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REVIEW

LABA/LAMA fixed-dose combinations in patients with COPD: a systematic review

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Objectives: The aim of this study was to assess the current evidence for long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) in the treatment of COPD.

Materials and methods: A systematic literature search of randomized controlled trials published in English up to September 2017 of LABA/LAMA FDCs vs LABA or LAMA or LABA/inhaled corticosteroid (ICS) FDCs in COPD patients was performed using PubMed, Embase, Scopus, and Google Scholar. Outcomes including forced expiratory volume in 1 second (FEV_1), Transition Dyspnea Index (TDI) scores, St George's Respiratory Questionnaire (SGRQ) scores, exacerbations, exercise tolerance (endurance time [ET]), inspiratory capacity (IC), and rescue medication use were evaluated.

Results: In total, 27 studies were included in the review. LABA/LAMA FDCs significantly improved lung function (FEV_1) at 12 weeks compared with LABA or LAMA or LABA/ICS. These effects were maintained over time. Significant improvements with LABA/LAMA FDCs vs each evaluated comparator were also observed in TDI and SGRQ scores, even if significant differences between different LABA/LAMA FDCs were detected. Only the LABA/LAMA FDC indacaterol/glycopyrronium has shown superiority vs LAMA and LABA/ICS for reducing exacerbation rates, while olodaterol/tiotropium and indacaterol/glycopyrronium have been shown to improve ET and IC vs the active comparators. Rescue medication use was significantly reduced by LABA/LAMA FDCs vs the evaluated comparators. LABA/LAMA FDCs were safe, with no increase in the risk of adverse events with LABA/LAMA FDCs vs the monocomponents.

Conclusion: Evidence supporting the efficacy of LABA/LAMA FDCs for COPD is heterogeneous, particularly for TDI and SGRQ scores, exacerbation rates, ET, and IC. So far, indacaterol/glycopyrronium is the LABA/LAMA FDC that has the strongest evidence for superiority vs LABA, LAMA, and LABA/ICS FDCs across the evaluated outcomes. LABA/LAMA FDCs were safe; however, more data should be collected in a real-world setting to confirm their safety.

Keywords: LABA, LAMA, fixed-dose combination, COPD, systematic review

Introduction

COPD is a chronic disease characterized by not fully reversible, commonly progressive airflow limitation. According to the WHO estimates, 65 million people have moderate-to-severe COPD worldwide. In 2005, COPD-related deaths accounted for 5% of worldwide deaths; the data certainly underestimated as the most epidemiological data that originate exclusively from high-income countries.[1] Based on current figures, WHO predicts a 30% increase in COPD deaths over the next 10 years, which will make COPD the third highest cause of death worldwide by 2030.[1]

Guidelines and recommendations aim at assisting physicians during the process of diagnosis and disease management so that any single COPD patient may receive

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the most appropriate medical care by adhering to evidence-based medicine. Bronchodilators are the mainstay of COPD treatment. Long-acting β_2-agonists (LABAs) or ultra-LABAs and long-acting muscarinic antagonists (LAMAs) are the preferred options for patients at different stages of the disease. Indeed, the most recent update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations states that 1) LABAs and LAMAs significantly improve lung function and dyspnea health status, and reduce exacerbation rates, and 2) combination treatment with LABA/LAMA increases forced expiratory volume in 1 second (FEV_1) and reduce COPD symptoms compared with monotherapy.[2] Both statements are provided with the highest strength of recommendation according to the level of evidence (level A).[2] Benefits of LABA/LAMA fixed-dose combinations (FDCs) are widely reported;[3–5] however, the availability of different FDC options approved for the treatment of COPD and the absence of head-to-head studies between all the available LABA/LAMA FDCs make choosing the most appropriate option difficult.

Therapeutic choice always depends on the evaluation of biological characteristics of the disease, symptoms, previous therapies and responses to them, health status, and last but not least patient preference. Therefore, the optimal therapy is the one drawn on the medical history of each patient. However, results from clinical trials, clinical practice, and guidelines are essential for an evidence-based medicine approach.

Patients' characteristics such as age, cognitive status, visual acuity, manual dexterity, manual strength, and coordination may influence the correct use of inhaler devices and, thus, the efficacy of inhaled medications. In fact, for several patients using a nebulizer, a pressurized metered dose inhaler or a dry powder inhaler device provides an easy-to-use and cost-effective therapy.[6]

This review will systematically and critically examine the available evidence on marketed LABA/LAMA FDCs or those under development in terms of clinical relevance for the management of COPD.

Materials and methods

Review questions

Is the evidence for the efficacy of LABA/LAMA FDCs for COPD the same across the literature?

Are the numbers of randomized controlled trials (RCTs) on LABA/LAMA FDCs and their clinical relevance the same across the literature?

Search strategy

This systematic review has been registered in PROSPERO (registration number: CRD42017070930; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=70930) and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1).[7] This systematic review satisfied all the recommended items reported by the PRISMA-P 2015 checklist.[8]

We undertook a comprehensive literature search for RCTs published in English and looking at the impact of LABA/LAMA FDCs in patients with COPD. The search was performed in PubMed, Embase, Scopus, and Google Scholar through to September 2017, in order to provide for relevant studies available up to September 30, 2017.

The terms "aclidinium," "formoterol," "glycopyrronium," "glycopyrrolate," "indacaterol," "olodaterol," "salmeterol," "tiotropium," "umeclidinium," and "vilanterol" were searched for the FDCs, and the term "chronic obstructive pulmonary disease" OR "COPD" was searched for the disease.

