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International Journal of Family & Community Medicine

Research Article
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The evidence of the use of oral N-acetylcysteine in the reduction and the prevention of exacerbations in chronic obstructive pulmonary disease

Abstract

Introduction: Exacerbations are responsible for the majority of morbidity, mortality and costs associated with chronic obstructive pulmonary disease. However, the evidence that oral mucolytics have an important clinical effect on this pathology is limited. The objective of this evidence-based review was to describe the current state of knowledge regarding the reduction and prevention of exacerbations in chronic obstructive pulmonary disease with the use of oral N-acetylcysteine.

Materials and methods: Research was performed on recommended scientific bases in English, Portuguese and Castilian, without restriction on the date of publication, with the MeSH words "Acetylcystein" and "Pulmonary Disease, Chronic Obstructive". Inclusion and exclusion criteria have been defined. The evaluation of the levels of evidence and the assignment of the recommendation forces were made through the scale Strength Of Recommendation Taxonomy.

Results: Seven articles were obtained through the methodology used: four systematic reviews and three guidelines. All studies concluded that the use of oral N-acetylcysteine decreases and prevents exacerbations in patients with chronic obstructive pulmonary disease.

Discussion: There are few studies that allow us to clearly recommend the use of oral N-acetylcysteine in patients with chronic obstructive pulmonary disease. Still, according to the existing studies and the usual clinical practice, there seems to be benefit with its use in the decrease and in the prevention of exacerbations in this group of patients.

Conclusions: Further studies are needed to evaluate the efficacy and the safety of oral N-acetylcysteine in the reduction and prevention of exacerbations in chronic obstructive pulmonary disease.

Keywords: chronic obstructive pulmonary disease, oral n-acetylcysteine, exacerbations, prevention, decrease

Volume 3 Issue 5 - 2019

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Received: August 10, 2019 | **Published:** October 03, 2019

Abbreviations: COPD, chronic obstructive pulmonary disease; CPG, clinical practice guidance; SR, systematic reviews; SORT, strength of recommendation taxonomy; NAC, N-acetylcysteine

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations. COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. They are classified as: mild (treated with short-acting-bronchodilators only), moderate (treated with short-acting-bronchodilators plus antibiotics and/or oral corticosteroids) or severe (patient requires hospitalization or visits the emergency room). The prevalence of COPD was higher in ≥40 year group compared to those <40. COPD exacerbations account for the greatest proportion of the total COPD burden. Spirometry is required to make the diagnosis; the presence of a post-bronchodilator forced expiratory volume in the first second/forced vital capacity (FEV1/FVC) <0.70 confirms the presence of persistent airflow limitation: GOLD 1 (mild–FEV1 ≥80% predicted); GOLD 2 (moderate – 50% ≤FEV1 ≤80%); GOLD 3 (severe – 30% ≤FEV1 ≤50%); and GOLD 4 (very severe – FEV1 < 30%). COPD is also classified by ABCD assessment tool, which provides information about previous history of exacerbation and the symptoms of the patient. The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.

Standard therapies for stable COPD include bronchodilators (such as b2 agonists, anticholinergics, and theophylline), corticosteroids, expectorants, and long-term oxygen therapy.[1] However, few pharmacological treatments have been proven to reduce clinical events, and none has been shown definitively to slow the decline in FEV1.[2–8] The hypersecretion of tracheobronchial mucus contributes to the symptoms of COPD and is associated with the increased risk of hospitalizations and the accelerated decline in forced expiratory volume in the first second. The exacerbations contribute to most

COPD morbidity, mortality and costs. These cause frequent hospital admissions, relapses and readmissions, contribute to mortality during or shortly after hospitalization, dramatically reduce quality of life, consume financial resources and accelerate a progressive decline in lung function, a cardinal feature of COPD. Mucolytics disrupt the mucus gel, generally by reducing its viscosity via alteration of the degree of cross linking or interaction between molecules. N-acetylcysteine (NAC) is a derivative of the amino acid L-cysteine, which is also commonly used as a mucolytic. It is used for COPD because of its antioxidant and anti-inflammatory properties.[2] However, the evidence that oral mucolytics have an important clinical effect, although widely used, in COPD patients is limited. Thus, it seems important to determine the evidence for their use in COPD patients. The purpose of this evidence-based review was to describe the current state of knowledge regarding prevention of COPD exacerbations with the use of oral NAC in this group of patients.

