Potential of doxofylline in the treatment of chronic obstructive airway diseases (Review)

SERGHEI COVANTSEV[1], DIANA POPARCEA[2], ANNA BUMBU[3], ALEXANDR CEASOVSCHIH[4,5], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[6], DEMETRIOS A. SPANDIDOS[7] and ALEXANDRU CORLATEANU[2]

[1]Federal State Autonomous Institution National Medical Research Centre 'Treatment and Rehabilitation Centre' of the Ministry of Health of The Russian Federation, Moscow 125284, Russia; [2]Division of Pneumology and Allergology, Department of Internal Medicine, State University of Medicine and Pharmacy Nicolae Testemitanu, Chisinau MD-2004, Republic of Moldova; [3]Department of Clinical Research and Development, Botkin Hospital, Moscow 125284, Russia; [4]Faculty of Medicine, 'Grigore T. Popa' University of Medicine and Pharmacy, Iasi 700115, Romania; [5]2nd Internal Medicine Department, 'Sf. Spiridon' Clinical Emergency Hospital, Iasi 700111, Romania; [6]Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, Athens 11527, Greece; [7]Laboratory of Clinical Virology, School of Medicine, University of Crete, Heraklion 71003, Greece

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Abstract. Doxofylline, a xanthine derivative introduced in 1987, was developed as an alternative to theophylline for the treatment of chronic respiratory disease, including chronic obstructive pulmonary disease and bronchial asthma, but also a promising agent with therapeutic potential, unique pharmacological profile, improved safety and tolerability, potential to decrease corticosteroid dependence and applicability in diverse healthcare settings, including resource-limited environments. The present review examines the utility of doxofylline as an effective bronchodilator, highlighting its improved tolerability profile, minimal drug interactions and distinct pharmacological activities, including its roles as a phosphodiesterase inhibitor, adenosine receptor antagonist and β-adrenergic receptor agonist, alongside its bronchodilator, antitussive and anti-inflammatory properties. The present review performed a comprehensive analysis of literature and a comparative evaluation of relevant clinical trials. By contrast with theophylline, whose clinical use has diminished due to its narrow therapeutic window and notable side effects, doxofylline demonstrates a more favorable safety profile and wider therapeutic range. Doxofylline not only enhances spirometric values and reduces the need for salbutamol administration but also exhibits fewer adverse effects, contributing to improved patient tolerance and adherence to treatment. Clinical findings further suggest significant improvements in lung function, exercise capacity and quality of life among patients treated with doxofylline. These results underscore its potential as a viable long-term therapeutic option, particularly in resource-limited settings, where it may reduce corticosteroid dependency and provide an effective, affordable and safer alternative to theophylline.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Pathophysiology, Laiko General Hospital, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, Athens 11527, Greece
E-mail: vaso_georgakopoulou@hotmail.com

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Contents

1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Obstructive Lung Disease (GOLD) guidelines as a common preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (1). According to a recent meta-analysis, the pooled prevalence of COPD is 15.47% in male and 8.79% in female patients (2).

Bronchial asthma (BA) is defined by the Global Initiative for Asthma as a heterogeneous disease usually characterized by chronic airway inflammation, defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary in duration and in intensity, together with variable expiratory airflow limitation (3). According to the World Health Organization, in 2019 asthma

affected ~262 million people worldwide and caused ~461,000 deaths (4). COPD and BA are highly prevalent, associated with significant morbidity and socio-economic impact and often overlap, complicating their clinical management (5).

Although a variety of treatment options exist for COPD and BA, there remains a pressing need for novel therapies capable of effectively suppressing chronic inflammation in the lungs (6,7). Theophylline, a purine-derived methylxanthine, exhibits smooth muscle relaxant and bronchodilator effects. It has been used in the management of BA and COPD, although its use is limited by a narrow therapeutic window and multiple drug-drug interactions, as reflected in current Global Initiative for Asthma and GOLD strategies (1,3).