Studies reporting the impact of the currently approved doses (European Medicines Agency and/or the United States Food and Drug Administration dosing) of LABA/LAMA FDCs vs LABAs or LAMAs or LABA/inhaled corticosteroid (ICS) FDCs on lung function (trough and peak FEV_1), dyspnea (assessed using Transition Dyspnea Index [TDI] scores), quality of life (assessed using St George's Respiratory Questionnaire [SGRQ] scores), COPD exacerbation rates, exercise tolerance (assessed by endurance time [ET]), inspiratory capacity (IC), and the use of rescue medication were included in this systematic review. Two reviewers independently checked the relevant studies identified from literature searches and databases. The studies were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Quality score

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of studies concerning the likelihood of biases related to randomization, double blinding, withdrawals, and dropouts.[9] Studies were considered of high quality if they had a Jadad score ≥3. Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

The quality of the publications was assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[10]

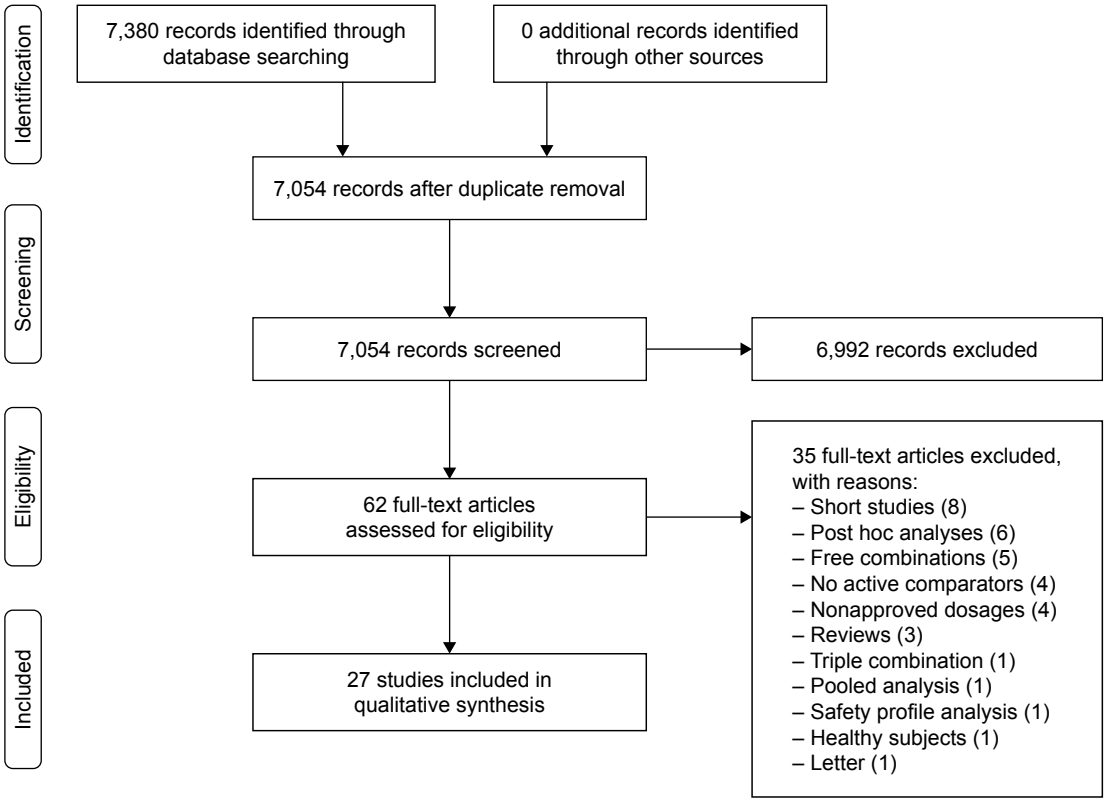

Figure 1 PRISMA flow diagram for the identification of studies included in the systematic review concerning the impact of LABA/LAMA FDCs in COPD.
Abbreviations: FDCs, fixed-dose combinations; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data extraction

Data from included studies were extracted and checked for study references, RCT registry number, study duration, doses of FDCs and comparators, FEV_1, TDI, SGRQ, COPD exacerbations, ET, IC, rescue medication, and Jadad score.

End points

The primary objective of this systematic review was to assess the impact of LABA/LAMA FDCs vs comparators on FEV_1, TDI and SGRQ (treatment duration ≥12 weeks; statistically significant improvement vs comparators), COPD exacerbations (treatment duration ≥52 weeks; statistically significant reduction of moderate–severe exacerbation rate and/or risk vs comparators and/or statistically significant increase of the time to the first exacerbation; exacerbations have been evaluated when included among the outcomes of RCTs and not if reported as adverse events [AEs]), ET and IC (treatment duration ≥3 weeks; statistically significant improvement vs comparators), and rescue medication (treatment duration ≥12 weeks; statistically significant reduction of puff/day vs comparators). The secondary objective was to assess the safety profile of LABA/LAMA FDCs vs comparators.

Strategy for data synthesis

A systematic narrative synthesis was performed on the results of the included studies (Table 1),[11–37] structured around the type of intervention, target population characteristics, type of outcome, and intervention content. The superiority of LABA/LAMA FDCs vs comparators was reported and discussed in agreement with the abovementioned criteria.

Results

Of the 62 potentially relevant studies identified in the initial search, 27 (44%) studies were deemed eligible for a qualitative analysis (Figure 1); their characteristics are summarized in Table 1. All the clinical trials were high-quality studies with a Jadad score ≥3. Patients enrolled in the selected clinical trials had to be able to correctly use the inhaler devices. Furthermore, the overall comorbidities were comparable among the studies. Table 2 shows the synthesis of the main pharmacological characteristics of LABAs, LAMAs, and ICS in the clinical trials included in this systematic review. Table 3 summarizes the studies in which LABA/LAMA combinations were significantly superior, similar, or inferior to comparators.

