Section: Pulmonology

Original Research Article

CLINICAL USE OF N-ACETYLCYSTEINE AND ACEBROPHYLLINE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A CROSS-SECTIONAL EXPERT-PRACTICE SURVEY AMONG INDIAN CLINICIANS

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory disorder associated with persistent airflow limitation, chronic airway inflammation, mucus hypersecretion and recurrent exacerbations. N-acetylcysteine has mucolytic and antioxidant properties, while acebrophylline possesses bronchodilator and muco-regulatory actions. Although both agents are used in respiratory practice, evidence describing how clinicians position their combined use in routine Indian COPD care remains limited. **Objective:** To assess clinicians' current practices and opinions regarding the use of N-acetylcysteine and acebrophylline combination therapy in COPD and related mucus-predominant airway conditions in Indian clinical settings.

Materials and Methods: A cross-sectional, questionnaire-based survey was conducted over a period of 10 months from November 2025 to August 2026 among 100 clinicians involved in the diagnosis and management of COPD and other obstructive airway disorders in India. A structured questionnaire evaluated diagnostic preferences, presenting symptoms, clinical indications for N-acetylcysteine–acebrophylline use, preferred treatment duration, expected onset of symptomatic benefit, mucus-management practices, adjunctive therapies and perceived adverse effects. Data were summarized using frequencies and percentages.

Results: Pulmonary function testing was preferred for COPD diagnosis by 68% of clinicians. Cough with sputum was the most commonly reported presenting symptom (40%). Fifty-one percent of respondents reported using the N-acetylcysteine–acebrophylline combination in COPD, while 44% reported its use in acute or chronic bronchitis. Bronchiolitis, emphysema and hyper-mucus secretion were commonly reported clinical settings for use of the combination. Forty-two percent preferred a treatment duration of 10–15 days, while 50% expected symptomatic improvement within approximately seven days. Seventy-seven percent considered the combination useful for mucus management. Gastrointestinal symptoms were the most frequently reported adverse effects.

Conclusion: The survey indicates that participating Indian clinicians commonly use N-acetylcysteine and acebrophylline as an adjunctive option in COPD and mucus-dominant airway disease. These findings represent prescribing preferences and clinical perceptions rather than evidence of comparative efficacy. Prospective patient-level studies are required to establish the incremental benefit, optimal duration and appropriate clinical phenotype for combination therapy.

Keywords: Acebrophylline, chronic bronchitis, chronic obstructive pulmonary disease, mucus hypersecretion, N-acetylcysteine, physician survey.

INTRODUCTION

Chronic obstructive pulmonary disease is a heterogeneous respiratory condition characterized by persistent respiratory symptoms and airflow obstruction resulting from abnormalities of the airways and/or alveoli. Spirometric confirmation remains essential for diagnosis, with persistent post-bronchodilator airflow obstruction forming the basis of objective disease confirmation.[1]

COPD remains an important global cause of mortality and disability. Tobacco exposure is a major preventable risk factor; however, household biomass exposure, ambient air pollution and occupational inhalational exposures are particularly relevant in low- and middle-income countries.[2] India has a substantial and heterogeneous COPD burden, with considerable variation related to geography, smoking prevalence, biomass exposure, occupational factors and socioeconomic conditions.[3-5]

The clinical expression of COPD extends beyond airflow limitation. Persistent cough, excessive sputum production, impaired mucociliary clearance, airway inflammation and oxidative stress contribute to symptom burden and recurrent exacerbations. Patients with a chronic bronchitic or mucus-predominant phenotype may therefore receive additional mucus-directed therapy alongside standard inhaled treatment.