An alternative to theophylline may be doxofylline, which is characterized by an improved tolerability profile and fewer notable drug-drug interactions. Doxofylline also exhibits distinct pharmacological properties compared with theophylline, characterized by improved safety, reduced central nervous system (CNS) stimulation, minimal cardiac effects and few drug interactions. Unlike theophylline, it does not require plasma concentration monitoring, making it more suitable for routine clinical use (8). Preliminary data suggest that doxofylline may demonstrate comparable or superior efficacy in the management of COPD and BA symptoms with better tolerability (8,9). Although its mechanisms of action (such as selective inhibition of phosphodiesterase (PDE), modulation of inflammatory mediators and adenosine receptor antagonism) have been described in previous studies, an integrated and up-to-date overview of its clinical potential, pharmacokinetic advantages and positioning in current therapeutic strategies is lacking (7,8). In addition, this therapeutic agent offers an effective and affordable alternative for patients who may face difficulties in accessing more expensive therapy, particularly in low- and middle-income countries where healthcare resources are limited (9).

The present review aimed to explore not only the established role but also the emerging potential of doxofylline in the management of COPD and BA. The present study aimed to summarize its pharmacological properties, therapeutic margin and safety profile, with emphasis on how these characteristics may differentiate it from classical methylxanthines and support its place in contemporary treatment strategies.

2. Materials and methods

A comprehensive literature search for published clinical trials evaluating the influence of doxofylline in patients with COPD and BA was conducted. The search terms included 'doxofylline' and 'theophylline' for the intervention, and 'chronic obstructive pulmonary disease', 'COPD' and 'bronchial asthma' for the disease. Databases searched were PubMed (from 1966 to January 2025; pubmed.ncbi.nlm.nih.gov/), ScienceDirect (from 1997 to January 2025; sciencedirect.com/), Google Scholar (from 2004 to January 2025; scholar.google.com/), and Web of Science (from 1900 to January 2025; https://www.webofscience.com/).

Inclusion criteria were as follows: i) Original clinical trials, including randomized controlled trials (RCTs), as well as meta-analyses or systematic reviews evaluating doxofylline in COPD and/or BA; ii) studies published in English and iii) studies reporting at least one clinical outcome [such as lung function, quality of life (QoL), exacerbation rate and safety]. Exclusion criteria were as follows: i) Non-clinical studies (*in vitro* or animal studies without clinical correlation); ii) case reports, editorials, letters or conference abstracts without full data and iii) articles with insufficient data or unavailable full text. Articles were assessed by two reviewers, with disagreements resolved by consensus.

The search initially identified 183 records. After removing 46 duplicates, 137 unique records were screened by title and abstract. Of these, 71 articles were excluded for irrelevance, leaving 66 full-text articles assessed for eligibility; 22 were excluded (non-clinical focus, inadequate outcome or insufficient data). Following full-text review, 44 studies met all inclusion criteria and were included in the present review.

3. Mechanisms of action and pharmacological properties

Chemical properties and pharmacodynamics. Doxofylline [7-(1,3-dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione] is a xanthine derivative introduced in 1987. Preclinical studies suggest that it modulates cAMP-associated pathways, with limited affinity for adenosine receptors and a less defined role in PDE inhibition compared with theophylline (10,11). Structurally, it differs from theophylline by the presence of a dioxalane group at position 7 (Fig. 1), which contributes to its improved tolerability and reduced drug-drug interactions (12,13).

PDE2A and cyclic (c)GMP-stimulated inhibition. PDE enzymes are key to cell signaling, hydrolyzing cyclic nucleotides such as cAMP and cGMP. PDE2A hydrolyzes both cAMP and cGMP, and its activity is further stimulated by cGMP, leading to preferential hydrolysis of cAMP under conditions of elevated cGMP (14).

