ORIGINAL ARTICLE

Evaluating the Safety and Effectiveness of Etophylline + Theophylline in Respiratory Disorders: A Real-World Multicenter Study (DRWE Study)

AGAM C VORA*, SURINDER K JINDAL†, RAJENDRA PRASAD‡, MOHANKUMAR THEKKINKATTIL#, PARAKKAL SUKUMARAN¥, PRALHAD PRABHUDESAI§, SANDEEP NAYAR£, RAJIV GARG¶, JUDO J VACHAPARAMBIL^, DEBOPAM CHATTERJEE€, PALAK GOSWAMI$

ABSTRACT

Context: Methylxanthines continue to play a role in the management of chronic respiratory diseases; however, real-world evidence on the etophylline-theophylline combination remains limited. **Aims:** To evaluate the safety and effectiveness of Deriphyllin (Fixed-dose combination of etophylline + theophylline manufactured by Zydus Healthcare Limited) as add-on therapy in patients with asthma, chronic obstructive pulmonary disease (COPD), and related respiratory disorders in routine clinical practice. **Settings and Design:** Prospective, multicenter, observational real-world study conducted across 400 sites in India. **Methods and Material:** A total of 4,001 adults (>18 years) newly initiated on etophylline + theophylline combination were followed for up to 3 months. The primary outcome was safety assessed through adverse event monitoring. Secondary outcomes included changes in modified Medical Research Council (mMRC) dyspnea grade, COPD Assessment Test (CAT), and Asthma Control Test (ACT) scores, along with physician global assessment and patient satisfaction. **Results:** The cohort (mean age 52.09 ± 13.56 years; 70.71% male) included asthma (52.84%) and COPD (38.67%) patients. Severe dyspnea (mMRC grades 3-4) decreased from 62.70% at baseline to 0.20% at 3-month follow-up ($\chi^2 = 5185.18$; $p < 0.0001$). CAT scores improved from 30.65 ± 4.8 to 9.32 ± 6.54 ($p < 0.0001$) for COPD patients and ACT scores from 12.58 ± 4.3 to 20.96 ± 2.64 ($p < 0.0001$) for asthma patients. Adverse events occurred in 7.17%, predominantly mild gastrointestinal symptoms. All patients underwent cardiac monitoring, and no arrhythmias were observed during the study period. Physician and patient satisfaction ratings were excellent/very good in 89.72% and 91.30% of cases, respectively. **Conclusion:** In this large real-world study, etophylline-theophylline as add-on therapy demonstrated clinically meaningful improvements in mMRC, CAT, and ACT scores exceeding minimal clinically important difference (MCID) thresholds, a favorable safety profile (7.17% adverse events; no cardiac arrhythmias), and high physician (89.72%) and patient (91.30%) satisfaction, supporting its role as a safe and effective first oral add-on option in persistent respiratory disease.

Keywords: Etophylline-theophylline, etophylline, theophylline, COPD, asthma, bronchodilator, real-world evidence

*Medical Director, Vora Clinic, Mumbai, Maharashtra, India
†Director, Jindal Clinics, Chandigarh, India
‡Director, Medical Education and Professor & Head, Dept. of Pulmonary Medicine, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India
#Senior Consultant Pulmonologist, One Care Medical Center, Coimbatore, Tamil Nadu, India
¥Emeritus Professor, Respiratory Medicine, Pushpagiri Medical College Hospital, Thiruvalla, Kerala, India
§Consulting Chest Physician, Lilavati Hospital, Bandra West, Mumbai, Maharashtra, India
£Principal Director and HOD – Chest and Respiratory Diseases, BLK-Max Super Speciality Hospital, New Delhi, India
¶Professor, Dept. of Respiratory Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India
^Chief Consultant Pulmonologist and Medical Superintendent, Sun Medical and Research Centre, Thrissur, Kerala, India
€Consultant Interventional Pulmonologist and Sleep Medicine Specialist, Apollo Multispeciality Hospital, Kolkata, West Bengal, India
$Medical Advisor, Medical Affairs, Zydus Life Sciences, Mumbai, Maharashtra, India
Address for correspondence
Dr Debopam Chatterjee
Consultant Interventional Pulmonologist and Sleep Medicine Specialist
Apollo Multispeciality Hospital; 58, Canal Circular Rd, Kadapara, Phoolbagan, Kankurgachi, Kolkata, West Bengal - 700 054, India
E-mail: doc.dchott10@gmail.com

Chronic respiratory diseases, particularly asthma and chronic obstructive pulmonary disease (COPD), represent a substantial global health burden affecting over 500 million individuals worldwide[1]. The Global Burden of Disease Study estimates that COPD alone accounts for 3.5 million deaths annually, ranking as the fourth leading cause of mortality globally[2]. Asthma affects approximately 262 million people worldwide, with substantial impact on quality of life, health care utilization, and economic productivity[3]. According to a World Health Organization (WHO) report, the burden of respiratory diseases is disproportionately severe in low- and middle-income countries, where India has the world's highest lung disease mortality rate (142.09 deaths per 100,000 population), accounting for 11% of all national

deaths, with lung disease deaths on the rise[4]. India accounts for 32% of global disability-adjusted life years due to chronic respiratory diseases[5]. Despite the availability of effective inhaled therapies, many patients with asthma have poor asthma control. Uncontrolled asthma presents a significant burden on the patient and society, and, for many, remains largely preventable[6].

Current treatment guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) emphasize a stepwise approach centered on inhaled bronchodilators and corticosteroids[7,8]. However, a substantial proportion of patients remain symptomatic despite guideline-directed therapy, necessitating consideration of additional therapeutic options[9]. Long-acting bronchodilators, while effective, may be inaccessible in resource-limited settings due to cost constraints, and some patients experience inadequate symptom control even with combination inhaled therapies[10,11].

The Indian subcontinent presents distinctive challenges that fundamentally impact respiratory disease management and therapeutic effectiveness. Critical inhaler technique errors occur in 86% of Indian patients with asthma and COPD, with only 14% performing all steps correctly[12]. This is consistent with global evidence, where research indicates that up to 90% of patients with asthma use their inhalers incorrectly depending on device and patient population, errors that are truly "critical" — defined as those which, if made, have a direct negative impact on clinical outcomes including uncontrolled asthma and increased exacerbation rates — have been empirically identified across all major inhaler device types including the pMDI, Turbuhaler, and Diskus/Accuhaler, and approximately 50% of patients who initially achieve correct technique fail to maintain it over time, with poor inhaler technique collectively accounting for one-quarter of all costs associated with inhaler use[13]. Furthermore, 75.3% of Indian asthmatics avoid inhalers due to social stigma and high cost, preferring oral medications despite potentially reduced effectiveness. Cost is a significant factor, as inhalers are often more expensive than oral medications and may not be consistently available in rural areas. Additional barriers include the use of controller medications (ICS) only during symptoms rather than as rescue medication stemming from inappropriate prescribing practices, complex and time-consuming regimens, and insufficient training in inhalation techniques. These region-specific factors create an urgent need for evidence-based oral bronchodilator alternatives that are culturally acceptable, technically accessible, cost-effective, and clinically effective in this population[14].