N-acetylcysteine is a thiol-containing mucolytic and antioxidant agent. It reduces mucus viscosity by disrupting disulfide bonds in mucoproteins and serves as a precursor for glutathione, thereby contributing to antioxidant defence. Long-term studies and meta-analyses have suggested that N-acetylcysteine may reduce COPD exacerbations in selected populations, although effects on lung function and quality of life have been inconsistent.[6-8]

Acebrophylline is a xanthine derivative with bronchodilator, anti-inflammatory and mucus-modifying properties. It has been used in obstructive airway diseases, including COPD and asthma. Comparative and short-term clinical studies have reported improvements in dyspnoea, sputum characteristics and respiratory symptoms with acebrophylline, although the overall evidence base is considerably smaller than that for standard inhaled COPD therapies.[9,10]

Despite the availability of evidence supporting the individual pharmacological actions of N-acetylcysteine and acebrophylline, substantially less evidence is available regarding their concurrent use as a combination in COPD. Available literature is particularly limited with respect to patient selection, prescribing duration, mucus-related indications and physician decision-making in routine Indian practice. The present study was therefore undertaken to describe current clinical practices and physician perceptions regarding N-acetylcysteine plus acebrophylline use in COPD and related mucus-dominant respiratory conditions in India.

Aim

To evaluate clinicians' current practices and opinions regarding the clinical use of N-acetylcysteine and acebrophylline combination therapy in COPD and associated obstructive airway conditions in Indian practice.

Objectives

1. To assess clinicians' diagnostic preferences, symptom patterns, clinical indications, preferred duration of therapy and expected onset of symptomatic benefit associated with N-acetylcysteine–acebrophylline use.
2. To assess clinicians' practices regarding mucus management, adjunctive medications and perceived adverse effects associated with the combination.

MATERIALS AND METHODS

Study design

A cross-sectional, questionnaire-based expert-practice survey was conducted among clinicians involved in the diagnosis and management of COPD and other obstructive airway diseases.

Study setting

The study was conducted among clinicians practicing across selected South Indian clinical settings.

Study duration

The study was conducted over a period of **10 months** , from **November 2025 August 2026**.

Study population

Clinicians involved in the routine diagnosis and management of adult patients with COPD, chronic bronchitis or other obstructive airway disorders were considered eligible for participation.

Sample size

A total of **100 clinicians** who completed the survey were included in the final analysis.

Sampling technique

A purposive sampling approach was used to invite clinicians with relevant experience in the management of obstructive airway diseases. Participation was voluntary.

Inclusion criteria

Clinicians were eligible if they were actively involved in the treatment of adult patients with COPD or related obstructive airway disorders, had relevant clinical experience, consented to participate and completed the questionnaire sufficiently for analysis.

Exclusion criteria

Duplicate responses, substantially incomplete questionnaires and responses from participants not involved in the clinical management of obstructive airway disease were excluded.

Questionnaire development

A structured questionnaire was used to obtain information regarding routine clinical practices related to COPD management.

The questionnaire domains were based on previously published Indian clinical-practice work evaluating the use of N-acetylcysteine and acebrophylline. The original published survey used a 20-question instrument to assess professional opinions regarding prescription patterns of the combination in COPD and bronchitis.

For the present study, the questionnaire focused on clinically relevant domains including:

- age groups commonly affected by COPD;
- preferred diagnostic investigations;
- common patient-reported symptoms;
- indications for N-acetylcysteine–acebrophylline therapy;
- respiratory conditions in which the combination was considered useful;
- usual treatment duration;
- expected onset of symptomatic improvement;
- perceived usefulness in mucus management;
- antibiotic selection when antibiotic therapy was clinically indicated;
- use of other adjunctive medication in patients with concomitant asthma, allergic or bronchitic symptoms;
- perceived adverse effects; and
- association of smoking with COPD in routine practice.

Questionnaire review and pilot assessment

The questionnaire was reviewed for clarity, clinical relevance and ease of interpretation before administration. A preliminary pilot assessment was undertaken among a small group of clinicians to identify ambiguous wording and improve questionnaire readability. Responses from the pilot assessment were not included in the final analysis.

Data collection

Eligible clinicians were invited to participate and were provided with the structured questionnaire. Participants were instructed to provide individual responses based on their routine clinical experience and prescribing practices.

No patient-identifying information was collected.

Primary outcome measures

The primary outcomes were:

1. proportion of clinicians reporting the use of N-acetylcysteine–acebrophylline in COPD and related obstructive airway conditions; and
2. proportion of clinicians considering the combination useful for mucus management.

