REVIEW ARTICLE

Erdosteine: Reigniting a Thiol Mucolytic for Management of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major health burden globally and in India. Oxidative stress plays a pivotal role in the pathogenesis of COPD, causing mucus hypersecretion, bronchoconstriction, and accelerated lung function decline. An important class of pharmacological agents that are often less discussed are the thiol mucolytic agents, which have a two-pronged effect of serving as both a mucolytic and an antioxidant. One of these agents which has reignited interest lately is erdosteine, with recent evidence demonstrating advantages over traditionally used N-acetylcysteine. In this review, we have summarized the key available evidence for the role of erdosteine in COPD, with takeaways on its place in therapy.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition distinguished by chronic respiratory symptoms (cough, sputum production, dyspnea, and/or exacerbations) due to airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) abnormalities, which lead to persistent, often progressive, airflow obstruction.[1] There are approximately 392 million COPD patients globally, with India and China alone accounting for >50% of the global burden.[2,3] Due to the disease impacting multiple facets of a patient's life, cornerstones of therapy include addressing the symptomatology, lung function, and quality of life (QoL), while also focusing on prevention and treatment of acute exacerbations of COPD (AECOPD).[1]

Oxidative Stress in Pathophysiology of Chronic Obstructive Pulmonary Disease

An important contributor to the pathogenesis of COPD is oxidative stress, which accelerates pulmonary aging and the decline in lung function.[4] Reactive oxygen species (ROS) also signal for pro-inflammatory cytokines and cause pulmonary tissue damage, which leads to bronchoconstriction and mucus hypersecretion.[5] Inspissated mucus in the larger airways causes increased sputum production and coughing, while in the peripheral airways, it causes airflow obstruction.[6] The net effect is a greater predisposition to disease exacerbation, accelerated decline in forced expiratory volume in 1 second (FEV_1), and decreased accessibility of inhaled medication in peripheral airways (Fig. 1).[4–6]

Drugs with a thiol moiety are frequently used in pulmonary medicine as mucolytics. However, their effects are also majorly due to their potent antioxidant effect.[7] Three thiol molecules have been extensively studied for COPD, namely, N-acetylcysteine (NAC), carbocysteine, and erdosteine, of which NAC and erdosteine are available in India.

Erdosteine—Pharmacological Perspectives

Erdosteine, a prodrug, is rapidly absorbed after oral administration and swiftly transformed through first-pass metabolism to its biologically active metabolite, N-thiodiglycolyl-homocysteine (M1).[8] The active metabolite, M1 (also known as MET1), acts *via* a two-pronged approach: as a mucolytic to enhance mucus clearance and as an antioxidant to reduce inflammation, thereby attenuating mucus production and protecting α1-antitrypsin activity (Fig. 2).[5,7–9] The net effect is an improvement in lung function and symptoms, with a reduction in the rate of COPD exacerbations (Fig. 2).[10] Other pleiotropic anti-inflammatory and antibacterial effects of erdosteine are mentioned in Table 1. The absorption of erdosteine is independent of food intake. Also, its pharmacokinetics are unaffected by age.[8]

Clinical Evidence with Erdosteine

Key Clinical Trials of Erdosteine

Fioretti and Bandera conducted a randomized, placebo-controlled, double-blinded trial in 132 patients with chronic bronchitis. Investigators studied the effect of erdosteine administration for 26 weeks (i.e., 6 months) in these patients. Findings revealed that erdosteine significantly reduced the rate and severity of exacerbations compared to placebo. Also, patients on erdosteine had fewer absent days at work compared to placebo.[5,12]

The ECOBES trial was a multicentric, double-blind, randomized trial involving 237 patients with an acute exacerbation of chronic bronchitis due to infective etiology. These patients were randomized to receive either erdosteine 300 mg twice daily or placebo for 10 days, in addition to amoxicillin 1500 mg/day. Patients who received erdosteine along with amoxicillin showed a more swift improvement in cough, sputum viscosity, and breathlessness compared to those receiving amoxicillin alone.[13]

Aubier and Berdah conducted a multicentric study in 170 patients with chronic bronchitis. Trial participants were randomized to receive either erdosteine 300 mg twice daily or placebo for a total duration of 3 weeks. Patients who received erdosteine had a significantly better global efficacy index (composite of cough frequency, cough severity, breathing difficulty, and dyspnea) compared to placebo. Furthermore, there was a significant reduction in the frequency and intensity of cough in patients who received erdosteine compared to placebo.[14]

