Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

CARE: Combination of Acetylcysteine and Acebrophylline in Moderate to Severe Asthma and COPD Patients

Raja Dhar[1], Rakesh K Chawla[2], Moumita Rahaman[1], Aditya K Chawla[2], Gaurav Chaudhary[2], Ashutosh Gautam[3], Rajat Singal[3]

[1]Department of Pulmonology, Birla Hospital, Kolkata, India; [2]Department of Respiratory Medicine, Critical Care, Sleep Medicine Interventional Pulmonology, Chawla Clinic, New Delhi, India; [3]Mankind Pharma Ltd, Okhla Phase III, New Delhi, India

Correspondence: Raja Dhar, Department of Pulmonology, Birla Hospital, Kolkata, 700 012, India, Email docaardee@yahoo.com

Objective: To assess the efficacy and safety of the combination of N-acetylcysteine and acebrophylline (Combination named Abiways), in patients with moderate to severe COPD and Asthma.

Materials and Methods: In this non-randomized, interventional, prospective, single-arm, post-marketing surveillance study, participants were administered Abiways as an add-on therapy for 90 days. The primary endpoint was Quality of Life, evaluated using the COPD Assessment Test (CAT) and Asthma Control Test (ACT) questionnaires. Secondary endpoints included mean FEV1 and FVC changes. Adverse events were recorded throughout the study.

Results: 97 (of 102 subjects enrolled) completed the study (76 COPD and 21 Asthma patients, respectively; mean age 57.9 ± 8.1 years; 33 females, 64 males). Overall, FEV1 improved significantly from 1.287L to 1.484L ($p < 0.001$) with similar statistical improvements in COPD (1.237 L to 1.414 L; $p = 001$) and asthma (1.477 L to 1.747 L; $p = 0.004$) subpopulations. COPD patients showed statistically significant improvements in CAT scores (17.2 ± 1.0 to 10.6 ± 0.9, $p = 0.0001$); however, such significance was not observed in the ACT scores for asthma patients. FVC remained unchanged in all subgroups. No severe adverse events were reported.

Conclusion: The combination of N-acetylcysteine and acebrophylline improves QoL in moderate to severe COPD patients and FEV1 in both COPD and asthma patients with a favorable safety and tolerability profile. The combination appears safe and effective for managing obstructive airway disease.

Keywords: COPD, asthma, N-acetylcysteine, acebrophylline, CAT score, FEV1, Abiways

Introduction

India, home to 18% of the global population, bears one-third of the total global health loss. Notably, the total disability-adjusted life years (DALYs) per person with chronic obstructive pulmonary disease (COPD) and asthma in India are 1.7 and 2.4 times higher than the global average, respectively.[1,2]

Bronchodilator therapy with long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) therapy remains the mainstay of respiratory obstructive disease management. Treatment guidelines recommend add-on therapy in patients with a history of frequent/severe exacerbations or in those with concomitant asthma.[3] For moderate-severe COPD, methylxanthines or mucolytics (Global Initiative for Chronic Obstructive Lung Disease, GOLD 2024, level B recommendation) may be added if exacerbations persist despite long-term control therapy,[3,4] while add-on or controller therapies are also considered for asthma[5] patients with persistent symptoms despite optimized treatment.[6]

N-acetylcysteine (NAC), a typical mucus-modifying medication has garnered significant attention in managing respiratory conditions characterized by excessive mucus production. The Placebo-controlled study on the efficacy and safety of N-acetylcysteine High dose in Exacerbations of Chronic Obstructive Pulmonary disease (PANTHEON) study[7] established the usefulness of NAC as a therapeutic approach in moderate to severe COPD. Acebrophylline is a

Received: 20 December 2024
Accepted: 23 April 2025
Published: 28 May 2025

preferrable add-on muco-regulator for both bronchial asthma and COPD in adults.[8,9] Acebrophylline is a combination of ambroxol + theophylline 7-acetate and is required only twice daily. It is claimed to be superior to theophylline due to inclusion of ambroxol in the compound and claimed to be better tolerated.[10]

