Efficacy and safety profile of xanthines in COPD: a network meta-analysis

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ABSTRACT Theophylline can still have a role in the management of stable chronic obstructive pulmonary disease (COPD), but its use remains controversial, mainly due to its narrow therapeutic window. Doxofylline, another xanthine, is an effective bronchodilator and displays a better safety profile than theophylline. Therefore, we performed a quantitative synthesis to compare the efficacy and safety profile of different xanthines in COPD.

The primary end-point of this meta-analysis was the impact of xanthines on lung function. In addition, we assessed the risk of adverse events by normalising data on safety as a function of person-weeks. Data obtained from 998 COPD patients were selected from 14 studies and meta-analysed using a network approach.

The combined surface under the cumulative ranking curve (SUCRA) analysis of efficacy (change from baseline in forced expiratory volume in 1 s) and safety (risk of adverse events) showed that doxofylline was superior to aminophylline (comparable efficacy and significantly better safety), bamiphylline (significantly better efficacy and comparable safety), and theophylline (comparable efficacy and significantly better safety).

Considering the overall efficacy/safety profile of the investigated agents, the results of this quantitative synthesis suggest that doxofylline seems to be the best xanthine for the treatment of COPD.

Introduction

Theophylline is one of the most widely prescribed drugs worldwide for the treatment of chronic obstructive pulmonary disease (COPD), not only because it is inexpensive and widely available, but also because it may benefit patients with COPD [1]. In fact, it improves both trough and peak forced expiratory volume in 1 s (FEV_1) and forced vital capacity in clinically stable COPD patients [2]. Furthermore, it is able to increase exercise tolerance [3, 4], probably because it reduces air trapping, suggesting an effect on peripheral airways [5], and this may explain why some patients with COPD may obtain considerable symptomatic improvement without any increase in spirometric values [6]. In patients

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with severe COPD, withdrawal of theophylline causes significant clinical deterioration despite therapy with other bronchodilators, indicating its added value [7]. Besides, compared with placebo, theophylline seems more effective over 12 months at reducing the frequency and duration of acute COPD exacerbations [8]. In addition, the use of theophylline leads to effects such as anti-inflammatory activity and improved diaphragm contractility, but their clinical relevance has not been firmly established [1].

Therefore, theophylline can have a role in the management of stable COPD [1]. However, recommendations for treating COPD with theophylline vary across national guidelines [9], probably because there are many controversies about its use [10], as it is less effective and well tolerated than inhaled long-acting bronchodilators and inhaled corticosteroids have a greater anti-inflammatory effect [1]. In most treatment guidelines, theophylline is relegated to second- or third-line therapy because of its narrow therapeutic window and propensity for pharmacological interactions [10], which makes its use challenging, especially in elderly patients with comorbidities receiving multiple classes of drug. Moreover, a recent meta-analysis of seven observational studies has suggested that theophylline slightly increases all-cause death in COPD patients [11].

Several other xanthines, such as aminophylline, bamiphylline and doxofylline, have been synthesised to be used clinically in various parts of the world for the treatment of respiratory disease, with the anticipation that such drugs would have greater efficacy than theophylline, but with improved side-effect profiles because of their different pharmacological profiles (table 1).

There is evidence that doxofylline, at least, is an effective bronchodilator for relieving airway obstruction and displays a better safety profile than theophylline, having a favourable risk-to-benefit ratio [12–14]. These findings suggest that it could be an attractive alternative to theophylline in the treatment of patients with COPD. However, doxofylline is not included in any guideline for management of COPD, probably also because most trials of doxofylline in people with COPD have used small numbers of participants. Undoubtedly, there is an evident dichotomy between the safety and efficacy profile of doxofylline that arises from clinical trials and positioning of this oral xanthine in the treatment of COPD.

Given the number of xanthines available for COPD and the absence of clinical trials that have directly compared all relevant agents, we performed a systematic review and network meta-analysis of randomised and nonrandomised clinical trials with the aim of evaluating their comparative efficacy and safety in patients with stable COPD.

Materials and methods

Search strategy

This network meta-analysis has been registered at PROSPERO (www.crd.york.ac.uk/PROSPERO identifier number CRD42017077901), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (figure S1A) [15]. This quantitative synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist [16].

Two reviewers (MC and LC) performed a comprehensive literature search for clinical studies evaluating the influence of xanthines in COPD patients. The PICO (patient problem, intervention, comparison and outcome) framework was used to develop the literature search strategy, as previously described [17].

TABLE 1 Main pharmacological characteristics of the xanthines investigated in this quantitative synthesis

	Adenosine receptors (antagonism, affinity)	PDE (inhibitory potency)	PI_3 kinase (inhibitory potency)	HDAC (inhibitory potency)
Bamiphylline	A_1/A_2 562-fold	NA	NA	NA
Doxofylline	A_1, A_{2A}, A_{2B} and A_3 >100 μM	PDE2A 100 μM other PDEs >100 μM (modest effect)	NA	HDAC1-11 no effect
Enprophylline	A_1 42–156 μM A_{2A} 38–81 μM A_{2B} 5–20 μM A_3 65–93 μM	PDE1-5 >100 μM (modest effect)	NA	NA
Theophylline and aminophylline (theophylline ethylenediamine)	A_1 10–30 μM A_{2A} 2–10 μM A_{2B} 10–30 μM A_3 20–100 μM	PDE3 98 μM PDE4 150 μM	100 μM	HDAC1-11 no effect

PDE: phosphodiesterase; PI_3: phosphoinositide-3; HDAC: histone deacetylase; NA: not available.