Methylxanthines, including theophylline and its derivatives, represent one of the oldest classes of bronchodilators with documented efficacy in obstructive airway diseases[15]. These agents exert their therapeutic effects through multiple mechanisms, including phosphodiesterase inhibition leading to increased cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), adenosine receptor antagonism, enhanced diaphragmatic contractility, and anti-inflammatory effects at therapeutic concentrations[16]. In addition to their bronchodilator effects, methylxanthines exhibit immunomodulatory properties, including activation of histone deacetylase, which may contribute to their therapeutic benefits[16].

A fixed-dose combination of etophylline (24-hydroxyethyl-theophylline) and theophylline offers theoretical advantages over theophylline monotherapy. Etophylline exhibits similar bronchodilator efficacy with potentially improved safety characteristics, including reduced central nervous system (CNS) stimulation and decreased gastrointestinal adverse effects. The combination formulation aims to optimize therapeutic benefit while minimizing dose-dependent adverse reactions commonly associated with higher theophylline concentrations. Additionally, sustained-release formulations provide prolonged therapeutic effect with convenient once- or twice-daily dosing, potentially improving medication adherence[17].

Indian real-world data indicate that oral add-on combinations, such as N-acetylcysteine with acebrophylline, may enhance symptoms and lung function in chronic respiratory disorders, though limited by small sample sizes and short durations[18].

Methylxanthines have a long history of use in respiratory treatment algorithms, yet contemporary real-world evidence on their effectiveness and safety remains sparse[19]. Existing data primarily come from controlled trials with strict criteria, limiting generalizability to diverse real-world patients[20]. Large-scale studies on etophylline-theophylline combinations are particularly scarce, highlighting gaps in efficacy and safety across varying severities, comorbidities, and therapies[21].

Validated instruments such as the COPD Assessment Test (CAT), Asthma Control Test (ACT), and modified Medical Research Council (mMRC) dyspnea scale enable standardized evaluation of symptom burden, functional limitations, and health status[22]. Patient-reported outcomes are increasingly recognized as key elements in comprehensive disease assessment, alongside objective physiological measures[23]. Real-world

evaluation of therapeutic interventions using these patient-centered measures offers valuable insights into clinical effectiveness from the patient's perspective[24].

The present study aims to address this evidence gap by conducting a large-scale, multicentric, prospective observational investigation of etophylline-theophylline safety and effectiveness in real-world clinical practice. We hypothesized that etophylline-theophylline, when added to existing respiratory therapy, would be associated with clinically meaningful improvements in validated patient-reported outcomes with acceptable tolerability in a diverse patient population with chronic respiratory disorders.

METHODS

Study Design

This prospective, observational, multicentric study was conducted across 400 clinics and hospitals in India between 15 May 2025 and 30 November 2025. The study comprised a 3-month enrollment period followed by patient-specific follow-up of up to 3 months from baseline, resulting in a total study duration of 6 months. Study visits included a baseline assessment (Visit 0), with follow-up assessments at Visit 1 (median: 27 days) and Visit 2 (median: 46 days) from baseline, reflecting real-world clinical practice.

Study Objectives

The primary objective of the study was to assess the safety of Deriphyllin (Etophylline + Theophylline) by monitoring adverse events and serious adverse events throughout the study period in patients with chronic respiratory disorders. The secondary objectives were to evaluate changes in dyspnea severity using the mMRC questionnaire from baseline to follow-up visits; to assess symptom control in COPD patients using CAT scores and in asthma patients using ACT scores; to measure overall treatment effectiveness based on global physician assessment and patient satisfaction through the subject satisfaction assessment; and to evaluate cardiac safety through electrocardiographic (ECG) monitoring and systemic safety through hematological and biochemical parameters.

Study Population

Eligible participants were adults aged >18 years of either gender with a diagnosis of respiratory conditions including asthma, COPD, chronic bronchitis with bronchospasm, chronic cough with bronchospasm, post-tuberculosis obstructive airway disease, or other chronic respiratory disorders. Participants required a clinical decision by their treating physician to initiate etophylline-theophylline as add-on therapy to ongoing treatment, with no prior etophylline-theophylline exposure.

Patients aged <18 years, hypersensitive to theophylline, etophylline, or etophylline-theophylline components, or using other methylxanthines were excluded from the study. Additional exclusions included significant cardiovascular conditions, active peptic ulcer disease, epilepsy, severe liver dysfunction, pregnancy or lactation, or physician-deemed unsuitability.

Ethical Committee Approval

Ethics approval was granted on 22 April 2025 by the Central Independent Ethics Committee (CIEC), Pune, India (IEC reference: ECR/390/Indt/MH/2024). All procedures followed the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrollment. The study was registered with the ISRCTN registry (ISRCTN11233269).

Study Procedure/Intervention

Patients received etophylline-theophylline (300 mg sustained release [SR], 450 mg SR, Retard 150 mg, or Retard 300 mg tablets) at physician discretion, dosed once-daily, twice-daily, or at bedtime. All formulations contained etophylline and theophylline in 3:3 ratio. Concomitant therapies (inhaled bronchodilators/corticosteroids) continued per real-world practice.

Data Collection/Assessments

Baseline (Visit 0) assessments included demographics, medical history (smoking/alcohol/comorbidities), vital signs (blood pressure [BP], pulse, peripheral capillary oxygen saturation [SpO_2]), symptoms, spirometry/6-minute walk test (6MWT) (where available), mMRC/CAT/ACT questionnaires, laboratory investigations (complete blood count [CBC], liver function tests [LFTs], serum creatinine) (where available), ECG (where available), and prescription details.

Follow-up (Visits 1 and 2) assessments repeated vital signs, questionnaires, spirometry/6MWT, laboratory investigations and ECG (where available), adverse events, global physician assessment, subject satisfaction, adherence, and therapy changes. Electrocardiography and laboratory investigations were performed at the discretion of the treating physician and were not mandatory for all participants.

Outcome Measures

Primary outcome was safety via adverse events/serious adverse events monitoring (system organ class, severity, causality, and ICH-defined serious adverse events)[25]. Secondary outcomes included mMRC (0-4 dyspnea grades)[26], CAT (0-40 health impact; minimal clinically important difference [MCID] ≥2)[27], ACT (5-25 control; MCID ≥3)[28], cough severity (CAT Q2/ACT Q3)[29], global physician assessment, (5-point)[30], subject satisfaction (5-point)[31], ECG parameters[32], and hematological/biochemical safety[33].

Statistical Analysis

The study targeted approximately 4,000 patients across 400 sites for robust real-world evidence (feasibility-based, no formal power calculation). Descriptive statistics used mean ± standard deviation (SD)/median (interquartile range) for continuous variables and number/percentage for categorical variables. Paired *t*-tests were used to analyze continuous outcomes (e.g., CAT and ACT scores), while the Wilcoxon signed-rank test was used for mMRC and cough scores, which are ordinal in nature. These tests were chosen to match the data distribution for each outcome. Chi-square trends assessed mMRC distribution. Subgroups were stratified by baseline inhaler use. Tests were two-tailed at α = 0.05 using SPSS version 25.0. Clinical significance used MCID thresholds.

