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Comparative efficacy of doxophylline-ambroxol combination versus aminophylline in the management of acute exacerbations of COPD: A retrospective case-control study

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Abstract: **Background**: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) manifests as sudden respiratory symptom aggravation and airflow decline, substantially elevating mortality risk, making therapeutic optimization crucial for patient outcomes. **Objectives**: To compare the clinical efficacy and safety of the combination therapy of Doxophylline ambroxol and Aminophylline monotherapy in the treatment of AECOPD. **Methods**: This retrospective study included 120 AECOPD patients admitted from April 2022 to April 2024. Patients were divided into two groups: the control group received aminophylline, while the study group received doxophylline and ambroxol for 10 days. Clinical efficacy, pulmonary function (FEV1, FVC, FEV1%, FEV1/FVC), inflammatory markers (CRP, PCT, WBC, NEUT%), blood gas parameters (PaO_2, $PaCO_2$), CAT and CCQ scores and adverse events were compared pre- and post-treatment. **Results**: Post-treatment, both groups showed significant improvements in FEV_1, FVC, FEV_1% and FEV_1/FVC compared to baseline (P<0.05), with the study group demonstrating superior outcomes (P<0.05). Inflammatory markers (CRP, PCT, WBC, NEUT%) decreased significantly in both groups, with greater reductions in the study group (P<0.05). Blood gas parameters (PaO_2, $PaCO_2$) improved in both groups (P<0.05), with more pronounced improvements in the study group (P<0.05). CAT and CCQ scores declined in both groups, but more substantially in the study group (P<0.05). No significant difference in adverse events was observed (P>0.05). **Conclusion**: Doxophylline-ambroxol combination therapy is more effective than aminophylline in improving pulmonary function and reducing inflammation in AECOPD, with equivalent safety.

Keywords: Ambroxol; Aminophylline; Acute exacerbation period; Chronic obstructive pulmonary disease; Clinical efficacy; Doxophylline

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a complex respiratory condition characterized by persistent and often worsening obstruction of airflow, resulting from pathological changes in either the bronchial airways (manifesting as chronic bronchitis) or the alveolar structures (leading to emphysema). This condition leads to persistent respiratory symptoms, including dyspnea, chronic cough, excessive mucus production and episodic worsening of the disease (Venkatesan, 2024). Globally, COPD ranks among the leading causes of morbidity and mortality, with an estimated 10.3% prevalence in individuals aged 30–79 years (Adeloye *et al.*, 2022). The clinical progression of COPD typically involves alternating periods of stability and acute exacerbations (AECOPD), which are characterized by a sudden worsening of respiratory symptoms (e.g., aggravated cough, increased sputum volume, purulent sputum and heightened breathlessness)(Baqdunes *et al.*, 2021). These episodes necessitate therapeutic intervention and are critical determinants of disease advancement. AECOPD significantly impairs patients' quality of life, escalates healthcare costs and raises mortality risk. Studies indicate that moderate-to-severe COPD patients suffer 1-3 annual exacerbations, with hospitalized cases facing a three-year mortality rate reaching 50% (Bertoletti *et al.*, 2023). Thus, developing more effective therapies is essential to enhance patient outcomes, reduce socioeconomic burdens and alleviate familial strain (Hosseinzadeh and Shnaigat, 2019).

The pathogenesis of COPD primarily involves oxidative stress, inflammatory airway responses, protease-antiprotease dysregulation and programmed cell death (Zhang *et al.*, 2023; Rosyid *et al.*, 2023). Current pharmacological management strategies consist of three key approaches: bronchodilators, anti-inflammatory agents and antimicrobial therapy.Bronchodilators, including β_2-

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agonists (e.g., salbutamol) and anticholinergics (e.g., ipratropium bromide), serve as first-line therapy by relaxing bronchial smooth muscles to alleviate airflow obstruction. During acute exacerbations, short-acting nebulized formulations are preferred for rapid symptom relief (El Hussein and Favell, 2023). Corticosteroids, administered systemically (orally or intravenously), help suppress airway and systemic inflammation, accelerating recovery and improving lung function and oxygenation. A 5-7 day regimen is typically recommended, though clinicians must carefully weigh benefits against potential adverse effects (e.g., hyperglycemia and infection risk), particularly in high-risk populations (Killeen and Wolfson, 2020; Georgiou *et al.*, 2024). Inhaled corticosteroids (ICS) may serve as an alternative in select patients, though their efficacy is often limited in severe airflow obstruction due to poor drug deposition. Antibiotics are indicated when bacterial infection is suspected (e.g., purulent sputum and worsening dyspnea), as they can expedite recovery and lower early relapse rates (Killeen and Wolfson, 2020). Despite these established therapies, clinical challenges persist. Some patients exhibit suboptimal responses to β_2-agonists, particularly during severe exacerbations (Yusuf *et al.*, 2022). Systemic glucocorticoids pose risks for diabetic, osteoporotic, or frail elderly patients, limiting their applicability. Furthermore, current treatments fail to address mucus hypersecretion-a critical pathological feature that exacerbates airway blockage and fosters bacterial growth, prolonging recoverye (Li *et al.*, 2024; Li *et al.*, 2020). Thus, novel therapies targeting bronchoconstriction, impaired mucociliary clearance and neutrophilic inflammation are urgently needed.

The therapeutic potential of theophyllines in COPD has regained attention. As classic bronchodilators, they exert effects via nonselective phosphodiesterase (PDE) inhibition, increasing intracellular cAMP and promoting bronchial smooth muscle relaxation. Beyond bronchodilation, theophyllines exhibit immunomodulation (inhibiting T-cell activation and cytokine release), enhanced diaphragmatic contractility and improved mucociliary clearance (Ivana and Clive, 2023; Nourian *et al.*, 2023). However, conventional aminophylline (theophylline-ethylenediamine complex), despite decades of use, has a narrow therapeutic window (effective serum concentration: 10-20 μg/mL), marked interindividual variability and frequent adverse effects (e.g., arrhythmias, seizures and even fatalities), limiting its utility. Doxophylline, a newer methylxanthine derivative, retains therapeutic benefits while offering improved safety through structural optimization. Key pharmacologic advantages include: Preferential PDE IV/V inhibition minimizes cardiovascular (PDE III) and CNS (PDE I/II) effects (Ivana and Clive, 2023; Giuzio *et al.*, 2023; Bhat *et al.*, 2020; Kazmi *et al.*, 2022). In vitro, doxophylline is 10-15 times more effective than aminophylline (Rogliani *et al.*, 2019). It suppresses neutrophil chemotaxis, ROS production and proinflammatory cytokines (e.g., TNF-α, IL-8), correlating with better outcomes in AECOPD (Chen *et al.*, 2022). Unlike aminophylline, it lacks adenosine receptor antagonism, reducing CNS/cardiovascular side effects and gastrointestinal intolerance (P<0.05) (Elgazar *et al.*, 2023). Clinical evidence supports these benefits. A randomized trial in AECOPD patients showed higher efficacy and fewer adverse events (arrhythmias, nausea/vomiting) with doxophylline (Cazzola *et al.*, 2024). A meta-analysis of 20 trials (n=820) confirmed significant FEV_1 improvement and superior safety. Evidence from eight systematic reviews demonstrated dosed theophylline's significant clinical advantages for COPD versus theophylline-ammonium (Cazzola *et al.*, 2018).