Namely, the "patient problem" included subject affected by stable COPD; the "intervention" regarded the administration of different xanthines; the effect of placebo and/or the values at baseline in clinical trials were used as "control"; and the assessed "outcomes" were the lung function, risk of adverse events, the therapeutic efficacy and dyspnoea. Thus, the terms aminophylline, bamiphylline, doxofylline, enprophylline and theophylline were searched for the drugs, and the terms chronic obstructive pulmonary disease or COPD were searched for the disease. The main pharmacological characteristics of the xanthines investigated in this quantitative synthesis are reported in table 1.

The search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Scopus, Google Scholar, Web of Science and ClinicalTrials.gov databases through February 2018, in order to provide for relevant studies available up to February 27, 2018. No language restriction was applied.

The clinical trials reporting the efficacy and/or safety profile of xanthines in COPD patients were searched in agreement with the following query translation: ["pulmonary disease, chronic obstructive"[medical subject heading (MeSH) terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR "copd"[All Fields]) AND (("bamiphylline"[Supplementary Concept] OR "bamiphylline"[All Fields]) OR ("enprophylline"[Supplementary Concept] OR "enprophylline"[All Fields]) OR ("doxofylline"[Supplementary Concept] OR "doxofylline"[All Fields]) OR ("theophylline"[MeSH Terms] OR "theophylline"[All Fields]) OR ("aminophylline"[MeSH Terms] OR "aminophylline"[All Fields]))].

Study selection

Published and unpublished clinical trials (both randomised and non-randomised) involving COPD patients and reporting the direct comparison between at least two different xanthines with regard to the efficacy and/or safety profile were included in this network meta-analysis.

Clinical trials reporting no direct comparison across xanthines, those not reporting data on efficacy and/or safety profile, and those available exclusively as abstracts were excluded by this network meta-analysis synthesis. Furthermore, nonclinical trials were excluded by this quantitative synthesis.

Two reviewers (MC and LC) independently checked the relevant studies identified from literature searches obtained from the abovementioned databases. The studies were selected in agreement with the abovementioned criteria, and any difference in opinion about eligibility was resolved by general consensus.

Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of the clinical trials concerning the likelihood of biases related to randomisation, double blinding, withdrawals and dropouts [18]. A Jadad score $\geqslant 3$ was defined to identify high-quality studies. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The risk of bias for the impact of xanthines on lung function and their safety profile in stable COPD patients was assessed *via* the consistency/inconsistency analysis to check whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [19]. Furthermore, the inconsistency of evidence was also assessed by quantifying the inconsistency factor, indicating whether one of the treatment had a different effect when it was compared with the others [20].

Meta-regression analysis was performed to examine the source of heterogeneity between studies and identify potential confounder covariates specifically for the impact of xanthines on lung function and the risk of adverse events [19].

The quality of the evidence concerning the impact of xanthines on lung function and the risk of adverse events was assessed in agreement with the grading of recommendations assessment, development and evaluation (GRADE) system [21].

Data extraction

Data from included studies were extracted and checked for study characteristics and duration, doses of xanthines, concomitant medications, disease characteristics, ethnicity, age, sex, lung function, safety, therapeutic efficacy, dyspnoea and Jadad score. Due to the complexity of this meta-analysis, data have been extracted in agreement with data extraction for complex meta-analysis (DECiMAL) recommendations [22].

End-points

The primary end-point of this meta-analysis was the impact of different xanthines on the change from baselines in FEV_1.

The secondary end-point were the risk of adverse events, *via* normalising the data on safety as a function of person-weeks, therapeutic efficacy (the rate of patients that achieved the 3rd or 4th rank in a four-point nonvalidated scale, or that achieved the 2nd or 3rd rank in a three-point nonvalidated scale, where the higher values represented greater therapeutic efficacy [23–27]) and the change from baseline in dyspnoea *via* the Medical Research Council scale [28] or a nonvalidated dyspnoea score that assessed dyspnoea using a four-point scale [29, 30]. More details concerning the scales used to assess the therapeutic efficacy and dyspnoea are reported in table S1.

Data analysis

This network meta-analysis was performed to compare the impact of specific xanthines in COPD patients by analysing the data extracted from studies that directly compared at least two different xanthines. Results are expressed as relative effect and 95% credible interval (95% CrI).

A full Bayesian evidence network was used (chains: 4; initial values scaling: 2.5; tuning iterations: 20 000; simulation iterations: 50 000; tuning interval: 10), and the convergence diagnostics for consistency and inconsistency was assessed *via* the Brooks–Gelman–Rubin method, as previously reported [31].

