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Therapeutic Role of Carbocysteine in Chronic Respiratory and Otorhinolaryngological Diseases: A Systematic Review and Meta-Analysis

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Abstract

Background: Carbocysteine is a mucoregulatory agent with anti-inflammatory properties used in chronic respiratory and otorhinolaryngological diseases. However, clinical evidence across indications remains heterogeneous. **Methods:** A systematic review and meta-analysis were conducted to assess the efficacy of oral carbocysteine in stable chronic conditions. PubMed, Cochrane Library, and ClinicalTrials.gov were searched up to February 2025. Eligible randomized controlled trials compared carbocysteine with placebo or standard treatments. Outcomes were meta-analyzed when reported in at least two studies. **Results:** Twenty RCTs were included. In COPD, a meta-analysis of incidence rates showed a pooled rate ratio of 0.48 (95% CI: 0.32 - 0.72; $p < 0.001$), reflecting a 52% reduction in exacerbations with carbocysteine. The mean number of exacerbations also declined significantly (SMD −3.39; 95% CI: −6.36 to −0.42; $p < 0.001$), alongside improvements in QoL (SMD −1.45; 95% CI: −2.43 to −0.48; $p < 0.001$). In otitis media with effusion, carbocysteine reduced effusion persistence and improved audiometric outcomes. In chronic bronchitis, benefits were observed in sputum viscosity and mucociliary clearance. Meta-analysis was not feasible in other conditions due to data limitations. **Conclusions:** Carbocysteine demonstrates consistent clinical benefits in COPD and otitis media with effusion. Further high-quality trials are warranted in other chronic indications.

Keywords

Carbocysteine, Chronic Respiratory Disease, Mucoregulation, COPD Exacerbations, Otitis Media with Effusion, Meta-Analysis

1. Introduction

Chronic respiratory and otorhinolaryngological diseases characterized by mucus hypersecretion and impaired clearance represent a significant burden on healthcare systems due to their recurrent nature and associated complications [1]. Conditions such as chronic bronchitis, chronic obstructive pulmonary disease (COPD), and recurrent otitis media are frequently linked to excessive mucus production, leading to persistent inflammation, increased susceptibility to infections, and disease progression [2]. Effective management strategies focus on improving mucus rheology, enhancing mucociliary clearance, and reducing exacerbations to improve long-term outcomes [3].

Carbocysteine is a mucoactive agent with both mucoregulatory and mucolytic properties, facilitating mucus clearance and reducing inflammation. Unlike classic mucolytics, which primarily degrade mucus structure, carbocysteine modifies its composition by promoting sialomucin secretion, reducing mucus viscosity and improving elasticity, which facilitates mucociliary clearance and drainage of secretions [4]. These properties make carbocysteine a therapeutic option in chronic respiratory and otorhinolaryngological conditions where mucus dysfunction plays a central role in disease progression [5].

Several randomized controlled trials (RCTs) have evaluated the effects of carbocysteine on clinical outcomes such as exacerbation rates and lung function parameters in COPD, sputum viscosity and expectoration ease in chronic bronchitis and cystic fibrosis, middle ear accumulation of serous fluid and mucus resolution in otitis media with effusion, and the need for surgical intervention such as grommet placement [6] [7]. However, the results have been inconsistent, with some studies showing significant benefits while others report limited or variable effects [8]. Given these discrepancies, a comprehensive systematic review and meta-analysis are necessary to synthesize the available evidence and provide a clearer understanding of the therapeutic role of carbocysteine in chronic disease management.

This systematic review aimed to assess the efficacy of carbocysteine compared to placebo or other treatments in patients with chronic mucus-related respiratory and otorhinolaryngological diseases. The primary objective was to evaluate its impact on mucus clearance, respiratory function, exacerbation prevention, and clinical symptom improvement. By analyzing data from multiple RCTs, this review provides evidence-based insights into the role of carbocysteine in chronic conditions where mucus hypersecretion and impaired clearance contribute to disease burden.

2. Materials and Methods

2.1. Search Strategy

A comprehensive literature search was conducted in February 2025 across PubMed, Cochrane Library, Embase, Scopus, and ClinicalTrials.gov to identify RCTs evaluating the effects of carbocysteine in chronic respiratory and otolaryngological

diseases. The search had no restrictions on language or publication years to ensure the inclusion of all relevant studies.

The search strategy utilized a combination of MeSH terms and free-text keywords, adapted to each database. Boolean operators (AND, OR) were applied to optimize search sensitivity and specificity. The key terms used included: Intervention-related terms: "Carbocysteine", "S-Carboxymethylcysteine", "Mucoregulator", "Mucoactive therapy", "Mucolytic agent". Chronic disease-related terms: "Chronic bronchitis", "Chronic cough", "Mucus hypersecretion", "Chronic airway disease", "pulmonary disease", "Exacerbations". Pathology-specific terms: "Chronic obstructive pulmonary disease", "COPD", "Cystic fibrosis", "Otitis media with effusion", "Recurrent otitis media", "Middle ear effusion". Clinical outcomes-related terms: "Lung function", "FEV1", "Airway clearance", "Sputum viscosity", "Expectoration", "Hearing loss", "Mucociliary clearance". To maximize the coverage of relevant studies, reference lists from included articles and systematic reviews were also manually screened.

2.2. Study Selection

This systematic review included only RCTs investigating the effects of carbocysteine in chronic mucus-related respiratory and otorhinolaryngological diseases. Observational studies, case reports, editorials, and animal studies were excluded to ensure a high level of evidence. Studies were required to compare carbocysteine to placebo, standard treatment, or other mucolytics. The included studies evaluated the systemic or inhaled use of carbocysteine, regardless of the dosing regimen. Trials that used concomitant medication to treat the underlying pathological condition were included, provided that these treatments were administered equally in both the intervention and control groups.

