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Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: A systematic review

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ABSTRACT

Background: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.
Methods: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.
Results: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV_1), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV_1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11–119). Finally, "triple therapy" increased FEV_1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, $p = 0.21$).
Conclusions: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prominent cause of disability and death worldwide [1]. As COPD is a progressive disease, guidelines recommended a stepwise approach to treatment [1,2]. Pharmacotherapy has improved substantially in the last decade. The availability of long-acting beta2-agonists (LABA), fixed combinations of inhaled corticosteroids (ICS) add to LABA, and long-acting muscarinic antagonists (LAMA), have allowed improved different outcomes of the disease. While short-acting beta2-agonists (SABA) are used for the relief of symptoms, inhaled LABA, LAMA, ICS and their combinations are reserved for maintenance treatment of patients with moderate to severe COPD [1,2] Although the relative benefits of which agent to use first have not been systematically studied, initial treatment of these patients with a LAMA (tiotropium) appears to be a rational approach than twice daily LABA [3,4]. However, when symptoms are not adequately controlled with monotherapy, guidelines recommended the addition of a LABA to a LAMA ("dual" long-acting bronchodilator therapy), the addition of an ICS to a LABA ("combined" therapy), or even a LABA plus an ICS to a LAMA ("triple" therapy), although data supporting these different therapeutic approaches are limited to date. The objective of this

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV_1, forced volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists; MID, minimal important difference; NNTB, number need to treat for benefit; NNTH, number need to treat for harm; OR, odds ratio; SABA, short-acting beta2-agonists; SAE, severe adverse effects; SGRQ, St. George Respiratory Questionnaire; TDI, transitional dyspnea index; WMD, weighted mean difference.

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systematic review is to assess the efficacy of these therapeutic combinations compared with tiotropium monotherapy in COPD patients.

2. Methods

2.1. Search and selection criteria

We identified studies from MEDLINE, EMBASE (January 1980 to May 2011) and the Cochrane Controlled Trials Register (CENTRAL) (first quarter 2011) databases using the following Medical Subject Headings, full text, and keywords (long-acting beta-2-agonists OR salmeterol OR formoterol OR indacaterol ORQAB-149 OR long-acting antimuscarinics agents OR tiotropium OR inhaled corticosteroids OR fluticasone OR budesonide OR ciclesonide OR mometasone OR beclomethasone AND chronic obstructive pulmonary disease. Also, we performed a search of relevant files from the drugs manufacturer's databases. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. The specific inclusion criteria were as follows: 1) adult patients aged greater than 40 years with stable COPD satisfying American Thoracic Society/European Respiratory Society [2], or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria [1]; 2) tiotropium plus LABA ("dual" long-acting bronchodilator therapy), LABA plus ICS ("combined" therapy) and tiotropium plus LABA plus ICS ("triple" therapy), all compared with tiotropium monotherapy; 3) studies with more than 2 weeks of duration; 4) randomized (parallel group or cross sectional) controlled trials without language restriction; 5) primary outcomes: forced volume in the first second (FEV_1) (pre and post bronchodilator test), use of rescue medications, health-related quality of life (HRQoL) (St. George Respiratory Questionnaire [SGRQ]) [5], dyspnea, and COPD exacerbations. Secondary outcomes measures: all-cause mortality, withdrawals during treatment period, and severe adverse effects (SAE). A serious adverse event was defined as any untoward medical occurrence that results in sometimes death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity [6].

2.2. Data abstraction and assessment of risk of bias

This systematic review was performed according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [7]. Titles, abstracts, and citations were independently analyzed by all reviewers. From full text, they independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The later was assessed according to recommendations outlined in Cochrane Handbook [8] for the following items: 1) allocation sequence generation; 2) concealment of allocation; 3) blinding of participants and investigators; and 4) handling of missing data. Each potential source of bias was graded as yes, no or unclear, relating to whether the potential for bias was low, high or unknown respectively. Disagreements were resolved by group consensus.

2.3. Data analysis

Outcomes were pooled using weighted mean differences (WMD) (continuous outcomes) or Mantel–Haenszel odds ratios (ORs) (binary outcomes). The precision of the mean estimates was quantified by the 95% confidence intervals (CIs). When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm (NNTH) was obtained. Heterogeneity was measured by the I^2 test [9] (<40% might be unimportant, 40%–60% might be moderate, and 60%–100% may be substantial) [8]. Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies in all outcomes [10]. In those outcomes that showed statistically significant differences but with moderate to substantial heterogeneity, 95% predictive intervals were calculated to address the distribution of true effects sizes [11]. Publication bias of primary outcomes was evaluated by visual inspection of funnel plots [12]. As a priori subgroup analysis, we explore the influence of type LABA (formoterol vs. salmeterol vs. indacaterol), and length of treatment (<24 weeks vs. ≥24 weeks). Subgroups were compared using the interaction test [13] $P \leq 0.05$ (2-tailed test) was considered significant. Meta-analysis was performed with the Review Manager 5.1.4 software (Cochrane IMS, 2011).