The EQUALIFE study was a multicentric, randomized, double-blinded, parallel-group trial that studied the effect of long-term erdosteine treatment in moderate COPD patients. In this study, 155 patients with moderate COPD were randomized to

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receive either erdosteine 300 mg twice daily or placebo for a total duration of 8 months. Erdosteine-treated patients experienced a significantly reduced number of AECOPDs and days of hospitalization. Additionally, there was significant improvement in health-related quality of life (HRQoL) in patients who received 8-month erdosteine treatment.[15]

Crisafulli and colleagues conducted a single-center, prospective, open-labeled pilot study in elderly patients (age >55 years) with bronchiectasis to study the additive effect of oral erdosteine (given for 15 days) over physiotherapy. Compared to patients who received physiotherapy alone, those who received erdosteine in addition to physiotherapy had a significantly better improvement in FEV_1 (by 200 mL) and forced vital capacity (FVC) (by 300 mL). There was also a significant reduction in mucus volume produced and mucus purulence.[16]

Moretti and Fagani conducted a single-center, single-blinded, randomized controlled trial (RCT) in patients hospitalized with AECOPD to determine if erdosteine had any benefits in the post-discharge period. Along with standard treatment, 40 patients hospitalized for AECOPD were randomized to receive either erdosteine 900 mg/day or a matching control. Treatment was continued for 10 days up to discharge. Patients who received erdosteine had a significant reduction in CRP (from 3.7 mg/dL at baseline to 0.8 mg/dL) after 10 days. Notably, at day 10, there was a 33% greater reduction in CRP in patients who received erdosteine (0.8 mg/dL) compared to the control group (1.2 mg/dL). Erdosteine treatment was associated with a 39% lower risk of exacerbations, an 83% relative risk reduction in the 60-day exacerbation rate [hazard ratio (HR) = 0.169, 95% confidence interval (CI) = 0.033–0.875] ($p = 0.034$), and a significant delay in time to first exacerbation at 1 and 2 months postdischarge ($p = 0.009$ at day 30, $p = 0.075$ at day 60) compared to matched controls. Hence, this study showed that erdosteine, added to standard care in hospitalized AECOPD patients, significantly reduced airway inflammation, improved AECOPD symptoms, and prolonged the time to the first exacerbation.[17]

Recently, interest in erdosteine was rekindled with the landmark RESTORE study (2017). It showed that in GOLD stage II and III COPD patients, treatment with erdosteine for 1 year significantly reduced the rate of all exacerbations by 19.4% and the rate of mild exacerbations by 57% (Fig. 3). The duration of exacerbations also reduced by 24.6% [9.5 ± 7.2 days in patients treated with erdosteine vs 12.6 ± 9.7 days in the control group; ($p = 0.023$)]. Notably, the reduction in exacerbations was irrespective of whether patients received background inhaled corticosteroids (ICS) or not.[18] This finding was in stark contrast to the BRONCHUS study, where NAC showed benefits only in those patients who were not receiving ICS.[19] Furthermore, significantly fewer patients treated with erdosteine required reliever medications compared to the control (10.2 vs 33.7%) ($p < 0.001$).[18]

In a *post hoc* analysis of RESTORE participants with moderate COPD (GOLD 2 subgroup), similar benefits were noted in