Eligible studies included patients diagnosed with chronic bronchitis, COPD, cystic fibrosis, obstructive sleep apnea syndrome (OSAS) and recurrent or persistent otitis media with effusion (OME). Studies focusing on acute respiratory infections or short-term symptom relief without long-term follow-up were excluded, as this review specifically aimed to evaluate the role of carbocysteine in chronic disease management. All included studies were required to assess clinical variables, such as sputum viscosity, expectoration ease, mucociliary clearance, lung function parameters (FEV1, FVC), exacerbation rates, middle ear effusion volume, hearing improvement, or need for surgical intervention.

The study selection process followed PRISMA guidelines, using a two-step screening process. First, two independent reviewers screened all retrieved records by title and abstract, applying broad eligibility criteria to exclude studies unrelated to carbocysteine or chronic disease management. Articles that passed this stage underwent a full-text review, where predefined inclusion and exclusion criteria were applied. Any disagreements between reviewers were resolved through discussion, and if consensus was not reached, a third reviewer was consulted.

Since most of the included studies were conducted many years ago, the original

authors were not contacted for additional information. To ensure comprehensive analysis, the reference lists of included studies and relevant systematic reviews were manually screened for additional trials that met the inclusion criteria.

2.3. Statistical Planning

A meta-analysis was conducted, incorporating both continuous and categorical data depending on the outcome analyzed. For continuous variables, means and standard deviations (SDs) were used to calculate standardized mean differences (SMDs) with 95% confidence intervals (CIs). For categorical variables, frequencies (n/N) were used to compute odds ratios (ORs) with 95% CIs.

To compare the incidence rates between the carbocysteine and placebo groups, a meta-analysis of rate ratios (RRs) was conducted. Incidence rates were calculated as the number of events per person-year in each study arm. The rate ratios and their corresponding standard errors (SEs) were computed using log-transformed values and pooled under a random-effects model to account for potential between-study heterogeneity. A continuity correction of 0.5 was applied when a study reported zero events in one of the treatment groups. Pooled estimates were presented as rate ratios with 95% confidence intervals (CIs).

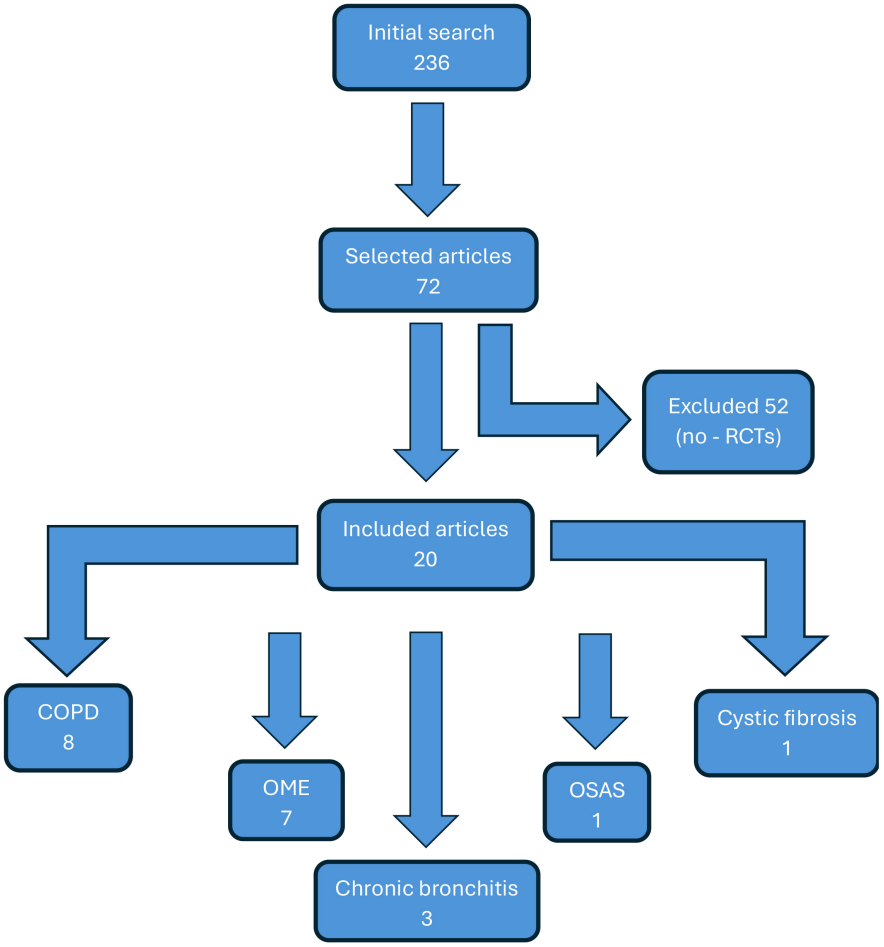
For all meta-analyses, effect sizes were pooled using both fixed-effects and random-effects models, depending on the level of heterogeneity observed. The fixed-effects model (inverse variance method) assumes that all studies estimate a common underlying effect size, weighting each study proportionally to its precision. The random-effects model (DerSimonian-Laird method) accounts for potential between-study variability, if the true effect may differ across studies. Given the expected clinical and methodological heterogeneity, the random-effects model was prioritized for primary analyses, while the fixed-effects model was used for sensitivity analyses.

To minimize heterogeneity, studies were grouped based on disease condition, comparison arm and outcome type. Chronic bronchitis simple (non-COPD) studies focused on outcomes related to sputum viscosity, mucociliary clearance, and expectoration. COPD studies assessed exacerbation rates, lung function parameters such as FEV1 and FVC, and symptom improvement. Cystic fibrosis studies evaluated mucus rheology and airway clearance. OME studies analyzed middle ear effusion resolution, hearing improvement, and the need for grommet placement. Studies on obstructive sleep apnea syndrome focused on outcomes related to airway patency, mucus clearance, and symptom improvement.

Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic, with I^2 values above 50% considered indicative of substantial heterogeneity. Sensitivity analyses were performed by excluding studies with a high risk of bias or those lacking a clearly defined control group. Publication bias was planned to be evaluated using funnel plots and Egger's test for asymmetry if at least ten studies had been available per outcome. All statistical analyses were performed using STATA, with statistical significance set at $p < 0.05$.