Material and methods

Search for Clinical Practice Guidance (CPG), Systematic Reviews (SR) and original articles in English, Portuguese and Castilian, without restriction on publication date, with the following MeSH terms: "Acetylcystein" and "Pulmonary Disease, Chronic Obstructive". The data sources used were: National Guideline Clearinghouse, Finder Guidelines, Canadian Medical Association Practice Guidelines Infobase, Cochrane Library, DARE - Database of Abstracts of Reviews of Effectiveness, Bandolier, British Medical Journal and PUBMED. The inclusion criteria were: adults, male and female, with the diagnosis of COPD, independently of *Gold* category. The exclusion criteria were: studies with mucolytic drugs other than NAC, such as inhaled mucolytics, carbocysteine, erdosteine, ambroxol or iodine-glycerol, and studies in patients with pulmonary pathology, other than COPD, such as asthma or cystic fibrosis. The intervention was the use of oral NAC in individuals who met the inclusion criteria. The assessment of evidence levels and the assignment of recommendation strengths were made using the Strength of Recommendation Taxonomy (SORT) scale.

Results

Seven articles were obtained: 4 SR and 3 CPG. The main results and the conclusions of the analyzed articles are presented in Table 1.

Table 1 Main outcomes and conclusions of the analyzed articles

Type of study	Authors (Year)	Description/Results/Conclusions	SORT
Pair wise and network Meta-analysis	Paola Rogliani, Maria G Matera, Clive Page, Ermanno Puxeddu, Mario Cazzola, Luigino Calzetta (2019)	1. Meta-analysis: Of the 60 articles retrieved by the primary search, full texts of 28 articles were screened and 7 studies were included in the analysis. All studies were described as randomized controlled trials.	1 B
		2. Objective: To access the efficacy of erdosteine, carbocysteine and NAC on acute exacerbation of COPD (AECOPD), duration of AECOPC, and hospitalization. The frequency of adverse events was also investigated	
		3. Inclusion criteria: COPD patients treated for more than 6 moths with oral formulations of erdosteine 600 mg/day, carbocysteine 1500 mg/day, and NAC 1200 mg/day were included in this meta-analysis.	
		4. Discussion: NAC therapy was associated with a significant reduction in the number of patients with at least 1 COPD exacerbation. No effects of NAC therapy on pulmonary function (FEV1 or FVC) or COPD exacerbation rate were observed. NAC therapy did not increase the occurrence of adverse drug effects. In subgroup analyses, both high-dose and low-dose NAC treatments reduced the number of patients with at least 1 exacerbation, but significant benefits were associated only with NAC durations ≥ 6 months, indicating that long-term NAC administration can reduce COPD exacerbation risk, regardless of dose. These results may imply that the use of NAC is helpful for COPD patients with frequent exacerbations in terms of reducing the duration of hospital stays, medical burdens, and the risk of hospital acquired pneumonia.	
CPG	Jadwiga A. Wedzicha, Peter M.A. Calverley, Richard K. Albert, Antonio Anzueto, Gerard J. Criner, John R. Hurst, Marc Miravitlles, Alberto Papi, Klaus F. Rabe, David Rigau, Pawel Sliwinski,	1. Guideline: The Task Force co-chairs who review the theme were selected by the European Respiratory Society (ERS) and American Thoracic Society (ATS). It employed a SR of the literature followed by the Grading of Recommendations Assessment, Development and Evaluation. Six randomised, placebo-controlled trials were analyzed.	2B
	Thomy Tonia, Jørgen Vestbo, Kevin C. Wilson, Jerry A. Krishnan	2. Objective: To verify if mucolytics should be prescribed to patients with stable COPD to prevent COPD exacerbations.	