Due to the characteristics of parameters besides the available data, the noninformative distributions specified the prior densities, in agreement with the Bayesian approaches to clinical trials and healthcare evaluation [32, 33]. Since the distributions were sufficiently vague, the reference treatment, study baseline effects and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, *via* heuristically determining a value for the outcome scale parameter (*i.e.* outcome scale S) [34, 35]. The posterior mean deviance of data points in the unrelated mean effects model were plotted against their posterior mean deviance in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent [36].

The efficacy/safety profile was assessed by plotting the summary findings regarding the relative efficacy and safety of specific xanthines comparisons, as previously described [37]. Furthermore, the probability that each intervention arm was the most effective than the others was calculated by counting the proportion of iterations of the chain in which each intervention arm had the highest mean difference, and the surface under the cumulative ranking curve (SUCRA), representing the summary of these probabilities, was also calculated. The SUCRA is 100% when a treatment is certain to be the best, and 0% when a treatment is certain to be the worst [31, 38].

A pooled analysis was performed to calculate the frequency of adverse events, ranked in agreement with the European Medicine Agency undesirable effects (section 4.8), as follows. Very common: $\geqslant$1/10; common $\geqslant$1/100 to <1/10; uncommon $\geqslant$1/1000 to <1/100; frequency not known if not calculable from the available data (www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/01/WC500137021.pdf). The overall adverse events frequency and the frequency of specific adverse events were compared across the investigated drugs.

OpenMetaAnalyst [39] and GeMTC [34] software were used for performing the network meta-analysis and meta-regression, OpenEpi [40] software for the pooled analysis, GraphPad Prism (La Jolla, CA, USA) software to graph the data, and GRADEpro software to assess the quality of evidence [21]. Statistical significance was considered to be $p<0.05$.

Results

Study characteristics

Data obtained from 998 COPD patients (47.94% treated with doxofylline, 24.82% treated with theophylline, 21.71% treated with aminophylline and 5.53% treated with bamiphylline) were selected from 14 studies [23–27, 29, 30, 41–47] published between 1987 and 2016. The relevant studies and patients' characteristics are described in table S2, and figure S1B shows the network across the xanthines involved in the Bayesian analysis.

All the meta-analysed clinical trials were published as full-text papers [23–27, 29, 30, 41–47]. Four studies had a Jadad score $\geqslant$3 [23, 24, 42, 45, 47], and 10 studies had a Jadad score $\geqslant$1 and <3 [25–27, 29, 30, 41, 43, 44, 46, 47]. The length of treatment ranged from 1 day to 12 weeks.

Network meta-analysis

Primary end-point

No significant differences were detected with regard to the change from baseline in FEV_1 across aminophylline, doxofylline, and theophylline. The subset analysis of the studies that expressed the change from baseline in FEV_1 as volume (mL or L) indicated that theophylline increased FEV_1 by 12.0 (95% CrI −142.5–173.7) mL *versus* doxofylline and 69.6 (95% CrI −211.6–348.2) mL *versus* aminophylline, and that doxofylline increased FEV_1 by 55.4 (95% CrI −212.5–310.5) mL *versus* aminophylline. In contrast, aminophylline, doxofylline and theophylline were both significantly ($p<0.001$) more effective than bamiphylline (figure 1a). Specifically, aminophylline, doxofylline and theophylline increased FEV_1 by 538.1 (95% CrI 122.6 –850.7) mL, 593.5 (95% CrI 271.1–791.6) mL and 604.3 (95% CrI 246.2–846.1) mL, respectively, *versus* bamiphylline ($p<0.001$).

Secondary end-points

Doxofylline was significantly ($p<0.001$) safer than both aminophylline and theophylline, whereas no difference resulted *versus* bamiphylline. No significant differences were detected with regard to the risk of adverse events across aminophylline, bamiphylline and theophylline (figure 1b).

When coupling relative effects for efficacy and safety, doxofylline appeared to be superior to aminophylline (comparable efficacy and significantly better safety), bamiphylline (significantly better efficacy and comparable safety) and theophylline (comparable efficacy and significantly better safety), as shown by the efficacy/safety analysis reported in figure 2a. The superiority of doxofylline over aminophylline, bamiphylline and theophylline was further confirmed by the combined efficacy/safety SUCRA analysis (figure 2b).

The SUCRA analysis also indicated that doxofylline was the most effective xanthine with regard to the impact on therapeutic efficacy (SUCRA value 0.71), followed by aminophylline (SUCRA value 0.49) and theophylline (SUCRA value 0.31). Doxofylline and aminophylline both elicited a greater beneficial impact on the improvement of dyspnoea score (SUCRA values 0.75 and 0.71, respectively), compared with theophylline (SUCRA value 0.04).

Pooled analysis of safety profile

The overall pooled analysis of the safety profile showed that the frequency of adverse events detected in COPD patients treated with doxofylline (22.0%) was significantly ($p<0.001$) lower than that found for both theophylline (61.7%) and aminophylline (54.55%).

The analysis of specific adverse events is reported in table 2, and showed that the most frequent adverse events were correlated with the administration of aminophylline (palpitations 12.73%, gastrointestinal discomfort 11.82% and insomnia 9.09%) and theophylline (nausea 10.8%, epigastralgia 9.1%, headache 8.6% and dyspepsia 7.3%). Generally, the frequency of specific adverse events induced by doxofylline was significantly ($p<0.05$) lower than that detected for both theophylline and aminophylline. The pooled analysis was not performed on bamiphylline since no data were available concerning the specific adverse events.