RESULTS

Patient Demographics and Baseline Characteristics

A total of 4,001 patients were enrolled across 400 participating sites during the 3-month enrollment period. The baseline demographic and clinical characteristics of study participants are shown in Table 1. The study population comprised predominantly male patients (n = 2,829; 70.71%) with a mean age of 52.09 ± 13.56 years. Mean anthropometric measurements were: weight 70.27 ± 11.08 kg, height 165.97 ± 7.8 cm, and body mass index (BMI) 25.39 ± 3.86 kg/m², indicating a generally normal weight population. The age distribution reflected typical chronic respiratory disease demographics, with the majority of patients in middle-to-older age groups. Most patients were nonsmokers (70.48%), and approximately 30% had current or former smoking history. Alcohol consumption was reported by 24.27% patients. The majority of patients completed at least one follow-up visit, enabling comprehensive safety and effectiveness evaluation.

Diagnostic Distribution

The diagnostic distribution (Table 2) revealed asthma as the predominant condition (52.84%), followed by COPD (38.67%). Other diagnoses included chronic bronchitis with bronchospasm (19.82%), chronic cough with bronchospasm (16.97%), post-tuberculosis obstructive airway disease (9.40%), interstitial lung disease (0.27%), and allergic bronchitis (0.15%). The overlap in diagnostic categories reflects real-world clinical practice, where patients may have multiple concurrent respiratory diagnoses.

Treatment Patterns

Etophylline-theophylline formulations and dosing

The treatment dosage patterns and frequency distribution of prescribed drugs are presented in Table 3. Among

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants

Characteristics	n or mean ± SD	Percentage (%)
Demographic characteristics		
Age (years)	52.09 ± 13.56	NA
Weight (kg)	70.27 ± 11.08	NA
Height (cm)	165.97 ± 7.8	NA
BMI (kg/m²)	25.39 ± 3.86	NA
Gender		
Male	2,829	70.71
Female	1,172	29.29
Smoking status		
Nonsmoker	2,820	70.48
Current smoker	614	15.35
Former smoker	567	14.17
Alcohol consumption		
No	3,030	75.73
Yes	971	24.27
Baseline clinical presentation*		
Cough (with or without sputum)	2,977	74.41
Wheezing	2,716	67.88
Chest tightness	2,495	62.36
Dyspnea (shortness of breath)	2,197	54.91
Nocturnal symptoms (cough/wheezing at night)	1,278	31.94
Episodes of exacerbation	136	3.40

*Multiple answers possible; SD = Standard deviation; NA = Not applicable; BMI = Body mass index.

the various formulations, etophylline-theophylline 300 mg SR was the most frequently prescribed (39.36%), followed by etophylline-theophylline Retard 150 mg (23.40%), etophylline-theophylline Retard 300 mg (22.94%), and etophylline-theophylline 450 mg SR (14.30%) (Fig. 1).

Table 2. Baseline Diagnostic Distribution of Patients*

Diagnosis	Frequency	Percentage (%)
Asthma	2,114	52.84
COPD	1,547	38.67
Chronic bronchitis with bronchospasm	793	19.82
Chronic cough with bronchospasm	679	16.97
Post-tuberculosis obstructive airway disease	376	9.40
Interstitial lung disease	11	0.27
Allergic bronchitis	6	0.15

*Multiple answers possible.

Table 3. Dosage Frequency of the Prescribed Drugs

Dosage frequency	Frequency	Percentage (%)
Once-daily	2,114	52.84
Twice-daily	1,777	44.41
Bedtime	110	2.75
Total	**4,001**	**100.00**

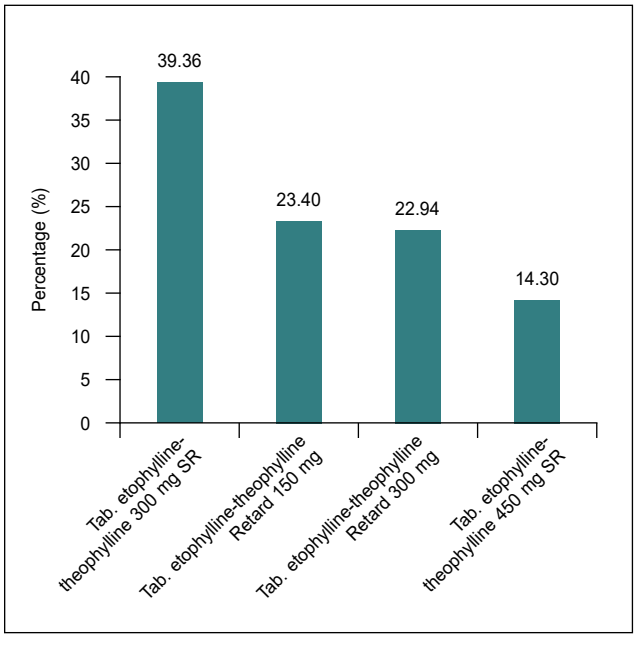

Figure 1. Proportional distribution of prescribed drugs.

With respect to dosing schedules, once-daily administration was most commonly prescribed (52.84%), followed by twice-daily dosing (44.41%), while bedtime dosing accounted for 2.75% of prescriptions (Table 3).

Follow-up assessments were conducted at a median interval of 27 days among 3,837 patients who completed the first follow-up visit and 46 days among 1,835 patients who completed the second follow-up visit from baseline.

Etophylline-theophylline 300 mg SR tablets were the most frequently prescribed formulation (39.36% of total prescriptions), with a strong preference for once-daily dosing, accounting for 62.80% of all once-daily prescriptions. The twice-daily dosing pattern was predominantly associated with etophylline-theophylline Retard formulations (150 mg and 300 mg), which collectively accounted for 83.4% of all twice-daily prescriptions. Notably, bedtime dosing was exclusively limited to SR formulations (300 mg and 450 mg SR). Among these, the 300 mg SR variant accounted for 72.73% of bedtime prescriptions (Table 4 and Fig. 2).

Follow-Up Intervals

Median time from baseline to Visit 1 was 27 days, and median time to Visit 2 was 46 days, demonstrating reasonable adherence to the planned visit schedule in real-world practice.

Efficacy Outcomes

Dyspnea severity (mMRC scale)

The mMRC dyspnea scale demonstrated remarkable improvement in 3,837 patients with available follow-up data. At baseline, 42.60% of patients experienced Grade 3 dyspnea, and 20.10% had Grade 4 dyspnea. Following the intervention, 46.50% achieved Grade 0 and 47.10% reached Grade 1. Severe dyspnea (grades 3-4) decreased from 62.70% at baseline to only 0.20% at the final follow-up, representing a statistically significant improvement in dyspnea severity ($\chi^2 = 5185.18$; $p < 0.0001$) (Table 5 and Fig. 3).