While doxophylline demonstrates notable bronchodilatory and anti-inflammatory properties, monotherapy remains insufficient to address the multifactorial pathology of AECOPD, particularly mucus hypersecretion and impaired clearance. This limitation has spurred interest in combining doxophylline with mucoactive agents, with ambroxol emerging as a promising candidate due to its pleiotropic effects (Ponugoti *et al.*, 2024). Ambroxol, a bromhexine metabolite, transcends its conventional classification as an expectorant. It modulates mucus dynamics by suppressing mucin (MUC5AC) production in glandular cells while enhancing chloride channel activity in ciliated epithelium, thereby improving mucociliary clearance (Kumar *et al.*, 2025; odriguez-Piñeiro *et al.*, 2023; Song *et al.*, 2022). Beyond its secretolytic action, ambroxol exhibits potent antioxidant activity by scavenging reactive oxygen and nitrogen species, mitigating oxidative damage in airways (Ahmadi *et al.*, 2024). Its anti-inflammatory properties include inhibition of pro-inflammatory cytokines (e.g., IL-1β, IL-8, TNF-α) and attenuation of neutrophil infiltration (Zhu *et al.*, 2023; Deng *et al.*, 2024). Additionally, ambroxol disrupts bacterial biofilms, augmenting antibiotic penetration into lung tissue (Wang *et al.*, 2020) and stimulates pulmonary surfactant production, optimizing alveolar stability (Li *et al.*, 2021). Clinical evidence indicates that ambroxol not only acts as an expectorant but also possesses anti-inflammatory properties, showing positive effects in preventing or treating acute exacerbations when used as an adjunctive therapy for COPD, particularly evidenced in in vitro and animal model studies for asthma treatment (Plomer and de Zeeuw, 2017). These findings suggest that the complementary mechanisms of both agents-doxophylline's bronchodilation and ambroxol's mucoregulatory and anti-inflammatory effects-may collectively enhance outcomes in AECOPD.

Based on the above background, This retrospective case-control study evaluates the efficacy and safety of doxophylline-ambroxol combination therapy versus aminophylline monotherapy in AECOPD. We hypothesize that the combination therapy of doxophylline and ambroxol outperforms monotherapy with aminophylline in enhancing pulmonary function (FEV_1, FVC, FEV_1%,

FEV_1/FVC), attenuating systemic inflammation (CRP, PCT, WBC, NEUT%), normalizing blood gases (PaO_2, $PaCO_2$) and improving quality of life (CAT, CCQ scores), without elevating adverse event risks. By analyzing these outcomes pre- and post-treatment, the synergistic effect and clinical efficacy of the combination therapy of doxophylline and ambroxol in AECOPD patients were clarified, improving quality of life, shortening hospitalization time and reducing readmission rates. This provides high-quality evidence-based evidence for the application of doxophylline ambroxol combination therapy in AECOPD management, promoting the acute exacerbation of COPD. The development of individualized and precise treatment strategies can reduce medical burden and ultimately improve patient prognosis and quality of life.

MATERIALS AND METHODS

Study design

This study adopted a retrospective controlled research design, selecting AECOPD patients admitted to the Respiratory Department of our hospital from April 2022 to April 2024 as the research subjects. A total of 162 patient data were extracted through an electronic medical record system, of which 42 patients were ultimately not included in the trial (25 patients did not meet the inclusion requirements, 4 refused to participate, 6 lost to follow-up and 7 for other reasons). A total of 120 patients completed the trial and were divided into study and control groups according to the treatment method, with 60 patients in each group. The design operation process is shown in fig. 1.

Ethical statement

The principles of the declaration of helsinki (DH) were strictly followed and all research procedures were in accordance with international ethical standards. All participants provided written informed consent; in emergency situations, their legal representatives or guardians were permitted to provide consent on their behalf. All data involved in the study were anonymized to ensure the privacy and confidentiality of the participants.

Inclusion and exclusion criteria

Inclusion criteria: Complies with AECOPD diagnostic criteria; 50-85 years old, with complete diagnosis and treatment records and follow-up data; There are typical symptoms such as worsening breathing difficulties, increased sputum volume and purulent sputum and the basic treatment plan needs to be adjusted; The severity of airflow restriction is GOLD level 2-4 ($30\% \leq FEV_1\%$, expected value<80%); Patients who require hospitalization but do not require immediate mechanical ventilation (CURB-65 score≤2); Capable of autonomous behavior and effective communication.

Exclusion criteria: Concurrent respiratory conditions, including bronchial asthma, bronchiectasis, active tuberculosis and lung cancer; Severe organ dysfunction (such as liver enzymes (ALT/AST)>3 times the upper limit of normal, creatinine clearance rate<30 mL/min, acute coronary syndrome or decompensated heart failure); Individuals allergic to theophylline, ambroxol, or antibiotics involved in research; Pregnant or lactating women, long-term users of immunosuppressants; Incomplete recording of key indicators such as lung function and inflammatory markers.

Intervention measures

Control group: Aminophylline injection (Henan Runhong Pharmaceutical Co., Ltd., national drug approval number H2023718, specification: 2 mL: 0.5 g): 0.25 g mixed with 100 mL of 5% glucose, intravenous drip (>30 minutes), once daily.

Study group

Doxophylline Injection (Heilongjiang Fuhe Pharmaceutical Group Co., Ltd., National Medical Products Administration Approval No. H20083758, specification: 20 mL: 0.3 g): Administer 0.3 g diluted in 100 mL of 0.9% NaCl solution via intravenous infusion (>30 minutes), once daily; Ambroxol injection (Shanxi Guorun Pharmaceutical Co., Ltd., national drug approval number H20203150, 2 mL: 15 mg): Dissolved in 5 mL of 0.9% sodium chloride injection for nebulized inhalation therapy, 15 minutes/time, 2 times/day.

The two treatment courses are uniformly 10 days. All drugs are controlled by infusion pumps and electrocardiograms are monitored during the infusion of theophylline drugs. In addition, all patients received routine treatment with AECOPD, Following the management protocol recommended by GOLD (2022) for COPD diagnosis, treatment and prevention (Christenson *et al.*, 2022), as follows: 1. Oxygen inhalation: low flow continuous oxygen administration, with oxygen delivery rate controlled at 1-2 L/min; 2. Anti-infection: Conventional treatment should be given to combat infection and specific medication should be selected based on changes in the patient's condition, clinical sputum culture and drug sensitivity test results, combined with actual conditions; 3. Bronchodilator therapy: Based on the severity of the patient's condition at the time of enrollment, a comprehensive evaluation is conducted and the recommended treatment strategy is implemented according to the guidelines. Usage method: nebulization inhalation: conventional nebulization drug combination, such as 3 mL of 0.9% saline injection+2.5ml of compound ipratropium bromide suspension+budesonide inhalation, frequency of use: twice a day; 4. Expectorants: selected according to the condition, including intravenous administration, oral expectorants, nebulization and other methods. Intravenous drip drugs often include ambroxol hydrochloride injection, while oral drugs include acetylcysteine effervescent tablets, ambroxol hydrochloride tablets, etc; 5. Anti inflammation: The application of glucocorticoids includes nebulized inhalation (budesonide) and intravenous infusion (methylprednisolone sodium succinate for injection).