Historically, COPD severity was assessed solely based on forced expiratory volume in 1 second (FEV1), a marker of airflow limitation. However, this approach may overlook the multidimensional effects of systemic inflammation on health. Consequently, in 2011, the GOLD Strategy developed a combined COPD assessment approach which categorizes patients based on airflow limitation (FEV1), symptoms (or COPD Assessment Test [CAT] score), and exacerbation history.[11] Research has demonstrated a correlation between CAT scores and FEV1% predicted, suggesting that CAT is linked to the severity of airflow limitation and GOLD classification in stable COPD patients.[12] Furthermore, CAT scores have shown predictive value for COPD exacerbations in high-risk patients.[13] Similarly, in asthma management, the Asthma Control Test (ACT) has been widely adopted to assess asthma control and serve as an appropriate measure for overall asthma impact.[14]

The mucolytic properties of NAC[15,16] and the mucociliary clearance induced by acebrophylline[17] are hypothesized to ameliorate airway obstruction in COPD and asthma, potentially leading to an enhanced QoL for these patients. Patient compliance is a crucial parameter in disease management. A cross-sectional Indian study reported that 48% of asthma patients were reluctant to undergo inhaler therapy,[18] highlighting the role and need of oral combination therapies. NAC combination is preferred for a variety of bronchitis conditions, emphasizing its effectiveness in managing not only acute exacerbations but also chronic manifestations such as hyper mucus secretion.[19] Acebrophylline combination may be used if asthma symptoms remain uncontrolled with ICS and long-acting β2-agonists.[20] However, there is a paucity of literature on the real-world efficacy of the oral combination, particularly in the moderate to severe disease subgroup from the Indian subcontinent. To address this knowledge gap, we conducted a prospective post-marketing surveillance study to evaluate QoL changes (evaluated through CAT and ACT questionnaire in COPD and asthma patients respectively) in subjects with moderate to severe COPD or asthma following adjunctive therapy with a combination of NAC and acebrophylline. Secondary objectives included assessing changes in FEV1 and Forced Vital Capacity (FVC).

Materials and Methods

This was a non-randomized, interventional, prospective, single-arm, post-marketing surveillance study conducted for 3 months. Patients with COPD or asthma visiting outpatient departments of selected hospitals of Kolkata and Delhi were enrolled for the study. The two centres were a private tertiary care hospital, CK Birla Hospital in Kolkata, and an outpatient clinic, Chawla Clinic, in New Delhi.

Ethical Approvals

The study was performed in compliance with the principles of the Declaration of Helsinki, the Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research, New Delhi 2006, Good Clinical Practice (GCP), and in compliance with local regulatory requirements. The study was conducted at 2 sites. One site is a tertiary care hospital and approval was taken from the respective ethics committee. The other site is a private clinical and does not have an attached EC; thus, approval was obtained form an independent ethics committee mentioned here. All participants provided written informed consent. EC approval numbers for the study were IEC/02/2023/APRV/05 (Calcutta Medical Research Institute, Kolkata) and GSER/2023/BMR-AP/020 (Good Society for Ethical Research, New Delhi).

We included 102 patients with moderate-to-severe COPD, as per GOLD guidelines[4] or moderate to severe asthma, as per Global Initiative for Asthma (GINA) guidelines (patients categorized as GINA 3–5)[21] and aged between 18 and 65 years of age. All patients were on inhalational therapy (either Muscarinic Antagonist, LAMA or Beta-Agonist, LABA for COPD, and LABA/ICS for asthma) and the combination tablet was used as an "add on" medication as first line of treatment.

Patients who had a history of auto-immune disease, epilepsy, active liver disease, severe renal impairment, concurrent corticosteroid use, a mental health diagnosis, difficulty speaking and completing the QoL questionnaire, hypersensitivity to the study drug, involvement in other clinical trials, intensive care unit (ICU) admission, severe renal impairment (including those receiving dialysis), patients with active liver disease (including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities), pregnant, breastfeeding, placed on concurrent use of corticosteroids, history of auto-immune disease or any other condition that might affect the interpretation of the study results were excluded from the study.