COPD Assessment (CAT scores)

Among patients with COPD who had available CAT data (n = 1,339), CAT scores demonstrated significant improvement (Table 6 and Fig. 4). The baseline mean CAT score was 30.65 ± 4.8, indicating a very high impact of disease on daily life. At study completion, the mean CAT score decreased to 9.32 ± 6.54, reflecting low-to-moderate disease impact. The mean reduction of 21.33 points was statistically significant (paired *t*-test:

Table 4. Proportional Distribution of All the SKUs as per the Dosage Pattern

Drug prescribed	Once-daily n (%)	Twice-daily n (%)	Bedtime n (%)	Total (%)
Tab. etophylline-theophylline 300 mg SR	1,325 (62.80)	170 (9.57)	80 (72.73)	1,575 (39.36)
Tab. etophylline-theophylline 450 mg SR	417 (19.76)	125 (7.03)	30 (27.27)	572 (14.3)
Tab. etophylline-theophylline Retard 150 mg	91 (4.31)	844 (47.50)	0	935 (23.4)
Tab. etophylline-theophylline Retard 300 mg	281 (13.32)	638 (35.90)	0	919 (22.94)
Total	**2,114 (100.00)**	**1,777 (100.00)**	**110 (100.00)**	**4,001**

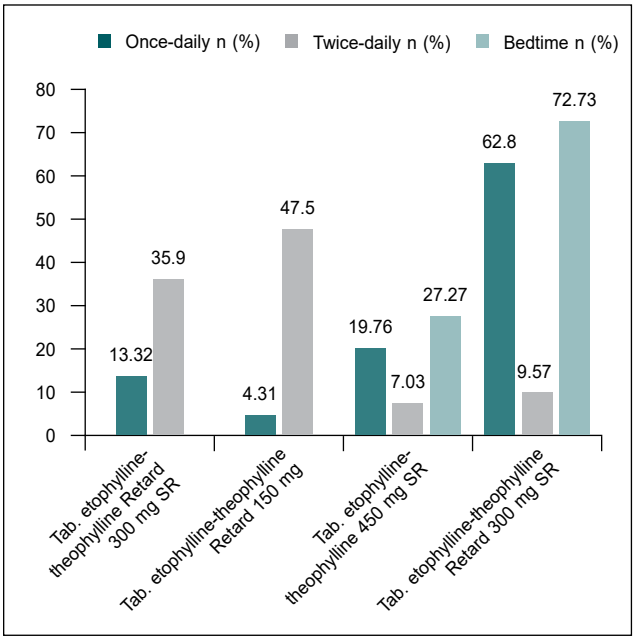

Figure 2. Dosage-wise distribution of the prescribed SKUs.

Table 5. Changes in mMRC Dyspnea Grade Distribution (n = 3,837)

mMRC Grade	Baseline n (%)	End of study n (%)	
Grade 0	0	1,786 (46.50%)	Chi-squared test for trends = 5185.18. p < 0.0001
Grade 1	289 (7.50%)	1,807 (47.10%)	
Grade 2	1,143 (29.80%)	238 (6.20%)	
Grade 3	1,635 (42.60%)	6 (0.20%)	
Grade 4	770 (20.10%)	0	

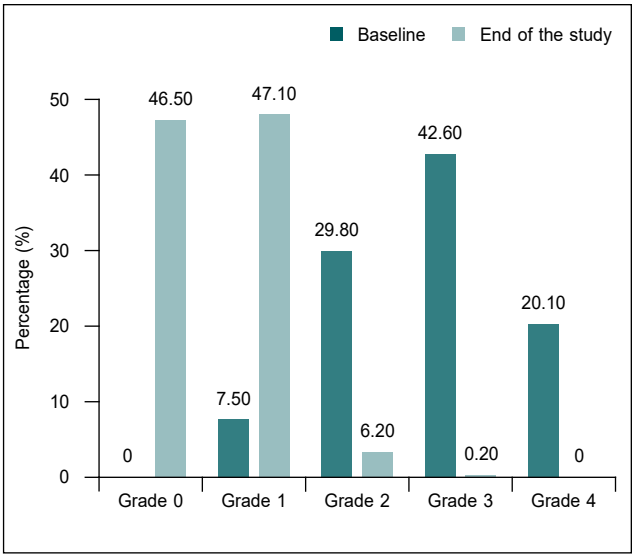

Figure 3. Comparison of mMRC grade for dyspnea.

Table 6. Changes in Disease-Specific Assessment Scores (CAT Score)

Baseline (mean ± SD)	End of the study (mean ± SD)	Paired *t*-test (Test value, p-value)
30.65 ± 4.8	9.32 ± 6.54	−64.33 (p < 0.0001)

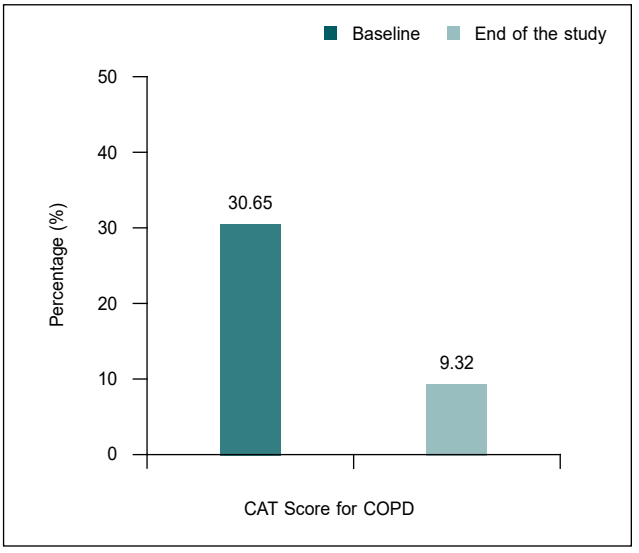

Figure 4. Comparison of CAT score.

t = −64.33, p < 0.0001) and substantially exceeded the MCID of 2 points, representing clinically meaningful improvement.

Asthma control (ACT scores)

Among participants with available ACT data (n = 2,984), ACT scores demonstrated significant improvement (Table 7 and Fig. 5). The baseline mean ACT score

Table 7. Changes in Disease-Specific Assessment Scores (ACT Score)

Baseline (mean ± SD)	End of the study (mean ± SD)	Paired *t*-test (Test value, p-value)
12.58 ± 4.3	20.96 ± 2.64	80.51 (p < 0.0001)

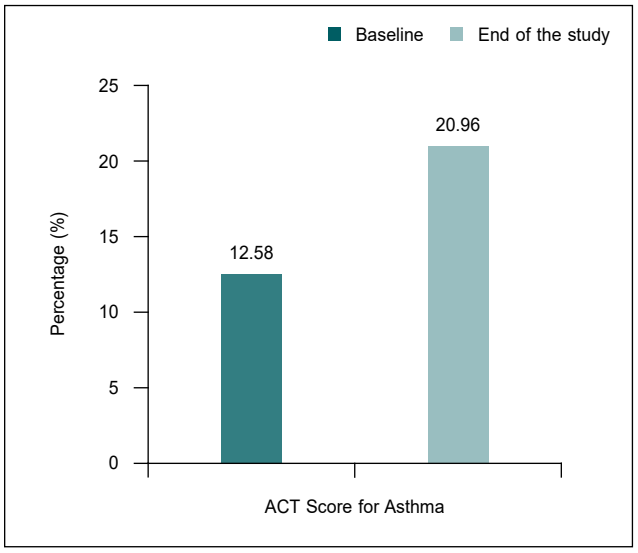

Figure 5. Comparison of ACT score.

was 12.58 ± 4.3, indicating uncontrolled asthma (ACT User's Guide, ≤15). At study completion, the mean ACT score increased to 20.96 ± 2.64, indicating well-controlled asthma (ACT User's Guide, ≥20)[24]. The mean improvement of 8.38 points was statistically significant (paired *t*-test: t = 80.51, p < 0.0001) and substantially exceeded the MCID of 3 points, indicating clinically meaningful improvement.

