



ISSN Print: 2664-8504
ISSN Online: 2664-8512
Impact Factor: RJIF 5.42
IJPRS 2024; 6(1): 01-05
www.pulmonologyjournals.com
Received: 02-01-2024
Accepted: 03-02-2024

Manjula S

Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Krishna Kumar M

Sr. General Manager, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Corresponding Author:

Manjula S

Sr. Vice President, Department of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

Expert opinion on the clinical use of N-acetylcysteine and acebrophylline for the management of chronic obstructive Pulmonary disease in Indian clinical settings

Manjula S and Krishna Kumar M

DOI: <https://doi.org/10.33545/26648504.2024.v6.i1a.21>

Abstract

Objective: The current survey-based study aims to assess the preferences and practices of healthcare professionals regarding the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) and bronchitis in Indian clinical settings, with a special focus on the use of N-acetylcysteine and acebrophylline (NAA) combination and their adjuvant therapies.

Methodology: The survey, conducted through a questionnaire consisting of 20 questions, collected opinions from specialists across India regarding the current practices and prescription patterns of the NAA combination for COPD management. Additionally, the survey investigated the recommendation of amoxicillin + clavulanic acid and montelukast + levocetirizine, alongside the NAA combination, for managing infections associated with bronchitis/COPD and mucus control.

Results: According to 68% of the 114 respondents, the diagnosis of COPD was based on the results of a pulmonary function test. Approximately 51% of the respondents recommended the NAA combination for COPD patients, while 44% preferred the combination to treat both acute and chronic bronchitis. According to 45% of the respondents, bronchiolitis is the most common disease that requires an NAA combination. The majority of respondents (42.10%) stated that they would recommend administering the NAA combination for a duration of 10 to 15 days. Additionally, 50% of the participants stated that this NAA combination treatment could lead to an improvement in COPD symptoms within 7 days. Furthermore, most of the participants recommended a combination of amoxicillin and clavulanic acid antibiotics, along with montelukast and levocetirizine, prescription as adjuvant therapy in conjunction with the NAA combination.

Conclusion: Experts emphasized the use of the NAA combination as a promising therapeutic approach for managing COPD patients and its potential benefits in addressing both acute and chronic bronchitis. Clinical improvement was noted after a week of using this medicine combination, which was reported to be helpful when administered for 10-15 days. Additionally, adjuvant therapies such as amoxicillin, clavulanic acid, montelukast, and levocetirizine are commonly recommended in conjunction with the NAA combination for effective mucus management in case of asthma/bronchitis/COPD.

Keywords: Chronic obstructive pulmonary disease, N-acetylcysteine, acebrophylline, bronchitis, bronchial asthma

Introduction

The Global Initiative for Obstructive Lung Disease defines chronic obstructive pulmonary disease (COPD) as a disease state marked by airflow restriction that is not entirely curable [1]. Obstructive bronchiolitis and emphysema, whose relative contributions vary from person to person, are a combination of small airway illnesses that leads to chronic airflow limitation in COPD [2].

In recent years, there have been significant advancements in the understanding and treatment of COPD. The disease is now recognized as the sixth most common global cause of poor health [3]. Historically, COPD has been associated with men over the age of 60 years, and it is primarily caused by smoking, resulting in a rapid decline in lung function with aging. Over 70% of COPD cases in high-income nations are caused by tobacco use. In low- and middle-income countries, household air pollution is a significant risk factor for COPD, accounting for 30-40% of the cases [3].

The use of pharmacological therapy in COPD has increased over the past few decades. To alleviate airflow restriction and reverse broncho-constriction in COPD, bronchodilators and anti-inflammatory medications are employed. Drug therapy aims to enhance lung function as well as the quality of life, exercise ability, and exacerbation prevention [4]. N-acetylcysteine, a typical antioxidant and mucus-modifying medication, has garnered significant attention in pharmaceutical research due to its potential therapeutic properties [5, 6]. Its mucus-modifying properties are particularly valuable in managing respiratory conditions characterized by excessive mucus production such as chronic bronchitis. A double-blind, randomized, placebo-controlled study by Stav and Raz observed that the administration of N-acetylcysteine to COPD patients led to an improvement in their physical performance. This improvement is likely attributed to reduced air trapping [7]. Adults with asthma and COPD can be treated with acebrophylline (A xanthine derivative) as a bronchodilator [8]. Acebrophylline alters mucus secretion by increasing 'sol' phase viscosity and decreasing 'gel' phase viscosity. It also promotes mucociliary clearance by enhancing ciliary motility [9]. Although there are some studies assessing the therapeutic effect of N-acetylcysteine and acebrophylline as monotherapy in reducing acute exacerbations in COPD patients, clinical evidence on the combination of N-acetylcysteine plus acebrophylline for the treatment of COPD is very limited [9-15]. In order to bridge the gap, the present study aims to gather expert opinions on the prescription practice of N-acetylcysteine and acebrophylline (NAA) combination for the treatment of COPD/bronchitis across the Indian settings.