The study was conducted for a period of 3 months. There were three visits for the study including a baseline visit and two follow up visits at 45 and 90 days, respectively. At visit 1 (baseline), eligible participants were given acetylcysteine 600 mg + acebrophylline 100 mg (the combination is already approved by Drugs Controller General of India [DCGI] for respiratory illness) oral tablets BID for 90 days as an add-on treatment to the standard treatment. Demographic data, including age, gender, height, weight and body mass index (BMI), was collected at baseline and a physical examination was done to record the medical and surgical history including co-morbidities, and the current medications. Vitals including systolic (SBP) and diastolic blood pressure (DBP), pulse rate and body temperature were obtained by qualified personnel with patient placed in supine position following adequate rest. Spirometry evaluation was done to record Forced Expiratory Volume (FEV1) and Forced Vital Capacity (FVC). Patient medical history was obtained, with special emphasis on respiratory medication that had been consumed in the past or continued till date alongside other concomitant diseases and smoking habits. Every patient was given a Quality-of-Life Evaluation COPD & Asthma specific questionnaire (CAT and ACT questionnaires were filled by the patients) to fill to record baseline QoL scores.

At visit 2 at day 45, general physical examination was done. At visit 3 or end of study visit at 90 days post study initiation, physical examination was done along with spirometric and QoL assessment (CAT and ACT scores). Safety data was collected throughout the study. Adverse events were regarded as treatment-emergent adverse events if they started on or after the date and time of administration of the first dose of the study drug, or if they were present prior to the administration of the first dose of the study drug and increased in severity during the study.

Endpoints

The study's primary endpoint was to monitor the improvement in QoL based on a validated questionnaire, CAT and ACT, for COPD and asthma, respectively. The secondary endpoints were to observe improvement or change in FEV1 and FVC scores from baseline to follow-up visits, along with the associated adverse events and serious adverse events (after the treatment with acebrophylline 100 mg + acetylcysteine 600 mg oral tablets BID for 90 days).

Statistical Analysis

102 patients were screened and enrolled. Study participants were summarized using descriptive statistics. Continuous variables were presented using mean/median and SD/quartiles, and categorical variables were reported as frequency and percentage. The analysis was performed on the intent-to-treat (ITT) population. The threshold for a clinically significant difference between baseline and follow-up was 2 and 3 units for CAT and ACT, respectively. The paired *t*-test was applied to see the FEV1 and FVC scores change between baseline and follow-up visits. The threshold for a clinically significant difference between the baseline (before the start of the treatment) and follow-up (after the treatment with acebrophylline 100 mg + acetylcysteine 600 mg oral tablets BID for 90 days) was 2 and 3 units respectively for CAT and ACT.

Results

Demographics

A total of 102 patients were enrolled in the study, out of which 97 (95.1%) completed the study, 3 (2.9%) patients were lost to follow-up, and 2 (2.0%) patients had consent withdrawals (Figure 1).

76 (78.4%) participants had moderate to severe COPD and 21 (21.6%) were moderately to severely asthmatic. The majority (66%) of the subjects were males. Notably, most subjects were non-smokers (67%). The baseline BMI was 25.9 ± 5.43 kg/m^2 (Table 1).

Quality of Life

The CAT score of the COPD population improved from 17.2 ± 1.02 at baseline to 10.6 ± 0.9 at 3 months, showing a statistically significant change of 6.6 units with a p-value of 0.0001 (Figure 2). No significant improvement was observed in the ACT scores at the end of the study in asthma patients (17.9 ± 0.9 baseline to 18.0 ± 1.1 at 90 days; p = 0.9611).