Table 1 Study characteristics and investigated outcomes

Study	Trial number identifier	Study duration (weeks)	FDCs	Comparators	Device	Main patients' characteristics	Investigated outcomes extracted from the studies							
							FEV_1 (trough, peak)	Dyspnea (TDI)	Quality of life (SGRQ)	Exacerbations	Exercise tolerance (endurance time)	Inspiratory capacity	Rescue medication	Jadad score
D'Urzo et al[11]	NCT01572792	52	FOR/ACL 12/400 μg	FOR 12 μg, ACL 400 μg	DPI: Genuair™/ Pressair®	Postbronchodilator FEV_1 (% predicted): 53.5; ≥1 AECOPD in the previous year (%): 21.2	Yes	Yes	Yes	Yes	No	No	Yes	5
Donohue et al[12]	NCT01437540	52	FOR/ACL 12/400 μg	FOR 12 μg	DPI: Genuair™/ Pressair®	Postbronchodilator FEV_1 (% predicted): 51.2; ≥1 AECOPD in the previous year (%): 24.5	Yes	No	No	Yes	No	No	Yes	4
Vogelmeier et al[13]	NCT01908140	24	FOR/ACL 12/400 μg	SAL/FLU 50/500 μg	DPI: Genuair™/ Pressair®, Accuhaler®	Postbronchodilator FEV_1 (% predicted): 53.3; ≥1 AECOPD in the previous year (%): 32.1; AECOPD in the previous year (n): 0.43	Yes	Yes	Yes	No	No	No	No	5
Singh et al[14]	NCT01462942	24	FOR/ACL 12/400 μg	FOR 12 μg, ACL 400 μg	DPI: Genuair™/ Pressair®	Postbronchodilator FEV_1 (% predicted): 54.3; AECOPD history: NA	Yes	Yes	Yes	No	No	No	Yes	4
D'Urzo et al[15]	NCT01437397	24	FOR/ACL 12/400 μg	FOR 12 μg, ACL 400 μg	DPI: Genuair™/ Pressair®	Postbronchodilator FEV_1 (% predicted): 53.5; AECOPD history: NA	Yes	Yes	Yes	No	No	No	Yes	3
Martinez et al[16]	NCT01854645, NCT01854658	24	FOR/GLY 9.6/18 μg	GLY 18 μg, FOR 9.6, TIO 18 μg	MDI: Co-Suspension Delivery Technology, non–Co-Suspension Delivery Technology; DPI: HandiHaler®	Postbronchodilator FEV_1 (% predicted): 51.5; AECOPD history: NA	Yes	No	Yes	No	No	No	Yes	4

Hanania et al[17]	NCT01970878	52	FOR/GLY 9.6/18 μg	GLY 18 μg, FOR 9.6, TIO 18 μg	MDI: Co-Suspension Delivery Technology, non–Co-Suspension Delivery Technology; DPI: HandiHaler®	FEV_1 at baseline (% predicted): 43.0; 1 AECOPD in the previous year (%): 16.1; ≥2 AECOPD in the previous year (%): 6.7	Yes	Yes	Yes	Yes	No	No	Yes	4
Vogelmeier et al[18]	NCT01985334	12	IND/GLY 110/50 μg	ICS/LABA, LABAs, LAMAs	NA	Postbronchodilator FEV_1 (% predicted): 63.6; 1 AECOPD in the previous year (%): 22.9; ≥2 AECOPD in the previous year (%): 0.6	Yes	Yes	No	No	No	No	Yes	3
Ferguson et al[19]	NCT01682863	52	IND/GLY 27.5/15.6 μg	IND 75 μg	DPI: Neohaler®	Postbronchodilator FEV_1 (% predicted): 54.4; 1 AECOPD in the previous year (%): 25.2; ≥2 AECOPD in the previous year (%): 7.6	Yes	No	No	Yes	No	No	Yes	4
Wedzicha et al[20]	NCT01782326	52	IND/GLY 110/50 μg	SAL/FLU 50/500 μg	DPI; NA, Accuhaler®	Postbronchodilator FEV_1 (% predicted): 44.1; 1 AECOPD in the previous year (%): 100; ≥2 AECOPD in the previous year (%): 19.3	Yes	No	Yes	Yes	No	No	Yes	5
Zhong et al[21]	NCT01709903	26	IND/GLY 110/50 μg	SAL/FLU 50/500 μg	DPI; Breezhaler®, Accuhaler®	Postbronchodilator FEV_1 (% predicted): 51.8; 1 AECOPD in the previous year (%): 20.7; ≥2 AECOPD in the previous year (%): 0.2	Yes	Yes	Yes	No	No	No	Yes	5

(*Continued*)

Table 1 (*Continued*)

Study	Trial number identifier	Study duration (weeks)	FDCs	Comparators	Device	Main patients' characteristics	Investigated outcomes extracted from the studies							
							FEV_1 (trough, peak)	Dyspnea (TDI)	Quality of life (SGRQ)	Exacerbations	Exercise tolerance (endurance time)	Inspiratory capacity	Rescue medication	Jadad score
Mahler et al[22]	NCT01727141, NCT01712516	12	IND/GLY 27.5/15.6 μg	IND 27.5 μg, GLY 15.6 μg	DPI: Neohaler®	Postbronchodilator FEV_1 (% predicted): 54.6; 1 AECOPD in the previous year (%): 24.2; ≥2 AECOPD in the previous year (%): 6.9	Yes	Yes	Yes	No	No	No	Yes	5
Beeh et al[23]	NCT01294787	3	IND/GLY 110/50 μg	TIO 18 μg	DPI: Breezhaler®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 55.9; 1 AECOPD in the previous year (%): 14.3; ≥2 AECOPD in the previous year (%): 2.4	No	No	No	No	Yes	Yes	No	5
Bateman et al[24]	NCT01202188	26	IND/GLY 110/50 μg	GLY 50 μg, IND 150, TIO 18 μg	DPI: Breezhaler®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 55.2; 1 AECOPD in the previous year (%): 19.3; ≥2 AECOPD in the previous year (%): 5.6	Yes	Yes	Yes	No	No	No	Yes	4
Wedzicha et al[25]	NCT01120691	64	IND/GLY 110/50 μg	GLY 50 μg, TIO 18 μg	DPI: Breezhaler®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 37.2; 1 AECOPD in the previous year (%): 76.0; ≥2 AECOPD in the previous year (%): 22.3	Yes	No	Yes	Yes	No	No	Yes	5
Vogelmeier et al[26]	NCT01315249	26	IND/GLY 110/50 μg	SAL/FLU 50/500 μg	DPI; Breezhaler®, Accuhaler®	Postbronchodilator FEV_1 (% predicted): 50.9; ≥1 AECOPD in the previous year (%): 0.2	Yes	Yes	Yes	No	No	No	Yes	5
Ferguson et al[27]	NCT01431274, NCT01431287	52	OLO/TIO 5/5 μg	OLO 5 μg, TIO 5 μg	SMI: Respimat®	Postbronchodilator FEV_1 (% predicted): 52.6; AECOPD history: NA	No	Yes	No	No	No	No	No	3