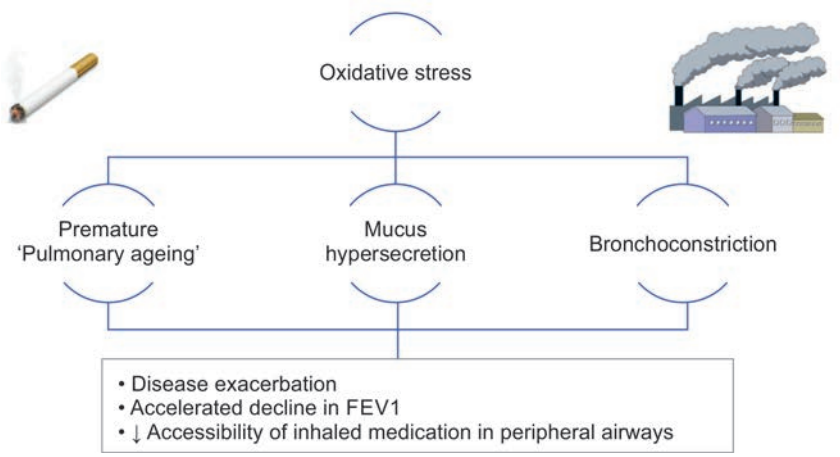


Fig. 1: Oxidative stress (which may arise due to risk factors like smoking or air pollution) can affect COPD pathogenesis at the cellular/genetic level. ROS cause telomere shortening, cellular senescence, DNA damage, mitochondrial dysfunction, decreased autophagy, stem cell exhaustion, decrease in anti-aging molecules, and auto-immune induction, resulting in premature pulmonary aging, mucus hypersecretion, and bronchoconstriction. The net effect is greater predisposition to disease exacerbation, accelerated decline in FEV_1, and decreased accessibility of inhaled medication in peripheral airways

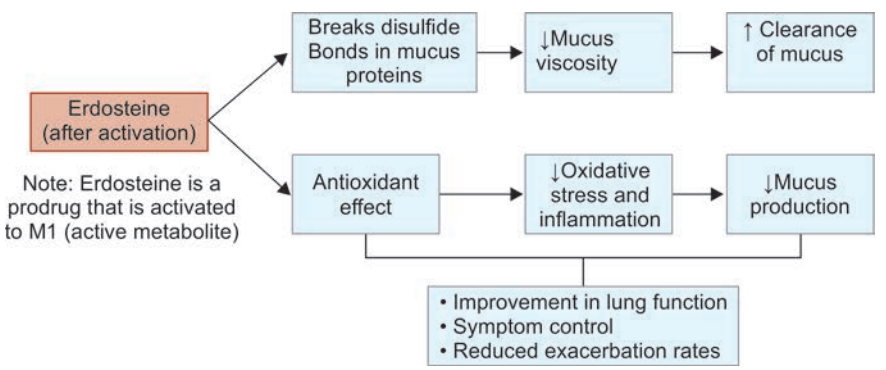


Fig. 2: Mechanism of action of erdosteine and resultant key clinical effects. Note that erdosteine is a prodrug that is converted to the active metabolite M1—which has a pharmacologically active—SH group. M1 exerts the pharmacological effects attributed to erdosteine, that is, mucolytic and antioxidant effects

Table 1: Other pleiotropic effects of erdosteine[5,11]

Anti-inflammatory activity	*Antibacterial activity*
↓ Cytokine release	↑ Antibiotic penetration
↓ Proteinase synthesis	↓ Biofilm formation
↓ Levels of pro-inflammatory proteins and activation of transcription factors	↓ Bacterial adhesion on epithelium

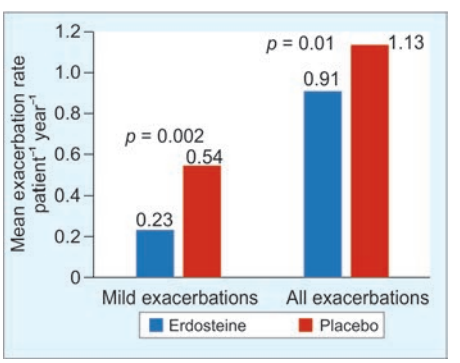


Fig. 3: In the RESTORE study, erdosteine reduced the rate of overall exacerbations by 19.4% and the rate of mild exacerbations by 57%[18]

the erdosteine arm, with a 47% reduction in the rate of exacerbations [0.27 vs 0.51 per-patient per-year (p = 0.003)] and a 26% shorter duration of exacerbations of COPD [9.1 vs 12.3 days, (p = 0.022)]. Patients who received erdosteine had a 58.3% reduction in the number (i.e., rate) of mild exacerbations [0.23 vs 0.53 per-patient per-year, (p = 0.001)] compared to the control group. Additionally, there was a significant prolongation of time to first exacerbation (p < 0.001) and an increase in mean exacerbation-free time by 51 days (p < 0.001) in the erdosteine group when compared to the control group. Of note, the beneficial effect of erdosteine on the rate of exacerbations was irrespective of baseline blood eosinophil counts.[20]