Concomitant Medication

Out of the total study population of 4,001 patients, 384 patients (9.60%) were receiving concomitant medications in addition to the primary treatment regimen, while 3,617 patients (90.40%) did not require any concomitant therapy (Table 8).

Among patients receiving concomitant medications (n = 384), 131 patients (34.1%) were prescribed inhaled therapies. The distribution of concomitant medications prescribed, as reported in the study records, is presented in Table 9.

These included respiratory, metabolic, cardiovascular, anti-infective, and other supportive medications. Budesonide, montelukast, formoterol-budesonide combinations, salmeterol, salbutamol, formoterol, and terbutaline-containing preparations were among the

Table 8. Distribution of Patients According to Concomitant Medication Status

Concomitant medication	Frequency	Percentage (%)
Yes	384	9.60
No	3,617	90.40
Total	**4,001**	**100.00**

Table 9. Proportional Distribution of the Concomitant Medication

Generic molecule name	Frequency	Percentage (%)
Budesonide	76	19.79
Metformin	63	16.41
Amoxicillin + Clavulanic acid	59	15.36
Montelukast	35	9.11
Azithromycin	24	6.25
Telmisartan	24	6.25
Formoterol + Budesonide	24	6.25
Amlodipine	18	4.69
Levothyroxine	18	4.69
Salmeterol	15	3.91
Salbutamol	20	5.21
Atorvastatin	11	2.86
Paracetamol	17	4.44
Ambroxol	6	1.56
Fexofenadine	6	1.56
Cilnidipine	6	1.56
Atenolol	6	1.56
Bisoprolol	6	1.56
Metoprolol	6	1.56
Olmesartan	6	1.56
Rabeprazole	6	1.56
Rosuvastatin	6	1.56
Sitagliptin	6	1.56
Tamsulosin	6	1.56
Formoterol	5	1.30
Terbutaline	4	1.04
Ambroxol + Guaifenesin	3	0.78
Rifampicin	2	0.52
Isoniazid	1	0.26
Nitroglycerin	1	0.26
Ranitidine	1	0.26
Telmisartan + Amlodipine	1	0.26
Rabeprazole + Domperidone	1	0.26

respiratory-related medications listed. Other commonly reported concomitant medications included metformin, amoxicillin-clavulanic acid, azithromycin, telmisartan, amlodipine, and lipid-lowering agents. Multiple concomitant medications may have been prescribed to the same patient.

Overall, the pattern of concomitant medication use suggests that while the majority of patients did not require additional therapy, those receiving concomitant treatment commonly required management of coexisting respiratory, metabolic, cardiovascular, or infectious conditions, consistent with real-world clinical practice in patients with chronic respiratory disorders.

Combination Therapy Analysis

Etophylline-theophylline demonstrated sustained effectiveness when administered concomitantly with inhaled medications. As shown in the overall efficacy analysis (Tables 5 and 6), etophylline-theophylline significantly improved disease-specific assessment scores in both COPD and asthma patients. Importantly, among patients receiving concomitant inhaler therapy, clinical improvement remained robust. In COPD patients using inhalers, CAT scores decreased from 29.73 ± 5.96 at baseline to 7.68 ± 4.54 at the end of the study (Wilcoxon test: −26.04; $p < 0.0001$). In asthma patients using inhalers, ACT scores increased from 11.77 ± 3.38 at baseline to 21.41 ± 1.72 at the end of the study (Wilcoxon test: 26.88; $p < 0.0001$). Collectively, these findings support the effectiveness of etophylline-theophylline when used alongside inhaled therapies, consistent with its role as an add-on treatment approach (Table 10).

Safety Outcomes

Adverse event incidence

Etophylline-theophylline demonstrated a favorable safety profile throughout the study duration (Table 11). Adverse drug reactions (ADRs) were reported in 287 of 4,001 patients (7.17%), while the majority (n = 3,714; 92.83%) experienced no adverse events during follow-up.

Among reported ADRs, gastrointestinal disturbances were most common, including nausea (5.05%), vomiting (3.35%), dry mouth (2.32%), and stomach upset (0.40%). CNS effects comprised insomnia (3.15%), headache (2.32%), and restlessness (0.50%). Cardiovascular effects included tachycardia (0.95%) and hypotension (0.12%) (Fig. 6). The majority of adverse events were mild-to-moderate in severity and did not require treatment discontinuation. Serious adverse events were rare, with

Table 10. Comparison of the CAT and ACT Scores Between Baseline and the End of the Study in Patients Using Inhalers

With inhalers	Baseline (mean ± SD)	End of the study (mean ± SD)	Wilcoxon test (p-value)
CAT Score for COPD	29.73 ± 5.96	7.68 ± 4.54	−26.04 ($p < 0.0001$)
ACT Score for asthma	11.77 ± 3.38	21.41 ± 1.72	26.88 ($p < 0.0001$)

Table 11. Distribution and Characteristics of Adverse Drug Reactions (N = 4,001)

Parameter	Frequency	Percentage (%)
Overall adverse events		
Yes	287	7.17
No	3,714	92.83
Nature of adverse drug reactions*		
Nausea	202	5.05
Vomiting	134	3.35
Insomnia	126	3.15
Dry mouth	93	2.32
Headache	93	2.32
Tachycardia	38	0.95
Restlessness	20	0.50
Stomach upset	16	0.40
Hypotension	5	0.12

*Multiple responses possible; percentages calculated based on total sample size (N = 4,001).

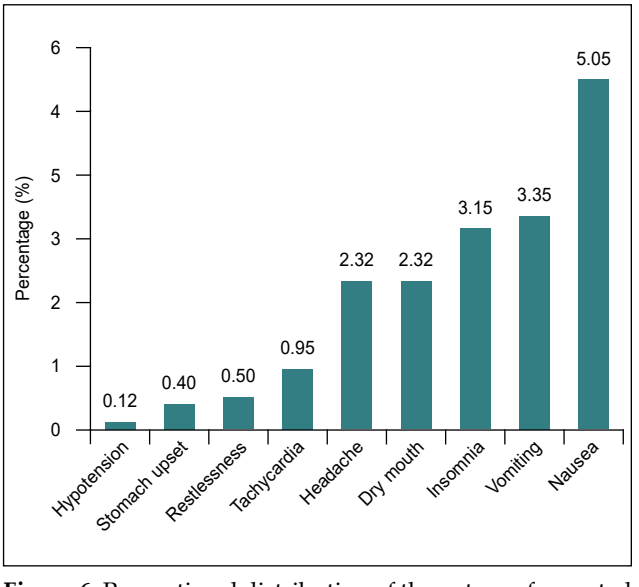

Figure 6. Proportional distribution of the nature of reported ADR.

hypotension occurring in only 5 patients (0.12% of total cohort). No deaths were reported during the study period.