Doxofylline may interfere with PDE activity (including PDE2A1; Fig. 2), potentially contributing to its bronchodilator and anti-inflammatory effects (10). However, other investigations did not confirm this mechanism, indicating that the role of PDE inhibition remains uncertain and requires further clarification (11,15). In contrast, theophylline exhibits a broader inhibitory profile, affecting PDE2A1, PDE3A and PDE10A1, which may contribute to its wider range of side effects, including nausea, vomiting, gastroesophageal reflux, headache, insomnia, tremor and potentially severe cardiac arrhythmia (11,16). These targeted actions enhance its efficacy and safety profile in managing respiratory disease.

Adenosine receptor A_{2A} antagonism. In the respiratory system, adenosine mediates bronchoconstriction and inflammatory responses through receptor activation. Theophylline serves as a non-selective antagonist of adenosine receptors, including the A_{2A} subtype, producing anti-inflammatory and bronchodilator effects (7). However, this non-selective antagonism is associated with adverse effects, such as CNS stimulation, cardiac arrhythmias (via A_1 receptor blockade), gastric hypersecretion, gastroesophageal reflux and diuresis. Additionally, paradoxical inhibition of adenosine A_{2A} receptor signaling may exacerbate inflammation (17).

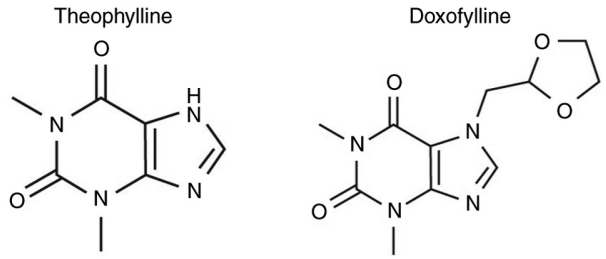

Figure 1. Chemical structure of theophylline and doxofylline [7-(1,3-dioxolan-2-ylmethyl)-3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione]. The presence of a dioxalane group at position 7 in doxofylline differentiates it structurally from theophylline, contributing to its improved safety and tolerability.

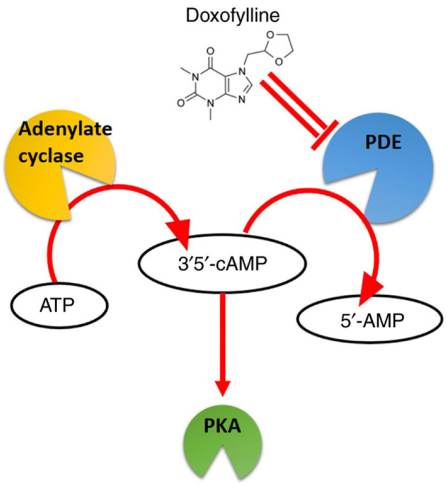

Figure 2. Mechanism of action of doxofylline via specific inhibition of cyclic GMP-stimulated PDE_2A. This inhibition contributes to maintaining high levels of cAMP, favoring bronchodilation and anti-inflammatory effects in the respiratory system. Unlike theophylline, doxofylline has specific selectivity for PDE_2A, thus decreasing side effects. PDE, phosphodiesterase; PKA, protein kinase A.