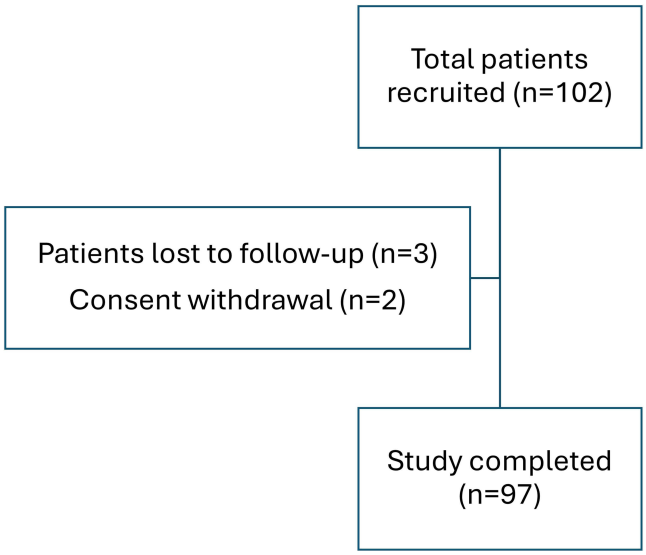

Figure 1 Flow Chart for Patient Disposition.

Improvement in FEV1 and FVC

Overall Population

For the total population of 97 patients, the mean FEV1 changed from 1.287 L at baseline to 1.484 L at 90 days, showing an increase of 0.197 L, which was statistically significant ($p < 0.001$). However, a non-significant change of 0.090 L (from 2.120 L at baseline to 2.210 L at 90 days) was observed for the FVC parameter. (Table 2)

Subgroup Analysis

Within the COPD population (78.4% patients), the change in FEV1 was improved from 1.237 ± 0.5L at baseline to 1.414 ± 0.5L at 90 days, showing a significant increase of 0.177 L ($p = 0.0001$), while the change in FVC (2.1 L at baseline to 2.2 L at 90 days) was not statistically significant ($p = 0.33$). (Figure 3a)

Table 1 Baseline Demographic Characteristics of Study Participants

Variable	Values (N=97)
Moderate to severe COPD	76 (78.4%)
Moderate to severe asthma	21 (21.6%)
Males	64 (65.9%)
Females	33 (34.0%)
Former smokers	32 (33.9%)
Non-smokers	65 (67.0%)
Current smokers	13 (13.4%)
Mean Age	57.9±8.1 years
Mean Weight	69.4±18.7 kg
Mean Height	160.6±10.2 cm
Mean BMI	5.9±5.4 kg/m^2

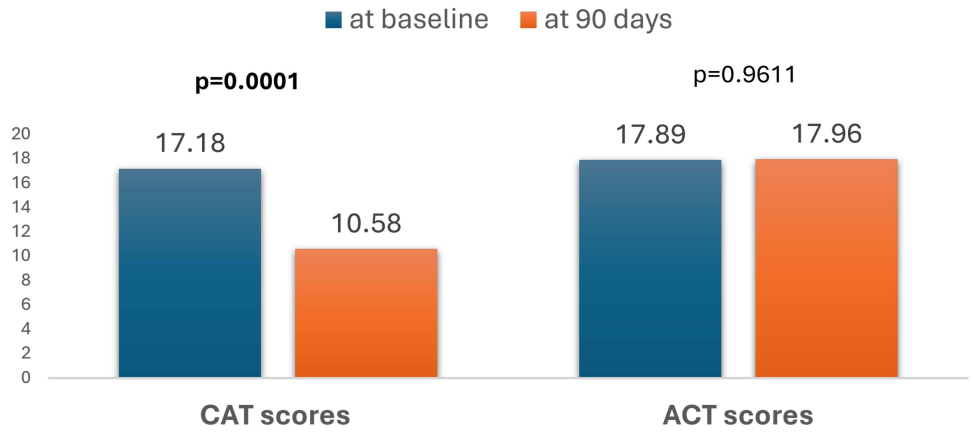

Figure 2 Change in quality of life (CAT scores in COPD patients and ACT in asthma patients) scores from baseline to 90 days of treatment in the overall population.

Among the asthma sub population (21.6%), the change in FEV1 improved from 1.477 ± 0.1L to 1.747 ± 0.3L, representing an increase of 0.270L, which was statistically significant (p = 0.004). The change was insignificant for the FVC parameter (2.3 L at baseline to 2.4 L at the end of the study; p = 0.83) at 90-day treatment (Figure 3b).