Secondary outcome measures

Secondary outcomes included:

- preferred COPD diagnostic modality; predominant presenting symptoms; clinical indications for use of the combination; treatment duration; expected onset of symptomatic benefit; antibiotic preferences when antibiotics were considered clinically indicated; use of adjunctive medication in associated asthma/allergic presentations; and perceived adverse effects.

Statistical analysis

Data were entered into a spreadsheet and checked for completeness before analysis.

Categorical variables were summarized using frequency and percentage. As the total sample comprised 100 respondents, absolute frequencies corresponded numerically to percentage values for most survey items.

The study was descriptive in nature. No inferential comparison between treatment groups was undertaken because the survey evaluated clinician practices and opinions rather than patient-level therapeutic outcomes.

Where appropriate, 95% confidence intervals for major proportions may be calculated in the final statistical analysis.

RESULTS

A total of 100 clinicians completed the survey and were included in the final analysis.

Pulmonary function testing was the most frequently preferred diagnostic investigation for COPD and was reported by 68 clinicians (68%). Chest radiography was selected by 22 clinicians (22%), while the remaining respondents reported other diagnostic approaches.

Among the commonly encountered symptoms, cough with sputum was reported most frequently.

Table 1: Commonly reported symptoms during COPD assessment

Symptom	n (%)
Cough with sputum	40 (40)
Cough without sputum	22 (22)
Breathlessness	22 (22)
Wheezing	14 (14)
Difficulty in climbing	1 (1)
Others	1 (1)
Total	**100 (100)**

Cough with sputum was the predominant symptom reported by participating clinicians, followed by breathlessness and cough without sputum.

Clinical use of N-acetylcysteine–acebrophylline

Fifty-one clinicians (**51%**) reported using the N-acetylcysteine–acebrophylline combination in patients with COPD. Forty-four percent reported its use in patients with acute or chronic bronchitis, while the remaining clinicians reported other respiratory indications.

Table 2: Conditions in which clinicians reported use of the NAA combination

Clinical condition	n (%)
Bronchiolitis	45 (45)
Emphysema	21 (21)
Hyper-mucus secretion	19 (19)
Diminished expiratory airflow	13 (13)
Others	2 (2)
Total	100 (100)

Bronchiolitis was the most frequently reported condition associated with NAA use in the questionnaire responses, followed by emphysema and hyper-mucus secretion. Because the term *bronchiolitis* may encompass different clinical contexts in adult practice, this result should be interpreted as a survey response rather than as a recommendation for routine COPD treatment.

Preferred duration of therapy

The most frequently reported duration of NAA therapy was 10–15 days, selected by 42% of clinicians. A duration of 15–30 days was reported by 32%, whereas 26% reported other durations.

Expected onset of symptomatic benefit

Half of the participating clinicians (50%) reported that they generally expected symptomatic improvement within approximately 7 days of initiating NAA therapy. Thirty-three percent reported an expected response at approximately 10 days, while 17% reported other time intervals.

These responses represent clinician perception and should not be interpreted as directly measured patient outcomes.

Table 3: Clinician opinion regarding the role of NAA in mucus management

Response	n (%)
Yes	77 (77)
No	22 (22)
No response/not attempted	1 (1)
Total	100 (100)

A majority of clinicians (77%) considered NAA useful as an adjunctive option in patients with excessive mucus production.

Table 4: Antibiotics reported by clinicians when antibacterial treatment was required

Antibiotic	n (%)
Amoxicillin–clavulanate	45 (45)
Azithromycin	24 (24)
Cefpodoxime	18 (18)
Cefuroxime	11 (11)
Other/not specified	2 (2)
Total	100 (100)

Amoxicillin–clavulanate was the most frequently reported antibiotic choice when clinicians considered antibiotic therapy necessary. These findings reflect prescribing preferences and do not imply that antibiotics should routinely accompany NAA treatment.