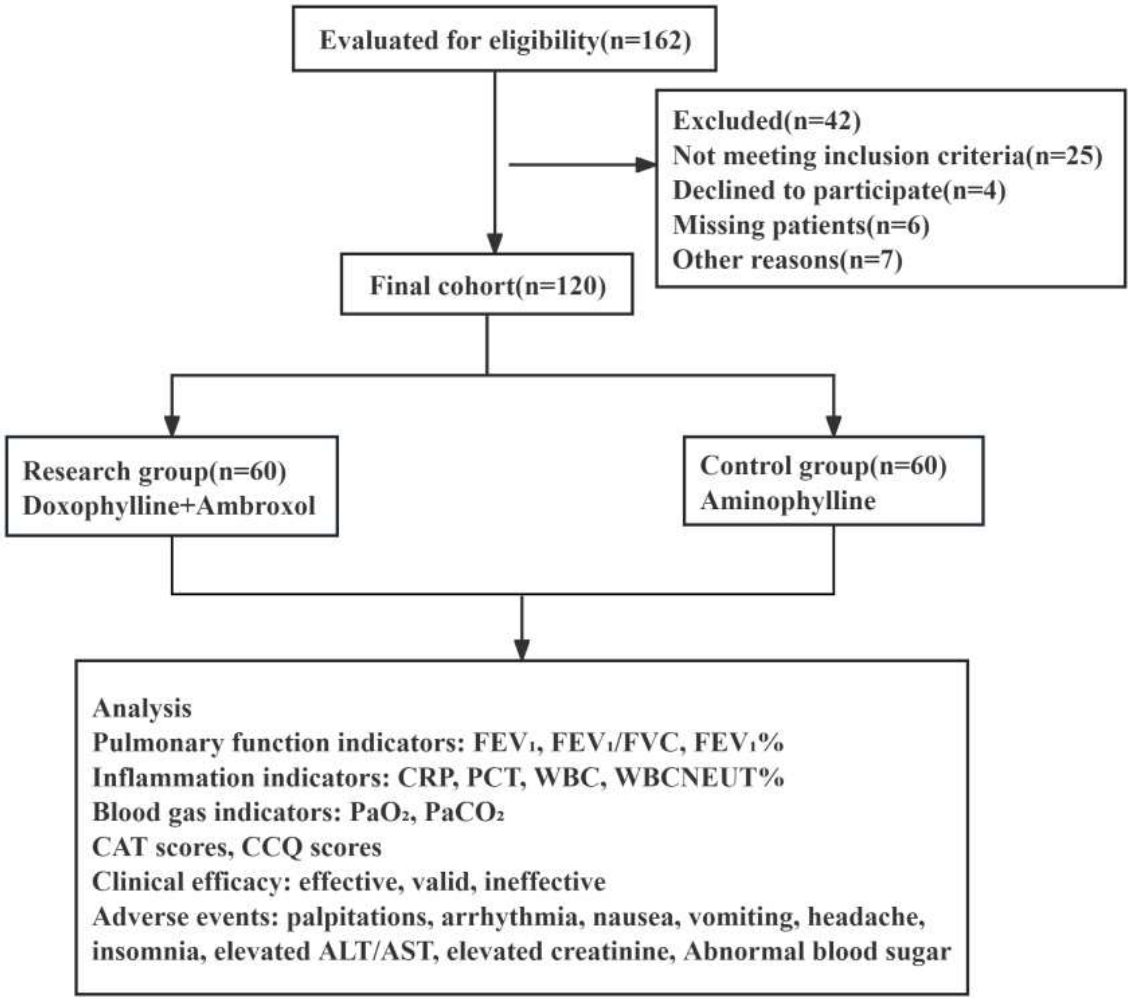

Fig. 1: Flow chart of the study

If nebulized inhalation of steroids cannot achieve therapeutic goals, timely intravenous infusion should be used to control the condition; 6. Symptomatic treatment: correct electrolyte imbalance, maintain acid-base balance, etc.

Evaluation indicators

(1) Collect baseline data of patients before treatment, including demographic characteristics, medical history, comorbidities and lifestyle habits, lung function indicators, inflammation indicators, arterial blood gas indicators, quality of life scores and severity of acute exacerbations.

(2) Referring to the "Chinese Expert Consensus on the Diagnosis and Treatment of Acute Exacerbation of COPD" (Cai *et al.*, 2014), a three-level evaluation standard was developed to compare the clinical efficacy of two groups of patients. Among them, significant effects: cough, phlegm and wheezing symptoms have basically disappeared, lung rales have disappeared and the CAT score has decreased by≥50%; Effective: Symptoms partially relieved, lung rales reduced, CAT score decreased by≥30%; Invalid: Symptoms and signs have not improved or worsened. Total effective rate=(number of significantly effective cases+number of effective cases)/total cases×100%.

(3) The lung function indicators were measured using a pulmonary function tester (Anhui Institute of Electronic Science, Anhui Medical Equipment Injection Standard 20192070007, model: PFT-B) and the first second forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC and FEV_1% of the estimated value were analyzed and compared between the two groups before and after treatment.

(4) Collect 2 mL of arterial blood from two groups of patients (both after 30 minutes without or without oxygen inhalation) and use a blood gas electrolyte analyzer (Shenzhen Kangli Biomedical Co., Ltd., Guangdong Medical Equipment Injection Standard 20172401147, model: BG-800A) to detect and compare the arterial oxygen partial pressure (PaO_2) and arterial carbon dioxide partial pressure ($PaCO_2$) before and after treatment between the two groups.

(5) Immunoturbidimetry (using the immunoturbidimetric assay kit from Jiangxi Yingda Biotechnology Co., Ltd., sensitivity: when the concentration of CRP in the sample is 5 mg/L, its absorbance value should be≥0.0500) was used

to detect C-reactive protein (CRP), enzyme-linked immunosorbent assay (using the enzyme-linked immunosorbent assay kit from Shanghai Future Industry Co., Ltd., sensitivity: 0.025 ng/mL) was used to detect serum procalcitonin (PCT) and a fully automated blood analyzer (produced by Shenzhen Mindray Co., Ltd., model: BC-6800Plus) was used to detect white blood cell count (WBC) and neutrophil percentage (NEUT%). Analyze and compare the improvement of inflammatory indicators between two groups of patients before and after treatment.

(6) Comparing the CAT scores of two groups of patients before and after treatment using the COPD Assessment Test (Jones *et al.*, 2009), covering 8 items such as cough, sputum, chest tightness and activity endurance, with each item scoring 0-5 points and a total score of 0-40 points. The higher the score, the heavier the symptom burden.

(7) The Clinical COPD Questionnaire (CCQ) (van der Molen *et al.*, 2003), was employed to assess and compare pretreatment and posttreatment scores between groups across three domains: symptom severity (4 items), functional capacity (4 items) and psychological impact (2 items), each assigned a score of 0-6. The total score=the sum of all item scores÷the number of questions, with 0-1 indicating low symptom burden and>1 indicating high symptom burden.

(8) Adverse reactions: In this study, adverse events and laboratory abnormalities were closely monitored and recorded throughout the treatment period, following a predefined monitoring protocol. The criteria for severity were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which classifies adverse events into five grades (1 to 5), ranging from mild to fatal. Record all adverse events during treatment, including cardiovascular events (palpitations, arrhythmias), gastrointestinal reactions (nausea, vomiting), neurological symptoms (headaches, insomnia) and allergic reactions; Laboratory abnormal events, including liver enzymes (ALT/AST>3×ULN), renal function (creatinine elevation>50% baseline) and abnormal blood glucose (random blood glucose>11.1 mmol/L) testing, are evaluated to assess drug safety.

Sample size calculation

We used G-power software for sample size estimation. During the estimation process, we selected an effect size of 0.5, set the significance level (α) to 0.05 (two tailed test) and set the statistical power (1-β) to 0.8.The power calculation determined a required sample of 54 participants per group, yielding a total study population of 108. The actual number of recruited experimental participants was 120, exceeding the planned sample size, thus meeting the statistical requirements of the research design.

Statistical analysis

Data analysis was performed using SPSS version 25.0, while study flow diagrams were created with Lucidchart. The Shapiro-Wilk test assessed data normality and variance homogeneity was evaluated using Levene's test. Normally distributed continuous variables are presented as $\bar{x}\pm s$. Between-group differences were analyzed with independent samples *t*-tests, while within-group comparisons employed paired *t*-tests and Cohen's d is used for effect size with a 95% confidence interval. Count data is expressed as frequency (percentage) [n, (%)] and chi square test or Fisher's exact test (expected frequency<5) is used for inter group comparison; The results for the patient's FEV_1, FVC, FEV_1/FVC, FEV_1%, PaO_2, $PaCO_2$, CRP, PCT, WBC, NEUT%, CAT score, CCQ score, etc. are all expressed as $\bar{x}\pm s$.; The incidence of adverse reactions was compared using the *chi square* test and all statistical tests were two-sided tests. $P<0.05$ indicates statistical significance.

