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Once-daily LABA/ICS combined inhalers versus inhaled long-acting beta2-agonists for people with chronic obstructive pulmonary disease (COPD) (Protocol)

Hidalgo M P, Celis CA, Rojas-Reyes MX, Dennis RJ

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[Intervention Protocol]

Once-daily LABA/ICS combined inhalers versus inhaled long-acting beta2-agonists for people with chronic obstructive pulmonary disease (COPD)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and safety of once-daily LABA/ICS in a combined inhaler versus once/twice-daily LABA for the treatment of COPD.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition that is associated with significant mortality and morbidity (GOLD 2015), being the fourth leading cause of death worldwide (WHO 2012). The primary risk factor for COPD is inhalation of agents such as tobacco or biomass smoke, but occupational dusts and fumes and exposure to air pollution have also been reported to be independent risk factors (Postma 2015). Inhalation of these agents is associated with airway inflammation, presenting as bronchiolitis and emphysema. These structural changes cause impairment of expiratory flow and lead to resting and exercise hyperinflation (Rossi 2015), and they are related to the occurrence of progressive symptoms, such as dyspnoea, cough and sputum production (Vestbo 2014).

The natural history of COPD is characterised by exacerbations or episodes of clinical and lung function deterioration associated with an increase in airway and systemic inflammation (Hurst 2009). Acute exacerbations are now the main outcome evaluated in clinical trials as they are associated with increased respiratory and cardiovascular mortality, long-term decline in lung function and poorer quality of life (Wedzicha 2014), effects that are greater in those patients who have a frequent exacerbator phenotype (Wedzicha 2013).

Pharmacological therapy for COPD is therefore aimed at improving lung function, exercise capacity and quality of life, relieving symptoms and preventing exacerbations (Woodruff 2015).

Description of the intervention

Bronchodilators are the main strategy in the pharmacological management of COPD and guidelines recommend a stepwise approach in which short-acting agents are used first; if symptoms persist or there are exacerbations, long-acting bronchodilators of different classes are recommended to maximise bronchodilation. Inhaled long-acting beta$_2$-agonists (LABA) or long-acting muscarinic antagonists (LAMA) are usually used (COPDX 2015; GOLD 2015; Miravitlles 2014; NICE 2010).

In patients with severe to very severe COPD who are symptomatic or experience frequent exacerbations, guidelines recommend inhaled corticosteroids (ICS) in combination with LABA and LAMA (COPDX 2015; GOLD 2015; Miravitlles 2014; NICE 2010).

The efficacy and safety of combined twice-daily LABA/ICS in one inhaler versus twice-daily LABA for the treatment of COPD has been reported and the data from 14 studies with 11,794 severe COPD patients have been reviewed (Nannini 2012).

Given that COPD patients with higher adherence experience fewer hospitalisations than those with lower adherence, there is a strong interest in determining the effects of a once-daily LABA/ICS combination therapy, in an attempt to simplify the treatment and, consequently, increase adherence to the prescribed therapy (Fuso 2013).

In May 2013, the US Food and Drug Administration (FDA) approved once-daily fluticasone/vilanterol via a dry powder inhaler for the long-term treatment of airflow obstruction in COPD patients and to reduce exacerbations in patients with a history of these events (FDA 2013). In 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended a marketing authorisation for the symptomatic treatment of adults with COPD with a post-bronchodilator forced expiratory volume in the first second (FEV_1) of less than 70% predicted normal and an exacerbation history despite regular bronchodilator therapy (EMA 2014). Additionally, there are several once-daily LABA and once-daily ICS under clinical development (Pelaia 2015).

Little is known about the efficacy and safety of once-daily LABA/ICS combination in COPD treatment in comparison with LABA monotherapy; this subject will be the focus of this review.

How the intervention might work

The efficacy of LABA/ICS combination in COPD has been well described (Pelaia 2015). ICS reduce the risk of exacerbations beyond that achieved by LABA, although the beneficial effect of the LABA/ICS combination over LABA alone is observed in the frequency of moderate COPD exacerbations (those requiring systemic corticosteroids or antibiotic treatment) but not in the frequency of severe exacerbations (hospitalisations) (D'Urzo 2015).