Table 5: Adjunctive medication reported in patients with associated asthma, bronchitic or allergic symptoms

Medication	n (%)
Montelukast + levocetirizine	52 (52)
Montelukast + fexofenadine	20 (20)
Montelukast alone	15 (15)
Fexofenadine alone	11 (11)
Other/not specified	2 (2)
Total	100 (100)

Montelukast plus levocetirizine was the most commonly reported adjunctive regimen. This response should be interpreted in the context of associated allergic or asthma-related symptoms and not as standard pharmacotherapy for COPD.

Perceived adverse effects

Gastrointestinal complaints including abdominal discomfort, nausea, vomiting and diarrhoea were the most frequently reported adverse effects, identified by 40% of clinicians.

Smoking and COPD

Ninety-six percent of respondents reported that COPD was commonly encountered among smokers in their clinical practice. This reflects clinician experience and does not exclude the important contribution of biomass exposure, occupational hazards and environmental pollution to COPD in India.

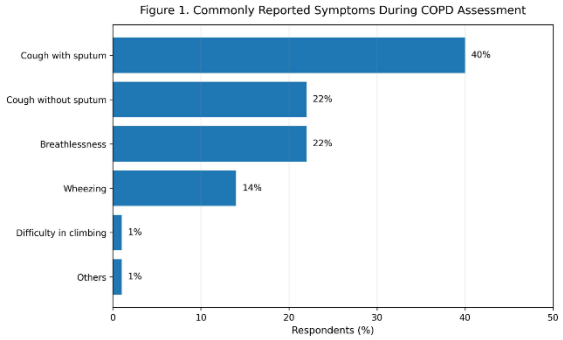


Figure 1: Common Symptoms During COPD Assessment

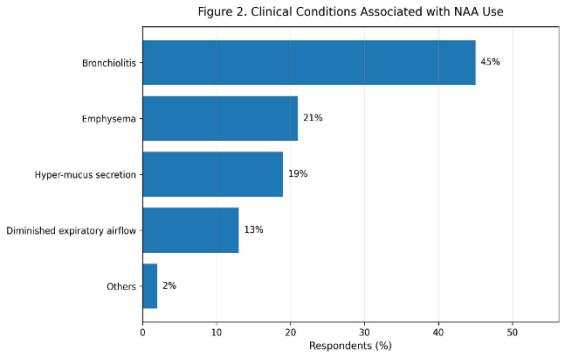


Figure 2: Clinical Conditions Associated with NAA Use

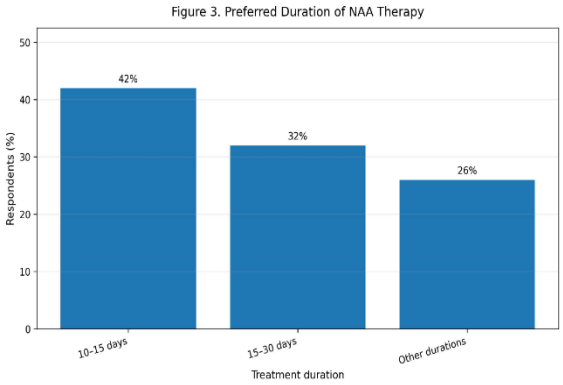


Figure 3: Preferred Duration of NAA Therapy

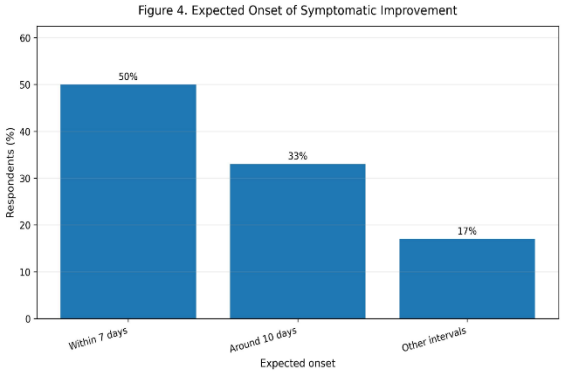


Figure 4: Expected Onset of Symptomatic Improvement

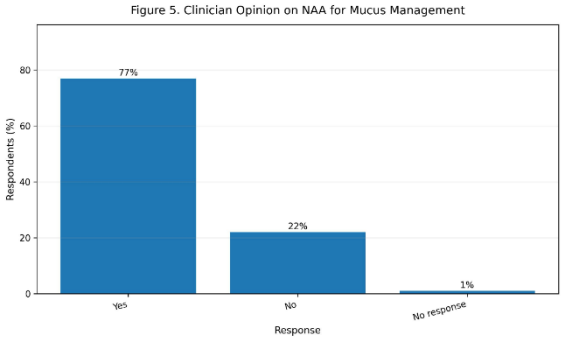


Figure 5: NAA for Mucus Management

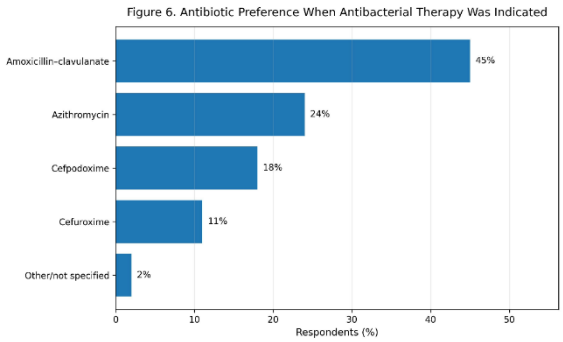


Figure 6: Antibiotic Preference

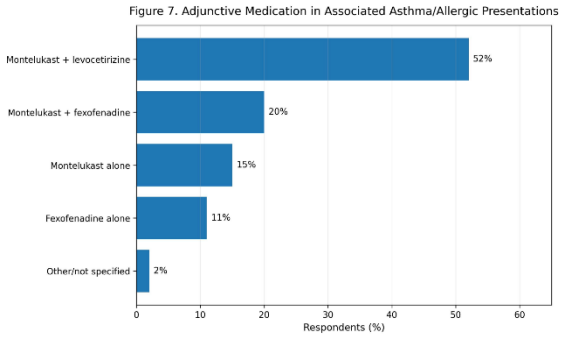


Figure 7: Adjunctive Medication Preference

DISCUSSION

This survey explored how Indian clinicians currently position N-acetylcysteine and acebrophylline in routine COPD practice. The main observations were the predominance of pulmonary function testing for diagnosis, frequent reporting of cough with sputum, substantial use of the NAA combination in COPD and bronchitis, short preferred treatment durations, and a strong perceived role in mucus management.