Safety

No significant adverse events were noted with the combination of acetylcysteine and acebrophylline (Abiways) during the 90-day treatment period. One subject reported weakness and a mild headache.

Discussion

QoL is a crucial endpoint in evaluating obstructive airway diseases, reflecting the patient's perspective on disease impact. This study uniquely explored the combined effects of two established mucolytics, NAC and acebrophylline, in managing COPD and asthma. The adjunctive therapy with these agents significantly enhanced QoL in COPD patients and improved FEV1 in all patients.

A 2024 meta-analysis by Papi et al[22] confirmed the significant association of NAC with the likelihood of experiencing an improvement in symptoms and/or QoL among 911 COPD patients (Odd's ratio [OR] = 2.82; 95% confidence interval [CI] CI 1.25–6.38). However, heterogeneity was observed between the studies in these analyses. Among the included studies, Tse et al[23] reported that eligible patients were enrolled four weeks post-exacerbation after appropriate treatment, with similar proportions receiving corticosteroids [ICS], LAMAs, and ICS/LABA before NAC therapy. Similarly, Pela

Table 2 Change in FEV1 and FVC from Baseline to 90 days of Treatment in the Total Population and Subgroups

	Baseline Parameter	n	Baseline (Mean±SD)	At 90 Days (Mean±SD)	p-Value
Total population	FEV1 (Litres)	97	1.287±0.5	1.484±0.5	<0.001*
	FVC (Litres)	97	2.120±0.6	2.210±0.7	0.33
COPD	FEV1 (Litres)	76	1.237±0.5	1.414±0.5	0.0001
	FVC (Litres)	76	2.070±0.6	2.170±0.7	0.33
Asthma	FEV1 (Litres)	21	1.477±0.1	1.747±0.3	0.004
	FVC (Litres)	21	2.300±0.6	2.350±0.6	0.083

Notes: *Statistically significant p-value.
Abbreviations: FEVI, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity.