Citation: Pereira I, Pinto AM, Silva AC, et al. The evidence of the use of oral N-acetylcysteine in the reduction and the prevention of exacerbations in chronic obstructive pulmonary disease. *Int J Fam Commun Med.* 2019;3(5):189–194. DOI: 10.15406/ijfcm.2019.03.00156

Table continued

Type of study	Authors (Year)	Description/Results/Conclusions	SORT
	(2017)2	3. Population: COPD patients who had moderate or severe airflow obstruction, who had a history of at least 2 exacerbations per year during the previous 2 years, who had a history of at least 1 exacerbation per year during the previous year, COPD regardless of whether or not they had any exacerbations during the previous year. 4. Intervention: The use of oral NAC for 1 or 3 years. 5. Potential benefits: Mucolytic therapy reduced hospitalizations and the number of COPD exacerbations per patient-year (an effect largely attributable to high-dose therapy), but not the proportion of patients who remained exacerbation-free. 6. Potential damage: None identified. 7. Main outcomes: When the data were pooled via meta-analysis, mucolytic therapy decreased the likelihood of hospitalization (14.1% versus 18.1%; risk ratio 0.76, 95% CI 0.59–0.97), indicating that 25 patients needed to be treated with mucolytics to prevent 1 hospitalization. When we segregated the analysis based upon dosage, the absolute and relative decreases in hospitalizations were similar among patients who received high-dose or low-dose mucolytic therapy compared with both doses pooled together, but due to smaller numbers of patients in each group, the confidence intervals widened to include no significant effect of the drug. The effect of mucolytic therapy on COPD exacerbations varied according to the method of measurement. Mucolytic therapy reduced the relative rate of exacerbations when assessed as the number of exacerbations per patient-year (rate ratio 0.79, 95% CI 0.65–0.95), although the absolute rate reduction was small (rate difference of 0.38 fewer exacerbations per patient-year, 95% CI 0.23 fewer to 0.54 fewer). The reduced rate of COPD exacerbations was largely attributable to high-dose mucolytic therapy (rate ratio 0.69, 95% CI 0.50–0.94), as trials that used low-dose mucolytic therapy did not find a significant relative rate reduction (rate ratio 0.87, 95% CI 0.66–1.14). Mucolytic therapy had no effect on COPD exacerbations when assessed as the proportion of patients who remained exacerbation-free (34.1% versus 32.4%; risk ratio 1.06, 95% CI 0.95–1.19). Mucolytic therapy had no demonstrable effect on mortality (1.3% versus 1.1%; risk ratio 1.15, 95% CI 0.55–2.43) or adverse events (26.9% versus 24.2%; risk ratio 1.11, 95% CI 0.91–1.35). The effect on quality of life could not be estimated via meta-analysis and the individual studies provided inconsistent results. For all outcomes, the estimated effects did not change substantially when the trials were pooled according to whether or not a history of exacerbations was required for enrolment. 8. Conclusion: NAC reduces the likelihood of hospitalization and, when given in high doses, may also reduce COPD exacerbations. No effect on mortality was shown, although there were low numbers of deaths in the trials to definitively determine the effect on mortality. Similarly, there is no evidence that mucolytic therapy increases adverse effects or alters quality of life. Determining the effects of mucolytic therapy in patients with mild or very severe COPD is an important research need, as the findings will help define the patient population most likely to benefit from mucolytic therapy. 9. Limitations: The overwhelming majority of patients had moderate or severe airflow obstruction; few patients had mild or very severe airflow obstruction. There was no information in any of the trials on the quantity of sputum production. In addition, the outcomes were limited by imprecise estimates, inconsistent results among the primary studies or both; these limitations diminished the panel's confidence in the estimated effects. As some of the studies included patients who were not on optimal inhaled therapy, the efficacy of mucolytics on top of maximal inhaled treatment has yet to be clearly established. 10. ERS/ATS recommendation: For patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with an oral mucolytic agent to prevent future exacerbations.	
SR and Meta-analysis	Kaushal Fowdar, Huan Chen, Zhiyi He, Jiujin Zhang, Xiaoning Zhong, Jianquan Zhang, Meihua Li, Jing Bai	1. Meta-analysis: Of the 574 articles retrieved by the primary search, full texts of 29 articles were screened and 12 studies were included in the analysis. All studies were described as randomized controlled trials.	1B