3. Results

Twenty RCTs [14–33] (including 6803 subjects) fulfilled the inclusion criteria (Fig. 1). Five trials were unpublished [19–21,23,24].

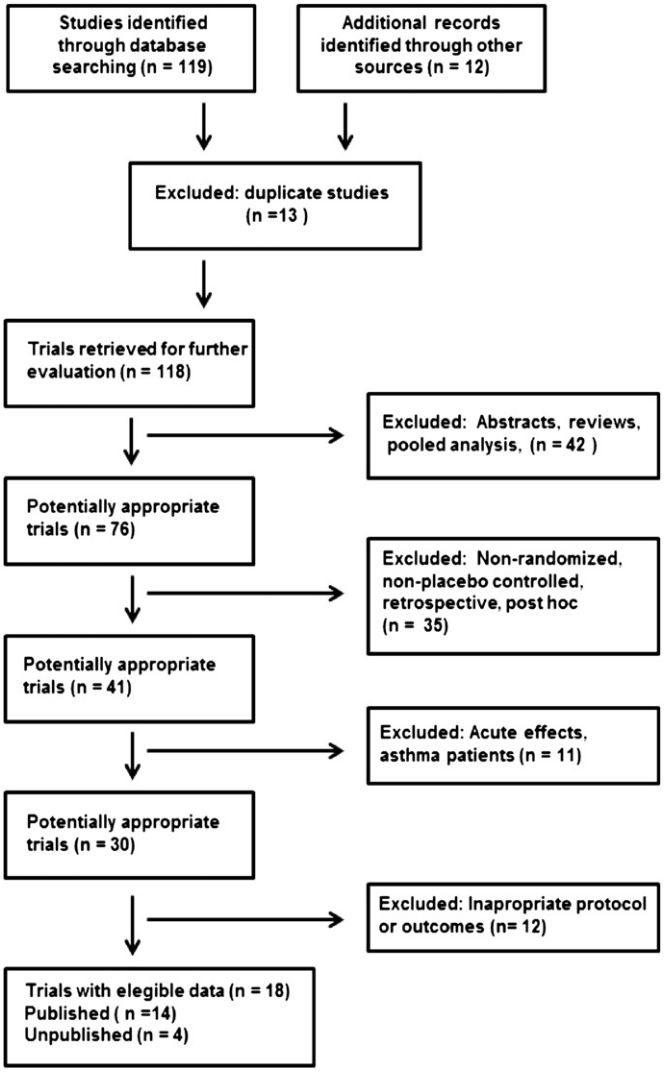

Fig. 1. Flowchart for identification of usable studies.

Table 1
Characteristics of included studies.