A previously published Indian survey involving 114 clinicians reported broadly similar prescribing patterns, including a preference for pulmonary function testing, use of NAA in COPD and bronchitis, a commonly preferred duration of 10–15 days and frequent use for mucus management.[11]

The similarity in practice patterns suggests that mucus-directed treatment continues to have a place in Indian respiratory practice. However, agreement among clinicians should not be interpreted as evidence of treatment efficacy.

The survey showed that cough with sputum was a prominent symptom and that 77% of clinicians considered NAA useful for mucus management. This is pharmacologically plausible, particularly for N-acetylcysteine, which reduces mucus viscosity and also acts as a precursor for glutathione.

Evidence for NAC in COPD, however, has not been uniform. In the BRONCUS trial, 523 patients were treated with NAC 600 mg daily or placebo for three years. No significant difference was observed in the overall annual decline in FEV1 or exacerbation rate, although subgroup findings suggested possible benefit in patients not receiving inhaled corticosteroids.[12]

Broader evidence has been more favourable but remains heterogeneous. A Cochrane review including 38 trials and 10,377 participants found that oral mucolytics produced a modest reduction in exacerbations, disability days and possibly hospitalisations, but had limited effects on lung function and health-related quality of life.[13]

A meta-analysis by Cazzola et al. involving 13 studies and 4,155 patients reported fewer exacerbations among patients receiving NAC, with an overall relative risk of 0.75. The authors also suggested that dose and the presence of established airflow obstruction may influence response.[14]

Other analyses have produced less favourable conclusions. A 2023 meta-analysis of nine randomized trials involving more than 2,000 participants found no statistically significant difference between NAC and placebo in several outcomes, including acute exacerbations, FEV1, FVC, SGRQ scores and adverse events.[15] This inconsistency illustrates why NAC should not be described as universally effective in COPD.

