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CONTRIBUTION OF BRONCHODILATOR COMBINATION THERAPIES TO COPD

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Objective: To determine the place in therapy of combination therapies of long-acting muscarinic antagonists (LAMA) and long-acting ß2 agonists (LABA) for the treatment of chronic obstructive pulmonary disease (COPD). **Methods:** We performed a review of data in EMA's European public assessment reports (EPAR) (www.ema.europa.eu) on the evaluation of marketed LAMA+LABA combinations. Reports on contributions to therapy by the Spanish Medicines and Health Devices Agency (www.aemps.gob.es) and evaluations by the UK NICE were also included (www.nice.org.uk). If additional information was required, corresponding published trial reports were reviewed. A literature search was performed on 04/01/2017. **Results and conclusions:** No clinically relevant differences were observed between LAMA+LABA combination therapies and LAMA monotherapy. The effectiveness of LAMA+LABA combinations in preventing exacerbations was only assessed with indacaterol / glycopyrronium, with modest results. The validity of comparative studies of LAMA+LABA vs. LABA+ corticosteroids was compromised by pre-trial exclusions of specific patients, and the inclusion of patients for whom a LABA+corticosteroid was contraindicated. A lack of scientific evidence exists to support the use of LAMA+LABA as first-choice therapy for COPD. **Keywords:** COPD, long-acting ß adrenoceptor agonists, LABA, long-acting anticholinergics, LAMA, double bronchodilator therapy.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease characterized by the long-term limitation of airflow. COPD is associated with an acute, chronic, inflammatory response in the airways and lungs after exposure to toxic particles or gases, primarily tobacco smoke. Disease severity depends on the frequency of exacerbations and extent of comorbidities. The prevalence and associated burden of morbidity and mortality with COPD are rather high.[1]

The most widely used guidelines for the management of this disease are the GOLD guidelines.[1] In pharmacological trials, inclusion criteria are frequently based on COPD staging as per GOLD criteria. The European Medicines Agency (EMA) performs evaluations based on GOLD guidelines.[2]

GOLD guidelines classify COPD severity according to the limitation of airflow, expressed as the percentage of forced expiratory volume in the first second (FEV1) following the administration of a bronchodilator, as compared to the theoretical value representing full function:

1. Mild: ≥ 80% predicted
2. Moderate: 50% to 79% predicted
3. Severe: 30% to 49% predicted
4. Very severe: < 30% predicted

In practice, FEV_1 < 50% has been traditionally used as the cut-off point for pharmacological therapy.

Pharmacological therapy is used to reduce symptoms, the frequency and severity of exacerbations and improve the health status and tolerance of the patient to physical exercise. There is no conclusive evidence supporting the effectiveness of any drug for COPD in preventing lung function deterioration in the long term.[1]

Inhaled bronchodilators are the first-choice drug therapy for COPD. Choices of drug therapies for COPD are based on GOLD stages,[3] which rely on spirometric values, the presence of exacerbations, and symptoms. The 2016 version of GOLD criteria introduced the use of the COPD Assessment Test (CAT). Dyspnea was assessed using the Modified British Medical Research Council scale (mMRC). Following these guidelines, patients were classified into four categories (A,B,C,D) (see table 1):

Grade A: low risk, less symptoms.
Grade B: low risk, more symptoms.
Grade C: high risk, less symptoms.
Grade D: high risk, more symptoms.

The GOLD guidelines established LAMA monotherapy as the therapy of choice for any stage of COPD requiring long-term therapy (table 1). This recommendation was based on studies with tiotropium, which report statistically significant differences in symptom improvement and the prevention of exacerbations after four years of treatment.[3,4] LABA + inhaled corticosteroids combination therapy was recommended as another first-choice therapy for patients with FEV1 <50% and/or more than one exacerbation per year or an exacerbation requiring hospitalization.

The 2017 GOLD guidelines[1] modified the "A,B,C,D" classification for pharmacological therapies, with the choice of drug therapy exclusively based on COPD symptoms and the presence of exacerbations. In the 2017 version, LAMA+LABA combination therapies are given more prominence, as they are recommended as initial therapy for group D, and as first-choice therapy for groups B and C (table 2).

Although the Spanish guide GesEPOC classifies COPD patients by phenotype,[5] inclusion criteria in clinical trials are not based on this classification and, consequently, there is no evidence supporting the indication of drug therapies by phenotype.

Additionally, indications for inhalers must be based both on the active ingredient and the device used, as the latter will determine the pulmonary deposition of the drug. If comparative studies are performed using different active ingredients as well as different devices, it is not possible to clearly differentiate between observed effects that are due to the substance or to the inhaler.

Table 1. First-choice drug therapy for stable COPD according to 2016 GOLD criteria (adapted from reference 3).

