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A Systematic Review and Meta-Analysis: The Long-Term Effects of Oral N-Acetylcysteine in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the world's most prevalent causes of morbidity and mortality. About 5.6% of Indonesians have COPD. Most COPD patients have mucus hypersecretion and inadequate mucus clearance, leading to airway obstruction. N-acetylcysteine (NAC) is a mucolytic drug with antioxidant and anti-inflammatory effects. Long-term oral NAC use in COPD remains controversial. We searched four databases to analyze the effects of oral NAC in COPD over a minimum six-month treatment. The data was analyzed through Review Manager 5.4. Eight randomized controlled trials, comprising 3.187 patients, were selected for inclusion in the study. NAC had a lower risk of exacerbations (RR 0.78, 95% CI 0.66-0.93; p=0.005), whether at high dose (1200mg/day) or low dose (600mg/day). The risk is higher at the high dose (RR 0.90, p=0.04) than at the low dose (RR 0.70, p=0.0002). NAC did not affect FEV1 (mean difference 4.71, 95% CI -3.20-12.61; p=0.24), and adverse events were the same as with placebo (RR 1.14, 95% CI 0.78-1.67; p=0.51). Long-term oral NAC reduces the risk of COPD exacerbations at any dose and was well tolerated.

Keywords: N-Acetylcysteine (NAC), chronic obstructive pulmonary disease (COPD), exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) has become the top three cause of death worldwide (Venkatesan, 2024). In 2012, COPD was responsible for over 3 million deaths, or 6% of all deaths worldwide. The prevalence and impact of COPD are predicted to increase in the forthcoming decades as a consequence of the continued contact with COPD risk factors and the growing age of the global population (Mathers & Loncar, 2006). COPD with acute exacerbations causes a rapid deterioration in lung function, impaired health status, reduced physical activity, and a heavy economic burden (Zheng et al., 2014).

The pathogenesis of COPD involves many factors. These include mucus hypersecretion, oxidative stress, and airway and lung inflammation ((Vestbo et al., 2013). N-acetylcysteine (NAC) is a potent mucolytic, reducing sputum viscosity and improving mucus clearance. Furthermore, NAC has anti-inflammatory, direct, and indirect antioxidant effects that may prove beneficial in the long-term treatment of COPD patients (Zheng et al., 2014; Huang et al., 2023).

COPD is a main cause of chronic illness and death globally, with many individuals suffering for years and dying prematurely from the disease or its complications. In fact, it is both a preventable and a treatable disease, therefore the issue of managing long-term therapy to stabilize the patient's condition is an important challenge (Mathers & Loncar, 2006). Due to the variability of the study population, dosage of NAC therapy, and duration of therapy, the efficacy of NAC in the long-term therapy of COPD patients was not sufficiently determined by the existing data (Huang et al., 2023). Thus, we performed this study in order to investigate the effects of oral NAC in COPD patients, particularly for therapy periods of six months or longer.

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Material and Methods

Literature searching

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to search the literature. We searched PubMed, ProQuest, Cochrane Library, and ScienceDirect from their earliest date to June 19, 2024. The keywords employed were synonyms and combinations of "N-acetylcysteine" and "Chronic Obstructive Pulmonary Disease".

To be included, an article had to meet the following criteria: (1) randomized controlled trials (RCT), (2) written in English (3) included patients diagnosed with COPD by spirometry, (4) compare the results of oral NAC with placebo in at least six months of treatment. Exclusion criteria were: (1) articles with a study design other than RCT, (2) articles with different outcome measures, and (3) articles not available in full text.

Outcome indicators

The main outcome was the total of subjects who experienced a minimum of one exacerbation within the observation time. An exacerbation was described as an episode of acutely deteriorating in the clinical manifestations of the respiratory tract that required further treatment. Secondary outcomes included pre- and post-study changes in FEV1 in mL and adverse events.

Data extraction

The authors extracted the data using a Microsoft Excel spreadsheet. The goal of the summarization process was to obtain a detailed description of each study. From the selected articles, the information collected was as follows: first author's name, year published, number of patients, age, sex, COPD stage, baseline FEV1%, daily NAC dose, NAC treatment duration, and concomitant therapy.

Methodological quality assessment

The articles reviewed in this paper were scored using the Modified Jadad Scores Scale (Table 1) (Jadad et al., 1996; Chen et al., 2014). In this scoring method, a maximum of 7 points was given. Articles were considered high quality if they scored >4, 3-4 were considered moderate quality, and <3 were considered low quality.