Methodology

A cross sectional, multiple-response questionnaire based survey among physicians specialized in COPD treatment in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet titled NAMO (N-acetylcysteine and Acebrophylline for the Management of Obstructive pulmonary disease) study was sent to the doctors who were interested to participate. The NAMO study questionnaire included 20 questions aimed at gathering professional opinions on the prescription patterns of NAA combination therapy for COPD management. The study was performed after obtaining approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to professionals across India based on their expertise and experience in treating COPD in the month of March 2022 for participation in this Indian survey. About 114 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. They were explicitly instructed to provide individual responses without consulting their colleagues. Before commencing the study, written informed consent was obtained from all survey participants.

Statistical Methods

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (Version 16.0.13901.20400).

Results

Out of the 114 respondents, 42% reported that COPD predominantly affects patients over 41 years of age, whereas nearly 32% stated that the disease is common in the 31-40 years age group. Majority of the respondents (67.54%) recommended the pulmonary function test as the preferred diagnostic method for COPD, while 22% preferred chest X-rays for COPD diagnosis. Approximately 40% of the respondents identified cough with sputum as the major symptom reported during COPD diagnosis (Table 1), whereas 2% of them stated cough without sputum and breathlessness as prominent symptoms during COPD diagnosis.

Table 1: Response to patient-reported symptoms during COPD diagnosis

Patient-reported symptoms during COPD diagnosis	Response rate (n=114)
Cough with sputum	46 (40.35%)
Cough without sputum	25 (21.92%)
Wheezing	16 (14.03%)
Breathlessness	25 (21.92%)
Difficulty in climbing	1 (0.87%)
Others	1 (0.87%)

Acetylcysteine was favored as monotherapy by approximately 39%, 27%, and 24% at preference rates of 20%, 30%, and 10%, respectively. Approximately 51% of the respondents reported that they recommend NAA combination to COPD patients, while 44% agreed that they recommend this combination to manage acute and chronic bronchitis (Figure 1).

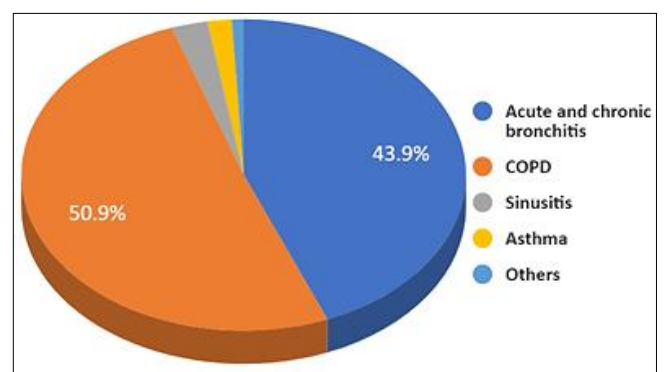


Fig 1: Response on the indications for recommending NAA combination

Bronchiolitis is identified as the most common condition requiring an NAA combination, as reported by 45% of the respondents. Moreover, 21% and 19% of the experts mentioned that they would prescribe this combination for patients with emphysema and excessive mucus secretion indications, respectively (Table 2). Approximately 42% of the respondents indicated a prescription duration of 10-15

days for the NAA combination, while 32% suggested a duration of 15-30 days for COPD patients. Regarding the onset of improvement, 50% of the experts believed that the

NAA combination could yield results within 7 days, whereas 33% indicated a clinical improvement after 10 days of NAA medication.

Table 2: Response on the conditions that require NAA usage in the clinical settings

Most common condition that requires NAA usage	Response rate (n=114)
Emphysema	24 (21.05%)
Bronchiolitis	51 (44.73%)
Exhibit diminished expiratory airflow	15 (13.15%)
Hyper mucus secretion	22 (19.29%)
Others	2 (1.75%)

Amoxicillin and clavulanic acid (Figure 2) are the most commonly utilized antibiotics in conjunction with the NAA combination for bronchitis/COPD treatment, as reported by 45% of the respondents. On the other hand, azithromycin, cefpodoxime, and cefuroxime were preferred as adjuncts by

24%, 18%, and 11% of the participants, respectively. Regarding asthma/bronchitis treatment, nearly 52% of the responders suggested montelukast + levocetirizine, while only 20% recommended a montelukast + fexofenadine combination (Figure 3).