O'Donnell et al[28]	NCT01533922, NCT01533935	6	OLO/TIO 5/5 μg	OLO 5 μg, TIO 5 μg	SMI: Respimat®	Postbronchodilator FEV_1 (% predicted): 52.0; AECOPD history: NA	No	No	No	No	Yes	Yes	No	3
Buhl et al[29]	NCT01431274, NCT01431287	52	OLO/TIO 5/5 μg	OLO 5 μg, TIO 5 μg	SMI: Respimat®	Postbronchodilator FEV_1 (% predicted): 50.0; AECOPD history: NA	Yes	No	Yes	No	No	No	Yes	3
Singh et al[30]	NCT01964352, NCT02006732	12	OLO/TIO 5/5 μg	TIO 5 μg	SMI: Respimat®	Postbronchodilator FEV_1 (% predicted): 55.1; AECOPD history: NA	Yes	Yes	Yes	No	No	No	No	3
Kerwin et al[31]	NCT01899742	12	VIL/UME 25/62.5 μg	TIO 18 μg	DPI: Ellipta®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 59.6; ≥1 AECOPD in the previous year (%): 34.0	Yes	Yes	Yes	No	No	No	Yes	5
Singh et al[32]	NCT01822899	12	VIL/UME 25/62.5 μg	SAL/FLU 50/500 μg	DPI: Ellipta®, Diskus®	Postbronchodilator FEV_1 (% predicted): 50.6; ≥1 AECOPD in the previous year (%): 0.0	Yes	Yes	Yes	No	No	No	Yes	5
Donohue et al[33]	NCT01817764, NCT01879410	12	VIL/UME 25/62.5 μg	SAL/FLU 25/250 μg	DPI: Ellipta®, Diskus®	Postbronchodilator FEV_1 (% predicted): 49.5; ≥1 AECOPD in the previous year (%): 0.0	Yes	Yes	Yes	No	No	No	Yes	5
Decramer et al[34]	NCT01316900, NCT01316913	24	VIL/UME 25/62.5 μg	VIL 25 μg, TIO 18 μg	DPI: Ellipta®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 47.4; ≥1 AECOPD in the previous year (%): 38.1	Yes	Yes	Yes	No	No	No	Yes	5
Maleki-Yazdi et al[35]	NCT01777334	24	VIL/UME 25/62.5 μg	TIO 18 μg	DPI: Ellipta®, HandiHaler®	Postbronchodilator FEV_1 (% predicted): 46.4; AECOPD history: NA	Yes	No	Yes	No	No	No	Yes	5
Maltais et al[36]	NCT01323660, NCT01328444	12	VIL/UME 25/62.5 μg	VIL 25 μg, UME 62.5 μg	DPI: Ellipta®	Postbronchodilator FEV_1 (% predicted): 51.3; AECOPD history: NA	Yes	No	No	No	Yes	Yes	Yes	4
Donohue et al[37]	NCT01313650	24	VIL/UME 25/62.5 μg	VIL 25 μg, UME 62.5 μg	DPI: NA	Postbronchodilator FEV_1 (% predicted): 47.4; AECOPD history: NA	Yes	Yes	Yes	No	No	No	Yes	4

Abbreviations: ACL, aclidinium bromide; AECOPD, acute exacerbation of COPD; DPI, dry powder inhaler; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone fumarate; FOR, formoterol fumarate; GLY, glycopyrronium or glycopyrrolate; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; NA, not available; OLO, olodaterol; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; SMI, soft mist inhaler; TDI, transition dyspnea index; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.

Table 2 Synthesis of the main pharmacological characteristics of LABAs, LAMAs, and ICS investigated in the clinical trials included in this systematic review

Drugs	Main pharmacological targets				Functional selectivity β_2/β_1 ratio	References
	β_2-AR					
	pKi	IA (% isoprenaline)	Onset of action (t½, minutes)	Duration of action (hours)		
LABAs						
Formoterol	8.06	95.0	5.9	0.93	130	55–61
Indacaterol	7.64	86.0	10.9	9.75	12.5	55–58, 60, 61
Olodaterol	9.14	88	NA	NA	65	55, 59, 61
Salmeterol	9.35	39.50	13.65	≈12	1,595	55–59
Vilanterol	9.42	70.00	3.45	NA	2,400	55, 56, 61
	M_3 mAChR				M_3/M_2 ratio	
	pKi	K_{off} (h^{-1})	Onset of action (t½, minutes)	Duration of action (hours)		
LAMAs						
Aclidinium	9.85	0.071	8.20	10.7	5.9	61–66
Glycopyrronium	9.28	0.11	8.72	6.1	16.5	61–65, 67
Tiotropium	9.72	0.091	10.2	27	8.7	61–65, 67
Umeclidinium	9.80	0.53	9.0	1.37	8.7	61, 63, 65, 68
	Relative lipophilicity	Receptor binding affinity (relative to binding affinity with dexamethasone =1)	Onset of action (t½, minutes)	Receptor complex half-life (hours)	Topical skin blanching potency (relative to dexamethasone =1)	
ICS						
Fluticasone	4.50	18.00	864	10.50	599.40	69, 70

Abbreviations: AR, adrenergic receptor; IA, intrinsic activity; ICS, inhaled corticosteroid; K_{off}, dissociation rate; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mAChR, muscarinic acetylcholine receptor; NA, not available; pKi, the negative logarithm to base 10 of the equilibrium dissociation constant; t½, residence half-life.

