exacerbation and symptom relief. Treatment with antioxidants requires long-term and regular administration. Early intervention might be essential to prevent the progress of COPD in terms of COPD exacerbation. Future studies are needed for patients with mild COPD (GOLD I).

Contributors

J-PZ, F-QW, Ch-XB, H-YW, JK, PC, W-ZY, L-JM, YG, and N-SZ were involved in the study design, recruitment of patients, and data collection. N-SZ, J-PZ, XL, LR, and MS were responsible for writing the manuscript. B-SW was responsible for the statistical analysis.

Conflicts of interest

Funding, medication, and payment for travel and hotels to attend the investigator's meeting for this study were supplied from Hainan Zambon Pharmaceutical. XL is employed by Hainan Zambon Pharmaceutical. LR and MS are employed by Zambon SpA. B-SW is an employee of MedKey (Shanghai) Med-Tec Development. All other authors declare that they have no conflicts of interest.

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