3. Results

3.1. Included Studies



COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial; OME: otitis media with effusion; OSAS: obstructive sleep apnea syndrome.

Figure 1. Search process and inclusion of studies.

The systematic search identified 236 studies, of which only 20 met the inclusion criteria after full-text review [9]-[27]. The included studies evaluated the effects of carbocysteine in chronic mucus-related respiratory and otorhinolaryngological diseases, with 8 studies focusing on COPD [9]-[16], 3 on chronic bronchitis without airflow obstruction [17]-[19], 1 on cystic fibrosis [20], 1 on OSAS [21], and 7 on OME [22]-[28]. The studies were published in English, French, Japanese, Polish, and Russian, reflecting a diverse body of international research on the therapeutic effects of carbocysteine (**Figure 1**). For COPD, the trials varied in the number of recruited patients, ranging from 16 to 709 subjects. Most studies included patients with confirmed COPD diagnosis based on functional criteria, with FEV1/FVC values below 70% and different degrees of airflow obstruction. In terms of intervention, carbocysteine doses ranged from 750 mg to 1500 mg per day, usually admin-

istered in two or three doses. Some studies compared carbocysteine to placebo [14] [16], while others evaluated it against another mucoregulator [10] or in combination with other therapies [11].

The follow-up duration varied significantly among the trials. The longest study [16] had a 12-month follow-up, whereas other studies assessed shorter-term efficacy, ranging from 7 days to 3 months [12] [13]. All studies recorded clinical variables related to COPD, including exacerbation frequency, lung function, sputum viscosity, quality of life, and respiratory symptoms. (**Table 1**)

Table 1. Summary of studies included in the COPD review evaluating carbocysteine in chronic respiratory diseases.

Study	Design	N (Total)	N (Carbocysteine)	N (Placebo/ Control)	Duration (months)	Primary Outcome
Zheng 2008	RCT, multicenter, double-blind, placebo-controlled	709	353	354	12	Exacerbations
Tatsumi 2007	RCT, single-center, open-label, controlled	142	72	70	12	Exacerbations, colds
Yasuda 2007	RCT, single-center, double-blind, placebo-controlled	156	78	78	12	Exacerbations, colds
Allegra 1996	RCT, double-blind, placebo-controlled	441	223	218	6	Exacerbations, acute illness days, antibiotics
Puchelle 1978	RCT, double-blind, placebo-controlled	20	10	10	0.5	Sputum viscosity, expectoration
Blaive 1993	RCT, double-blind, active comparator (Letosteine)	47	23	24	1	Sputum viscosity, expectoration
Edwards 1976	RCT, single-blind, placebo-controlled	82	27	26	3	Sputum volume, viscosity
Distefano 1990	RCT, double-blind, combination therapy (Carbocysteine + Sobrerol)	16	8	8	0.5	Sputum characteristics

RCT: randomized controlled trial; N: number of patients; COPD: chronic obstructive pulmonary disease.

For chronic bronchitis, the three RCTs included in this review evaluated the efficacy of carbocysteine in this patient population. These studies included 24, 20, and 109 patients, respectively, all diagnosed with simple chronic bronchitis without significant airflow obstruction. The trials used a placebo-controlled design to assess the impact of carbocysteine on sputum viscosity, mucociliary clearance, lung function, and respiratory symptoms. The duration of treatment varied: one study [17] administered carbocysteine-lysine at a dose of 2.7 g/day for 4 days; another [18] used oral carbocysteine at 375 mg three times daily for 10 days; and the third [19] provided oral carbocysteine at 750 mg three times daily for six months. In the short-term studies, mucus samples were collected before and after treatment, and their rheological properties were analyzed. In the long-term trial, lung function was monitored monthly using PEFR, and data on acute exacerbations

were also collected.

For cystic fibrosis, one randomized, single-blind, comparative study evaluated the effects of SCMC-Lys versus ambroxol hydrochloride (ABX) in 26 patients with confirmed cystic fibrosis and predominant respiratory involvement [20]. The study included both pediatric and adult patients, with dosing adjusted accordingly (SCMC-Lys: 900 mg TID for adults and 270 mg TID for children; ABX: 33 mg TID for adults and 10 mg QID for children). The treatment period lasted 80 days, during which clinical symptoms, sputum properties, arterial blood gases, and pulmonary function were assessed.

For OSAS, one RTC trial assessed the effects of carbocysteine compared to continuous positive airway pressure (CPAP) in 40 patients with moderate to severe OSAS [21]. Patients were randomly assigned to receive either 1500 mg of oral carbocysteine daily or CPAP therapy for six weeks. The study evaluated changes in polysomnographic parameters, oxidative stress markers, and endothelial function.

The studies evaluating the effects of carbocysteine in OME varied in design, sample size, and follow-up duration [22]-[28]. The number of participants ranged from 38 to 250 children, with most studies including pediatric patients aged between 3 and 14 years. Some trials focused specifically on children with chronic otitis media with effusion and adenoid hypertrophy, while others included broader populations with middle ear effusion. The treatment regimens differed among studies, with carbocysteine administered either as a monotherapy or as part of a combined approach with other therapies such as decongestants or antihistamines. Dosing strategies varied, with most studies using S-carboxymethylcysteine (SCMC) syrup at a dosage of 125 mg/5 mL, given three times daily for periods ranging from 4 to 12 weeks.

The control groups consisted of either placebo [24] [25] [27] or alternative treatments such as antihistamine-decongestant combinations [26]. The primary outcomes assessed included the resolution of middle ear effusion, improvement in audiometric parameters, and reduction in the need for surgical intervention, such as tympanostomy tube insertion.