SPIROMETRY	RECOMMENDED FIRST-CHOICE THERAPY		EXACERBATIONS / YEAR
FEV_1 ≥50%	**GOLD A** Short-acting anticholinergic, if required or Short-acting beta2-agonist, if required	**GOLD B** LAMA or LABA	≤1
FEV_1 <50%	**GOLD C** LAMA or inhaled corticoid + LABA	**GOLD D** LAMA and/or inhaled corticoid + LABA	≥2 ≥1 with hospitalization
Symptoms	Mild symptoms CAT <10 mMRC 0-1	Moderate symptoms CAT ≥10 mMRC ≥2	

Table 2. First-choice drug therapy for stable COPD according to 2017 GOLD criteria (adapted from reference 1).

EXACERBATIONS / YEAR	RECOMMENDED INITIAL THERAPY	
≤1	**GOLD A** 1 bronchodilator	**GOLD B** LAMA or LABA
≥2 ≥1 with hospitalization	**GOLD C** LAMA	**GOLD D** LAMA + LABA
Symptoms	Mild symptoms CAT <10 mMRC 0-1	Moderate symptoms CAT ≥10 mMRC ≥2

Rationale for the use of bronchodilator combination therapies

The combination of different classes of bronchodilators has been reported to be superior to increasing the dose of bronchodilator monotherapy in terms of efficacy and safety.[1] However, this is contradicted by the fact that LAMAs are already at full dose in the combinations available on the market (table 1). Adding another bronchodilator does not necessarily provide clinically relevant differences (100 mL-FEV1 increase), as response in patients with moderate-to-severe COPD is limited.[6] Thus questions remain concerning the rationale for use of combination therapy.

Methods

A review was performed of relevant clinical trial results on marketed LAMA+LABA combination therapies evaluated in EMA's European public assessment reports (EPAR) (www.ema.europa.eu). Evaluations of a product's place in therapy (IPT) by the Spanish Medicines and Health Devices Agency (www.aemps.gob.es) and evaluations by the UK

Table 1. Marketed drug therapies for moderate-to-severe COPD.

MEDICINE (BRAND NAME)	DOSING	TREATMENT COST/DAY (€)
LAMA		
Tiotropium (Spiriva *Handihaler*)	18 mcg/24 h	1.64
Tiotropium (Spiriva *Respimat*)	5 mcg/24 h	1.59
Tiotropium (Braltus Zonda)	10 mcg/24 h	1.31
Glycopyrronium (Enurev, Seebri, Tovanor *Breezhaler*)	44 mcg/24 h	1.59
Umeclidinium (Incruse *Ellipta)*	55 mcg/24 h	1.51
Aclidinium (Bretaris, Eklira *Genuair*)	322 mcg/12 h	1.59
LABA + inhaled corticosteroid		
Salmeterol/fluticasone (Seretide, Anasma, Inhaladuo, Plusvent *Accuhaler;* Airflusal *Forspiro)*	50/500 mcg/12 h	1.38
Formoterol/beclometasone (Foster, Formodual *Nexthaler;* Formodual)	12/200 mcg/12 h	1.72
Formoterol/budesonide (Symbicort, Rilast *Turbuhaler*; Bufomix *Easyhaler;* Biresp, Duoresp *Spiromax*)	9/320 mcg/12 h	1.71
Vilanterol/fluticasone (Relvar *Ellipta*)	22/92 mcg/12 h	1.72
LAMA+LABA		
Glycopyrronium/indacaterol (Ultibro, Ulunar, Xoterna *Breezhaler*)	43/85 mcg/24 h	2.87
Umeclidinium/vilanterol (Anoro, Laventair *Ellipta*)	55/22 mcg/24 h	2.34
Aclidinium/formoterol (Duaklir, Brimica *Genuair*)	340/12 mcg/12 h	2.34
Tiotropium/odolaterol (Spiolto, Yanimo *Respimat*)	5/5 mcg/24h	2.73

Table 2. Outcomes of studies assessing bronchodilator effects for COPD.

OUTCOME	MINIMAL CLINICALLY RELEVANT DIFFERENCE
FEV_1	100-ml increase
Transition dyspnea index, TDI	1-unit increase
St George's Respiratory Questionnaire, SGRQ	4-point reduction
Exacerbation index	20% reduction (NICE)[9]
Exacerbation index	1/year reduction (EMA EPAR aclidinium/formoterol, pag. 98)[6]
Exacerbation index	15% reduction (FLAME trial)[10]

NICE were also included (www.nice.org.uk). If additional information was needed, the corresponding trial report was reviewed. The literature search was performed on 04/01/2017.

Aggregated data are presented whenever possible. When the "p" value but not the confidence interval was reported, the latter was calculated using the Altman et al. method.7 Additional statistic calculations were performed using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration).