https://doi.org/10.2147/JAA.S513358

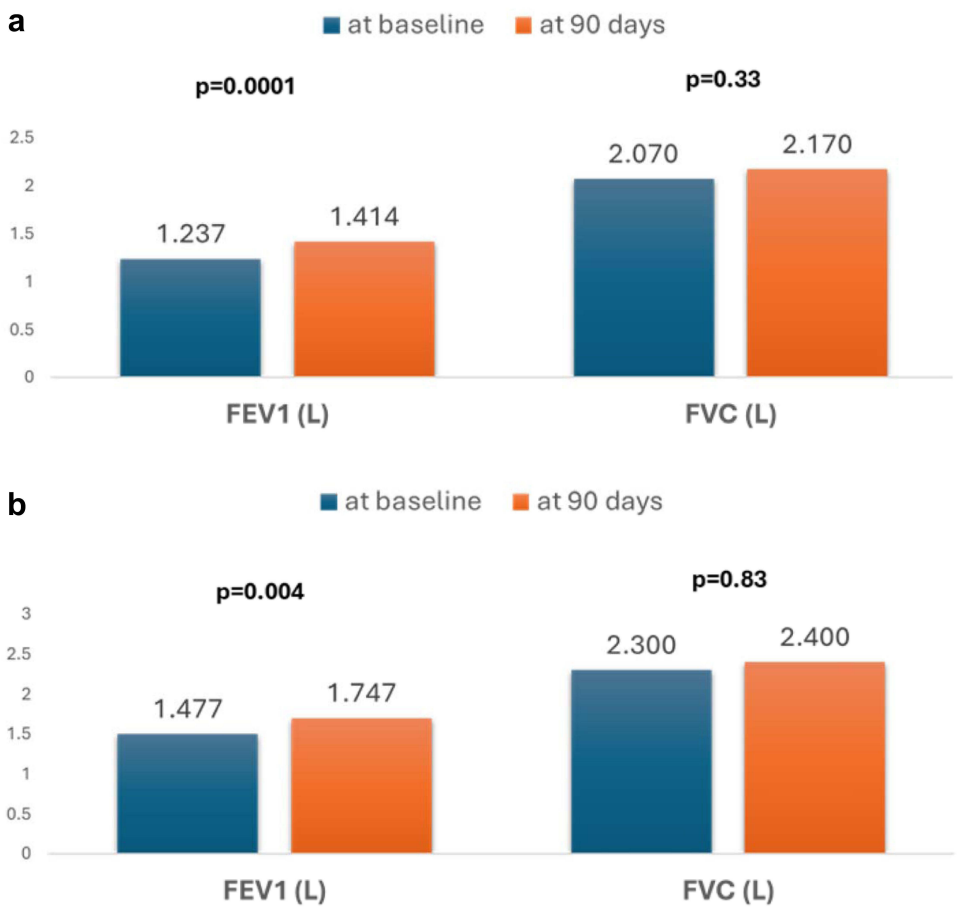

Figure 3 (**a**) FEV1 and FVC from baseline to 90 days of treatment in COPD subpopulation. (**b**) FEV1 and FVC from baseline to 90 days of treatment in the Asthma subpopulation.

and colleagues[24] demonstrated significant QoL improvements in NAC-treated patients with moderate to severe COPD, with 65% reporting better QoL compared to only 29% in the placebo group. These findings suggest that NAC may alter the natural history of moderate to severe COPD providing symptomatic relief.

To further analyse the quantum of the treatment's impact, we assessed the change in FEV1 value from baseline to 90 days, observing a significant improvement in lung physiology and function; however, the change in FVC was non-significant. This improvement aligns with the meta-analysis by Jiang et al,[25] which reported significantly higher FEV1 in NAC-treated COPD patients, a critical factor given the progressive decline in FEV1 in COPD. An Indian study conducted by Bachh AA et al[26] further substantiates the benefits of NAC. The research revealed that consistent NAC use over four months led to notable improvements in patients with moderate to severe COPD. Specifically, the study observed a significant reduction in exacerbations and hospital admissions, alongside measurable enhancements in lung function parameters with no reported adverse effects.

Acebrophylline, similarly, has shown promise in COPD management. In line with our findings. Tapadar SR et al reported consistent FEV1 improvement with 100 mg acebrophylline twice daily, alongside fewer cardiovascular side effects than theophylline. The drug's efficacy in enhancing blood gas parameters further supports its role in COPD treatment.[27] The benefits of acebrophylline extend beyond its anti-inflammatory properties. Studies have demonstrated its positive impact on blood gas parameters, with a significant increase in PaO_2 and a decrease in $PaCO_2$ in COPD subjects. These rheological properties contribute to its overall efficacy in managing COPD symptoms.[28] With successful management of COPD, this pathophysiology may be arrested or improved to some extent, attributing to the improved FEV1 in the present study.

FEV1 improvement represents the airflow maintenance in both small and large airways. Consequently, a decrease in FEV1 is associated with an increased risk of severe exacerbations of asthma. Therefore, the regular monitoring of pulmonary function is crucial, especially in asthma patients who may not perceive their symptoms until airflow

obstruction is severe. The significant improvement seen in the mean FEV1 in asthma subjects in this study is consistent with other Indian studies on acebrophylline[29] and improvement in breathlessness with NAC 600 mg in acute bronchitis.[30]

Our study did not demonstrate significant QoL improvements in the asthma subgroup, which differed from the findings of Sharma et al evaluating the efficacy of acebrophylline[29] This discrepancy may be due to differences in study design and patient populations. Our study focused on moderate to severe asthma subjects followed over 90 days, compared to Sharma et al's 4-week study, in which no distinction was made in the grades of asthma. Moreover, our study included a small number of asthma subjects (n = 21), nearly one-third of the latter's study (n = 75).

Regarding safety, no significant adverse effects were reported. A single subject reported weakness and mild headache. Treatment compliance was high, with a 95% completion rate, indicating excellent patient tolerability.

Strengths of the Study

This study is the first to suggest the therapeutic value of the NAC and acebrophylline combination in improving QoL and lung function parameters in COPD and asthma patients from the Indian subcontinent.