More recent randomized evidence has again suggested potential benefit in selected populations. A multicentre double-blind trial published in 2024 randomized 968 patients with mild-to-moderate COPD to NAC 600 mg twice daily or placebo for two years, providing contemporary evidence regarding its effects on exacerbations and lung function in earlier-stage COPD.[16]

The latest 2026 systematic review and meta-analysis provides an especially useful contemporary perspective. Cai et al. included 14 randomized controlled trials involving 2,856 patients and reported that NAC was associated with a modest reduction in acute exacerbations overall (RR 0.87, 95% CI 0.79–0.96). Importantly, the analysis did not establish consistent improvement across all physiological and quality-of-life outcomes.[17]

Taken together, these findings support a cautious interpretation of the present survey. NAC may be useful as adjunctive therapy in selected patients, particularly those with chronic bronchitic or mucus-predominant disease, but this should not be extrapolated to the entire COPD population.

The clinicians in our survey most commonly preferred treatment for 10–15 days, and half expected symptomatic improvement within approximately one week. These responses appear to relate more to short-term relief of mucus-related symptoms than to prevention of future COPD exacerbations.

Evidence from acute exacerbation settings supports the possibility of short-term biological effects. Zuin et al., in a randomized placebo-controlled study of 123 patients with acute COPD exacerbation, evaluated NAC 600 mg/day and 1200 mg/day for 10 days and found greater normalization of C-reactive protein with NAC, particularly at the higher dose.[18]

A later meta-analysis examining NAC in acute exacerbations also reported improvement in several outcomes, although marked heterogeneity was present for some pulmonary-function measures, limiting certainty.[19] These data reinforce the need to distinguish short-term symptomatic or inflammatory effects from long-term disease modification.

The second component of the combination, acebrophylline, has a considerably smaller evidence base. Available studies suggest bronchodilator and mucus-modifying activity, but most are relatively small and older.

In a comparative Indian study, Tapadar et al. randomized 40 patients with moderate COPD to acebrophylline or sustained-release theophylline in addition to tiotropium. Both treatments improved clinical and spirometric parameters, while acebrophylline showed a more favourable adverse-effect profile for some cardiovascular symptoms.[9]

Agliati evaluated 30 COPD patients receiving acebrophylline 100 mg twice daily for 14 days and reported improvement in cough, dyspnoea, expectoration, mucus characteristics and several respiratory-function parameters. Three patients reported epigastric discomfort, but treatment discontinuation was not required.[10]

These studies offer a rationale for clinicians' perception of benefit in mucus-dominant disease, but they do not establish that combining acebrophylline with NAC produces additive or synergistic benefit. That distinction is important because direct comparative trials of the combination remain limited.

The present survey also found that amoxicillin–clavulanate was the antibiotic most frequently selected when clinicians considered antibacterial therapy necessary. This should not be interpreted as support for routine antibiotic administration in patients receiving NAA. Antibiotics should remain reserved for clinically appropriate situations in which bacterial infection or an antibiotic-responsive COPD exacerbation is suspected.

Potential interactions between NAC and antimicrobial activity have also been investigated experimentally. Landini et al. demonstrated that high concentrations of NAC could alter the activity of certain antibiotics in vitro, including reduced activity of carbapenems under some experimental conditions.[20] These laboratory findings should not be directly extrapolated to routine oral prescribing, but they further argue against assuming universal pharmacological synergy between NAC and antibiotics.

The frequent reporting of montelukast plus levocetirizine probably reflects treatment of associated allergic disease, asthma or overlapping upper-airway symptoms rather than COPD itself. The result should therefore be viewed as a description of real-world prescribing behaviour rather than a recommendation for routine COPD therapy.

Gastrointestinal symptoms were the main adverse effects identified by participating clinicians. Similar gastrointestinal intolerance has been described with both NAC and acebrophylline, although NAC is generally well tolerated in randomized COPD studies.