Table continued

Type of study	Authors (Year)	Description/Results/Conclusions SORT
	(2017)3	2. Objective: To evaluate the effect of NAC on exacerbations of COPD. 3. Inclusion criteria: Patients with stable COPD; COPD diagnosis involved spirometric demonstration of a post- bronchodilator forced expiratory volume in the first second /forced vital capacity (FEV1/ FVC) ratio 0.7, intervention with orally administered NAC for ≥ 4 weeks in addition to standard therapy; inclusion of a control group of patients receiving placebo or standard therapy (e.g., b2 agonists, anticholinergics, and theophylline); randomized or cross-over controlled trial design; and examination of the number of patients with at least 1 exacerbation as the primary outcome, and other effect indexes as the secondary outcomes. 4. Discussion: In this quantitative synthesis of current literature both erdosteine, carbocysteine, and NAC fulfilled the primary endpoint represented by the reduction in the risk of AECOPD. Considering exclusively the high-quality RCTs that did not introduce significant heterogeneity in the pairwise meta-analysis, this study indicates that the mean effect estimate of the overall impact of mucolytic/antioxidant agents reached the minimal clinically important difference (MCID: ≈0.75 RR) in reducing the risk of AECOPD compared to placebo. In any case, the results of pairwise meta-analysis seem to be affected by a certain level of publication bias that was mainly related with the results extracted from the study of Tse et al., as confirmed by both funnel plot and Egger's test analyses. Although was found no significant difference across the investigated drugs with respect to their protective effect against AECOPD, the SUCRA analysis resulting from the network meta-analysis indicated that erdosteine was the most effective agent, followed by carbocysteine and NAC. Interestingly, the consistency/inconsistency analysis showed that the network meta-analysis was not affected by significant bias. The superiority of erdosteine with respect to carbocysteine and NAC was also confirmed by the NNT analysis, that provided significant NNT values for erdosteine but neither for carbocysteine nor for NAC, when compared to placebo. 5. Conclusion: The current evidence suggests that the overall efficacy/safety profile of erdosteine is superior to that of both carbocysteine and NAC. However, future head-tohead studies performed on the same COPD populations are needed to definitely confirm the results of this quantitative synthesis.
SR and Meta-analysis	Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG (2017)	1. Meta-analysis to evaluate the impact of the mucolytic drugs in COPD. It includes randomized clinical trials with at least 3 months of duration. Investigates the effects of mucolytic drugs in acute COPD exacerbations. 2. Main outcomes: To establish if the treatment with NAC reduces the frequency of the exacerbations and/or disability days in patients with COPD. 3. Results: The mucolytic drugs significantly reduced the risk of exacerbations versus placebo (11 analyzed studies: odds ratio (OR) 0,51, CI 95% 0,39-0,67; p < 0,001). One of the most effective mucolytic drugs was NAC (SUCRA 68.0–79.0%). Only NAC 1.200 mg/day significatlively protected against exacerbations versus placebo (2 studies were analyzed: OR 0,56, IC 95% 0,35-0,92; p < 0,05; high quality of evidence).