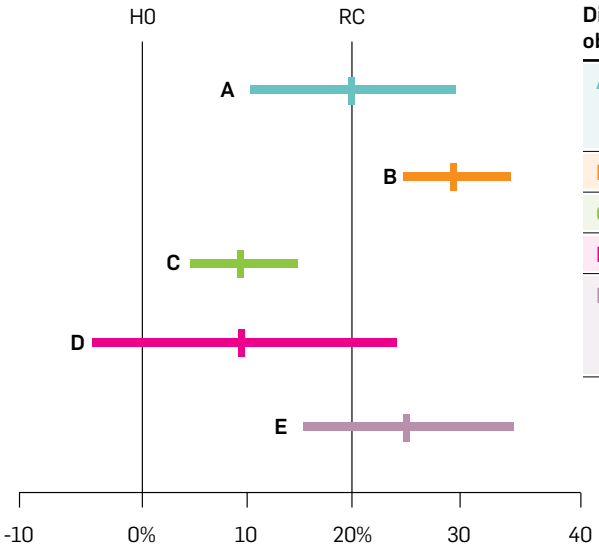
Outcomes

Assessment of bronchodilator effect was based on the results in FEV1, which is a surrogate endpoint weakly correlated with health status.[1]

Clinically relevant outcomes include dyspnea, as assessed using the transition dyspnea index (TDI), health-related quality of life as assessed by St. George's Respiratory Questionnaire (SGRQ), and number of exacerbations.[8] (Table 2).

Cut-off values were established by NICE for placebo-controlled comparative studies. Agencies use these values for comparative studies with inhalators.

Figure 1. Minimal clinically relevant difference and statistical significance [adapted from Argimon JM. *El intervalo de confianza: algo más que un valor de significación estadística.* Med Clin (Barc) 2002;118(10):382-4].



	Difference observed	Statistical significance	95% CI	Interpretation
A	20%	ES	+10 to + 30%	Inconclusive Potentially important (observation = relevant)
B	30%	ES	+25 to +35%	Important
C	10%	ES	+5 to +15%	Not important
D	10%	NS	+5 to +25%	Inconclusive
E	25%	ES	+15 to +35%	Inconclusive Potentially important (observation > relevant)

Theoretical results of a trial comparing an active therapy vs placebo where effects are measured on the basis of differences in percentages of recovery. Investigators consider that the minimal clinically relevant difference is 20%. H0: null hypothesis; CR: difference in clinical relevance; NS: not statitically significant (p> 0.05); SS: statistically significant (p< 0.05).

Comparators

Trials with LAMA+LABA combination therapies included patients with moderate, severe, or very severe COPD (GOLD groups B, C and D). Before LAMA+LABA therapies were approved, the therapy of choice for any stage of COPD was LAMA in monotherapy, whereas bronchodilator + corticosteroid were indicated for groups C and D. For the purposes of this review, only drugs approved for COPD at approved dose levels listed in drug label information were considered (table 1).

Trials

According to the EMA, as COPD is a chronic disease, the duration of trials assessing the effects of a drug on symptoms and lung function must be at least 12 weeks. Moreover, the effects of a therapy on exacerbations must be assessed in follow-up studies of at least 12 months of duration.[8] Based on this criterion, only trials of a minimum duration of 12 weeks to assess effects on symptoms and 12 months to evaluate effects on exacerbations were considered.

Assessment of clinically relevant effects of LAMA+LABA combination therapies

The selected trials included patients with moderate, severe or very severe COPD according to GOLD criteria. Unless otherwise indicated, studies listed in the tables were double-blind, with a duration of 24 to 26 weeks.

Lung function

The primary outcome of most studies was lung function. The most frequently used outcome was change in pre-dose FEV_1 after 24-26 weeks of treatment, that means FEV_1 change at the lowest concentration reached by the drug before the next dose is administered. Table 3 below describes the differences observed between the two groups. The minimal clinically relevant difference was established at 100ml.

In some studies, the primary outcome was area under the curve for FEV_1. For clarity, only pre-dose FEV_1 values are presented.

Table 3. Effects on lung function.

COMBINATION, n	COMPARATOR, n	DIFFERENCE IN PRE-DOSE FEV_1 VALUE (95%CI)	CLINICAL RELEVANCE	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 474	Glycopyrronium, 473	90 ml (60 to 110)	Unclear	[11]EPAR page 49
Glycopyrronium/indacaterol, 474	Tiotropium Handihaler® [a], 480	80 ml (50 to 100)	No	[11]EPAR page 49
Umeclidinium/vilanterol, 837	Umeclidinium, 418	64 ml (33 to 95)	No	[2]EPAR page 228
Umeclidinium/vilanterol, 837	Tiotropium Handihaler®, 418	62 ml (32 to 93)	No	[2]EPAR page 228
Aclidinium/formoterol, 620	Aclidinium, 598	29 ml (4 to 54)[b]	No	[6]EPAR page 73
Tiotropium/olodaterol, 1018	Tiotropium Respimat®, 1018	61 ml (40 to 82)[c]	No	[12]NICE
LAMA+LABA vs LABA+corticoide				
Glycopyrronium/indacaterol, 258	Salmeterol/fluticasone, 264	103 ml (65 to 141)	Unclear	[13]ILLUMINATE
Glycopyrronium/indacaterol, 1597	Salmeterol/fluticasone, 1595	62 ml (48 to 77)	No	[10]FLAME Apend. page 45 52 weeks
Aclidinium/formoterol, 468	Salmeterol/fluticasone, 463	-14 ml (-44 to 16)	No	[14]AFFIRM COPD
Umeclidinium/vilanterol, 1060	Salmeterol/fluticasone, 1059	90 ml (70 to 110)	Unclear	[15]12 weeks