Study	Design	Location and duration (weeks)	Patients, *n* (% male), and % of all patients that completed the study	Mean age, y	Mean baseline FEV_1,% predicted	Current Smoker %	Use of ICS (%)	Selected comparisons	Outcomes measured
Aaron et al. [14]	R,DB, PG	MC, (54)	449, (32), 61	68	39	28	No	T 18 μg OD vs. T/SA 18 μg OD/50 μg TD vs. T 18 μg OD + SA/FL 50/500 μg TD	CE (M), HRQoL, DSP, FEV_1, AE
Bateman et al. [15]	R,DB, PG	MC, (6)	107 (71)	62	47	51	No	T 18 μg OD vs. SA/FL 50/500 μg TD	FEV_1, RU, AE
Cazzola et al. [16]	R,DB, PG	SC, (12)	90 (90), 91	66	38	82	No	T 18 μg OD vs. T 18 μg OD + SA/FL 50/500 μg TD vs. SA/FL 50/500 μg TD	FEV_1
Hanania et al. [17]	R,DB, PG	MC, (6)	155 (61), 90	65	46	46	46	T 18 μg OD vs. FO 20 μg (Neb) TD + T 18 μg OD	FEV_1 (M), RU, DSP, CE, HRQoL, AE
Hoshino and Ohtawa [18]	R,PG	SC (12)	46 (93),87	73	61	NS	No	T 18 μg OD vs. SA/FL 50/250 μg TD + T 18 μg OD	FEV_1, HRQoL.
GSK SCO 40034 [19]	R,DB, PG	MC, (12)	125 (74), 93	64	< 70	NS	NS	T 18 μg OD vs.SA/FL 50/500 μg TD	FEV_1, DSP, RU, AE
GSK SCO 30008 [20]	R,DB, PG	SC, (4)	55 (68), 98	59	30–80	61	No	T 18 μg OD vs. SA/FL 50/500 μg TD	Mucociliary clearance rate (M), FEV_1, RU, DSP, AE
GSK ADC111114 [21]	R,DB,PG	MC, (24)	342, (47), 78	61	40–80	NS	No	T 18 μg OD vs. SA/FL 50/250 μg TD + T 18 μg OD	FEV_1, AE
Kurashima et al. [22]	R,CO	SC, (16)	84 (99), 93	70	64	NS	No	T 18 μg OD vs. SA/FL 50μg/400 μg TD	FEV_1, HRQoL
Novartis CQAB 149B2341 [23]	R,DB, PG	MC, (12)	1134 (69), 94	64	30–65	NS	No	T 18 μg OD vs. T 18μg + IND 150 μg OD	FEV_1, AE
Novartis CQAB149B 2351 [24]	R,DB, PG	MC (12)	1142 (65), 94	63	30–65	NS	No	T 18 μg OD vs. T 18μg + IND 150 μg OD	FEV_1, AE
Singh et al. [25]	R,DB, CO	MC, (13)	41 (77), 80	63	47	47	0	T 18 μg OD vs. SA/FL 50/500 μg TD + T 18 μg OD vs. SA/FL 50/500 μg TD	FEV_1, DSP, RMU, AE
Tashkin et al. [26]	R,DB, PG	SC, (6)	129 (67), 87	65	38	37	Yes	T 18 μg OD vs. FO 20 μg (Neb) TD + T 18 μg OD	FEV_1, HRQoL, CE, DSP, RU, AE
Tashkin et al. [27]	R,DB, PG	MC, (12)	255 (66), 89	64	30–80	48	27	T 18 μg OD vs. FO 12 μg TD + T 18 μg OD	FEV1, HRQoL, CE, DSP, RU, AE
Terzano et al. [28]	R,SB, CO	SC, (4)	80 (61), 85	68	50	0	NS	T 18 μg OD vs. FO 12 μg TD + T 18 μg OD	FEV_1, DSP, RU
van Noord et al. [29]	R,DB, CO	MC, (20)	74 (79), 96	65	37	NS	89	T 18 μg OD vs. FO 12 μg + T 18 μg OD	FEV_1, CE, RU
van Noord et al. [30]	R,DB, CO	MC, (24)	95 (80), 91	64	39	26	85	T 18 μg OD vs. SA 50 μg TD + T 18 μg OD	FEV_1, DSP, CE, RU
Vogelmeier et al. [31]	R,DB, PG	SC,(24)	428 (79), 87	63	51	NS	Yes	T18 μg OD vs. FO 10 μg TD + T 18 μg OD	FEV_1 (M), HRQoL, RU, CE, AE
Wedzicha et al. [32]	R,DB, PG	MC, (104)	1323 (82), 61	64	31	38	No	T18 μg OD vs. SA/FL 50/500 μg TD	CE (M), HRQoL, FEV_1, AE
Welte et al. [33]	R,DB, PG	MC, (12)	665 (75), 91	62	38	56	No	T18 μg OD vs. FO/BU 9/320 μg TD + T 18 μg OD	FEV_1 (M), HRQoL, RU, CE, AE

AE = adverse effects; BU = budesonide; CO = cross over; COPD = chronic obstructive pulmonary disease; CE = COPD exacerbations; DB = double blind; DSP = dyspnea; FO = formoterol; FL = fluticasone; HRQoL = health-related quality of life; IND = indacaterol; FEV_1 = forced expiratory volume in the first second; M = main outcome; MC = multi center; Neb = nebulized; OD = once daily; PG = parallel group; R = randomized; RU = rescue medication use; SA = salmeterol; SC = single center; T = tiotropium; TD = twice daily.

Ten studies compared tiotropium plus LABA (salmeterol, formoterol or indacaterol) vs. tiotropium [14,17,23,24,26–31], seven compared salmeterol/fluticasone vs. tiotropium [15,16,19,20,22,25,32], and six studies compared tiotropium plus LABA/ICS (salmeterol/fluticasone or formoterol/budesonide) vs. tiotropium [14,16,18,21,25,33]. Three studies included two different comparisons (Table 1) [14,16,25]. Trials enrolled patients with stable COPD that met moderate to very-severe GOLD criteria (average baseline FEV_1 of 41% predicted) [1]. The mean age of patients was 64 years (72% of males). There were only four long-term trials (≥24 weeks) [14,30–32]. Allocation concealment was adequate in 8 studies [14–16,19–21,27,32] and data were not collected for patients who withdraw in twelve studies (Table 2) [14–16,18,19,23,24,27–30,32]. Ten trials were sponsored by the pharmaceutical industry [15,19–21,23,24,27,29,33].