3.2. Meta-analysis: Carbocysteine vs Placebo

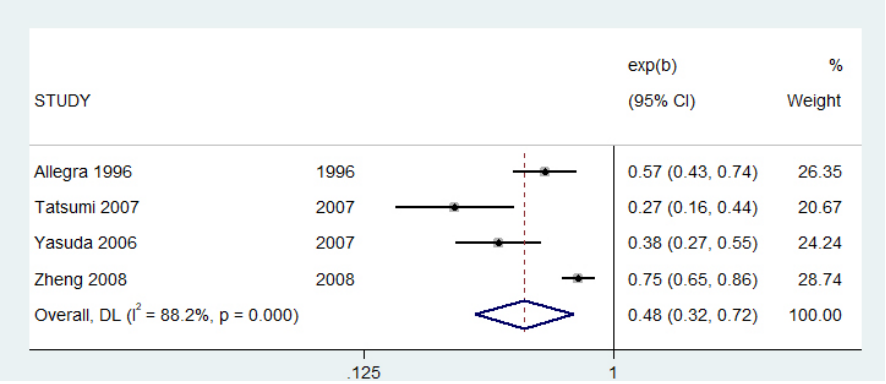
To enable meta-analytic pooling, only outcomes consistently reported across two or more trials were included in the quantitative synthesis, while study-specific results were excluded from this section.

3.2.1. Chronic Obstructive Pulmonary Disease (COPD)

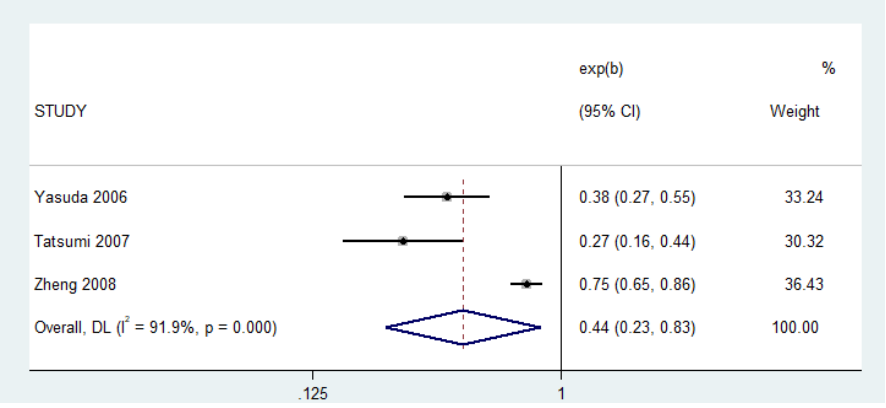
Incidence rate of exacerbations

A meta-analysis of incidence rates comparing carbocysteine to placebo showed a pooled RR of 0.48 (95% CI: 0.32 - 0.72; $p < 0.001$), indicating a significant 52% reduction in exacerbations in the carbocysteine group. Despite substantial heterogeneity among the included studies ($I^2 = 88.2\%$), all individual trials consistently favored carbocysteine, reinforcing the robustness of its therapeutic benefit across different populations and clinical settings. (**Figure 2A**)

To assess the robustness of the findings, a sensitivity analysis was performed excluding the earliest study, which differed from the others in having a shorter follow-up period (6 months versus 12 months) and being conducted more than a decade prior to the remaining trials. After excluding this study, the pooled RR remained directionally consistent and statistically significant (RR = 0.44; 95% CI: 0.23 - 0.83; $p < 0.001$), confirming that the observed benefit was not driven by this single data point (Figure 2B). However, the level of heterogeneity increased rather than decreased ($I^2 = 91.9\%$), suggesting that variability among the more recent studies remained substantial despite the exclusion. This further underscores the importance of considering clinical and methodological differences across trials when interpreting the pooled effect.



(A)



(B)

Figure 2. (A) Meta-analysis of carbocysteine versus placebo: incidence rate of exacerbations in patients with COPD; (B) Sensitivity analysis excluding the oldest study with shortest follow-up: incidence rate of exacerbations in patients with COPD.

Mean number of exacerbations

A meta-analysis of four RCTs evaluated the effect of carbocysteine on the mean number of exacerbations. A random-effects model was applied due to high heterogeneity ($I^2 = 99.6\%$, $p < 0.0001$). The pooled SMD was −3.39 (95% CI: −6.36 to −0.42; $p < 0.001$), indicating a significant reduction in the mean number of exac-

erbations among patients receiving carbocysteine. (Figure 3)

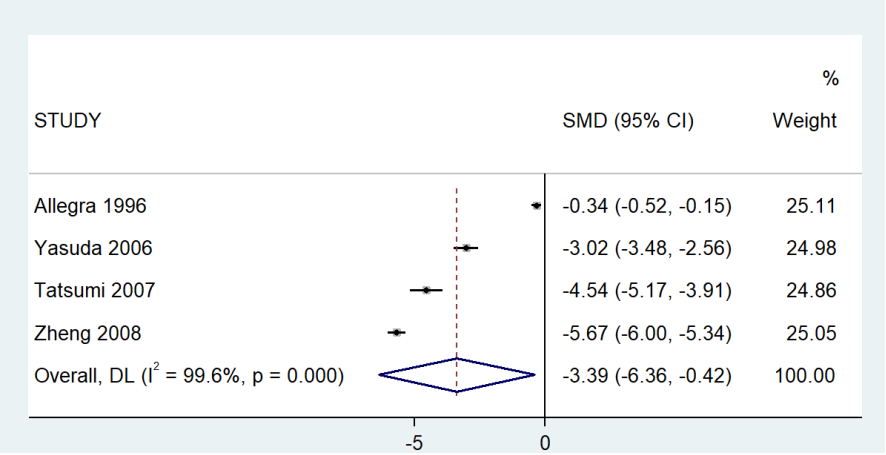


Figure 3. Meta-analysis of the mean number of exacerbations in patients with COPD: carbocysteine versus placebo.