(a) Open label treatment.
(b) Comparative study not reported in the EPAR. Statistical analysis performed for the purposes of this review.
(c) Meta-analysis of the main clinical trials performed for this review.

Dyspnea

The transition dyspnea index (TDI) measures changes in the severity of dyspnea on a -9 to +9 scale. The lower the value, the more severe the impairment. The minimal clinically relevant difference is 1 point. TDI was a secondary outcome in all included trials.

Table 4. Effects on dyspnea.

COMBINATION, n	COMPARATOR, n	DIFFERENCE IN TDI (95%CI)	CLINICAL RELEVANCE	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 432	Glycopyrronium, 435	0.21 (-0.17 to 0.59)[a]	No	[11]EPAR page 50
Glycopyrronium/indacaterol, 432	Tiotropium Handihaler® [b], 445	0.51 (0.14 to 0.88)[a]	No	[11]EPAR page 50
Umeclidinium/vilanterol, 837	Umeclidinium, 418	0.3 (-0.1 to 0.7)	No	[2]EPAR page 229
Umeclidinium/vilanterol, 837	Tiotropium Handihaler®, 418	0.1 (-0.3 to 0.5)	No	[2]EPAR page 229
Aclidinium/formoterol, 604	Aclidinium, 594	0.44 (0.08 to 0.79)	No	[6]EPAR page 75
Tiotropium/olodaterol, 992	Tiotropium Respimat®, 978	0.36 (0.09 to 0.62)	No	[12]NICE page 13
Tiotropium/olodaterol, 393	Tiotropium Respimat®, 385	0.59 (0.22 to 0.97)	No	[12]NICE page 17 12 weeks
LAMA+LABA vs LABA corticosteroid				
Glycopyrronium/indacaterol, 258	Salmeterol/fluticasone, 264	0.76 (0.26 to 1.26)	Unclear	[13]ILLUMINATE
Aclidinium/formoterol, 423	Salmeterol/fluticasone, 414	-0.00 (-0.46 to 0.46)	No	[14]AFFIRM COPD
Umeclidinium/vilanterol, 1060	Salmeterol/fluticasone, 1059	0.18 (-0.14 to 0.49)	No	[16,17]12 weeks[c]

(a) 95%CI calculated for this review.
(b) Open label treatment.
(c) Meta-analysis of the main clinical trials performed for this review.

Health-related quality of life

Health-related quality of life was assessed by the St. George Questionnaire (SGRQ) on a 0 to 100 scale. The higher the score, the poorer the quality of life. The minimal clinically relevant difference is 4 points. It is a secondary outcome in most included clinical trials, except for trials with tiotropium/olodaterol.

Table 5. Effects on health-related quality of life.

COMBINATION, n	COMPARATOR, n	DIFFERENCE IN SGRQ (95%CI)	CLINICAL RELEVANCE	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 729	Glycopyrronium, 739	-2.07 (-4.23 to 0.09)[a]	Unclear	[18,19]ClinicalTrials.gov, NCT01120691 64 weeks
Glycopyrronium/indacaterol,729	Tiotropium Handihaler® [b],737	-2.69 (-4.85 to -0.53)[a]	Unclear	[18,19]ClinicalTrials.gov, NCT01120691 64 weeks
Glycopyrronium/indacaterol, 475	Glycopyrronium, 475	-1.18 (-3.07 to 0.71)[a]	No	[20,21]ClinicalTrials.gov-NCT01202188
Glycopyrronium/indacaterol, 475	Tiotropium Handihaler®[b], 483	-2.13 (-3.73 to -0.53)[c]	No	[22]NICE
Umeclidinium/vilanterol, 837	Umeclidinium, 418	-0.67 (-2.43 to 1.10)	No	[2]EPAR page 233
Umeclidinium/vilanterol, 837	Tiotropium Handihaler®, 418	0.17 (-1.58 to 1.93)	No	[2]EPAR page 233
Aclidinium/formoterol, 594	Aclidinium, 584	-0.79 (-2.20 to 0.62)	No	[6]EPAR page 77
Tiotropium/olodaterol, 1029	Tiotropium Respimat®, 1033	-1.23 (-2.31 to -0.15)	No	[12]NICE[d]
Tiotropium/olodaterol,393	Tiotropium Respimat®, 384	-2.10 (-3.47 to -0.72)	No	[12]NICE[d] page 17 12 weeks
LAMA+LABA vs LABA+corticosteroid				
Glycopyrronium/indacaterol, 258	Salmeterol/fluticasone, 264	-1.24 (-3.33 to 0.85)	No	[13]ILLUMINATE
Glycopyrronium/indacaterol, 1602	Salmeterol/fluticasone, 1593	-1.3 (-2.1 to -0.4)	No	[10]Flame_apend_page 46 52 weeks
Aclidinium/formoterol, 468	Salmeterol/fluticasone, 463	1.0 (-0.8 to 2.8)	No	[14]AFFIRM COPD
Umeclidinium/vilanterol, 1060	Salmeterol/fluticasone, 1059	-0.08 (-1.34 to 1.18)	No	[15]12 weeks