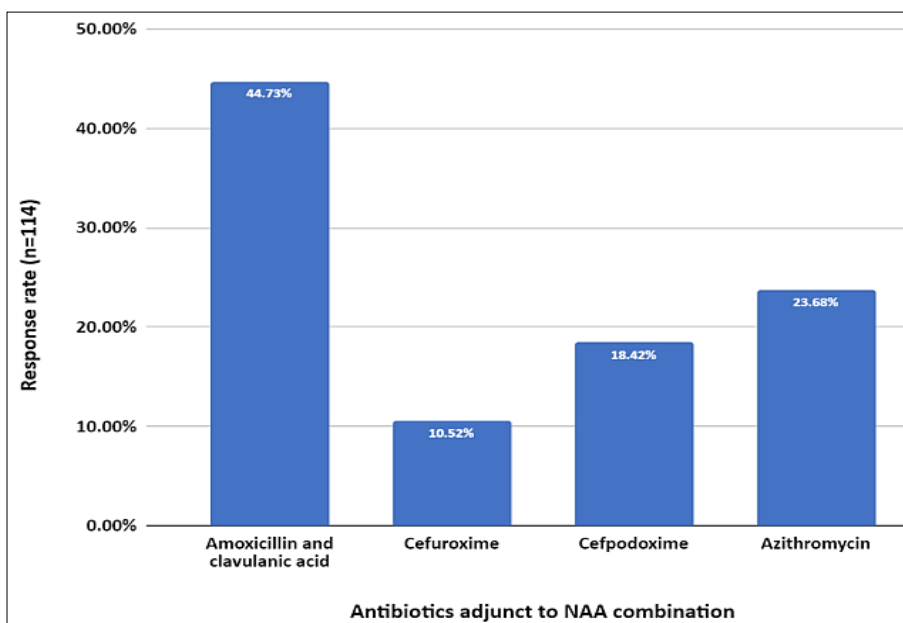


Fig 2: Response on the antibiotic preference along with NAA for infectious management of bronchitis/COPD

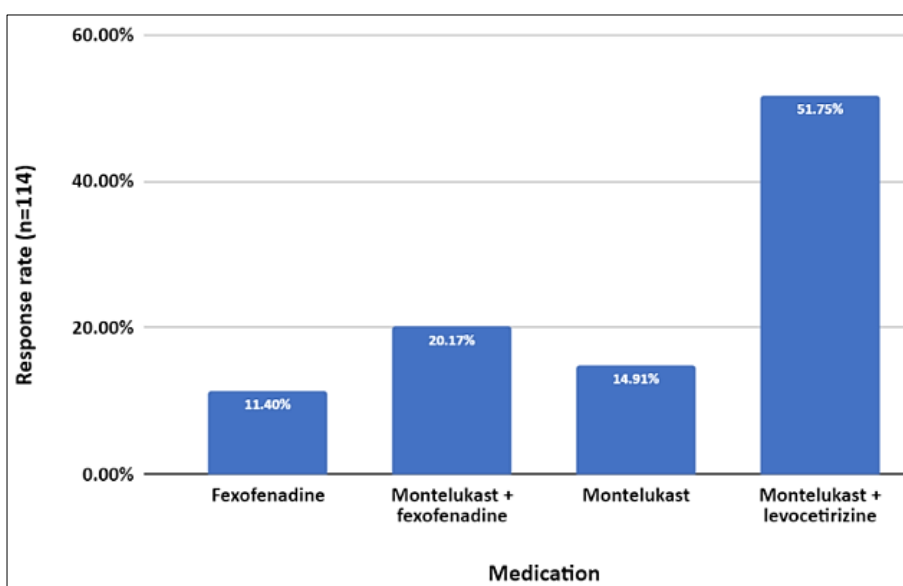


Fig 3: Response on the medication preferred along with NAA for asthma/bronchitis

Nearly 59% of the participants stated that they would prescribe acebrophylline and montelukast for the treatment

of COPD. About 24% of them recommended this combination for treating asthma patients as well. However,

experts also recommended this combination therapy for the treatment of acute bronchitis. The majority of the responders (77.19% out of 114 respondents) have agreed that they recommend NAA combination therapy for effective mucus management (Table 3).

Table 3: Response on the recommendation of NAA combination for the effective mucus management

Recommendation of NAA combination for the effective mucus management	Response rate (n=114)
Yes	88 (77.19%)
No	25 (21.92%)
Not attempted	1 (0.87%)

A significant proportion of experts (40%) reported abdominal discomfort, nausea, vomiting, and diarrhea as the adverse effects of taking NAA combination therapy. COPD is commonly diagnosed among smokers, as reported by the majority of the study participants (96%).