Indian evidence also supports the feasibility of NAC administration in stable COPD. Salve and Atram evaluated NAC together with home-based physical activity in an Indian randomized study and examined its effects on health-related quality of life.[21] Although this study cannot establish efficacy of the NAC–acebrophylline combination, it provides locally relevant clinical experience with NAC.

The strong association between smoking and COPD reported by clinicians is consistent with established disease epidemiology. Nevertheless, COPD in India should not be viewed as a disease confined to smokers. Biomass smoke, occupational exposures, ambient pollution and previous respiratory insults remain important, particularly among never-smokers and rural populations.

Overall, the current findings suggest that clinicians primarily position NAA as a supportive, mucus-directed treatment rather than as a replacement for established inhaled COPD therapy. This appears pharmacologically reasonable, but the strength of supporting evidence differs substantially between the two components. NAC has been studied in multiple randomized trials and meta-analyses, whereas acebrophylline is supported mainly by smaller clinical studies.

Most importantly, direct clinical evidence specifically demonstrating an incremental benefit from the NAC–acebrophylline combination remains limited. Future investigations should therefore compare the combination against each component individually and against guideline-directed COPD therapy.

Strengths of the Study

The study addresses a practical area in which prescribing behaviour appears to be ahead of the available combination-specific clinical evidence.

It evaluates several dimensions of real-world practice, including diagnostic preferences, symptom patterns, indications for use, treatment duration, mucus management, associated medications and perceived adverse effects.

The study also separates physician perception from therapeutic efficacy, thereby reducing the risk of drawing inappropriate causal conclusions from a cross-sectional survey.

Limitations

The principal limitation is that this was a clinician-opinion survey rather than a patient-level clinical study. Consequently, the findings cannot establish the efficacy, safety, superiority or synergistic effect of N-acetylcysteine plus acebrophylline.

The purposive sampling strategy may have introduced selection bias and may limit generalizability to all clinicians treating COPD in India.

The relatively modest sample size may not adequately capture regional or specialty-related differences in practice.

Survey responses may also be influenced by recall bias, personal prescribing preference and previous exposure to particular therapeutic approaches.

No objective patient outcomes such as spirometry, CAT score, mMRC score, exacerbation rate, hospitalization rate or quality-of-life measurements were collected.

The study did not compare clinicians according to specialty, years of experience or geographic region. Future surveys should include these variables to determine whether prescribing patterns vary across clinician subgroups.

Finally, direct evidence for the NAC–acebrophylline combination remains much less extensive than evidence for NAC alone.

Future Directions

Future studies should prospectively evaluate the combination in clearly defined COPD phenotypes, particularly patients with chronic bronchitis, troublesome sputum production and recurrent exacerbations.

A comparative clinical study should ideally include

1. standard COPD treatment alone;
2. standard treatment plus NAC;
3. standard treatment plus acebrophylline; and
4. standard treatment plus NAC and acebrophylline.

Relevant outcomes should include annualized exacerbation rate, time to first exacerbation, CAT score, mMRC dyspnoea grade, sputum volume or sputum-related symptom scores, FEV1, rescue-medication use, hospitalizations, treatment discontinuation and adverse events.

Longer follow-up would help determine whether short-term mucus-related symptomatic improvement translates into meaningful reduction in exacerbation burden or improvement in quality of life.

CONCLUSION

This cross-sectional survey indicates that N-acetylcysteine and acebrophylline are commonly positioned by participating Indian clinicians as adjunctive therapy in COPD and mucus-dominant respiratory conditions.

Pulmonary function testing was the preferred diagnostic approach, while cough with sputum was a commonly reported clinical feature. More than half of respondents reported using the combination in COPD, and approximately three-fourths considered it useful for mucus management. A treatment duration

of 10–15 days and perceived symptomatic improvement within approximately one week were commonly reported.

These observations represent prescribing practices and clinician perceptions rather than patient-level evidence of efficacy. Available literature provides a stronger evidence base for NAC than for acebrophylline, while direct evidence supporting additional benefit from their combined administration remains limited.

Prospective comparative trials are required to define the patient phenotype most likely to benefit, the optimal treatment duration, long-term safety and whether combination therapy provides clinically meaningful benefit beyond either agent used individually.

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