Quality of life

The effect of carbocysteine on quality of life was assessed in a meta-analysis of two RCTs. Due to substantial heterogeneity (I^2 = 95.1%, p < 0.0001), a random-effects model was used. The pooled analysis demonstrated a significant benefit in favor of carbocysteine (SMD −1.45; 95% CI: −2.43 to −0.48; p < 0.001), suggesting a clinically meaningful improvement despite notable variability between studies. (Figure 4)

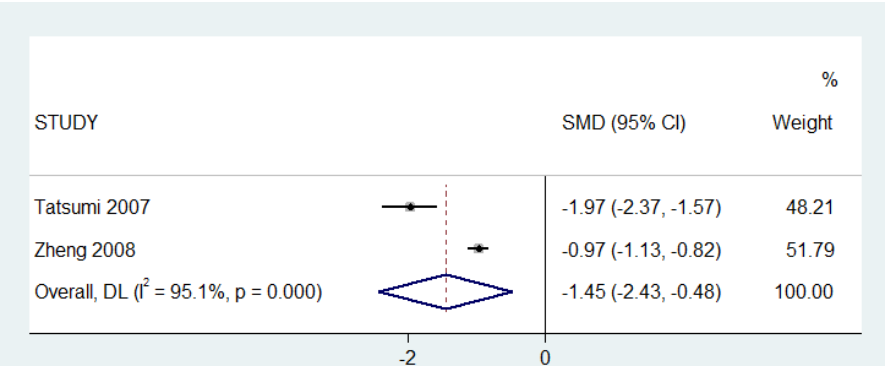


Figure 4. Meta-analysis of the impact of carbocysteine versus placebo on quality of life in patients with COPD.

Adverse events

The safety profile of carbocysteine was assessed through a meta-analysis of four RCTs. A fixed-effects model was used given the absence of significant heterogeneity (I^2 = 0.0%, p = 0.620). The pooled OR was 0.93 (95% CI: 0.64 - 1.35; p > 0.05), indicating no significant difference in adverse event rates between carbocysteine and placebo. These findings suggest that carbocysteine is well tolerated and does not increase the risk of adverse events. (Figure 5)

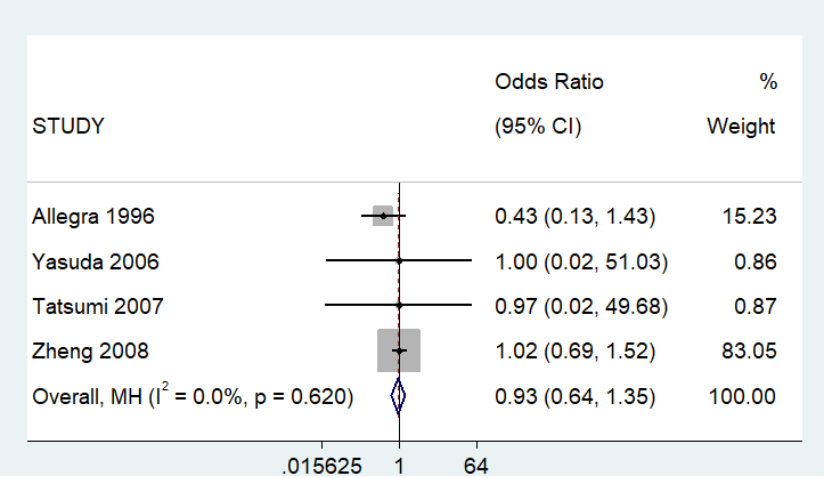


Figure 5. Meta-analysis of adverse events in patients with COPD: carbocysteine versus placebo.

Common colds

Two RCTs evaluating the incidence of common colds were included in a meta-analysis. A random-effects model was applied, with moderate heterogeneity detected (I^2 = 68.2%, p = 0.076). The combined rate ratio was 0.47 (95% CI: 0.35 - 0.63; p < 0.001), indicating a significant 53% reduction in the risk of common colds with carbocysteine compared to placebo. (Figure 6)

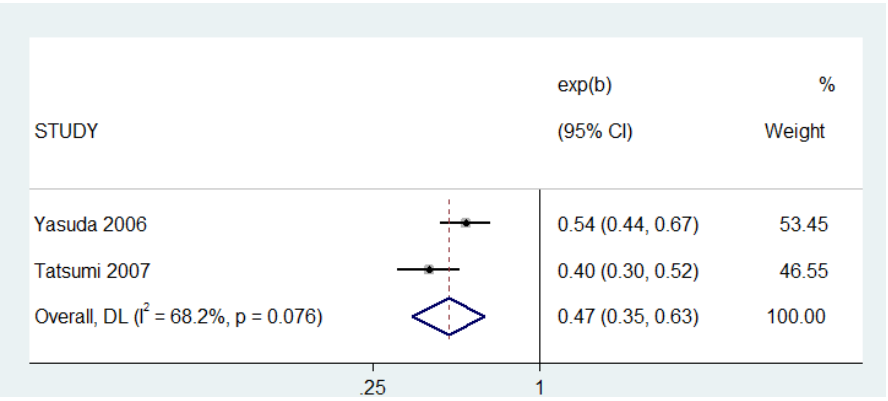


Figure 6. Meta-analysis of the incidence of common colds in patients with COPD: carbocysteine versus placebo.

Although a small number of COPD trials included active comparators, such as N-acetylcysteine or combination therapies (e.g., carbocysteine plus sobrerol), no more than one study was available per comparator with sufficiently similar design and outcomes to allow meta-analysis. These studies are not discussed individually, to avoid overinterpretation and preserve consistency in the level of evidence presented for this specific condition.