RESULTS

Comparison of baseline information

The trial enrolled 120 AECOPD patients, allocated equally between experimental and control arms (n=60 per group) according to therapeutic intervention. The comparison results of baseline characteristics showed that the two groups of patients were all in demographic characteristics (age, gender, BMI), medical history characteristics (COPD course, annual acute exacerbations), complications and living habits (hypertension, diabetes, smoking history, drinking history), lung function indicators (FEV_1, FVC, FEV_1%, FEV_1/FVC), inflammatory indicators (CRP, PCT, WBC, NEUT%), blood gas analysis (PaO_2, $PaCO_2$), quality of life scores (CAT scores, CCQ scores) and acute exacerbation severity grading and other baseline indicators. No statistically significant difference was observed (all $P>0.05$), demonstrating comparable baseline characteristics between the treatment groups prior to intervention. See table 1.

Comparison of clinical efficacy between two groups

Post-intervention assessment revealed significantly better outcomes in the research group (95% efficacy; 38 markedly improved, 19 improved, 3 ineffective) compared to controls (78.3% efficacy; 22 markedly improved, 25 improved, 13 ineffective), with statistically significant between-group differences ($P=0.003$). Therefore, the combination therapy of doxophylline and ambroxol can achieve comprehensive optimization of clinical efficacy, enabling more AECOPD patients to achieve significant therapeutic effects while significantly reducing the proportion of ineffective treatments and has important clinical application value. See table 2.

Analysis of lung function indicators

Prior to therapy, the groups were well-matched in terms of airflow limitation severity (all spirometric indices $P>0.05$). Post-treatment analysis demonstrated superior gains in the experimental arm, with statistically significant between-group differences emerging in all measured parameters (all $P<0.05$).

Table 1: Comparison of baseline characteristics between two groups of patients [$\bar{x}\pm s$, (n, %)]

Indicators	Study group (n=60)	Control group (n=60)	statistic(χ^2/t)	*P-value*
Demographic Characteristics				
Age (years)	65.8 ± 8.2	66.3 ± 7.9	t=-0.338	0.736
Male (n, %)	38 (63.3%)	35 (58.3%)	χ^2=0.330	0.565
BMI (kg/m²)	22.1 ± 3.0	21.8 ± 2.8	t=0.562	0.575
Medical History Characteristics				
COPD duration (years)	9.2 ± 3.5	8.9 ± 3.8	t=0.447	0.656
Number of acute exacerbations per year (times)	2.5 ± 0.9	2.6 ± 1.0	t=0.596	0.574
Comorbidities & Habits				
Hypertension (n, %)	25 (41.7%)	28 (46.7%)	χ^2=0.31	0.579
Diabetes (n, %)	14 (23.3%)	11 (18.3%)	χ^2=0.48	0.488
Smoking history (n, %)	42 (70.0%)	40 (66.7%)	χ^2=0.16	0.692
Alcohol History (n, %)	18 (30.0%)	15 (25.0%)	χ^2=0.38	0.538
Lung Function				
FEV_1(L)	0.98 ± 0.22	1.02 ± 0.25	t=-0.919	0.360
FVC(L)	2.02±0.45	2.08±0.47	t=-0.710	0.479
FEV_1(%)	30.06 ± 6.75	31.29 ± 7.67	t=-0.930	0.354
Inflammatory Indicators				
CRP(mg/L)	32.5 ± 9.8	34.1 ± 10.2	t=-0.868	0.387
PCT(μg/L)	0.38 ± 0.12	0.41 ± 0.15	t=-1.167	0.245
WBC($\times10^9$/L)	11.2 ± 2.6	11.8 ± 2.9	t=-1.183	0.239
NEUT%	78.5 ± 6.3	79.2 ± 7.1	t=-0.566	0.573
Blood Gas Analysis				
PaO_2(mmHg)	58.3 ± 7.5	56.9 ± 8.2	t=0.967	0.335
$PaCO_2$(mmHg)	49.6 ± 6.8	50.3 ± 7.1	t=-0.547	0.585
Quality of Life Score				
CAT scores (points)	26.4 ± 4.2	25.8 ± 4.6	t=0.740	0.461
CCQ scores (points)	4.1 ± 0.9	4.0 ± 1.0	t=0.572	0.569
Acute Exacerbation Severity (n, %)			χ^2=0.82	0.664
Grade I (mild)	12 (20.0%)	15 (25.0%)		
Grade II (moderate)	35 (58.3%)	32 (53.3%)		
Grade III (severe)	13 (21.7%)	13 (21.7%)		

Table 2: Comparison of clinical efficacy between two groups ($\bar{x} \pm s$)

Groups	n	Markedly efficacy	Efficacy	Inefficacy	Overall effective rate	χ^2	*P-value*
Study group	60	38 (63.3%)	19 (31.7%)	3 (5.0%)	57 (95.0%)	8.72	0.003
Control group	60	22 (36.7%)	25 (41.7%)	13 (21.6%)	47 (78.3%)		

This treatment advantage was particularly evident in FEV_1 measurements (research group: 1.31±0.26 L; control group: 1.18±0.27 L, P=0.012), indicating that the treatment plan of the research group can more effectively improve patients' airway obstruction; The FVC of the research group increased significantly to 2.52±0.46 L compared to the control group's 2.37±0.52 L (P=0.037), indicating that the research group has a greater advantage in improving total lung ventilation; The research group achieved a post-treatment FEV_1/FVC ratio of 50.8±2.7%, surpassing the clinically significant 50% threshold (P=0.007 vs control). This transition from severe to moderate airflow obstruction suggests a substantially reduced risk of daily respiratory compromise. Furthermore, while FEV_1% values approached moderate COPD thresholds in the study group, the control group maintained severe classification, demonstrating superior comprehensive pulmonary enhancement in the intervention cohort. The results indicate that the combination therapy of doxophylline and ambroxol can more effectively alleviate airway obstruction and improve ventilation function. See table 3.

Comparison of inflammatory indicators

Initial inflammatory status was well-balanced between groups, as evidenced by statistically equivalent baseline values for all measured biomarkers (all P>0.05). While anti-inflammatory effects were observed in both arms post-intervention, the magnitude of reduction proved significantly more pronounced in the study group (all P<0.001).

Table 3: Comparison of lung function indicators before and after treatment between two groups ($\bar{x} \pm s$)

Parameters	Visit	Mean ± SD		Statistics	Mean difference	95% CI		Effect size	*P-value*
	n=60/ group	Study group	Control group			Lower	Upper		n=60/gruop
FEV_1(L)	Before treatment	0.98 ± 0.22	1.02 ± 0.25	-0.919	-0.04	-0.13	0.05	FEV_1(L)	Before treatment
	After treatment	1.31 ± 0.26*	1.18 ± 0.27*	2.544	0.130	0.03	0.23		After treatment
FVC(L)	Before treatment	2.02 ± 0.45	2.08 ± 0.47	-0.710	-0.06	-0.25	0.13	FVC(L)	Before treatment
	After treatment	2.52 ± 0.46*	2.37 ± 0.52*	2.107	0.15	0.01	0.29		After treatment
FEV_1/ FVC(%)	Before treatment	48.5 ± 1.8	48.8 ± 2.7	-0.832	-0.300	-1.13	0.53	FEV_1/ FVC(%)	Before treatment
	After treatment	50.8 ± 2.7*	49.7 ± 1.5*	2.746	1.100	0.31	1.89		After treatment
FEV_1%	Before treatment	30.06 ± 6.75	31.29 ± 7.67	-0.930	-1.230	-3.84	1.38	FEV_1%	Before treatment
	After treatment	40.18 ± 7.98*	36.20 ± 8.28*	2.690	3.980	1.05	6.91		After treatment