Discussion

Experts indicated that COPD was frequently observed in subjects over the age of 41 years and pulmonary function test was preferred for diagnosing COPD. The majority of the respondents recommended the NAA combination for a variety of bronchitis conditions, emphasizing its effectiveness in managing not only acute exacerbations but also chronic manifestations such as hyper mucus secretion. There are numerous studies highlighting the use of N-acetylcysteine for reducing acute exacerbations in COPD patients [10-13]. The survey findings can be considered as the first of their kind suggesting the therapeutic value of the NAA combination, as there was no clinical evidence on the combination of NAA for the treatment of COPD.

Among the antibiotics, the combination of amoxicillin and clavulanic acid stands out as the most preferred choice when used in conjunction with the NAA combination for the treatment of bronchitis and COPD. For addressing asthma and bronchitis, the combination of montelukast and levocetirizine has been recommended. In cases involving severe pulmonary obstruction, allergic broncho pulmonary aspergillosis, individuals with asthma-COPD overlap syndrome, as well as patients with a history of smoking, an expert review published by Krishan *et al.* reported a preference for the combination of montelukast and acebrophylline.¹⁶ Due to the antioxidant and anti-inflammatory properties of N-acetylcysteine, its combined administration with antibiotics is commonly indicated for the treatment of lower respiratory tract infections [17].

Oral N-acetylcysteine has gained significant recognition as a potent and efficient mucolytic agent. It serves as a precursor for innate glutathione reservoir, actively supporting the scavenging of reactive oxygen species. It also exerts control over cell signal transmission and gene expression linked to inflammation through redox-sensitive pathways. By restoring the equilibrium between cell oxidation and antioxidation in COPD cases, NAC plays a pivotal role in preventing the intensity of the inflammatory response. Studies have demonstrated that the administration of higher doses of NAC (1200 mg daily) was linked to a reduction in the occurrence of acute COPD exacerbations and subsequent hospital readmissions [18]. For COPD patients with concurrent chronic bronchitis, a randomized placebo-controlled trial reported apparent clinical advantages of

using N-acetylcysteine alone as a monotherapy [19]. However, a 600 mg once daily dosage of this monotherapy was found to be effective in improving the quality of life in Indian COPD patients, according to a randomized controlled trial [20]. On the other hand, acebrophylline monotherapy was also proven to have a clinical improvement in dyspnoea, amount of sputum, and frequency of reliever medication [9]. While there is substantial literature evidence to corroborate the efficacy of N-acetylcysteine monotherapy and acebrophylline monotherapy, the available literature pertaining to the combined efficacy of N-acetylcysteine and acebrophylline (NAA) was very limited. Further research employing larger sample sizes and randomized controlled trials was imperative to substantiate and validate the synergistic effects of NAA combination therapy.

The survey results highlighted that combined NAA therapy stands out as the most effective treatment for patients with COPD. The key strengths of the study include a comprehensive assessment of NAA therapy efficacy and the use of a meticulously created and validated questionnaire for survey. The findings from the survey offer valuable insights for making informed decisions aimed at achieving optimal treatment outcomes in individuals with COPD. However, it is crucial to acknowledge that the present study has certain limitations. The study's relatively small sample size could potentially limit the extent to which the results can be generalized. Moreover, given that the conclusions rely on expert opinions, there exists a potential for bias to influence the outcomes.

Conclusion

The survey findings highlighted the NAA combination as a promising strategy for managing COPD patients, showing potential advantages in treating both acute and chronic bronchitis. Improvement is often noted within a week of starting this combination therapy, with a recommended duration of 10-15 days. The experts recommended the use of adjuvant therapies like amoxicillin + clavulanic acid, montelukast, and levocetirizine along with the NAA combination for the effective management of mucus in cases of asthma, bronchitis, and COPD.

Acknowledgement

We would like to thank all the consultants who were participated in this study.

References

1. Agusti A, Celli BR. GOLD 2023: What's New, Doc? Arch Bronconeumol. 2023 Apr 1;59(4):193-4.
2. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2007 Sep 15;176(6):532-55.
3. Chronic obstructive pulmonary disease (COPD) [Internet]. [Cited 2023 Aug 2]. Available from: [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))
4. Senior RM, Pierce RA, Atkinson JJ. Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology, Pathogenesis, and α 1-Antitrypsin Deficiency. In: Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, *et al.*, editors.