3.2.2. Chronic Bronchitis without Obstruction

Reduction of sputum viscosity

A meta-analysis of two RCTs assessed the impact of carbocysteine on sputum viscosity in patients with chronic bronchitis without airflow obstruction. A random-effects model was used due to substantial heterogeneity (I^2 = 87.8%, p = 0.004). The pooled SMD was −2.67 (95% CI: −5.28 to −0.05; p < 0.05), confirming a significant reduction in sputum viscosity with carbocysteine treatment. (Figure 7)

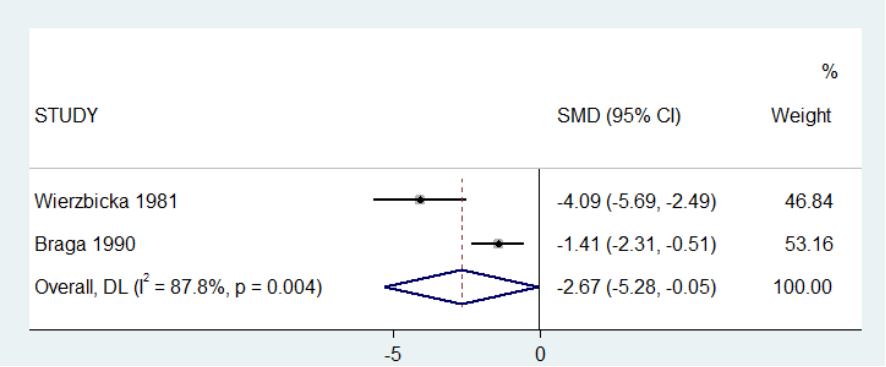


Figure 7. Meta-analysis of carbocysteine versus placebo on sputum viscosity reduction in patients with chronic bronchitis without obstruction.

3.2.3. Otitis Media with Effusion (OME)

Resolution OME

A meta-analysis of two RCTs evaluated the effect of carbocysteine on OME resolution. A fixed-effects model was applied due to a lack of heterogeneity (I^2 = 0.0%, p = 0.574). The pooled OR was 1.45 (95% CI: 1.00 - 2.11; p = 0.050), indicating a borderline statistically significant benefit in favor of carbocysteine. (Figure 8)

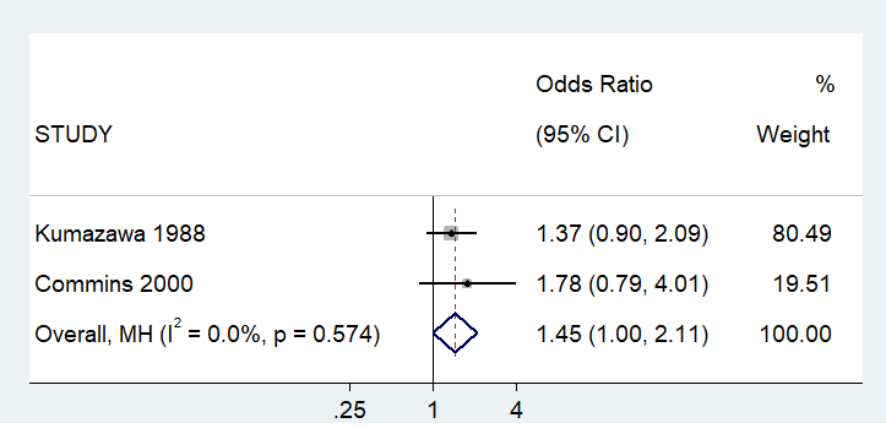


Figure 8. Meta-analysis of resolution rates in otitis media with effusion: carbocysteine versus placebo.

Audiometric improvement

The effect of carbocysteine on audiometric outcomes in patients with OME was assessed in two RCTs. Using a fixed-effects model (I^2 = 0.0%, p = 0.573), the pooled OR was 1.52 (95% CI: 1.02 - 2.27; p = 0.038), demonstrating a significant

improvement in hearing thresholds with carbocysteine compared to placebo. (Figure 9)

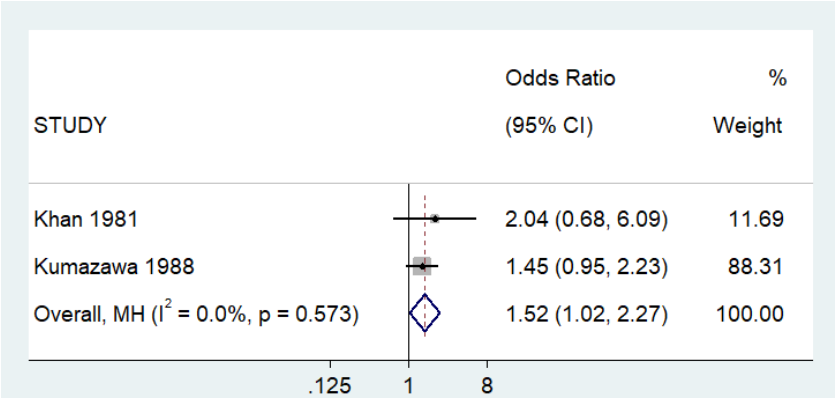


Figure 9. Meta-analysis of improvement in audiometry in patients with otitis media with effusion: carbocysteine versus placebo.

3.3. Non-Comparative Evidence: Indications with One Available RCT

3.3.1. Cystic Fibrosis

Only one study was identified evaluating carbocysteine lysine salt monohydrate (SCMC-Lys) in cystic fibrosis, so a meta-analysis could not be performed. The trial compared SCMC-Lys and ambroxol hydrochloride (ABX) in 26 patients over 80 days, showing similar efficacy in reducing sputum viscosity and elasticity and improving oxygenation.

In the SCMC-Lys group, sputum viscosity significantly decreased from 5002 ± 736 to 3493 ± 411 mPas ($p < 0.01$), while sputum elasticity was reduced from 401 ± 59 to 311 ± 40 G ($p < 0.05$). Oxygenation improved, with PaO_2 increasing from 36.1 ± 2.1 to 40.7 ± 2.0 mmHg ($p < 0.01$) and HbO_2 saturation rising from 64.1 ± 3.6 to 69.5 ± 3.5% ($p < 0.02$). Lung function showed significant gains, with tidal volume increasing from 74.5 ± 5.0 to 78.8 ± 4.8% ($p < 0.005$), FEV_1 from 65.3 ± 8.2 to 68.2 ± 8.1% ($p < 0.02$), and PEF from 63.9 ± 5.8 to 68.2 ± 2.2% ($p = 0.05$).

Notably, SCMC-Lys significantly improved cough symptoms ($p < 0.05$), a benefit not observed with ABX, suggesting a potential advantage in enhancing expectoration. No adverse events were reported in either group.