Limitations of the Study

The study's limitations include a small asthma cohort, possibly lack of a control group, and a relatively short duration of 3 months, all of which may introduce selection bias and limit the generalizability of the findings.

Conclusion

The findings of this study underscore the potential of the combination of acetylcysteine and acebrophylline as an effective therapeutic approach for managing obstructive airway diseases, demonstrating significant improvements in FEV1 in both COPD and asthma patients. Additionally, the observed enhancement in quality of life among COPD patients further substantiates the clinical efficacy of this combination. Notably, the treatment was well-tolerated, with no safety concerns and good patient compliance. Future large-scale studies, particularly with a broader asthma population, are warranted to provide deeper insights into its long-term benefits and applicability.

Acknowledgments

The authors acknowledge Mankind Pharma for funding this study and Dr. Punit Srivastava and Dr. Esha Singh of Mediception Science Pvt Ltd (www.mediception.com) for supporting the preparation of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Singh S, Salvi S, Mangal DK, et al. Prevalence, time trends and treatment practices of asthma in India: the Global Asthma Network study. *ERJ Open Res*. 2022;8(2):00528–2021. doi:10.1183/23120541.00528-2021
2. Salvi S, Kumar GA, Dhaliwal RS, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Glob Health*. 2018;6(12):e1363–74. doi:10.1016/S2214-109X(18)30409-1
3. Miravitlles M, Matsunaga K, Dreher M. Stepwise management of COPD: what is next after bronchodilation? *Ther Adv Respir Dis*. 2023;17:17534666231208630. doi:10.1177/17534666231208630
4. Goldcopd. Global Initiative for Chronic Obstructive Lung Disease - GOLD. 2024. Available from: https://goldcopd.org/2024-gold-report/. Accessed Jun 11, 2024.
5. IMA. Recommendations-for-management-of-asthma-in-primary-care-22-12-2020.pdf. 2025. https://ima-india.org/ima/pdfdata/Recommendations-for-management-of-asthma-in-primary-care-22-12-2020.pdf. Accessed May 14, 2025.