Table 3 Studies in which LABA/LAMA combinations were significantly superior ↑, similar ≈, or inferior ↓ to comparators

LABA/LAMA FDC	Comparators	Trough FEV_1	Peak FEV_1	TDI	SGRQ	Exacerbations	Exercise tolerance	Isotime IC	Rescue medication use
Formoterol/aclidinium 400/12 μg BID via Genuair	LABA monotherapy	↑: [12, 14, 15]	↑: [14, 15]	↑: [11, 15]	≈: [11, 14, 15]	≈: [11, 12]			≈: [11, 12, 14]
	LAMA monotherapy	↑: [15] ≈: [11, 14]	↑: [14, 15]	↑: [11] ≈: [15]	≈: [11, 14, 15]	≈: [11]			↑: [14, 15] ≈: [11]
	LABA/ICS	≈: [13]	↑: [13]	≈: [13]	≈: [13]				≈: [13]
Formoterol/glycopyrrolate 8/9.6 μg (two actuations) BID via pMDI	LABA monotherapy	↑: [16, 17]	↑: [16, 17]	↑: [17]	≈: [16, 17]	≈: [17]			↑: [16j] ≈: [17]
	LAMA monotherapy	↑: [16a, 17]	↑: [16, 17]	↑: [17f]	↑: [16f and h, 17f]	≈: [17]			↑: [16k, 17]
	LABA/ICS								
Indacaterol/glycopyrronium 110/50 μg OD via Breezhaler or 27.5/15.6 μg BID via Neohaler	LABA monotherapy	↑: [18b, 19, 22, 24]	↑: [22, 24]	↑: [18b, 22] ≈: [24]	↑: [22] ≈: [24]	≈: [19]			↑: [18b, 22, 24] ≈: [19]
	LAMA monotherapy	↑: [18b, 22, 24, 25]	↑: [22, 24]	↑: [18b, 22, 24g]	↑: [22, 24g, 25]	↑: [25f]	≈: [23]	↑: [23]	↑: [18b, 22, 24, 25]
	LABA/ICS	↑: [18, 20, 21, 26]	↑: [21, 26]	↑: [18, 26] ≈: [21]	↑: [20] ≈: [21, 26]	↑: [20]			↑: [18, 20, 26] ≈: [21]
Olodaterol/tiotropium 5/5 μg OD via Respimat	LABA monotherapy	↑: [29]		↑: [27, 29]	↑: [29]		↑: [28]	↑: [28]	↑: [29]
	LAMA monotherapy	↑: [29, 30c]		↑: [27, 29, 30]	↑: [29, 30i]		≈: [28]	↑: [28]	↑: [29]
	LABA/ICS								
Vilanterol/umeclidinium 62.5/25 μg OD via Ellipta	LABA monotherapy	↑: [34, 36d, 37]	↑: [34, 37]	≈: [34, 37]	≈: [34, 37]				≈: [34, 37]
	LAMA monotherapy	↑: [31, 34, 35, 36d, 37]	↑: [34, 35, 37]	≈: [31, 34, 37]	↑: [35] ≈: [31, 34, 37]				↑: [31, 34l, 35, 37]
	LABA/ICS	↑: [32, 33e]	↑: [32, 33e]	≈: [32, 33]	≈: [32, 33]				≈: [32] ↑: [33m]

Notes: a, not superiority vs TIO in PINNACLE1; b, comparator means LABA or LAMA; c, nonsuperiority vs TIO in OTEMTO1; d, data not shown and not reported significance; e, comparator means SFC 50/250 μg; f, nonsuperiority vs TIO; g, nonsuperior to glycopyrronium; h, nonsuperiority in PINNACLE2; i, nonsuperiority vs TIO in OTEMTO2; j, nonsuperiority vs formoterol in PINNACLE1; k, nonsuperiority vs glycopyrrolate in PINNACLE1; l, nonsuperiority in Study 2; m, nonsuperiority in DB2114930.

Abbreviations: BID, twice daily; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second; IC, inspiratory capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OD, once daily; pMDI, pressurized metered dose inhaler; SFC, salmeterol/fluticasone; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnea index; TIO, tiotropium.

FEV_1

LABA/LAMA FDCs were associated with significant improvements in the morning predose trough FEV_1 and peak FEV_1 compared with their LABA or LAMA comparators (high quality of evidence, GRADE ++++). These effects were maintained over time.

Formoterol/aclidinium was found superior to formoterol, but not consistently superior to aclidinium in terms of trough FEV_1,[10,12,14,15] whereas the gain in peak FEV_1 reached with formoterol/aclidinium was significant vs both formoterol and aclidinium.[14,15]

Formoterol/glycopyrrolate was found superior to both formoterol and glycopyrrolate in improving peak and trough FEV_1;[16,17] however, it did not reach superiority vs tiotropium in one study.[16] Olodaterol/tiotropium was found superior to both olodaterol and tiotropium in improving trough FEV_1;[29,30] however, it did not reach superiority vs tiotropium in one study.[30] No trials reporting superiority of olodaterol/tiotropium for improving peak FEV_1vs LABA or LAMA monotherapy were identified. Both indacaterol/glycopyrronium and vilanterol/umeclidinium have shown superiority vs LABA (indacaterol and vilanterol, respectively) or LAMA (glycopyrronium and tiotropium or umeclidinium and tiotropium, respectively) in terms of improving peak FEV_1,[22,24,34,35,37] as well as improving trough FEV_1.[18,19,22,24,25,31,34–37]

LABA/LAMA FDCs also showed significant superiority in improving trough FEV_1 and peak FEV_1vs the LABA/ICS comparator salmeterol/fluticasone (SFC; moderate quality of evidence, GRADE +++). One trial demonstrated the superiority of formoterol/aclidinium to SFC 50/500 μg at improving peak FEV_1; however, superiority in morning predose FEV_1 was not reached.[13] Four trials showed superiority of indacaterol/glycopyrronium vs SFC FDC at improving trough FEV_1,[18,20,21,26] while two trials demonstrated superiority of indacaterol/glycopyrronium vs the same LABA/ICS at improving peak FEV_1.[21,26] Two trials comparing vilanterol/umeclidinium with SFC FDC, although at a lower dose in one study,[33] demonstrated superiority at improving both trough FEV_1 and peak FEV_1.[32,33]

No trials comparing the effects of formoterol/glycopyrrolate or olodaterol/tiotropium with a LABA/ICS on lung function were identified.