(a) Statistical analysis performed for this review.
(b) Open label treatment.
(c) 95%CI calculated for this review.
(d) Primary endpoint of trials.

Exacerbations

According to the EMA, as COPD is a chronic disease, the duration of studies performed to assess the effects of drugs on exacerbations must be at least 12 months.[8] The only trials which met this requirement were a trial with glycopyrronium/indacaterol and another with tiotropium/olodaterol, but only the former had exacerbations as the primary outcome. The patients included in this study (SPARK[18]) had severe or very severe COPD. Disease severity in the remaining studies ranged from moderate to very severe.

Exacerbation was defined as a worsening of symptoms over two consecutive days. It was considered "moderate" if treated with systemic corticosteroids or antibiotics, and as "severe" if hospitalization or an emergency department visit was required.

Table 6. Effects on all exacerbations.

COMBINATION, n	COMPARATOR, n	ARR (95%CI)	RAR (IC95%)	CLINICAL RELEVANCE	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA					
Glycopyrronium/indacaterol, 729	Glycopyrronium, 739	0.85 (0.77 to 0.94)	0,60 (0,24 a 0,93) fewer exacerbations / patient-year	Unclear[b]	[18]SPARK 64 weeks
Glycopyrronium/indacaterol, 729	Tiotropium Handihaler® [a], 737	0.86 (0.78 to 0.94)	0,58 (0,24 a 0,88) fewer exacerbations / patient-year	Unclear[b]	[18]SPARK 64 weeks
LAMA+LABA vs LABA+corticoide					
Glycopyrronium/indacaterol, 1651	Salmeterol/ fluticasone, 1656	0.88 (0.82 to 0.94)	0,50 (0,25 a 0,74) fewer exacerbations/ patient-year	Unclear[c]	[10]FLAME[d] 52 weeks

(a) Open label treatment.
(b) NICE establishes 20% as the minimal clinically relevant difference.
(c) The minimal clinically relevant difference established in the trial was 15%.
(d) Primary outcome of the trial.

Table 7. Effects on moderate or severe exacerbations.

COMBINATION, n	COMPARATOR, n	RR (95%CI)	ARR (95%CI)	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 729	Glycopyrronium, 739	0.88 (0.77 to 0.99)	0,11 (0,01 a 0,25) fewer exacerbations /patient-year	[18]SPARK[a] 64 weeks
Glycopyrronium/indacaterol,729	Tiotropium Handihaler® [b], 737	0.90 (0.79 to 1.02)	No significant differences	[18]SPARK[a] 64 weeks
Tiotropium/olodaterol, 1029	Tiotropium Respimat®, 1033	0.92 (0.77 to 1.10)[c]	No significant differences	[12]NICE 52 weeks
LAMA+LABA vs LABA corticoide				
Glycopyrronium/indacaterol, 1651	Salmeterol/fluticasone, 1656	0,83 (0.75 to 0.91)	0,21 (0,11 a 0,30) fewer exacerbations /patient-year	[10]FLAME 52 weeks

(a) Primary outcome of the trial.
(b) Open label treatment.
(c) 95%CI calculated for this review.

The EMA concluded that the difference obtained with glycopyrronium/indacaterol was negligible and insufficient to consider it effective in reducing exacerbations, as no significant differences had been observed as compared with tiotropium monotherapy.

Table 8. Effects on severe exacerbations.

COMBINATION, n	COMPARATOR, n	RR (95%CI)	ARR (95%CI)	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 729	Glycopyrronium, 739	0.81 (0.60 to 1.10)	No significant differences	[18]SPARK 64 weeks
Glycopyrronium/indacaterol, 729	Tiotropium Handihaler® [a], 737	1.16 (0.84 to 1.61)	No significant differences	[18]SPARK 64 weeks
Tiotropium/olodaterol, 1029	Tiotropium Respimat®, 1033	1.14 (0.76 to 1.72)[b]	No significant differences	[12]NICE 52 weeks
LAMA+LABA vs LABA corticoide				
Glycopyrronium/indacaterol, 1651	Salmeterol/fluticasone, 1656	0.87 (0.69 to 1.09)	No significant differences	[10]FLAME 52 weeks

(a) Open label treatment.
(b) 95%CI calculated for this review.