The percentage of patients that withdrew from the clinical trials due to adverse events was significantly ($p<0.001$) higher in the subjects treated with theophylline (10.0%) compared with those treated with doxofylline (2.6%). Overall, the reported adverse events that led to study discontinuation were dyspepsia, epigastralgia, nausea and palpitations. No data are available concerning the withdrawal due to adverse events for the other investigated xanthines.

Bias and quality of evidence

The analysis of inconsistency showed that no significant discrepancy exists between direct and indirect evidences for both efficacy (inconsistency factor −0.05, 95% CrI −0.64–0.69; $p\geqslant0.05$) and safety profile (inconsistency factor −1.39, 95% CrI −4.69–0.73; $p\geqslant0.05$). The consistency/inconsistency analysis indicated that all points fit adequately with the line of equality (efficacy R^2 0.99, slope 0.99, 95% CI 0.92–1.07; safety: R^2 0.95, slope 1.26, 95% CI 0.86–1.66) (figure S2).

The meta-regression model of the effect estimates resulting for FEV_1 indicated that neither the total dose (study duration × daily dose) of xanthines administered to COPD patients during the studies, nor the route of administration, lung function, ethnicity and Jadad score were significant ($p>0.05$) confounder variables that may have altered the results of this meta-analysis. The meta-regression model of the effect estimates resulting for adverse events indicated that neither lung function, nor ethnicity and Jadad score represented effect modifiers. Conversely, the total dose of xanthines administered during the studies (coefficient −0.08, $p<0.001$) and the route of administration (oral *versus i.v.* coefficient 1.41, $p<0.001$) were significant confounding factors for the frequency of adverse events (figure S3).

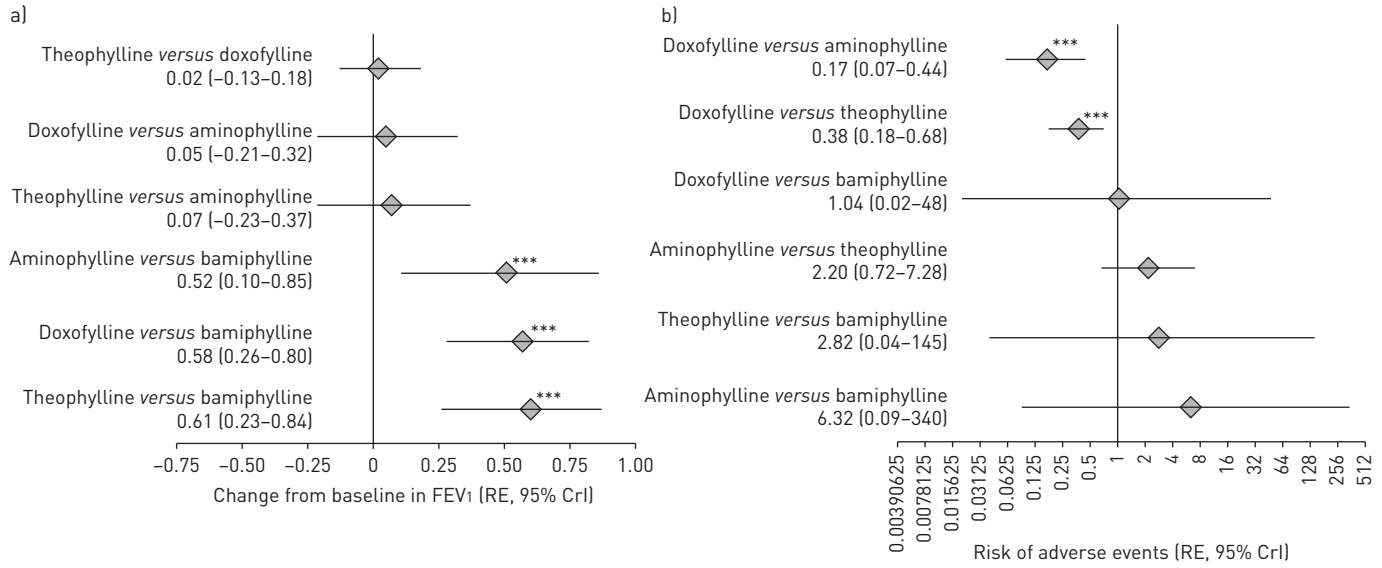

FIGURE 1 Impact of xanthines on change from baselines in a) forced expiratory volume in 1 s (FEV_1) and b) the risk of adverse events. RE: relative effect; CrI: credible interval. ***: p<0.001 *versus* comparators.

The GRADE analysis of the change from baseline in FEV_1 indicated moderate quality of evidence (+++) for the use of doxofylline *versus* theophylline/aminophylline, low quality of evidence (++) for the use of doxofylline *versus* bamiphylline and very low quality of evidence (+) for the use of theophylline *versus* aminophylline/bamiphylline and aminophylline *versus* bamiphylline.