TDI

LABA/LAMA FDCs were also associated with a significant improvement in TDI scores at 12 weeks compared with their LABA or LAMA comparators (high quality of evidence, GRADE ++++).

Formoterol/aclidinium was found to be superior to both formoterol[11,15] and aclidinium in one study[11] at improving TDI scores from baseline; however, it did not reach superiority vs aclidinium in one study.[14] Formoterol/glycopyrrolate also demonstrated superiority at improving TDI scores from baseline vs formoterol or glycopyrrolate in one trial, but it was not superior to tiotropium in the same study.[17] Olodaterol/tiotropium was found to be superior to olodaterol[27,29] or tiotropium,[27,29,30] and indacaterol/glycopyrronium was found to be superior to indacaterol[18,22] (except in one study[23]) or LAMAs (glycopyrronium or tiotropium).[18,22,24] It must be noted that in one trial the LABA and LAMA comparators were combined in a single group.[18] Vilanterol/umeclidinium has not demonstrated to be superiority to vilanterol or umeclidinium and/or tiotropium at improving TDI scores, even if different trials evaluated this improvement.[31,34,37]

Compared with an LABA/ICS FDC, LABA/LAMA FDCs have shown significant improvements in TDI at 12 weeks (low quality of evidence, GRADE ++). However, when the LABA/LAMA FDCs were analyzed separately, important differences between the compounds were found. Only indacaterol/glycopyrronium has been shown in two trials,[18,26] to significantly improve TDI scores (not significantly different in one[20] vs SFC FDC). Formoterol/aclidinium[13] and vilanterol/umeclidinium[32,33] both failed to demonstrate superiority vs SFC FDC, even when compared with a lower ICS dose in one trial.[33]

No trials comparing the effects of formoterol/glycopyrrolate or olodaterol/tiotropium with a LABA/ICS FDC on TDI scores were identified.

SGRQ

LABA/LAMA FDCs had significant improvements in SGRQ at 12 weeks compared with their LABA or LAMA comparators (moderate quality of evidence, GRADE +++).

Formoterol/glycopyrrolate was found to be superior at improving SGRQ scores to glycopyrrolate monotherapy in two trials but was not superior to tiotropium and to formoterol monotherapy in the same studies.[16,17] Olodaterol/tiotropium was found to be superior to both olodaterol[29] and tiotropium[29,30] at improving SGRQ scores. Indacaterol/glycopyrronium was found to be superior to indacaterol[22] or glycopyrronium and/or tiotropium[22,24,25] at improving SGRQ scores, while vilanterol/umeclidinium was found to be superior to umeclidinium in one study[35] (similar to umeclidinium or tiotropium in three studies,[30,33,36] but not superior to vilanterol).[33,36] Formoterol/aclidinium did not demonstrate superiority vs formoterol or aclidinium at improving SGRQ vs baseline.[10,13,14]

Concerning LABA/LAMA FDCs' impact on SGRQ compared with the LABA/ICS comparator, only indacaterol/glycopyrronium, in one trial, has demonstrated superiority to SFC FDC[20] (not significantly superior in two studies).[20,25] No trials comparing the effects of formoterol/glycopyrrolate or olodaterol/tiotropium with an LABA/ICS FDC on SGRQ scores were identified. Formoterol/aclidinium[13] and vilanterol/umeclidinium[32,33] vs SFC FDC failed to demonstrate superiority, even when compared with a lower ICS dose in one trial.[33]

COPD exacerbations

LABA/LAMA FDCs have shown significant improvements in the rate of moderate/severe COPD exacerbations over 52 weeks compared with LAMA or LABA/ICS FDC (very low quality of evidence, GRADE +). However, of the LABA/LAMA FDCs, only indacaterol/glycopyrronium has demonstrated superiority to both an LAMA (glycopyrronium, not statistically different vs tiotropium)[25] and LABA/ICS FDC (SFC)[20] in the reduction of exacerbation rates. No trials comparing the effects of formoterol/aclidinium, vilanterol/umeclidinium, formoterol/glycopyrrolate, or olodaterol/tiotropium with any of the LABA, LAMA, or LABA/ICS FDC on moderate/severe exacerbation rates were identified.

Exercise tolerance and IC

Olodaterol/tiotropium has demonstrated superiority to olodaterol or tiotropium monotherapy at improving isotime IC and superiority to olodaterol monotherapy at improving ET,[28] while indacaterol/glycopyrronium significantly improved isotime IC vs tiotropium[23] (moderate quality of evidence, GRADE +++). No published trials comparing the effects of formoterol/aclidinium, vilanterol/umeclidinium, or formoterol/glycopyrrolate with any of the LABA, LAMA, or LABA/ICS FDCs on ET or IC were identified.

Rescue medication use

LABA/LAMA FDCs showed significant improvements on the use of rescue medication over 12 weeks compared with LABA or LAMA (high quality of evidence, GRADE ++++).