Serious adverse events

Serious adverse events are defined as a reaction that results in death, requires hospitalization or prolongation of existing hospitalization or results in persistent or significant disability or incapacity.[23] This variable combines efficacy and safety, as it includes serious COPD exacerbations. In trial reports and EPARs, no statistical analyses were available for this outcome. A statistical analysis was specifically performed for the purposes of this review.

Of note, the percentage of patients with serious adverse events was much higher in studies of a duration ≥ 12 months, which supports the recommendation that long-term trials are performed in order to assess treatment benefits and harmful effects.

Table 9. Effects on serious adverse events.

COMBINATION, n	COMPARATOR, n	RR (95%CI)	ARR	REFERENCE / OBSERVATIONS
LAMA+LABA vs LAMA				
Glycopyrronium/indacaterol, 729 (22,9%)	Glycopyrronium, 740 (24,2%)	0.95 (0.79 to 1.14)	No significant differences	[22]NICE 64 weeks
Glycopyrronium/indacaterol,729 (22,9%)	Tiotropium Handihaler® [a],737 (22,4%)	1.02 (0.85 to 1,24)	No significant differences	[22]NICE 64 weeks
Glycopyrronium/indacaterol, 474 (4,6%)	Glycopyrronium, 473 (6.1%)	0.76 (0.44 to 1.30)	No significant differences	[21]SHINE
Glycopyrronium/indacaterol, 474 (4,6%)	Tiotropium Handihaler® [a], 480 (4,0%)	1.17 (0.64 to 2.14)	No significant differences	[21]SHINE
Umeclidinium/vilanterol, 1124 (5,1%)	Umeclidinium, 576 (5,0%)	1.01 (0.65 to 1.56)	No significant differences	[2]EPAR page 268
Umeclidinium/vilanterol, 1124 (5,1%)	Tiotropium Handihaler®, 423 (5,2%)	0.97 (0.59 to 1.61)	No significant differences	[2]EPAR page 268
Aclidinium/formoterol, 1111 (9,8%)	Aclidinium, 721 (7,4%)	1.33 (0.97 to 1.83)	No significant differences	[6]EPAR page 103
Tiotropium/olodaterol, 1029 (16,4%)	Tiotropium Respimat®, 1033 (16,7%)	0.99 (0.81 to 1.20)	No significant differences	[12]NICE page 14 52 weeks
LAMA+LABA vs LABA corticoide				
Glycopyrronium/indacaterol, 258 (5,2%)	Salmeterol/fluticasone, 264 (7,7%)	0.69 (0.42 to 1.12)	No significant differences	[15]
Glycopyrronium/indacaterol, 1678 (18,4%)	Salmeterol/fluticasone, 1680 (19,9%)	0.92 (0.80 to 1.06)	No significant differences	[10]FLAME page 2231 52 weeks
Aclidinium/formoterol, 467 (7,5%)	Salmeterol/fluticasone, 466 (7,1%)	1.06 (0.67 to 1.67)	No significant differences	[14]AFFIRM COPD
Umeclidinium/vilanterol, 1060 (2,3%)	Salmeterol/fluticasone, 1059 (2,4%)	1.00 (0.44 to 2.26)	No significant differences	[15]12 weeks

(a) Open label treatment.

LAMA+LABA vs. LAMA

Although the bronchodilator effect of LAMA+LABA vs. LABA monotherapy was the primary outcome in most trials, the clinical relevance of the improvements achieved is generally questionable or negligible.

Also, differences in dyspnea are all below thresholds for clinical relevance. No statistically significant differences have been observed either with glycopyrronium / indacaterol or with umeclidinium/vilanterol vs. glycopyrronium or umeclidinium monotherapy, respectively.

Similar results have been observed regarding health-related quality of life. Differences were not statistically significant in most trials, and no clinically relevant differences have been observed with any combination therapy as compared with monotherapy.

Effects on exacerbations have only been assessed in one trial with glycopyrronium/indacaterol. This trial reported a slight improvement as compared to glycopyrronium, which could not be demonstrated as compared to tiotropium. As differences were negligible, the EMA did not approve the introduction of the indication "reduction of exacerbations" in the product information for this medicine.

In terms of safety, both LABA and LAMA can cause cardiovascular adverse events (arrhythmias, atrial fibrillation and tachycardia) in some patients. LABA can induce clinically significant cardiovascular problems due to increased heart rate, blood pressure, prolongation of the QT interval and hypokalemia. Patients with uncontrolled cardiovascular disease or changes in heart conduction were excluded from trials. Therefore, the increased cardiovascular risk associated with LABA+LAMA cannot be established.