3.1. Tiotropium plus LABA compared with tiotropium monotherapy

Data from ten trials [14,17,23,24,26–31] showed that the use of "dual" long-acting bronchodilator therapy (formoterol, salmeterol or indacaterol plus tiotropium) was associated with significantly increases in mean final pre-bronchodilator FEV_1 (70 mL), mean change in pre-bronchodilator FEV_1 from baseline (60 mL), mean final post-bronchodilator FEV_1 (130 mL), and mean change in post-bronchodilator FEV_1 from baseline (130 mL), compared with tiotropium monotherapy (Table 3). In the same way, "dual therapy" reported greater reductions in the use of rescue medication (−0.75 puffs/day) and dyspnea, and a significantly improvement in HRQoL (−1.81 units in the SGRQ). However, "dual" therapy did not significantly reduce the rate of COPD exacerbations (25.8%) in comparison with tiotropium monotherapy (27.3%). The rate of exacerbations (per 100 patient-years) was 32.1 in the LABA/tiotropium group and 33.1 in the tiotropium group. However, a post-hoc subgroup analysis showed that "long duration" studies (≥24 weeks) present a non-significant decrease (OR = 0.72; (95% CI, 0.44, 1.19) compared with "short duration" studies (OR = 1.76; 95% CI, 0.64, 4.79). Also, there was no significant difference in the number of prematurely discontinued patients between the "dual therapy" group (16.7%) and the tiotropium group (17.0%). SAE and pneumonia were reported by 3.9% and 0.47% of patients receiving "dual therapy", and 3.5% and 0.45% of patients receiving tiotropium ($p = 0.69$, and $p = 0.99$) respectively. In the same way, there were no significant differences of withdrawals due to adverse events (4.8% vs. 5.8%) or treatment failure (3.9% vs. 3.5%). Of all the outcomes that showed statistically significant differences, only three presented a moderate to substantial degree of heterogeneity. In these cases, 95% prediction intervals reflected the uncertainly of these estimates (Table 3). The post-hoc subgroup analysis showed that factors such as type of LABA (salmeterol, formoterol and indacaterol) and duration of treatment (<24 weeks vs. ≥24 weeks) did not influence the effect of mean final pre-bronchodilator FEV_1 ($p = 0.47$ and $p = 0.26$ respectively). A visual inspection of funnel plot of pulmonary function outcomes did not reveal any asymmetry, suggesting the absence of publication bias.

Table 2
Risk of bias of the eligible studies.

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?
Aaron et al. [14]	Yes	Yes	Yes	No
Bateman et al. [15]	Yes	Yes	Yes	No
Cazzola et al. [16]	Yes	Yes	Yes	No
Hanania et al. [17]	Yes	Unclear	Yes	Yes
Hoshinio and Ohtawa [18]	Unclear	Unclear	No	No
GSK SCO 40034 [19]	Yes	Yes	Yes	No
GSK SCO 30008 [20]	Yes	Yes	Yes	Yes
GSK ADC 111114 [21]	Yes	Yes	Yes	Yes
Kurashima et al. [22]	Yes	Unclear	No	Yes
Novartis CQAB1 49B2341 [23]	Yes	Unclear	Yes	No
Novartis CQAB 149B2351 [24]	Yes	Unclear	Yes	No
Singh et al. [25]	Yes	Unclear	Yes	Yes
Tashkin et al. [26]	Yes	Unclear	Yes	Yes
Tashkin et al. [27]	Yes	Yes	Yes	No
Terzano et al. [28]	Yes	Unclear	Yes	No
van Noord et al. [29]	Yes	Unclear	Yes	No
van Noord et al. [30]	Yes	Unclear	Yes	No
Vogelmeier et al. [31]	Yes	Unclear	No	Yes
Wedzicha et al. [32]	Yes	Yes	Yes	No
Welte et al. [33]	Yes	No	Yes	Yes