The GRADE analysis of the risk of adverse events indicated high quality of evidence (++++) for the use of doxofylline *versus* theophylline/aminophylline and very low quality of evidence (+) for the use of

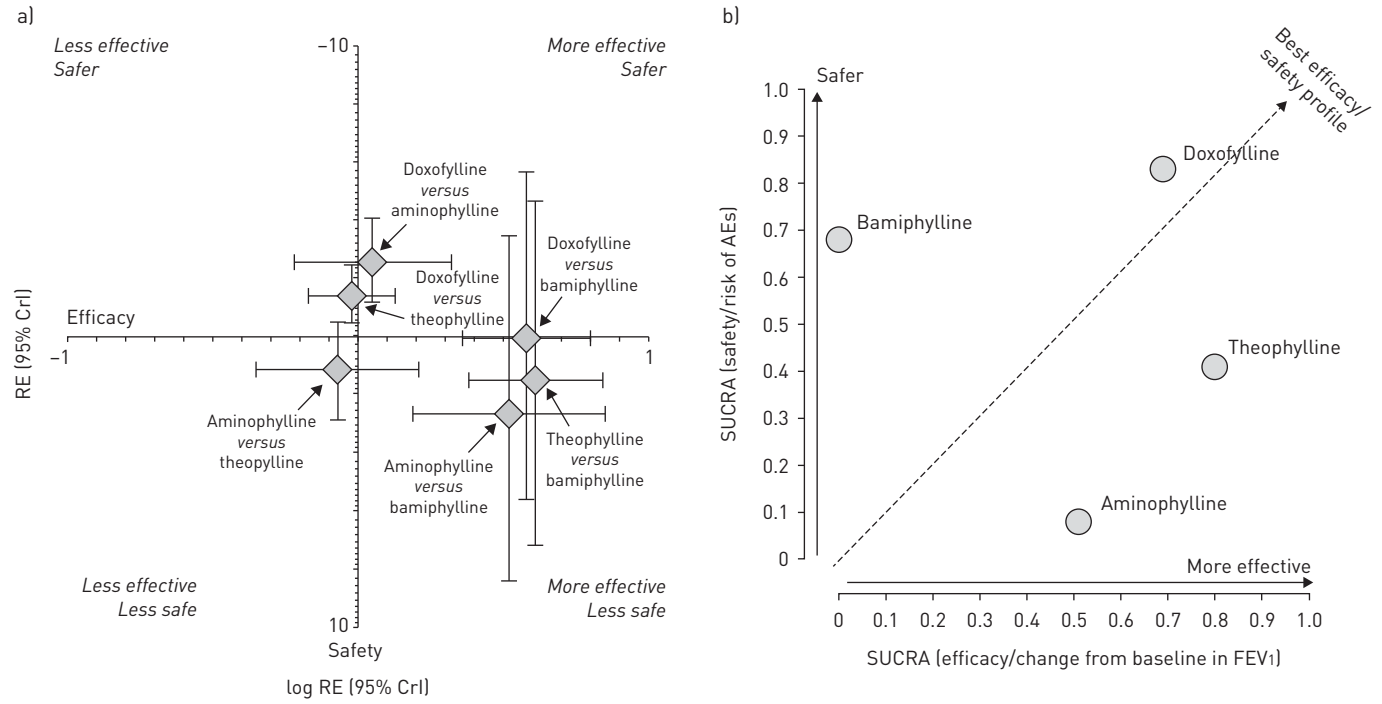

FIGURE 2 Summary findings regarding the efficacy/safety profile across xanthines in chronic obstructive pulmonary disease patients. a) Combined plot of the change from baseline in forced expiratory volume in 1 s (FEV_1) and the risk of adverse events (AEs) of specific xanthine comparisons. b) Combined efficacy/safety SUCRA (surface under the cumulative ranking curve) analysis of specific xanthines. RE: relative effect; CrI: credible interval.

TABLE 2 Pooled analysis of adverse events extracted from the studies on xanthines administered in chronic obstructive pulmonary disease patients and ranked by frequency in agreement with European Medicines Agency guidelines [64]