Table 1. Modified jadad scores scale

	Items	Points
Randomization	Appropriate	2
	Did not describe the details of randomization	1
	Inappropriate	0
Concealment	Appropriate	2
	Did not describe the details of concealment	1
	Inappropriate	0
Blinded	Appropriate	2
	Did not describe the details of blinded	1
	Inappropriate	0
Withdraw or drop-out	Described	1
	Did not describe	0

Data analysis

A statistical analysis was conducted using the Review Manager 5.4.1 software. The risk ratio (RR) was applied to assess the risk of exacerbations and the adverse events caused by NAC during the treatment period. The mean difference was used to assess the difference in FEV1 between pre- and post-study.

Results and Discussion

Study selection

The database search initially identified 624 articles. Following the removal of duplicates, 128 studies were excluded. An additional 435 studies were excluded after a preliminary review of titles and abstracts. Following a comprehensive examination of the full texts, 53 studies were excluded, and finally, eight studies were selected for analysis. The main reasons for excluding articles were treatment duration of less than six months (2 articles), post hoc analysis (6 articles), observational studies (2 articles), protocol studies (5 articles), inappropriate outcome (11 studies), review studies (15 articles), and studies with no full text available (12 articles). The details of the article selection process based on the PRISMA guidelines are shown in Figure 1.

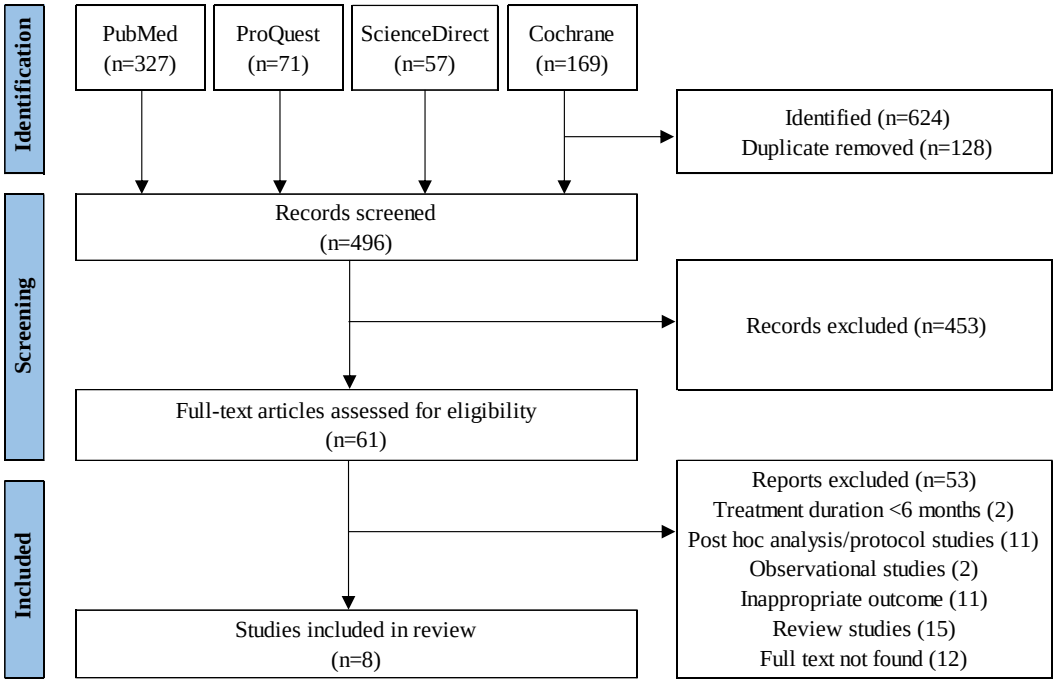

Figure 1. PRISMA Flow Chart

Features of the included articles

Eight RCTs with 3187 patients with COPD were part of this review. Table 2 showed the baseline information of the selected studies. Patients included had the oldest mean age reported by Tse et al. (2013), which was 71.0 ±1.1 in the NAC arm and 70.8 ±1.1 in the placebo arm, while Hansen et al. (1994) reported the youngest mean age which was 51.1 for the NAC arm and 51.7 for the placebo arm. The greatest percentage for male patients was in the study by Tse et al. (2013), 93% in the NAC arm and 94% in the placebo arm. The included articles had participants with different stages of COPD and concomitant therapies.

Zheng et al. (2014) included subjects with the lowest mean FEV1% at baseline, which was 49.08±11.9 in the NAC group and 48.8±11.7 in the placebo group. Four trials by Pela et al. (1999), Bachh et al. (2007), Decramer et al. (2005), and Schermer et al. (2009) used NAC dosed at 600 mg/day, while four other trials by Zheng et al. (2014), Tse et al. (2013), Hansen et al. (1994), and Ran et al. (2023) used NAC dosed at 1200 mg/day. The duration of therapy varies from 6 months to 36 months.