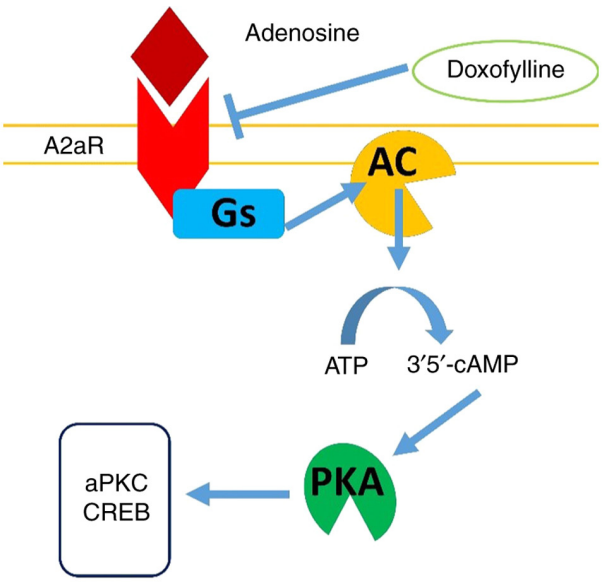

Figure 3. Interaction of doxofylline with the A_2AR pathway. Modulation of this signaling may contribute to bronchodilation and attenuation of airway inflammation in bronchial asthma and chronic obstructive pulmonary disease. A_2A R, adenosine A_2A receptor; AC, adenylate cyclase; PKA, protein kinase A; CREB, cAMP response element-binding protein; aPKC, atypical protein kinase C.

Unlike theophylline, doxofylline demonstrates a low affinity for adenosine A_1 and A_2 receptors and does not antagonize calcium channel blockers, which may explain its decreased cardiac adverse effects (17). Selective inhibition of PDE, along with its unique chemical structure featuring the dioxalane group, may contribute to its improved safety profile. Studies indicate that its effect on the A_2A receptor decreases airway inflammation and promotes bronchial relaxation, thereby supporting its efficacy in treating BA and COPD (10,18) (Fig. 3).

Interaction with β_2-adrenergic pathways. β_2-adrenergic receptor agonists are widely used as bronchodilators in BA and COPD due to their role in G-protein-mediated smooth muscle relaxation in the bronchial tree, resulting in bronchodilation (19,20). While doxofylline does not act as a direct β_2-agonist, it may enhance bronchodilation by potentiating the effects of β_2-agonists via increased intracellular cAMP availability (10).

Theophylline enhances bronchodilation by potentiating the effects of β_2-agonists, increasing intracellular cAMP levels. This synergistic effect is beneficial in combination therapies for patients with severe BA or COPD. Inhaled bronchodilators, including β_2-agonists and antimuscarinics, are critical for managing COPD at all stages and are essential for BA treatment (21).

Doxofylline also enhances the bronchodilator effects of β_2-agonists. Studies highlight its lower side-effect profile compared with theophylline, positioning it as a safer option for long-term management (13,18). Doxofylline, in conjunction with β_2-agonists, achieves effective bronchodilation without the notable adverse effects associated with high-dose theophylline (10).

Histone deacetylase (HDAC) inhibition. HDAC enzymes regulate gene transcription by remodeling chromatin structure. Decreased HDAC2 activity is associated with corticosteroid resistance in COPD and BA, underscoring the clinical relevance of this pathway (22,23).

Low-dose theophylline has been reported to restore HDAC2 activity, thereby enhancing the transcriptional suppression of pro-inflammatory genes and improving corticosteroid responsiveness (7).

Unlike theophylline, the role of doxofylline in HDAC pathways remains uncertain; its improved safety profile is attributed to the presence of the dioxalane group, which reduces interaction with PDEs and adenosine receptors while maintaining anti-inflammatory activity (10,24).

Protein kinase C (PKC) inhibition. PKC is a family of enzymes that serves an essential role in cell processes, including proliferation, differentiation and inflammation. PKC inhibitors interfere with PKC activity, modulating these processes and offering therapeutic potential in inflammatory disease (25). Theophylline has demonstrated anti-inflammatory effects

Table I. Pharmacological properties of doxofylline and theophylline.