	Doxofylline			Theophylline			Aminophylline		
	Adverse events	Rank	Statistical notes	Adverse events	Rank	Statistical notes	Adverse events	Rank	Statistical notes
Subjects n		391			232			110	
Palpitations	3 (0.77)	+	Lower frequency *versus* theophylline* and aminophylline***	7 (3.02)	++	Higher frequency *versus* doxofylline*, lower frequency *versus* aminophylline***	14 (2.73)	+++	Higher frequency *versus* doxofylline*** or theophylline***
Gastrointestinal discomfort	3 (0.77)	+	No difference *versus* theophylline (NS), lower frequency *versus* aminophylline***	2 (0.86)	+	No difference *versus* doxofylline (NS), lower frequency *versus* aminophylline***	13 (11.82)	+++	Higher frequency *versus* either doxofylline*** and theophylline***
Insomnia	3 (0.77)	+	Lower frequency *versus* theophylline** and aminophylline***	11 (4.74)	++	Higher frequency *versus* doxofylline**, no difference *versus* aminophylline (NS)	10 (9.09)	++	Higher frequency *versus* doxofylline***, no difference *versus* theophylline (NS)
Nausea	15 (3.84)	++	Lower frequency *versus* theophylline***, no difference *versus* aminophylline (NS)	25 (10.78)	+++	Higher frequency *versus* doxofylline*** or aminophylline**	1 (0.91)	+	No difference *versus* doxofylline (NS), lower frequency *versus* theophylline**
Epigastralgia	21 (5.37)	++	A signal of lower frequency *versus* theophylline (p=0.07), no difference *versus* aminophylline (NS)	21 (9.05)	++	A signal of higher frequency *versus* doxofylline (p=0.07), no difference *versus* aminophylline (NS)	6 (5.45)	++	No difference *versus* doxofylline (NS) or theophylline (NS)
Headache	12 (3.07)	++	Lower frequency *versus* theophylline**, no difference *versus* aminophylline (NS)	20 (8.62)	++	Higher frequency *versus* doxofylline** or aminophylline*	1 (0.91)	+	No difference *versus* doxofylline (NS), lower frequency *versus* theophylline*
Other	1 (0.26)	+	Lower frequency *versus* theophylline***	18 (7.76)	++	Higher frequency *versus* doxofylline***	0 (FNK)	FNK	NC
Dyspepsia	12 (3.07)	++	Lower frequency *versus* theophylline*	17 (7.33)	++	Higher frequency *versus* doxofylline*	0 (FNK)	FNK	NC
Anxiety	1 (0.26)	+	Lower frequency *versus* theophylline* or aminophylline**	5 (2.16)	++	Higher frequency *versus* doxofylline*, no difference *versus* aminophylline (NS)	5 (4.55)	++	Higher frequency *versus* doxofylline**, no difference *versus* theophylline (NS)
Arrhythmia	2 (0.51)	+	No difference *versus* theophylline (NS), a signal of lower frequency *versus* aminophylline (p=0.06)	2 (0.86)	+	No difference *versus* doxofylline (NS) or aminophylline (NS)	4 (3.64)	++	A signal of higher frequency *versus* doxofylline (p=0.06), no difference *versus* theophylline (NS)
Flushing	0 (FNK)	FNK	NC	0 (FNK)	FNK	NC	4 (3.64)	++	NC
Tremors	1 (0.26)	+	Lower frequency *versus* theophylline*	5 (2.16)	++	Higher frequency *versus* doxofylline*	0 (FNK)	FNK	NC
Vomiting	1 (0.26)	+	A signal of lower frequency *versus* theophylline (p=0.07)	4 (1.72)	++	A signal of higher frequency *versus* doxofylline (p=0.07)	0 (FNK)	FNK	NC
Tachycardia	0 (FNK)	FNK	NC	3 (1.29)	++	NC	0 (FNK)	FNK	NC
Anorexia	3 (0.77)	+	No difference *versus* theophylline (NS)	3 (1.29)	++	No difference *versus* doxofylline (NS)	0 (FNK)	FNK	NC
Chest pain	2 (0.51)	+	No difference *versus* theophylline (NS)	3 (1.29)	++	No difference *versus* doxofylline (NS)	0 (FNK)	FNK	NC
Sweating	1 (0.26)	+	No difference *versus* theophylline (NS)	3 (1.29)	++	No difference *versus* doxofylline (NS)	0 (FNK)	FNK	NC
Diarrhoea	0 (FNK)	FNK	NC	0 (FNK)	FNK	NC	1 (0.91)	+	NC

Continued

TABLE 2 Continued

	Doxofylline			Theophylline			Aminophylline		
	Adverse events	Rank	Statistical notes	Adverse events	Rank	Statistical notes	Adverse events	Rank	Statistical notes
Hypotension	0 (FNK)	FNK	NC	0 (FNK)	FNK	NC	1 (0.91)	+	NC
Dizziness	1 (0.26)	+	No difference *versus* theophylline (NS)	2 (0.86)	+	No difference *versus* doxofylline (NS)	0 (FNK)	FNK	NC
Dry mouth	2 (0.51)	+	No difference *versus* theophylline (NS)	1 (0.43)	+	No difference *versus* doxofylline (NS)	0 (FNK)	FNK	NC
Excitation	0 (FNK)	FNK	NC	1 (0.43)	+	NC	0 (FNK)	FNK	NC
Constipation	2 (0.51)	+	NC	0 (FNK)	FNK	NC	0 (FNK)	FNK	NC

Data are presented as n or n (%), unless otherwise stated. +: uncommon ⩾1/1000 to <1/100; ++: common ⩾1/100 to <1/10; +++: very common ⩾1/10. NS: nonsignificant (p>0.05); FNK: frequency not known; NC: not calculable. *: p<0.05; **: p<0.01; ***: p<0.001.

doxofylline *versus* bamiphylline, theophylline *versus* aminophylline/bamiphylline and aminophylline *versus* bamiphylline (table 3).