Cardiac safety assessment

Comprehensive ECG monitoring was performed in 456 patients across multiple time points. ECG assessments were available at baseline (n = 456), 28 days (n = 249), and 46 days (n = 179). All ECG recordings consistently demonstrated normal sinus rhythm throughout the study period. No arrhythmias, conduction disturbances, or other clinically significant ECG abnormalities assessed as related to etophylline-theophylline were observed at any assessment point. Cardiac safety profile was favorable, with tachycardia occurring in 0.95% (38/4,001) and hypotension in 0.12% (5/4,001) of patients.

Treatment Satisfaction

Global physician assessment

Treating physicians rated overall treatment outcomes very favorably (Table 12 and Fig. 7). The majority assessed outcomes as "excellent" (61.23%) or "very good" (28.49%), with combined excellent/very good ratings accounting for 89.72% of assessments. "Good" ratings were assigned in 213 cases (5.32%) and "fair" in 12 cases (0.30%). No physician rated treatment outcomes as "poor" (0.00%), while NA ratings were recorded in 186 cases (4.66%).

The high proportion of "excellent"/"very good" ratings (89.72%) reflects strong physician satisfaction with treatment outcomes and suggests meaningful clinical improvements recognized by treating clinicians. The concordance between objective outcome measures (CAT, ACT, mMRC) and the global physician assessment supports the validity and clinical relevance of the observed improvements; NA ratings were recorded in 186 cases (4.66%), and no physician rated outcomes as "poor" (0.00%).

Patient satisfaction assessment

Patient-reported satisfaction closely mirrored physician assessments, demonstrating strong alignment between clinical and patient perspectives (Table 13 and Fig. 8). Patients rated satisfaction as "excellent" in 2,501 cases

Table 12. Global Physician Assessment (N = 4,001)

Global physician assessment	Frequency	Percentage (%)
Excellent	2,450	61.23
Very good	1,140	28.49
Good	213	5.32
Fair	12	0.30
Poor	0	0.00
NA	186	4.66
Total	**4,001**	**100.00**

Table 13. Patient Satisfaction Assessment (N = 4,001)

Patient satisfaction assessment	Frequency	Percentage (%)
Excellent	2,501	62.51
Very good	1,152	28.79
Good	288	7.20
Fair	48	1.20
Poor	12	0.30
Total	**4,001**	**100.00**

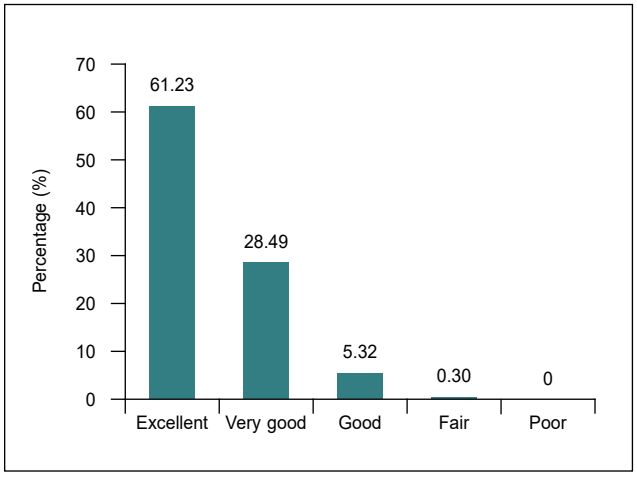

Figure 7. Global physician assessment.

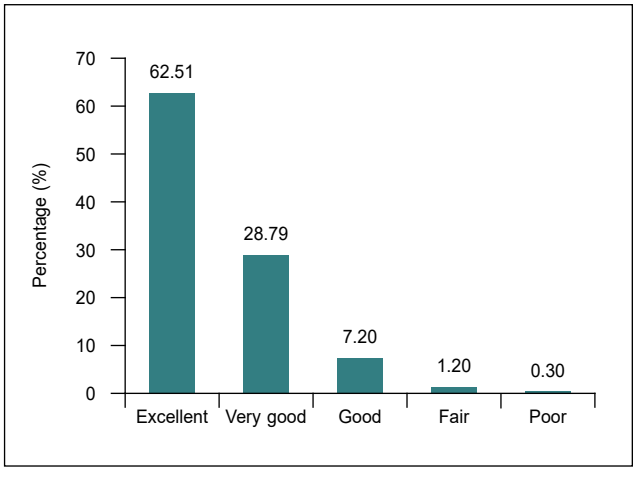

Figure 8. Patient satisfaction assessment.

(62.51%) and "very good" in 1,152 cases (28.79%), yielding combined excellent/very good ratings of 91.30%. "Good", "fair", and "poor" ratings were reported by 288 patients (7.20%), 48 (1.20%), and 12 (0.30%) patients, respectively.

DISCUSSION

This multicentric, real-world observational study of 4,001 patients across 400 Indian sites demonstrates that etophylline-theophylline achieved substantial clinical improvements with favorable tolerability as add-on therapy for chronic respiratory disorders. The study showed CAT score improvements of 21.33 points ($p < 0.0001$), ACT score increases of 8.38 points ($p < 0.0001$), and exceptional mMRC improvements, with 93.60% achieving grades 0-1 versus 7.50% at baseline ($\chi^2 = 5185.18$; $p < 0.0001$). Adverse events occurred in only 7.17% (287 of 4,001 patients) of patients, predominantly mild gastrointestinal symptoms, with no cardiac arrhythmias. Treatment satisfaction was high, with 89.72% of physicians and 91.30% of patients rating outcomes as excellent or very good. In the subgroup receiving concomitant inhaled medications (add-on therapy), etophylline-theophylline demonstrated CAT improvements of 22.05 points and ACT improvements of 9.64 points.

The 21.33-point CAT improvement observed in this study substantially exceeds typical bronchodilator trials (1.5-4.5 points) and pulmonary rehabilitation programs (3-7 points), representing approximately threefold greater improvement than previously reported theophylline add-on therapy studies (21.33 vs. 6.6 points). The marked improvements likely reflect the severe baseline symptom burden (CAT 30.65), additive effects when combined with existing therapy, and multiple mechanisms of action of the combination therapy. The ACT improvement of 8.38 points exceeds typical inhaled corticosteroid–long-acting beta-2 agonist (LABA) combinations (2-5 points), achieving well-controlled asthma (ACT ≥20) in patients with very poor baseline control. The mMRC improvements in the current study were remarkable, with severe dyspnea (grades 3-4) decreasing from 62.70% to 0.20%. While individual bronchodilators typically improve mMRC by 0.5-1.0 grades, this study demonstrated shifts spanning 2-3 grades, improvements typically observed only with intensive interventions.