Note: * *P*<0.05: statistically different from before treatment within the group

Table 4: Comparison of inflammatory indicators before and after treatment between two groups ($\bar{x} \pm s$)

Parameters	Visit	Mean ± SD		Statistics	Mean difference	95% CI		Effect size	*P-value*
	n=60/gruop	Study group	Control group			Lower	Upper		
CRP(mg/L)	Before treatment	32.5 ± 9.8	34.1 ± 10.2	-0.868	1.6	-2.4	5.6	0.15	0.387
	After treatment	10.8 ± 3.5*	20.5 ± 6.2*	-10.464	10.25	9.3	11.2	1.93	<0.001
PCT(μg/L)	Before treatment	0.38 ± 0.12	0.41 ± 0.15	-1.167	0.03	-0.02	0.08	0.22	0.245
	After treatment	0.07 ± 0.03*	0.18 ± 0.07*	-11.123	11.07	9.5	12.64	2.04	<0.001
WBC($\times 10^9$/L)	Before treatment	11.2 ± 2.6	11.8 ± 2.9	-1.183	0.6	-0.4	1.6	0.22	0.239
	After treatment	7.3 ± 1.4*	9.8 ± 2.1*	-7.607	7.43	6.8	8.06	1.4	<0.001
NEUT%	Before treatment	78.5 ± 6.3	79.2 ± 7.1	-0.566	0.7	-1.73	3.13	0.1	0.573
	After treatment	65.2 ± 5.8*	72.6 ± 6.5*	-6.525	6.52	5.2	7.84	1.2	<0.001

Note: * *P*<0.05: statistically different from before treatment within the group

The differential response was most clinically apparent in CRP reduction, where research participants attained mean levels of 10.8±3.5 mg/L versus 20.5±6.2 mg/L in conventional treatment recipients, indicating that the study group has a greater advantage in reducing systemic inflammatory response; The PCT of the research group decreased to 0.07±0.03 μg/L, while the control group only decreased to 0.18±0.07 μg/L, indicating that the research group had a more significant effect in controlling infection related inflammation; The research group demonstrated significantly lower leukocyte counts post-treatment (7.3±1.4 $\times 10^9$/L) compared to control subjects (9.8±2.1 $\times 10^9$/L; *P*<0.001), indicating that the study group can more effectively reduce inflammation related leukocytosis; The research group achieved significantly lower NEUT% (65.2±5.8%) compared to controls (*P*<0.001), demonstrating superior modulation of innate immune responses. The combination therapy of doxophylline and ambroxol has a more comprehensive and significant anti-inflammatory effect, which may improve the prognosis of AECOPD patients and reduce inflammation mediated lung tissue damage through more effective anti-inflammatory mechanisms. See table 4.

Table 5: Comparison of blood gas indicators before and after treatment between two groups ($\bar{x}\pm s$)

Parameters	Visit	Mean ± SD		Statistics	Mean difference	95% CI		Effect size	*P-value*
	n=60/group	Study group	Control group			Lower	Upper		
PaO_2 (mmHg)	Before treatment	58.3 ± 7.5	56.9 ± 8.2	0.967	1.4	-1.44	4.24	0.18	0.335
	After treatment	73.6 ± 6.8*	65.4 ± 7.3*	6.314	6.82	4.27	9.37	0.97	<0.001
$PaCO_2$ (mmHg)	Before treatment	49.6 ± 6.8	50.3 ± 7.1	-0.547	-0.7	-3.21	1.81	-0.1	0.585
	After treatment	41.2 ± 5.1*	46.7 ± 6.1*	-5.323	-5.43	-7.44	-3.42	-0.98	<0.001

Note: * P<0.05: statistically different from before treatment within the group

Table 6: Comparison of CAT scores before and after treatment between two groups ($\bar{x}\pm s$, points)

Parameters	Visit	Mean ± SD		Statistics	Mean difference	95% CI		Effect size	*P-value*
	n=60/group	Study group	Control group			Lower	Upper		
CAT scores	Before treatment	26.4 ± 4.2	25.8 ± 4.6	0.740	0.6	-0.98	2.18	0.14	0.461
	After treatment	18.1 ± 3.8*	21.7 ± 4.1*	-4.946	-3.6	-4.95	-2.25	-0.96	<0.001

Note: * P<0.05: statistically different from before treatment within the group

Table 7: Comparison of CCQ scores before and after treatment between two groups ($\bar{x} \pm s$, points)

Parameters	Visit	Mean±SD		Statistics	Mean difference	95% CI		Effect size	*P-value*
	n=60/gruop	Study group	Control group			lower	upper		
Symptom scores	Before treatment	4.2 ± 0.8	4.1 ± 0.9	0.637	0.1	-0.23	0.43	0.12	0.526
	After treatment	1.8 ± 0.5*	2.9 ± 0.7*	-9.829	-1.1	-1.32	-0.88	-1.81	<0.001
Functional status scores	Before treatment	4.3 ± 0.9	4.0 ± 1.0	1.712	0.3	-0.28	0.88	0.32	0.089
	After treatment	2.0 ± 0.6*	3.1 ± 0.8*	-8.442	-1.1	-1.36	-0.84	-1.56	<0.001
Mental state scores	Before treatment	3.8 ± 1.0	3.9 ± 1.1	-0.520	-0.1	-0.5	0.3	-0.1	0.604
	After treatment	1.5 ± 0.4*	2.7 ± 0.7*	-11.438	-1.2	-1.41	-0.99	-2.11	<0.001

Note: *P<0.05: statistically different from before treatment within the group

Blood gas index analysis

Pretreatment arterial blood gas analysis revealed comparable impairment in gas exchange between groups, with no significant differences in PaO_2 and $PaCO_2$ (both P>0.05). Post-intervention, while both cohorts demonstrated improvement, the research group exhibited superior enhancement in oxygenation parameters (all P<0.001). Notably, the experimental arm achieved mean PaO_2 levels of 73.6±6.8 mmHg versus 65.4±7.3 mmHg in controls, reflecting clinically meaningful improvement in oxygen uptake, indicating that the research group can more effectively improve patients' oxygenation status and reduce the risk of hypoxemia; The $PaCO_2$ of the research group decreased significantly to 41.2±5.1 mmHg, which was significantly lower than the 46.7±6.0 mmHg of the control group, indicating that the research group has more advantages in promoting CO_2 excretion and correcting hypercapnia.

Table 8: Comparison of Incidence of Adverse Reactions between two groups (n,%)

Groups	Adverse event			Laboratory anomalies		
	Cardiovascular events (palpitations, arrhythmia)	Gastrointestinal reactions (nausea, vomiting)	Neurological symptoms (headache, insomnia)	Elevated ALT/AST	Abnormal blood sugar levels	Elevated blood creatinine (Cr)
Study group(n=60)	2 (3.3%)	8 (13.3%)	2 (3.3%)	1 (1.7%)	0 (0%)	0 (0%)
Control group(n=60)	6 (10.0%)	6 (10.0%)	7 (11.7%)	2 (3.3%)	1 (1.7%)	1 (1.7%)
χ^2	2.857	0.37	3.273	0.343	1.017	1.017
P-value	0.091	0.543	0.070	0.558	0.313	0.313

Therefore, it indicates that the treatment plan of the research group can simultaneously optimize oxygenation and ventilation, reducing the risk of respiratory failure. See table 5.

CAT score comparison

Baseline CAT scores showed no intergroup difference (P=0.461), confirming equivalent initial symptom severity. Post-intervention, while both groups demonstrated significant reductions (P<0.001), the study group achieved superior symptom control (mean reduction: 8.3 points) compared to controls (4.1-point decrease), with statistically significant between-group differences. This greater magnitude of improvement reflects the intervention's enhanced capacity to alleviate AECOPD symptoms and improve quality of life. See table 6.