3.2. LABA plus ICS compared with tiotropium monotherapy

Data from seven studies [15,16,19,20,22,25,32] showed that LABA/ICS (salmeterol/fluticasone in all studies) combination produced small but significant increases in pre-bronchodilator FEV_1 measures compared with tiotropium (Table 4). Contrary, there were no significant differences in post-bronchodilator FEV_1 measures. Additionally, the LABA/ICS combination reduced significantly the use of rescue medication (−0.40 puffs/day), and significantly improved HRQoL (−2.07 units in the SGRQ). There was no significant difference in the number of patients that suffered COPD exacerbations between groups. The exacerbation rate (per 100 patient-years) was 31.9 in the LABA/ICS group and 30.5 in the tiotropium. However, there were more SAE and cases of pneumonia in patients on LABA/ICS (25.3% and 7.4%) than in those on tiotropium (20.4% and 3.4%). The NNTHs were 20 (95% CI, 11–119) and 25 (95% CI, 15–66) respectively. Finally, there were no significant differences in the withdrawals of any cause. However, data from one study [28] showed more all-cause deaths on tiotropium (38/665) than on salmeterol/fluticasone (21/658) (OR = 0.54; 95% CI 0.32–0.94). Except for post-bronchodilator FEV_1 outcomes and dyspnea, the heterogeneity was low or null.

3.3. LABA/ICS plus tiotropium compared with tiotropium monotherapy

Finally, six studies comparing LABA/ICS (salmeterol/fluticasone or formoterol/budesonide) plus tiotropium vs. tiotropium monotherapy [14,16,18,21,25,33] were assessed. Data showed further increases in pre and post-bronchodilator FEV_1 measures with "triple" therapy compared with tiotropium monotherapy (Table 5). Also, "triple therapy" improved HRQoL significantly more than did therapy with tiotropium (−3.95 units in the SGRQ), and decrease the rate of COPD exacerbations, although in a non-significant way (OR = 0.65; 95% CI: 0.36 to 1.19, $p = 0.17$). There were non-significant differences in dyspnea, SAE, pneumonia and withdrawals of any cause. Five measures (pre-bronchodilator FEV_1, HRQoL, dyspnea, exacerbations, and total withdrawals) showed statistical heterogeneity. In the case of pre-bronchodilator FEV_1, although most of the 95% predictive interval is above zero indicating the treatment will be beneficial in most settings, the interval falls below zero, and so in some settings the treatment may actually be ineffective. Contrary, for HRQoL, the interval is entirely below zero and shows that "triple" therapy will be beneficial when applied in at least of 95% of the individual study settings (Table 5).

Table 3
Effect of LABA plus tiotropium ("dual" long-acting bronchodilator therapy) vs. tiotropium monotherapy on different COPD outcomes.

Outcome	References	*N*	Mean duration, weeks (range)	Measure 95% CI	*p*	I^2 %	95% prediction interval
Mean final pre-bronchodilator FEV_1 (mL)	[14,17,22,23,25,28]	2969	17 (4–54)	WMD = 70 (50, 90)	0.0001	0	
Mean change in pre-bronchodilator FEV_1 (trough) from baseline (mL)	[14,26,27,29]	1003	23 (6–54)	WMD = 60 (30, 100	0.0003	82	−165, 35
Mean final post-bronchodilator FEV_1 (mL)	[14,22,23,25,29]	2701	23 (12–54)	WMD = 120 (100, 140)	0.0001	0	
Mean change in post-bronchodilator FEV_1 (peak) from baseline (mL)	[17,28,29]	439	11 (4–20)	WMD = 130 (100, 150)	0.0001	0	
Mean rescue medication (puffs/day)	[17,25–30]	1357	10 (4–24)	WMD = −0.75 (−1.17, −0.32)	0.0006	90	−2.04, 0.55
Final change in SGRQ	[14,15,25,26,30]	1205	20 (6–54)	WMD = −1.81 (−3.11, −0.51)	0.006	9	
TDI	[14,25–27,29]	981	24 (12–54)	WMD = −1.15 (−1.81, −0.48)	0.0007	66	−2.55, 0.26
Patients with COPD exacerbations	[14,17,25,26,28–30]	1501	30 (4–54)	OR = 0.94 (0.57, 1.57)	0.82	68	
Serious adverse effects	[14,17,22,23,25,26,30]	2273	17 (6–54)	OR = 1.02 (0.71, 1.48)	0.90	0	
Pneumonia	[14,25]	433	33 (13–54)	OR = 1.00 (0.10, 9.73	0.99	0	
Prematurely discontinued patients	[14,17,22,23,25,26, 28–30]	3774	17 (4–54)	OR = 0.96 (0.77, 1.20)	0.73	0	
Withdrawals due to adverse events	[14,17,22,23,25,26]	3490	17 (6–54)	OR = 0.99 (0.62, 1.59)	0.96	31	
Withdrawals due to treatment failure	[14,22,23,26,30]	3206	22 (6–54)	OR = 1.04 (0.54, 2.03)	0.90	0	

COPD = Chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; *N* = number of subjects; LABA = long-acting β_2-agonists; OR = Odds ratio; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.