Table continued

Type of study	Authors (Year)	Description/Results/Conclusions	SORT
		4. Conclusions: The results of this meta-analysis demonstrate that the mucolytic drugs are effectively protecting COPD patients from the exacerbations of the disease, being this effect more benefic when the treatment was implemented for a year or more.	
		5. Possible Limitations: Specific differences in study designs and patient characteristics, such as history of exacerbations and ethnicity. The lung function and the use of corticosteroids didn't influence the analysis.	
CPG	Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK (2015)4	1. Guideline: Review of 27 systematic reviews, 8 of which were considered potentially relevant.	2B
		2. Objective: To describe the current state of knowledge regarding the prevention of acute exacerbations in COPD.	
		3. Population: COPD patients.	
		4. Intervention: The use of oral NAC.	
		5. Potential benefits: The prevention of acute exacerbations in COPD.	
		6. Potential damage: In patients with COPD and chronic bronchitis NAC is well tolerated, except in rare patients with adverse gastrointestinal effects.	
		7. Main outcomes: Worsening of lung function, quality of life, urgent care/hospitalization and healthcare costs.	
		8. Conclusion: In patients with moderate to severe COPD with a history of ≥ 2 exacerbations in the previous 2 years, the treatment with oral NAC is suggested for the prevention of acute COPD exacerbations.	
CPG	Management of Chronic Obstructive Pulmonary Disease Working Group. Washington (DC): Department of Veterans Affairs, Department of Defense (2014)5	1. Guideline: Searching in electronic databases and in unpublished data - 94 studies met the inclusion criteria.	2B
		2. Population: The COPD patients were classified into 2 groups: patients with frequent exacerbations (≥ 2/year), defined as those which needed corticosteroid and/or antibiotic prescription, hospitalization or going to emergency room; and patients without frequent exacerbations.	
		3. Intervention: The use of oral NAC.	
		4. Main outcomes: Quality of life, morbidity, dyspnea, functional capacity, rate and/or severity of exacerbation, mortality, health care utilization, rigor of diagnostic tests, symptomatology burden, disease progression.	

Table continued

Type of study	Authors (Year)	Description/Results/Conclusions	SORT
		5. Conclusion: There is insufficient evidence to recommend for or against the use of NAC preparations available in the United States in patients with stable and confirmed COPD who maintain respiratory symptoms.	
SR	Poole PJ, Black PN (2002)6	1. Were selected randomized, double-blind controlled trials.	1B
		2. Inclusion criteria: Individuals > 20 years of age and chronic bronchitis/COPD, with regular use for ≥ 2 months of oral mucolytics.	
		3. Exclusion criteria: Studies on inhaled mucolytic drugs, combinations of mucolytics with antibiotics or bronchodilators, deoxyribonucleases, proteases, and studies in patients with asthma or cystic fibrosis.	
		4. Main outcomes: Number of exacerbations per patient/month, days of illness and days of antibiotic use.	
		5. Results:	
		5.1. Twenty-three of the 27 studies that met the selection criteria included data on the main outcomes;	
		5.2. Twenty-one studies were made in patients with chronic bronchitis and 2 in patients with COPD;	
		5.3. The follow-up period was from 2 to 24 months (average of 6 months);	
		5.4. The studies were carried out in: Italy (11), United Kingdom (4), Sweden (2), Europe (2), Germany (2), Denmark (1) and United States of America (1);	
		5.5. The mucolytic drugs were better compared to placebo in reducing exacerbations per patient/month ($p < 0.001$), days of disease ($p < 0.001$), and days of antibiotic use ($p < 0.001$) for a 95% confidence interval .	
		6. Conclusion: In patients with chronic bronchitis or COPD, the mucolytic drugs reduce the exacerbations, the days of illness and the days of antibiotic use.	
		7. Possible limitations: The lung function did not improve and the hospitalization rates were not reported.	

Discussion

There are few studies to clearly recommend the use of oral NAC in COPD patients. Still, according to existing studies and usual clinical practice, there appears to be benefit from the use of oral NAC in both reducing and preventing exacerbations in this patient group, when in combination with optimized traditional COPD treatment.

Conclusion

Further randomized, controlled, double-blind studies with larger samples and longer-term evaluation are needed to more consistently assess the efficacy and the safety of oral NAC in decreasing and preventing exacerbations in patients with COPD.

Acknowledgments

None.

Conflicts of interest

The author declares there is no conflict of interest.

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