Comparison of CCQ ratings

Initial scores across symptomatic, functional and psychological domains showed no intergroup differences (all P>0.05), confirming comparable pretreatment status. Post-therapy analysis revealed significantly greater multidimensional improvement in the study group (all P<0.001), with symptom scores decreasing to 1.8±0.5 compared to 2.9±0.7 in controls, demonstrating the intervention's holistic therapeutic advantage, indicating that the treatment plan of the research group has more advantages in relieving core symptoms such as cough, sputum production and difficulty breathing; The functional status score of the research group improved to 2.0±0.6, a decrease of 53.5% compared to the control group (3.1±0.8), indicating that the research group can more effectively improve patients' daily activity ability and reduce the impact of diseases on their lives; The mental state score of the study group decreased to 1.5±0.4, significantly better than the control group's 2.7±0.7, indicating that the study group had a more significant effect in alleviating psychological symptoms such as anxiety and depression. Therefore, the study group's combined treatment plan can better achieve the improvement of patients' overall quality of life. See table 7.

Security evaluation analysis

In total, there were 12 adverse events and 1 laboratory abnormality in the research group, while the control group experienced 19 adverse events and 4 laboratory abnormalities. The specific adverse events and their severity grading are detailed in table 8. The research group showed a better safety trend in cardiovascular events and neurological symptoms. The incidence of gastrointestinal reactions and laboratory abnormalities was similar between the two groups. Notably, no instances of hyperglycemia or renal dysfunction were detected in the experimental arm, contrasting with single cases observed for each parameter in controls. These laboratory abnormalities showed no statistically significant between-group difference in occurrence rates (all P>0.05), indicating that combination therapy has no synergistic toxicity and good safety. In addition, all recorded adverse events were graded for severity according to the CTCAE v5.0 criteria and all were found to be Grade 1 (mild). No adverse events of higher grades were observed. This indicates that in this study, both treatment regimens demonstrated high safety profiles and did not trigger severe drug-related adverse reactions.

DISCUSSION

Acute worsening of COPD most commonly manifests as a rapid decline in pulmonary function and symptom burden, including increased difficulty breathing, worsening cough, increased sputum and/or purulent sputum, which require changes in the patient's medication regimen and additional treatment measures. Utilizing a retrospective case-control methodology, this investigation comprehensively assessed the therapeutic benefits and safety profile of doxophylline-ambroxol combination therapy versus conventional aminophylline monotherapy in AECOPD management. Analysis revealed superior clinical improvement across multiple outcome measures in the combination therapy cohort compared to monotherapy such as lung function indicators (FEV_1, FVC, FEV_1/FVC, FEV_1%), inflammatory markers (CRP, PCT, WBC), blood gas parameters (PaO_2, $PaCO_2$) and quality of life scores (CAT, CCQ) than the monotherapy group (P<0.05) and did not increase the incidence of adverse reactions. These findings provide new evidence-based medicine for the treatment of AECOPD.

FEV_1, FVC, FEV_1/FVC and FEV_1% are common lung function indicators that reflect a patient's lung ventilation function. The lower the level of these indicators, the more severe the patient's condition. In this study, Statistical comparisons revealed the doxophylline regimen produced significantly larger increases across all measured spirometric parameters versus conventional aminophylline therapy (all $P<0.05$), with between-group differences most pronounced in FEV_1% predicted. These findings substantiate doxophylline's enhanced capacity to restore lung function in elderly AECOPD populations. This result is consistent with previous studies emphasizing the stronger bronchodilator effect of doxycycline. The meta-analysis by Zhang(Zhang, 2023) showed that doxophylline improved FEV_1 in AECOPD patients by 0.15-0.25 L compared to aminophylline, attributed to its higher phosphodiesterase (PDE) selectivity and fewer adenosine receptor-mediated side effects. The expectorant and anti-inflammatory properties of ambroxol may further promote the improvement of lung function. The RCT conducted by William *et al*.(Poncin *et al.*, 2025) established that ambroxol administration enhanced pulmonary function recovery (FEV_1) in acute exacerbations via its secretolytic and bronchodilatory properties. The current findings provide additional evidence for a therapeutic synergy between doxophylline's bronchodilatory effects and ambroxol's mucoregulatory action in AECOPD management, which may be the reason for the more significant improvement in lung function in the combination therapy group.

In the acute exacerbation stage of COPD, the activation of neutrophils promotes the release of enzymes such as elastase and peroxidase, which not only participate in the pathological and physiological processes of airway inflammation and emphysema, but also stimulate the transition and secretion of mucin proteins, leading to increased airway obstruction (Beeh *et al.*, 2024). In this study, the CRP level in the research group decreased by 66.8% and PCT decreased by 81.6%, significantly better than the control group's 39.9% and 56.1%. This result is highly consistent with research published in 2025, which suggests that key genes involved in oxidative stress play a central role in the progression of COPD inflammation and effective anti-inflammatory treatment can reduce CRP by 60%-70% (Wang *et al.*, 2025). More noteworthy is that in this study, PCT was reduced to 0.07±0.03 μg/L, reaching the "exclusion of bacterial infection" threshold (<0.1 μg/L), which is consistent with the clinical standards recommended by the "Sepsis Guidelines" and provides laboratory evidence for reducing antibiotic abuse (Schuetz, 2023). Doxophylline exerts anti-inflammatory effects by inhibiting pro-inflammatory cytokines and neutrophil infiltration. Ambroxol further enhances this effect by inhibiting neutrophil elastase and reducing oxidative stress. These two substances are key drivers of neutrophil inflammation in COPD. The synergistic suppression of inflammatory cascades by this dual-agent regimen not only explains our clinical findings but also establishes a pathophysiological basis for combination therapy in AECOPD.

The results of blood gas analysis directly reflect the patient's respiratory function status. The CAT score and CCQ score are widely used in clinical practice to assess the severity of COPD patients and evaluate their treatment outcomes. Arterial blood gas analysis revealed the combination therapy group achieved a mean PaO_2 of 73.6±6.8 mmHg post-treatment, breaking the 70 mmHg tissue hypoxia warning line, which can alleviate complications related to hypoxemia (such as pulmonary hypertension). $PaCO_2$ decreased to 41.2±5.1 mmHg and both indicators were significantly better than the control group. 81.7% of patients' $PaCO_2$ decreased to≤45 mmHg, below the correction point for hypercapnia, indicating effective CO_2 clearance and reduced risk of respiratory acidosis. Meet the "dual blood and gas standards" standard of the AECOPD Respiratory Support Expert Consensus (2024)(Zhou *et al.*, 2024). It has significant clinical implications. Clinical practice has shown that Doxophylline has more advantages than Aminophylline in relieving airway spasms and improving respiratory symptoms in patients and has high safety, which has been recognized by clinical practice and patients(Zhang *et al.*, 2022). Wang *et al*.(Wang *et al.*, 2025) found that the combination therapy with ambroxol resulted in an increase in PaO_2 levels and a decrease in $PaCO_2$, which improved the respiratory status of patients, consistent with the results of this study. In addition, the CAT score of the research group decreased by 8.3 points and 80% of patients fell to a low symptom burden state (<20 points). The CCQ symptom score improved to 1doxophylline.8 points, reflecting a basic relief of dyspnea and cough. These results are supported by previous research. Vashishth *et al*. (Vashishth *et al.*, 2024) found that compared to aminophylline, patients treated with had reduced nighttime awakenings and improved exercise tolerance. Kardos et al.(Kardos *et al.*, 2018) showed that ambroxol can reduce cough frequency and further promote symptom relief. This study confirmed the improvement of psychological status through CCQ psychiatric score in combination therapy, which is crucial for long-term management of COPD. While our study demonstrates significant improvements in CAT and CCQ scores, indicating better symptom control and quality of life in the short term, we acknowledge that these instruments are designed for chronic assessment. The 10-day treatment period is insufficient to draw definitive conclusions about long-term improvements. Future studies with longer follow-up periods are necessary to fully evaluate the sustained benefits of the doxophylline-ambroxol combination therapy on quality of life in patients with AECOPD.