3.3.2. Obstructive Apnea Syndrome (OSAS)

Only one study was identified evaluating carbocysteine in OSAS, so a meta-analysis could not be performed. The Wu *et al.* (2016) trial randomized 40 patients with moderate to severe OSAS to receive carbocysteine (1500 mg/day) or continuous positive airway pressure (CPAP) for six weeks, assessing polysomnographic parameters, oxidative stress biomarkers, and endothelial function.

In the carbocysteine group, the Apnea-Hypopnea Index (AHI) significantly decreased from 43.3 ± 7.2 to 29.8 ± 6.5 events/hour ($p < 0.01$), indicating an improvement in sleep-disordered breathing. Daytime sleepiness, measured by the

Epworth Sleepiness Scale (ESS), improved from 10.18 ± 4.28 to 6.82 ± 3.66 ($p < 0.01$). Additionally, endothelial function, assessed via flow-mediated dilation (FMD), significantly improved from 6.12 ± 1.45% to 8.35 ± 1.57% ($p < 0.01$), suggesting a beneficial effect on vascular health.

These results indicate that carbocysteine may reduce apnea severity and improve sleep-related symptoms in OSAS patients, potentially due to its mucoregulatory and anti-inflammatory properties. However, as CPAP remains the gold standard treatment, further studies are needed to clarify the clinical relevance of carbocysteine in OSAS management.

4. Discussion

This systematic review and meta-analysis evaluated the efficacy of carbocysteine in chronic mucus-related respiratory and otorhinolaryngological diseases, including COPD, chronic bronchitis, cystic fibrosis, OME, and OSAS. The findings suggest that carbocysteine provides clinical benefits in several of these conditions, particularly in reducing exacerbation rates, improving mucus clearance, and enhancing functional outcomes such as lung function and hearing.

In COPD, carbocysteine significantly reduced the frequency of exacerbation, reinforcing its role as a mucoregulatory therapy in chronic airway disease. The magnitude of this effect was substantial across the studies analyzed, with most trials reporting a consistent reduction in exacerbation risk compared to placebo. These findings support the hypothesis that carbocysteine helps stabilize COPD by reducing mucus accumulation and its associated inflammatory response, which are key contributors to disease progression and exacerbation frequency [29] [30]. Additional evidence from previous meta-analyses supports this effect, further confirming the therapeutic value of carbocysteine in preventing COPD exacerbation [31].

Some studies also reported potential improvements in respiratory function and symptom control, though these effects were less consistent. Patients receiving carbocysteine experienced improved mucus clearance and reduced respiratory discomfort, which may translate into better disease management and quality of life [32]. Several clinical guidelines also support this approach, recommending the use of oral mucolytic agents such as carbocysteine in patients with COPD and moderate to severe airflow obstruction who continue to experience exacerbation despite optimal inhaled therapy, particularly in those with chronic bronchitis phenotype [33].

The benefits observed with carbocysteine in reducing COPD exacerbations are likely explained by its mucoregulatory and anti-inflammatory properties. Unlike classic mucolytics that primarily degrade mucus structure, carbocysteine modulates its composition by increasing the secretion of sialomucins, leading to a more fluid and easily expectorated mucus [4]. This effect enhances mucociliary clearance, which is often impaired in COPD due to chronic inflammation and oxidative stress [34]. As demonstrated in our study, this mucoregulatory action may

contribute to the observed reduction in exacerbations and improvement in respiratory stability.

Oxidative stress is a key factor in corticosteroid resistance in COPD, as it reduces the activity of histone deacetylase 2 (HDAC2), an enzyme essential for the anti-inflammatory effects of inhaled corticosteroids [35]. Carbocysteine has been shown to restore HDAC2 activity, thereby enhancing corticosteroid efficacy in reducing lung inflammation [36]. Additionally, in vitro studies using bronchial epithelial cells exposed to cigarette smoke extracts demonstrated that carbocysteine decreases the production of reactive oxygen species (ROS) and upregulates nuclear factor Nrf2, which controls the expression of antioxidants and cytoprotective genes [37]. By modulating oxidative and inflammatory pathways, carbocysteine may enhance the therapeutic effects of corticosteroids, a mechanism that aligns with the reduction in exacerbation rates observed in our meta-analysis. These findings reinforce its potential role as an adjunctive therapy in COPD management [38].

In this way, the combination of carbocysteine with inhaled corticosteroids has been associated with a greater reduction in exacerbations in patients with moderate to severe COPD compared to corticosteroids alone [39]. Beyond its effects on airway inflammation, cellular senescence in bronchial epithelial cells, a process accelerated in COPD due to chronic oxidative stress, contributes to persistent airway inflammation by inducing the senescence-associated secretory phenotype (SASP). Studies suggest that carbocysteine can counteract this process by restoring the expression of protective proteins such as SIRT1 and FOXO-3, which regulate oxidative stress responses and cellular longevity [40].

Even more, experimental studies with bronchial epithelial cells have shown that carbocysteine promotes cell proliferation and reduces the accumulation of senescence markers such as p21, suggesting that it may help preserve epithelial function and slow COPD progression [41]. This effect could have important implications for disease trajectory, as it may contribute to maintaining airway integrity and limiting persistent inflammation caused by senescent cells [42]. The ability of carbocysteine to reduce exacerbations, as demonstrated in our meta-analysis, may be partially attributed to these protective effects at the cellular level, reinforcing its therapeutic potential in COPD.

Viral infections, particularly those caused by rhinovirus, influenza, and respiratory syncytial virus, are among the most common triggers of COPD exacerbation. Carbocysteine may have a protective role in this context, as it has been shown to modulate innate immune responses, reduce oxidative stress, and regulate pathogen-recognition receptors such as TLR4 in bronchial epithelial cells exposed to cigarette smoke [32]. Oxidative stress contributes to epithelial barrier dysfunction, facilitating viral entry and increasing susceptibility to infections. Given its antioxidant and anti-inflammatory properties, carbocysteine may help preserve epithelial integrity and limit viral replication, thereby reducing the impact of viral infections on COPD exacerbations [43]. As demonstrated in our meta-analysis, the re-

duction in exacerbations with carbocysteine suggests that its benefits extend beyond bacterial infections, potentially mitigating viral-induced exacerbations as well. These findings indicate that carbocysteine acts not only as a mucoregulatory agent but also as a potential immunomodulator, further supporting its role in comprehensive COPD management strategies [44].