LAMA+LABA vs LABA+corticosteroid

The LABA + inhaled corticosteroid combination is recommended for severe or very severe COPD (GOLD C and D) inadequately controlled with bronchodilators.[1] The use of corticosteroids must be restricted to this indication, as they increase the risk of pneumonia.[3] This combination has been demonstrated to reduce the risk of exacerbations and provide a statistically significant improvement in quality of life in trials of a duration of up to three years.[24]

Relevant characteristics of included trials

In the pre-trial phase of the FLAME study, previous therapy was discontinued and replaced with tiotropium (LAMA) for four weeks. During this phase, 30% of patients were excluded, which may have resulted in the selection of patients with good tolerance and response to LAMA. This trial almost exclusively included patients with GOLD B (24%) and D disease (75%).[10] It is worth recalling that GOLD criteria do not recommend the use of inhaled corticosteroids for GOLD B disease due to the increased risk of pneumonia.[1,3]

The 26-week trial ILLUMINATE comparing indacaterol/glycopyrronium with salmeterol/fluticasone also involved a pre-trial phase where patients were treated with ipratropium (anticholinergic) as instructed plus salbutamol as needed. A total of 38% of patients were excluded from this phase of the trial, which may have led to an enrichment of patients which good tolerance to anticholinergics.[13]

Reflections on the market approval and evaluation process

The variability of data provided on LAMA+LABA combination therapies in the EPARs is surprising. As tiotropium/olodaterol was not approved in Europe through a centralized procedure involving the European Medicines Agency (EMA), an EMA EPAR is not available. In some studies, the most relevant comparisons are not reported, no statistical analysis is provided, or the *p* value but not the confidence interval is shown. This makes it difficult to determine the magnitude of differences, where appropriate. Limited data are provided on the effects of authorized combinations on exacerbations.

These limitations hinder the work of agencies that aim to establish the contribution of new combinations to therapy, as is the case of evaluations by the Spanish Grupo Coordinador de Posicionamiento Terapéutico (IPT) (www.aemps.gob.es), UK NICE (www.nice.org.uk), the French agency HAS (www.has-sante.fr) and the German agency IQWiG (www.iqwig.de). These agencies merely transcribe the data provided in EPARs and acknowledge the limited data available.

FEV$_1$ is poorly correlated with symptoms and health-related quality of life

LAMA monotherapy is a therapeutical option for any COPD stage

LAMA and LABA can cause cardiovascular adverse events

LAMA+LABA have not been clearly demonstrated to provide clinically relevant improvements as compared to LAMA monotherapy

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Annex

Figure 1 shows the number of COPD patients treated with long-acting inhaled agents in 2016. The number of patients treated with corticosteroids is remarkably high. GOLD guidelines do not recommend the administration of corticosteroids due to the increased risk of pneumonia.

Figure 1. COPD patients treated with long-acting inhaled agents in Navarre, Spain (categories are not mutually exclusive).