Property	Doxofylline	Theophylline
Mechanism of action	Selective inhibition of PDE2A1 activity; increases intracellular cAMP by decreasing its breakdown, promoting bronchodilation and anti-inflammatory effects	Non-selective PDE inhibition, adenosine receptor antagonism
Indication	Bronchodilator used in asthma and chronic obstructive pulmonary disease	Asthma, COPD, chronic bronchitis
Dosage and administration	400 mg p.o., immediate-release tablet, 2-3 times daily	300-600 mg daily, administered in 2-3 doses
Absorption bioavailability	90-100%	62-96%
Therapeutic drug concentration for chronic bronchitis	8-20 μg/ml	5-15 μg/ml
Time to peak concentration	1.5-2 h	1-2 h
Steady state within 6 h	9.43 μg/ml	5-15 μg/ml
AUC	69.5 μg h/ml	87 μg h/ml
Protein binding	48%	40-60%
Distribution half-life	1.5 h	8.7 h
Volume of distribution	0.81 l/kg	0.3-0.7 l/kg
Metabolism sites and kinetics	Liver (>90% of the administered dose), primarily CYP3A4	Liver, primarily CYP1A2, CYP2E1
Metabolites	Hydroxyethyltheophylline (inactive)	1,3-dimethyluric acid, 1-methylxanthine
Renal excretion	<4%	10-13%
Total body clearance	5.4 l/h	0.65 l/h/kg
Elimination half-life	6 h	8 h

AUC, area under the curve; cAMP, cyclic AMP; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; p.o., per os; PDE, phosphodiesterase.

through PKC inhibition. By modulating inflammatory pathways, it decreases airway inflammation and improves respiratory function in patients with BA and COPD (7).

Doxofylline also exhibits PKC inhibitory properties. PKC inhibition potentiates its anti-inflammatory effects, making it a more specific and safer option compared with theophylline for the long-term management of chronic respiratory disease (18,24).

Mechanisms of anti-inflammatory effects. Doxofylline significantly decreases inflammatory response by blocking several inflammatory pathways, such as lipopolysaccharides (LPS)-induced thioredoxin-interacting protein/NOD-like receptor protein 3 (NLRP3) inflammasome activation, leading to decreased IL-1β and IL-18 release (26,27). In addition, it has been shown to reduce the need for steroid use in patients with bronchial inflammation by decreasing eosinophilic and neutrophilic infiltration in lung tissue, accompanied by inhibition of nitric oxide and prostaglandin E2 production (24,28).

Doxofylline decreases LPS-induced lung inflammation in mice (24) and inhibits NLRP3 inflammasome activation in human bronchial epithelial cells (26). Furthermore, rat models confirm that doxofylline may attenuate leukocyte adhesion to the vessel wall and migration of vascular endothelial cells via inhibition of IL-6 and tumor necrosis factor-α release, highlighting its potential role in managing inflammatory respiratory conditions (10,17).

Pharmacological and pharmacokinetic properties of doxofylline. The pharmacological and pharmacokinetic profiles of doxofylline and theophylline reveal notable differences in their mechanisms of action, indications and administration (Table I).

Doxofylline achieves effective bronchodilation at a dosage of 400 mg administered two to three times daily, whereas theophylline requires more variable dosing, typically 300-600 mg daily in 2-3 doses (29). In terms of pharmacokinetics, doxofylline shows high oral bioavailability of 90-100%, compared with 62-96% for theophylline (30), has been reported to reach therapeutic plasma concentrations of 8-20 μg/ml in chronic bronchitis, compared with theophylline's narrower therapeutic range of 5-15 μg/ml (31). However, unlike theophylline, doxofylline generally does not require routine plasma monitoring because of its more favorable pharmacokinetic stability and wider safety margin.

The time to peak concentration for doxofylline is 1.5-2.0 h, with a distribution half-life of about 1.5 h, compared with a longer elimination half-life for theophylline (8.7 h). Doxofylline exhibits moderate protein binding (~48%) and a relatively high volume of distribution (0.81 l/kg), compared with theophylline (40-60% and 0.3-0.7 l/kg, respectively) (30). Its metabolism occurs predominantly in the liver, with >90% of the administered dose metabolized primarily via cytochrome P450 3A4 (CYP3A4), producing inactive metabolites (30), whereas theophylline is metabolized primarily by CYP1A2 and CYP2E1, yielding active metabolites (31).