Table 2. Features of the included articles

Author	Country	n		MJS	Age (mean±SD)		Men (%)		COPD stage	FEV1% baseline (mean±SD)		NAC daily dose (mg)	Duration (months)	Concomitant therapy
		NAC	P		NAC	P	NAC	P		NAC	P			
Zheng 2014	China	504	502	7	66.1±8.7	66.4±8.8	82	81	2,3,4	49.08±11.9	48.8 ±11.7	1200	12	①②③④⑤⑥
Tse 2013	Hong Kong	58	62	7	71.0 ±1.1	70.8 ±1.1	93	94	1,2,3,4	60.6 ±3.2	58.6 ±2.7	1200	12	①②③④⑤⑥
Pela 1999	Italy	85	84	3	66± 10.1	66± 8.4	80	71	2,3	56.8±19.69	59.3 ±18.6	600	6	①②③⑥⑦
Bachh 2007	India	50	50	3	62.6 ±6.2	60.1 ±7.3	76	80	2,3	52.1±10.1	51.3 ±9.6	600	12	①②③④⑤⑥
Decramer 2005	Europe	256	267	7	62±8	62±8	79	79	2,3	57±9	57±9	600	36	①②③④⑤⑥
Schermer 2009	Nether-land	96	96	3	59.2 ±9.2	59.6 ±10.1	78	68	1,2,3	68.1±13.9	71.4 ±17.1	600	36	①②③⑥
Hansen 1994	Den-mark	75	78	6	51.1	51.7	40	46	1	NA	NA	1200	6	NA
Ran 2023	China	464	460	6	62.5 ±8.4	62.6±8.0	89	88	1,2	82.4±15.8	82 ±16.8	1200	24	①②③④⑤⑥

① Inhaled Corticosteroid ② Long-acting beta-agonist ; ③ Short-acting beta-agonist; ④ Short-acting muscarinic antagonist; ⑤ Long-acting muscarinic antagonist; ⑥ Theophylline; ⑦ Oral corticosteroid

MJS: Modified Jadad Scales; NAC: N-acetylcysteine; P: Placebo; FEV1%: Forced Expiratory Volume 1 s % predicted; NA: Not Available

Quality assessment

Modified Jadad Scales Scores were used in this study. Five articles were high quality, while the other three were moderate quality with a score of 3 (Table 1).

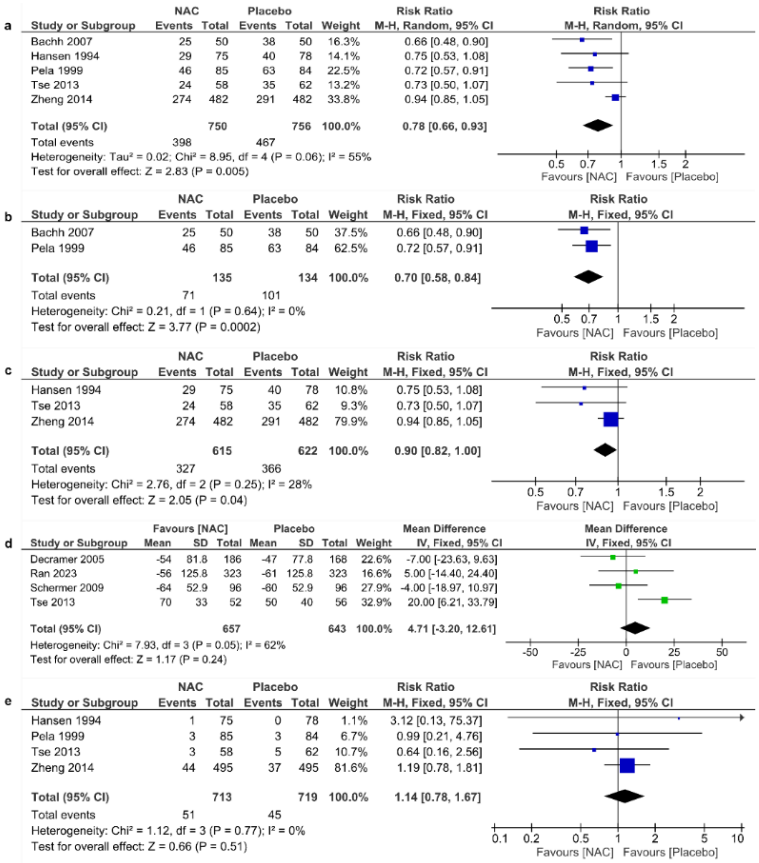

Figure. 2. a. Forest plot for at least one exacerbation in all included studies, b. Forest plot for at least one exacerbation in low-dose (600mg/day) NAC, c. Forest plot for at least one exacerbation in high-dose (1200mg/day) NAC, d. Forest plot for change in FEV1, e. Forest plot for adverse events.