Patients receiving concomitant inhaled medications demonstrated maintained or even enhanced effectiveness compared to the overall population. As add-on therapy to inhaled medications, etophylline-theophylline maintained effectiveness with CAT improvements of 22.05 points and ACT improvements of 9.64 points, suggesting a genuine additive benefit through complementary mechanisms: inhaled medications provide direct airway effects while methylxanthines stimulate ciliary beat frequency and augment airway fluid and mucus secretion, producing an overall enhancement of mucociliary clearance[34].

The safety profile observed in this study compares favorably with traditional methylxanthines. Historical concerns regarding theophylline relate primarily to its narrow therapeutic index[35]. While theophylline monotherapy adverse event rates typically includes gastrointestinal events like nausea, vomiting, and CNS effects such as seizures and tremors commonly reported[36].

The overall adverse event rate of 7.17% was low and compares favorably with safety profiles reported for established inhaled COPD therapies including LABAs, LAMAs and inhaled corticosteroids[37]. Gastrointestinal and CNS adverse events were infrequent, with nausea (5.05%), vomiting (3.35%), insomnia (3.15%), and headache (2.32%) representing the most commonly reported reactions. These findings are consistent with the known adverse-effect profile of theophylline, although the overall incidence observed in the present study was low[38]. Cardiovascular adverse events were uncommon, with tachycardia reported in only 0.95% of patients (38/4,001), and ECG monitoring performed in 456 patients demonstrated no arrhythmias, conduction abnormalities, or other clinically significant treatment-related ECG changes during follow-up, supporting the favorable cardiac safety profile observed despite the recognized potential for methylxanthine-associated cardiovascular effects[39].

The favorable safety profile, including absence of cardiac arrhythmias and low adverse event incidence, supports use in routine clinical practice among patients with chronic respiratory diseases[40,41]. While caution remains appropriate in patients with cardiovascular disease, seizure disorders, or peptic ulcer disease (as per exclusion criteria)[42], the medication appears well-tolerated in general respiratory disease populations. The maintained effectiveness when added to inhaled medications validates etophylline-theophylline as true add-on therapy rather than a monotherapy substitute[31]. This supports guideline recommendations for methylxanthines as add-on options when symptoms persist despite optimized inhaled therapy[43,44] with current data providing robust real-world evidence supporting this approach.

This contributes to bronchodilation and modulates inflammatory responses, as adenosine promotes bronchoconstriction and inflammatory mediator release in airways; theophylline activates histone deacetylase 2[45]; these mechanisms explain the synergistic benefits observed when etophylline-theophylline is combined with inhaled corticosteroids. Methylxanthines improve diaphragmatic contractility and reduce respiratory muscle fatigue[46]. The 3:1 etophylline-theophylline ratio optimizes these mechanisms while minimizing adverse effects, allowing for effective therapeutic action with improved tolerability, as evidenced by the low adverse event incidence in this study.

Study strengths include large sample size (4,001 participants), multicentric design (400 sites), real-world approach, multiple validated outcome measures, and comprehensive safety monitoring. Limitations include the nonrandomized open-label design, 3-month follow-up duration, absence of a control group which precludes definitive causal inference and region-specific conduct that may affect generalizability despite enhancing real-world applicability. Objective lung function measurements (spirometry, FEV_1) were not systematically collected, limiting the ability to correlate patient-reported outcomes with physiological improvements.

However, validated patient-related outcome measures (CAT, ACT, mMRC) are recognized as clinically meaningful endpoints that capture real-world treatment impact.

The substantial attrition between visits (54.1% did not complete Visit 2) likely reflects several factors common in real-world observational studies: (1) clinical improvement leading patients to deprioritize follow-up visits or (2) logistical challenges in routine practice, (3) the observational nature precluding strict visit adherence requirements.

The remarkably high patient satisfaction rates (>91% excellent/very good) emphasize that objective improvements in validated outcome measures translated to subjectively meaningful benefits from the patient perspective. This concordance between objective efficacy outcomes and subjective satisfaction represents a key strength of the study and supports the clinical relevance of observed improvements. The minimal proportion of poor satisfaction ratings (0.30%) suggests that treatment was well-tolerated and perceived as beneficial by the vast majority of patients, even accounting for the 7.17% who experienced adverse events.

The panel discussions based on interim DRWE study data at NAPCON Jaipur on 15th November 2025 and NAPCON Patna on 12th December 2025 further reiterated the value of large-scale Indian real-world evidence on theophylline + etophylline in guiding respiratory practice. The study findings and expert discussions supported the combination of etophylline + theophylline as a safe, effective, and practical first add-on option in selected obstructive airway disease patients, particularly those who remain symptomatic despite inhaled therapy or face inhaler-related barriers. The key message from these sessions was clear: evidence-based respiratory care must also be patient-centric, adaptable, and grounded in real-world clinical realities.

Importantly, Visit 1 retention (95.9%) was excellent, and sensitivity analyses in the Visit 2 cohort demonstrated sustained benefits, suggesting that findings are robust despite attrition. The exceptional concordance between objective measures and patient satisfaction (91.30% rating treatment excellent/very good) indicates clinically meaningful improvements valued by patients, supporting the role of etophylline-theophylline as effective, well-tolerated add-on therapy for chronic respiratory disorders.

CONCLUSIONS

This large-scale, multicentric real-world study demonstrates that etophylline-theophylline, as an add-on therapy, achieves substantial clinical benefits in chronic respiratory disorders, with improvements that exceed the MCID threshold for key outcome measures. The sustained efficacy observed in patients receiving concomitant inhaled medications validates etophylline-theophylline's role as an effective add-on therapy, offering a complementary approach for patients with persistent symptoms despite optimized inhaled treatments.

Key Message: In a large real-world cohort of 4,001 patients across 400 Indian centers, etophylline-theophylline as add-on therapy produced clinically meaningful improvements in CAT, ACT, and mMRC scores exceeding established MCIDs, with a low adverse event rate (7.17%), no observed cardiac arrhythmias, and high physician and patient satisfaction.

Conflicts of interest: None.

REFERENCES

1. Wu Y, Liu C, Ge W, Qiu Y, Zhang Z, Qin K. Exploring health consequences of Asthma-COPD overlap syndrome in a national study. Sci Rep. 2026;16(1):2416.
2. Xu J, Xu H, Zhang D, Deng X, Bian Y, Xu Y, et al. Global, regional and national trends in burden of chronic obstructive pulmonary disease from 2000 to 2021 and the prediction for 2030. Chron Respir Dis. 2026;23:14799731261432520.