4. Discussion

Long-acting bronchodilators (LAMA or LABA) are prescribed as a maintenance therapy for moderate COPD [1,2]. When symptoms are not adequately controlled with monotherapy, guidelines recommended the addition of LABA to LAMA ("dual" long-acting bronchodilator therapy), or the addition of ICS to LABA ("combined" therapy), or even a LABA plus ICS to a LAMA ("triple" therapy). Given the different mechanisms and duration of actions of these agents, they have the potential to provide better outcomes than the individual agents. To our knowledge this is the first systematic review performed to assess and compare the efficacy and safety of these three different therapeutic combinations in comparison with tiotropium monotherapy.

First, we found that the use of "dual" long-acting bronchodilator therapy (formoterol, salmeterol or indacaterol plus tiotropium) is associated with significant increases in pre and post-bronchodilator FEV_1 outcomes compared with tiotropium monotherapy. In particular, the improvements of pre and post-bronchodilator FEV_1 measures exceeded the predefined minimal important difference (MID) of 100 mL [34]. This therapy was also associated with significant reductions in the use of rescue medication (less than 1 puff/day) and dyspnea (a decrease greater than the threshold value of 1 point of TDI). However, the clinical relevance of the significant improvement in HRQoL seems uncertain because it did not reach the predefined MID range (−2.4 to −5.6 of SGRQ units) [34]. Conversely, "dual" bronchodilator therapy failed to significantly reduce the risk of COPD exacerbations compared with tiotropium. This fact could be a very important limitation of "dual therapy" because acute exacerbations are associated with significantly impaired health status, faster disease progression and have a huge impact on health care services in terms of activity and costs [35]. However, this result should be considered with caution because this outcome presented substantial statistical heterogeneity. Additionally, post-hoc analysis suggests that "long duration" studies with "dual therapy" could reduce the rate of COPD exacerbations. Finally, there were no differences in terms of SAE (pneumonia) and withdrawals between both therapies. In spite of the absence of a significant reduction in COPD exacerbations, the improvements in pulmonary function, dyspnea, and use of rescue

Table 4
Effect of LABA plus ICS ("combined" therapy) vs. tiotropium monotherapy on different COPD outcomes.

Outcome	References	*N*	Mean duration, weeks (range)	Measure 95% CI)	*p*	I^2 %
Mean final pre-bronchodilator FEV_1 (mL)	[15,24]	164	9 (6–12)	WMD = 60 (10, 120)	0.03	0
Mean change in pre-bronchodilator FEV_1 (trough) from baseline (mL)	[15,16,19,20,24]	404	8 (4–12)	WMD = 60 (10, 100)	0.01	0
Mean final post-bronchodilator FEV_1 (mL)	[15,22,25]	320	11 (6–16)	WMD = 40 (50, 130)	0.38	78
Mean change in post-bronchodilator FEV_1 (peak) from baseline (mL)	[15,20,22–25,32]	1698	24 (4–104)	WMD = 20 (30, 70)	0.40	69
Mean rescue medication (puffs/day)	[15,16,19,20,25]	404	9 (4–13)	WMD = −0.40 (−0.76, −0.03)	0.03	0
Final change in SGRQ	[22,32]	1479	60 (16–104)	WMD = −2.07 (−2.49, −1.64)	0.0001	0
TDI	[19,20,25]	237	10 (4–13)	WMD = −0.42 (−0.96, 0.03)	0.13	71
Patients with COPD exacerbations	19,25,32	802	43 (12–104)	OR = 1.12 (0.90, 1.40)	0.31	0
Serious adverse effects	[15,19,20,32]	1610	31 (4–104)	OR = 1.33 (1.04, 1.69)	0.02	0
Pneumonia	[20,32]	1378	54 (4–104)	OR = 2.22 (1.35, 3.63)	0.002	0
Prematurely discontinued patients	[16,19,20,25,32]	1620	29 (4–104)	OR = 0.90 (0.45, 1.80)	0.77	34
Withdrawals due to adverse events	[15,19,20,25,32]	1667	28 (4–104)	OR = 1.02 (0.73, 1.44)	0.90	0
Withdrawals due to treatment failure	[19,32]	1448	58 (12–104)	OR = 0.80 (0.50, 1.29)	0.36	0

COPD = Chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroids; n = number; LABA = long-acting β_2-agonists; OR = Odds ratio; *N* = number of subjects; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.