Discussion

The results of our network meta-analysis demonstrate that doxofylline seems to be the best xanthine in the treatment of COPD. The SUCRA analysis has shown that doxofylline was the most effective xanthine with regard to the impact on therapeutic efficacy, followed by aminophylline and theophylline. Although no significant differences have been detected with regard to the change from baseline in FEV_1 across aminophylline, doxofylline and theophylline, doxofylline and aminophylline elicited a greater beneficial impact on the improvement of dyspnoea score compared to theophylline. Moreover, doxofylline was significantly safer than both aminophylline and theophylline. The superiority of doxofylline over aminophylline, bamiphylline and theophylline has further been confirmed by the combined efficacy/safety SUCRA analysis. It is noteworthy that the meta-regression has shown that both the lung function and the total dose of xanthines administered during the studies, which can be translated as the expression of the severity of COPD, did not influence the results.

Although improving lung function is not an objective of COPD management [10], it is the primary end-point most frequently used by regulatory authorities in interpreting drug efficacy in COPD trials. A minimal clinically important difference (MCID) of 100 mL for pre-dose or trough FEV_1 has been proposed, based on clinical anchoring to end-points such as exacerbations, perception of dyspnoea and decline in lung function [48]. This MCID was largely achieved with aminophylline, doxofylline and theophylline when compared with bamiphylline, but not across them. The diversity of the tools used to evaluate the impact of treatments on dyspnoea makes the evaluation of the real clinical impact of the different xanthines on this symptom much more problematic. However, to rank the treatments for an outcome, we used SUCRA probabilities, which express as a percentage the efficacy of every intervention relative to an imaginary intervention that is always the best without uncertainty. Thus, large SUCRA scores might indicate a more effective intervention [32, 39]. The high SUCRA ranking of doxofylline suggests that it is more effective than theophylline in reducing dyspnoea. Interestingly, the combined efficacy/safety SUCRA analysis documented the superiority of doxofylline over aminophylline, bamiphylline and theophylline.

The results of the present meta-analysis are not surprising considering that doxofylline should not be assumed just as another theophylline [14]. It is now well established that doxofylline possesses a distinct pharmacological profile from theophylline (table 1 and figure S4). In fact, it does not elicit any significant effect on any of the known phosphodiesterase isoforms, lacks significant adenosine receptor antagonism, does not cause a direct effect on any of the known histone deacetylase enzymes, and interacts favourably with β_2-adrenoceptors [49, 50].

Theophylline is inexpensive and widely available, and it might improve the action of another bronchodilator or even be a sufficient bronchodilator by itself in certain patients [51]. Furthermore, a potent anti-inflammatory effect at lower doses, which suggests the drug may be useful as a steroid-sparing therapy in patients with severe COPD, has been identified [1]. Nevertheless, because of its toxicity at levels close to the therapeutic range [9], theophylline is rarely used as a first-line COPD medication [1]. However, in low doses theophylline can still be considered to be an add-on therapy in those patients with severe or very severe COPD. In fact, the Spanish COPD guidelines (GesEPOC) 2017 [52] relegate it to

TABLE 3 GRADE (grading of recommendations assessment, development and evaluation) evidence profile: impact of xanthines on change from baseline in forced expiratory volume in 1 s (FEV_1) and risk of adverse events in chronic obstructive pulmonary disease (COPD) patients

	Quality assessment: impact of xanthines in COPD					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Change from baseline in FEV_1						
Should doxofylline *versus* theophylline be used in COPD patients?	Serious[#]	Not serious	Not serious	Serious[¶]	Dose response gradient	⊕⊕⊕○ Moderate
Should doxofylline *versus* aminophylline be used in COPD patients?	Serious[#]	Not serious	Not serious	Serious[¶]	Dose response gradient	⊕⊕⊕○ Moderate
Should doxofylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Not serious	Not serious	None	⊕⊕○○ Low
Should theophylline *versus* aminophylline be used in COPD patients?	Very serious[#]	Not serious	Serious[+]	Serious[¶]	Publication bias strongly suspected[§]	⊕○○○ Very low
Should theophylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Very serious[f]	Not serious	Very strong association, publication bias strongly suspected[##]	⊕○○○ Very low
Should aminophylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Very serious[f]	Not serious	Very strong association, publication bias strongly suspected[##]	⊕○○○ Very low
Risk of adverse events						
Should doxofylline *versus* theophylline be used in COPD patients?	Serious[#]	Not serious	Not serious	Not serious	Strong association, dose response gradient	⊕⊕⊕⊕ High
Should doxofylline *versus* aminophylline be used in COPD patients?	Serious[#]	Not serious	Not serious	Not serious	Very strong association, dose response gradient	⊕⊕⊕⊕ High
Should doxofylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Serious[+]	Serious[¶]	Publication bias strongly suspected[§]	⊕○○○ Very low
Should theophylline *versus* aminophylline be used in COPD patients?	Very serious[#]	Not serious	Serious[+]	Serious [¶]	Publication bias strongly suspected[§]	⊕○○○ Very low
Should theophylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Very serious[f]	Serious[¶]	Publication bias strongly suspected[##]	⊕○○○ Very low
Should aminophylline *versus* bamiphylline be used in COPD patients?	Very serious[#]	Not serious	Very serious[f]	Serious[¶]	Publication bias strongly suspected[##]	⊕○○○ Very Low

GRADE working group grades of evidence: high quality (we are very confident that the true effect lies close to that of the estimate of the effect); moderate quality (we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low quality (our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect); very low quality (we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect). [#]: confirmed by Jadad score values; [¶]: credible intervals cross the threshold between recommending and not recommending treatment; [+]: drugs tested head-to-head in a small population; [§]: data from direct comparison of small studies; [f]: drugs not tested head-to-head; [##]: data from indirect comparison of small studies.

third-line treatment, mainly in high-risk patients who continue to be dyspnoeic following dual bronchodilator therapy. In addition, the French-Language Respiratory Society (Société de Pneumologie de Langue Française) proposes its use for patients with dyspnoea on long-acting bronchodilators [53].