Renal excretion of doxofylline is minimal, with <4% of the dose excreted unchanged in urine, compared with 10-13% for theophylline. Doxofylline has a total body clearance of 5.4 l/h and an elimination half-life of ~6 h, whereas theophylline shows a clearance of ~0.65 l/h/kg (equivalent to ~2.6-3.0 l/h in adults) and an elimination half-life of approximately 8 h, which may be further prolonged in patients with hepatic or cardiac impairment (30,31).

4. Doxofylline in chronic obstructive airway disease

Doxofylline in COPD. COPD is a prevalent and debilitating respiratory condition that imposes a notable global burden. According to the Global Burden of Disease 2019 study, COPD was the third leading cause of death worldwide, responsible for 3.23 million deaths and affecting ~212 million people (32). This highlights the socio-economic and public health challenges associated with COPD. Effective management of COPD involves a combination of bronchodilators and anti-inflammatory medications aimed at improving lung function and enhancing the quality of life (QoL) in affected patients (32).

Theophylline has been a cornerstone in the treatment of COPD and BA since its introduction in 1937. However, due to its narrow therapeutic window and associated safety concerns, the GOLD Management Strategy guidelines (33) recommend its use only in patients who do not benefit from other bronchodilators or those unable to afford alternative treatments. In this context, doxofylline, a newer methylxanthine derivative, has emerged as a promising alternative (1). Unlike theophylline, doxofylline exhibits distinct pharmacological properties, including minimal effects on PDE isotypes, negligible antagonism at adenosine receptors and no impact on HDAC pathways. While not a direct β_2-agonist, doxofylline may potentiate β_2-adrenergic bronchodilation via increased intracellular cAMP (10,13).

In a clinical study involving 154 patients with COPD, doxofylline was compared with theophylline and demonstrated improvements in baseline spirometric parameters; doxofylline was better tolerated, with fewer side effects and lower dropout rates due to adverse events (34). A subset analysis of high-quality trials confirmed an improvement in FEV_1 of 239 ml (35). Grading of Recommendations Assessment, Development, and Evaluation analysis provided high-quality evidence for the impact of doxofylline on FEV_1 and moderate-quality evidence for its safety profile in COPD (35). Furthermore, an analysis of RCTs reported a significant increase in forced expiratory volume in 1 sec (FEV_1) of 8.2% and 324 ml from baseline with doxofylline (35).

Studies evaluating the effects of doxofylline in severe COPD have demonstrated its efficacy in decreasing respiratory symptoms such as dyspnea and cough and improving exercise tolerance (13,36,37). These findings underscore the rationale for using doxofylline in the treatment of COPD, with a superior efficacy-to-safety profile compared with theophylline (13,34,36).

The safety profile of doxofylline is a critical factor in the management of COPD, particularly given the disease association with significant declines in health-related (HRQoL). Improvements in HRQoL are key indicators of treatment success. Doxofylline is associated with HRQoL improvement (36), consistent with broader evidence on HRQoL determinants in COPD (38). Patients receiving 400 and 800 mg doses of doxofylline demonstrated significant decrease in symptom scores, including cough (77.35 and 97.43%. respectively), shortness of breath (77.60 and 95.90%. respectively) and chest tightness (86.29 and 98.40%. respectively) following 4 weeks of treatment (37). Consistent findings were observed in another study evaluating the combination of doxofylline with inhaled corticosteroids and long-acting bronchodilators, which resulted in significant improvements in QoL score and reductions in the frequency of exacerbation (36).

Doxofylline represents a promising therapeutic alternative for the long-term treatment of COPD. Its enhanced efficacy and safety profile, combined with better tolerability and improvement in lung function and QoL, position it as a safe and effective alternative to traditional therapies for COPD (34,39).