Formoterol/glycopyrrolate was superior to formoterol[16] (but not superior in one study)[16] or glycopyrrolate and/or tiotropium,[16,17] indacaterol/glycopyrronium was superior to indacaterol[18,22,24] (not significantly different in one study)[18] as well as to glycopyrronium and/or tiotropium,[18,22,24,25] and olodaterol/tiotropium was superior to olodaterol[29] or tiotropium[29] at reducing the need for rescue medications at 12 weeks. Formoterol/aclidinium was superior to aclidinium in two studies,[13,14] but not in another one,[10] nor was superior to formoterol at improving rescue medication use.[14,15] Similarly, vilanterol/umeclidinium was superior to tiotropium and/or umeclidinium, but not superior to vilanterol at improving rescue medication use.[31,34,35,37]

Compared with LABA/ICS FDCs, LABA/LAMA FDCs significantly improved rescue medication use at 12 weeks overall; however, differences between LABA/LAMA FDCs compounds were found (low quality of evidence, GRADE ++). Only indacaterol/glycopyrronium in three studies[18,20,26] (not in one)[20] and vilanterol/umeclidinium in one study[32] demonstrated superiority vs SFC FDC (not in another study)[31] at improving rescue medication use (it must be noted that in one trial the dose of SFC was 50/250).[33] One trial comparing formoterol/aclidinium with an SFC FDC[13] did not find any significant improvements in rescue medication use at 12 weeks. No studies comparing the effects of formoterol/glycopyrrolate or olodaterol/tiotropium with an LABA/ICS FDC on rescue medication use were identified.

Safety

LABA/LAMA FDCs are a safe therapeutic approach in patients with COPD. Current literature shows that combining an LABA with an LAMA does not increase the risk of AEs or serious AEs (SAEs) compared with their individual components.[5,38] Furthermore, LABA/LAMA FDCs have been shown to have a comparable safety profile to LABA/ICS FDCs.[5]

LABA/LAMA FDCs also do not significantly increase the risk of cardiovascular SAEs compared with their individual components.[9] Intriguingly, some of the LABA/LAMA FDCs showed a numerical trend in protecting against cardiovascular SAEs, whereas other combinations showed a signal in increasing the risk of cardiovascular SAEs.[9] The frequencies of SAEs and deaths in RCTs of LABA/LAMA FDCs are low. However, while COPD makes it difficult to perform studies that are adequately powered to detect the real safety profile of LABA/LAMA FDCs, it appears that the cardiac safety of LAMA/LABA FDCs could be lower in COPD patients who have concomitant cardiovascular diseases, prolonged corrected QT interval, or polypharmacy.[39]

In any case, we have to highlight that the occurrence of rare/uncommon SAEs may be related to several individual patient characteristics and that COPD patients with comorbidities are usually excluded from RCTs. In fact, a recent observational study of a cohort of 31,138 patients with COPD

who added an LAMA to an LABA, or vice versa, indicated that adding a second long-acting bronchodilator does not increase the risk of most cardiovascular events in the real-world-setting treatment of COPD. However, the authors detected a modest, although significant, increase in the risk of heart failure.[40] To confirm these data from meta-analyses and observational studies, high-quality, large, RCTs including patients with COPD and cardiovascular comorbidities are warranted.[39]

Moreover, also the drug formulations and the characteristics of the specific devices may modulate the frequency of SAEs and lead to potential imbalance of the safety profile in favor of some LABA/LAMA FDCs rather than others.[41,42] In fact, while some inhaler devices deliver fine particles leading to increased lung deposition, others deliver greater particles that induce oropharyngeal deposition of drugs. The latter condition may result in a greater systemic absorption of bronchodilators, with a potential increased risk of AEs.[41,42]

Discussion

The main aim of this systematic review was to investigate whether the evidence for the efficacy and safety of all marketed LABA/LAMA FDCs or those under development is comparable, in terms of the number of RCTs and outcomes. We found that evidence supporting the use of different LABA/LAMA FDCs for the management of COPD is heterogeneous.

In the era of evidence-based medicine, we rely on the literature to identify the best approach to treat patients, and systematic reviews are a valuable tool to define a clear picture of current literature on LABA/LAMA FDCs. Several systematic reviews and meta-analyses have been conducted and published regarding the effect of the LABA/LAMA class on different outcomes such as changes in FEV_1, patient-reported outcomes, and safety,[5,9,43,44] but none of them was focused on producing a tool to easily identify which (if not all) LABA/LAMA FDCs have demonstrated superior results when compared with single bronchodilators (LABA or LAMA) or LABA/ICS. If the goal of treatment is, eg, to reduce dyspnea, using the results of this systematic review, we can now choose which FDC has shown to improve this outcome; again, if the focus is to reduce exacerbations, we can easily find the right answer to this question in the results of this review.

Overall, LABA/LAMA FDCs have shown superiority regarding lung function improvement vs comparators. However, at difference with others, indacaterol/glycopyrronium and vilanterol/umeclidinium were the only FDCs demonstrating statistical superiority vs LABA and LAMA monotherapies and LABA/ICS in terms of improvements in trough FEV_1, which is the most commonly investigated (and requested by health authorities) outcome in studies on COPD.

Regarding TDI improvement, indacaterol/glycopyrronium has shown superior results vs each comparator, but surprisingly vilanterol/umeclidinium did not show any superiority vs LABA or LAMA or LABA/ICS FDCs, even if many trials evaluated this outcome. Similarly, significant improvements in SGRQ scores were only demonstrated with indacaterol/glycopyrronium, while other LABA/LAMA FDCs (particularly formoterol/aclidinium and vilanterol/umeclidinium) showed no advantage over LABA, LAMA, or LABA/ICS FDCs.

One of the biggest differences between the different LABA/LAMA FDCs is their effect on COPD exacerbation rates, with only indacaterol/glycopyrronium demonstrating superiority at improving COPD exacerbation rates vs LAMA or LABA/ICS FDCs. One Cochrane review found a significant heterogeneity analyzing this outcome for different LABA/LAMA FDCs and concluded that it is still not clear whether only indacaterol/glycopyrronium prevents COPD exacerbations or all LABA/LAMA FDCs are able to prevent these events.[45] In our opinion, studies investigating the superiority of LABA/LAMA FDCs at preventing COPD exacerbations vs LABA monotherapy are not needed as it is already proven that LAMAs[46,47] and LABA/ICS FDCs[48] are superior to LABAs for this outcome. As indacaterol/glycopyrronium demonstrated better exacerbation prevention vs both LAMA (glycopyrronium) and LABA/ICS (SFC), the demonstration of superiority vs any LABA seems to be irrelevant.