A second *post hoc* analysis on the entire RESTORE dataset revealed that in patients with moderate-to-severe AECOPD, erdosteine-treated patients (vs placebo) required a lesser mean duration of corticosteroid treatment (11.4 days in the erdosteine arm vs 13.3 days in the control arm). Also, 14.4% fewer patients required antibiotics + oral corticosteroids (p < 0.001) in the erdosteine arm as compared to the control. An improvement in QoL was also noted in the erdosteine arm, with greater improvement in SGRQ scores irrespective of the severity of exacerbation.[21]

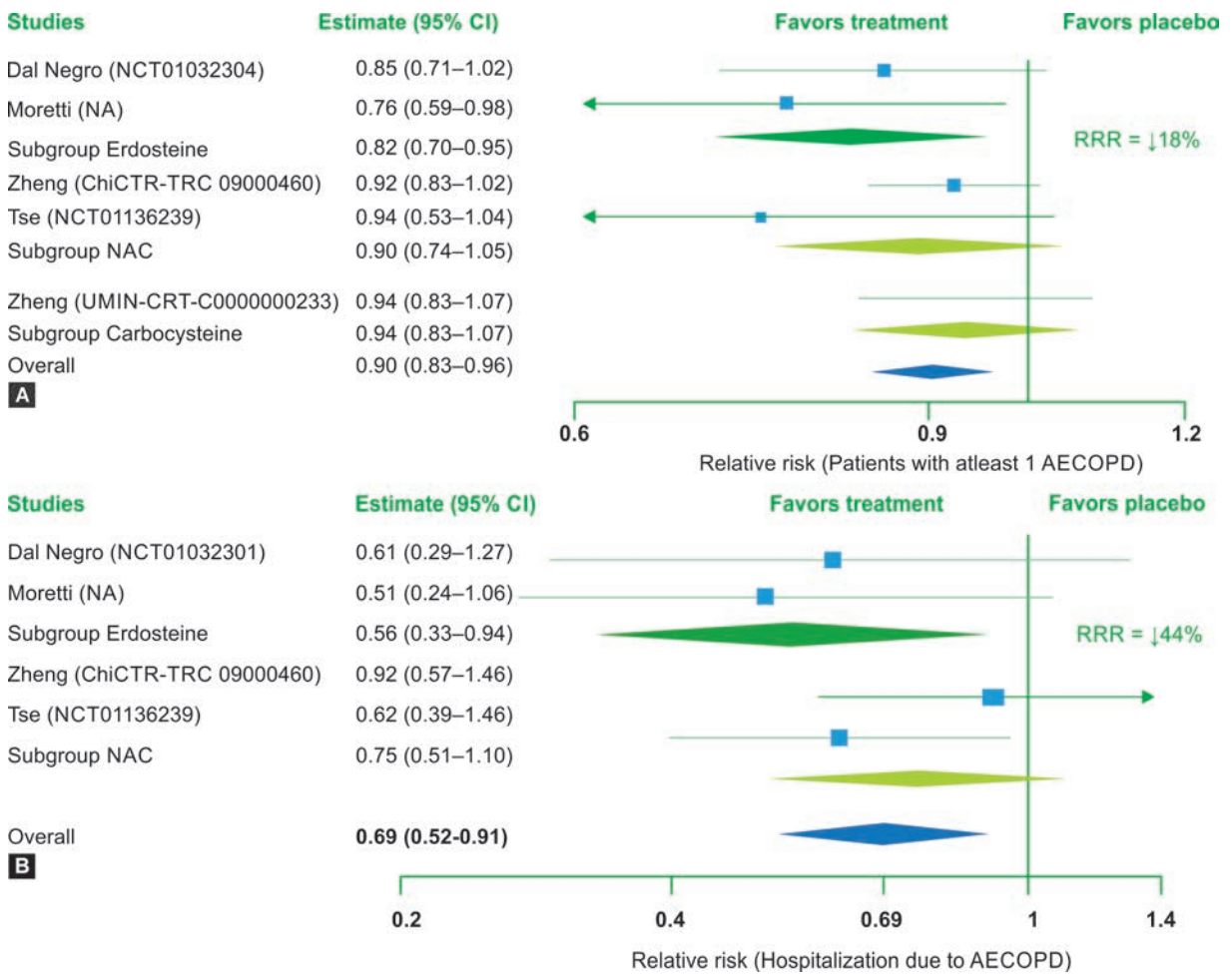
Summary and details of key clinical trials of erdosteine in COPD are summarized in Table 2.