The current opinion is that the benefit from combining ICS and LABA might be due to a synergistic interaction (Bateman 2014), the mechanism for which has not yet been fully understood. There is evidence that ICS increase the expression of cell surface receptors and the transcription of the beta$_2$-adrenoceptor gene. Instead, LABAs increase the anti-inflammatory effects of ICS by improving the translocation of glucocorticoid receptors from the cytoplasm to the nucleus after activation by corticosteroids (Cazzola 2010).

The addition of ICS to LABA is recommended for the treatment of severe/very severe COPD with frequent exacerbations (two or more per year) (group C and D of the current GOLD guidelines) (GOLD 2015). Use of LABA/ICS could also be considered in patients with the asthma-COPD overlap syndrome and in those with moderate COPD and persistent exacerbations despite treatment with a long-acting bronchodilator (Koblizek 2013).

The risk/benefit ratio has to be carefully assessed when considering treatment with ICS in patients with COPD. The most frequent ICS side effects include dysphonia, skin bruising and oral candidiasis. In general, these effects have not been severe enough to alter management, but they appear to increase with higher doses and with cumulative exposure. Additional adverse effects of ICS include osteoporosis, diabetes and cataracts (Battaglia 2014).

A meta-analysis involving 31,397 participants in 43 long-term randomised controlled trials (RCTs) showed a significantly increased risk of pneumonia with the use of fluticasone or budesonide in COPD without an effect on mortality (Kew 2014).

Why it is important to do this review

In COPD, the optimum combination of agents with beneficial effects on symptoms, quality of life and exacerbations has not been established (COPDX 2015; GOLD 2015; Miravitlles 2014; NICE 2010).

A recent meta-analysis that evaluated twice-daily LABA/ICS in one inhaler versus twice-daily LABA for treatment of COPD analysed the data from 11,794 people with severe COPD in 14 RCTs and brings into question the superiority of LABA/ICS over LABA in preventing exacerbations (Nannini 2012). The effects on severe exacerbations (hospitalisations) were inconsistent and the treatments had similar effects on mortality. Quality of life, symptoms scores, rescue medication use and FEV_1 improved more on LABA/ICS than on LABA, but the differences were probably not clinically significant. There was an increased risk of pneumonia with the use of LABA/ICS, so for an individual patient this would need to be balanced against the effect on exacerbations (Nannini 2012).

As LABA/ICS therapy is considered an important strategy for treating severe/very severe COPD with frequent exacerbations, there is a strong interest in determining the efficacy and safety of a once-daily LABA/ICS combination, in an attempt to simplify treatment and increase adherence (Fuso 2013).

This is a crucial issue in the treatment of COPD patients because those with low adherence experience more hospitalisations and higher healthcare costs than those with high adherence behaviour (van Boven 2014).

The effectiveness and safety of once-daily LABA/ICS combination versus once/twice-daily LABA in COPD is not known.

OBJECTIVES

To assess the effectiveness and safety of once-daily LABA/ICS in a combined inhaler versus once/twice-daily LABA for the treatment of COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel-group randomised controlled trials (RCTs) reported as full-text articles, as well as those published as abstracts only and unpublished data.

Types of participants

We will include all participants with a diagnosis of stable COPD (GOLD 2015; smoking history of ≥ 10 pack-years and a post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%) and we will record the definitions for each study.

Types of interventions

We will include trials comparing:

- once-daily LABA/ICS (fluticasone/vilanterol 100/25 µg or 200/25 µg; mometasone/indacaterol 400/500 µg) in a combination inhaler versus once-daily LABA (indacaterol 150 µg or 300 µg; vilanterol 25 µg; olodaterol 5 µg);
- once-daily LABA/ICS (fluticasone/vilanterol 100/25 µg or 200/25 µg; mometasone/indacaterol 400/500 µg) in a combination inhaler versus twice-daily LABA (formoterol 9 µg; salmeterol 50 µg).

Types of outcome measures

Primary outcomes

1. Acute exacerbations of COPD, defined as need for treatment with oral steroids, antibiotics or both (moderate exacerbations) or hospital admission for a COPD exacerbation (severe exacerbations).
2. Respiratory health-related quality of life (HRQoL) as measured by the Chronic Respiratory Questionnaire (CRQ) or St. George's Respiratory Questionnaire (SGRQ).
3. Pneumonia, defined as treatment or hospital admission for pneumonia.