The benefits observed in COPD are consistent with findings in chronic bronchitis without airflow obstruction, where carbocysteine also demonstrated improvements in mucus clearance and symptom relief [7]. Patients with chronic bronchitis often experience persistent mucus hypersecretion, leading to chronic cough, airway irritation, and an increased risk of infections. The studies analyzed in this review suggest that carbocysteine effectively reduces sputum viscosity, facilitating expectoration and alleviating respiratory discomfort. These effects were observed across different treatment durations and were generally well tolerated, reinforcing the role of mucoregulatory therapy in chronic bronchial conditions even in the absence of airflow limitation [45].

Similarly, cystic fibrosis is a condition characterized by abnormally thick and dehydrated mucus that contributes to chronic infection and progressive lung function decline. Although only one study was available, it suggested that carbocysteine improved sputum rheology and oxygenation, facilitating airway clearance in these patients. The study also reported an improvement in cough symptoms, which may indicate enhanced mucus mobilization and reduced airway obstruction. While these findings are promising, the lack of additional trials prevents a comprehensive assessment of its role in cystic fibrosis. Further research is needed to determine whether carbocysteine provides sustained clinical benefits or should be considered as an adjunct to standard mucolytic therapies in this population [46].

The positive effects of carbocysteine on mucus clearance and respiratory function extend to OSAS, where airway obstruction is often exacerbated by mucus accumulation and inflammation. Although only one study was available, its findings suggest that carbocysteine may contribute to reducing apnea severity and improving sleep-related symptoms, likely due to its ability to enhance mucus clearance and reduce airway resistance [47]. Patients receiving carbocysteine experienced improvements in sleep quality and daytime alertness, indicating potential benefits beyond airway patency. While these results support the hypothesis that mucoregulatory therapy could play a role in OSAS management [48], further studies are required to determine its clinical significance, particularly in comparison to standard treatments such as CPAP. Nevertheless, based on current evidence, carbocysteine should not be considered a replacement for CPAP, but rather a potential adjunct or alternative for patients who are unable or unwilling to tolerate positive airway pressure therapy.

The effects of carbocysteine on mucus clearance and fluid regulation observed in chronic respiratory diseases also appear relevant in OME, where middle ear fluid accumulation leads to hearing impairment and an increased risk of recurrent

infections [49]. The findings from this review suggest that carbocysteine may enhance the resolution of middle ear effusion, potentially by modulating mucus composition and improving mucociliary transport in the Eustachian tube. Although the overall benefit was modest, the consistency of results across studies suggests that carbocysteine could be a useful adjunctive therapy in selected patients with persistent OME [50].

Beyond effusion resolution, some studies also reported improvements in audiometric outcomes, indicating that carbocysteine may contribute to functional recovery by promoting fluid clearance from the middle ear. However, the magnitude of these effects varied, with some trials showing clearer benefits than others. This variability may be influenced by factors such as disease chronicity, baseline severity, and treatment duration. Therefore, further trials are needed to determine which patient subgroups may derive the greatest benefit and how it compares to standard treatment options [51].

While the overall findings are encouraging, certain limitations of this meta-analysis warrant consideration. A substantial degree of heterogeneity was observed in some pooled analyses, particularly those evaluating exacerbation rates and quality of life in COPD. As noted in the previous paragraph, this variability may be partly explained by differences in study design, baseline populations, treatment duration, dosing regimens, and outcome definitions. Additional clinical sources of heterogeneity may include variability in baseline disease severity (some trials included patients with FEV_1 as low as 25% of predicted, while others involved milder cases with values closer to 70%) as well as differences in COPD phenotype, such as the predominance of chronic bronchitis or emphysematous patterns. In some studies, the use of concomitant bronchodilators or corticosteroids was allowed, while in others it was restricted or not reported, adding further variability in treatment context. These factors were inconsistently described across trials and likely contributed to the differences in effect size observed. Moreover, many of the included trials were conducted several decades ago, during which diagnostic criteria, standard of care, and reporting standards differed significantly from current practice. These factors may have contributed to methodological inconsistencies and between-study variability. Nevertheless, the direction of the treatment effect consistently favored carbocysteine across studies, which strengthens the validity of the findings despite statistical heterogeneity. The reproducibility of favorable outcomes across diverse settings and populations supports the robustness of the therapeutic benefit observed.

Despite these limitations, the findings offer practical guidance for clinical decision-making. From a clinical perspective, the current evidence suggests that carbocysteine is most likely to benefit patients with chronic respiratory conditions characterized by mucus hypersecretion and recurrent exacerbations, particularly those with COPD and chronic bronchitis phenotypes. Patients with frequent exacerbations despite inhaled therapy, poor mucus clearance, or intolerance to high-dose inhaled corticosteroids may be good candidates. The favorable safety profile

and oral administration also make carbocysteine a pragmatic option for older adults or those with polypharmacy concerns. These findings support its role as an adjunctive, long-term mucoregulatory therapy in carefully selected patient populations.

In summary, this systematic review and meta-analysis support the therapeutic potential of carbocysteine in chronic respiratory and otorhinolaryngological diseases, particularly in reducing exacerbations, improving mucus clearance, and enhancing functional outcomes. The findings suggest that carbocysteine may play a valuable role as an adjunct therapy, not only due to its mucoregulatory effects but also through its anti-inflammatory and immunomodulatory properties, which may contribute to better disease control and symptom relief.

Nonetheless, further high-quality research is needed, particularly in indications with limited evidence, such as cystic fibrosis and obstructive sleep apnea. Future studies should aim to identify the patient subgroups most likely to benefit, refine treatment regimens, and clarify the mechanisms underlying the clinical effects of carbocysteine.

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Conflicts of Interest

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