Meta-analysis

A meta-analysis of 15 RCTs by Cazzola and Floriani showed that treatment with erdosteine resulted in significant symptom amelioration (sputum viscosity, cough intensity, catarrh ronchi, cough frequency) in patients with chronic bronchitis/COPD. Treatment with erdosteine was associated with double the chance of treatment success in comparison to placebo [odds ratio (OR) = 2.08, 95% CI = 1.09–3.96] or other mucolytics (OR = 2.19, 95% CI = 1.03–4.69).[22]

A 2018 meta-analysis of 10 studies, which included 1,278 patients with chronic bronchitis and COPD, established that erdosteine reduced the risk of exacerbations by 35% [relative risk (RR) = 0.65, 95% CI = 0.50–0.83] and even the risk of hospitalizations for COPD by 44% (RR = 0.56, 95% CI = 0.33–0.94). Erdosteine-treated patients also had a 29% lower risk of experiencing at least one exacerbation of COPD (RR = 0.71, 95% CI = 0.57–0.89). Patients treated with erdosteine had a lesser duration of AECOPD and a lengthened time period to first COPD exacerbation.[23]

A meta-analysis of seven RCTs was conducted by Rogliani and colleagues involving 2,753 COPD patients, comparing the efficacy of 3 thiol mucolytics—NAC, carbocysteine, and erdosteine. Only erdosteine, but not NAC, reduced the risk of experiencing at least one AECOPD by 18% (RR = 0.82, 95% CI = 0.70–0.95) and the risk of hospitalization for AECOPD by 44% (RR = 0.56, 95% CI = 0.33–0.94) (Fig. 4). The number needed to treat (NNT) for preventing one AECOPD was also the least for erdosteine (10.11) compared to NAC (15.69) and carbocysteine (30.92). The network meta-analysis revealed that among the three mucolytics studied, erdosteine



Figs 4A and B: Comparative meta-analysis of mucolytics in COPD showed that only erdosteine, but not NAC, reduced the risk of experiencing at least one acute exacerbation of COPD (p < 0.01) (RRR = 18%) (A). Also, only erdosteine, but not NAC, reduced the risk of hospitalization due to acute exacerbation of COPD (p < 0.05) (RRR = 44%) (B) (Adapted from Rogliani et al.)[24]

Table 2: Summary of key clinical trials[5,12–21]

Authors + trial name	*Trial design*	*Study duration*	*No. (n)*	*Disease condition*	*Results/takeaways*
Fioretti and Bandera (1991)[12]	Double blind, randomized	26 weeks	132	Chronic bronchitis	Erdosteine showed better reduction (vs placebo) • ↓ Rate of exacerbations • ↓ Severity of exacerbations • ↓ Number of days of work-absenteeism
Marchioni et al. ECOBES (1995)[13]	Multicenter, double-blind, randomized	10 days	237	Acute exacerbation of chronic obstructive bronchitis	Erdosteine with amoxicillin vs amoxicillin alone—faster improvement in: • Breathlessness • Cough • Sputum viscosity
Aubier and Berdah (1999)[14]	Multicenter, double-blind, randomized, parallel group	3 weeks	170	Stable chronic obstructive bronchitis with hypersecretion	Erdosteine better outcomes than placebo (statistically significant) for: • ↑ Global efficacy index (cough frequency + cough severity + breathing difficulty + dyspnea) • ↓ Cough intensity • ↓ Cough frequency
Moretti et al. EQUALIFE (2004)[15]	Multicenter, double-blind, randomized, parallel group	32 weeks	124	Stable moderate COPD	Erdosteine vs placebo showed significant • ↓ Number of AECOPDs • ↓ Hospitalization days due to AECOPD • ↑ In HRQoL • ↓ COPD-related disease cost per patient
Crisafulli et al. (2007)[16]	Single-center, prospective, parallel, open label, pilot study	15 days	30	Elderly patients (age >55 years) with bronchiectasis and chronic mucus hypersecretion	Erdosteine added to physiotherapy had significant ($p < 0.05$) improvement (vs only physiotherapy) on: • ↑ FEV_1 (200 mL) • ↑ FVC (300 mL) • ↓ Mucus volume produced • ↓ Mucus purulence At day 15, significant improvements were observed in 6MWT, VAS cough, and VAS dyspnea ($p < 0.01$) in both groups
Moretti and Fagnani (2015)[17]	Single center, prospective, randomized, controlled, single-blind study	Treatment for 10 days Duration of study—60 days	40	Patients hospitalized for AECOPD	At day 10, mean serum CRP significantly reduced by: • 78% compared to baseline in the erdosteine group (from 3.7 mg/dL to 0.8 mg/dL) • 33% greater reduction vs control group (0.8 vs 1.2 mg/dL) Improvements in symptom score and FEV1 were greater in erdosteine group vs control group Compared to control arm, erdosteine was associated with: • 39% lower risk of exacerbations • 83% risk reduction in 60-day exacerbation rate (HR = 0.169, 95% CI = 0.033–0.875) ($p = 0.034$) • Significant delay in time to first exacerbation (logrank test $p = 0.009$ and 0.075 at days 30 and 60 respectively)
Dal Negro et al. RESTORE (2017)[18]	Multicenter, double-blind, randomized, parallel group	52 weeks	445	Stable COPD (GOLD stage II and III)	Erdosteine vs placebo[18] • ↓ Rate of all AECOPD by 19.4% [0.91 vs 1.13 per-patient per-year ($p = 0.01$)] • ↓ Rate of mild AECOPD by 57.1% [0.23 vs 0.54 per-patient per-year ($p = 0.002$)] • ↓ Duration of AECOPDs by 24.6% [9.5 ± 7.2 days with erdosteine vs 12.6 ± 9.7 days with placebo; ($p = 0.023$)] • ↓Reliever medication use—erdosteine (10.2% patients) vs placebo (33.7% patients) ($p < 0.001$) • Improvement in subject and physician severity scores ($p = 0.022$ and $p = 0.048$, respectively) Of note: • Reduction in exacerbations was irrespective of background ICS use (contrast to NAC studies where similar benefits are only observed in patients not receiving ICS)[19]