Safety is an important dimension in evaluating treatment plans. While the overall adverse event rates did not differ

significantly between groups (all $P>0.05$), the experimental regimen demonstrated a more favorable trend in cardiovascular stability and neurological tolerability. This safety feature is particularly important for COPD patients who require long-term treatment. It is worth noting that the study group did not observe any cases of abnormal blood glucose and renal function, while the control group had one case each. Based on the efficacy data, the research group demonstrated a better benefit risk ratio, which provides important evidence for its clinical application. Zhou and Hu (Zhou and Hu, 2021) investigated the efficacy and adverse drug reactions of ambroxol in the treatment of elderly COPD complicated with pulmonary infection and found that drug combination did not increase adverse reactions, demonstrating high safety. The study by Jiang *et al*.(Jiang *et al.*, 2021) also supports that the combination therapy of Doxophylline and other drugs has good safety and does not increase adverse reactions in patients with AECOPD. These findings align with existing evidence, demonstrating that theophylline-ambroxol combination therapy maintains a favorable safety profile without elevating medication-associated risks.

CONCLUSION

In summary, this study confirms that the treatment plan of the research group has significant clinical advantages in AECOPD patients. The research results provide clinical doctors with a more effective, safe and reliable treatment option, which has important practical value in improving the short-term prognosis and enhancing the quality of life of AECOPD patients. Notwithstanding the positive therapeutic effects observed, certain constraints of this research should be noted: firstly, the follow-up time is relatively short, making it impossible to evaluate long-term efficacy and safety; Secondly, the limited sample size may affect the detection of rare adverse reactions; Thirdly, without conducting subgroup analysis, it is impossible to evaluate the differences in therapeutic efficacy among patients with different characteristics. Future research can extend follow-up time to evaluate long-term efficacy; Expand sample size to verify security; Conduct subgroup analysis to identify advantageous populations and explore individualized treatment plans.

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Author's contribution
Chendong Ma, Qunchao Zhu: Edited and refined the manuscript with a focus on critical intellectual contributions.
Gangwei Zhou, Si Wan: Developed and planned the study, performed experiments and interpreted results.
Gangwei Zhou, Jiaru Jiang: Participated in collecting, assessing and interpreting the date.
Fei Shen, Sicong Jiang: Made significant contributions to date interpretation and manuscript preparation.
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Data availability statement
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical approval
This study was approved by the Ethics Committee of The First People's Hospital of Jiashan (Approval No.2025-083).

Conflict of interest
The authors declare that they have no financial conflicts of interest.

REFERENCES

Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A and Rudan I (2022). Global, Regional and National Prevalence of and Risk Factors for, Chronic Obstructive Pulmonary Disease (COPD) in 2019: A systematic review and modelling analysis. *Lancet Respir Med*. **10**(5): 447-58.

Ahmadi E, Afrooghe A, Soltani ZE, Elahi M, Shayan M, Ohadi MAD and Dehpour AR (2024). Beyond the lungs: Exploring diverse applications of bromhexine and ambroxol. *Life Sciences*. **353**: 122909.

Baqdunes MW, Leap J, Young M, Kaura A and Cheema T (2021). Acute exacerbation of chronic obstructive pulmonary disease. *Crit Care Nurs Q*., **44**(1): 74-90.

Beeh KM, Scheithe K, Schmutzler H and Kruger S (2024). Real-world effectiveness of fluticasone furoate/ umeclidinium/vilanterol once-daily single-inhaler triple therapy for symptomatic COPD: The ELLITHE non-interventional trial. *Int J Chron Obstruct Pulmon Dis*., **19**: 205-16.

Bertoletti L, Couturaud F, Sanchez O and Jimenez D (2023). Pulmonary embolism and chronic obstructive pulmonary disease. *Semin Thromb Hemost*. **49**(8): 809-15.

Bhat A, Ray B, Mahalakshmi AM, Tuladhar S, Nandakumar DN, Srinivasan M, Essa MM, Chidambaram SB, Guillemin GJ and Sakharkar MK (2020). Phosphodiesterase-4 enzyme as a therapeutic target in neurological disorders. *Pharmacol. Res*., **160**: 105078.

Cai BQ, Cai SX, Chen RC, Cui LY, Feng YL, Gu YT, Huang SG, Liu RY, Liu GN, Shi HZ, Shi Y, Song YL, Sun TY, Wang CZ, Wang JL, Wen FQ, Xiao W, Xu YJ, Yan XX, Yao WZ, Yu Q, Zhang J, Zheng JP, Liu J and Bai CX (2014). Expert consensus on acute exacerbation of chronic obstructive pulmonary disease in the People's

Republic of China. *Int J Chron Obstruct Pulmon Dis*. **9**: 381-95.

Cazzola M, Calzetta L, Barnes PJ, Criner GJ, Martinez FJ, Papi A and Gabriella MM (2018). Efficacy and safety profile of xanthines in COPD: A network meta-analysis. *Eur Respir Rev*. **27**(148): 180010.

Cazzola M, Page CP, Calzetta L, Rogliani P and Matera MG (2024). Doxofylline: Advancing and empowering equitable asthma and COPD management beyond tradition. *Advanced Therapeutics*. **8**: 7.

Chen ZY, Lin YM, Wu JH, Zhang XQ, Zhang Y, Xie WX, Chu SQ and Li Y (2022). Effect of doxofylline on pulmonary inflammatory response and oxidative stress during mechanical ventilation in rats with COPD. *BMC Pulm Med*. **22**(1): 66.

Christenson SA, Smith BM, Bafadhel M and Putcha N (2022). Chronic obstructive pulmonary disease. *Lancet*. **399**(10342): 2227-42.

Deng H, Zhu S, Yu F, Song X, Jin X and Ding X (2024). Analysis of predictive value of cellular inflammatory factors and T cell subsets for disease recurrence and prognosis in patients with acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*., **19**: 2361-69.

El Hussein MT and Favell D (2023). A mnemonic for managing acute exacerbations of chronic obstructive pulmonary disease. *Jaapa*. **36**(8): 11-14.

Elgazar AA, El-Domany RA, Eldehna WM and Badria FA (2023). Theophylline-based hybrids as acetyl cholinesterase inhibitors endowed with anti-inflammatory activity: Synthesis, bio evaluation, in silico and preliminary kinetic studies. *RSC Adv*. **13**(36): 25616-34.

Georgiou A, Ramesh R, Schofield P, White P and Harries TH (2024). Withdrawal of inhaled corticosteroids from patients with COPD; Effect on exacerbation frequency and lung function: A Systematic Review. *Int J Chron Obstruct Pulmon Dis*. **19**: 1403-19.

Giuzio F, Bonomo MG, Catalano A, Infantino V, Salzano G, Monné M, Geronikaki A, Petrou A, Aquaro S, Sinicropi MS and Saturnino C (2023). Potential Pde4b inhibitors as promising candidates against sars-cov-2 infection. *Biomol Concepts*. **14**(1): doi: 10.1515/bmc-2022-0033.

Hosseinzadeh H and Shnaigat M (2019). Effectiveness of chronic obstructive pulmonary disease self-management interventions in primary care settings: A systematic review. *Aust J Prim Health*. **25**: PY18181.

Ivana Stolfa and Clive Page (2023). Phosphodiesterase inhibitors and lung diseases. *Advances in Pharmacology*, pp.55-81.