Table 5
Effect of LABA plus ICS plus tiotropium ("triple" therapy) vs. tiotropium monotherapy on different COPD outcomes.

Outcome	References	N	Mean duration, weeks (range	Measure 95% CI)	*p*	I^2 %	95% rediction interval
Mean final pre-bronchodilator FEV_1 (mL)	14,18,25,33	1,059	22 (12-54)	WMD = 90 (40,140)	0.0005	0	
Mean change in prebronchodilator FEV_1 (trough) from baseline (mL)	14,16,18,21,26,33	1461	20 (6-54)	WMD = 110 (60,150)	0.0001	83	−233,33
Mean change in postbronchodilator FEV_1 (peak) from baseline (mL)	21,26,33	1053	11 (6-16)	WMD = 130 (110,150)	0.0001	0	
Final change in SGRQ	14,18,33	991	26 (12-54)	WMD = 3.95 (6.18,-1.73)	0.0005	81	−5.41,−2.49
TDI	14,26	353	30 (6-54)	WMD = 0.99 (2.99,1.00)	0.33	81	
Patients with COPD exacerbations	14,21,33	1,303	27 (12-54)	OR = 0.65 (0.36,1.19)	0.17	75	
Serious adverse effects	14,21,33	1,303	27 (12-54)	OR = 0.68 (0.40,1.14)	0.14	0	
Pneumonia	14,33	961	33 (12-54)	OR = 1.27 (0.30,5.36	0.74	0	
Prematurely discontinued patients	14,21,33	1,033	26 (12-54)	OR = 0.65 (0.37,1.12)	0.12	71	
Withdrawals due to adverse events	14,21,33	1,033	26 (12-54)	OR = 1.01 (0.59,1.74)	0.96	0	
All-cause mortality	14,33	961	33 (12-54)	OR = 1.79 (0.54,5.89)	0.34	0	

COPD = Chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonists; N = number of subjects; OR = Odds ratio; SGRQ = Saint George Respiratory Questionnaire; TDI = Transitional dyspnea index; WMD = weighted mean difference.

medication, and even in HRQoL of combine tiotropium with a LABA, probably is better than adding an ICS in moderate to severe COPD.

Secondly, data comparing "combined" inhaled therapy (salmeterol/fluticasone) with tiotropium monotherapy showed modest but significant effects on mean pre-bronchodilator FEV_1 outcomes, use of rescue medication, HRQoL, and dyspnea compared with tiotropium monotherapy. However, these improvements were statistically but not clinically significant. Additionally, we found no difference in the exacerbation rate between groups, suggesting that both reduced the rate in a similar way. However, "combined" therapy" was associated with significantly increased rates of SAE (one of every 20 patients treated) and pneumonia (one of every 25 patients) in concordance with previous studies [36–38]. It is interesting to point out that these adverse effects were not accompanied by a significant increase of exacerbations, or deaths. The risk of pneumonia could be related to the fact that ICS achieve locally high concentrations in the lung, increasing the risk of pneumonia due to their immunosuppressive effects [39]. Actually, six of the seven studies included in this comparison used a high dose of fluticasone (1000 μg/d) [15,16,19–22,24,31]. In fact, inhaled fluticasone at dosages of 1000 μg/d exerts effects on serum cortisol levels that are equivalent to 10 mg of prednisone, a dose that may double the risk of pneumonia in patients with arthritis [40]. In summary, salmeterol/fluticasone and tiotropium seemed to achieve similar results to tiotropium monotherapy in terms of effectiveness but not safety.

And thirdly, patients treated with tiotropium plus LABA/ICS ("triple therapy") may have additional benefits in those with severe and very severe COPD. Thus, "triple therapy" provided a greater improvements in change post-bronchodilator FEV_1 from baseline that exceeded the MID (130 mL). In the same way, the HRQoL showed a decrease of 3.95 points of SGRQ that was not significantly inferior to MID [34]. Also, we found significant improvements in pre-bronchodilator FEV_1 outcomes although they did not reach their MIDs. Of the three therapeutic approaches studied, this is the only one that showed a non-significant decrease in the rate of COPD. Finally, there were no significant differences in safety and withdrawals between both therapies. Surprisingly, the presence of inhaled steroids in the triple therapy was not associated with an increase in the incidence of pneumonia, suggesting a protective effect of tiotropium. However, due to the low number of trials included in the analysis, the efficacy and safety of "triple therapy" remains uncertain. Thus, on the basis of only two trials [14,33] "triple therapy" was associated with a non-significant increase of all-cause mortality compared with tiotropium (1.4% vs. 0.8%).