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Authors + trial name	*Trial design*	*Study duration*	*No. (n)*	*Disease condition*	*Results/takeaways*
Calverly et al. *Post hoc* analysis of RESTORE (2019)[20]	Multicenter, double-blind, randomized, parallel group	52 weeks	254	Stable COPD (*post hoc* analysis of GOLD 2 subgroup, that is, spirometrically moderate COPD	Erdosteine vs placebo • ↓ 47% lesser rate of exacerbations (mean) [0.27 vs 0.51 exacerbations per-patient per-year ($p = 0.003$)] • ↓ 58.3% lesser rate of mild exacerbations [0.23 vs 0.53 per-patient per-year ($p = 0.001$)] • ↓ 26% shorter mean duration of exacerbations [9.1 vs 12.3 days ($p = 0.022$)]. • ↑ Time to first exacerbation by 7.7% [182 days for erdosteine vs 169 days for placebo ($p < 0.001$)] • ↑ Mean exacerbation-free time was increased by 51 days ($p < 0.001$) Of note: • Beneficial effect of erdosteine was maintained irrespective of baseline blood eosiniphil count
Calverly et al. *Post hoc* analysis of RESTORE (2022)[21]	Multicenter, double-blind, randomized, parallel group	52 weeks	445	Stable COPD (GOLD stage II and III)	In patients with moderate-to-severe AECOPD, erdosteine-treated (vs placebo) had: • ↓ Mean duration of corticosteroid treatment (11.4 days vs 13.3 days) ($p = 0.043$) • ↓ 14.4% lesser patients required antibiotics + OCS ($p < 0.001$) GOLD 2 patients who exacerbated (erdosteine vs placebo) • ↑ SGRQ total scores regardless of exacerbation severity

Table 3: Summary of meta-analyses studies[22–24]

Authors (year)	*Disease*	*Number of studies (n = patients)*	*Key results*
Cazzola, Floriani and Page (2010)[22]	Chronic bronchitis or COPD	15 RCTs ($n = 1046$)	• ↓ Cough frequency • ↓ Cough intensity • ↓ Sputum viscosity • ↓ Difficulty to expectorate • ↓ Catarrh ronchi at auscultation • More than double odds of treatment success vs other mucolytics (OR = 2.19, 95% CI = 1.03–4.69) • More than double odds of treatment success vs placebo (OR = 2.08, 95% CI = 1.09–3.96)
Cazzola et al. (2018)[23]	Chronic bronchitis and COPD	10 studies ($n = 1278$)	• ↓ 35% reduced risk of exacerbations (RR=0.65, 95% CI = 0.50–0.83) • ↓ 29% reduced risk of experiencing at least one exacerbation (RR = 0.71, 95% CI = 0.57–0.89) • ↑ Time to first exacerbation • ↓ Duration of AECOPD • ↓ 44% reduced risk of hospitalization for COPD (RR = 0.56, 95% CI = 0.33– 0.94)