Secondary outcomes

1. Dyspnoea scores: defined by the modified Medical Research Council (mMRC) or Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) dyspnoea domain. We will also include other valid dyspnoea scales.
2. Lung function: change from baseline in trough FEV_1 and forced vital capacity (FVC).
3. Rescue medication use.
4. Exercise capacity: six-minute walking test.
5. Mortality.
6. Severe adverse events and cardiovascular events.
7. Other adverse events: upper respiratory tract infections, oral candidiasis, nasopharyngitis, sinusitis, dysphonia, headache, ocular events.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group and contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO (Appendix 1).
We will search all records in the CAGR using the search strategy presented in Appendix 2.
We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will identify trials through the use of the LILACS/BIREME database, the main respiratory journals and meeting abstracts (American Thoracic Society (ATS), European Respiratory Society (ERS) annual meetings).
We will check the reference lists of all primary studies and review articles for additional references.
We will conduct a search of ongoing clinical trials in the ClinicalTrials.gov registry (www.ClinicalTrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) and clinical trial databases of

pharmaceutical companies manufacturing once-daily LABA/ICS combination inhalers.

Data collection and analysis

Selection of studies

Two review authors (MXR and CC) will independently screen titles and abstracts for all potential studies identified as a result of the search and they will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'.

We will retrieve the full-text study reports/publications; two review authors (RD and CC) will independently screen the full-text articles, identify studies for inclusion and identify and record the reasons for exclusion of ineligible studies.

We will resolve disagreements through discussion or, if required, we will consult a third review author (PH).

We will identify and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review.

We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (MXR and CC) will extract study characteristics and outcome data from included studies.

We will resolve disagreements by consensus or by consultation with a third review author (RD).

We will extract the following study characteristics:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals and date of study.
2. Participants: N, mean age, age range, gender, severity of COPD, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes and time points reported.
5. Funding for trial and notable conflicts of interest of trial authors.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way.

We will input all the data collected to Review Manager 5 (RevMan 2014).

We will double-check that data are entered correctly by comparing the data presented in the systematic review with those provided in the study reports. A second review author (PH) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (MXR and CC) will independently assess risk of bias for each study and make a judgement of 'low', 'high' or 'unclear' risk of bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will assess risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We will resolve disagreements by consensus or by consultation with another review author (PH).

We will summarise risk of bias judgements across different studies for each of the domains listed in the 'Risk of bias' table.

Quality of evidence

We will assess the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. This methodological approach considers RCTs as high-quality evidence that may be rated down by limitations in any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. The GRADE approach results in an assessment of the quality of a body of evidence as one of four grades (Guyatt 2011):

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

One review author (CC) will independently assess the quality of the body of evidence found for each of the outcomes that we identified as critical or important for clinical decision-making. Following the GRADE approach, if study authors did not take measures to ensure concealment of allocation, randomised assignment, completed follow-up or blinded outcome assessment, we will downgrade the quality of evidence because of design limitations.

We will evaluate consistency by the similarity of point estimates, the extent of overlap of confidence intervals (CI) and using statistical criteria including a test for heterogeneity (I^2 statistic). We

will downgrade the quality of evidence when inconsistency across study results is present, being large and unexplained (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation).
We will assess precision with the 95% CI around the pooled estimate and the calculation of optimal information size.
When trials are conducted in populations other than the target population, or the interventions assessed or outcomes measured differ from those included in the review question, we will downgrade the quality of evidence because of indirectness.
We will include the results of this assessment, as well as the information on the effect measures, in the GRADEpro software to develop a 'Summary of findings' table that will be included in the final report.

Measures of treatment effect

When multiple trial arms are reported in a single trial, we will include only the relevant arms (once-daily LABA/ICS versus once-daily or twice-daily LABA).
For acute exacerbations reported as a dichotomous variable, we will use the risk ratio as the measure of treatment effect. If data on exacerbations are reported as time free of exacerbation or time to first exacerbation, we will use the hazard ratio. If rates of exacerbation are reported, we will analyse these using rate ratios. We will report all measures of treatment effect with the corresponding 95% CIs.
To compare the treatment effect on respiratory health-related quality of life (HRQoL) we will summarise those RCTs reporting on the same scale (CRQ or SGRQ) using the standardised mean difference. For this outcome we will narratively describe skewed data reported as medians and interquartile ranges.
We will report the treatment effect on pneumonia using the risk ratio at follow-up.