3. Zhang L, Jiang H, Yang G, Zhang J, Yuan S, Chen J, et al. Global, regional and national burden of asthma from 1990 to 2021: a systematic analysis for the Global Burden of Disease Study 2021. BMJ Open Respir Res. 2025;12(1):e003144.
4. Respiratory Therapy. India tops world in lung disease deaths. 2015 Jul 10. Available from: https://respiratory-therapy.com/department-management/clinical/india-tops-world-lung-disease-deaths/. Accessed June 6, 2026.
5. India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Glob Health. 2018;6(12):e1363-74.
6. Busse WW, Kraft M. Current unmet needs and potential solutions to uncontrolled asthma. Eur Respir Rev. 2022;31(163):210176.
7. Venkatesan P. GOLD COPD report: 2026 update. Lancet Respir Med. 2026;14:e14-e15.
8. Dubin S, Patak P, Jung D. Update on asthma management guidelines. Mo Med. 2024;121(5):364-7.
9. Kankaanranta H, Lahdensuo A, Moilanen E, Barnes PJ. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. Respir Res. 2004;5(1):17.
10. Stolbrink M, Thomson H, Hadfield RM, Ozoh OB, Nantanda R, Jayasooriya S, et al. The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review. Lancet Glob Health. 2022;10(10):e1423-42.
11. Chen S, Small M, Lindner L, Xu X. Symptomatic burden of COPD for patients receiving dual or triple therapy. Int J Chron Obstruct Pulmon Dis. 2018;13:1365-1376.
12. Sodhi MK. Incorrect inhaler techniques in Western India: still a common problem. Int J Res Med Sci. 2017;5(8):3461-5.
13. Bosnic-Anticevich SZ, Cvetkovski B, Azzi EA, Srour P, Tan R, Kritikos V. Identifying critical errors: addressing inhaler technique in the context of asthma management. Pulm Ther. 2018;4(1):1-12.
14. Swarnakar R, Dhar R. Call to action: addressing asthma diagnosis and treatment gaps in India. Lung India. 2024;41(3):209-16.
15. Shukla D, Chakraborty S, Singh S, Mishra B. Doxofylline: a promising methylxanthine derivative for the treatment of asthma and chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2009;10(14):2343-56.
16. Tilley SL. Methylxanthines in asthma. Handb Exp Pharmacol. 2011;(200):439-56.
17. Sankar K, Chavala SD, Sumalata C. Comparative study of efficacy and adverse effect profile of theophylline and etofylline combination versus doxofylline in patients with COPD. Sch J App Med Sci. 2015;3(1):310-7.
18. Dhar R, Chawla RK, Rahaman M, Chawla AK, Chaudhary G, Gautam A, et al. CARE: combination of acetylcysteine and acebrophylline in moderate to severe asthma and COPD patients. J Asthma Allergy. 2025;18: 827-834.
19. Scurek M, Brat K. A narrative review of theophylline: is there still a place for an old friend? J Thorac Dis. 2024;16(5):3450-60.
20. Herland K, Akselsen JP, Skjønsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med. 2005;99(1):11-9.
21. Cazzola M, Calzetta L, Barnes PJ, Criner GJ, Martinez FJ, Papi A, et al. Efficacy and safety profile of xanthines in COPD: a network meta-analysis. Eur Respir Rev. 2018;27(148):180010.
22. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.
23. Kocks JWH, Seys SF, van Duin TS, Diamant Z, Tsiligianni IG. Assessing patient-reported outcomes in asthma and COPD patients: which can be recommended in clinical practice? Curr Opin Pulm Med. 2018;24(1):18-23.
24. De Simón Gutiérrez R, Castro RP. Narrative review of the role of patient-reported outcomes and inhaler handling errors in the control of asthma and COPD. Curr Allergy Asthma Rep. 2022;22(11):151-61.
25. MedDRA. Maintenance and Support Services Organization (MSSO). Introductory Guide MedDRA Version 24.1. September 2021. Available from: https://alt.meddra.org/files_acrobat/intguide_24_1_English.pdf. Accessed June 6, 2026.
26. MDCalc. MMRC (Modified Medical Research Council) Dyspnea Scale. Available from: https://www.mdcalc.com/calc/4006/mmrc-modified-medical-research-council-dyspnea-scale. Accessed June 6, 2026.
27. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med. 2014;2(3):195-203.
28. van Dijk BCP, Svedsater H, Heddini A, Nelsen L, Balradj JS, Alleman C. Relationship between the Asthma Control Test (ACT) and other outcomes: a targeted literature review. BMC Pulm Med. 2020;20(1):79.
29. River ENT. Cough Severity Index (CSI). Available from: https://river-ent.com/wp-content/uploads/2021/04/riverent_form_coughseverityindex_fillable-2-1.pdf. Accessed June 6, 2026.
30. CDISC. Static physician global assessment. Available from: https://www.cdisc.org/kb/examples/static-physician-global-assessment-75269644. Accessed June 6, 2026.
31. Chrystyn H, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD. Respir Med. 2014;108(2):358-65.
32. Agarwal RL, Kumar D, Gurpreet, Agarwal DK, Chabra GS. Diagnostic values of electrocardiogram in

chronic obstructive pulmonary disease (COPD). Lung India. 2008;25(2):78-81.

33. Carmona-Aparicio L, Coballase-Urrutia E, Orozco-Ibarra M, Serrano-García N, Caballero-Salazar S, Ramírez-Pérez M, et al. Hematological and biochemical alterations induced by sub-acute administration of permethrin in rats. J Xenobiot. 2025;15(6):183.
34. Wanner A. Effects of methylxanthines on airway mucociliary function. Am J Med. 1985;79(6A):16-21.
35. Dinesh V, Varshini DR, Mohanan AA, Amrithanand VT. Navigating the storm: a case of severe theophylline toxicity and its management. Med Rep. 2025;12:100191.
36. Journey JD, Bentley TP. Theophylline toxicity. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532962/
37. Koarai A, Sugiura H, Yamada M, Ichikawa T, Fujino N, Kawayama T, et al. Treatment with LABA versus LAMA for stable COPD: a systematic review and meta-analysis. BMC Pulm Med. 2020;20(1):111.
38. Miravitlles M, Auladell-Rispau A, Monteagudo M, Vázquez-Niebla JC, Mohammed J, Nuñez A, et al. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. Eur Respir Rev. 2021;30(160):210075.
39. Zhang C, Zhang M, Wang Y, Xiong H, Huang Q, Shuai T, et al. Efficacy and cardiovascular safety of LAMA in patients with COPD: a systematic review and meta-analysis. J Investig Med. 2021;69(8):1391-8.
40. Lal D, Manocha S, Ray A, Vijayan VK, Kumar R. Comparative study of the efficacy and safety of theophylline and doxofylline in patients with bronchial asthma and chronic obstructive pulmonary disease. J Basic Clin Physiol Pharmacol. 2015;26(5):443-51.
41. Barnes PJ. Theophylline in chronic obstructive pulmonary disease: new horizons. Proc Am Thorac Soc. 2005;2(4):334-9; discussion 340-1.
42. Gottwalt B, Tadi P. Methylxanthines. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559165/
43. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2024 report. GOLD; 2024. Available from: https://goldcopd.org/2024-gold-report/. Accessed June 9, 2026.
44. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. GINA; 2025.
45. Ohar J, Putcha N, Bradshaw M. Asthma-chronic obstructive pulmonary disease overlap: diagnostic and management challenges. J Fam Pract. 2018;67(10 Suppl):S46-51.
46. Fujii Y. Treatment of diaphragmatic fatigue with inhaled aminophylline therapy in an experimental canine model: an open-label, dose-ranging, pharmacologic study. Curr Ther Res Clin Exp. 2003;64(9):725-32.

■■■■