Doxofylline in BA. The literature supports doxofylline as an effective and safe methylxanthine for the treatment of BA, with a superior efficacy-to-safety profile compared with theophylline (13,36).

A meta-analysis demonstrated that doxofylline is more effective than theophylline in decreasing daily BA events and preventing adverse reactions (13). Similar findings were reported in other studies, which highlighted improvements in spirometric parameters, decreased consumption of salbutamol and fewer undesirable side effects or treatment dropouts (13,18). In patients with BA responsive to salbutamol, particularly those with features overlapping with COPD, increases in spirometric values-including slow and forced vital capacity (FVC), FEV_1, forced expiratory flow at 25-75%, and peak expiratory flow rate-have also been reported, consistent with evidence from bronchodilator response studies in BA and Asthma-COPD Overlap (ACO) (40).

Although a meta-analysis found no notable difference between doxofylline and theophylline in terms of FEV_1 improvement, doxofylline is superior in reducing the need for salbutamol as a rescue medication (13). Moreover, the LESDA long-term trial demonstrated that one year of doxofylline therapy in asthmatic patients significantly improved FEV_1, reduced daily asthma event rates, and decreased salbutamol usage, with a favorable safety profile (41).

Doxofylline has also proven to be a rapid and effective bronchodilator in mechanically ventilated patients with acute respiratory failure and airflow obstruction. It is associated with a decrease in respiratory resistance and intrinsic positive end-expiratory pressure, thereby improving the mechanical efficiency of respiratory muscles at lower lung volumes (42).

Table II. Estimated monthly costs of therapies used in bronchial asthma and chronic obstructive pulmonary disease.

Therapy	Estimated monthly cost, €	Remarks	(Refs.)
Doxofylline (400 mg twice daily)	5-15	Widely available; generic options	(1,30)
Theophylline (300-400 mg twice daily)	5	Narrow therapeutic window	(1,31)
LABA (such as salmeterol)	35-65	Inhaler; moderate accessibility	(1,3)
LAMA (such as tiotropium)	45-65	Inhaler; limited access in low-income countries	(1,3)
ICS/LABA combination (such as Symbicort)	55-75	Moderate to high cost	(1,3)
Biological agents (such as omalizumab)	800	For severe cases only; hospital-based administration	(3,4)

Costs may vary by country, manufacturer and reimbursement scheme. Data were obtained from international guidelines [Global Initiative for Chronic Obstructive Lung Disease 2019, Global Initiative for Asthma 2024, World Health Organization (WHO) databases, and DrugBank]. LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

A meta-analysis involving 820 patients from 20 RCTs demonstrated that doxofylline significantly improves FEV_1, with fewer adverse events (35). Another meta-analysis examining the efficacy and safety of xanthines in BA reported that while doxofylline is no more effective than aminophylline or theophylline in improving baseline FEV_1, it is superior in alleviating dyspnea and significantly safer than both aminophylline and theophylline (13).

Drug interactions and safety considerations. As with other methylxanthines, doxofylline is associated with potential drug interactions. Concomitant use of doxofylline with certain drugs such as erythromycin, troleandomycin, lincomycin, clindamycin, allopurinol, cimetidine, ranitidine, propranolol, is not recommended. These agents may decrease the hepatic clearance of xanthines, leading to elevated plasma levels of doxofylline (8,10,17). Additionally, doxofylline should not be co-administered with other xanthine derivatives to avoid competitive inhibition at enzymatic metabolization sites, which may further slow drug clearance (30).

Adverse effects associated with doxofylline are typically mild and may include gastrointestinal disturbances such as nausea and vomiting, as well as CNS symptoms such as headache and dizziness. Notably, doxofylline has a reduced incidence of cardiovascular side effects, including tachycardia and palpitations, compared with other xanthines (30).