Jiang T, Zhan M and Wei W (2021). Effects of budesonide combined with doxofylline on procalcitonin and brain natriuretic peptide in acute phase of Copd. *J. Xinjiang Med. Univ.,* **44**(5): 591-94.

Jones PW, Harding G, Berry P, Wiklund I, Chen WH and Kline Leidy N (2009). Development and First Validation of the COPD Assessment test. *Eur Respir J*. **34**(3): 648-54.

Kardos P, Beeh KM, Sent U, Mueck T, Grater H and Michel MC (2018). Characterization of differential patient profiles and therapeutic responses of pharmacy customers for four ambroxol formulations. *BMC Pharmacol Toxicol*., **19**(1): 40.

Kazmi I, Al-Abbasi FA, Afzal M, Nadeem MS, Altayb HN, and Gupta G (2022). Phosphodiesterase-4 inhibitor roflumilast-mediated protective effect in sepsis-induced late-phase event of acute kidney injury: A narrative review. *Pharmaceuticals (Basel)*. **15**(7): 899.

Killeen BM and Wolfson AB (2020). Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary diseases. *Acad Emerg Med*. **27**(11): 1201-02.

Kumar S, Corkran M, Cheema Y, Scull MA and Duncan GA (2025). Aav-Mediated muc5ac sirna delivery to prevent mucociliary dysfunction in asthma. *Gene Ther*. **32**(5): 508-16.

Li H, Song S and Kong Z (2021). Regulatory effects of andrographolide on lung tissue inflammation and Th17/Treg in rats with chronic obstructive pulmonary disease induced by smoking and lipopolysaccharide. *J. Biomater. Tissue Eng.,* **11**(3): 513-19.

Li J, Ma J, Tian Y, Zhao P, Liu X, Dong H, Zheng W, Feng S, Zhang L, Wu M, Zhu L, Liu S and Zhao D (2020). Effective-component compatibility of bufei yishen formula II inhibits mucus hypersecretion of chronic obstructive pulmonary disease rats by regulating Egfr/Pi3k/Mtor signaling. *J Ethnopharmacol*., **257**: 112796.

Li K, Song Z, Yue Q, Wang Q, Li Y, Zhu Y and Chen H (2024). Disease-specific transcriptional programs govern airway goblet cell metaplasia. *Heliyon*. **10**(13): e34105.

Nourian YH, Salimian J, Ahmadi A, Salehi Z, Karimi M, Emamvirdizadeh A, Azimzadeh Jamalkandi S and Ghanei M (2023). Camp-Pde Signaling in COPD: Review of cellular, molecular and clinical features. *Biochem Biophys Rep*., **34**: 101438.

Odriguez-Piñeiro AM, Jaudas F, Klymiuk N, Bähr A, Hansson GC and Ermund A (2023). Proteome of Airway Surface Liquid and Mucus in Newborn Wildtype and Cystic Fibrosis Piglets. *Respir Res*., **24**(1): 83.

Plomer M and De Zeeuw J (2017). More than expectorant: New scientific data on ambroxol in the context of the treatment of bronchopulmonary diseases. *MMW Fortschr Med*. **159**(Suppl 5): 22-33.

Poncin W, Schrøder C, Oliveira A, Herrero-Cortina B, Cnockaert P, Gely L, Osadnik C, Reychler G, Mechlenburg I and Spinou A (2025). Airway clearance techniques for people with acute exacerbation of COPD: a scoping review. *Eur. Respir. Rev.,* **34**(175): 240191.

Ponugoti SS, Shah H, Chopada A, Thakur VP, Bagwe PV, Oak M, Kulkarni R, Chavarkar G, Charwekar Y and

Joshi SV (2024). Ambroxol hydrochloride: A comprehensive review on industrial-scale synthesis, pharmacological aspects & Amp; Therapeutic Applications. *Chemistry Select*, **9**(40): e202401887.

Rogliani P, Calzetta L, Ora J, Cazzola M and Matera MG (2019). Efficacy and safety profile of doxofylline compared to theophylline in asthma: A meta-analysis. *Multidiscip Respir Med*., **14**: 25.

Rosyid AN, Saputra PBT, Purwati DD, Ulhaq AUD, Yolanda S and Djatioetomo YCED (2023). Neutrophil elastase in the pathogenesis of chronic obstructive pulmonary disease: A review. *Curr. Respir. Med. Rev.,* **19**(1): 29-35.

Schuetz P (2023). How to best use procalcitonin to diagnose infections and manage antibiotic treatment. *Clin Chem Lab Med*. **61**(5): 822-28.

Song D, Iverson E, Kaler L, Boboltz A, Scull MA and Duncan GA (2022). Muc5b mobilizes and Muc5ac spatially aligns mucociliary transport on human airway epithelium. *Sci Adv*., **8**(47): eabq5049.

Van der Molen T, Willemse BW, Schokker S, Ten Hacken NH, Postma DS and Juniper EF (2003). Development, validity and responsiveness of the clinical COPD questionnaire. *Health Qual Life Outcomes*., **1**: 13.

Vashishth A, Sharma G, Sarkar A, Kadian M, Jain M and Kumar A (2024). Doxophylline, a non-selective phosphodiesterase inhibitor, protects against chronic fatigue-induced neurobehavioral, biochemical and mitochondrial alterations. *Neurochem Res*., **50**(1): 34.

Venkatesan P (2024). Gold COPD Report: 2024 Update. *Lancet Respir Med*., **12**(1): 15-16.

Wang F, Cui B and Song J (2025). The application value of terbutaline combined with ambroxol hydrochloride in the acute exacerbation period of chronic obstructive pulmonary disease. *Clini. Med*., **45**(02): 96-98.

Wang L, Tkhilaishvili T, Bernal Andres B, Trampuz A and Gonzalez Moreno M (2020). Bacteriophage-antibiotic combinations against ciprofloxacin/ceftriaxone-resistant *Escherichia coli in vitro* and in an experimental galleria mellonella model. *Int J Antimicrob Agents*. **56**(6): 106200.

Wang S, Zhong M, Deng X, Liu C, Tan Y, Qian B and Zhong M (2025). Based exploration of the diagnostic value of oxidative stress-related key genes in chronic obstructive pulmonary disease. *Cell Biol Toxicol*., **41**(1): 69.

Yusuf AP, Zhang JY, Li JQ, Muhammad A and Abubakar MB (2022). Herbal medications and natural products for patients with Covid-19 and diabetes mellitus: potentials and challenges. *Phytomed Plus*. **2**(3): 100280.

Zhang MZ, Zhang RY, Liu J and Wang W (2023). Advances in the role of autoimmune mechanisms in chronic obstructive pulmonary disease. *Zhonghua Jie He He Hu Xi Za Zhi.*, **46**(11): 1131-36.

Zhang S, Chen L and Ye J (2022). Effect of doxofylline combined with ambroxol hydrochloride on serum Il-33 /Sst2 Axis expression in elderly patients with stable chronic obstructive pulmonary disease. *Clinical and Basic Bridging Research,* **38**(04): 291-95.

Zhang Z (2023). Zu Viel Sitzen, Zu Wenig Bewegung. *Deutsche Heilpraktiker-Zeitschrift*. **18**(7): 24-27.

Zhou Z, Wang Y, Wang Y, Yang B, Xu C, Wang S and Yang W (2024). A diagnostic nomogram for predicting hypercapnic respiratory failure in patients with acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*., **19**: 1079-91.

Zhou Z and Hu G (2021). Efficacy and adverse drug reactions of ambroxol hydrochloride in the treatment of chronic obstructive pulmonary disease with pulmonary infection in the elderly. *Chin J of Clinical Rational Drug Use*., **14**(31): 35-36.

Zhu T, Xiao X, Dong Y and Yuan C (2023). Neferine alleviates ovalbumin-induced asthma Via Mapk signaling pathways in mice. *Allergol Immunopathol (Madr)*. **51**(3): 135-42.