This study met most of the methodological criteria suggested for systematic reviews [7]. Inclusion criteria were clearly defined. Several relevant databases were searched for published and unpublished articles in any language. Attempts were made to minimize error and bias in the process of study selection, data extraction and quality assessment. Trial quality was formally assessed, included appropriate criteria, and the results were clearly reported. The assessment indicated the variable quality of the included studies. In some cases (especially in comparisons between LABA/ICS and "triple" therapy with tiotropium monotherapy), the use of the funnel plot technique was not reliable due to the small number of studies. Accordingly, publication bias cannot be excluded. One third of outcomes explored showed evidence of substantial heterogeneity. Because a "random-effects" model was used, we assumed a priority that exist heterogeneity, so we needed to consider not only the mean effect size and its confidence interval (precision), but also how the true effects are distributed about this

Table 6
Summary of the three combined therapies assessed on main COPD outcomes.[a]

Combination	FEV_1	Dyspnea	Health-related quality of life	COPD exacerbations	SAE
LABA + tiotropium vs. tiotropium ("dual" therapy)	↑ (SD-A)	↓ (SD-A)	↑ (SD-B)	=("Long duration" studies suggest a reduction compared with "short duration" studies)	
LABA/ICS vs. tiotropium ("combined" therapy)	↑ (SD-B)	↓ (SD-B)	↑ (SD-B)		↑ (SD)
LABA/ICS + tiotropium vs. tiotropium ("triple" therapy)	↑ (SD-A)	↓ (NSD)	↑ (SD-A)	↓ (NSD)	↑ (NSD)

↑ improvement; ↓ decrease; = no difference.
[a] A = the improvement exceeded predefined minimal important difference (MID); B = the improvements did not reach the MID; NSD = statistically non-significant difference; SD = statistically significant difference.

mean. Thus, prediction intervals were calculated to address the distribution of true effect sizes. However, there were large differences among the studies included, as regards many factors which have large influence on the outcomes and results: duration of the study (from 4 to 104 weeks), sample size (from 43 to more than thousand), and outcomes considered. Thus, these facts might affect the ability to detect changes in relevant variables such as the rate of exacerbations.

In summary, this systematic review suggests (Table 6): 1) "Dual" long-acting bronchodilator therapy (tiotropium plus salmeterol, formoterol or indacaterol) is potentially a good pharmacological approach to improve clinical results in stable moderate COPD patients when symptoms are not adequately controlled with tiotropium monotherapy; however, there is limited evidence to support the long-term benefits and to demonstrate its potential to reduce exacerbation frequency; 2) Despite its effects on FEV_1, use of rescue medication, HRQoL, and dyspnea, overall salmeterol/fluticasone combination had a similar impact than tiotropium on patients with severe stable COPD, but with an increased risk in SAE and pneumonia; and 3) The evidence that emerges from a limited number of studies suggested a beneficial effect of "triple therapy" over tiotropium monotherapy on patients with severe and very severe COPD. Caution is warranted when interpreting these conclusions given the low number, the variable quality of the included trials, and the possibility of publication bias. Decisions about drug treatment should take into consideration the frequency of exacerbations in the particular patient and the potential for adverse effects (including a risk of pneumonia with ICS) and costs.

Further large, long-term randomized controlled trials comparing these combined pharmacological approaches with tiotropium are required to confirm the extent of these benefits and to assess the new and emerging pharmacological options for maintenance treatment. Specific future research should examine the long-term efficacy and safety of the different combinations of bronchodilators and ICS, as well as their effects on the natural history of COPD when used early in the disease progression. Data from the literature are still scarce and most studies are too short to generate strong messages that can help the clinician in selecting a correct therapeutic approach.

Appendix

Role of authors

Dr. Rodrigo: 1) has made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; 2) has drafted the submitted article and revised it critically for important intellectual content, and 3) has provided final approval of the version to be published.

Dr. Plaza: 1) has made substantial contributions to conception, design, and interpretation of data; 2) has revised the article critically for important intellectual content, and 3) has provided final approval of the version to be published.

Dr. Castro-Rodriguez: 1) has made substantial contributions to conception, design, and interpretation of data; 2) has revised the article critically for important intellectual content, and 3) has provided final approval of the version to be published.

Conflict of interests

Dr. Rodrigo has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Dr. Esteve SA, Merck Sharp & Dome, and Admiral. Dr. Plaza has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline, Dr. Esteve SA and Merck Sharp & Dohme. Dr. Castro-Rodriguez has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Merck Sharp & Dohme, GlaxoSmithKline, and Astra Zeneca.

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