- Fishman's Pulmonary Diseases and Disorders [Internet]. 5th ed. New York, NY: McGraw-Hill Education; 2015 [cited 2023 Aug 2]. Available from: accessmedicine.mhmedical.com/content.aspx?aid=1122358782
5. Ueno T, Yamada M, Igarashi Y, Ogawa T. N-acetyl cysteine protects osteoblastic function from oxidative stress. *Journal of Biomedical Materials Research Part A*. 2011;99A(4):523–31.
 6. Gerrits CMJM, Herings RMC, Leufkens HGM, Lammers JWJ. N-acetylcysteine reduces the risk of re-hospitalisation among patients with chronic obstructive pulmonary disease. *European Respiratory Journal*. 2003 May 1;21(5):795–8.
 7. Stav D, Raz M. Effect of N-Acetylcysteine on Air Trapping in COPD: A Randomized Placebo-Controlled Study. *CHEST*. 2009 Aug 1;136(2):381–6.
 8. Garcia Morales OM, Rojas-Reyes MX, Dennis RJ. Oral xanthine derivatives (theophylline and doxofylline) for patients with stable chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2017 Aug 3;2017(8):CD012748
 9. Tapadar SR, Das M, Chaudhuri AD, Basak S, Mahapatra AB. The effect of acebrophylline vs sustained release theophylline in patients of copd-a comparative study. *Journal of clinical and diagnostic research: JCDR*. 2014 Sep;8(9):MC11.
 10. Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, *et al*. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest*. 2013 Jul 1;144(1):106–18.
 11. Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, *et al*. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): A randomised, double-blind placebo-controlled trial. *The Lancet Respiratory Medicine*. 2014 Mar 1;2(3):187–94.
 12. Decramer M, Mólken MR van, Dekhuijzen PR, Troosters T, Herwaarden C van, Pellegrino R, *et al*. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): A randomised placebo-controlled trial. *The Lancet*. 2005 Apr 30;365(9470):1552–60.
 13. Gerrits CMJM, Herings RMC, Leufkens HGM, Lammers JWJ. N-acetylcysteine reduces the risk of re-hospitalisation among patients with chronic obstructive pulmonary disease. *European Respiratory Journal*. 2003 May 1;21(5):795–8.
 14. Zambon SpA. A Phase III, Multi-centre, Randomized, Rater- and Patient-blind, Placebo- and Active-controlled, Parallel Group Clinical Trial to Compare the Efficacy and Safety of 1-week Treatment of Intravenous N-acetylcysteine (NAC) 600 mg Twice Daily (Active Test Treatment), Ambroxol Hydrochloride 30 mg Twice Daily (Active Control Treatment) and Placebo as Expectorant Therapies in Adult Chinese Patients With Respiratory Tract Diseases and Abnormal Mucus Secretions [Internet]. clinicaltrials.gov; 2022 Apr [cited 2023 Aug 3]. Report No.: NCT03843541. Available from: <https://clinicaltrials.gov/study/NCT03843541>
 15. Agliati G. Effects of a Short Course of Treatment with Acebrophylline on the Mucus Rheological Characteristics and Respiratory Function Parameters in Patients Suffering from Chronic Obstructive Pulmonary Disease. *J Int Med Res*. 1996 May 1;24(3):302–10.
 16. Krishna NH, Nene A, Modi M, Reza T, Songara A, Deshmukh V. Expert opinion on montelukast and acebrophylline combination in the management of asthma. *Indian Journal of Allergy, Asthma and Immunology*. 2021 Dec;35(2):48.
 17. Landini G, Di Maggio T, Sergio F, Docquier JD, Rossolini GM, Pallecchi L. Effect of High N-Acetylcysteine Concentrations on Antibiotic Activity against a Large Collection of Respiratory Pathogens. *Antimicrobial Agents and Chemotherapy*. 2016 Nov 21;60(12):7513–7517.
 18. Tian H, Zhou Y, Tang L, Wu F, Deng Z, Lin B, *et al*. High-dose N-acetylcysteine for long-term, regular treatment of early-stage chronic obstructive pulmonary disease (GOLD I–II): study protocol for a multicenter, double-blinded, parallel-group, randomized controlled trial in China. *Trials*. 2020 Dec;21:1-0.
 19. Zhang L, Xiong Y, Du L. Efficacy and Safety of N-Acetylcysteine for Chronic Obstructive Pulmonary Disease and Chronic Bronchitis. *BioMed Research International*. 2022 Jun 26;2022:e9133777.
 20. Salve VT, Atram JS. N-acetylcysteine combined with home based physical activity: effect on health related quality of life in stable COPD patients-a randomised controlled trial. *Journal of Clinical and Diagnostic Research: JCDR*. 2016 Dec;10(12):OC16.