Efficacy and safety outcomes

Five studies involving 1556 patients (750 receiving NAC therapy and 756 in the control group) reported the number of patients who experienced at a minimum of one acute COPD exacerbation (Zheng et al., 2014; Tse et al., 2013; Hansen et al., 1994; Pela et al., 1999; Bachh et al., 2009). Number of patients with at a minimum of one exacerbation differed significantly between groups (RR 0.78, p=0.005, I2=55%) (Figure 2.a). The results of the subgroup analysis of NAC doses (600mg/day and 1200mg/day) are illustrated in Figures 2.b and 2.c. There was a statistical difference in the number of subjects who reported at a minimum of one exacerbation between the groups receiving NAC and those receiving placebo., both at the 600mg/day dose (RR 0.70, p=0.0002, I2=0%) and the 1200mg/day dose (RR 0.90, p=0.04, I2=28%).

Four studies with 1300 participants (657 patients receiving NAC therapy and 643 control patients) evaluated the pre- and post-study difference in FEV1 volume in milliliters (Tse et al., 2013; Decramer et al., 2005; Schermer et al., 2009; Ran et al., 2023). Between patients in both treatment arms, no significant differences in FEV1 were found (mean difference 4.71, 95% CI -3.20-12.61, p=0.24, I2 = 62%) (Figure 2.d). Four studies involving 1432 patients (713 treated with NAC, 719 controls) reported adverse events (Zheng et al., 2014; Tse et al., 2013, Hansen et al., 1994, Pela et al., 1999). The adverse events observed between both groups were not found to be statistically significantly different (RR 1.14, 95% CI 0.78-1.67; p=0.51, I2=0%) (Figure 2.e).

Our study demonstrated that the use of oral NAC for more than six months was related to a significant decrease in the risk of exacerbations compared with the placebo group (RR 0.78, 95% CI 0.66-0.93; p=0.005). Previous reviews have also demonstrated that NAC may decrease the risk of exacerbations in COPD patients, but these studies included NAC use at all treatment durations (Jiang et al., 2021, Cazzola et al., 2015, Papi et al., 2024, Shen et al., 2014). Fowdar et al. demonstrated that long-term treatment with NAC (≥6 months) decreased the frequency of exacerbations, but this study included older studies (before 1990) in which COPD was diagnosed without spirometry (Fowdar et al., 2017).

Oxidative stress is elevated in COPD patients, contributing to inflammatory pathogenesis, particularly upon the occurrence of exacerbations (Venkatesan, 2024). NAC has both direct and indirect antioxidant effects. The direct effect is due to the interaction between the free thiol group and the electrophilic group of reactive oxygen species (ROS). The indirect antioxidant effect is associated with its function as a glutathione (GSH) precursor, which protects against toxins (Bachh et al., 2007).

Our subgroup analysis showed that both the 600 mg/day and 1200 mg/day doses had a reduced risk of exacerbations compared to placebo, but the risk was slightly higher for those taking 1200 mg daily (RR 0.90, p=0.04) compared to those taking 600 mg daily (RR 0.70, p=0.0002). A review by Sadowska et al. (2007) pointed out that NAC has been shown to effectively suppress oxidative stress at concentrations both low and high, in both acute (in vitro) and chronic (in vivo) administration. The slightly higher risk of exacerbation in the high-dose group that was shown in this study may be due to one of the included study in the high-dose group, that is by Zheng et al. (2014) had a much higher sample size compared to other two studies (Table 2), but the FEV_1% baseline is the lowest compared to others. This means that the subjects included in the Zheng et al. trial may have had worse baseline conditions than others, so that the risk of exacerbation was higher to begin with.

No significant difference was found between the change in FEV_1 in patients treated with NAC or placebo for at least 6 months (mean difference 4.71, 95% CI -3.20-12.61; p=0.24). This result is consistent with the previous study by Huang et al. NAC is not a bronchodilator, so it may not be able to increase lung function or slow down the deterioration of lung volume in patients with COPD (Huang et al., 2023).

Our study also found that the adverse events that occurred in both groups were not statistically different (RR 1.14, p=0.51). Commonly reported adverse events include gastrointestinal symptoms, respiratory tract infection, pruritus, dizziness, dry mouth, muscle pain, pyrosis, and anorexia (Zheng et al., 2014; Tse et al., 2013; Hansen et al., 1994; Pela et al., 1999).

Our study is limited in several ways. First, the number of included articles in the subgroup (high or low dose) was too small. Second, the eight studies had heterogeneous concomitant COPD treatment and COPD stage. Future studies are needed that consider concomitant treatments such as inhaled corticosteroids and baseline COPD stage, as these may have an impact on exacerbations. There is also a need for more studies with high and low dose NAC in the long-term treatment period.

Conclusion

Long-term treatment with oral NAC decreases the risk of COPD exacerbations, regardless of the dose used. Oral NAC can be considered an important and well-tolerated therapeutic agent that can be included in the standard COPD therapy plan.

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