Given the pharmacological profile of doxofylline [49, 50]; its significant anti-inflammatory activity that can result in significant steroid sparing activity, as documented at least in both an allergic and a nonallergic murine model of lung inflammation [54]; its documented clinical activity [12–14]; and, above all, the results of the present meta-analysis, there is a clear need to understand what is the room in the treatment of COPD for a xanthine that induces the same, if not even better, therapeutic effects of theophylline but with a totally different safety profile. Specifically, the rate of study withdrawal due to adverse events such

as dyspepsia, epigastralgia, nausea and palpitation was approximately four-fold higher in COPD patients treated with theophylline than in those treated with doxofylline.

Meta-analysis is an analytical technique designed to summarise the results of multiple studies in order to effectively increase sample size and provide valid pooled effect estimates [55]. It can be considered a systematic study of the currently available studies undertaken to answer specific questions or hypotheses [56]. In this regard, meta-analyses are mainly focused on questions ideally intended to solve clinical problems in agreement with the PICO strategy [17, 57]. Actually, the network meta-analytical approach is an extension of traditional pairwise meta-analysis. It represents a novel and effective statistical method that permits to incorporate clinical evidence from both direct and indirect treatment comparisons in a complete network of trials in order to assess the efficacy and risk of adverse events of multiple interventions [58]. Furthermore, the network meta-analytical approach permits to report the treatment rankings *via* the SUCRA method, a simple numerical summary to supplement the graphical display [59]. As already mentioned, this method facilitates the interpretation of the effect estimates resulting from indirect/mixed comparisons, and it can be important for clinicians who wish to know what is the best treatment for certain clinical conditions [58].

Despite the several advantages that a network meta-analysis can provide with respect to the real impact of different xanthines in the treatment of stable COPD patients, this quantitative synthesis has also some limitations, which mainly stem from the quality of reported data.

First of all, we must point out that xanthines have mostly been compared to placebo rather than active agents; trials were relatively small; and most studies are old, *i.e.* performed at a time when none of the current reference inhaled treatments were available. Clearly, this means that the results of our meta-analysis do not allow the placement of xanthines within the global COPD therapeutic framework. However, theophylline, being cheap and widely available, remains one of the most widely prescribed drugs for COPD treatment in developing countries [60]. Doxofylline, which presently is used in some regions of the world, can offer an alternative safer treatment, because of the lower risk of adverse events when compared with conventional "high-dose" theophylline, making blood monitoring unnecessary.

Another important limitation of the present meta-analysis relates to the lack of information on important outcomes such as exacerbations. Xanthines are considered to have no role in the acute exacerbation of COPD because a lack of solid information and, in effect, the last European Respiratory Society/American Thoracic Society document on prevention of COPD exacerbations did not mention xanthines [61]. Only two studies have compared oral theophylline with placebo to explore its capacity in reducing the frequency of COPD exacerbations, with contrasting results [62, 63]. No study has evaluated the impact of aminophylline, bamiphylline and doxofylline in reducing the frequency of COPD exacerbations.

Furthermore, it was impossible to establish whether there is any difference between slow- and rapid-release preparations of aminophylline or theophylline when compared with doxofylline. In addition, data in the literature did not allow us to evaluate the impact of duration of exposure to medications and that of comorbid conditions on our results. The adverse events relative to the concomitant medications remain unknown, but we must point out that the total dose of xanthines administered during the studies and the route of administration have influenced our scores.

Despite these limitations, we believe that this network meta-analysis provides valuable information on the efficacy and safety of doxofylline in people with stable COPD. It is our opinion that the use of an orally active drug that is safe, effective and relatively inexpensive, as doxofylline is, must be encouraged, particularly for those COPD patients who find inhalers difficult to use or who do not get adequate control from other pharmacological classes. In any case, we would encourage further randomised clinical trials of doxofylline to investigate the use of this drug to reduce acute exacerbations and hospitalisations due to COPD as an alternative to more expensive combined therapies, and certainly as an alternative to theophylline.

Conflict of interest: M. Cazzola reports personal fees from ABC Farmaceutici, outside the submitted work, and received personal fees to perform the meta-analysis and write the article. L. Calzetta reports personal fees from ABC Farmaceutici, during the conduct of the study, and received personal fees to perform the meta-analysis and write the article. M.G. Matera reports personal fees from ABC Farmaceutici, outside the submitted work. She is also a consultant at ABC Farmaceutici and was supported to write the article.

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