In terms of drug interactions, doxofylline safety profile is favorable due to its limited interaction with CYP450 enzymes, reducing the likelihood of significant interactions with other medications metabolized via this pathway (8,10,17,30), although caution is advised when co-administering doxofylline with other xanthine derivatives to prevent potential additive effects.

Overall, improved therapeutic window and reduced adverse effect profile make doxofylline a safer alternative to traditional methylxanthines in the management of respiratory conditions.

Cost considerations. COPD continues to represent a significant economic burden despite therapeutic advances, particularly in resource-limited regions. Doxofylline is a cost-effective option compared with other commonly used bronchodilators in the treatment of COPD and BA (Table II). For example, the average monthly price of doxofylline at usual doses (400 mg twice daily) is €5-15 (1,30). In comparison, tiotropium, a commonly used inhaled anticholinergic, has an estimated monthly cost of €45-65, while inhaled formoterol and budesonide-based inhaled combinations are €55-75/month (1,3). Salmeterol, either as monotherapy or in combination with fluticasone, incurs a monthly cost of €35-65, depending on dosage and formulation (1,4).

Despite being inexpensive (~€5/month), theophylline is limited by its narrow therapeutic window and increased risk of side effects, requiring close monitoring. In this context, doxofylline offers an advantageous balance between efficacy, superior safety profile and economic sustainability. Therefore, compared with riskier options (such as theophylline) and costly modern therapy, doxofylline represents a viable and affordable therapeutic alternative.

5. Future considerations

The present review has certain limitations. First, the data presented are mainly from studies published in English, which may introduce a selection bias. Second, methodological variability between the included studies in terms of design, study population, doses administered and treatment duration limits the possibility to draw generalizable conclusions. To the best of our knowledge, there is a lack of recent studies on certain pharmacological aspects of doxofylline. In addition, the lack of recent meta-analyses and direct comparisons with modern biological therapies decreases the ability to position doxofylline in relation to state-of-the-art treatments. Therefore, further multicenter and independent research is needed to validate the conclusions.

Future research on doxofylline should focus on long-term safety and efficacy studies across diverse populations, including pediatric and elderly patients, to ensure its broad applicability. Comparative studies with newer bronchodilators and anti-inflammatory agents are needed to define

its role in combination therapy, particularly in severe and overlapping respiratory conditions. Exploring pharmacogenomic factors, biomarkers of treatment response and its potential in non-respiratory indications may provide insights into personalized medicine. Additionally, economic analyses and cost-effectiveness studies, especially in low- and middle-income countries, may support its global adoption. Further mechanistic research into doxofylline pathways, such as selective PDE inhibition and HDAC activity, may unlock novel therapeutic potential.

6. Conclusion

Doxofylline represents a notable advancement in the treatment of chronic respiratory diseases such as COPD and BA. By contrast with theophylline, whose use has diminished due to its narrow therapeutic window and associated side effects, doxofylline offers a more favorable safety profile and wider therapeutic margin (8,10). Meta-analyses and clinical studies have demonstrated that doxofylline not only enhances spirometric parameters and decreases the need for salbutamol administration but also results in fewer adverse effects, thereby improving patient tolerance and compliance (13,36,38). Clinical evidence highlights significant improvements in lung function, exercise capacity and QoL among patients treated with doxofylline (17). Its ability to improve airway function and exert anti-inflammatory effects, coupled with its rapid bronchodilator activity in acute situations, underscores its potential as a therapeutic alternative (9,14). Moreover, doxofylline decreases glucocorticoid dependence and promotes long-term inflammation control, with a low incidence of adverse reactions, making it a safer option for clinical use (10,36). The present review may help clarify the clinical role of xanthine derivatives in COPD, particularly regarding the safety concerns and narrow therapeutic window of theophylline (10,13,38).

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Authors' contributions

SC, ACe and ACo conceived the study. SC, DP, AB, ACe, ACo, VEG and DAS performed the literature review and wrote the manuscript SC and ACo revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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