Rogliani et al. (2019)[24]	COPD	7 RCTs ($n = 2753$)	• Rank of Effectiveness (by SUCRA): Erdosteine > carbocysteine > NAC, that is, efficacy of erdosteine was rated the highest
			• Only erdosteine, but not NAC reduced
			  • ↓ 44% reduced risk of hospitalization due to AECOPD (RR = 0.56, 95% CI = 0.33–0.94) ($p < 0.05$)
			  • ↓ 18% reduced risk of experiencing at least 1 exacerbation of COPD (RR = 0.82, 95% CI = 0.70–0.95) ($p < 0.01$)
			• NNT to prevent 1 AECOPD was 10.11 for erdosteine, 15.69 for N-acetyl cysteine and 30.92 for carbocysteine.

had the highest efficacy (Fig. 5).[24] Summary and details of key meta-analysis studies with erdosteine in COPD are summarized in Table 3.

Consensus and Guideline Recommendations

A 2020 European Delphi Consensus on mucolytics in COPD consistently rated the use of erdosteine the highest. The panel also recommended that approved doses of mucolytic agents could be recommended for regular use in COPD patients with a bronchitic phenotype.[25] As per GOLD 2024 Guidelines, regular treatment with mucolytics such as erdosteine, carbocysteine, and NAC reduces the risk of exacerbations in select populations (level B). Based on RESTORE study evidence, GOLD 2024 Guidelines also mention that erdosteine may have a significant effect on exacerbations irrespective of concurrent treatment with ICS (in contrast to NAC, which showed no benefits in patients who received ICS).[1,19]

Place in Therapy

Erdosteine may find its place in the management of COPD, particularly in patients with chronic bronchitis and mucus hypersecretion. Its dual action as a mucolytic and antioxidant addresses two critical aspects of COPD pathophysiology—mucus

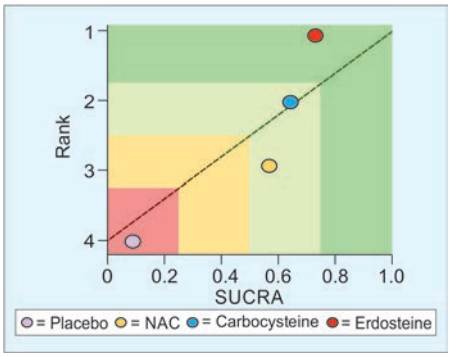

Fig. 5: Ranking plot resulting from the network meta-analysis in which treatments were plotted on the X-axis according to SUCRA (score of 1 being the most effective) and on the Y-axis according to the rank of being the best treatment (score of 1 being the most effective). Hence, erdosteine was the most effective drug, followed by carbocysteine and NAC (adapted from Rogliani et al.)[24]

clearance and oxidative stress reduction. Clinical studies have demonstrated its effectiveness in reducing the frequency and severity of AECOPD, improving lung function, and enhancing patients' quality of life.[12–24] Additionally, erdosteine has shown benefits irrespective of concurrent inhaled corticosteroid use, positioning it as a valuable therapeutic option as an add-on therapy in the long-term management of COPD, especially in the mucus-secreting phenotype.

Future Directions

The BETTER Trial (Trial Reg. No. ACTRN12621000315819) will investigate the effect of erdosteine in children and adults with bronchiectasis between the ages of 2 and 49 years. The study will inform us whether regular treatment with erdosteine is able to reduce the number of exacerbations and improve QoL in patients with bronchiectasis.[26]

Conclusion

There is a significant patient burden of COPD globally and within India. Though the mainstay pharmacotherapeutic agents in COPD are essential, thiol-mucolytics deserve special attention not only due to their mucolytic properties, but also their strong antioxidant effect. Erdosteine has a potent antioxidant effect which is beneficial in COPD management, both for short-term use as a mucolytic and in the long term for the prevention of AECOPD. Meta-analysis evidence has shown clear benefits over NAC and hence may be considered the thiol-mucolytic agent of choice for COPD patients in clinical practice.

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