Regarding exercise tolerance and isotime IC, more data supporting LABA/LAMA FDCs are needed as this is an important outcome impacting the quality of life of COPD patients. Olodaterol/tiotropium has shown superiority vs LABA regarding isotime IC and ET, while indacaterol/glycopyrronium was superior to LAMA regarding isotime IC. Actually, a pairwise and network meta-analysis conducted by Calzetta et al documented that LABA/LAMA combination was superior to the monocomponents in increasing both ET and IC, providing support to the double bronchodilation strategy for the increase of exercise tolerance in COPD patients.[43] One suggestion for future trials is to combine double bronchodilation and exercise training; this could bring superior results in terms of ET. Actually, as shown by Ofir et al[49] COPD patients often stop exercise for leg discomfort, so optimizing bronchodilation with an LABA/LAMA FDC

may result in prolonging exercise duration or shifting the locus of symptom limitation from dyspnea to leg fatigue. As such, combining exercise training (to improve limb muscle fatigue) with double bronchodilation may produce superior results in terms of exercise tolerance for COPD patients.

We were able to detect some differences between different LABA/LAMA FDCs; in fact, some LABA/LAMA FDCs showed significant benefits on specific outcomes, but several inconsistencies in the evidence supporting the efficacy of LABA/LAMA FDCs were found; these were likely caused by differences in study design, comparators, outcomes, and patient populations or by differences existing between the LABA/LAMA FDCs. Being aware of these differences allows us to choose the FDC that has been shown to improve a specific outcome that appears to be critical in a given patient.

The 2018 GOLD Report recommends the use of two bronchodilators for Group B patients with persistent breathlessness on monotherapy and Group C patients with persistent exacerbations, and indicates LABA/LAMA combinations as preferred treatment in Groups D patients.[50] The present systematic review supports the GOLD algorithm, as LABA/LAMA FDCs have shown superiority vs any comparators for the vast majority of evaluated outcomes; yet, the step-up strategy recommended by the GOLD report is supported by this systematic review for the same reason. The superiority shown by some LABA/LAMA FDCs vs LABA/ICSs for the majority of evaluated outcomes is supporting the GOLD 2018 report, as current evidence is in favor of the double bronchodilation strategy for both efficacy and safety reasons. As acknowledged by the GOLD committee, long-term treatment with ICS (especially fluticasone) could be associated with the risk of pneumonia and other adverse effects. Therefore, LABA/LAMA seems an overall safer and more effective option for COPD patient management.

Potentially an early start with a fast-acting LABA/LAMA FDC at the time of COPD diagnosis could lead to rapid improvements in symptoms. Prompt symptom relief will give reassurance of effectiveness and could be a key factor in patient compliance, thus likely improving adherence to the prescribed medications that are usually very low in COPD patients, with a negative influence on outcomes. This approach is supported by the GOLD 2018 report that states that, for patients with severe breathlessness, initial therapy with two bronchodilators may be considered.[50]

The focus of this study was to compare the LABA/LAMA FDC in COPD patients, and the results must be interpreted in the light of the population enrolled in these trials. Of course, in asthmatic and ACO patients, an accurate evaluation of an ICS-containing regimen is mandatory.

From a safety standpoint, the current evidence suggests that LABA/LAMA FDCs are a safe therapeutic approach in COPD patients. While the choice of a specific LAMA/LABA FDC should not be based on the specific safety profile, postmarketing surveillance and observational studies are welcomed to adequately clarify the safety of any LABA/LAMA FDC in daily clinical practice. A recent study on 284,220 LABA–LAMA-naïve patients with COPD has shown an increased risk of a severe cardiovascular disease event within 30 days of initiation of LABA or LAMA therapy.[51] However, the risk was reduced in the longer term. Therefore, this study highlights the importance of a careful early management of COPD after the introduction of LABA or LAMA therapy.

We did not perform any meta-analysis to compare the different LABA/LAMA FDCs as it was not the objective of the study. In our opinion, a statistically significant difference vs comparators could help to establish the superiority of one treatment over another, given the lack of universally accepted clinically relevant differences between active treatments. However, it must be pointed out that statistically significant superiority does not always mean difference in clinical relevance.

Finally, although no further studies could formally be considered in this systematic review as the methodological criteria already registered in PROSPERO (CRD42017070930) set the literature search at the end of September 2017, we cannot overlook recent RCTs on triple FDC therapy including an ICS plus an LABA plus an LAMA, such as the TRIBUTE and IMPACT studies,[52,53] which provided relevant findings concerning the efficacy and safety of adding an ICS to the double bronchodilation therapy in the management of COPD patients. Interestingly, the triple therapy demonstrated a greater protective effect against COPD exacerbations in patients with higher blood eosinophil levels, as further confirmed by the SUNSET study[54] that aimed to evaluate the impact of de-escalation from the long-term triple therapy to indacaterol/glycopyrronium in nonfrequently exacerbating COPD patients.

Conclusion

Evidence supporting the efficacy of different LABA/LAMA FDCs and their clinical relevance for the management of COPD are heterogeneous across the literature, particularly for improvements in TDI and SGRQ scores, and even more for exacerbation prevention, and changes in ET and IC. Furthermore, not all LABA/LAMA FDCs have shown

superiority over LABA/ICS for most of the evaluated outcomes. Based on the published evidence, the equivalence of all LABA/LAMA FDCs cannot be established. Indacaterol/glycopyrronium is so far the LABA/LAMA combination supported by the more robust evidence of superiority vs LABA, LAMA, and LABA/ICS across the evaluated outcomes.

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Author contributions

All authors provided substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; drafted the article; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the authors revised the manuscript critically for important intellectual content and approved the version to be published.

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