6. Shah BK, Singh B, Wang Y, Xie S, Wang C. Mucus Hypersecretion in Chronic Obstructive Pulmonary Disease and Its Treatment. *Mediators Inflamm*. 2023;2023:8840594. doi:10.1155/2023/8840594
7. Zheng JP, Wen FQ, Bai CX, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med*. 2014;2(3):187–194. doi:10.1016/S2213-2600(13)70286-8
8. Pozzi E. Acebrophylline: an airway mucoregulator and anti-inflammatory agent. *Monaldi Arch Chest Dis*. 2007;67:106–115. doi:10.4081/monaldi.2007.498
9. Pattanayak S, Sheel S, Kumar V. Acebrophylline Is A Better Choice Of Drug Over Theophylline For Patients With Asthma, COPD And Bronchitis Patients. *Int J Pharm Sci*. 2023;1(9):1.
10. Gain R, Rk TA, Sen P, V A. Comparison of Efficacy and Safety of Theophylline, Doxophylline and Acebrophylline as an Add-On in the Management of Chronic Obstructive Pulmonary Disease. *J Evol Med Dent Sci*. 2020;9(04):191–194.
11. Safka KA, Wald J, Wang H, McIvor A, McIvor L. GOLD Stage and Treatment in COPD: a 500 Patient Point Prevalence Study. *Chronic Obstr Pulm Dis COPD Found*. 2016. 4(1):45–55.
12. Ghobadi H, Ahari SS, Kameli A, Lari SM. The Relationship between COPD Assessment Test (CAT) Scores and Severity of Airflow Obstruction in Stable COPD Patients. *Tanaffos*. 2012;11(2):22.
13. Lee SD, Huang MS, Kang J, et al. The COPD assessment test (CAT) assists prediction of COPD exacerbations in high-risk patients. *Respir Med*. 2014;108(4):600–608. doi:10.1016/j.rmed.2013.12.014
14. van Dijk BCP, Svedsater H, Heddini A, Nelsen L, Balradj JS, Alleman C. Relationship between the Asthma Control Test (ACT) and other outcomes: a targeted literature review. *BMC Pulm Med*. 2020;20(1):79. doi:10.1186/s12890-020-1090-5
15. Gerrits CMJM, Herings RMC, Leufkens HGM, Lammers JWJ. N-acetylcysteine reduces the risk of re-hospitalisation among patients with chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21(5):795–798. doi:10.1183/09031936.03.00063402
16. Decramer M, Rutten-van Mölken M, Dekhuijzen PNR, 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. *Lancet Lond Engl*. 2005;365 (9470):1552–1560. doi:10.1016/S0140-6736(05)66456-2
17. Agliati G. Acebrophylline in the treatment of chronic obstructive pulmonary disease. *Curr Ther Res*. 1995;56(2):169–175. doi:10.1016/0011-393X (95)85042-2
18. Sulaiman SP, Panicker V. Attitudes of patients with asthma on inhaler use- a cross-sectional study from south Kerala. *J Evid Based Med Healthc*. 2017;4(26):1505–1509. doi:10.18410/jebmh/2017/294
19. Manjula S, Krishna Kumar M. Expert opinion on the clinical use of N-acetylcysteine and acebrophylline for the management of chronic obstructive Pulmonary disease in Indian clinical settings. *Int J Pulm Respir Sci*. 2024;6(1):01–5. doi:10.33545/26648504.2024.v6.i1a.21
20. 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 J Allergy Asthma Immunol*. 2021;35(2):48. doi:10.4103/ijaai.ijaai_4_22
21. Ginasthma. GINA-2024-Strategy-Report-24_05_22_WMS.pdf. Available from: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. Accessed 2024 Jun 12.
22. Papi A, Alfano F, Bigoni T, et al. N-acetylcysteine Treatment in Chronic Obstructive Pulmonary Disease (COPD) and Chronic Bronchitis/Pre-COPD: distinct Meta-analyses. *Arch Bronconeumol*. 2024;60(5):269–278. doi:10.1016/j.arbres.2024.03.010
23. Tse HN, Raiteri L, Wong KY, et al. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest*. 2013;144(1):106–118. doi:10.1378/chest.12-2357
24. Pela R, Calcagni AM, Subiaco S, Isidori P, Tubaldi A, Sanguinetti CM. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. *Respir Int Rev Thorac Dis*. 1999;66(6):495–500.
25. Jiang C, Zou J, Lv Q, Yang Y. Systematic review and meta-analysis of the efficacy of N-acetylcysteine in the treatment of acute exacerbation of chronic obstructive pulmonary disease. *Ann Palliat Med*. 2021;10(6):6564576–6566576. doi:10.21037/apm-21-1138
26. Bachh A, Shah N, Ahmed Z, Pandey D, Dar KA, Haq I. Effect of oral N-acetylcysteine in COPD - A randomised controlled trial. *JK Pract*. 2007;14:12–16.
27. Tapadar SR, Das M, Chaudhuri AD, Basak S, Mahapatra ABS. The Effect of Acebrophylline vs Sustained Release Theophylline in Patients of COPD- A Comparative Study. *J Clin Diagn Res JCDR*. 2014;8(9):MC11–4. doi:10.7860/JCDR/2014/8176.4869
28. 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;24(3):302–310. doi:10.1177/030006059602400311
29. Sharma A, Adiga S, Chogtu B, Mohapatra AK, Magazine R. Comparing the Efficacy and Influence on the Quality of Life of Three Classes of Drugs Used in Bronchial Asthma - A Prospective Study. *J Clin Diagn Res JCDR*. 2014;8(9):HC13–5. doi:10.7860/JCDR/2014/8999.4877
30. Singh A, Shah HJ, Pariyani J, Shinde KV, Kumar P. A Comparative Study to Assess Efficacy and Safety of NAC Combination and NAC in Patients of Productive Cough with Acute Bronchitis. *Ind J Respir Care*. 2023;12(3):254–258. doi:10.5005/jp-journals-11010-1065