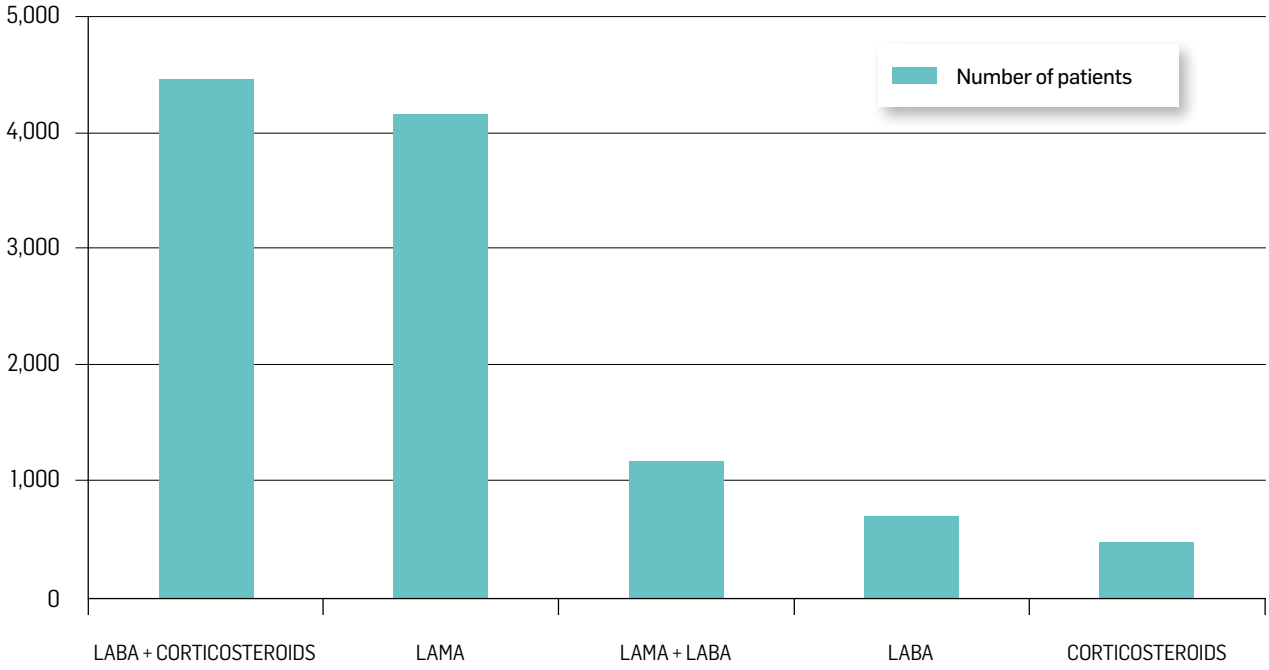
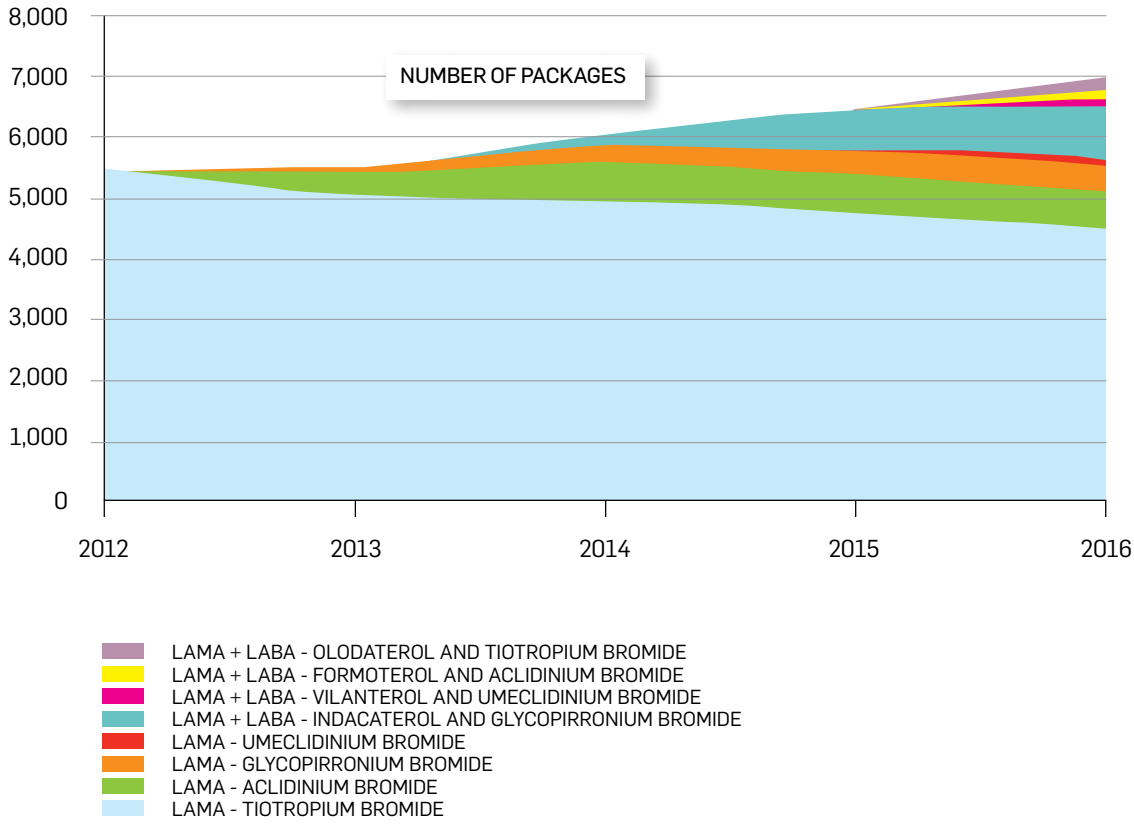


Figure 2. Evolution of the use of LAMA and LAMA + LABA.



Conclusions

No clinically relevant differences were observed between LAMA+LABA and LAMA in monotherapy.

The effectiveness of LAMA+LABA combinations in preventing exacerbations was only assessed as a primary outcome with indacaterol/glycopyrronium (vs. monotherapy), with unclear results. Effects of other combinations on exacerbations are unknown.

The validity of comparative studies of LAMA+LABA vs. LABA+ corticosteroids was compromised by the exclusion of patients prior to randomization and the inclusion of patients for whom a LABA+corticosteroid combination was contraindicated.

There is currently a lack of evidence supporting the use of LAMA+LABA as first-choice therapy, although patients who are unresponsive to monotherapy could benefit from these combinations.

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