Unit of analysis issues

We will use dichotomous data using participants (rather than events) as the unit of analysis to avoid counting the same participant more than once.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible.
We will perform a sensitivity analysis to assess how the changes in assumptions may affect the results if data are judged to be 'not missing at random'.
We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will evaluate the possible sources of clinical heterogeneity (i.e. if treatments, participants and the underlying clinical question are similar enough among trials). If we identify substantial clinical heterogeneity we will consider reporting by subgroups.
We will use the I^2 statistic to measure statistical heterogeneity among the trials in each analysis. Heterogeneity might not be important (I^2 statistic value of 0% to 40%); it may be moderate (I^2 statistic of 30% to 60%); it may be substantial (I^2 statistic of 50% to 90%); or it may be considerable (I^2 statistic of 75% to 100%).
We will consider a Chi^2 test P value of less than 0.10 indicative of statistical heterogeneity.

Assessment of reporting biases

We will assess possible reporting biases on two levels: within-study and between-studies.
We will examine within-study selective outcome reporting as a part of the overall 'Risk of bias' assessment.
We will attempt to find protocols for included studies and compare the outcomes stated in the protocols with those reported in the publications. We will compare the outcomes listed in the methods section of a publication with those for which results are reported if protocols are not found.
We will contact study authors for clarification if we identify indications of reporting bias.
We will create a funnel plot of effect estimates against their standard errors (SE) to assess possible between-studies reporting bias if there are at least 10 studies included in the review. We will consider possible explanations if we find asymmetry of the funnel plot.

Data synthesis

We will perform a fixed-effect meta-analysis for the estimation of pooled effects (for effectiveness and safety outcomes).
We will perform a random-effects meta-analysis if we identify important statistical heterogeneity among the results of included studies (I^2 statistic from 40% to 60%). If substantial or considerable unexplained heterogeneity (> 60%) is present we will not perform meta-analysis (see Assessment of heterogeneity).

'Summary of findings' table:

We will create a 'Summary of findings' table to report the primary and secondary outcomes identified above.
We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (Brozek 2008). We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes and we will make comments to aid the reader's understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We will present the primary outcomes in subgroup analyses. We plan to carry out the following subgroup analyses if data are available.

- Different once-daily ICS/LABA combinations.
- Subgroup analysis based on baseline COPD severity: severe/very severe versus mixed population.
- Length of follow-up (less than six months versus six months or longer).
- Participants with baseline ICS use versus participants without baseline ICS use.

We will use the formal test for subgroup interactions provided in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

- A comparison based on our 'Risk of bias' assessments.
- A comparison of results from fixed-effect models versus results from random-effects models.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 2. Search strategy to identify relevant records from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 combin* NEAR inhaler*
#8 fluticasone* AND vilanterol*
#9 mometasone* AND indacaterol*
#10 QMF149
#11 GW685698 AND GW642444
#12 FF AND VI:ti,ab
#13 MF AND IM:ti,ab
#14 FDC:ti,ab
#15 once NEXT daily
#16 steroid* OR corticosteroid* or ICS
#17 (long-acting* or long NEXT acting*) NEAR beta*
#18 #15 AND #16 AND #17
#19 #7 OR #8 or #9 or #10 or #11 or #12 or #13 or #14 or #18
#20 #6 AND #19

[In search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD]

CONTRIBUTIONS OF AUTHORS

María Ximena Rojas and Carlos Celis wrote the first draft of the protocol. Patricia Hidalgo and Rodolfo Dennis commented and contributed to the protocol and approved it before its publication.

DECLARATIONS OF INTEREST

CC received payment for lectures in June 2014 from Astra Zeneca and November 2014 from Novartis and expenses for conference attendance in May 2014 from Astra Zeneca, Novartis and Boehringer.

MXR has no conflict of interest in the present review.

PH has no conflict of interest in the present review.

RJD has no conflict of interest in the present review.

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Logistic support

External sources

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